# A Review On Various Herbal Plants And Behavioral Model's On Parkinson's Disease

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***Abstract-*** *Parkinson's disease is a chronic neurodegenerative disorder with a myriad of motor and non-motor symptoms. Its management is essentially palliative, and it can extend to three to four decades. Device-assisted therapy including deep brain stimulation, apomorphine pump, and levodopa gel intestinal infusion, have significantly improved management of advanced Parkinson's disease. The condition is associated with damage to the dopaminergic neurons inthe substantia nigra pars compacta, a great decrement of dopamine neurotransmitter in the striatum, and a deficiency of tyrosine hydroxylase; the rate-determining enzyme during dopamine formation. Various approaches , including genetic manipulations and toxin-induced insults, aim to recapitulate both motor and non-motor aspects of PD in animal models. Parkinson's disease (PD) is the world's most widespread chronic neuron degenerative motion condition affecting more than 10 million people. The characteristic hallmark of PD involves a progressive loss of dopaminergic neurons in the brain's Substantial Nigra.*

***Keywords:*** Parkinson's disease, Levodopa, Dopamine agonists, Non-motor symptoms, Genetic models of PD, Motor impairment, Herbal Drug treatment

## I. INTRODUCTION

Parkinson's disease is the second most prevalent neurodegenerative disease worldwide .[1] This condition is illustrated for the loss of up to seventy percent of the dopaminergic neurons in the substania nigra pars compacta (SNc), a huge decrease in dopamine (DA) in the striatal neurons. [2] Parkinson's disease (PD) is an age- related neurodegenerative disorder that pathological feature is basically related on the progressive degradation of dopamine production in substantia nigra. The clinical manifestation include bradykinesia (especially having difficulties in initiating movement), hypokinesia (lose of facial expression), rigidity, rest tremor (pill- rolling movement of the forearm) and non- motor features including depression, psychosis autonomic dysfunction.[3]

## II. CLASSIFICATION

**I. Drugs affecting brain dopaminergic system**

a) Dopamine precursor : Levodopa (l-dopa)
b) Peripheral decarboxylase inhibitors : Carbidopa, Benserazide.
c) Dopaminergic agonists: Bromocriptine, Ropinirole, Pramipexole
d) MAO-B inhibitor: Selegiline, Rasagiline
e) COMT inhibitors: Entacapone, Tolcapone
f) Glutamate (NMDA receptor) antagonist (Dopamine facilitator): Amantadine.

**II. Drugs affecting brain cholinergic system**

**a)** Central anticholinergics: Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.
**b)** Antihistaminics : Orphenadrine, Promethazine [4]

## III. PATHOLOGY OF IDIOPATHIC IN A PARKINSON'S DISEASE:

The dominant pathology of idiopathic Parkinson's disease(PD) isprimarily a loss of dopamine-producing cells in the substantia nigra in the midbrain, followed by degeneration of nigrostriatal pathway, depriving basal ganglia of dopamine required to facilitate all motor activities.[5]

**1. Macroscopic Pathology**

Depigmentation of the substantia nigra pars compacta (SNpc):

- The midbrain appears pale due to loss of neuromelanin-containing dopaminergic neurons in the SNpc.
- Locus coeruleus depigmentation may also occur.

**2. Microscopic Pathology**

- Loss of dopaminergic neurons:
  Primarily in the SNpc, leading to reduced dopamine levels in the striatum (especially the putamen).
- Lewy neurites:
  Abnormal neuritic processes containing α-synuclein.

**3.Braak Staging of PD Pathology**

Proposed by Heiko Braak, it describes the sequential progression of α-synuclein pathology:

- **Stage 1–2:** Involvement of the medulla and olfactory bulb (preclinical phase).
- **Stage 3–4:** Spread to midbrain (SNpc) and limbic areas (onset of motor symptoms).
- **Stage 5–6:** Involvement of neocortex (cognitive and neuropsychiatric symptoms).

**4. Neurochemical Changes**

- Dopamine deficiency in the striatum is the primary cause of motor symptoms.
- Secondary changes in other neurotransmitter systems: acetylcholine,serotonin, andnorepinephrine also contribute to non-motor symptoms.[6]


**Fig :- 1 [7] - Pathology of idiopathic in a Parkinson`s disease**

## IV. DIAGNOSIS OF PD

Presently, the diagnosis of Parkinson's is primarily based on the common symptoms outlined above. There is no X-ray or blood test that can confirm the disease. However, noninvasive diagnostic imaging, such as positron emission tomography (PET) can support a doctor's diagnosis. Conventional methods for diagnosis include.

- The presence of two of the three primary symptoms
- Responsiveness to Parkinson's medications, such as levodopa.[8]

## V. COMMON SYMPTOMS

- Tremor or the involuntary and rhythmic movements of the hands, arms, legs and jaw
- Muscle rigidity or stiffness of the limbs – most common in the arms, shoulders or neck
- Gradual loss of spontaneous movement, which often leads to decreased mental skill or reaction time, voice changes, decreased facial expression, etc.


**Fig:- 2 -Symptoms of Parkinson`s disease**

## VI. CAUSES OF PARKINSON'S DISEASE

- **Neurotransmitter Death**

The brain'ssubstansia nigra produce dopamine. If the dopaminergic neurons that secrete dopamine begin to die rapidly, the amount of dopamine in the body declines, resulting in Parkinson's symptoms.

- **Gene Abnormality**

The much more similar inherited cause of Parkinson's disease is a single genetic mutation in the LRRK2 gene.

## VII. TREATMENT OF PARKINSON'S DISEASE

Pharmacologic treatments for Parkinson's disease motor symptoms are primarily dopamine based. Levodopa preparations, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors are useful initial therapies. For young individuals with prominent tremors, anticholinergic agents (e.g., trihexyphenidyl) are useful, but caution is required because of the potential for adverse events, particularly relating to cognition. More than 40% of individuals treated with oral dopamine agonists (ropinirole, pramipexole) experience impulse control disorders (e.g., gambling, compulsive spending, abnormal sexual and eating behaviors, compulsive medication use, and lobbyism). [9]

## VIII. VARIOUS PLANTS USE ON ANTI-PARKINSONIAN ACTIVITIY

The herbal medicines were listed in table 3, which, according to their families, species and part of the plant used in treatment, have been shown to be effective on PD.

| Sr. No | Plant Name | Families | Species | Plant Part |
|---|---|---|---|---|
| 1 | Chrysanthemumindicum | Asterceae | C.indicum | Whole plant |
| 2 | Trifolium | Fabaceae | Trifoliumpratense | Whole plant |
| 3 | Tripterygium | Celastraceae | TripterygiumwilfordiiHookF. | Root & bark |
| 4 | Bacopa | Plantaginaceae | Bacopa monnieri | Whole plant |
| 5 | Gynostemma | Cucurbitaceae | Gynostemmapentaphyllum [Thunb] Makino | Leaves |
| 6 | Clausena | Rutaceae | Clausena lansium | Leaves |
| 7 | Cynodon | Poaceae | Cynodondactylon | Plant extract |
| 8 | Centella | Apiaceae | Centalla asiatica | Whole plant |
| 9 | Ocimum | Lamiaceae | Ocimum sanctum | Whole plant |
| 10 | Plumbago | Plumbaginacea | Plumbago scandens | Whole plant |
| 11 | Cassia Tora | Fabaceae | Sanna tora | Seed |
| 12 | Ginkgo biloba | Ginkgoaceae | G.biloba | Whole plant |
| 13 | Panax ginseng | Araliaceae | Panax ginseng | Whole plant |

### 8.1 CHRYSANTHEMUMINDICUM

**Fig 3:- Chrysanthemumindicum**

The indicum Chrysanthemum L. The extract is protective against lipopolysaccharideinduced cytotoxicity in SH-SY5Y cellular model and BV-2 microglial cells of Parkinson's disease and 1-methyl-4-phenylpridinium ion 5.Because of the greater identification of natural products, medicinal plants are in high demand in both developed and developing countries, and they are sometimes the only source of health care.Herbal sources have been used to cure a variety of ailments since ancient times .[10], [11]

### 8.2 TRIFOLIUM

**Fig 4:- Trifolium**

Red clover extract applies to the pre-tense plant known as Trifolium. Iso-flavones: red clover- Pratensein, formononetin and daidzein help to protect the nerves from dopaminergic LPSinduced neuronal damage. Biochanin A, an estrogenic red clover bioflavonoids, improves the consumption of dopamines. Red clover extract slightly lesson the scale of the lesion.[10], [12]

### 8.3 TRIPTERYGIUM

**Fig 5:- Tripterygium**

Common Threewingnut Root (CTR) is a dried root of Triptery-gium wilfordii Hook F. CTR extract protects dopaminergic neurons against lipopolysaccharide-induced inflammatory Dismissal. Effect and toxicity are two important aspects of drugs. Among the compounds obtained from plants or natural sources,Agents with remarkable efficacy and potential toxicity have attracted much attention in recent years. [10], [13]

### 8.4BACOPA

**Fig 6:- Bacopa**

Bacopa monnieri pretreatment of dopaminergic N27 cell lines demonstrated reduction of ROT-induced oxidative stress and cell death (in rotenone-Motivated mouse model), normalization of oxidative marker rates (ROS, malondialdehyde and hydroperoxide rates), restoration of GSH levels, dopamine levels, cytosolic antioxidant enzyme activity levels and neurotransmitter function.In a bioassay for paraquatoxidative tension it confers sometimes tremendous resistance.[10], [14]

**8.5GYNOSTEMMA**

**Fig 7:-Gynostemma**

Gynostemma pentaphyllum herbal ethanol extract demonstrates neuroprotective effects on PD type 6-OHDA-lesioned rat . Gypenosides, The G's saponins. Pentaphyllum, defensive dopaminergic neurons in primary culture or in the extensive PD mouse model against oxidative damage iInduced by MPP+ 22.Gynostemma pentaphyllum (Thunb.) Makino is a creeping perennial herb that belongs to the family Cucurbitaceae. As a well-known edible and medicinal plant, GP has a long history of application in oriental medicine since the Ming dynasty . The famous classical book of Chinese material medica, Compendium of Materia Medica, first recorded the usage and curative effect of GP.[10], [15]

**8.6 CLAUSEN**

**Fig 8:- Clausen**

Clausena lansium is native fruit tree from southern China. Care in progress with Bu-7 a flavonoid fromClausena lansium leaves, decreased apoptosis induced by rotenone, mitochondrial potentialand Added protein phosphorylation induced by rotenone .[10], [16]

**8.7 CYNODON**

**Fig 9 :- Cynodon**

The traditional use of cynodon dactylon is in Ayurveda. Cynodon dactylon 's anti-Parkinson activity attenuated the motor defects and shielded the brain from oxidative stress in the PD model of rotenone-induced Parkinson's rats. Weed control is a major challenge nowadays, considering the urgent need to feed a growing population, while reducing the environmental impacts of food production.[10], [17]

**8.8 CENTELLA**

**Fig 10:-Centella**

Centella asiatica (Gotu Kola) is an Ayurvedic traditional medicine. Centella asiatica is protective against Parkinsonism Induced by MPTP. This works according to showing antioxidant involvement in brain area of the hippocampus and corpus striatum. Centella asiatica, also known as Gotu Kola, Bua-bok, Tiger grass, or Indian Pennywort , is an herbaceous perennial plant member of the Apiaceae family, also known as Umbelliferae.[10], [18]

**8.9 OCIMUM**

**Fig 11:-Ocimum**

Ocimum tenuiflorum or tulasi (Ocimum sanctum). Ocimum sanctum leaf extract has aneuroprotective effect on a catalepsy caused by haloperidol in albino mice. O. Sanctum extract has a neuropro-tective effect on parkinsonism induced by rotenone and a catalepsy induced by haloperidol in rats and muscle rigidity in mice. [10], [19]

**8.10 PLUMBAGO**

**Fig 12:-Plumbago**

The Plumbago scandens is a plumbago genus. Plumbago's crude ethanolice extract and complete acetate fraction works against Parkinsonism by reducing locomotive operation, catalepsy, and palpebral ptosis. It has been reported that many plants naturally produce secondary metabolites, commonly referred to as phytochemicals or biologically active compounds which are essential for plant metabolism but play a great role in the plants' protection mechanism (Ascensao et al., 1997).[10], [20]

**8.11 CASSIA TORA**

**Fig 13:- Cassia Tora**

Cassia Cassiae Semen is the seed of dry, mature Cassia obtusifolia L. Tora Cassia L. (Tora C.). Alaternin, a part of C. Tora has powerous peroxynitrite-scavenging, stated to be PD, and attenuates neuronal cell death from transient cervical hypoper fusion in mice35. Cassiae Semen extract has beneficial properties in PD models of 6-OHDA-induced neurotoxicity in PC12 cells and MPTP-induced neuronal degeneration in the PD form of the mouse, as well as seed extract in hippocampalcultures of the mouse. [10], [21]

**8.12 GINKGO BILOBA**

**Fig 14:- Ginkgo biloba**

Ginkgo Folium is Ginkgo biloba L's entire, dried leaf. In software PD mice G. Biloba 761 attenuates the neuro

degeneration of the nigrostriatal pathway induced by MPTP and has an inhibitory effect on oxidative stress .In Cells of PC12, G. Biloba extract has protective effects against 6-hydroxydopamine induced parkinsonism on paraquat-induced apoptosis and PD rat models Ginkgo biloba L., known as a "living fossil,"has been utilized for over 2000 years as a therapeutically valuable plant for human health . The name "Ginkgo" is derived from a Japanese word, while the term "biloba" refers to the characteristic two-lobed shape of its leaves. [10], [22]

### 8.13 PANAX GINSENG

**Fig 15:- Panax ginseng**

The dry root and rhizome of Panax ginseng C is Ginseng Radix Et Rhizoma. Mey, A. Mey. Ginseng extract G115 has been significantly pro-tected against neurotoxic effects of MPTP and MPP+ in rodents. Ginseng saponins have enhanced the growth of dopaminer-gineuroblastoma cells SK-N-SH .Ginseng has an inhibitory function in MPP+ accumulation in dopaminergic neurons, suppresses oxidative stress caused by dopamine autoxidation and attenuates apoptosis caused by MPP+ and Growth factor for nerves (NGF) potenzia.[10], [23]

## IX. VARIOUS BEHAVIORAL METHODS FOR PARKINSON'S DISEASE

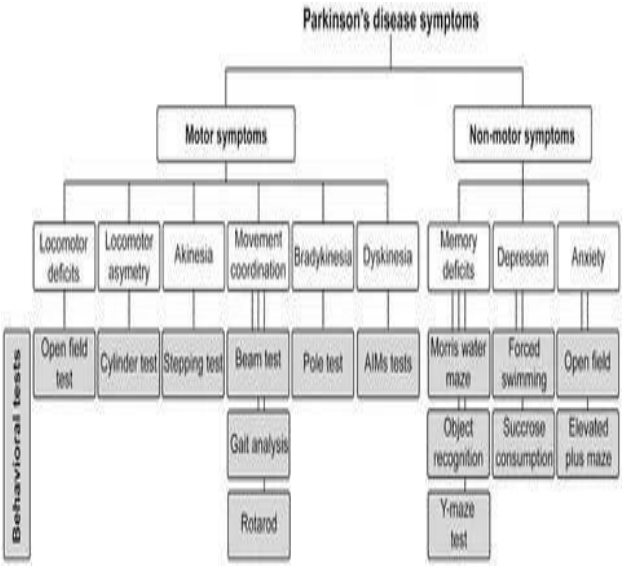


**Fig 16:- Various behavioral methods for Parkinson`s diseas**

### 9.1 Motor behavioral tests

Motor manifestations of PD encompass bradykinesia and akinesia, marked by diminished or absent movements alongside muscle rigidity and stiffness. These assessments involve diverse motor tasks, including: (i) tests for spontaneous movement (such as the free movement test,cylinder test, initiation movement test, pole test, beam traversal test, gait test, and adhesive removal test), (ii) evaluation of abnormal involuntary movements (AIMs) associated with akinesia and catalepsy, and (iii) assessment of rotational behavior using the rotarod test.[24]

### a)Open field test (OFT)

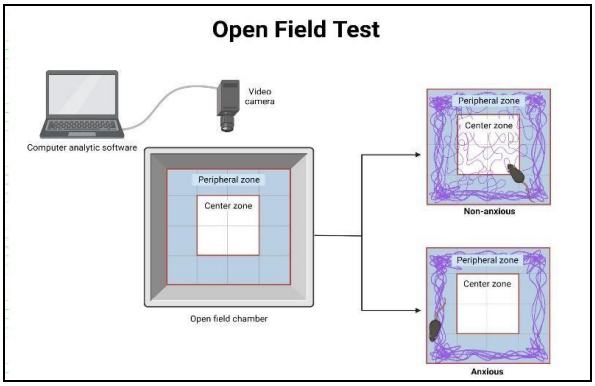


**Fig 17:-Open field test**

Open Field was a circular arena, made of plastic; the floor was divided by a marker into compartments with a

central area. Each rat was then scored for the locomotor activity, which was expressed as the sum of lines crossed plus the number of balances. A score for exploratory behavior was given,which was the sum of the number of times the rat passed through central area plus the duration of time the rat stayed in the central area, finally, an anxiety score was calculated, equal to the sum of urine and feces spots .[25]

**b) Cylinder test**

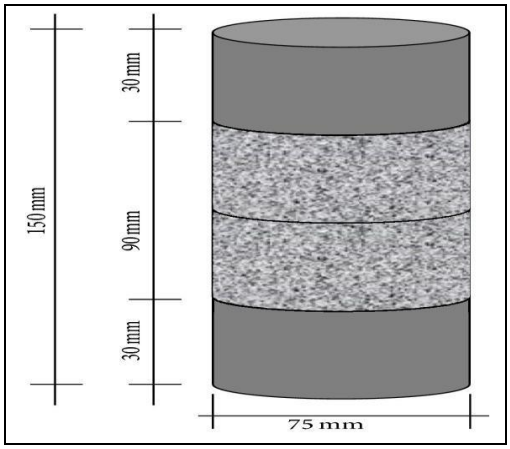


**Fig 18:- Cylinder test**

Locomotor asymmetry represents a key motor phenotype of PD, characterized by the initial onset of symptoms affecting one side of the body, which persists as the most prominently affected side throughout the course of the disease, even as the other side bectest affected.[26]In rodent models, locomotor asymmetry, sensorimotor coordination, and forelimb use are evaluated using the cylinder test . [27]

**c) Stepping test**

Deficits in forepaw movements have been shown to effectivel model parkinsonian akinesia, and the type of test commonly used to examine this phenomenon is referred to as the stepping test.As the disease advances to the middle stages, there is a noticeable reduction in the number of steps, reflecting increasing difficulty with gait and mobility. In the advanced stages, severe akinesia often develops, where individuals struggle to initiate movements, resulting in minimal or no steps being taken. [28]

**d) Beam test**

Several types of beam tests have been adapted to examine hind limb coordination in rodent models, providing a means to assess motor coordination in animal models of Parkinson's disease (PD).In the early stages of PD, rodents show a slight increase in traversal time. As the disease progresses to the middle stages, they experience frequent slips and longer traversal times. In the advanced stages,rodents often become unable to traverse the beam without falling. [29]

**e) Pole test**

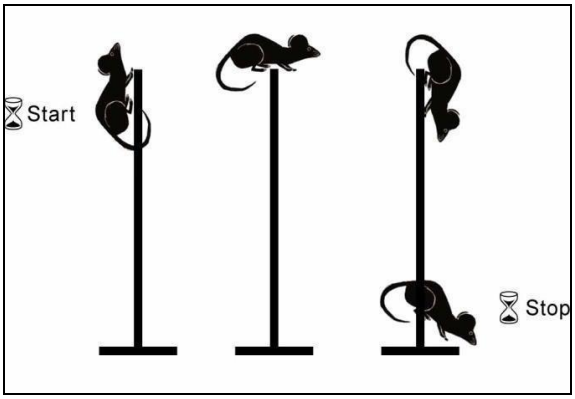


**Fig 19:- Pole test**

Another highly sensitive test aimed at examining bradykinesia, nigrostriatal dysfunction and motor coordination in PD mice is known as the pole test. During the early stages, mice demonstrate a slight increase in the time it takes to descend the pole, reflecting mild motor impairment. In the middle stages, there are noticeable delays and hesitations as the motor deficits become more pronounced. In advanced stages, significant delays, or a complete inability to descend the pole are observed, indicating severe motor dysfunction . [30]

**e) AIMs test**

The AIMs test has been used to reflect and measure dyskinesia,and catalepsy in rodent models of PD after administration of drugs like L-DOPA . The AIMs test has been described in depth by Cenci et al., and is classified into different subtypes based on the type of measurement of the behavioral abnormality. These subtypes include measurements of: (i) locomotive dyskinesia also known as controversive rotational response characterized by the increase in locomotion, which is dependent on the contralateral side of treatment, (ii) contralateral twisted posturing of both the neck and upper body, [31]

**f) Rotarod test**

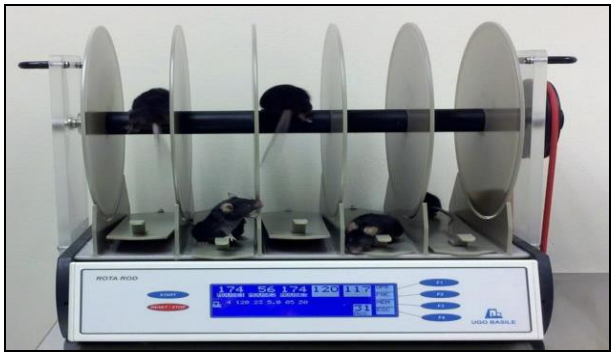

**Fig 20:- Rotarod test**

The rotarod test is one of the oldest and best-defined methods to assess behavioral deficits in rodent models of PD, and this test was first described by Dunham and Miya in 1957 . In the advanced stages, there is a significant reduction in the time spent on the rod, often accompanied by frequent falls, mirroring the severe motor dysfunction seen in advanced PD in humans.[32]

### 9.2 Non- motor behavioral tests

**a) Morris water maze test (MWMT)**

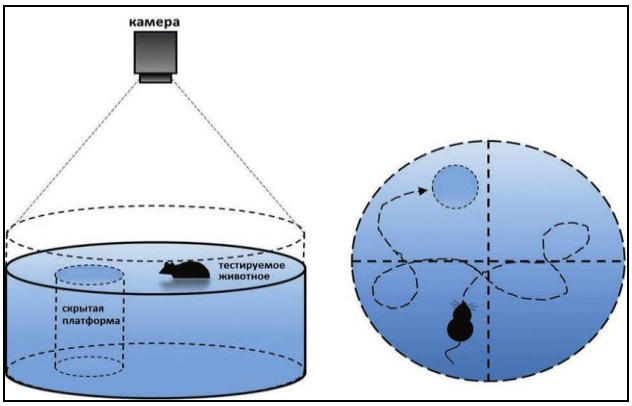


**Fig 21:- Morris water maze test (MWMT)**

Working and spatial memory can be assessed using the Morris water maze, which involves a circular pool filled with opaque water and a hidden platform placed just below the surface. Rodents are placed in the pool, and the test then measures the capacity of the animal to make use of external spatial cues to locate the platform placed in the pool . As the disease progresses to the middle stages, more noticeable impairments in learning and memory become apparent, with rodents requiring longer times or exhibiting inconsistent navigation
strategies. [33]

**b) Forced swimming test (FST)**

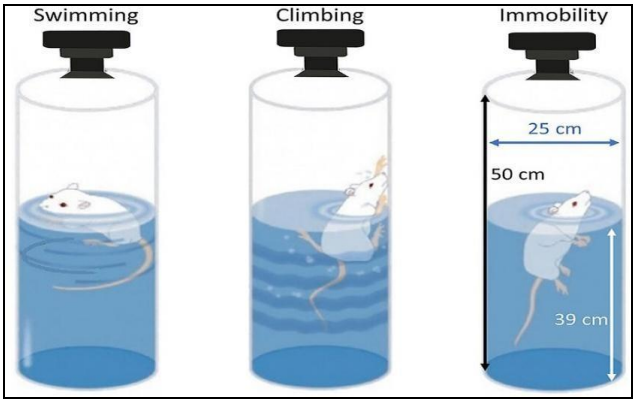


**Fig 22:- Forced swimming test (FST)**

The FST is one of the most used tests to evaluate depression-like behavior in mice and rats. In early stages of PD, rodents exhibit a slight increase in immobility time during the FST, indicating emerging depression-like behavior. This behavioral assay consists of placing the animal in a vertical plexiglass cylinder filled with water, and after 24 h of training, a short session of around 5 min is carried out. The rodent's despair is analyzed by measuring the total duration of immobility duringthe test.[34]

**c) Open field test**

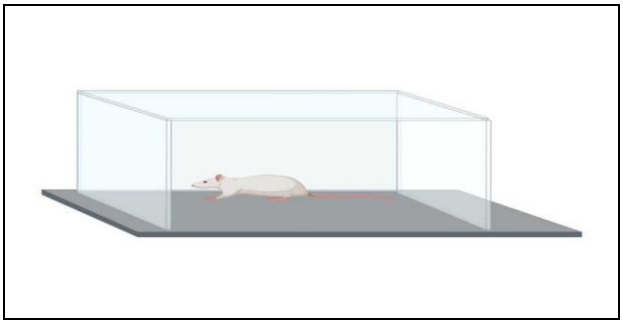

**Fig 23:-Open field test**

Open field test results revealed not only an increase in activity, but also reduced anxiety like behavior in transgenic A53T mouse models ). These studies show that A53T mice seemed to develop an age-related anxiolytic-like phenotype. In fact, 12-month-old A53T mice showed to spend more time in the center as compared to either WT or younger A53T mice . Similarly, another study showed that mice overexpressing the human WT α-syn (Thy1-α-syn) tend to have more center entries and exploration time when compared to WT mice.[35]

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