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# SCREENING OF ANTI-ALZHEIMER'S ACTIVITY OF USTUKHUDDUS AGAINST SCOPOLAMINE INDUCED NEUROCOGNITIVE IMPAIRMENT IN MICE MODEL

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**ABSTRACT**
Alzheimer's disease is categorised as a neurocognitive clutter. As of the year 2021, it was anticipated that 46.8 million people all over the globe were adapting with dementia. The clinical signs of Alzheimer's malady incorporate trouble in problem-solving and executing commonplace chores at domestic. Alzheimer's infection could be a neurological sickness that dynamically declines over time. The predominant A species within the amyloid plaques that are characteristic of Alzheimer's infection. The advancement of viable pharmaceutical treatment for Alzheimer's is still in its earliest stages, and the sickness remains serious. Alzheimer's illness is characterised by a wide extend of behavioral side effects, counting a sleeping disorder, confusion, disturbance, uneasiness, and savagery. There are presently a number of Alzheimer's infection antibodies beneath improvement, with the trust that they would lighten a few of the related cognitive side effects.

**KEYWORDS:** Alzheimer's disease, Characteristic and Pharmaceutical treatment.

## 1. INTRODUCTION

### Dementia

Dementia is a neurodegenerative disorder characterized by progressive andcontinuous loss of cognitive functions. The neuropsychiatric symptoms include apathy; agitation and depression. As the disorder progresses, the patient gradually becomes dependent on others to perform routine daily activities. Various underlying diseases or disorders are the root cause of the syndrome of dementia. Each of these disorder or disease is characterized by a specific signs and symptoms in combination with a presumed underlying neuropathology.[1]

Dementia has a major negative effect on people's functioning, independence, and the need for care. This in turn is placing a heavy burden on families, communities and society, with the cost of care often paid for out-of-pocket. Thepersonal, social and economic consequences of dementia are enormous. Dementia leads to increased care costs for governments, communities, families and individuals, and to losses in productivity for economies. The cost of care for dementia, estimated at US$ 604 billion per year in 2010, is growing at a faster rate than the prevalence of the disease.[2]

As of the year 2015, it was anticipated that 46.8 million people all over the globe were adapting with dementia It is basic to pick up an understanding of the variables that contribute to dementia as well as the improvement of medicines for the condition due to the truth that the number of individuals over the age of 60 is anticipated to extend around the world by 1.25 billion by the year 2050, accounting for 22% of the whole populace of the world.[3]

Neurons are central to the proper functioning of the human brain since they play a critical role in communication. During childhood, neural stem cells produce the majority of neurons, the number of which is significantly reduced in adulthood. Although neurons are not immortal, the progressive loss of neurons, neuron structure, and/or their functions, known as neurodegeneration, is central to the pathophysiology of several brain disorders and is also a major health concern.[4] Neurodegeneration is associated with dysfunction of the synapse, neural network, and the deposition of physiochemically altered variants of proteins in the brain. Diseases with neurodegeneration as their hallmark feature are collectively termed NDs.[5-6]

The most common NDs include Alzheimer's disease, Parkinson's disease, prion disease, Amyotrophic lateral sclerosis, motor neuron disease, Huntington's disease, spinal muscular atrophy, and spinocerebellar ataxia.[5-9]

Cognitive functioning is a major health factor that impacts an individual's ability to live independently and is a key factor determining the quality of life.

It can be related as a process where functional

awareness of reality occurs, thisis where the interest of close connection of understanding and language comes from.

On psychological grounds, the word cognition may be defined as an integrated process which involves learning, memory, attention etc., including the complex areas of perception, language, reasoning and intelligence.

Among older adults, cognitive function varies widely with aging. Generally, some cognitive functions are relatively stable with aging, including vocabulary and knowledge of world events[10] whereas other cognitive functions, particularly those that rely on mental processing speed and attention, working memory, executive function, and verbal recall, decline with age[11-14]

These decrements in cognitive functioning with aging have been related to changes in underlying neuroanatomic structures, such as decreases in white matter integrity and decreased volumes of the caudate, cerebellum, hippocampus, prefrontal cortex, and medial temporal lobes.[5-7]

Neurocognitive functions are cognitive functions associated with specific pathways or loci within the brain and are affected by different disease processes and Testing specific neurocognitive functions can be used to deduce which areas of the brain are involved when cognitive problems are suspected.

Therefore, neurocognitive dysfunction has been the center of attention in many medical conditions.[18]

Any marked observable difference's which causes memory loss, difficulty communicating, experiencing difficulty in handling daily tasks, confusion, changes in personality traits, and mood or behavioral symptoms is a strong indicator of neurocognitive impairment.

Examples of neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, fronto-temporal dementia and the spinocerebellar ataxias. These diseases vary in their pathophysiology – with some causing memory and cognitive impairments and others affecting a person's ability to move, speak and breathe.[19]

**Definition**

Neuro-degeneration may be defined as a process where the functional units of brain (neurons), spinal cord and the peripheral nervous system start to undergo deterioration and eventually lose their functionality causing neurological impairment due to which various cognitive functions are disturbed.

Neurodegenerative diseases such as Alzheimer's (AD), Parkinson's (PD), and Huntington's diseases (HD) and amyotrophic lateral sclerosis (ALS) make up a group of pathologies characterized by separate etiologies with distinctmorphological and pathophysiological features.

Neuronal degeneration predominantly starts with degeneration in specific neuronal populations like dopaminergic neurons in PD, striatal neurons in HD, and cortical and hippocampal neurons in AD, these diseases share similar cognitive declines in the later stage of the disease.[20]

Neurodegeneration is a pivotal feature of a broad range of devitalizing, incurable diseases that comes under the category of neurodegenerative diseases.[20]

**Dementia: A brief overview**

Dementia refers to a syndrome that is characterized by progressive deterioration of cognitive functions. The neuropsychiatric symptoms include apathy;agitation and depression. As the disorder progresses, the patient gradually becomes dependent on others to perform routine daily activities. Various underlying diseases or disorders are the root cause of the syndrome of dementia. Each of these disorder or disease is characterized by a specific signs and symptoms in combination with a presumed underlying neuropathology.[1]

Learning and memory are two fundamental cognitive functions that confer us the ability to accumulate knowledge from our experiences.[22]

Learning refers to acquisition of any new information about the event in particular surroundings and subsequent retrieval of this information is referredto as memory[25] Memory, one of the most complex functions of the brain, comprises of multiple components such as perception/ sensation, registration, consolidation, storage, retrieval and decay/forgetting.[24-25] Memory may be sensory (registration), short-term memory and long-term memory.[26] Consolidation refers to the process of conversion of short-term memory to longterm memory.[27] Sensory memory (registration) is defined as a process of sensory perception and an ability to retain the perceived sensory signals in the sensory areas of the brain for relative short interval of time, following actual sensory experience.[1]

Dementia may occur due to both anatomical and biochemical changes in the brain. The behavioral and psychological symptoms of dementia include agitation/irritability/mood labiality, anxiety, apathy, delusion, depression symptoms, disinhibition, euphoria, hallucinations, loss of appetite and sleep disturbances.[28]

Dementia has been etiologically associated with numerous heterogeneous conditions and is categorized in few subtypes according to its causes.

**Table 1: Types of dementiaalzheimer's disease.**

| | |
|---|---|
| Cortical Dementias | Alzheimer's disease,<br>Dementia with Lewy bodies,<br>Fronto-temporal dementia:<br>(a) A behaviouralvariant,<br>(b) A language variant |
| Sub-cortical dementias | • Parkinson's disease,<br>• Huntington's disease,<br>• Wilson's disease,<br>• Normal pressure hydrocephalus |
| Mixed dementias and dementia in disseminated brain diseases: | **Vascular dementia:**<br>(I) Large vessel vascular dementia:<br>(a) Multi-infarctdementia<br>(b) Strategic infarct dementia<br>(ii) Small-vessel vascular dementia:<br>(a) Subcortical: It is involved in Binswanger disease, CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy.<br>(b) Cortical and subcortical: It is involved in hypertensive, arteriolosclerotic angiopathy, amyloid angiopathies and collagen-vascular disease.<br>**(iii)** Hypoperfusive vascular dementia:<br>(iv) Hemorrhagic vascular dementia: |
| Infection associateddementia | HIV dementia: HIV dementia (HIVD) is likely to become more common, considering the rise in HIV infection. |
| Creutzfeldt-Jakob Disease | It is a dementia with an extremely rapid course, caused bytransmissible infectious agent, the prion. Cognitive deterioration is progressive, widespread and accompanied by pyramidal and extrapyramidal signs i.e myoclonic jerks, ataxia and muscle rigidity |
| Neurosyphilis | It may evolve into different types of dementia if left untreated. The most severe form is general paresis, often evident 15-20 years after the original infection. |
| Metabolic and | Progression of dementia is usually dependent on the chronicity of the metabolic or toxic condition, and the further course tends to be diseasespecific. |
| Neoplastic-associateddementia: | Neoplastic diseases (depending upon tumor location, extent as well as rapidity of tumor growth) essentially may produce any kind of neuropsychiatric symptoms. |
| Dementia following traumatic brain injury | Traumatic brain injury may cause variety of cognitive difficulties. The severe trauma with loss of consciousness is called as post-traumatic amnesia. |
| Psychiatric disorders associated dementia | The relationship between dementia and depression is complex. Pseudodementia is a term used to describe the condition of depressed patients who perform poorly on cognitive tasks because of lack of interest and motivation. However, dementia syndrome of depression (DSD) occurs during episodes of severe mood disorders |

Alzheimer's disease (AD) was identified more than 100 years ago. It is adegenerative disease of the brain and the most common cause of dementia in older people, accounting for 60% to 80% of cases of late-life cognitive dysfunction.[29,30,31]

It is a progressive neurodegenerative disease, characterized by progressive cognitive deterioration together with declining activities of daily living and behavioral changes.[32]

Alzheimer's disease is an unavoidable neurological disorder in which the death of brain cells causes memory loss and cognitive decline and ultimate dementia.[33]

It is a gradual neurodegenerative condition caused by neuronal cell death, and it typically starts in the entorhinal cortex in the hippocampus,[34] it may be understood as a progressive, irreversible neurodegenerative condition impacting cognition, function, and behavior.[35]

AD follows a progressive disease continuum that extends from an asymptomatic phase with biomarker evidence of AD (preclinical AD), through minor cognitive (mild cognitive impairment [MCI]) and/or neurobehavioral (mild behavioral impairment [MBI]) changes to, ultimately, AD dementia. A number of staging systems have been developed to categorize AD across this continuum. While these systems vary in terms of how each stage is defined, all encompass the presence/ absence of pathologic Aβ and NFTs, as well as deficitsin cognition, function, and behavior.[36-38]

As a result, subtle but important differences exist in the nomenclature for each stage of AD depending on the selected clinical and research classifications

Preclinical AD, as the earliest stage in the AD continuum, comprises a long asymptomatic phase, in which individuals have evidence of AD pathology but no evidence of cognitive or functional decline, and their daily life is unaffected.[37]

The duration of preclinical AD can vary between individuals, but typically lasts 6–10 years depending on the age of onset.[39-40]

The risk of progression from preclinical AD to MCI due to AD (with/without MBI) depends on a number of factors, including age, sex, and apolipoprotein E (ApoE) status.[40,41]

However, not all individuals who have underlying AD pathology will go on to develop MCI or AD dementia.[42,43]

**History**

The credit for first time describing a dementing condition, which later became known as Alzheimer's disease, goes to German physiatrist and neuropathologist Dr. Alois Alzheimer. Alzheimer disease (AD) an aggressive form of dementia, manifesting in memory, language and behavioral deficits.[44-45]

According to the World Health Organization (WHO) estimates, the over all projected prevalence in global population will quadruple in the next decades, reaching 114 million patients by 2050.[46]

Apart from having a great social impact, this would clearly lead to increased economic burden to healthcare systems worldwide.[47-48]

It is currently estimated that 46.8 million people worldwide have dementia with an estimated global cost of dementia care at US$818 billion in 2010.[49]

By 2030 it is estimated that there will be 74.7 million people with dementia, and the cost of caring for these individuals could rise to some US$2 trillion. There are no effective options available at present for prevention and treatment of Alzheimer disease despite all scientific reports. Alzheimer's disease progresses gradually and can last for decades.

**Epidemiology**

The global prevalence of dementia has been estimated to be as high as 24 million, and is predicted to double every 20 years until at least 2040. As the population worldwide continues to age, the number of individuals at risk will also increase, particularly among the very old.[50]

In 2016, approximately 47 million people live with dementia across the globe. Alzheimer's is the single most common cause of dementia, comprising 70% of all cases. The majority of the patients with Alzheimer's have late-onset (around 65 years of age or later), and few have early-onset during 40's or 50's.

Geographical distribution of Alzheimer's is slightly skewed. The western European countries and North America has the highest prevalence of Alzheimer's, followed by China, Latin America, and Western-Pacific countries. The incidence rates also depict similar picture, except for the fact that Latin America has a relatively higher incidence of Alzheimer's compared to thewestern European countries.

**Risk factors**

Alzheimer's dementia is a multifactorial disease, in which older age is the strongest risk factor, suggesting that the aging-related biological processes may be implicated in the pathogenesis of the disease.

Furthermore, the strong association of AD with increasing age may partially reflect the cumulative effect of different risk and protective factors over the lifespan, including the effect of complex interactions of genetic susceptibility, psychosocial factors, biological factors, and environmental exposures experienced over the lifespan.[51]

**Age**

Age is the only most serious risk factor for causing AD and one of the non- modifiable risk factors. Most instances of AD are seen in the elderly population, ages 65 years or above. Around 5% of individuals have an AD with the age of 65 and 74 and for those more than 85, the danger increments to 50%.[52]

**Gender**

Women overcount than men with regards to Alzheimer's disease. As per an investigation, a woman is approximately 1.5 to 3 times higher at risk of getting AD than a man. Chances increment after menopause. Since ladies generally livelonger than men, and the appearance of Alzheimer's disease increase with age, this could likewise be a factor.

**Family history**
Alzheimer's disease frequently runs in the family. On the off chance that you have a parent, or youngster with the sickness, you're bound to create it yourself. Your danger goes up if different relatives have Alzheimer's. this could be because of genes, way of life factors, or a mix of both.

**Apolipoprotein E (Apoe)**
Several studies have emphasised the importance of genes involved in cholesterol transfer as risk factors for AD such as apolipoprotein E (APOE), apolipoprotein C1 (APOC1), and apolipoprotein J (APOJ) (clusterin) suggesting deterioration of cholesterol homeostasis.[53]

**Genetics**
The most common form of EO-FAD (early - onset familial Alzheimer's disease) is associated with mutations of the PSEN1/2 genes (Presenilin 1 and 2 (PSEN1/2). Full length PSEN is composed of nine trans-membrane domains located on the endoplasmic reticulum.

Endoproteolytic cleavage of PSEN and assembly into γ-secretase complex is followed by transport to the cell surface, thus potentially influencing APP (Amyloid precursor protein (APP) processing.[54]

Mutant PSEN1 may interact with APP by enhancing 42-specific-γ-secretase cleavage of normal APP resulting in increased deposition of Aβ.[55]

**Epigenetic factors**
Epigenetic factors, i.e., heritable changes in gene expression which do notinvolve DNA coding sequences, have also been identified which may alter allelic expression in a significant number of the genes involved in AD.[56]

**Traumatic brain injury**
TBI could cause damage to the BBB resulting in leakage of plasma proteins and sensitization of the immune system to brain antigens normally isolated from them. Subsequently, a number of studies reported a connection between head injury and AD. In survivors of head injury, APP is observed in neuronal cell bodies and in dystrophic neurites surrounding Aβ deposits, as observed in AD.[57] Subsequently, it was shown that specific neurons in the medial temporal lobe (MTL) secreted large quantities of APP and that there were more APP-immunoreactive neurons in these areas in TBI.[58]

Hence, increased expression of APP in head trauma cases may be an acute- phase response to neuronal injury,[59] the overexpression of APP leading to the deposition of Aβ. Several acute-phase proteins are localised within Aβ deposits in AD including amyloid-P, complement factors, and α-antichymotrypsin.[60]

The relationship between TBI and AD is further emphasised by the discovery of the tauopathy chronic traumatic encephalopathy (CTE), a neurodegenerative disorder believed to result directly from repetitive brain injury.[61,62]

**Mitochondrial dysfunction**
Although not discussed specifically by Henderson,[62] theories suggesting that mitochondrial dysfunction may be involved in AD have a long history. Hence, distorted mitochondria accompanied by a decline in cerebral metabolic rate are present in early AD. In addition, there is a deficiency of enzymes involved in carbohydrate utilization including such mitochondrial markers as phosphofructokinase (PFK) and pyruvate dehydrogenase.[64]

As a consequence, chronic hypoperfusion could induce oxygen stress via the production of reactive oxygen species (ROS) and result in mitochondrial failure and AD.[65]

Moreover, part of the familial aggregation of AD may reflect excess maternal versus paternal inheritance consistent with mitochondrial inheritance.

The possibility of a genetic origin of mitochondrial dysfunction in AD has also led to the formulation of a 'mitochondrial cascade hypothesis' (MCH), in which it is mitochondrial dysfunction that is the initial event leading to AD pathology.[66]

**Role of environment for AD:**
A few investigations demonstrate a role for environmental consequences for AD development. In a recent audit, Richard Mayeux and Yaakov stern summed up the role of diet, exercises, or diseases that possibly assume a role in the development of Alzheimer's disease. Environmental factors affecting AD include:
Temperature sensitivity, Isolation, ummet needs, and Noise, Overstimulation, boredom etc.

**Neuropathology**
Brain atrophy caused by neuronal loss is a prominent pathological feature of Alzheimer's disease (AD). Amyloid β (Aβ), the major component of senile plaques, is considered to play a central role in neuronal cell death.[75]

Loss of the large pyramidal cells of the association neocortex and hippocampus, along with plaques and tangles, is fundamental to the neuropathology of Alzheimer's disease. The pathophysiology of alzheimers disease is identified with the injury and demise of neurons, starting in the brain's hippocampus area that is associated with memory and learning, then atrophy influences the whole brain. Alois alzheimer's first portrayed the presence of neurofibrillary tangles inside neurons, senile/feeble plaques between neurons, degeneration of neurons, gross diffuse cerebral cortex atrophy, and cerebral vessels atherosclerosis, and still, these keep on being the standard pointers of Alzheimer's

illness.[67]
The clinical manifestation of AD is considered to correlate with the degree of neuronal loss in brain, particularly in hippocampus and cerebral neocortex.

In addition to neuronal loss, two pathognomonic changes are commonly observed in AD brains: extracellular senile plaques and intraneuronal neurofibrillary tangles (NFT).[68,69]

Amyloid β (Aβ), a major constituent of senile plaques, is produced from amyloid precursor protein (APP) by enzymatic cleavage with β - and γ- secretases.[70,71]

While β-secretase works as a single protein, presenilin (PS) is a component of a protein complex that functions as γ-secretase.[72,70,73,74,71]

AD is a neurodegenerative disorder characterized clinically by progressive deterioration of cognition, behavior, and functionality that impairs activities of daily living significantly. Morphologically, the disease is characterized by brain atrophy and by enlarged cerebral ventricles. From a biochemical point of view, the most clear-cut and consistent finding is a deficit of the cholinergic system, decreased levels of choline acetyltransferase, and other cholinergic markers. Histologically, AD is characterized by extracellular deposits, called cerebral plaques, composed of a dense proteinaceous core containing the Ab peptide surrounded by dead and damaged neurons. The other typical histopathologic hallmarks of AD are the neurofibrillar tangles within neurons, formed mainlyby a filamentous, hyperphosphorylated form of the microtubule-associated protein t. Whereas most cases of AD occur sporadically, approximately 5% of patients develop the disease early as a result of fully penetrant autosomal dominant gene mutations.[76]

**Pathophysiology of alzhimer's disease:**
Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdala, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also with subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus. The deposition of tangles follows a defined pattern, starting from the trans-entorhinal cortex; consequently the entorhinal cortex, the CA1 region of the hippocampus and then the cortical association areas, where frontal, parietal and temporal lobes are particularly affected. The extent and placement of tangle formation correlates well with the severity of dementia, much more so than numbers of amyloid plaques.[77]

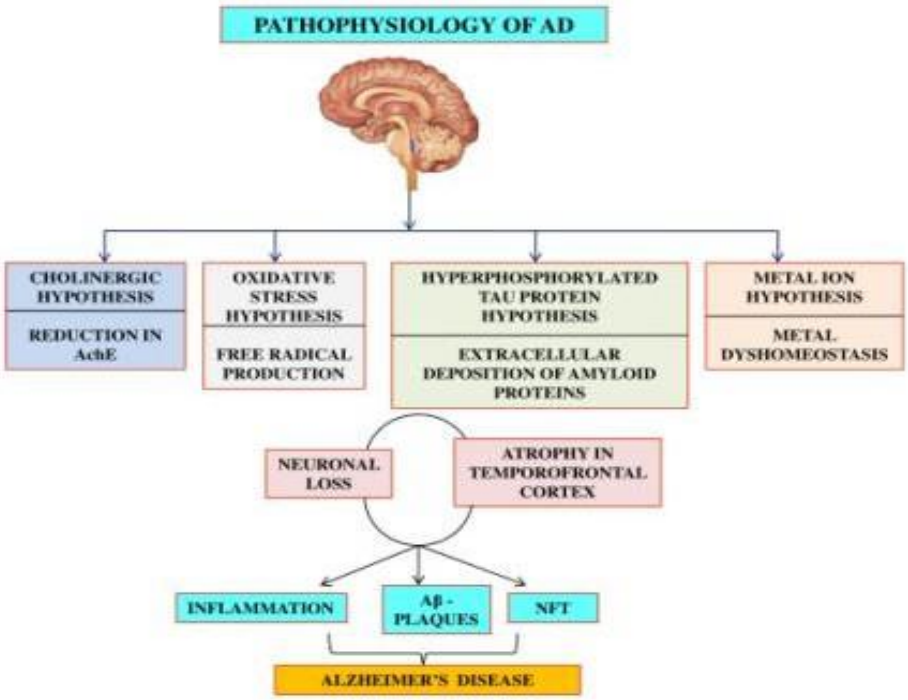


**Figure 1: pathophysiology of alzheimer's.**

The accretion of tau proteins correlates very closely with cognitive decline and brain atrophy, including hippocampal atrophy.

In the neuropathology of Alzheimer's disease there is a loss of neurons and atrophy in temporofrontal cortex, which causes inflammation and deposit the amyloid plaques and an abnormal cluster of protein fragments and tangledbundles of fibers due to this there is an increase in the presence of monocytes and macrophages in cerebral cortex and it also activates the microglial cells in the parenchyma.[78]

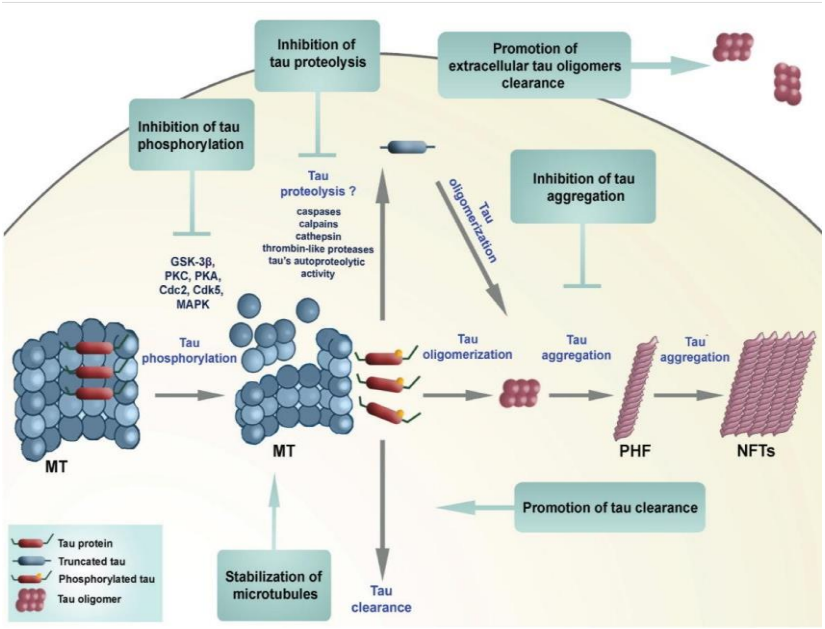


**Figure 2: Tau protein aggregation.**

**Hyperphosphorylated tau Protein and Amyloid β hypothesis**

One of the main pathological features of AD is the formation of senile plaques (SP), which is caused by amyloid beta (Aβ) deposition. Normally, Aβ are soluble small peptides, which are produced by the splitting of the precursor protein of amyloid (APP) by the action of α-secretase, β-secretase and γ- secretase. The imbalance between β-amyloid (Aβ) production and clearance leads to various types of toxic oligomeric, namely protofibrils, fibrils and plaques depending upon the extent of oligomerization. The reason of the formation of Aβ is still unclear, but the sequence, concentration and conditions of stability of Aβ are important factors.[79]

The pathophysiology of Alzheimer's disease is credited to a number of factors such as the cholinergic dysfunction, amyloid/tau toxicity and oxidative stress/ mitochondrial dysfunctions.[80]

**Oxidative stress hypothesis**

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced in many normal and abnormal processes in humans, they play dual role as both have beneficial functions in cellular signaling pathways and venomous processes that can lead to damage of cellular structures (includingcell membrane, lipid, protein, and DNA). The high oxygen consumption of the brain, which utilizes 20% more oxygen than other mitochondrial respiratory tissues, means that the brain is more vulnerable to oxidative stress. The neuron is the basic functional unit of the brain, which contains a large number of polyunsaturated fatty acids. It can interact with ROS, leading to the lipid peroxidation reaction and molecular apoptosis, in addition, less glutathione in neurons is also one of the causes of oxidative stress injury.[79]

Metal ion hypothesis Metal dyshomeostasis is involved in the progression and pathogenesis of diseases, including neurodegerative diseases and cancer. Ionosphere and metal chelators are well known modulators of transition metal homeostasis, and a number of these molecules are used in clinical trials. Metal- binding compounds are not the only drugs capable of targeting transition metal homeostasis.[81]

**Cholinergic hypothesis**

Among the mechanisms related to the onset and evolution of AD, a extremely studied hypothesis is the cholinergic hypothesis, which was the first theory related to AD pathogenesis.[82,83]

In general, the brain of AD carriers presents, in addition to the histopathological markers previously described, atrophy, synaptic loss and deficiency in central neurotransmission. There is overall degeneration of basal forebrain neurons.[84]

In the beginning of the disease there is loss of the cholinergic neurons in the basal nucleus and in the entorhinal cortex, but in the advanced stage of AD, more than 90% of the cholinergic neurons of the basal nucleus are lost.[85]

Bartus and Emerich (1999) [86] point out that according to the cholinergic hypothesis, the abnormal or impaired functioning of the cholinergic system proves capable of inducing a memory deficiency in animal models, similar to AD. According to this hypothesis, the destruction of cholinergic neurons in the basal forebrain and the loss of central cholinergic transmission leads to the appearance of cognitive and non-cognitive symptoms in patients with AD.[85] It is also observed that the cholinergic hypothesis is also characterized by: a marked decrease in acetyltransferase concentration responsible

for the synthesis of acetylcholine in the cortex and hippocampus; and due to the loss of cholinergic neurons in the Meynert basal nucleus.[87] The cholinergic hypothesis also corroborates that the dysfunction and cell death of neurons responsible for the maintenance of specific transmission systems leads to the deficiency of Ach, noradrenaline and serotonin.[88]

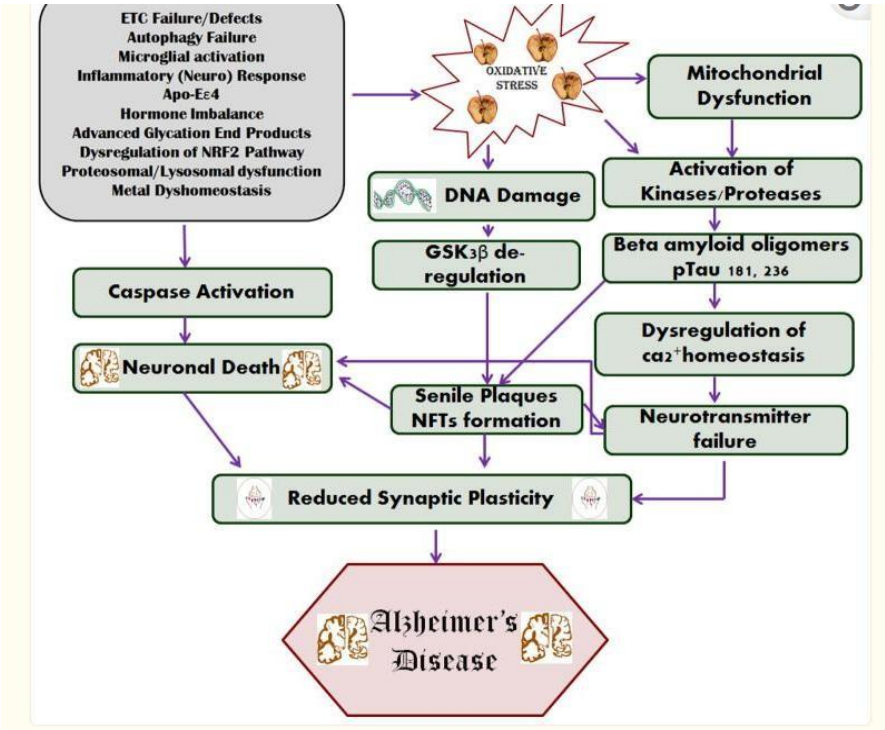


**Figure 3: Neurotransmitters in alzheimer's diseaseGlutaminergic system in Alzheimer's disease.**

Glutamate uptake and recycling system is an important factor that determines the availability of glutamate for signaling processes. Unfortunately, in AD, this system can be severely weakened. In AD patient, a decrease in the glutamate transporter capacity and protein expression and a selective loss of vesicular glutamate transporter (VGluT) were seen.[90]

Glutamate is the major excitatory neurotransmitter in the CNS (approximately 8–10 mM/kg), and is found in more than 80% of all neurons.[91,92,94]

It is involved in most normal brain function, especially in the cortical and hippocampal regions, which deal with cognition, memory and learning[95] among other functions.

Glutamate also plays a major role in the development of the central nervous system, as well as synapse induction and elimination, cell migration, differentiation and death.[96-97]

Most of the glutamate in the brain is located intracellularly inside nerve terminals and only a tiny fraction of this glutamate is normally present outsideor between the cells.[98-100]

The extracellular elevation of glutamate causes alterations in the glutamate- mediated neurotransmission, activating receptors and inducing the depolarization of neurons which in turn triggers a sequence of intracellular events that conclude in Ca2+ and Na2+ influx. This leads to the exocytosis of glutamate and ultimately cell death, which correlates with the loss of memory function and learning ability in AD patients.[101-102]

**Diagnosis**

The diagnosis of AD performed in an initial stage of the disease is essential to ensure that the patient has good living conditions.[103]

For this, the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) and established standards by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) concomitant with Alzheimer's Disease and Related Disorders Association (ADRDA) are used.[104]

These neuropsychological tests and psychometric tests, in various fields, analyze the cognitive functions of patients. In addition, blood tests, structural neuroimaging, molecular and functional neuroimaging, cerebrospinal fluid, electroencephalogram (EEG) and evoked potentials are performed. Genetic studies are also important complementary tests that can integrate a more complete diagnosis of the disease.[105]

According to the Diagnostic and Statistical Manual of

Mental Disorders IV, Text Revision, AD requires the following: new onset memory impairment,[106] cognitive disturbance, such as aphasia, apraxia, agnosia, or executive functioning; and[107] a gradual, progressive course that results in significant functional impairment.

Fluorodeoxyglucose-positron emission: tomography (PET), scans show areas of the brain region in which nutrients are poorly metabolized. Identifying patterns of degeneration; areas of low metabolism: can help distinguish betweenAD and other types of dementia.

Amyloid PET imaging can measure the burden of amyloid deposits in the brain. This imaging is primarily used in research but may be used if a person has unusual or very early onset of dementia symptoms.

Tau PET imaging, which measures the burden of NFTs in the brain, is only used in research.

Neuropsychological tests help with diagnosis, such as Mini Mental State, ADAS (Alzheimer's disease Assessment Scale) with its cognitive subscale and non-cognitive subscale, Dementia Questionnaire, Neurological Examination, Blessed Dementia Rating Scale, Dementia Rating Scale, Information-Concentration-Memory Test, Haschinsky Scale. Some scales such as Neuropsychiatric Inventory, Brief Psychiatric Rating Scale, Behaviour Rating Scale for Dementia, ADAS, non-cognitive subscale and the Cohen-Mansfield Agitation Inventory evaluate psychiatric symptoms. Brain computed axial tomography (CAT) gives information about the brain cortical and subcortical atrophy, the ventricular enlargement, the vascular injuries, the tumors and the hydrocephalia. If the patient's personality allows us to do so, it is convenient to ask nuclear magnetic resonance as this let, us observe injuries of the white substance especially in one of the subtypes of the AD and in vascular dementia. The hyperintensity of white substances (leucoaraiosis) can be inherent to the aging process, or other pathological process. The cortical – subcortical injuries can be better appreciated than in CAT. Functional studies such as the Single Photon Emission Computed Tomography (SPECT), and the Positron Emission Tomography (PET) allow us to detect alterations in the neuronal metabolism. In AD, the hypoflow or the hypometabolism appears in temporal and parietal cortex, making it global with the evolution of the disease.
The multifocal or localized injuries are typical of the vascular dementia.[108-111]

**Alzheimer's disease treatment**
The early treatment will improve the quality of life of the patient. The pharmacological treatment in early stages of the disease is useful to improve thecognitive disorders, to slow down the advance of the deficit and to diminish the psychiatric symptoms such as agitation, depression and psychosis.[112]

**Non Pharmacological Treatment**
Non-pharmacological treatments consist of the care of the patient through the implementation of psychotherapeutic and stimulation interviews. The adaptation of the context, the work with the family, and persons in charge are very important. Psycho-education is important as it can produce some behavioral changes, and it can diminish the need of a symptomatic treatment in the same way that an organized routine can be established, the avoiding of isolation, the cognitive stimulus when it is possible and the affective contention.[113]

Pharmacological Treatment A) Neurotransmission dysfunction treatment B) Neuronal metabolism disorder C) Compounds under research

**A) Cholinesterase inhibitors:**
This pharmacological group is the most studied for the treatment of AD. The cholinesterase inhibitors improve the cholinergic transmission inhibiting the enzyme in a reversible, pseudoreversible or irreversible way. They have a moderate effect in patients at early stage of the disease, and its long-term use delays the advance of the cognitive deterioration.[113–118]

The favorable answer predictor would be the following: - slight to moderate stage of the disease - late onset - absence of Apo E, allele 4.[119]

The cholinesterase inhibitor medications are: tacrine, rivastigmine, donepezil and galantamine.

They must be used with caution in patients with bradycardia, heart block, peptic ulcer or asthma. Due to the fact that a cholinergic deficit is related to the appearance of the psychiatric symptoms of AD, there are studies that support the hypothesis that administrating cholinesterase inhibitors symptoms such as apathy, psychosis, disinhibition, agitation could be improved regulating the cholinergic transmission in the frontal, temporal, and orbitofrontal areas.

The nucleus basalis has projections to the cerebral cortex, the limbic and paralimbic system would be like a station between the emotional and the cognitive.[120-122]

**Tacrine** or tetra-hidro-aminoacridine (THA) is a reversible inhibitor of the cholinesterase. Eight studies controlled with placebo have shown effectiveness since 1981. Some of them show significant improvement.[123-127]

Tacrine is metabolized in liver (in cytochrome P450 of the system 1A2) it has a half-life of 2-4 hours. The most important side effects of tacrine are nausea, vomits, stomachache, anorexia, bradicardia, mialgias, ataxia and the increase of hepatic enzymes especially the transaminase glutamic-oxalacetic in 40 % of the cases already studied. It cannot be used in patients with hepatic deficiency.

**Donepezil** is a reversible inhibitor of the cholinesterase more potent than tacrine. In 2 double-blind studies that involved 900 patients between 50 and 90 years of age with slight to moderate dementia, it has been observed a cognitive improvement or detention of the decline evaluated by the ADAS scale or by MMSE during 15 and 30 weeks. The used doses were 5 to 10 mg daily.[128-131]

**Donepezil** is absorbed almost 100% orally, it has a peak between 3 or 4 hours after taking it. It is joined to plasmatic proteins in a 96 % of the cases without displacing other drugs; it is metabolized in liver by cytochrome P450 by 2D6, and 3A4 in a slow way, and not saturated. It is still not known if it can induce insome degree, the hepatic enzymatic system, but the inductors at 2D6 and 3A4 levels can increase the elimination of donepezil. Another part is excreted through the kidney. Its average half-life is 70 hours so it can be taken once a day. The side effects are: nausea, vomits, diarrhea, anorexia, insomnia, fatigue and cramps. Bradicardia, syncope, increase of gastric heartburn, bronchospasm, and convulsions are less frequent. It seems that there is some tolerance to the negative side effects in high doses (10 mg daily), as it has been seen that after 6 weeks a reduction of the negative side effects has been appreciated.

**Rivastigmine** is an inhibitor of the brain selective carbamate acetylcholinesterase. Its function is pseudoirreversible and makes the inhibition of acetylcholinesterase persistent even though the drug has been eliminated. The half-life is 1 hour and the effect duration is 10 hours. This is due to the fact that in case of the union of the acetylcholine and the enzyme in the acetate site, the hydrolization is quick, and the enzyme is regenerated in microseconds. Instead, the disassociation of the drug from the carbamate site is much more slower and in the same process it is split, making a phenolic compound that is eliminated through the kidney. It has selectivity through the central acetylcholinesterase, with slight inhibition of the peripheral acetylcholinesterase(30-40% inhibition).

**Rivastigmine** is absorbed orally within 1 hour after its administration, and it is joined in a weak way to the plasma proteins and it easily goes through the hematoencephalic barrier. Its metabolism is through hydrolysis by the esterases implicated in its mechanism of action. 90% is eliminated in 24 hours through the kidneys. Due to its hepatic metabolism, it has a low index of pharmacologic interaction.

**Galantamine** is the newest reversible inhibitor of the cholinesterase that has an allosteric modulatory action on the nicotine receptors. The presynaptic activation of the latter increases the release of acetylcholine, glutamate, monoamines and GABA. So, it has a dual action: it has proved effectiveness over the cognitive symptoms and the psychiatric symptoms, of AD.[132-133] It has a half-life of 7 hours. It is metabolized by cytochrome P450 and glucuronidation, and also excreted in urine without changes. Two double-blind studies (1,500 patients with Alzheimer's slight to moderate level of the disease during 6 months) have proved effectiveness on the cognitive symptoms and the global functioning with doses of 16 to 32 mg daily.[134-135] The negative side effects are: nausea, vomits, anorexia and shaking. The drug is well tolerated when the dose is increased gradually. Other inhibitors of the cholinesterase that are under research are eptastigmine, huperzine and velnacrine.

**NNMDA antagonists Memantine** is a non-competitive NMDA antagonist. It blocks the calcium channels of such receptor, and in this way it stops the entrance of calcium to the neurons and the toxicity that it produces; besides, it isan agonist of the AMPA receptor. In double-blind studies there has been an improvement in the cognition and in the behavior. Its now in phase III studies in the United States. The side effects are: vomits, restlessness, dizziness, tiredness, vertigo. The dose is 15 to 20 mg daily.[112]

**Plants used in the treatment of alzheimer's disease**

A number of scientific researches have been carried out on medicinal herbs. Herbs have anti- inflammatory and antioxidant activities that may be used in thetreatment of AD. Alzheimer's patients have an acetylcholine deficiency.

Anti-inflammatory herbs may reduce inflammation of the brain tissue in Alzheimer's: German chamomile, Ginseng, licorice, turmeric, and white willow bark. Acetylcholine is a neurotransmitter that plays a key role in cognitive function and reasoning. The brains of those with mild-to-moderate Alzheimer's disease, a progressive type of dementia, have abnormally low acetylcholine concentrations. This means that any compound that enhances the cholinergic system in the brain may be useful in treating Alzheimer's disease and similar brain malfunctions.[136]

**Curcuma longa L. (Zingiberaceae)**

Curcuma longa (Turmeric, Harida) has been used as a source of Curcumin (diferuloylmethane), an orange-yellow component of turmeric or curry powder. Studies have proved that Curcumin has anti- inflammatory and antioxidant activities, and it helps in combating Alzheimer's Disease (AD). Regular consumption of this herb helps in keeping the mind balanced.[137]

The dose of curcumin can be reduced by making it to colon targeting.[138]

**Ginkgo biloba L. (Ginkgoaceae)**

Ginkgo Biloba is the best known herb for Alzheimer's disease and its associated symptoms. In controlled clinical trials, using a placebo and control group, ginkgo biloba extracts showed therapeutic benefits in

Alzheimer's, similar to prescription drugs such as Donepezil or Tactrin, with minimal undesirable side effects.[139]

The chief chemical constituent of gingko biloba is gingkolides and it is a pertinent antioxidant, with neuroprotective and cholinergic activities that help in the management of AD. Ginkgo biloba improves protection against Aβprotein-induced oxidative damages (degrading hydrogen peroxide, preventing lipids from oxidation, and trapping the reactive oxygen species).[140]

**Rosmarinus officinalis (Lamiaceae)**

Rosemary (Satapatrika) contains the following natural COX-2 inhibitors: Apigenin, carvacrol, eugenol, oleanolic acid, thymol, and ursolic acid. 'If a synthetic COX-2 inhibitor could prevent Alzheimer's disease, so could a natural COX-2 inhibitor,' according to Duke 2007. In addition, Rosemary contains nearly two dozen antioxidants and another dozen anti- inflammatory compounds. Some of the strongest antioxidant substances in the herb are carnosic acid and ferulic acid, which have even greater reported antioxidant activity than the widely common synthetic antioxidants butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA).[141]

Rosemary can be used as a tea, in shampoo, or in bath water, because it can be absorbed through the skin.[142]

**Matricaria recutita (Asteraceae)**

German Chamomile is said to stimulate the brain, dispel weariness, calm the nerves, counteract insomnia, aid in digestion, break up mucus in the throat and lungs, and aid the immune system. Chamomile can relieve anxiety, and in higher doses, leads to drowsiness, according to the University of Maryland Medical Center.[143]

**Melissa officinalis L. (Lamiaceae)**

Historically, Melissa officinalis (lemon balm) was believed to sharpen memory. Lemon balm can also temporarily improve cognitive decline as well as improve the mood for Alzheimer's patients. Another study addressing the use of lemon balm for Alzheimer's Disease, concluded that Melissa officinalis is one ofseveral plants that may be useful in the prevention and treatment of Alzheimer's disease due to its ability to inhibit acetylcholinesterase and its antioxidant activity.[142-143]

**Glycyrrhiza glabra (Fabaceae)**

Alzheimer's disease is characterized by neuronal loss and the presence of extracellular senile plaques, whose major constituent is amyloid-β peptide (Aβ). In this study, we investigated the effects of a water extract of licorice (Yashti- madhuka) on Aβ25-35-induced apoptosis in PC12 cells. Results suggest that GWE exerts a protective effect against apoptotic neuronal cell death induced byAβ fragments. Extract from the licorice root is reported to treat or even prevent brain cell death in diseases like Alzheimer's and its associated symptoms.[145]

**Galanthus nivalis L. (Amaryllidaceae)**

The chief chemical constituent of the Galanthus nivalis L. (common snowdrop) is Galanthamine, and this is an isoquinoline alkaloid. Acetylcholinesterase (AChE) inhibitors, which are also called 'anticholinesterase drugs', have been recently approved as an promising treatment approach for AD. Galanthamine has been found to be the long- acting and specific inhibitor of the AChE enzyme and to potentiate cholinergic nicotinic neurotransmission by allosterically modulating the nicotinic acetylcholine receptors, which may be of additional value in the treatment of AD.[146,147]

**Commiphora whighitti (Burseraceae)**

Commiphora whighitti (Guggulu), a plant resin, contains the major constituent of guggulipid, which is guggulsterone. The guggulipid has been seen to be a potential cognitive enhancer for improvement of memory in scopolamine- induced memory deficits.[148]

Commiphora whighitti acts on impairment in learning and memory and decreased choline actyl transferase levels in hippocampus. However, Commiphora whighitti shows maximum effects on memory functions and the potential for dementia disorder.[149]

**Lipidium meyenii walp (Brassicaceae)**

Lipidium Meyenii (maca), is known as Maca. Maca shows beneficial improvement in memory and learning. Black maca improves experimental memory impairment, induced by ovariectomy, due in part, to its antioxidant andAChE inhibitory activities. Results demonstrated that black maca can enhance learning and memory in OVX (ovariectomized) mice and this effect might be related, at least in part, to its ability to reduce LPO (Lipid peroxidation) and AChE in OVX mice.[150]

**Ashwagandha (Withania somnifera)**

It is a member of the Solanaceae family, and its root is commonly used for medicinal purposes. A prior study found that ashwagandha possesses cholinergic action.[15] The potential of ashwagandha to boost acetylcholine levels in the brain contributes to its memory-enhancing and cognition- improving properties. According to molecular modelling research, withanamides A and C bind to Aβ and prevent fibril formation.[152] It was also discovered that with anamides prevented amyloid plaques from damaging activated neuronal cells.[152,153,154] In human neuroblastoma cells, ashwagandha methanol extract stimulated the growth and development of the neural network.[155] In verified AD mice, per-oral administration of Withania root extract reversed behavioural deficits and prevented the formation of Aβ plaque.[156] The overexpression of the low-density lipoprotein receptor-related protein in the liver has been connected to Ashwagandha's effects [156]. The roots of ashwagandha help the body's defensive

mechanism in cases of chronic disease by enhancing cellular immunity and neutralising the cytotoxic cascade's fatal mediators, such as cytokines and ROS.[157,158]

The revelation of modern solutions for Alzheimer's illness, a few of which have been utilized within the past for other neurodegenerative ailments (such as the anti-viral medicine amantadine, which has been utilized to treat Parkinson's infection), is exceptionally promising. Aniracetam, piracetam, and pramiracetam are cases of nootropics, whereas choline esterase inhibitors, such as donepezil and rivastigmine, are illustrations of choline esterase inhibitors, which are ordinarily utilized to upgrade memory, disposition, and conduct. Concurring to the Globe Wellbeing Organization (WHO), more than 80 percent of the populace of the world employments conventional home grown pharmaceutical as their major source of healthcare. Since modern medicines have such discernible total and changeless impacts, there has been an outstanding development in later a long time toward the utilize of home grown medications as an elective.[159]

It is common information that India, with its colossal biodiversity and knowledge-rich old conventional therapeutic frameworks such as Ayurveda, Siddha, and Unani, as well as nearby wellbeing conventions, offers a strong establishment for the use of a huge number of plants within the common healthcare of the country's populace. It was appeared that the alkaloids indole - 3-alkylamines and carbolines in Desmodiumgangeticum had organic activities such as an anticholinesterase, smooth muscle stimulant, and central apprehensive framework stimulant reaction. In expansion, they explored the chemical make-up of the roots and found the nearness of three pterocarpenoids: gangetin, gangetinin, and desmodin separately.

**Gangetin**, a pterocarpan, has been appeared to have anti-fertility impacts by interferometer with the movement of antacid phosphatase in uterine discharges. It is accepted to be successful within the treatment of neurological sicknesses as well as having activities such as antiulcer, antioxidant, cardiotonic, antiinflammatory, and antinociceptive. As a result, it is imperative to examine the potential of conventional solutions to treat an assortment of cognitive maladies. The root of Desmodiumgangeticum includes a number of chemical components, the foremost imperative of which are gangetin, gangetinin, and desmodin.[160]

There are around 38 particular species of **Desmodium** that have been recorded in India, two of which are utilized in society pharmaceutical all over the globe. These incorporate Desmodiumgangeticum and Desmodiumadscendens. A critical and well investigated species of the sort Desmodium, Desmodiumgangeticum is used in conventional Indian pharmaceutical, outstandingly Ayurvedic pharmaceutical. It is one of the species within the class Desmodium. Alkaloids, flavonoids, and pterocarpinoids make up the lion's share of Desmodiumgangeticum's constituents. Brahmi, Ashwagandha, Curcumin, Arcoruscalamus, Shankhpushpi, and Zingiber are fair few of the Ayurvedic solutions which will offer assistance soothe the indications of Alzheimer's infection.

After the early discovery and control of physical components (diabetes, hypertension, and hyperlipidemia), the foremost fruitful demonstrate of treatment for Alzheimer's malady will likely incorporate the application of multifaceted, disease-modifying intercessions to anticipate the early and proceeded misfortune of neurons and to diminish the poisons that result in further cell deterioration. Within the conclusion, the foremost effective demonstrate of treatment for Alzheimer's infection will likely incorporate early location and control of physical components (diabetes, hypertension, and hyperlipidemia.

This plant is considered to be one of the Dashamoola (roots) of Ayurveda, and it is an fundamental component of numerous well-known Ayurvedic drugs, such as Dashamoolarishta (for frailty, hemorrhoids, and liver infection), Chyavanaprasha (for avoiding the maturing handle and acting as an antioxidant), Dhanwantharam Kuzhambu (for treating neurological conditions such as neuritis and neuralg (it makes a difference to battle tiredness, weariness, push and maturing). The objective of this investigate was to decide whether or whether the root of the Desmodiumgangeticum (fabaceae) plant, which was utilized as a creature show in this ponder, may be advantageous within the treatment of Alzheimer's infection.[161

## 2. REVIEW OF LITERATURE

**Evaluation of anti-alzheimer activity of alcoholic extract of costus pictus d. don leaves in wistar albino rats**

**Authors**

**Pasha khooshbu**

**Objective:** The aim was to assess the effect of anti-Alzheimer's activity of the alcoholic extract of *Costus pictus* D. Don Leaves in Alzheimer induce Wistar albino rats.

**Methods:** In the present study, the efficacy of an Extract of *Costus pictus* D. Don (ECPDD) was evaluated against scopolamine-induced Alzheimer in the Wistar albino rat. Donepezil at a dose of 2.5 mg/kg, ECPDD was given in rat at a dose of 100 mg/kg body weight, 150 mg/kg body weight, and 200 mg/kg body weight. Anti-Alzheimer activity was assessed by victimization novel object recognition test, elevated plus maze, and Y-maze. And by biochemical test like neurotransmitter esterase activity, catalase activity, malonyldialdehyd and glutathione assays.

**Results:** Results showed that extracts treatment prevents Alzheimer and increases the level of acetylcholine,

catalase, glutathione peroxidase, and phytochemical studies identified the presence of flavonoid and alkaloid in the ECPDD.

**Conclusion:** According to the results, it was concluded that the leave of *C. pictus* D. Don has significant anti-Alzheimer activity due to the presence of potent antioxidants such as flavonoid and anticholinesterase enzyme present in alkaloids.

**A Rat Model of Alzheimer's Disease Based on Abeta$_{42}$ and Pro-oxidative Substances Exhibits Cognitive Deficit and Alterations in Glutamatergic and Cholinergic Neurotransmitter Systems**

**Tomas Petrasek**

Alzheimer's disease (AD) is one of the most serious human, medical, and socioeconomic burdens. Here we tested the hypothesis that a rat model of AD (Samaritan; Taconic Pharmaceuticals, USA) based on the application of amyloid beta$_{42}$ (Abeta$_{42}$) and the pro-oxidative substances ferrous sulfate heptahydrate and L-buthionine-(S, R)-sulfoximine, will exhibit cognitive deficits and disruption of the glutamatergic and cholinergic systems in the brain. Behavioral methods included the Morris water maze (MWM; long-term memory version) and the active allothetic place avoidance (AAPA) task (acquisition and reversal), testing spatial memory and different aspects of hippocampal function. Neurochemical methods included testing of the NR1/NR2A/NR2B subunits of NMDA receptors in the frontal cortex and CHT1 transporters in the hippocampus, in both cases in the right and left hemisphere separately. Our results show that Samaritan ratstm exhibit marked impairment in both the MWM and active place avoidance tasks, suggesting a deficit of spatial learning and memory. Moreover, Samaritan rats exhibited significant changesin NR2A expression and CHT1 activity compared to controls rats, mimicking the situation in patients with early stageAD. Taken together, our results corroborate the hypothesis that Samaritan rats are a promising model of AD in its early stages.

**Neuroprotective activity of *Ulmus pumila* L. in Alzheimer's disease in rats; role of neurotrophic factors**

**Rehab A.Hussein**

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders which affects the hippocampus and cortical neurons leading to impairment of cognitive ability. Treatment of AD depends mainly on acetylcholinesterase inhibitors, however, a novel therapeutic approach is introduced based on the maintenance of neuronal viability and functionality exerted through neurotrophic factors. In the current study, *Ulmus pumila* L. leaves alcoholic extract was investigated for its neuroprotective activity in $AlCl_3$-induced AD in rats. Rats were orally treated with $AlCl_3$ (17 mg/kg) for 4 weeks followed by *U. pumila* extract (150 mg/kg b.wt.) for another 6 weeks. Treatment of neuro-intoxicated rats with *U. pumila* extract resulted in a significant regulation in neurotrophic factors; brain derived neurotrophic factor and transforming growth factor-β and pro-inflammatory cytokine; TNF. It also induced an elevation in serum levels of monoamine neurotransmitters; norepinephrine, dopamine and serotonin and a decline in brain acetlycholinesterase activity. *U. pumila* extract also showed potent antioxidant activity as indicated by the declined malondialdehyde and elevated reduced glutathione, catalase and super oxide dismutase levels in AD rats' brains. Histological improvement was detected in the cerebral cortex, the hippocampus and striatum of the treated rats. The phytochemical analysis of *U. pumila* extract revealed high contents of flavonoids and phenolics and the major compounds were isolated and chemically characterized. Additionally, *U. pumila* extract and the isolated compounds exerted prominent activity in *in-vitro* acetylcholinesterase inhibition assay withkaempferol-3-O-β-glucoside being the most potent compound showing $IC_{50}$ of 29.03 ± 0.0155 µM. A molecular docking study indicated high affinity of kaempferol-3-O-β-robinobioside on acetylcholine esterase binding site with estimated binding free energy of –8.26 kcal/mol.

**Anti-Alzheimer's Activity of aqueous extract of leaves of Murrayakoenigii in Aluminium chloride Induced Neurotoxicity in rats**

**B. Maheswari Reddy**

Objective: The present study was aimed to evaluate the protective effect of Murrayakoenigii on aluminium chloride (AlCl3) induced neurobehavioral and pathological changes in Alzheimeric rats. Methods: Wistar albino rats were selected in this study and were divided into 6 groups (6each). Group I animals received saline and were considered as control. Group II rats were administered with AlCl3 (40mg/kg b.w, oral) for 35 days. Group III rats were treated with standard Vitamin E (100mg/kg b.w, p.o) and AlCl3 (40mg/kg b.w, oral). Group IV, V,VI received aqueous extract of leaves of Murrayakoenigii (100mg/kg b.w, p.o,200mg/kg b.w, p.o,400mg/kg b.w, p.o) and inducing agent AlCl3 (40mg/kg b.w, oral) .The rats were given respective treatment for 35 days and behavioural parameters were determined on the 35th day. On the 35th day the rats were sacrificed and anti-oxidant parameters, brain acetylcholinesterase content were determined. Results: Oral administration of aqueous extract of leaves of Murrayakoenigii at doses 100,200, 400mg/kg body weight showed improvements in behavioural parameters when compared to AlCl3 induced rats; showed increase in superoxide dismutase, catalase, reduced glutathione and decreased levels of malondialdehyde and also a showed decrease in brain acetylcholinesterase content when compared to AlCl3 induced rats. Conclusion: This study strongly suggested that M koenigii could possibly restore the altered neurological capacities and antioxidant power in rats, and it could even be a good alternative to chemical medicines against AlCl3 induced

neurotoxicity

**A novel synthetic compound shows antioxidant and anti-inflammatory activity and alleviates cognitive deficits in rats for the treatment of Alzheimer's disease**

**Jing Xie**

**Background:** Alzheimer's disease (AD) is a progressive dementia, and β- amyloid (Aβ) accumulation is widely regarded as the primary pathogenesis of AD. A new synthetic compound, 8-hydroxyquinoline-resveratrol derivative (E)- 5-(4-hydroxystyryl)quinolin-8-ol (10c) was evaluated as a possible anti-ADagent.

**Method:** (I) The total amount of ROS in SH-SY5Y cells was detected by dichlorofluorescein diacetate (DCFH-DA), and the antioxidant activity and neuroprotective effect of 10c in SH-SY5Y cells were evaluated; (II) Griess reagent was used to test the activity of Compound 10c against NO production in LPS-induced BV-2 microglial cells; (III) An automatic digital stereotaxic instrument was used to inject $A\beta_{25-35}$ into the brain to establish an AD animal model to evaluate the protective effect of compound 10c on $A\beta_{25-35}$-induced learning and memory dysfunction in rats.

**Results:** 10c exhibited far more potent antioxidant activity for both exogenous and endogenous reactive oxygen species (ROS) than trolox, resveratrol, and CQ (ROS production: 10c with 26.23% at 1.5 μM; resveratrol with 82.17% at 2.5 μM; CQ with 78.52% at 10 μM). 10c also shows good neuroprotective effectsas an endogenous antioxidant in neuroblastoma cells. Moreover, Compound 10c also demonstrated effective inhibition of nitric oxide (NO) production($IC_{50}$ =3.10 μM) and IL-1β production in BV-2 microglial cells which were treated with lipopolysaccharide (LPS). In the water maze test, the numbers of rats who crossed the former platform were increased significantly in both the 10c group (5.7±1.6) and positive control group (CQ, 5.1±1.7). Meanwhile, both 10c (43.8±5.5 s) and CQ (44.1±6.6 s) treatment could significantly prolong the time rats spent in the target quadrant compared to the vehicle-treated model group. These results demonstrated that 10c could alleviate the learning and memory dysfunction of rats induced by $A\beta_{25-35}$ to a certain extent.

**Conclusions:** Altogether, compound 10c is a promising compound for thetreatment of AD.

**Exploring the Effect of *Phyllanthus emblica* L. on Cognitive Performance, Brain Antioxidant Markers and Acetylcholinesterase Activity in Rats: Promising Natural Gift for the Mitigation of Alzheimer's Disease**

**Uddin M.S.**

Neurodegenerative diseases are incurable and debilitating conditions that result in the progressive degeneration of nerve cells, which affect the cognitive activity. Currently, as a result of multiple studies linking Alzheimer's disease (AD) to oxidative damage, the uses of natural antioxidant to prevent, delay, or enhance the pathological changes underlying the progression of AD has received considerable attention. Therefore, this study was aimed at examining the effect of ethanolic extracts of *Phyllanthus emblica* (EEPE) ripe (EEPEr) and EEPE unripe (EEPEu) fruits on cognitive functions, brain antioxidant enzymes, and acetylcholinesterase (AChE) activity in rat. The effects of EEPEr and EEPEu fruits (i.e., 100 and 200 mg/kg b.w.) were examined in Swiss albino male rats for 12 days and its effect on cognitive functions, brain antioxidant enzymes, and AChE activity determined. Learning and memory enhancing activity of EEPE fruit was examined by using passive avoidance test and rewarded alternation test. Antioxidant potentiality was evaluated by measuring the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase, reduced glutathione (GSH), glutathione-S-transferase, and the contents of thiobarbituric acid reactive substances (TBARS) in entire brain tissue homogenates. AChE activity was determined using colorimetric method. Administration of the highest dose (i.e., 200 mg/kg b.w.) of EEPEr fruit significantly ($p < 0.01$) and both lowest and highest doses (i.e., 100 and 200 mg/kg b.w.) of EEPEu fruit markedly ($p < 0.05$, $p < 0.001$) increased step- through latency in rats on 6th, 11th, and 12th day with respect to the control group. For aforementioned doses, the percentage of memory retention (MR) was considerably ($p < 0.05$, $p < 0.01$) increased in rats on 10th, 11th, and 12th days with respect to the control group. The extract, particularly highest dose (i.e., 200 mg/kg b.w.) of EEPEr fruit markedly ($p < 0.05$) and lowest and highest doses (i.e., 100 and 200 mg/kg b.w.) of EEPEu fruit significantly ($p < 0.01$) increased the correct responses in rats on 6th, and 12th day related to the control group. In case of this test, the percentage of MR was significantly ($p < 0.05$, $p < 0.01$) increased in rats treated with aforementioned doses on 12th day with respect to the control group. The highest dose (i.e., 200 mg/kg b.w.) of EEPEr fruit suggestively ($p < 0.05$) and both lowest and highest doses (i.e., 100 and 200 mg/kg b.w.) of EEPEu fruit suggestively ($p < 0.05$, $p < 0.01$, $p < 0.001$) increased the levels of SOD, CAT, GSH, GSH-Px and expressively ($p < 0.01$) decreased the TBARS level compared to the control group. Treatment with the highest dose (i.e., 200 mg/kg b.w.) of EEPEr fruit significantly ($p < 0.05$) and both lowest and highest doses (i.e., 100 and 200 mg/kg b.w.) of EEPEu fruit markedly ($p < 0.01$, $p < 0.001$) decreased the level of AChE activity compared to that of the control group. The present study shows that EEPE fruit possesses an excellent source for natural cognitive enhancer which could be developed in the treatment of AD and other neurodegenerative diseases.

**Evaluation of neuroprotective effects of *Canna indica* L against aluminium chloride induced memory impairment in rats**

**Prachi S. Ojha**

Memory disorders are the progressive neurological

disorder, mainly causing dementia, memory loss and cognitive dysfunctions. The current study is aimed to experimentally validate the crude extract of *Canna indica* aerial parts (CIA) and root (CIR) against aluminium chloride induced altered memory in rats. Initially, methanolic extract of CIA, hydroalcoholic extract of CIR, and their combination of CIA + CIR were screened for *Invitro* antioxidant activity via 2,2-diphenyl-1-picrylhydrazyl (DPPH) and nitric oxide (NO) assays, acetylcholinesterase (AChE) inhibitory assay and were also screened for their memory enhancing activity by *in-vivo* models such as elevated plus maze (EPM), morris water maze (MWM), cooks pole climb (CPC), Actophotometer, novel object recognition (NOR), and T-maze. Aluminium chloride ($AlCl_3$) (17 mg/kg/day p.o.) for 21 days, was used as an Alzheimer's disease inducing agent and Donepezil (AChE inhibitor) as a standard treatment agent. The AChE, butyrylcholinesterase (BChE) activity and malondialdehyde (MDA) level were significantly increased, and glutathione (GSH), total protein (TP), catalase (CAT), and Dopamine were decreased only in $AlCl_3$ treated rats and treatment with CIA 200 mg/kg and CIA + CIR 200 mg/kg significantly reversed these mechanisms.Histopathology of cortex and hippocampus was examined at 40× magnification, indicating maintain of integrity and architecture of CA1 and CA3 neuronal cells compared to control and standard groups. The in vivo studies of interospective and exteroceptive behavior models (EPM), MWM, CPC, Actophotometer, NOR, T-maze revealed that $AlCl_3$ administration enhanced transfer latency (TL), escape latency time (ELT) and decreases locomotion, discriminatory index, and percentage alternation respectively. However, treatment with CIA and CIA + CIR 200 mg/kg highly significantly reversed the pathological changes of disease, extracts of *Canna indica* of both root and aerial parts phyto constituents are rich in flavonoids, phlobatannins, anthocyanin pigments, saponins, alkaloids, steroids, terpenoids etc. Which will decipher the acetylcholinestrase inhibitory, antioxidant and anti-inflammatory activity, will ameliorate the pathological state of Alzheimer disease.

## 3. AIM AND OBJECTIVES

**Aim:** The aim of the experiment is to estimate the Anti-alzheimer's activity of ustukhuddus against scopolamine induced neurocognitive impairment in mice model

**Objectives**

The main purpose of the study is to estimate the anti alzheimer activity ofustukhuddus

In the present study we are using a natural product for the treatment of AD.

**Experimental design**

- **Procurement of ustukhuddus**

Collection and authentication of Ustukhuddus.

Extraction of ustukhuddus by Soxhlet Extraction using ethanol. This extraction will be subjected to Phytochemical screening.

- **Animals required**

In this investigation, 1 month old swiss albino mice weighing between 25-30grams was employed.

The neurocognitive impairment in mice is induced by administering Scopolamine 2mg/kg body weight i.p in 0.5% w/v CMC

## 4. MATERIALS AND METHODS EXPERIMENTAL DESIGN

**Procuring of the ustukhuddus**

The gathering and confirmation of the Ustukhuddus. The ethanoloc extract wasprepared by maceration method of extraction. The powdered form of 100gm of dried plant part is dissolved in 1000ml of ethanol and kept at room temperature for 48 hours, and is shaken several times.

After 48hours the extract is filtered through Whattman filter paper and then the solvent is distilled at 65 C in rotary evaporator.

The final extract is dissolved in CMC and is administered.

The taking after sorts of creatures are required: a male Swiss pale skinned person For the purpose of this investigate, we'll be utilizing mice that weigh between 20 and 25 g. The current examination will make utilize of a add up to of thirty mice. The neurocognitive disability in mice is created by intraperitoneal organization of scopolamine at a dosage of 2 mg/kg of body weight in 0.5% weight-based concentration of CMC.

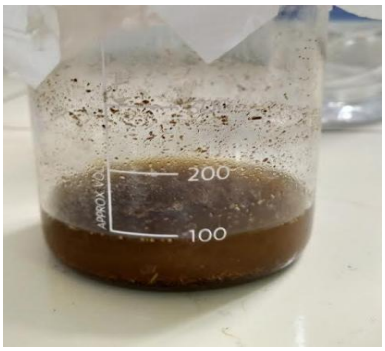


**Figure 4: Dried flowers of ustukhuddus. Figure 5: extraction by maceration.**

**Experimental protocol methodology**

Scopolamine initiated Neurocognitive impedance The mice will be conveyed equally among five bunches of six mice each, for a add up to of thirty mice. Scopolamine ought to be managed thirty minutes taking after the test, or standard pharmaceutical treatment, whichever comes to begin with. Creatures inGather I (Typical Control) will be encouraged their standard nourishment and will be given 0.5%w/v CMC within the vehicle orally at a measurement of 1 mlper 100 g of body weight.

| Groups | Drug and dose |
|---|---|
| Group 1 CONTROL GROUP | Normal diet and vehicle 0.5%w/v CMC by p.o. At a dose of 1ml/100gm body weight. |
| Group II NEGETIVE CONTROL GROUP | Scopolamine 2mg/kg body weight in 0.5%w/v CMC by p.o. |
| Group III STANDARD GROUP | Scopolamine 2mg/kg body weight + Donepezil HCL 5mg/kg body weight. |
| Group IV TREATMENT GROUP | Scopolamine 2mg/kg body weight + ethanolic extract of Ustukhuddus 200mg/kg body weight in 0.5%w/v CMC by p.o. |
| Group V TREATMENT GROUP | Scopolamine 2mg/kg body weight + ethanolic extract of ustukhuddus 400mg/kg body weight in 0.5%w/v CMC by p.o |

**Figure 6: methodology.**

**Methods**

The another segments will talk about the testing approach for behavioral and memory tests, as well as the course of action of medicines and biochemical request into brain zones. Examens de Comportement Memory, cognitive capacity, and mental action were assessed utilizing the raised also labyrinth, shaft climbing, and rota pole tests individually. Rats' locomotor movement was measured employing a computerized photo actometer for comparison's sake. Knowledge and memory are being tried here. The Raised Furthermore labyrinth exam, the Post climbing test, and the Rota rod test were utilized to assess the participant's information and memory picks up. The lion's share of the time, analysts utilize these examinations to explore how rats procure data and work their memories.

**A) The method of the elevated plus maze**

The raised additional maze was utilized as the exteroceptive behavioral show (meaning the boost was found exterior the body) to assess the learning and memory capacities of rats. The device is able to oblige both the two open arms (16 cm x 5 cm) as well as the two secured arms (16 cm x 5 cm x 12 cm). The arms increased from a middle arrange that measured 5 centimetres by 5 centimetres, and the maze was raised to a stature of 25 centimetres above the ground. On the primary day of the competition, each creature was situated at theconclusion of an open arm, with its back to the stage's middle.

The length of time that the animal took to move into one of the bolted arms utilizing all four of its legs was recorded as the trade inertia (TL) for that animal. The recording of TL took put on the primary day. On the off chance that the animal did not enter into one of the secured arms inside 90 seconds, it was tenderly constrained into one of the two secured arms, and the time remaining was numbered as 90 seconds. After being given ten seconds to investigate the labyrinth, the mammoth was escorted back to its domestic walled in area after being given the opportunity to do so. On minute day15, memory conservation was inspected after a delay of 24 hours after the beginning day explore.

**Morris water maze**

Around the exterior of the swimming pool, there were four particular starting areas that were set up. On each of the five preparing days, each of the four begin areas was utilized once in a grouping that was considered to be pseudo- random. The water labyrinth was arranged in a huge room that included a assortment of extra visual clues for the maze. At the starting of the test, the creature was put into the water at one of the beginning places so that it was confronting the side of the pool. Within the occasion that the creatures were incapable to distinguish the stage inside 120 seconds (for rats) or 60 seconds (for mice), the analyst would tenderly set it there and let it to stay for 30 seconds. For a period of five days in a push, each creature was put through a every day session comprising of, within the case of rats, four trials each day and,within the case of mice, three trials each session. It was decided that the "Elude Inactivity Time," or ELT, required to reach the concealed stage within the water maze was a degree of learning.

**Table no. 2: Morris water maze descriptionpole climbing method.**

| Stage | Relevant | Type | Example |
|---|---|---|---|
| Simple Discrimination (SD) | High | Odour, Taste | Cinnamon,Vanilla |

| | | | |
|---|---|---|---|
| Compound Discrimination (CD) | High | Odour, Taste | Nutmeg, Lemon |
| IntradimensionalShift (IDS) | High | Odour, Taste | Clove, Ginger |
| ExtradimensionalShift (EDS) | High | Odour, Taste | Cinnamon, butterscotch |

**B) Rotarod method**

Misfortune of engine coordination is one of the foremost conspicuous side effects of the condition. This exam is required in arrange to have get to to it. The rats were set on a rota pole, and the reasonable rotational speed was chosen for them (25 rpm). Some time recently doing the genuine examination, the animal was put through a development test for a entirety miniature. We took note of how frequently the rodent slipped off the spinning pole whereas it was being watched

**Rotarod technique**

**Check for evidence of locomotor activity**

This serves as an marker of whether a individual is alert or mindful of their mental exercises. A advanced photoactometer will be utilized to create the assurance. A check will be taken each time the living being devastates a parcel of the light pillar that strikes the photo cells on its surface. The movements of each person animal will be followed and logged for five minutes independently, and the comes about may be detailed as tallies for five minutes per animal.

**The locomotor technique**

**Experimental models**

Scopolamine butyl bromide was managed intra peritoneally (i.p.) to rats in allof the exploratory bunches with the special case of the typical bunch. This was exhausted arrange to commence the foremost vital and principal perspective of AD. a) Scopolamine convinced ALZD in rats. Scopolamine, a muscarinic receptor adversary, was weakened in typical saline (0.9% NaCl) and managed intravenously at a rate of one millilitre per kilogramme of the patient's body weight. The creatures were assessed for their conduct five minutes after accepting an infusion of scopolamine on a every day premise for a period of thirty days.

**C) Donepezil therapy in rats.**

An Hurt inhibitor known as donepezil, at a measurements of 0.75 mg/kg, was ground up and combined with an conventional salt arrangement containing 0.9% sodium chloride. It was managed orally at a volume of 1 millilitre per kilogramme of body weight. The rats within the control bunch were allowed this privilege. Plant Extricate administration: Prior to the behavioural tests, the rats within the testing bunches (bunches 4-11) were given different sums of ethanolic and fluid extricates of Cassia obtusifolia. These extricates were made from the Cassia obtusifolia plant.

**Biochemical estimation**

After the behavioral considers were wrapped up, the biochemical parameters of oxidative thrust and cholinergic work were tried in all of the bunches that were given the medicine. After thirty days had passed since the starting of the test,the creatures were set in a drying up room where they were permitted to breathe in carbon dioxide. By puncturing the critters' retroorbital films with capillary tubes, blood tests were extricated from the animals. In arrange to extricate serum, blood tests from different sorts of living beings were centrifuged at arate of 1000 insurgencies per diminutive for a period of 15 minutes. The serum was inspected in arrange to decide the levels of anti-oxidants such as GSH, MDA, Turf, and NO. Hurt was too measured.

Taking after the collection of blood tests, the creatures were put beneath anesthesia with an overabundance of ether. It'll be rapidly dismembered, washed totally with NS, dried, and weighed once it has been evacuated from each living species with its intaglio brain. For the purposes of histological examination, each brain test will be protected by settling it in a 10% formalin arrangement or a Na3PO4 buffer.

**Estimation of acetylcholinesterase activity**

The technique of Ellmanet al., 1961723, was used to determine acetylcholinesterase activity.

The principle behind this is using a spectrophotometer, the rise in yellow color generated by thiocholine when it interacts with di-this-nitrobenzoate (DTNB) with an absorbance of 412 nm was used to determine acetylcholinesteraseactivity.

**Procedure**

A 0.4 ml aliquot of the homogenate is put to a cuvette containing 2.6 ml phosphate buffer (0.1 ml pH 8) and 100 l of DTNB for AChE measurement. By bubbling air, the contents of the cuvette were well mixed, and the absorbance was measured in a spectrophotometer at 412nm. The baseline reading was taken when the absorbance reached a steady value. Then 20 l of the substrate (acetyl thiocholine iodide) was added, and the change in absorbance was monitored for 10 minutes at 2-minute intervals. As a result, the change in absorbance per minute is calculated.

**Estimation of lipid peroxidation**

The production of lipid peroxide was measured using the Niehaus (1968)124 technique.

**Principle**

Malondialdehyde (MDA) is a breakdown product of peroxidized lipids that is measured using the Trichloroacetic acid- Thiobarbituric acid- Hydrochloric acid (TCA-TBA HCl) reagent (absorption maximum at 535 nm).

**Procedure:**

In 0.1 M Tris HCl buffer, pH 7.5, the tissue

homogenate was produced. About 1 mL of the homogenate was mixed well with 2 mL of the TCA-TBA-HCl reagent. In a boiling water bath, the solution was heated for 15 minutes. Centrifugation at 3000 rpm for 10 minutes was used to remove the flocculent precipitate after it had cooled. The sample's absorbance was measured at 535 nm against a blank that did not include any tissue homogenate. 1.56 X 105 M–1cm-1 is the extinction coefficient of MDA.

**Antioxidant defense status**

**1. Superoxide dismutase**

Superoxide dismutase is a metal-containing antioxidant enzyme that converts damaging oxygen free radicals to oxygen and hydrogen peroxide during normal metabolic cell processes.

The technique of Kono (1978)[21] was used to calculate superoxide dismutase levels.

**Principle**

Under aerobic circumstances, the reduction of Nitro Blue Tetrazolium (NBT) to blue formazan mediated by hydroxylamine hydrochloride was measured. The amount of inhibition of NBT reduction by superoxide anions, which are formed by photo-oxidation of hydroxylamine hydrochloride, was used as a measure of enzyme activity when superoxide dismutase was added.

**Procedure**

1.3ml of 50 mM sodium carbonate solution with 0.1 mM EDTA (pH 10.0), 0.5 ml of 96 MofNBT, and 0.1 ml of 0.6 percent triton-X-100 made up the reaction mixture. The reaction was started by adding 0.1 ml of 20 mM hydroxylamine hydrochloride (pH 6.0) to the reaction mixture, and the rate of NBT reduction was measured for around 30 seconds in the absence of the enzyme source. Small aliquots of supernatant were then introduced to the test and reference cuvettes, which were both devoid of hydroxylamine hydrochloride. Finally, the percentage inhibition in the rate of NBT reduction was calculated, and one unit ofthe enzyme was defined as the inverse of the quantity of protein (mg) necessary to inhibit the rate of NBT reduction by 50%.

**2. Glutathione-S-Transferase**

Glutathione-S-transferase is a metabolic enzyme best known for catalyzing the conjugation ofthe reduced form of glutathione (GSH) to xenobiotic substrates for detoxification purposes. The technique of Habig et al., 1974126, was used todetermine glutathione-Stransferase. As a substrate, 1-chloro-2,4-dinitrobenzene (CDNB) is utilized.

**Principle**

GST catalyzes the production of a glutathione-chloro-2,4 dinitrobenzene conjugate, which was detected at 340 nm (E 340 = 9.6Mm-1 cm-1).

**Procedure**

0.1ml of 1 m MCDNB (freshly produced) was added to 2.75 ml of 0.1 M phosphate buffer (pH 6.5). The volume was then increased to 3 ml by adding 0.1 ml of 1 mM GSH (freshly produced) and 50 l samples. CDNB's glutathione conjugate absorbs the most light at 340 nm. The extinction coefficient of 9.6 Mm-1 cm-1 was achieved using the Jasco V double beam spectrophotometer. The absorbance was measured every minute for a total of five minutes. The blanks represented a non-enzymatic interaction of GSH with the relevant substrate in allcircumstances. The CDNB solution was diluted in ethanol with care taken to ensure that the alcohol content in the assay mixture did not exceed 5%, and the reference cuvette should contain 0.1 M phosphate buffer (pH 6.5).

**Estimation of nitric oxide**

Nitric oxide concentration evaluation (NO) NO could be a free radical that's capable for making oxidative push. It is characterised by the nearness of unpaired electrons. Nitrite (NO2) and nitrate (NO3) are two steady and terminal products of NO digestion system. They may be used as roundabout markers to dissect the nearness of NO. Nitrite contains a negative charge, while nitrate encompasses a positive charge. The amounts of NO items were given in moles.

## 5. RESULTS

**Table No. 3: Phytochemical screeningbehavioural tests: Elevated plus maze method.**

| Chemical constituent | Test | Extract |
|---|---|---|
| Tannins | Ferric chloride test | + |
| | Lead acetate test | + |
| | Acetic acid sol. | - |
| | Dil. Iodine sol. | + |
| Alkaloids | Mayer’s test | + |
| | Dragendroff’s test | + |
| | Hager’s test | + |
| | Wagner’s test | + |
| Glycoside | | |
| **A.Cardiacglycosides** | Baljet’s test | + |
| | Legal’s test | + |
| | Keller-killiani test | + |
| | Liebermann’s test | + |

| | | |
|---|---|---|
| **B. Steroids** | Salkowski test | + |
| | Liebermann-burchard test | + |
| | Liebermann's test | + |
| **C.Saponins** | Foam test | + |
| **D. Flavonoids** | Schinoda test | + |
| | Lead acetate test | + |
| | NaOH test | + |
| **E. Anthraquinones** | Borntrager's test | - |
| | Modified-borntrager'stest | + |
| Carbohydrates | Molisch test | + |
| | Fehling's test | - |
| | Benedict's test | - |
| Proteins | Biuret's test | - |
| | Millon's test | - |

**Table no. 4: Elevated plus maze method.**

| Treatments | Open ArmEntries | Percentage decreasedin Open arm entries |
|---|---|---|
| Group-1 | 14.27 | 1 |
| Group-2 | 16.28 | 0.876 |
| Group-3 | 14.21 | 0.995 |
| Group-4 | 13.28 | 0.930 |
| Group-5 | 12.89 | 0.903 |
| **SD** | 0.115 | |
| **SEM** | 0.0346 | |

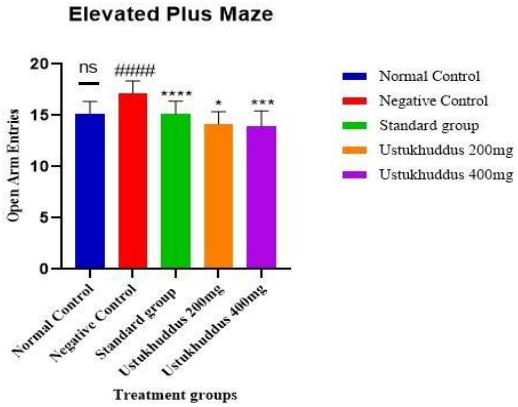


**Figure no. 7: Elevated plus maze test effect of extracts on pole climbing method.**

**Table No. 5 Pole climbing method.**

| Treatments | Pole Climbing |
|---|---|
| Group-1 | 45 |
| Group-2 | 43 |
| Group-3 | 44 |
| Group-4 | 36 |
| Group-5 | 33 |
| **SD** | 0.8776 |
| **SEM** | 0. 2646 |

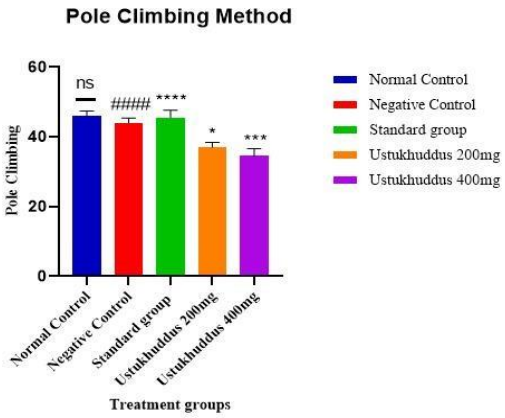


**Figure no. 8 Pole climbing methodmorris water maze.**

**Table no. 6: Morris water maze.**

| Groups | Simple Discrimination (SD) | Compound Discrimination (CD) | Intradimensional Shift(IDS) | Extradimensional Shift (EDS) |
|---|---|---|---|---|
| Group-1 | 7.2±0.13 | 5.8±0.19 | 3.8±0.11 | 2.4±0.27 |
| Group-2 | 3.4±0.11 | 2.4±0.34 | 4.6±0.26 | 4.9±0.23 |
| Group-3 | 4.6±0.34 | 5.3±0.18 | 2.3±0.19 | 4.2±0.35 |
| Group-4 | 5.3±0.14 | 3.8±0.21 | 4.7±0.24 | 7.2±0.28 |
| Group-5 | 6.2±0.26 | 7.5±0.28 | 5.7±0.39 | 5.6±0.21 |

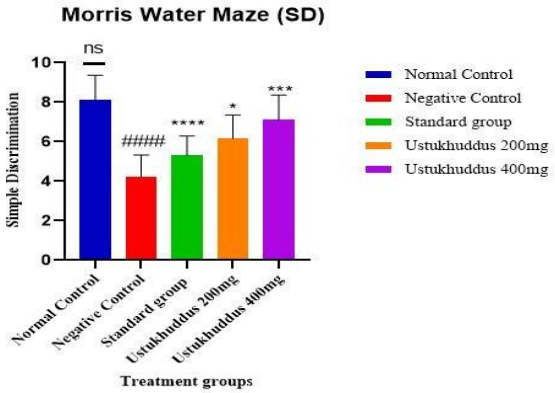


**Figure no. 9: Morris water maze (SD).**

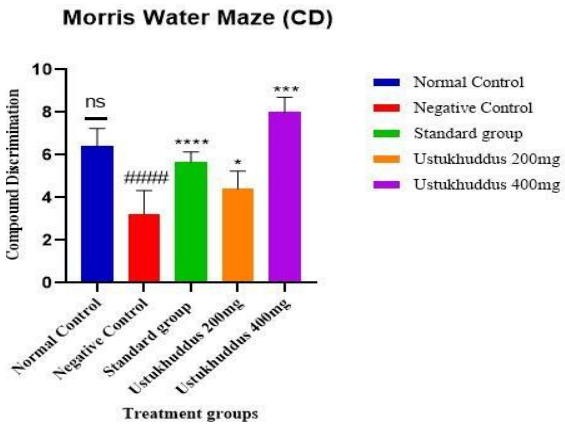


**Figure no. 10: Morris water maze (CD).**

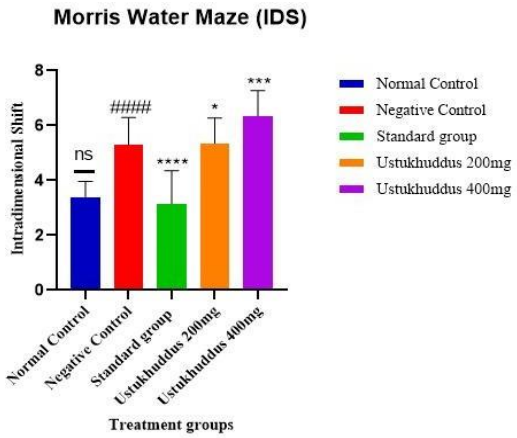


**Figure no. 11 Morris Water Maze (IDS).**

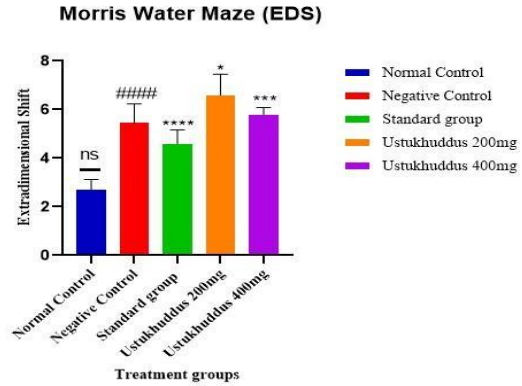


**Figure no. 12: Morris water maze (EDS).**

**Effect of extracts on rotarod test**

**Table no. 7: Rotarod test.**

| Groups | 1st Day | 7th Day | 14th Day | 21st Day |
|---|---|---|---|---|
| Group-1 | 55 | 53 | 49 | 46 |
| Group-2 | 27 | 21 | 16 | 12 |
| Group-3 | 35 | 29 | 26 | 22 |
| Group-4 | 48 | 39 | 27 | 23 |
| Group-5 | 32 | 24 | 21 | 20 |

**Effect of extracts on rotarod method**

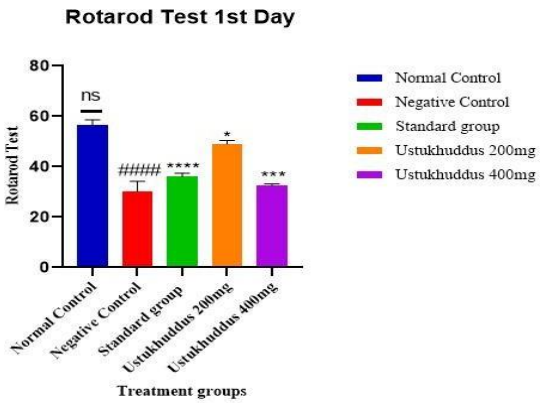


**Figure no. 13: Rotarod Test (Day 1).**

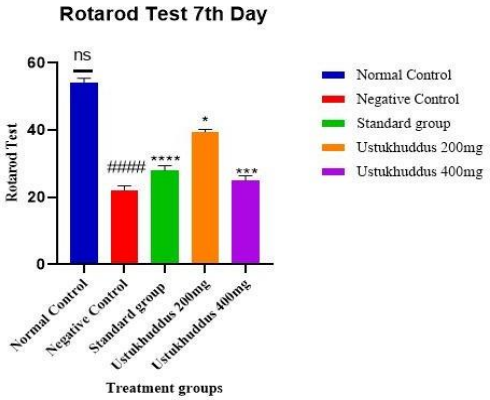


**Figure no. 14: Rotarod Test (Day 7).**

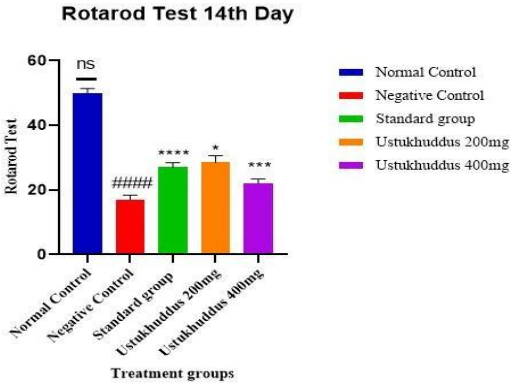


**Figure no. 15: Rotarod Test (Day 14).**

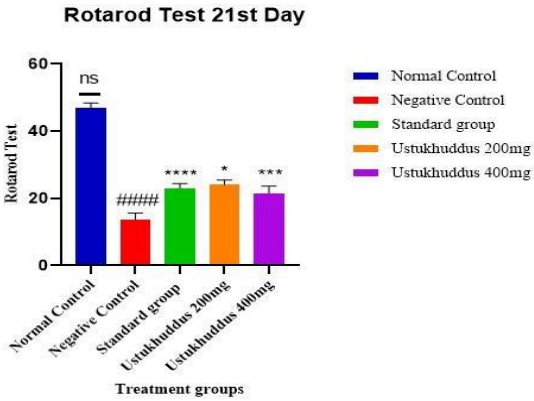


**Figure no. 16: Rotarod Test (Day 21) Effect of Extracts on Locomotor Activity test.**

**Table No. 8: Locomotor activity test.**

| Treatments | Active Pokes (300 secs) | Beam Breaks |
|---|---|---|
| Group-1 | 300 | 55 |
| Group-2 | 300 | 67 |
| Group-3 | 300 | 54 |
| Group-4 | 300 | 47 |
| Group-5 | 300 | 42 |
| **SD** | | 9.511 |
| **SEM** | | 2.867 |

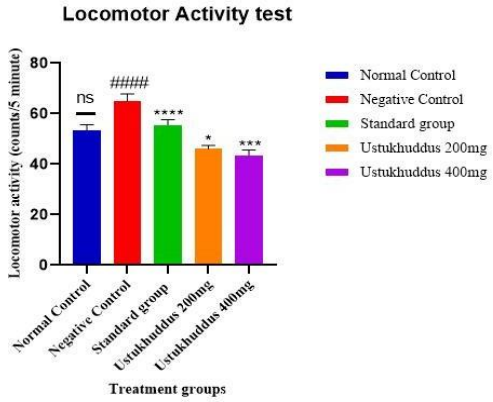


**Figure no. 17: Locomotor activity test Effect of Extracts on acetylcholinesterase (AChE) activity.**

**Table No. 9: AChE activity.**

| Treatments | Cerebellum | Hippocampus | Cortex |
|---|---|---|---|
| Group-1 | 0.29 | 0.49 | 0.17 |
| Group-2 | 0.17 | 0.46 | 0.23 |
| Group-3 | 0.24 | 0.48 | 0.24 |
| Group-4 | 0.25 | 0.42 | 0.25 |
| Group-5 | 0.23 | 0.38 | 0.16 |

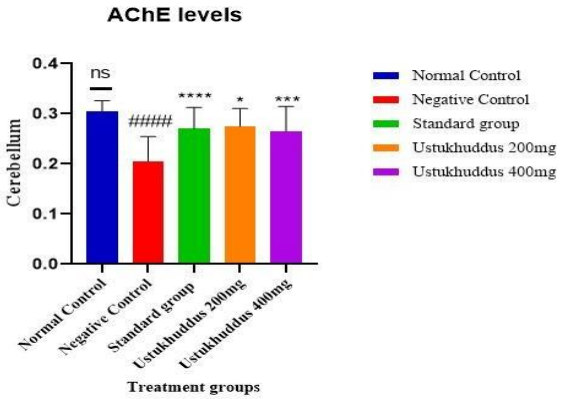


**Figure no. 18: AChE levels (Cerebellum).**

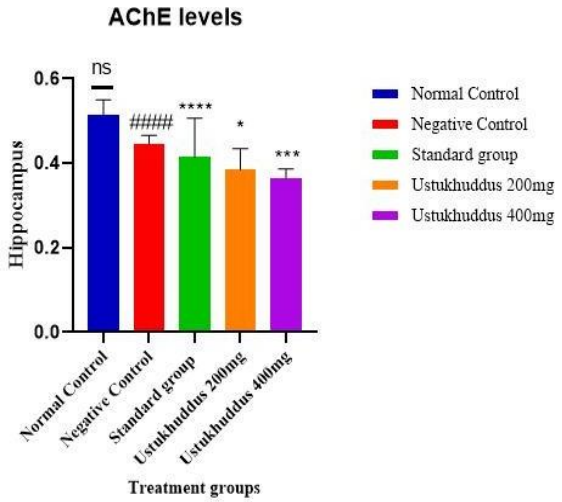


**Figure no. 19: AChE levels (Hippocampus).**

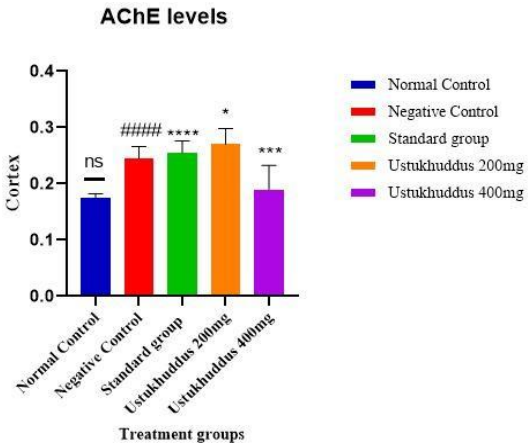


**Figure no. 20: AChE levels (Cortex).**

**Effect of Extracts on Malondialdehyde (MDA) Level**

**Table No. 10: MDA Level.**

| Treatments | MDA |
|---|---|
| Group-1 | 0.346 |
| Group-2 | 0.382 |
| Group-3 | 0.351 |
| Group-4 | 0.347 |
| Group-5 | 0.358 |

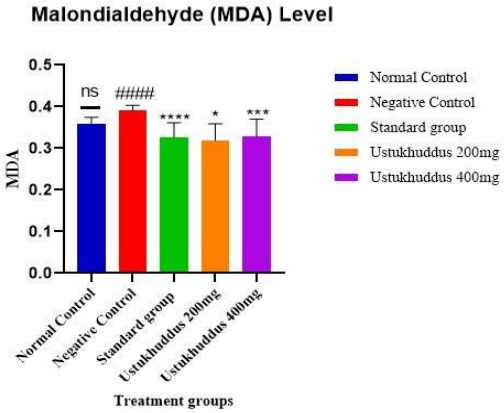


**Figure no. 21 MDA levels.**

**Effect of extricates on *in-vivo* antioxidants**

**Table No. 11: In-vivo antioxidants.**

| Group | GSH (Glutathione µg/mg) | SOD(unit/mn/ mgprotein) | NO(µ/mgprotein) |
|---|---|---|---|
| Group-1 | 7.95 | 0.37 | 16.17 |
| Group-2 | 8.49 | 0.49 | 14.54 |
| Group-3 | 8.36 | 0.88 | 12.49 |
| Group-4 | 10.94 | 1.33 | 13.64 |
| Group-5 | 11.68 | 1.39 | 12.18 |

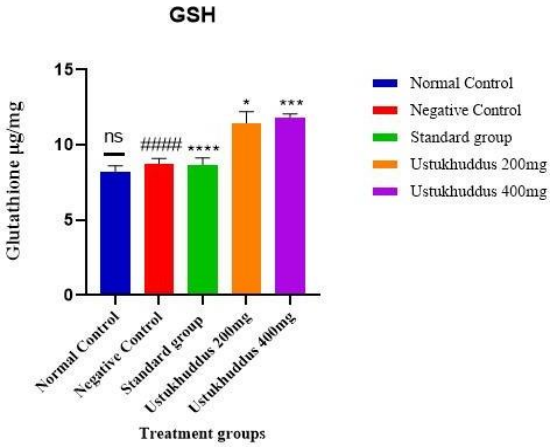


**Figure no. 22: GSH levels.**

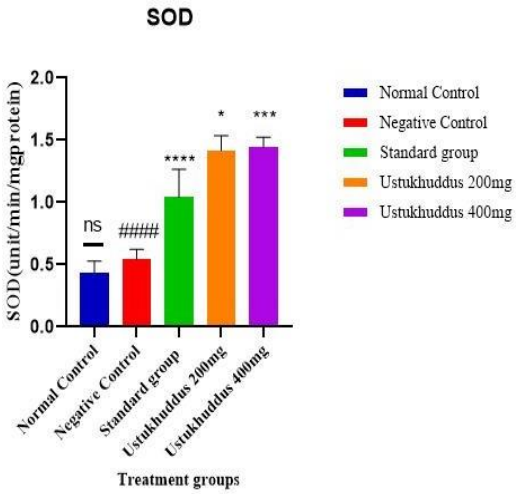


**Figure no. 23: SOD levels.**

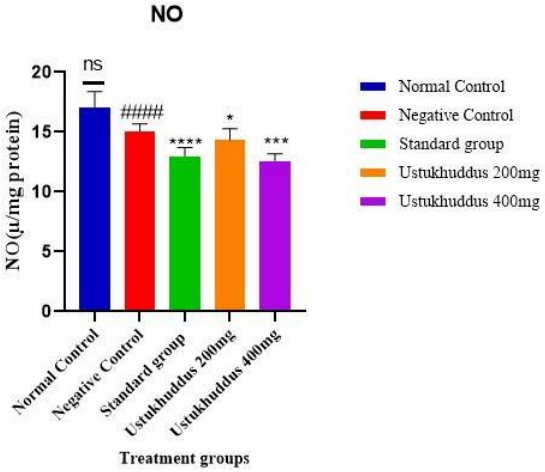


**Figure no. 24: NO levels.**

**Histological studies**

**Group 1:** The hippocampus has been shown to have rotting foci or apoptotic neurons. Experts in the dentate gyrus show extensive degeneration and apoptotic neurons. Meninges in the brain began to deteriorate and eventually die. Gliosis of the essential prefrontal projection.

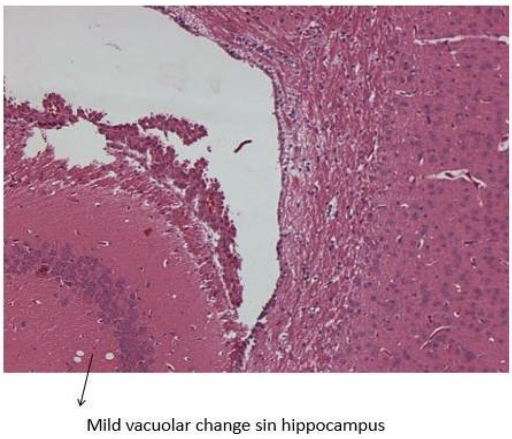


**Figure no. 25 Group 1**

**Group 2:** Necrosis foci or neuronal apoptosis have been seen in the hippocampus. There are several different types of apoptotic neurons and degenerative changes in Dentate gyrus gurus. Both thinning and bleeding were seen in brain meningeas.

Prefrontal cortex focal gliosis..

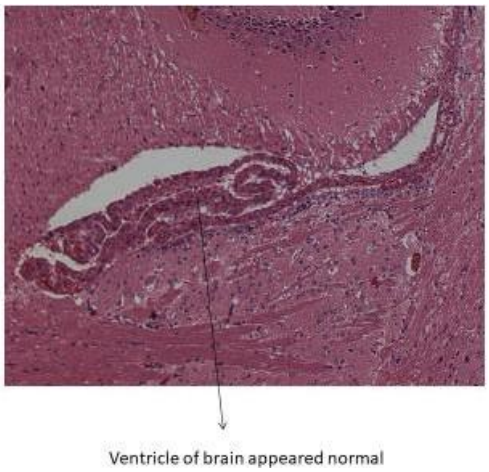


**Figure no. 26 Group 2**

**Group 3:**
Alarming claims of widespread suffering and death were presented. Cortical focusal gliosis increased in number. When the meninges of the brain come into contact, it is well-known that a tiny amount of death occurs.

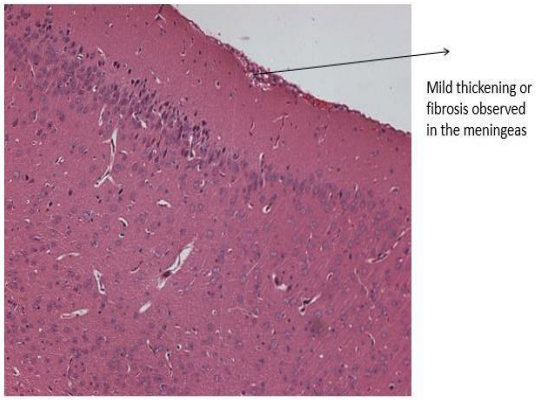


**Figure no. 27 Group 3**

**Group 4:** It is widely recognised that several foci of necrotic or apoptotic neurons, as well as glial cell invasion and provocative cells, are seen. The Dentate Gyrus underwent subtle degenerative alterations that

were tracked by researchers. Make sure there is no accumulation of fluid in the ventricles.

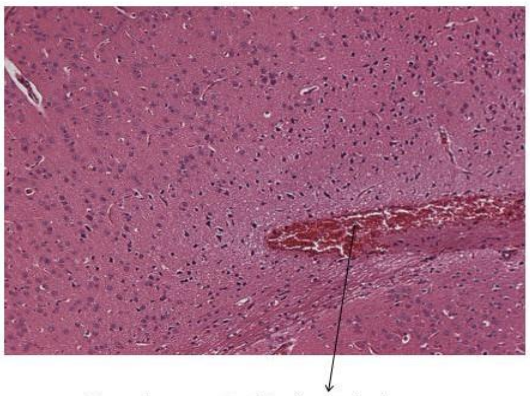


**Figure no. 28 Group 4**

**Group 5:** There's a lot of death going on in the brain's ventricles. An area of the frontal cortex has haemorrhages. Points of intense cell accumulation due to inflammation. The dentate gyrus has been linked to both neuronal apoptosis andvacuolar degeneration.

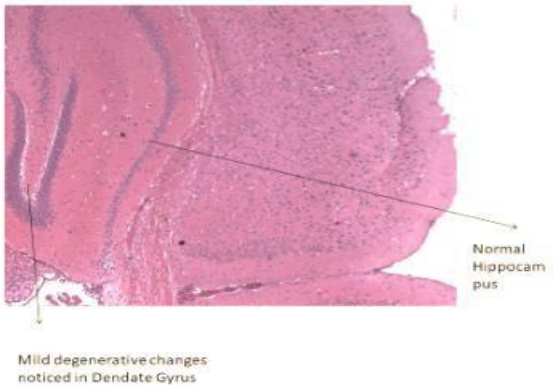


**Figure no. 29 Group 5**

## 5. DISCUSSION

Alzheimer's infection could be a neurological sickness that dynamically declines over time. Cognitive decay, odd conduct, changes in identity, and in the long run passing are the conclusion results of this illness. Memory isfundamental for life since it permits life forms to keep track of the things they've learned and alter their behaviour appropriately. In the event that acetylcholine is show within the neocortex, it may offer assistance with memory and learning issues. The number of people with dementia is anticipatedto generally fourfold each 20 a long time, from its 2015 tall of 46.8 million individuals, agreeing to the World Alzheimer Report 2015.

Alzheimer's malady is the foremost common form of dementia within the elderly. ALZD is a natural brain clutter that causes persistent, dynamic inability and is characterised by disturbances in a assortment of cognitive forms, counting memory, judgment, introduction, comprehension, learning capacity, and dialect. There are three particular neuropathological highlights of Alzheimer's malady. Amyloid beta protein plaques. There has been cell passing and basic changes within the brain. The advancement of viable pharmaceutical treatment for Alzheimer's is still in its earliest stages, and the sickness remains serious.

Cancer prevention agents incorporate vitamin E (tocopherol), selegiline (a monoamine oxidase inhibitor), phenolics (curcumin), tannins (gallic corrosive), and polyphenolics (ferulic corrosive) all work together to dodge cognitive disarranges by diminishing free radical era. There are presently a number of Alzheimer's infection antibodies beneath improvement, with the trust that they would lighten a few of the related cognitive side effects. Pterocarpan gangetin has anti-fertility impacts by repressing uterine soluble phosphatase. Antiulcer, antioxidant, cardiotonic, antiinflammatory, antinociceptive, and useful in neurological issues are as it were few of its implied properties. Brahmi, Ashwagandha, Curcumin, Arcoruscalamus, Shankhpushpi, Zingiber, etc. are as it were few of the Ayurvedic solutions that have been appeared to be compelling in treating Alzheimer's.

Alzheimer's illness treatment models that center on distinguishing and tending to physical hazard components early on are more likely to be successful within the long run. The nature of Alzheimer's illness makes it exceptionally unlikely that a single treatment or mediation will be able to turn around the condition. Most current strategies are equipped on facilitating the burden of cognitive decrease by facilitating behavioral indications and postponing the onset of cognitive decay. Alzheimer's illness is characterised by a wide extend of behavioral side effects, counting a sleeping disorder, confusion, disturbance, uneasiness, and savagery. The essential objective of this inquire about was to evaluate the anti-dementia impacts of ustukhuddus.

Pale skinned Swiss male. In this try, mice weighing 20-25 g were utilized. Infusing 2 milligrammes of scopolamine into the intramuscular space in 0.5% weight-per-volume (w/v) CMC causes neurocognitive harm in mice. Mice are tried both some time recently and after treatment utilizing a hoisted furthermore labyrinth, a morris water labyrinth, and an actophotometer to decide their level of behavioral action. There were an add up to of 30 mice, part over 5 bunches of 6 rats each.

## 6. CONCLUSION

The standard bunch was decided to be more successful and secure, be that as it may the discoveries of the raised furthermore labyrinth illustrate that group 5 with the more prominent measurements has more strength as since of more grounded restorative impact. Locomotor movement and the morris water labyrinth tests created comparative outcomes. In common, the unani pharmaceutical. An execution of Ustukhuddus, it appears, may complement routine pharmaceuticals by acting as an adjuvant.

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