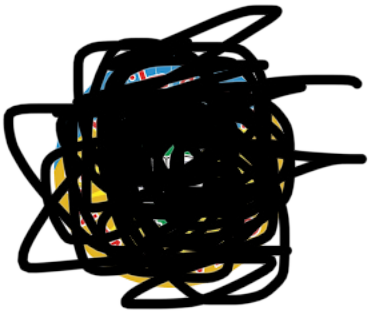

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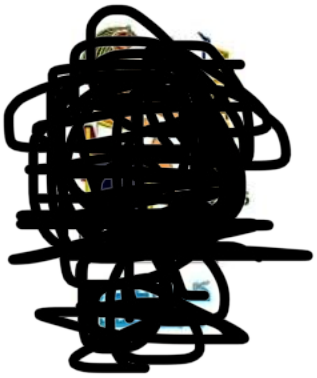

Using Drosophila as a model for neurodegenerative diseases

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Acknowledgment

First and foremost, I want to give the most praise and thankful to Allah for all the great blessings he has given me, and I would not have reached where I am today except with Allah's grace. the second is thankful to my mother, father, and brother for encouraging me and being proud of all the simple achievements I achieved, and I am very grateful to my supervisor:

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Professor of Entomology, Zoology Department
Faculty of Science, Tanta University.
who helped me to develop this work until it reached what it is now.

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1. Introduction

The term neurodegenerative divides into two syllables (neuro) which refers to nerve cells and neurons and (degeneration)which refers to tissues and organs losing structure and function this term refers to any pathological condition affecting the neurons although there is no clear definition for this term.

There are a couple hundred neurodegenerative diseases known to us now but classifying them is very hard because different diseases affect different parts of the brain which causes different symptoms, so the only categorization of these diseases is based on dominant clinical features or the damaged lesion of the brain or both [1].

The most recognizable diseases are Alzheimer's, tau's disease, ALS, Parkinson's disease, and Huntington’s Disease.

1. Alzheimer's disease: affects older people more and causes dementia

2. Parkinson's disease affects the motor motion of the body

3. Tau disease: is very similar to Alzheimer's and associated with tau protein.

Hallmarks for these diseases are few and mainly connected to some proteins in the nerve cells' head or axon, the elevation of these proteins indicates early signs of having a neurodegenerative disease like

1. Aβ which is derived from the transmembrane amyloid precursor protein and found in synapsis

2. Tau which is a microtubule-associated protein involved in the assembly

3. α-synuclein that is expressed in pre-synaptic nerve terminals and stabilization of microtubules, localized mainly in axons in the central nervous system

4.TAR DNA-binding protein which is involved in RNA regulation [2]

2. Chapter one: Alzheimer

Alzheimer's is a chronic aggressive neurological disease, that usually affects people older than 65 years old with an average duration of 5-10 years and can extend up to 20 years, affecting wide areas of the brain, especially the cerebral cortex then slowly progresses to the frontal lobes this disease is maybe caused by aging and environmental circumstances. Still, there is a small portion of people who have an autosomal dominant inherited Alzheimer which kicks in early on (age 45 for men). in this group, a mutation occurs in some genes encoding (APP, and PS2) which causes the overproduction in A*B* [3]

There are two major neurological changes in the brain.

1)Positive lesion which is caused by accumulation of neurofibrillary tangles and amyloid plaques

2)Negative lesion due to major loss in neurons neuropils and synapsis [4]

2.1. There are two main hypotheses for Alzheimer's.

a) amyloid cascade hypothesis in which the cortical plaques of the brain became full of abnormal amyloid-beta peptide deposition, Aβ is generated by proteolytic processing of the β-amyloid precursor protein (APP) in addition to Tau protein phosphorylation Aβ deposits lead to plaques creation, the amyloid fibrils accumulated in the cell’s outer space and grouped into a globe shape. Amyloid-β can also be deposited in media and referred to as Cerebral Amyloid Angiopathy.

b) The mitochondrial cascade hypothesis which tries to explain the clinical, biochemical, and histological parts of Alzheimer's by the dysfunctional mitochondria and its effect on aging

mitochondrion is a subcellular organelle that is responsible for ATP production and since neurons require high energy, low ATP levels are a sign of cell death, which can occur due to mutation or dysfunction of proteins that cause mitochondrial fusion

Scientists think that the main reason for Alzheimer's is more likely to be the accumulation of amyloid-beta peptide protein [5],[6]

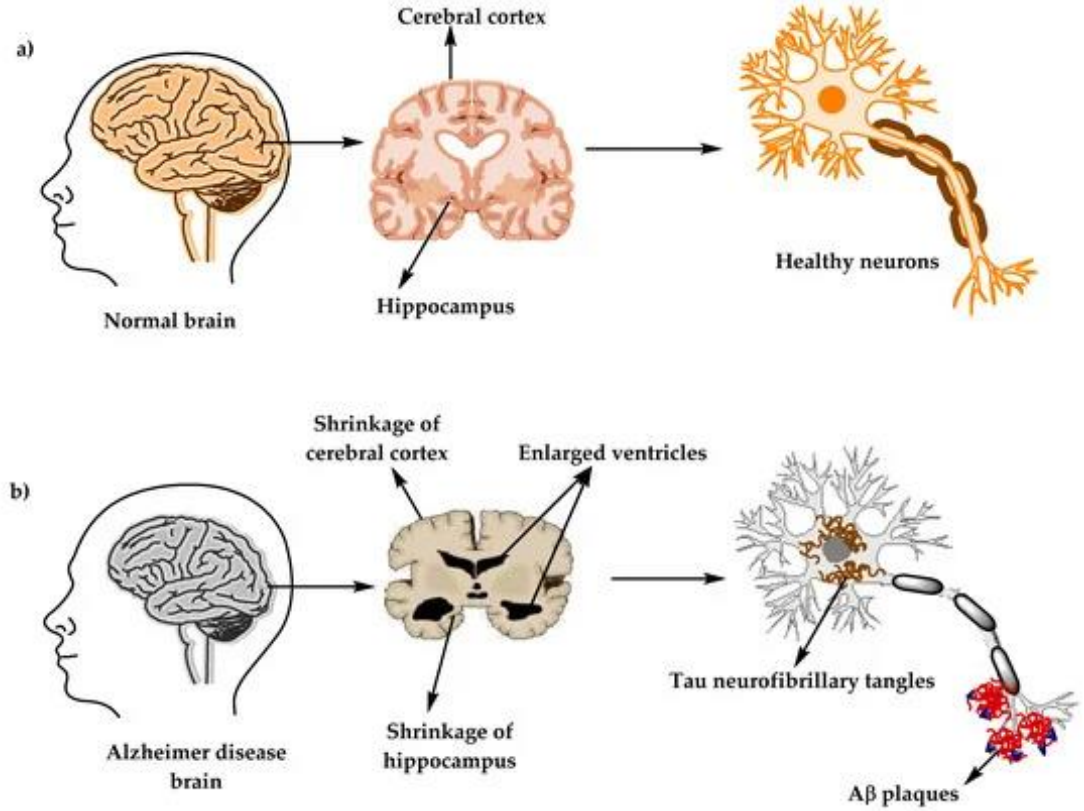

Figure 1. The physiological structure of the brain and neurons in (a) healthy brain and(b) brain after Alzheimer's disease

2.2. **Hallmarks of Alzheimer**

Usually appears one year before the start of the symptoms

1. App

presence of senile plaques and neurofibrillary tangles. These senile plaques are composed of β amyloid (Aβ), a proteolytic fragment of the Amyloid Precursor Protein (APP)

2. Tau and p-tau

neurofibrillary tangles are composed primarily of tau, a microtubule-associated protein which is one of the gnomic features of AD

3. Isoprostanes

Isoprostanes are the end-products of lipid peroxidation, particularly F2-isoprostanes, which increase the frontal and temporal cortex of AD patients

4. Inflammatory markers

Like protease inhibitors which allow the accumulation of protein Protease is a protein that breaks down proteins) [7]

2.3. Symptoms of Alzheimer's vary from psychotic symptoms like delusion and hallucination which are correlated with neurofibirally tangles, apathy which is a lack of motivation, depression, disturbance in sleep time [8] addition to dementia, memory loss, loss of language and time [9]

2.4 Risks for Alzheimer

a recent study determined that good lifestyle habits and management of comorbidities may lead to a lower risk of dementia so staying away from risk factors decreases the probability of having AD

1. vascular diseases

The cerebrovascular and neurovascular networks control some brain mechanisms, so any dysfunction leaves patients at high risk for AD

2. TYPE 2 diabetes

Occur due to insulin resistance that B cells try to overcome by secreting excessive amounts of insulin but at the same time burden the B cells causing T2D, which is considered a high risk for AD

3. Traumatic brain injury

Cause brain damage, periods of unconsciousness, and amnesia

4. epilepsy

A neurological disorder that causes continuous and sudden seizures leaves patients at high risk for AD because the causes brain damage, cognitive declines, and neuropathological changes

5. depression

Mental health diseases that may alter brain chemistry, are considered a critical risk for AD

In addition to obesity, age, environmental factors, and genetic factors [10]

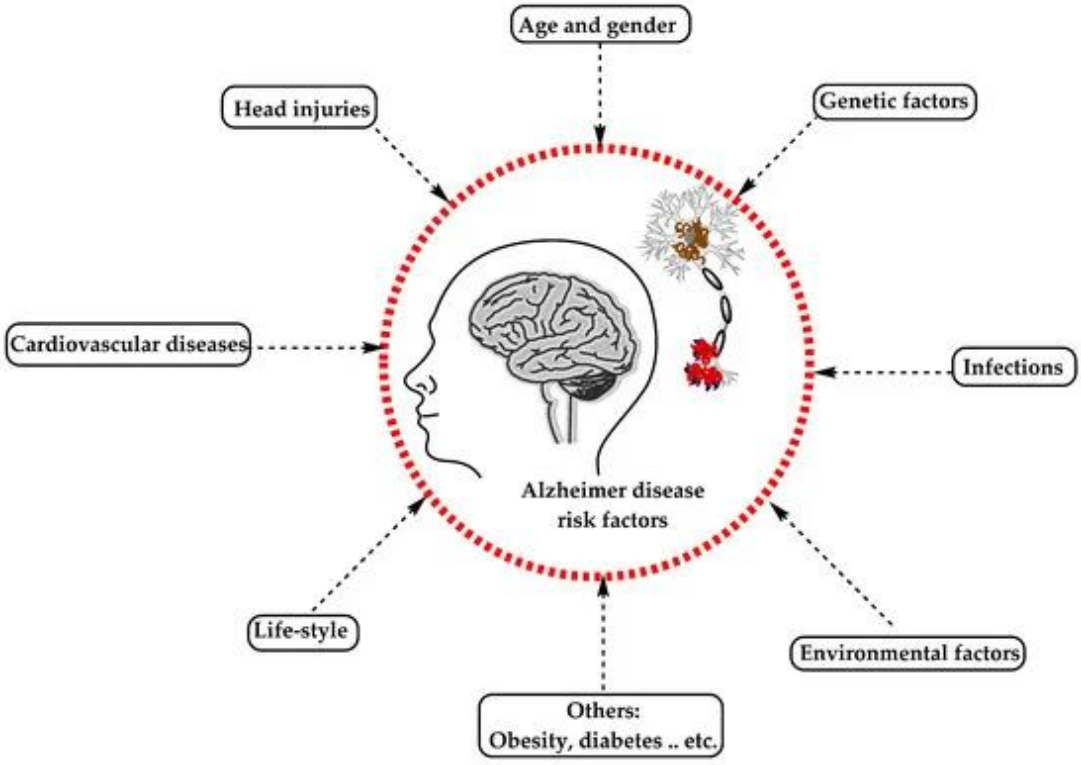

Figure 2. The risk factors for Alzheimer's disease [9].

Drosophila (fruit fly) has hundreds of years of genetic research on it and due to its well-known anatomy and complex yet known nervous system and brain and having 13,600 coding genes on only four chromosomes it's considered a perfect model for studying neurodegenerative diseases like Alzheimer [11]

Drosophila has a very human-like central nervous system when we over-expressed human APP and BACE genes in the Drosophila central nervous system. Biochemical, neuroanatomical, and behavioral analyses indicate that these flies exhibit aspects of clinical AD neuropathology and symptomology. These include the generation of $A\beta_{40}$ and $A\beta_{42}$, the presence of amyloid aggregates, dramatic neuroanatomical changes, defects in motor reflex behavior, and memory defects. [12]

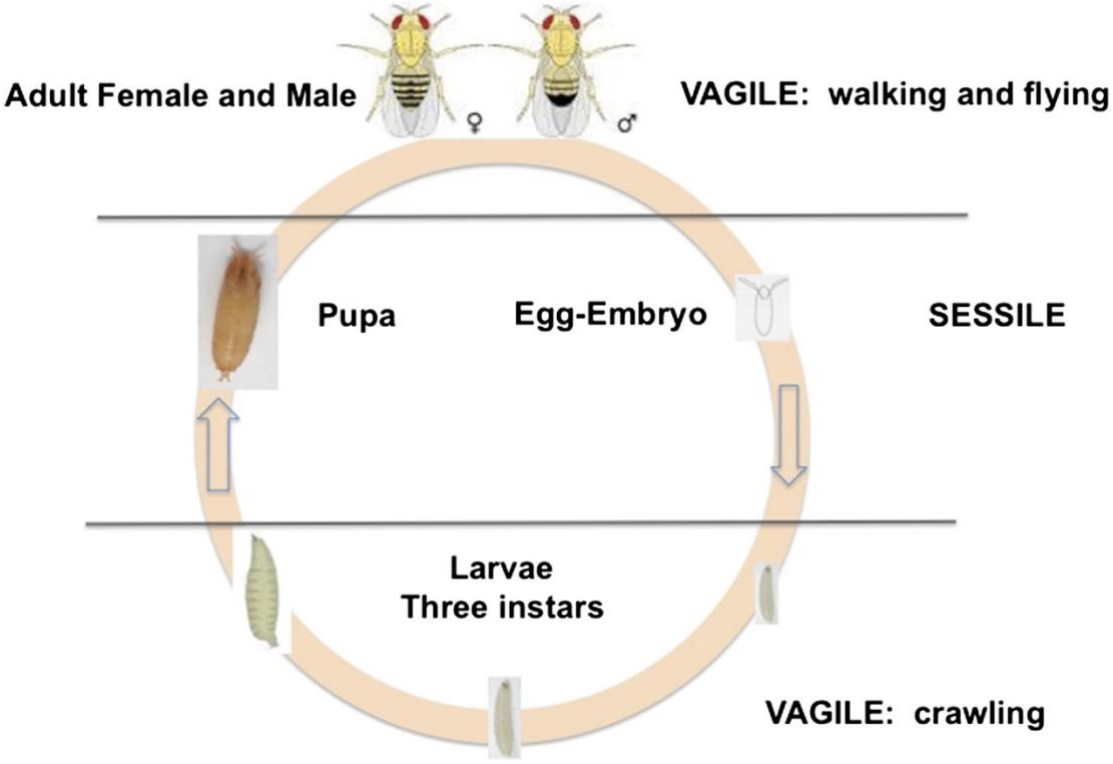

Figure 3: Drosophila life cycle [13]

2.5. The treatments

1- It was found that The therapeutic drugs that reduce the production of amyloid B peptide have side effects so scientists have tried another way that clears the peptide by preventing it from accumulating in the brain one of these drugs is doxycycline which is an antibiotic and when it was used on drosophila flies with (AB42) it did not only improve the lifespan of the flies but also slow the progression of locomotor deficits, doxycycline prevents AB fibrillization and produces the generation of small non-

amyloid structures that were nontoxic as determined by the lack of (caspase 3) activation in a neuroblastoma cell line which confirm that doxycycline also prevent toxicity of amyloid B by measuring the rough eye phenotype transgenic fly with E22G which is a variant for *AB* 42 [14]

2-Researches has been done on traditional herbal medicine, which has been used for the management of neurodegenerative disorders the treatment of neurosis, insomnia, and dementia called Yi-Gan-San (YGS) and by examining the antioxidant capacity and cytotoxicity of YGS treatment by using 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) in alleviating Aβ neurotoxicity Drosophila melanogaster in Vivo, flies under we discovered that YGS treatments showed a greater survival rate, better climbing speed, and lower Aβ42 aggregation in Drosophila brain tissues [15]

3- luteolin therapeutic potential for Alzheimer's disease

An experiment was conducted on luteolin which is (3′,4′,5,7-tetrahydroxy flavone) is a flavone naturally occurring as a glycosylated form, and is present in different fruits and vegetables using drosophila wild type human Aβ42 with ,drosophila was exposed to luteolin mixed with their diet at concentrations 5,10,15,20 μm measuring the climbing abilities, activity patterns ,life span and proteins activities in the brain of treated and untreated flies and after doing Histopathology of *Drosophila* brain sections was done by performing thioflavin-S, bielschowsky's silver and toluidine blue staining ,it was found that A dose-dependent increase in the life span, delay in the loss of climbing ability as well as activity was observed in AD flies exposed to luteolin compared to unexposed AD flies in addition to a significant dose-dependent reduction in the expression of Aβ42 peptides in AD fly groups exposed to 10, 15 and 20μm of luteolin improving cognitive dysfunction, increasing lifespan, reducing oxidative stress which confirm that luteolin is a good potential treatment for AD [16]

4- using new syntheses acetylcholinesterase inhibitor named JXP-1 as a potential treatment for AD

Acetylcholinesterase is an enzyme found in postsynaptic junctions in muscles and nerves, terminates neuronal transmission and breaks down neurotransmitters (acetylcholine).

An experiment was conducted using drosophila fly in vivo as a model, the drug was added to food dissolved in water as 1/5 of food volume, and newly emerged flies aged 0–24 h were collected and placed into fresh food vials containing 5 ml of fly food. Each vial contained a total of 20 flies. At least 100 flies per genotype were analyzed it was found that XJP-1 treatment improves the life span of flies, reduces the number of amyloid plaques in the brain, and reduces amyloid aggregation by ACHE inhibition, so XJP-1 is considered an effective and potent AD drug candidate, which efficiently rescues AD symptoms in flies [17]

5- testing kaempferol as a potential treatment for AD using drosophila as a model, kaempferol is a natural flavanol found in a variety of plants like beans

Drosophila flies with AD were allowed to feed on the diet with kaempferol at concentrations of 10,20,30,40 μm for 30 days then the climbing abilities, phototaxis suppression, and oxidation stress were studied alongside the acetylcholinesterase activity and it was found that exposure to kaempferol delay loss of climbing abilities, memory, reduce the oxidation stress and acetylcholinesterase activity, so kaempferol is a possible therapeutic agent for AD [18]

6- testing apolipoprotein E memetic neurodegeneration as a potential treatment for AD using drosophila as a model

ApoE-mimetic peptides are involved in lipid transport and metabolism, and likely play a critical role in some transport to and from neurons for the maintenance of cell membranes and synapses and repair injuries, are well known to display anti-inflammatory and neuroprotective effects in the central nervous system, we tested whether the apoE-mimetic peptides could modify neurodegeneration, and cognitive functions in transgenic *Drosophila* models of AD by in vivo delivery of peptide into brain cells by penetration of (a 16-amino acid peptide derived from

the *Drosophila* Antennapedia homeodomain protein, Antp) to carry (apoE peptide-COG133) into brain cells(able to cross the blood-brain barrier) and we discovered that The development of neurodegeneration and cognitive deficits was corrected by injections of COG133 (novel mimetics of so it was considered as a potentially promising treatment for AD[19]

7- apigenin effects on drosophila model of Alzheimer's disease

Apigenin is a trihydroxy flavone that is flavone substituted by hydroxy groups at positions 4′, 5, and 7 and widely found in vegetables, fruits, herbal plants, parsley, celery, and chamomile it possesses anti-oxidant activity, neuroprotective, anti-inflammatory and anti-Aβ aggregation properties in addition to its ability to cross the blood-brain barrier, its effect was studied on fly expressing wild-type human *AB42* the results showed a delay in the loss of climbing abilities and reduction in oxidation stress also improving in mitochondrial dysfunction in comparison with the control flies, so apigenin Is considered a good potential treatment or complementary treatment for AD [20]

8- effects of SU-HE-XIANG WAN on drosophila model for Alzheimer's disease

suHeXiang Wan (SHXW) is a Chinese traditional medicinal prescription that consists of 15 crude herbs,(SHXW) has been prescribed to treat central nervous, depression, seizures, infantile convulsion, and stroke so an experiment was conducted to determine if we can use it as a treatment for Alzheimer by using drosophila flies express human Aβ42 in their neurons alongside it's modified product that called KSOP1009, flies were kept on the media containing 5 μg/ml of KSOP1009 and as a result, Aβ42-induced eye degeneration, apoptosis, and the locomotive dysfunctions were suppressed so both (SHXW) and its new product is a potential treatment for AD [21]

9-testing withana somnifera as a potential treatment for Alzheimer's disease

Withania somnifera (Ashwagandha) also known as Indian ginseng, is a sub-tropical herb that originated in India and has been recognized to boost

neuronal function and reduce stress and anxiety, we use Drosophila melanogaster as a model to study the effect of Ashwagandha against lifespan of Alzheimer's disease flies, to create AD flies male come across with virgin female carrying AB42, kept in corn-based meal supplemented with 20 mg/mL Ashwagandha (root extract) (Himalaya, India). Seven days post-mating, the parents were removed, and the pupae were left until F1 emerged. The F1 will express the Aβ42 protein in their compound eyes leading to rough eye phenotype (REP) which is the treated flies and repeating the process without feeding it ashwagandha to create the untreated flies and having a control flies, The degree of REP was evaluated for all F1 to determine the effect of Ashwagandha recording the number of dead F1 daily, that study reveals that Ashwagandha treated AD Drosophila showed significant improvement in their REP compared to the untreated flies. Moreover, Ashwagandha also promotes longevity in AD flies, so Ashwagandha is considered a potential treatment for AD [22]

10- Effects of *Gardenia jasminoides* extracts on drosophila flies with AD

The evergreen flowering plant commonly known as gardenia and capa jasmine, Herbal extracts have been extensively used worldwide for their application on memory improvement, so it was tested against the memory loss induced by human Abeta protein over-expression in the fruit fly, the extracts that are rich with gardenia yellow, geniposide, and garden-side components which show therapeutic effects on memory loss especially when adding ardenoside into a formula of *Ganoderma lucidum*, *Panax notoginseng* and *Panax ginseng*, the results showed that the two components did not alter the accumulation of Abeta proteins but suppressed the expression of related genes in the brain in addition to reducing memory loss so it's considered as a potential treatment for AD [23]

11-the effects effect of nordihydroguaiaretic acid (NDGA) on the Drosophila as a model of Alzheimer's disease

Nordihydroguaiaretic acid (NDGA), is a phenolic lignan derived from the leaves and twigs of the shrub Creosote bush, *Larrea* tridentata which is

known as chaparral and greasewood in the USA, and gobernadora (governess), and hediondilla, an experiment was conducted on a drosophila fly that expresses wild-type of human AB-42 AD flies were exposed to 20,40,60,80 µm for NDGA for 30 days, NDGA results increasing life span, delay the loss of climbing ability, prevent the memory loss and reduced oxidative stress in the brain of AD flies but did not influence the expression nor the aggregation of AB-42 so it's considered as a potential treatment for AD [24]

3. Chapter two: Parkinson's disease

Parkinson's disease (PD) is a clinical syndrome of Parkinsonism that starts suddenly and usually affects one side of the body before moving and spreading all over the body causing a combination of motor problems (bradykinesia), rigidity, and loss of reflexes. [25].

PD is the second most common neurodegenerative disease after Alzheimer’s disease (AD), with a prevalence of approximately 0.5–1% among those 65–69 years of age, rising to 1–3% among persons 80 years of age and older. With an aging population, both the prevalence and incidence of PD are expected to increase by more than 30% by 2030, which will result in both direct and indirect costs to both society and the economy.[26]

Parkinson's disease is caused by a loss of nerve cells in the part of the brain called the substantia nigra.

Nerve cells in this part of the brain are responsible for producing a chemical called dopamine. Dopamine acts as a messenger between the parts of the brain and nervous system that help control and coordinate body movements. If these nerve cells die or become damaged, the amount of dopamine in the brain is reduced. This means the part of the brain controlling movement cannot work as well as normal, causing movements to become slow and abnormal. The loss of nerve cells is a slow process. The symptoms of Parkinson's disease usually only start to develop when around 50% of the nerve cell activity in the substantia nigra has been lost.[27]

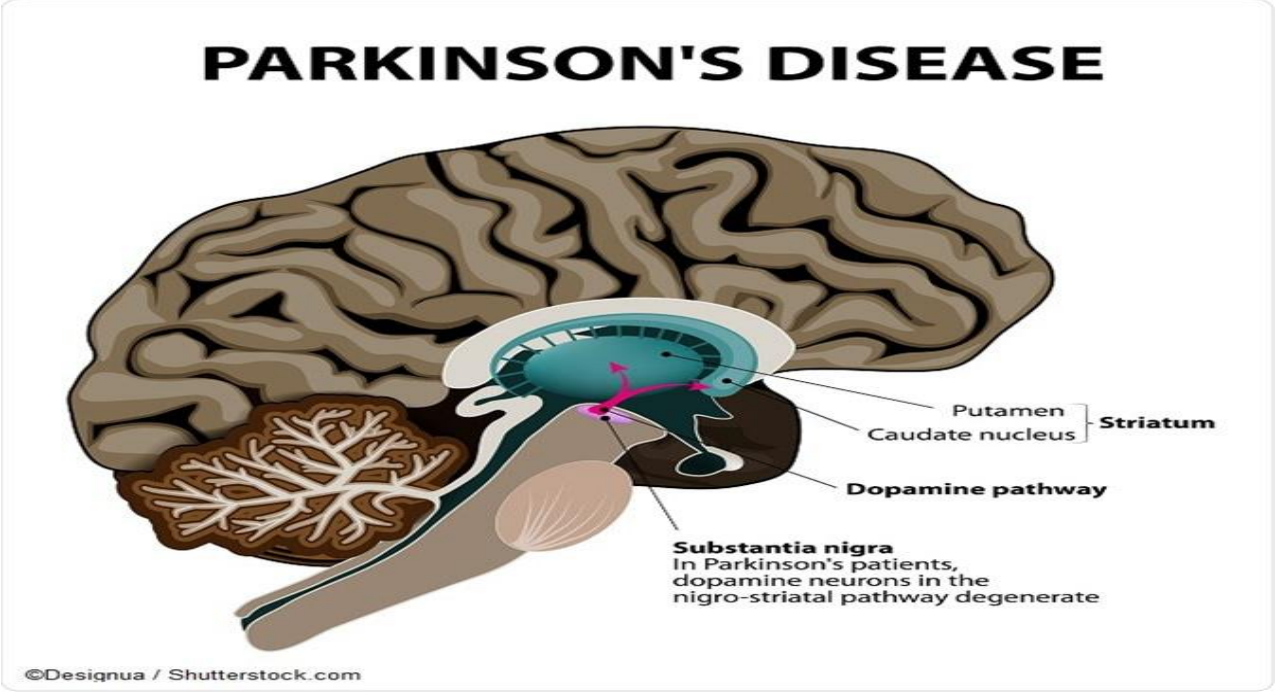

Figure 3 : dopamine pathway in Parkinson's patient brain

In Parkinson's disease, the nerve cells called neurons in the brain gradually break down or die. Many of the symptoms of Parkinson's are due to a loss of neurons that produce dopamine. When dopamine levels decrease, it causes irregular brain activity, leading to problems with movement and other symptoms of Parkinson's disease.

3.1. The cause of Parkinson's disease is unknown, but several factors appear to play a role, including

- Genes
- Environmental risks
- The presence of Lewy bodies: Clumps of specific substances within brain cells are microscopic markers of Parkinson's disease. These are called Lewy bodies, and researchers believe these Lewy bodies hold an important clue to the cause of Parkinson's disease.
- Alpha-syncluic proteins found in Lewy bodies accumulate in a clumped form that cells cannot break down [28]

3.2 Hallmarks of Parkinson's disease

- Age (dominant factor): ~ 1% of people older than 60 are affected. At the age of 80 years, the prevalence rises to 3%.
- Genetic risk factors: we know of 28 distinct chromosomal regions that are related to PD, for only six of these regions have the underlying genes that cause common monogenic forms of PD identified, namely *SNCA(α-synuclein)* and (*LRRK2) for* autosomal dominant, and (*PINK1)*, *PARK7(DJ-1)*, *(ATP13A2)*, and (*PARK2)*

- *Environmental risk factors: exposure to environmental toxins increases the risks for PD, especially* side product produced in the synthesis of the narcotic drug meperidine, namely 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which causes irreversible Parkinsonism in addition to various insecticides like paraquat which was helpful in the determination of the pathogenesis of PD, and it's linked to mitochondria dysfunction
- α-Synuclein aggregation: α-Synuclein is the major protein component of Lewy bodies, Aggregated α-synuclein (in the form of Lewy bodies or Lewy neurites) interferes with the mechanisms of microtubule-based sub-cellular transport, thus causing synaptic dysfunction and other disruptions to neuronal homeostasis.
- Lysosomal and proteasomal dysfunction: which is the Dysfunction of molecular and organelle degradation pathways, studies investigating the lysosomal enzyme β-glucocerebrosidase to facilitate the accumulation of dysfunction mitochondria and α-synuclein.
- Iron and other metals: PD is significantly linked to a disturbance of iron metabolism.
- Mitochondrial dysfunction
- Synaptic dysfunction: synaptic function requires tight control of intracellular processes such as neurotransmitter packaging, energetic homeostasis, and Ca^{2+} buffering [29]

3.3 The Common symptoms of Parkinson's disease include.

- Tremor or the involuntary and rhythmic movements of the hands, arms, legs, and jaw
- Muscle rigidity or stiffness of the limbs – most common in the arms, shoulders, or neck
- Gradual loss of spontaneous movement often leads to decreased mental skill or reaction time, voice changes, decreased facial expression, etc.
- Gradual loss of automatic movement, which may lead to decreased blinking, decreased frequency of swallowing and drooling
- A stooped, flexed posture with bending at the elbows, knees, and hips
- Unsteady walk or balance
- Depression or dementia [30]

3.4 In addition to complications like

- Depression and emotional changes
- thinkings difficulties
- Swallowing problems
- Chewing problems
- Sleeping disorders
- Bladder problems
- Smell dysfunction.
- Pain
- Fatigue

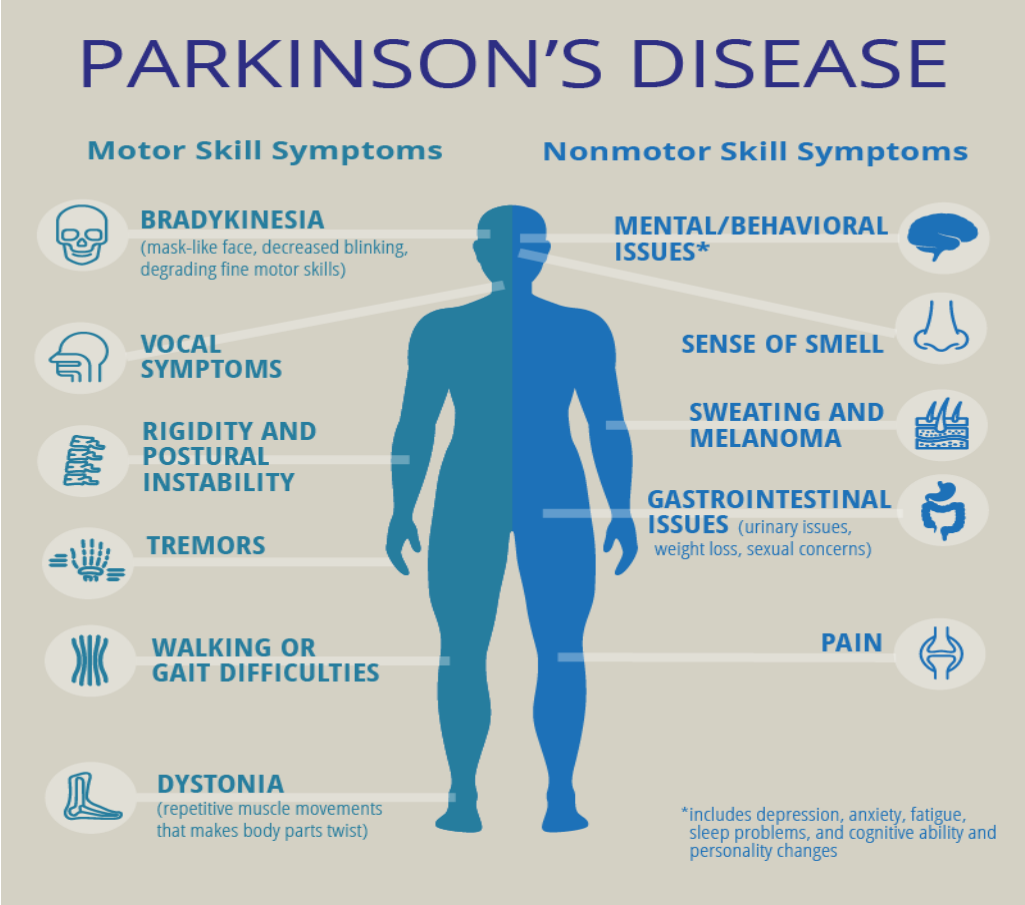

Figure 4: motor and non-motor symptoms of Parkinson's [31]

3.5 Stages of Parkinson's disease

1. Non-motor aspect of the experience of daily tasks

symptoms like dementia, depression, anxiety, and other mental ability- and mental health-related issues. Appears

2. The motor aspect of experiencing daily tasks

affects movement-related tasks and abilities. It includes your ability to speak, eat, chew and swallow, dress and bathe.

3. motor examination
   usually when the disease is diagnosed due to difficulties in speaking, facial expressions, stiffness and rigidity, walking gait and speed, balance, movement speed, tremors

4. motor complicates

in which symptoms appear all day long and greatly affect daily life tasks [32]

3.6 There are two types of Parkinson's, causatively speaking

Primary Parkinsonism

1. Familial Parkinson's: inherited, caused by genetic mutations

2. Idiopathic Parkinson's: there is no clear reason why it happens

Secondary Parkinsonism

This condition is happening because of another medical condition

1. Vascular Parkinsonism: occurs when blood flow to certain parts of the brain is weak
2. Post-traumatic Parkinsonism occurs because of repeated brain damage
3. Drug-induced Parkinsonism occurs when a drug interferes with how the body uses or induces dopamine
4. Toxin-induced Parkinsonism: toxic substances can destroy very specific types of brain cells
   which contain dopamine-sensitive neurons
5. Normal pressure hydrocephalus occurs when you have too much cerebrospinal fluid (CSF) inside your skull, which puts pressure on parts of your brain areas responsible for walking and controlling your bladder.
6. Post-encephalitis Parkinsonism occurs because of an infection that causes encephalitis.[33]

There are two ways to turn drosophila flies into the model for PD either by toxin exposure or by causing mutation in their genes that resemble human genes that are associated with PD

Drosophila as a model for Parkinson's disease

several studies have been performed to model PD-associated neuron loss by neurotoxin intoxication in flies, the most popular parkinsonian neurotoxins being 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and paraquat

chronic exposure to the pesticide rotenone, a mitochondrial complex I inhibitor, recapitulated key aspects of sporadic PD in Drosophila since it resulted in neurodegenerative and behavioral defects

flies that were treated with rotenone showed dose-dependent motor deficits as well as selective loss of DA neurons in all the brain clusters.

paraquat exposure caused reduced lifespan in flies as well as movement disorders such as resting tremors, rotational behaviors, and postural instability, which mirror PD symptoms

3.7 The reasons for using drosophila as a model for PD

- α-Synuclein in drosophila is a small (140 amino acids) but abundant neuronal protein that is particularly enriched in presynaptic terminals but with age, it results in neuron loss and progressive loss of climbing abilities
- The parkin gene as its mutation was found in autosomal Parkinson's disease patients' families and was found in drosophila to understand its role null mutants were generated and showed that loss of parkin causes mitochondrial defects, degeneration of indirect flight muscles, hypersensitivity to oxidative and environmental stress, male sterility, reduced lifespan, but the accumulation of it caused neurodegeneration in flies
- PINK1 also it's a mutation associated with autosomal Parkinson's and targets the mitochondria, the pink1 gene in the fly contains a protein that resembles the human pink1 protein, and pink1 mutant flies share

phenotypic similarities with the parkin mutant They also exhibited male sterility, muscle degeneration, hypersensitivity to oxidative stress, mitochondrial defects, reduced lifespan, and DA neuronal degeneration accompanied by locomotor defects.

- DJ-1 the mutation of that gene is associated with rare familial PD and has been considered as a biomarker for neurodegenerative disease as well as cancer because this mutation causes oxidation damage, this gene was also found in flies and its mutation causes oxidative damage which increases as the fly age and may lead to neuron loss and risks of having PD
- LRRK2 mutation is the most common genetic cause of PD and is associated with a dominant form of the disease that encodes many complex proteins, how LRRK2 mutation causes PD is still unknown, but it's known that mutation of LRRK2 increases kinase activities, the expression of human LRRK2 in flies led to inconsistent results however led to neuron loss [34]

3.8The treatments

Studies were made about a treatment (however most of these treatments aim at symptom management and slow down the progress of the disease) for Parkinson's disease by using drosophila as an experimental model like

1. Polyscias fruticose is a plant species that includes the araliaceous family that is used as a medicinal plant and has great therapeutic characteristics specially panax species enhancing the body's immunity system, improving male fertility, preventing fatigue, nourishment, increasing appetite, sleeping well, increasing work capacity, gaining weight, and antidote *Polyscias fruticose* leaves were also used to assist in the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases because of improving symptoms of tremor, loss of balance, insomnia, memory impairment, nervous tension, and nervous breakdown in addition to being antistress, improve memory, antioxidant, hypoglycemic, hepatoprotective, hypolipidemic, antifungal, and antibacterial effects

P. fruticose has been reported to contain saponins, alkaloids, glycosides, polyphenols, flavonoids, tannins, vitamins (C, B_1, B_2, and B_6), and amino acids in addition to secondary metabolizing compounds with antioxidant effects

Assessing the human brain is difficult so scientists experiment on drosophila especially One among the *Drosophila* model for PD, a PD fly model by knocking down dUCH (*Drosophila* ubiquitin carboxyl-terminal hydrolase), a homologous gene of UCH-L1 in humans not only on larva but on adult flies as well, this model could display pathophysiological features and mimic PD symptoms including mobility defects such as difficulty in walking, slow movement, tremor, and progressive DA neuron degeneration that experiments led to seconding the hypothesis that says that p. fruticose leaves extract used as a treatment results in improvement on PD and overall is a strong potential as a PD treatment [35]

2. testing the five ayurvedic herbs as a treatment for PD on drosophila melanogaster

These herbs include e Zandopa (containing Mucuna pruriens), Withania somnifera, Centella asiatica, Sida cordifolia, and Bacopa Monnier mixing these herbs with chemical like. Levodopa (L-DOPA, 3,4-dihydroxy-Lphenylalanine) and vitamin C powder (L-ascorbic acid, Fruit flies were cultured on food containing individual herbs or herbal formulations Food containing treatment was made by mixing the powdered herbs or the chemicals, a combination of all five herbs, Tests were performed in both PINK1 mutant flies and healthy wild-type (WT) flies.

the symptoms in PINK1 mutants were measured by testing their climbing ability. Fourteen days after the flies were originally placed on food with treatment, testing first-generation offspring as well this study showed that B. MONNIER is a promising treatment or complementary treatment for PD as it is improving the climbing abilities of drosophila and cognitive improvement occurred [36]

3. testing curcumin as a treatment for Parkinson's disease

Curcumin is the principal curcuminoid of the spice turmeric (*Curcuma longa*), a member of the ginger family whi9ch have a pharmacological properties beside delaying the loss of climbing ability in the PD model flies so an experiment was conducted in which Transgenic fly lines that expresses wild-type human synuclein (h-*α*S) under control in neuron ,all The flies were cultured on standard *Drosophila* food containing 0.83% agar, 4.72% corn meal, 4.16% sugar, and 1.67% yeast at 25°C then lies were exposed separately to different doses of curcumin in final concentration of 25, 50, and 100 *μ*m in addition to a dose of dopamine , The data collected for the male flies by *Drosophila* activity monitor and showed that the exposure of PD flies to 25, 50, and 100 *μ*m of curcumin showed a dose-dependent significant delay in the loss of activity pattern, reduction in lipid peroxidation, protein carbonyl content, apoptosis, and increase in the life span so it was considered as a potential treatment for PD [37]

4. testing Y-oryzanol as a treatment for Parkinson's disease

γ-oryzanol is present in rice bran oil and contains a mix of steryl-triterpenyl esters of ferulic acid, The microflora in the hindgut can hydrolyze these compounds, releasing ferulic acid for absorption or degradation, flies were exposed to rotenone to stimulate the symptoms of PD then flies were exposed to γ-oryzanol which resulted in ORY 25 μm + ROT 500 μm flies. Flies were exposed to the diet containing ROT and ORY for 7 days, the ORY acted on this model by restoring dopamine levels in the heads of flies and the activity of the enzyme acetylcholinesterase and improving motor function of flies in addition to improving antioxidant defenses, preventing oxidative stress, mitochondrial dysfunction and preventing the lethality induced by rotenone so it is considered as a potential treatment or complementary treatment for PD [38]

5. testing kaempferol as a treatment for PD

Kaempferol was added to the diet of flies that have induced AD at concentrations of 10, 20, 30, and 40 µm and the effect was studied on various cognitive and oxidative stress markers, The results of the study showed that kaempferol delayed the loss of climbing ability in addition to the activity of PD flies in a dose-dependent manner compared to unexposed PD flies. A dose-dependent reduction in oxidative stress markers was also observed, Molecular scan results revealed that kaempferol binds to human alpha-synuclein at specific sites which might result in the inhibition of alpha-synuclein aggregation and prevent the formation of Lewy bodies, so it is a promising treatment for PD [39]

6. Testing the effects of minocycline as a treatment for PD

Minocycline ((MC), a second-generation tetracycline drug), a tetracycline derivative, exerts ameliorative effects in neurodegenerative disease models that are known to be clinically safe, an experiment was conducted using drosophila with parquet-induced PD, Fed on filter paper saturated with one of the following solutions: 5% sucrose, 5% sucrose with 1 or 10 mM paraquat, minocycline HCl at varying concentrations, which resulted in increasing the life span, stopping the mobility defects, improvement in survival of dopaminergic neurons and decreasing the oxidative stress so it was considered as a potential treatment for PD [40]

4.Summary

Alzheimer's disease is a neurodegenerative condition characterized by the loss of neurons, neurons, and synapses, leading to negative lesions in the brain. Two main hypotheses for Alzheimer's are the amyloid cascade hypothesis, focusing on abnormal amyloid-beta peptide deposition, and the mitochondrial cascade hypothesis, linking dysfunctional mitochondria to the disease, Parkinson's disease is a neurological disorder characterized by the loss of nerve cells in the brain's substantia nigra, leading to a reduction in dopamine levels. Dopamine plays a crucial role in controlling body movements by acting as a messenger between different brain regions. As the disease progresses, movements become slow and abnormal due to impaired dopamine function, Drosophila's genetic simplicity and similarity to humans make it a valuable model for studying neurodegenerative diseases, Researchers using Drosophila (fruit flies) have provided insights into Alzheimer's and Parkinson's treatments, with genetically modified flies showing characteristics of the disease.

الملخص

مرض الزهايمر هو حالة عصبية تتميز بفقدان الخلايا العصبية والمحابس، مما يؤدي إلى تشكيل آثار سلبية في الدماغ. تظهر فرضيتان رئيسيتان لمرض الزهايمر، وهما فرضية تسلسل الأميلويد، التي تركز على ترسيب ببتيد أميلويد بيتا غير الطبيعي، وفرضية تسلسل الميتوكوندريا، التي تربط بين ميتوكوندريا غير صحية والمرض، مرض باركنسون هو اضطراب عصبي يتميز بفقدان خلايا الأعصاب في نواة المنطقه السوداء بالدماغ، مما يؤدي إلى تقليل مستويات الدوبامين. يلعب الدوبامين دورًا حاسمًا في التحكم في حركة الجسم عن طريق تصرفه كرسول بين مناطق الدماغ المختلفة. مع تقدم المرض، تصبح الحركات بطيئة وغير طبيعية بسبب ضعف وظيفة الدوبامين، بساطة الوراثة والشبه بين الذبابة المنزلية والإنسان تجعل منه نموذجًا قيمًا لدراسة الأمراض العصبية، قدم الباحثون الذين استخدموا الذبابة المنزلية (ذباب الفاكهة) رؤيه جيده على علاجات الزهايمر وباركنسون، حيث أظهر الذباب المعدل وراثيًا سمات المرض.

5.References

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