Role of Pinus gerardiana Wallichex D. Don seed in the management of Neurodegenerative disorders

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Abstract- **The dominant chemicals present in the seed of Pinus gerardiana Wallichex D. Don, Oleic acid (OA) a monosaturated fatty acid and Linoleic acid (LA) a polysaturated fatty acid. Both being unsaturated fats have beneficial properties as anti- inflammatory and Neuroprotective agents along with several therapeutic effects. Oleic acid demonstrates the potency to reduce the prolyl endopeptidase activity in brain amyloidogenesis, follow up by the multiple protective effects in pathways critical to the formation of β-amyloid plaques in brain of the mice suffering from the Alzheimer's disease (AD). Also, it has been observed that the frontal cortex and hippocampus of AD brains have a substantial reduction in monounsaturated fatty acids (FAs), including OA. This all indicates that the OA is beneficial in the prevent and management of Alzheimer's disease. Oleic acid along with Linoleic acid have been efficacious for the management and prevention of Parkinson's disease (PD) as, lipid droplets (LDs) can be destroyed in two ways later on: lipolysis and lipophagy. Lipolysis is a sort of neutral degradation carried out by cytoplasmic enzymes. Lipophagy is the acidic destruction of LDs by autophagy, either micro- or macro-autophagy. The latter step begins with the formation of a phagophore that contains all or a portion of the LDs, giving rise to a lipoautophagosome, which unites with a lysosome to form the autolysosome, which degrades the LDs. LDs and autophagy markers might accumulate in brain cells throughout the aging process, under stressful situations, neurons increase lipid synthesis and astrocytes increase LD accumulation, potentially due to a neuron-astrocyte connection involved in lipid metabolism. A number of researches suggests that LDs may act as a free radical sink. As a result, it may have an antioxidant and protective function in the pathogenesis of Parkinson's disease. Several fatty acids, on the other hand (e.g., linoleic or oleic acid), influence LD levels via modulating autophagic flux and LD biogenesis. Hypothetically it can be said that the increased quantity of LDs operates as free radical scavengers. The increased lipophagy clearance might then operate as an antioxidant mechanism. Hence it can be postulate that both OA and LA are adept enough to manage or prevent the Parkinson's disease. Furthermore, aside from the clinical motor characteristics, modest cognitive impairment, primarily executive dysfunction, with secondary visuospatial and memory problems, may be detected in the early stages of illness. It was coming to know from several researches that around 20-40% of patients, with these issues may progress to dementia, which is a significant risk factor for caregiver distress, poor quality of life, and nursing facility placement. Progressive dysexecutive syndrome, attentional impairments, fluctuating cognition, and psychotic symptoms are common characteristics of dementia in Parkinson's disease (PD-D). This implements that the association between PD and Dementia. people with Alzheimer's disease suffer from both short-term memory impairment and problems forming new material in long-term storage. Alzheimer's disease is usually regarded as a cause of presenile dementia, whereas so-called "senile dementia" (Age 65+) was formerly overlooked by both the general public and medical practitioners, but it is now known that AD affects individuals of all ages. Hence the association between the Alzheimer's disease. To preserver with this, it can be said that the Pinus gerardiana seed might be suggesting in the management of Neurodegenerative disorders.**

Keywords: **Pinus gerardiana Wallichex D. Don, Chilgoza, Linoleic acid, Oleic acid, Free radicals, Anti-inflammatory, Neuroprotective Neurodegenerative disorders.**

Introduction

Medicinal plants have long been acknowledged as a significant source of medicines, as a means of curing human ailments and preserving health. Due to lower costs and fewer side effects, the use of green medicines is growing exponentially [1].

Five species of pines are indigenous to India viz. Pinus roxburghii (Chir pine), Pinus wallichiana (Blue pine), Pinus kesiya (Khasi pine), P. gerardiana (Chilgoza pine) and P. merkussi (Teriasserian pine). Out of these the three-pine

species grow wild in the Indian Himalayas. Pinus roxburghii, Pinus wallichiana, and Pinus gerardiana are examples of pine tree [2].

Pinus roxburghii (Chir pine) is one of the most important conifers in India. It is distributed from 450 m to 2300 m attitude in the Himalayas in Afghanistan, Pakistan, India, Nepal and Bhutan. In India, the species occurs extensively in Jammu and Kashmir, Himachal Pradesh and Uttarakhand and in a few parts of Sikkim, West Bengal and Arunachal Pradesh. The species is well known for its resin and timber. Artificial regeneration as well as natural regeneration take place through seeds [3].

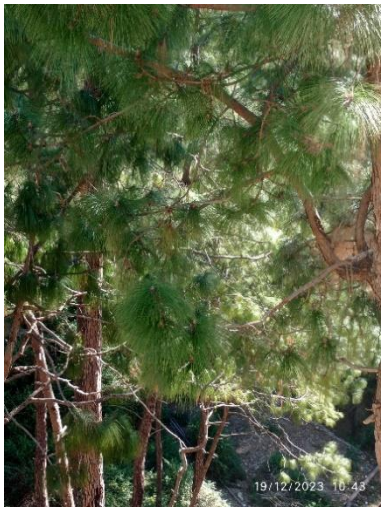


Image of Pinus roxburghii **Pinus roxburghii needles**

Sagwal (1984) studied cone and seed morphology using individual cones of two trees of Chir pine.

Cone length, diameter and weight were found to vary considerably with respect to tree. Number of seeds per cone was influenced by cone length and weight.

In accordance to that the mean fresh weight and repeatabilities of different populations of Chir pine in Himachal Pradesh

Representation of the Mean cone fresh weight [3]

Population	Mean cone fresh weight (g)	Repeatability of cone (fresh weight SE)
Mastgarh (Nurpur Forest Division)	168.55	0.73 0.10
Kalhel (Chamba Forest Division)	169.89	0.70 0.11
Chamba (Chamba Forest Division)	191.78	0.38 0.14
Banikhet (Dalhousie Forest Division)	154.17	0.45 0.14
Vrindavan (Nurpur Forest Division)	147.90	0.38 0.14
Bakloh (Dalhousie Forest Division)	134.86	0.45 0.14
Average	161.19	0.52

$CD_{0.05}$ for mean cone fresh weight = 34.83

Representation of the repeatability [3]

Character	Kalhel		Chamba		Average
Cone dry weight	0.7477	0.0998	0.4738	0.1523	0.610
Cone diameter	0.1265	0.1075	0.3134	0.1514	0.220
Cone length	0.7048	0.1112	0.4098	0.1546	0.557
No. of seeds	0.2896	0.1383	0.0527	0.1026 #	0.171
Seed weight per cone	0.4920	0.1440	0.1013	0.1161 #	0.296
100-seed weight	0.6968	0.1132	0.5622	0.1434	0.629

# indicates that repeatability is not significant.

Pine cone

Pinus wallichiana Jackson (Blue pine), a member of subsection *Strobi*, is a haploxylon pine also known as *Pinus griffithii*, *Pinus excelsa*, and *Pinus chylla*. It ranges throughout the Himalaya Mountains, extending beyond them to eastern Afghanistan, northeastern Baluchistan (West Pakistan), northern Burma, and Yunnan Province, China with some interruptions. It is an important component of the middle- and high-elevation Himalayan forests, especially in the drier inner valleys (Critchfield and Little, 1966; Mirov, 1967) [4].

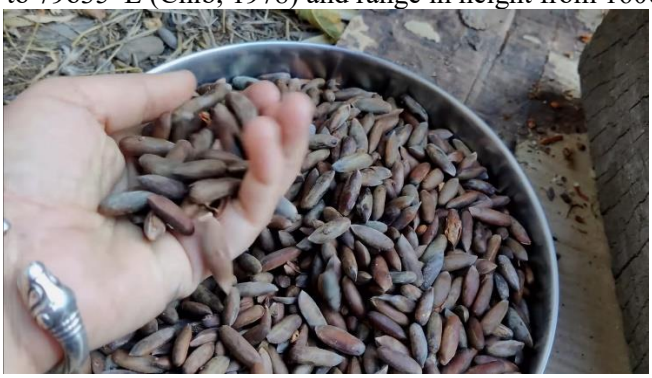
Blue Pine is one of the greatest commercially important and commonly distributed pine species in the Hindukush Himalayas. On the globe, the species is distributed in longitudinal range between 68oE to 100oE, latitudinal range between 25oN to 36oN and the altitudinal range from between 1500 to 3800 m. Pinus wallichiana prefer low temperature and may occur at high altitudes in low rainfall areas and at low altitudes (less than 2,800 m) in high rainfall areas in pure or mixed forests and known as Kail in timber trade [5].

Pinus Wallichiana Cone and pine needles

Pinus gerardiana Wallich ex. D. Don. (Chilgoza) is a prominent medicinal plant used to treat a variety of ailments in traditional medicine. It is known as the "Champion of the Rocky Mountains" [6]. Pinus gerardiana is an indigenous and endangered pine of the northern Himalayas. It is the only conifer in India that is traded for its nuts. It is a vital element of the ecosystem, customs, and culture of Kinnaur District in Himachal Pradesh, as well as a secondary source of income for Kinnaura tribes [7].

Pinus gerardiana needles

Pinus gerardiana (P. gerardiana) is also known as "chilgoza or neoza pine." The world's dispersion is limited to mountain ranges in the east of India, Pakistan, and Afghanistan, as well as dispersed sections of the Himalayan Hindu Kush (30o to 37o N latitude and 66o to 80o E longitude). The Northwest Himalayas in India extend from latitude 31o 55 'to latitude 32o05′ N and longitude 77o 45 'to 79o35′ E (Chib, 1978) and range in height from 1600 to 3300 meters"[1].



Freshly harvested and collected Chilgoza Seed

Chilgoza trees reach medium heights (17 to 27 m) and have a dbh of 2-4 m. The branches have glabrous bark and are thin and horizontal.[1] Three needle-shaped, dark green leaves are grouped in a cluster. The female cones, which are ovoid and covered in tough woody scales, are longer than the male ones. These cylindrical, dark brown seeds typically ripen in October and have a pointed top [8].

Kinnaur natives climbing the Chilgoza tree to harvest fresh cones

DESCRIPTION –

a) Macroscopic: Off-white in colour; oval in shape and pointed at the micropylar end; ranging from 1.5 to 2 cm long; oleaginous; possess a delicate terebinthine flavour; odour sweet.

b) Microscopic: TS is circular in outline shows epidermis covered with cuticle followed by wide ground tissue; collapsed layer; inner parenchymatous region which has 8 to 10 vascular bundles arranged in a ring, cells of the ground tissue are filled with starch grains and oil globules; vascular bundles consist of a centrally located xylem encircled by a phloem, with an external bundle sheath [9].

Freshly harvested and collected cones of Pinus gerardiana

TAXONOMICAL CLASSIFICATION

Kingdom Plantae	Plants
Sub -kingdom	Trachiobionate-Vascular plants
Super division	Spermatophyta-Seed plants
Division	Coniferophyta-conifers
Class	Pinopsida
Order	Pinales
Family	Pinaceae-Pine family
Species	Pinus gerardianaWall. ex D Don–chilghoza pine SYNONYMS – Cilagoja

REGIONAL LANGUAGE NAMES

Eng. : Chilgoza pine, Edible pine, Neosa pine

Guj. : Chilgojhaa

Hin. : Chilgozaa, Neoza, Gunobar, Rhee
Kan. : Chilgojha
Mal. : Chilgojha
Mar. : Chilgoza, Galgoja
Ori. : Chilgojha
Pun. : Mirrigalgoj, Mirri, Chiri, Chirrigalgoja
Tel. : Chilgoja
Urd. : Chilgozah

Table1: Taxonomical classification of Pinus gerardiana and its synonyms. [10]

List of the chemical constituents present in the seeds of the Pinus gerardiana plant

S.No.	Part	Chemical constituents	References
1.	Seed	Linoleic acid , Unsaturated fatty acids, Oleic acid	[11], [12]
2.	Seed	Vitamin E (α-tocopherol)	[12]
3.	Seed	Albumenoids and Oil starch	[6]
4.	Seed	Polyphenols, Xanthenes, Carotenoids	[13]
5.	Seed	Gallocatechin, Catechin, Lutein, Lycopene	[14]
6.	Seed	Epicatechin, Catechin, Taxifolin dihydroquercetin, Quercetin and Phenolic acids	[15]
7.	Seed	Vitamins: Thiamine (B1), Beta carotene, Riboflavin (B2), Pantothenic acid (B5), Niacin (B3), Vitamin B6(Pyridoxine), Vitamin k, Folate (B9), and Minerals including Magnesium, Calcium, Manganese, Phosphorous, Potassium, Iron, Zinc.	[15]
8.	Seed	Palmitic (3.7%), Stearic acid (1.2%), Oleic acid (52.3%) and Linoleic (42.8%), Palmito-dilinolein (2.4 %), Palmito-oleolinolein (2.4 %), Triolein 3-4 %, Dioleolinolein (47.4 %), Stearo-oleolinolein (3.2 %), trilinolein (0.4 %), Oleiodilinolein (32.5 %)	[16] [17, 18].

USES OF THE CHEMICAL CONSTITUENTS OF PINUS GERARDIANA:

1) **Linoleic acid (LA)**: Human arterial pressure has been demonstrated to decrease in response to polyunsaturated fatty acids of the omega-6 series, as have a number of experimental hypertension models [19]. There is confirmation that LA has neuroprotective properties in vitro and in vivo against Parkinson's disease [20].

2) **Oleic acid (OA):** Oleic acid is a mono-unsaturated omega-9 fatty acid found in plants as in olive oil and nuts[21] and animals. Oleic acid is used in pharmaceuticals as an excipient and in aerosol goods as an emulsifying or solubilizing agent. It may slow the progression of adrenoleukodystrophy, a deadly condition affecting the brain and adrenal glands, as well as improve memory**[22].** It is also known that oleic acid has an influence on the cardiovascular system by decreasing the rate of myocardial infarction, platelet aggregation, and TXA2 production, as well as lowering systolic blood pressure [23].

3) **α-tocopherol (Vit.E):** Alpha-tocopherol, one of vitamin E's eight isoforms, is nature's most effective fat-soluble antioxidant [24] .

For cancer the ability of vitamin E, particularly α -tocopherol, to reduce free radical damage, induce apoptosis, and influence oncogene expression makes it a promising target for chemotherapeutic techniques.[24] Vitamin E, in addition to enhancing apoptotic pathways, can also suppress tumour survival factors such as protein kinase C (PKC).[25] α-TS has been named the most effective form of vitamin E in the adjuvant therapy of cancer due to its demonstrated efficacy in multiple cancer cell tests and encouraging outcomes from early clinical trials.[26] when combined with additional micronutrients used in chemotherapy or radiation, such as vitamin C, retinoic acid, and carotenoids [27].

4) Xanthenes: A unique group of tricyclic chemicals that include oxygen is known as xanthenes. (Aza)xanthene derivatives shown biological activity as neuroprotectors, antitumors, and antimicrobials, among other things, demonstrating the nucleus' adaptability for many biological uses [28].

5) **Carotenoids**: In cells, tissues, and entire animals, carotenoids improve the immune response, prevent mutagenesis, reduce induced nuclear damage, and protect against numerous neoplastic processes. Carotenoids also protect tissue from photo-induced damage. Under certain circumstances, several carotenoids, particularly -carotene, quench highly reactive singlet oxygen and can impede free radical-mediated processes. Consumption of carotenoid-rich fruits and vegetables has been linked to a lower risk of some types of cancer, notably lung cancer, in epidemiological studies [29].

6) Catechin: Catechins are naturally occurring polyphenolic compounds found in food and medicinal plants. A growing body of research has linked the consumption of catechin-rich foods to the prevention and treatment of chronic disorders in humans, such as inflammatory bowel disease (IBD). Some studies have shown that catechins can significantly inhibit excessive oxidative stress via either direct or indirect antioxidant effects and promote the activation of antioxidative substances such as glutathione peroxidases (GPO) and glutathione (GSH), thereby reducing oxidative damage to the colon. Furthermore, catechins can regulate the infiltration and proliferation of immune-related cells such as neutrophils, colonic epithelial cells, macrophages, and T lymphocytes, hence reducing inflammatory relationships and providing advantages to IBD.[30]

7) Lutein: One of the most common carotenoids in both the natural world and the human diet is lutein. It is highly concentrated as macular pigment in the foveal retina of primates, where it works in conjunction with zeaxanthin to reduce blue light exposure, offer protection from photo-oxidation, and improve visual function. Recently, research on lutein has moved beyond the retina to examine its potential effects on brain growth and function. Only primates build up lutein in the brain, and nothing is known about its physiological significance or distribution.[31]

As previously noted, the only caroteoids that are preferentially deposited in the fovea to create the macular pigment are lutein and its isomer zeaxanthin. Given that the retina, like the brain, is made up of neural tissue, lutein is being studied for its potential significance in cognitive function.[32-34]

8) **Lycopene:** Lycopene is a tetraterpene chemical and one of the carotenoids. It is basically acknowledged as a strong antioxidant and a carotenoid that is not a pro-vitamin A. Cancer recurrence, diabetes mellitus, cardiac difficulties, oxidative stress-mediated malfunctions, inflammatory events, skin and bone illnesses, hepatic, neurological, and reproductive abnormalities have all been reported to be significantly improved by lycopene. Additionally, toxicity and safety are reviewed, as well as its protective properties against the recommended concentrations of toxic agents.[35]

9) Epicatechin: A natural flavonoid is epicatechin. It has been demonstrated that eating epicatechin lowers blood sugar levels in diabetic people. Epicatechin's anticancer effects were linked to its antioxidant, antiangiogenic, and direct cytotoxic effects on cancer cells. Epicatechin is a viable contender as a replacement, despite the fact that its precise mode of action is currently under investigation.[36]

10) Taxifolin dihydroquercetin: Taxifolin (3,5,7,3,4-pentahydroxy flavanone or dihydroquercetin) is a flavonoid. Promising pharmacological actions were demonstrated by taxifolin in the treatment of malignancies, oxidative stress, microbial infections, inflammation, and liver and cardiovascular diseases. Compared to other activities, the anti-cancer activity was more noticeable.[37]

11) Quercetin: One of the flavonoids with antioxidant qualities is quercetin. It is said that quercetin has numerous positive health impacts, including preventing diseases like osteoporosis, lung cancer, and cardiovascular disease.[38]

12) **Phenolic acids**: As phenolic acids are a subclass of plant phenolics, they have resonance stabilized structures and phenol moieties. Through radical scavenging, the H-atom donation in phenolic acids results in antioxidant properties. Dietary polyphenols, or natural antioxidants, include phenolic acids as a major class. They perform a number of tasks, such as defense, development, and plant growth. They are building blocks for other important bioactive compounds that are frequently employed in the food, cosmetics, and pharmaceutical sectors. Oxidative stress is the source of these dietary antioxidants' defences against the growth and progression of pathological diseases.[39]

13) **Thiamine**: Thiamine, often known as vitamin B1, is now recognized as being essential for energy metabolism. It was discovered as a result of early study on the 'anti-beriberi component' found in rice polishing. Following its synthesis in 1936, it prompted several years of investigation to determine its activity in curing beriberi.[40]

14) Beta carotene: Beta-carotene's health benefits and dietary needs are linked. This orange-red pigment has been extensively studied for its ability to treat a variety of chronic conditions, including cancer, cystic fibrosis, and COVID-19. However, due to multiple reported twin outcomes, this class of phytoconstituents has seen a significant study deficit.[41]

15) Riboflavin: Riboflavin has also been linked to the protection of a wide range of health problems, including migraine, anaemia, cancer, hyperglycaemia, hypertension, diabetes mellitus, and oxidative stress, either directly or indirectly. Riboflavin shortage has a significant impact on iron absorption, tryptophan metabolism, mitochondrial dysfunction, gastrointestinal system, brain dysfunction, and vitamin metabolism in general, as well as skin diseases.[42]

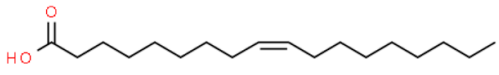
16) Pantothenic acid: Pantothenic acid (vitamin B5) is a B-complex vitamin that is water soluble. It is biologically significant due to its incorporation into coenzyme A and acyl carrier protein, both of which are important in fatty acid metabolism**.[43]** It has been hypothesized that pantethine has a positive impact on hyperlipidaemia [44].

17) Niacin: Niacin, also known as nicotinic acid, has long been used to treat cardiovascular disease and lipid abnormalities. Niacin boosts apo A-I-containing lipoproteins (high-density lipoprotein [HDL]) and has a positive effect on apolipoprotein (apo) B-containing lipoproteins (e.g., very-low-density lipoprotein [VLDL], low-density lipoprotein [LDL], and lipoprotein[a]) [45].

18) Pyridoxine: Pyridoxine (vitamin B6) is a cofactor in numerous enzymatic pathways involved in amino acid metabolism, with pyridoxal 5-phosphate being the most physiologically active form. Pyridoxine has been used as an antidote to isoniazid overdose, Gyromitra mushroom or fake morrel (monomethylhydrazine) toxicity, and hydrazine exposure **[46].**

19) **Vitamin k**: Vitamin K has long been associated with blood coagulation, as it is required for the posttranslational alteration of seven proteins involved in this cascade. However, it is also involved in the development of additional 11 or 12 proteins that play various functions, including the control of connective tissue calcification. Because this procedure is biologically necessary in bones [47].

Uses of oleic acid (OA)



Structure of Oleic acid [48]

Anti- inflammatory effect of oleic acid: OA is the most prevalent FA in healthy persons, present in adipocytes, cell membranes, and plasma[49]. Endogenous OA is present as a component of hormone synthesis and cellular membranes[50]. Inflammatory-related illnesses benefit from an OA-rich diet. It influences the immune system by activating many immunological competent cell pathways [51].

- **Oleic acid for Eye Inflammation:**

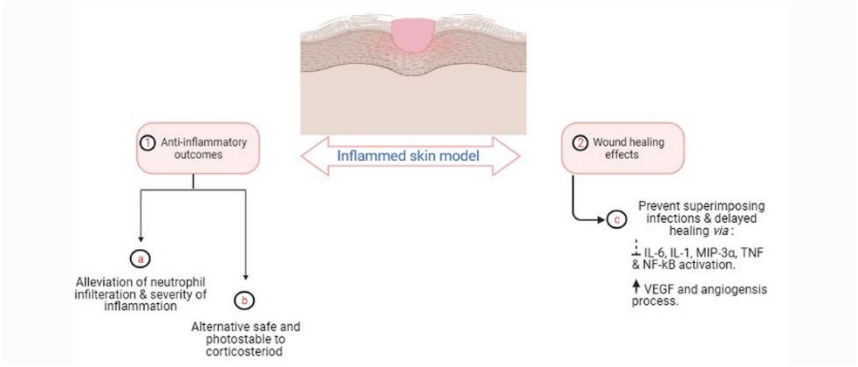
In male Wistar rats, OA has an anti-inflammatory impact against hyperlipidaemia-induced retinal inflammation. A high OA diet for 90 days reduced the levels of proinflammatory blood and retinal cytokines such as IL-1-α**,** TNF- α, and MCP-1. It also reduced serum C reactive protein (CRP), serum pro-inflammatory eicosanoids (LTC4, LTB4, and PGE2), and retinal expression of BLT-1, EP-4, EP-1, and COX-2 in comparison to control rats on a low lard rich diet[51, 52]. It has been proven that OA has the potential to improve both hydrophilic and lipophilic compound ocular medication delivery[53]. Furthermore, some studies have shown that lipid-based lubricants can help reduce certain dry eye symptoms[54]. Because of its anti-inflammatory properties, enhancement of medication distribution, and improvement of dry eye symptoms, OA addition to topical ophthalmic treatments warrants further research in some eye conditions [55].

- **Oleic acid for Skin Inflammation**

OA has been demonstrated to reduce skin inflammation via changing the function of neutrophils in immunity; however, binding to albumin reduces its anti-inflammatory action. A research looked at the effect of incorporating OA into nano-structured lipid carriers (OA-NLC) on anti-inflammatory properties. The results demonstrated that in the presence of albumin, the OA-NLC aborted elastase release and superoxide formation, indicating that enhanced nano-formulation influence on OA anti-inflammatory action that has yet to be documented for other activities. The use of OA-NLC as an ointment on the skin reduced neutrophil infiltration and the degree of skin irritation [50, 56]. OA is important in wound healing because it induces fast wound closure, which is necessary to avoid superimposing infections and delayed healing. The administration of OA to wounds in Wistar rats resulted in a faster proliferative stage, epithelial cell regeneration, and appropriate collagen and keratin synthesis. Furthermore, neovascularization was boosted during the early inflammatory phase due to an increase in vascular endothelial growth factor (VEGF) production, which plays an important role in the angiogenesis process [57]. After 1 hour of wound development, OA increases NF-B and TNF- α production in rats. However, a drop in IL-6, IL-1, and MIP-3 levels, as well as NF-B release, was detected 24 hours after wounding, indicating that OA accelerates the inflammatory processes of wound healing [56]. For the treatment of UV-induced skin irritation, OA can be used instead of corticosteroids. OA was added to semisolid Lanette® or Pemulen® TR2 preparations. After repeated doses at 24, 48, and 72 hours after UVB exposure, both formulations decreased ear edema in mice. Glucocorticoid receptors appeared to be involved in the anti-inflammatory effect. The

authors proposed using OA as a possible alternative to glucocorticoids since it is safe and does not cause photosensitivity even at relatively high doses (13%) [58].

FIG 1 [55]



Summary of oleic acid (OA) action pathways in controlling skin inflammation and wound healing effects

- **Oleic acid for Lung Inflammation**

Pneumonitis is a broad word that refers to inflammation of lung tissue. Noninfectious causes of lung inflammation are usually referred to as pneumonitis by physicians. Lung inflammation can be transient or chronic, and the reasons range from environmental factors to infections and disorders such as asthma and bronchitis [59]. Damage to Lungs from OA is a widely used model that closely reflects human illnesss [60]. However, OA has been shown to have anti-inflammatory properties against active neutrophils. Through neutrophil suppression, OA-based nanosystems protected mice from acute respiratory distress syndrome [61].

- **Oleic acid over management and treatment of Sepsis**

Sepsis is a medical disorder induced by a severe infection with systemic inflammation[62] . Sepsis can be characterized by inflammatory and metabolic changes that result in enormous cytokine production, oxidative stress, and organ dysfunction. Plasma non-esterified fatty acids (NEFA) are elevated in severe systemic inflammatory response syndrome. Several NEFA are toxic to cells, activating Toll-like receptors and inhibiting Na+/K+-ATPase, resulting in lung damage[63].

Monocytes and neutrophils generate the cytokines Interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), and Interleukin- 10 (IL-10), which form the storm during sepsis [64-66].

Septic mice displayed increased amounts of TNF- α, IL-1, and IL-10 in the peritoneal lavage compared to controls, but omega-9 pretreatment significantly reduced TNF- α and IL-1 levels in septic mice. Surprisingly, IL-10 levels rose in the peritoneal lavage of septic mice given omega-9. Despite the fact that omega-9 administration modified cytokine response and neutrophil formation in the peritoneal cavity, omega-9 pretreatment did not impede bacterial clearance via the innate immune response. Pretreatment with omega-9 improved bacterial clearance in the peritoneum [67].

In septic mice, omega-9 regulated the immunological response. Omega-9 reduced proinflammatory cytokine production, raised IL-10 production, decreased neutrophil migration and accumulation at the site of infection, and enhanced bacterial clearance [67]. In mice treated to cecal ligation and puncture (CLP), oleic acid alleviated clinical symptoms, prolonged survival, avoided liver and kidney impairment, and lowered NEFA plasma levels [63]. As a result, an omega-9-enriched diet as a supplementary meal may be recommended in patients with infections, and it may add to the additional benefits of eating unsaturated fatty acid-rich diets [67]. Or it can be suggested that OA might help with sepsis by reducing metabolic dysfunction, which supports the advantages of diets high in monounsaturated fatty acids (MUFA) [63].

- **Ulcerative colitis and intestinal inflammation**

Ulcerative colitis (UC) is an inflammatory bowel disease that produces stomach ulcers and inflammation in the gastro intestinal tract. UC arises when the lining of the colon or rectum becomes irritated. Pathogenesis of that illness is influenced by genetic susceptibility, dysregulated immunological responses, epithelial barrier abnormalities, and environmental variables. Despite the fact that there is no cure, medicine can greatly lessen the disease's signs and symptoms and lead to long-term remission[68].

Experimentally induced UC rats acorn-fed ham rich in OA in a study to lessen the load of meat products diet in instances of ulcerative colitis. Diet affected the gut microbiota, with a considerable increase in bacterial species with anti-inflammatory capabilities (Alistipes, Blautia, Dorea, and Parabacteroides). When compared to rats fed a conventional vegetable diet, it also had a powerful anti-inflammatory effect, which helped to avoid UC symptoms such as macroscopic score of colitis, disease activity index, density of inflammatory cells in colon, epithelium alteration in colon mucosa, proinflammatory IFN- and IL-17 levels, and myeloperoxidase titers in colon[69].

- **Neuroprotective activity of Oleic acid**

Recent research has shown that oleic acid is required for proper brain growth and functioning. During brain development, oleic acid is needed to synthesise myelin phospholipids[70] . It functions as a neurotrophic factor by stimulating axonal and dendritic development, improving neuronal migration and aggregation, and enabling synapse formation[71-74]. When compared to normal brain tissue, there is a considerable decrease in oleic acid in the brains of people with Alzheimer's disease and major depressive disorder [75, 76]. Oleic acid has been demonstrated to diminish amyloidosis in Alzheimer's disease in vitro and animal models[77]. As well as to reduce the harmful effects of 7-ketocholesterol, a lipid peroxidation product that is elevated in individuals with neurological disorders [78]. After cerebral ischaemia, oleic acid reduces the inflammatory responses of microglia, which cause neuronal death [79].
Oleic acid is an endogenous agonist of peroxisome proliferator-activated receptor gamma (PPAR-), a nuclear receptor superfamily ligand-activated transcription factor [80]. PPAR- has been proposed as a therapeutic target for neuroprotection in cerebral ischaemia, in addition to its well-established involvement in regulating glucose and lipid metabolism [81]. In animal models of cerebral ischaemia, the treatment of PPAR-agonists offers neuroprotection and enhances neurological capabilities[82-85].
Based on these data, it can be hypothesized that oleic acid had neuroprotective effects in cerebral ischaemia, and that these benefits may be exerted via PPAR- activation.[86]

- **Oleic acid for Liver Inflammation**

Liver inflammation develops when a disease-causing microorganism or medication assaults liver cells. Hepatitis is an inflammation of the liver. Hepatitis is usually caused by a virus, but it can also be caused by an autoimmune condition. Alcohol, pollutants, and certain drugs can all damage the liver and induce inflammation. Hereditary diseases, as well as chronic bile flow restriction, can potentially cause hepatitis. The intensity, management, and result of liver inflammation are all determined by the kind of hepatitis. Chronic liver inflammation may induce fibrosis, cirrhosis, and hepatocellular cancer[87].
By stimulating multiple signaling pathways in hepatic parenchymal cells, OA can help avoid endoplasmic reticulum (ER) stress, mitochondrial dysfunction, inflammation, insulin resistance, and oxidative stress. The following are the most essential routes that contribute to liver damage resolution or prevention: (1) induction of the nuclear factor erythroid 2-related factor 2 (Nfr2), which results in antioxidant signals; (2) suppression of (NF-B), which prevents the cellular inflammatory response; and (3) suppression of the PERK signaling pathway, which results in autophagy, ER stress, and lipogenic response prevention[88]. By decreasing pyroptosis and ER stress, OA also lowers hepatocellular lipotoxicity produced by palmitic acid[89].

- **Insulin resistance (IR) and Type 2 Diabetes Mellitus (T2DM)**

One of the most important causes in the development and activation of IR and T2DM is mitochondrial dysfunction, which can result in inefficient fatty acid oxidation (FAO). OA increased FAO gene expression by deacetylating PGC1 via PKA-dependent stimulations of the SIRT1-PGC1 complex. OA also reduced the expression of inflammatory mediators E-selectin and sICAM, upregulated free fatty acid receptor-4 (FFAR4), promoted M2 expression, decreased phosphate and tensin homolog (PTEN), increased adiponectin, and downregulated protein phosphatase 2A (PP2A). OA also reduced IR and T2DM by enhancing cell and endothelial function, oxidative stress, hypothalamus function, glucolipotoxicity, apoptosis, and enzyme dysregulation[90]. It is unknown if combining OA with anti-diabetic medications such as metformin would result in a synergistic effect[55].

- **Anti-cancer activity of Oleic acid**

Numerous studies have revealed that OA inhibits cellular growth in a variety of tumor cell types. OA suppressed HER2 overexpression, a well-known oncogene implicated in the genesis and progression of a variety of human malignancies. OA is also involved in intracellular calcium signalling pathways associated to apoptosis and growth stimulation in cancer cells. The processes driving OA-induced apoptosis are connected to an increase in intracellular caspase 3 activity and the formation of ROS [91, 92]. OA inhibited cancer activity in human esophagus cells (HEC) by numerous methods, including reducing cell proliferation, cellular migration, and adhesion characteristics, which were mediated by activating tumor suppressor genes (p27, p21, and p53). Although OA treatment of HEC had no effect on the number of colonies, it significantly reduced colony size. Furthermore, OA is known for its anti-proliferative activity in various forms of cancer, such as colorectal cancer, where OA caused apoptosis, and breast cancer via modulating HER2 gene expression[93]. Nonetheless, further research employing in vivo animal grafting models is needed to establish OA anti-tumor effects. In tongue squamous cell carcinoma (TSCC), OA has anti-cancer effects and mechanisms. The results showed that OA effectively inhibited the growth of TSCC cells. It significantly accelerated cell cycle G0/G1 arrest, lowered Bcl-2 and Cyclin D1 expression, and raised the fraction of apoptotic cells, all while increasing p53 expression and caspase-3 cleavage. OA also resulted in the production of autolysosomes and a reduction in p62 expression as well

as the LC3 I/LC3 II ratio. Furthermore, after OA treatment, p-mTOR, p-Akt, p-4E-BP1, p-S6K, and p-ERK1/2 expression in TSCC cells was significantly decreased. The study indicated that OA has anti-cancer action in TSCC via increasing autophagy and apoptosis by blocking the Akt/mTOR signaling pathway[94]. Other macromolecules with which OA interacts and exerts its anti-cancer activities include proteins such as -lactalbumin and lactoferrins. A combination of OA and Gc protein-derived macrophage activating factor (GcMAF) was demonstrated to have a considerable impact on immune system activation and tumor mass reduction in patients with advanced cancer[95]. The stimulation of macrophages by GcMAF is associated with the release of nitric oxide. Furthermore, OA synergistically boosted the effectiveness of cancer medicines. For example, OA enhanced the effectiveness of Herceptin, a breast cancer treatment that targets the HER-2/neu gene[96]. Furthermore, n-butyl and phenyl OA derivatives inhibited cell proliferation in human HT-29 colon and MCF-7 breast cell lines[97]. Other OA analogues might be synthesized to aid in the discovery of even more potent anti-tumor medicines based on OA using in silico drug modeling or combinatorial chemistry[55].

Oleic acid on Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent form of dementia and an irreversible neurological ailment that causes increasing cognitive deterioration. Extracellular senile plaques constituted of beta-amyloid (Aβ) deposits, intracellular neurofibrillary tangles, and brain atrophy are the neuropathological hallmarks of AD [98]. Proteolytic activity of β-secretase (BACE1) and β -secretase from a single transmembrane amyloid precursor protein (APP) produces Aβ residues. When produced in low amounts, Aβ not only shields the lipid from peroxidation, but it also plays a causative role in synapse and neuronal plasticity, which is the basis for learning and memory [99]. Various experimental and genetic studies, however, indicated that aberrant extracellular Aβ deposition is a critical and likely causative element that begins the neurotoxic cascade in AD [100].

Despite the fact that the molecular processes underpinning Aβ toxicity are mostly unclear, the damage caused by Aβ may entail a number of mechanisms such as oxidative stress, mitochondrial malfunction, an increase in intracellular Ca2+, and inflammation [101]. Aβ causes oxidative stress, which increases BACE1 gene expression, resulting in Aβ overproduction and the generation of reactive oxygen species (ROS), resulting in several pro-apoptotic and inflammatory signalling cascades that result in progressive degenerative cognitive abnormality [102, 103] .

According to current research, nuclear factor-κB (NF-κB) is essential for the release of proinflammatory cytokines in response to Aβ. Numerous molecules and factors, including cytokines, chemokines, proinflammatory transcription factors, proinflammatory enzymes, adhesion molecules, and vascular endothelial growth factor (VEGF), regulate inflammation at the molecular level, with NF-κB serving as the central regulator [99]. NF-B activation involves the phosphorylation and destruction of I-κBs via the I-κB kinases (IKK) complex. When I-κB is phosphorylated, the resulting NF-κB is translocated to the nucleus and binds to B binding sites in the promoter regions of target genes, inducing the transcription of proinflammatory and neurotoxic mediators such as inducible nitric oxide synthase (iNOS), cyclooxygenase (COX-2), tumor necrosis factor-α (TNF-α), prostaglandin E2 (PGE2), and nitric oxide (NO) [104]. Furthermore, NF-κB activation and the subsequent release of proinflammatory cytokines has been clinically linked to neuronal degeneration in Alzheimer's disease [105].

A significant body of investigations has shown a protective [106-108] in addition to detrimental implications [109-111] effects of oleic acid on neurological conditions such as AD. For instance, it has been observed that the frontal cortex and hippocampus of AD brains have a substantial reduction in monounsaturated fatty acids (FAs), including OA [106, 108]. Additionally, it has been demonstrated that OA considerably reduces prolyl endopeptidase activity [107]; the functional relevance of prolyl endopeptidase in brain amyloidogenesis is suggested by the dramatically elevated levels of this enzyme in AD brains [112]. Uncertainty exists on the clinical and physiological underpinnings of how OA influences AD. Furthermore, no prior research has looked at cholesterol-free diets combined with low fat consumption and enhanced omega-3 fatty acids [113].

(Amtul, Westaway, Cechetto, & Rozmahel, 2011) here reported, for the first time, multiple protective effects in pathways critical to the formation of amyloid plaques in the brains of AD mice fed a low-fat/+OA diet. These findings imply that controlling dietary OA consumption can provide a fresh method of lowering AD risk [113].

As a result, due to this potential of OA in Reducing /inhibiting the formation of amyloid plaques, Aβ-induced neurotoxicity and consequent neuroinflammation might be a beneficial avenue in the reducing the risk factor and/or prevention of AD.

Alzheimer's Disease

Introduction

Since there is no long-term cure for Alzheimer's disease (AD), the WHO has designated AD as a "global public health priority." The etiology of AD and its potential therapeutic targets are now just well-defined notions and hypotheses. On the basis of this idea, drugs slow down the advancement of disease pathology. For individuals over 60, AD is the main

cause of dementia. Alzheimer's affects between 50 and 75 percent of dementia patients. Based on global statistical data, women are more likely than men to get AD, and the risk rises with age[114].

Aetiology

While the majority of AD appears to be sporadic, a rare (<0.5%) familial type of AD is caused by mutations in three genes: presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP). Typically, symptoms appear between the ages of 30 and 50, sooner than in sporadic AD[115]. A complicated interaction between hereditary and environmental variables is thought to be the cause of "typical" late-onset Alzheimer's disease. It is currently estimated that hereditary factors account for around 70% of the risk of AD. The single greatest risk factor for sporadic AD is the APOE gene, which has three variants: ε2, ε3, and ε4. When compared to non-ε4 carriers, ε4 heterozygotes have an odds ratio (OR) for AD of around 3, which increases to approximately 12 in homozygotes[116]. More than 20 genetic risk factors have been found by genome-wide association studies involving hundreds of samples. These variables are linked to pathways involved in endosomal vesicle recycling, inflammation, and cholesterol metabolism[117]. Specifically, it is now understood that a major factor in the pathophysiology of AD is microglial activation in response to amyloid accumulation. Together, these relatively common risk genes may nearly quadruple case prediction from chance when aggregated into a polygenic risk score, even though each gene alone only slightly increases risk[118].

Several lower frequency genes that carry a relatively high risk for AD have also been identified using focused genetic techniques and next-generation sequencing research, which are shedding light on the pathophysiology of the disease. Vascular risk factors can either directly impact the development of AD pathology or vascular damage might "double-hit" the likelihood of clinical AD by superimposing cerebrovascular damage[119].

Pathology

Neurofibrillary tangles (NFTs) and amyloid plaques are the hallmarks of Alzheimer disease. Furthermore, cerebral amyloid angiopathy often coexists with neuropil threads, dystrophic neurites, related astrogliosis, and microglial activation[120]. Neurodegeneration with synaptic and neuronal loss leads to macroscopic atrophy as a result of these pathogenic processes. Mixed pathology, which combines vascular disease and Lewy bodies, is common, especially in the elderly[121]. Indeed, even in fAD patients, Lewy body pathology frequently coexists, the cause for which is unknown[122]. There is growing recognition of TDP-43 pathology as a significant co-pathology[123].

Amyloid plaques are extracellular accumulations mostly formed of improperly folded Aβ with 40 or 42 amino acids (Aβ40 and Aβ42), two byproducts of APP metabolism. Because of its increased rate of fibrillization and insolubility, A42 is more common in plaques than Aβ40. Amyloid deposition may not necessarily follow a predictable pattern of development, although it often begins in the isocortex and only later affects subcortical regions. Unlike NFTs, amyloid plaques affect the entorhinal cortex and hippocampal formations to a lower extent Aβ has several different staging systems, such as those from Braak and Braak [124], and the Thal criteria[125] and as well as the Alzheimer Disease Registry Consortium (CERAD)[126].

Neurofibrillary tangles are mostly made up of paired helical filaments made of hyperphosphorylated tau. Tau disease usually originates in the medial temporal lobe's allocortex (entorhinal cortex and hippocampus) before extending to the associative isocortex. Primary sensory, motor, and visual regions are often spared. Because neuronal and synapse loss often follow tangle formation, clinical characteristics and severity of Alzheimer's disease are better connected with NFT pathology[120], whereas -amyloid pathology hits a peak early in the disease's clinical phase[127]. Several criteria for the pathological diagnosis of Alzheimer's disease have been presented. Early attempts with amyloid plaques or NFTs were hampered by a lack of specificity or sensitivity[128]. Previous pathological criteria for Alzheimer's disease developed by the National Institute of Aging and the Reagan Institute combined the CERAD neuritic plaque score with the Braak and Braak NFT staging to create three diagnosis categories: high, intermediate, and low probability. Only in combination with a dementia diagnosis may an AD diagnosis be established if criteria for a high or intermediate chance of AD were satisfied[129]. One shortcoming of this method is that it did not address those who died with a significant burden of Alzheimer's disease pathology but no clinical symptoms. Neuropathological recommendations updated by the National Institute on Aging and the Alzheimer's Association (NIA-AA) try to address this, admitting the possibility of a mismatch between the clinical picture and neuropathological alterations[130].

Pathogenesis

The amyloid hypothesis, the most widely accepted theory of AD pathogenesis, proposes that the accumulation of pathological forms of A produced by sequential cleavage of the APP in the brain by the α - and β -secretase enzymes is the primary pathological process, driven by an imbalance between Aβ production and Aβ clearance. The production of NFTs and subsequent neuronal dysfunction and neurodegeneration are assumed to be downstream processes, possibly driven by inflammation[131]. Genetics provides strong evidence for a pivotal function for Aβ: all fAD mutations cause a relative overproduction of toxic types of β-amyloid and are involved in either Aβ synthesis or processing. On the other hand, a lifetime reduction in APP cleavage by β-secretase is caused by an APP missense mutation (A673T), which lowers the clinical risk of AD[132]. Like many other risk genes, ApoE plays a role in amyloid clearance in sporadic illness[119].

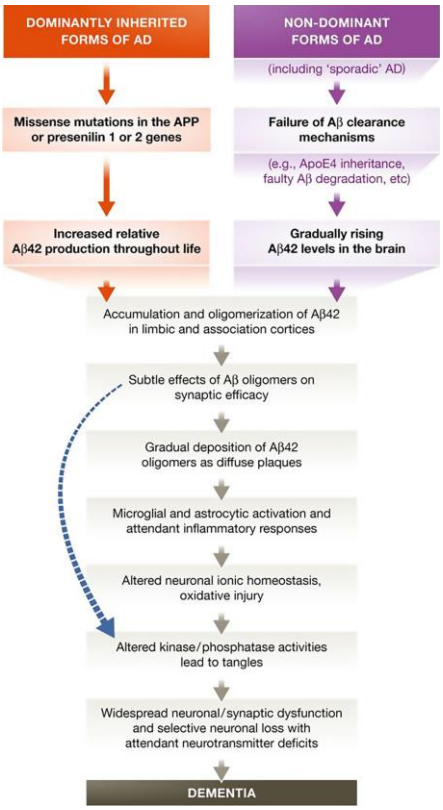


Figure 3 (A summary of the key pathogenic events that lead to Alzheimer's disease, as hypothesized by the amyloid hypothesis. The curved blue arrow suggests that Aβ oligomers can directly cause synaptic and neuritic damage, as well as trigger tau hyperphosphorylation and activate detrimental inflammatory pathways.) [119]

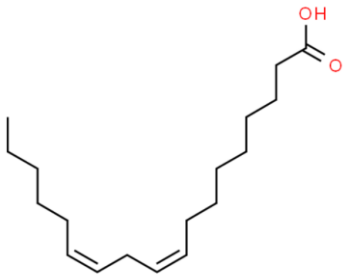
While fibrillar amyloid within dense-core plaques was thought to be important in the development of Alzheimer's disease, it is now thought that soluble A oligomers are the most pathological forms: oligomers purified from AD brains and applied to neurons in vitro inhibit long-term potentiation, cause synaptic dysfunction, damage dendritic spines, and cause neuronal death [133, 134]. Human oligomers also promote neurotic degeneration and hyperphosphorylation of tau at AD-relevant epitopes in cultured neurons [135]. Plaques may thus function as a'reservoir' from which amyloid oligomers disseminate, or as a protective mechanism, sequestering harmful Aβ series until they reach a physiological saturation point [136].

While Aβ accumulation is required for a diagnosis of AD, the fact that a considerable number of older people die with significant -amyloid deposition but no symptoms indicates that it is not sufficient for AD dementia. The Aβ soluble oligomer:plaque ratio may be smaller in people with asymptomatic amyloidosis than in patients with Alzheimer's disease dementia, lending credence to the idea that plaques operate as a protective reservoir [137]. Tau is undoubtedly an important component of the process that leads to AD, as indicated by the necessity for both Aβ and tau pathology for an AD diagnosis, as well as the strong relationship between neurodegeneration and tau burden. However, whereas tau gene mutations cause tau buildup and a range of neurodegenerative dementias on the frontotemporal dementia spectrum [138], unlike mutations in β-amyloid genes, tau mutations do not cause AD on their own [119].

With the development of biomarkers of Aβ and tau disease in cerebrospinal fluid (CSF) and positron-emission tomography (PET), various research have been conducted to investigate the evolution and interplay of these illnesses in vivo. Such research in both healthy older people and patients with sporadic Alzheimer's disease [139], as well as fAD [140]. give more evidence that amyloid pathology develops several years before clinical symptoms and predates changes in CSF tau and tau PET, which are thought to precede changes in magnetic resonance imaging (MRI) and, lastly, clinical symptoms [139]. These models, which have led to new criteria for AD as discussed below, continue to evolve as more data become available; and while there is considerable evidence that β-amyloid is upstream of tau pathology in AD, some healthy elderly individuals show evidence for tau pathology without -amyloid, which may be part of the normal aging process or reflect a non-AD neurodegenerative pathway [141]. The processes by which AD proteins target some parts of the brain but not others, as well as how they proliferate throughout the brain, are of great interest. It has been demonstrated that abnormally folded tau and Aβ can cause structurally normal peptides to undergo conformational changes, similar to what happens in prion disease. Trans-synaptic transmission of these is possible between neurons [142]. The location of the initial pathogenic event may then decide which cortical networks are impacted, explaining the phenotypic variation found in AD through differential network collapse [119].

While amyloid and tau pathology are undoubtedly important in the pathogenesis of AD, it is unknown how the two are related mechanistically. A number of lines of evidence imply that the innate immune system is important in the etiology of Alzheimer's disease and may offer this relationship. At postmortem, activated microglia co-localize with amyloid plaques [119]. A number of Alzheimer's disease risk genes, such as CR1, CD33, and TREM2, are implicated in immune system pathways [143, 144]. Clinical investigations utilizing PET ligands that bind to active microglia give additional in vivo evidence for the role of neuroinflammation in Alzheimer's disease [145, 146]. The topic of whether (or when) neuroinflammation is beneficial, harmful, or both may depend on illness stage and genotype, and yet to be completely resolved.

Lenoleic acid uses:



Structure of linoleic acid [147]

- **Neuroprotective and anti-inflammatory effects in Parkinson's disease:**

Parkinson's disease (PD) is a prevalent neurodegenerative ailment that is clinically characterized by resting tremor, stiffness, bradykinesia, and postural instability [148]. Dopaminergic neuronal loss, particularly in the Substantia nigra pars compacta (SNpc), and gliosis (pathological proliferation of reactive glial cells) are the two main characteristics of Parkinson's disease (PD) [149, 150]. Aside from the clinical motor characteristics, modest cognitive impairment, primarily executive dysfunction, with secondary visuospatial and memory problems, may be detected in the early stages of illness, these issues may eventually lead to dementia. [151]. The precise processes behind the enormous mortality of dopaminergic nigrostriatal neurons are unknown, but oxidative stress, inflammation, and mitochondrial malfunction may all play a significant role [148]. Furthermore, autophagic flux changes, proteostasis loss, and the link between the two changes all play important roles in the development of Parkinson's disease [152]. Lipid metabolism changes, particularly changes in lipid droplet dynamics, have recently been significant in Parkinson's disease pathogenesis. Modification of lipid metabolism has emerged as a potential treatment strategy for this condition [153, 154].

Lipid droplets (LDs) are cellular organelles composed of a neutral lipid core surrounded by a phospholipid monolayer containing several proteins from the perilipin family on their surface [155]. The primary constituents of these LDs are triacylglycerides, which are generated in the endoplasmic reticulum by a number of enzymes, including the diacylglyceroltransferases (DGAT) [156]. These LDs can be destroyed in two ways later on: lipolysis and lipophagy. Lipolysis is a sort of neutral degradation carried out by cytoplasmic enzymes. Lipophagy is the acidic destruction of LDs by autophagy, either micro- or macro-autophagy. The latter step begins with the formation of a phagophore that contains all or a portion of the LDs, giving rise to a lipoautophagosome. This lipoautophagosome unites with a lysosome to form the autolysosome, which degrades the LDs [157]. The link between Parkinson's disease and lipid metabolism (LD biogenesis and lipophagy) has received little attention. (Shimabukuro et al.) proposed that LDs and autophagy markers might accumulate in brain cells throughout the aging process [158]. Other researchers have shown that under stressful situations, neurons increase lipid synthesis and astrocytes increase LD accumulation, potentially due to a neuron-astrocyte connection involved in lipid metabolism [159, 160]. Surprisingly, a growing body of research suggests that LDs may act as a free radical sink[161-163]. As a result, it may have an antioxidant and protective function in the pathogenesis of Parkinson's disease. Several fatty acids, on the other hand (e.g., linoleic or oleic acid), influence LD levels via modulating autophagic flux and LD biogenesis [164, 165].

These data all point to the significance of LDs in the pathogeny of Parkinson's disease. Still, more research into the relationships between these processes is required. Hypothetically it can be said that the increased quantity of LDs operates as free radical scavengers. The increased lipophagy clearance might then operate as an antioxidant mechanism. By the experimentation done by (Alarcon-Gil, Sierra-Magro et al. 2022), in vitro and in vivo PD models were used to confirm the neuroprotective and anti-inflammatory effects of LA. LA seems to be an antioxidant, LD biogenesis stimulator, and lipophagy inducer. This unique method of action for LA opens the door to the creation of new therapeutics for Parkinson's disease [20].

Dementia in Parkinson's disease

Parkinson's disease (PD) is a slowly developing neurodegenerative disorder that is primarily characterized by the degeneration of dopaminergic neurons in the ventral tegmental area and the substantia nigra, along with varying losses of integrity in the central noradrenergic (locus coeruleus), cholinergic (nucleus basalis of Meynert), and serotonergic (dorsal raphe nuclei) systems. These abnormalities can cause a wide range of behavioral problems, both motor and non-motor [151]. Aside from the clinical motor characteristics, modest cognitive impairment, primarily executive dysfunction, with secondary visuospatial and memory problems, may be detected in the early stages of illness. From (Bosboom, Stoffers, and Wolters 2004) it was coming to know that around 20-40% of patients, with these issues may progress to dementia, which is a significant risk factor for caregiver distress, poor quality of life, and nursing facility placement. Progressive dysexecutive syndrome, attentional impairments, fluctuating cognition, and psychotic symptoms are common characteristics of dementia in Parkinson's disease (PD-D). It is believed that a mix of cortical and subcortical alterations led to it [151].

Moerover, there are four categories comprise the recommended clinical diagnostic criteria for PD-D, which are rooted in core findings, linked clinical aspects, symptoms that cast doubt on the diagnosis, and features incompatible with a PD-D diagnosis. Probable PD-D is identified when all four criteria are satisfied in a satisfactory manner; potential PD-D is identified when clinical features are abnormal or there are unresolved uncertainties. These definitions are based on generally accessible testing, even though they are operational and open to modification in light of new information. The inclusion criteria can be used in multicenter, worldwide investigations of cognitive and other nonmotor aspects of Parkinson's disease (PD), clinicopathological correlations, and therapy interventions [166].

Dementia in Alzheimer's disease

(Miller (1973)) provided the demonstration that people with Alzheimer's disease suffer from both short-term memory impairment and problems forming new material in long-term storage. These findings are explored in particular in connection to the hypothesis that, because the pathological alterations in Alzheimer's disease are most visible in the hippocampal area, involvement of the hippocampus may explain the memory problem[167].

Alzheimer's disease is usually regarded as a cause of presenile dementia, whereas so-called "senile dementia" (Age 65+) was formerly overlooked by both the general public and medical practitioners, but it is now known that AD affects individuals of all ages [168].

Conclusion

On the basis of the rational from different source it is clear that the main chemical constituents present in the seed of Pinus gerardiana Wallichex are effective neuroprotective and can be used for the management/ prevention of neurological disease/ Cognitive disorder like Alzheimer's disease and Parkinson's disease. Along with that it is also came to know that Parkinson's disease and Alzheimer's disease can either lead/ cause or increase the severity of Dementia in their own respective pathways/ ways. So, it can be hypothesized that consumption of Chilgoza (Pinus gerardiana Wallichex seed) can be helpful in the prevention and either in the prevention of neurodegenrative disorders as Dementia, Parkinson's disease, Alzheimer's disease etc. it is concluded that further studies needed to done on various scales to understand the mechanism of action of pinus gerardiana wallichex seed.

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