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Memory Enhancing Activity of Ginger (*Zingiber officinale*), Its Treatments in Dementia and Alzheimers Disease

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ABSTRACT

As people live longer, they are becoming more susceptible to age-related ailments. Dementia patients throughout the world are crying out for better treatments, but the ones currently on the market do not meet those demands. Natural compounds, which have been used in traditional medicine due to their good effects and high tolerance, have recently grabbed the attention of the scientific community. Ginger (Zingiber officinale) has been shown to have anti-and anti-anti-vascular Alzheimer's dementia properties, two of the most common and devastating dementias. On Alzheimer's disease and vascular dementia models and in some human trials, ginger compounds were found to be therapeutic. These studies all point to a role for Ginger in both the treatment and prevention of this illness. Most people with Alzheimer's (AD) notice a decline in their cognitive abilities, although it is a neurological condition that affects the elderly in particular.Amyloid-beta buildup and tau hyperphosphorylation, as well as a lack of neurotransmitter balance, as well as cell death and inflammation, all contribute to the development of this disease. Finding new Alzheimer's disease medicines that can also alleviate side effects and pharmacokinetic difficulties is a desirable goal. Phytochemicals, which have been widely used by humans, can be used to fight a wide variety of ailments. Zingiber officinale, Gingeroids, Shogaoids, and Bornols were examined for memory problems. – Following the initial screening process, clinical trials are conducted in vitro. Intervening mechanisms like oxidative stress and apoptosis are among the most frequently addressed ones. A new study has linked Alzheimer's disease pathogenesis to signalling pathways. In vivo studies and clinical trials aid in the clarification of test findings and results scores in the area of cognitive functioning. Many conventional aspects of ginger intake in AD also appear in the current review. Ginger and its constituents' pharmacological and therapeutic properties will need to be studied in more depth in order to help treat and prevent memory problems.

Keywords- Zingiber officinale, Alzheimer's disease, Degenerative disease, Dementia, Neuroprotective.

I. INTRODUCTION

Dementia is a condition marked by an age-related deterioration in cognitive abilities and a loss of one's sense of self-determination. As a general rule, dementia is marked by memory loss, problem-solving impairment, and language difficulties, as well as a considerable decrease in mental processes [1]. An estimated 50 million individuals worldwide suffer from dementia, and that number is expected to grow by 82 million by 2030 and by 152 million by 2050. A new instance of dementia is diagnosed every three seconds, according to the Global Dementia Observatory Reference Guide. For the diagnosis of dementia or "major neurocognitive disorder" (DSM-5), there must be severe cognitive impairment in at least one of the following: memory, attention, language, motor programming, perception of objects, space-time perception, and executive functioning[2]. Neurodegeneration is the most common cause of dementia among the elderly. Alzheimer's disease (AD), Lewy body dementia (LBD), vascular dementia (VD), frontotemporal lobar degeneration (FTLD), and parkinson's disease (PD) are the most frequent types of degenerative dementia. Because of their non-neurodegenerative nature and the fact that they can be reversed with treatment, a category of dementias is worth mentioning. Non-neurodegenerative dementia with mild cognitive impairment can be induced by vitamin deficiencies, hypothyroidism, normal pressure hydrocephalus, persistent alcohol misuse, chemotherapy, infections, intracranial formations, traumatic brain injury, and mental illness [3]. Behavioral and psychological symptoms, such as aggressiveness, agitation, and depression, are common in people with dementia [4-6]. Degenerative neurodegenerative disease Alzheimer's disease (AD) results in a profound decline in both memory and cognitive function. Synapse loss, neurofibrillary tangles (NFTs), senile plaques, and neuronal dysfunction are all symptoms of Alzheimer's disease (AD). When the amyloid protein (A) aggregates, it causes neuronal damage. Damage to cholinergic function, glutamate-mediated excitotoxicity, oxidative stress, and inflammatory responses are some of the other suggested pathways. After the age of 60, it is expected that the frequency of dementia doubles every ten years [7]. Several investigations have shown that ginger has a wide range of pharmacological properties. 6-gingerol has mostly been linked to gastroprotective,

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immunomodulatory, anti-allergy, and hepatoprotective actions. Ginger also contains antioxidant, anticarcinogenic, antihyperglycemic, neuroprotective, and antiemetic properties [8].

For centuries, ginger (Zingiber officinalis Roscoe) has been used as a spice and a medicinal herb. Ginger root can help ease or treat a number of common symptoms, such as a cold or a headache. Ginger includes phenolic and terpene compounds, as well as other bioactive components. In order to understand the wide range of bioactivities of ginger, we can look to the phenolic compounds found in gingerols and shogaols. Ginger has recently been found to have antioxidant, anti-inflammatory, antibacterial, and anticancer effects[9]. Many disorders, including Alzheimer's, cardiovascular disease, and obesity as well as chemotherapy-induced nausea and emetic have been demonstrated to benefit from ginger's antioxidant properties.

II. PHYTOCHEMICAL PROPERTIES OF ZINGIBER OFFICINALE

More than 400 types of ginger compounds, including carbohydrate and lipids as well as the elements of terpenes, have been found in studies. Ginger's chemical components can be split into two categories: pungent and aromatic. An aromatic compound that is pungent in nature is pinene; aromatic compounds that are more flavorful include camphene and cumene, borneol and bisabolene, and zingiberol [10].

Essential oils are usually the place to find ginger's biologically active components. Studies reveal that whether ginger rhizomes are fresh or dried, heat treatment or variations in drying processes alter the efficiency of the essential oil and the structure of its chemical components [11]. Ginger oil made from dried rhizomes, for example, has a higher concentration of chemical components than fresh ginger oil. Fresh ginger rhizomes are believed to contain the most active elements, gingerols, although dried ginger rhizomes contain more shogaols [12]. The rhizomes of ginger can be used for a variety of purposes. As a vegetable, fresh ginger is most commonly consumed. Only immature rhizomes can be used to preserve ginger in syrup or brine. Most of it is shipped out to other countries. The mature rhizome of dried ginger is used as a spice. The flavour and perfume of the rhizomes become more pronounced as they age. Direct spice is a kind of dried ginger. Ginger oil and oleoresin are produced from dried ginger [13].

Ginger's essential oil is mostly composed of monoterpene hydrocarbons, oxygenated monoterpenes, and sesquiterpene hydrocarbons produced by steam distillation (1–2.5 percent). Zingerone, shogaols, and gingerols impart ginger's distinct flavour. Sesquiterpenoids are the primary constituents of ginger's essential oil, with -zingiberene accounting for 30–70 percent of the total, and a smaller percentage of sesquiterpenoids such as -sesquiphellandrene, -bisabolene, and -farnesene. Ginger glycolipids and diterpenes are also present. Gingerol [14] is the most pungent of the gingerols. -gingerol is an oily liquid that is found in the fresh rhizome and is the most prevalent component in the rhizome. Shogaols, which are nonvolatile phenylpropanoid-derived chemicals from gingerols, are responsible for the pungency of dried or cooked ginger. One other unpleasant ingredient is zingerone, a spicy-sweet scent that develops during the drying process. Acrid resinous compounds (5–8 percent) are also present in ginger [15]. Fresh ginger has 80.9 percent water, 12.3 percent carbs, 2.3 percent protein, 0.9 percent fat, 2.4 percent fibre, and 1.2 percent minerals in its nutrient profile. In addition to minerals such as iron, calcium, and phosphorus, the ginger rhizome is also rich in vitamins including niacin, thiamine, and riboflavin.

III. PHARMACOKINETICS AND BIOAVAILABILITY

To have an effect on the body, dietary gingerols that have been consumed must be present in the blood and tissues. Compound distribution to different tissues is affected by numerous mechanisms, including solubility and potential breakdown in digestive fluid and enterocyte membrane permeability; permeability of enterocyte membrane; protein efflux; and/or pre-systemic gut and/or hepatic metabolism [16].

Due to ginger's weak bioavailability, its nutritional and therapeutic utility in nutraceuticals or fortified food products is limited. As lipid-soluble chemicals, gingerols and their derivatives are expected to be well absorbed by diffusion across the intestinal epithelium. Because of the low solubility of their chemical structure, they must first reach the brush boundary cells before they can be absorbed. However, before this can occur, they must be solubilized in an aqueous solution. For example, the concept Bioaccesibility is related to this phenomenon because it describes the amount of ingested nutrients that are available for absorption, which is different from the concept Bioavailability that represents a step forward in terms of how much ingested nutrients reach the general circulation and specific sites where they can have an effect. A compound's ability to have an effect on the body is first limited by its bioaccessibility[17-19].

Gingerols, unlike flavonoids and other glycosylated substances, are not degraded by intestinal brush boundary glycosidase enzymes, unlike flavonoids. There's a downside to this, though, as P-glycoprotein substrates gingerols. The outer membranes of enterocytes in the small intestine, as well as in the liver, brain, and kidney, are strongly abundant in this protein. In many cases, it serves as a major barrier to drug absorption in the digestive tract [20].

In the liver, gingerols undergo "first-pass effect" metabolism after absorption via the hepatic portal vein. Due to the fact that they have exceptionally short half-lives and are subject to Phase II conjugative processes, such as glucuronidation and sulphation, they are more likely to be excreted from the bile or the kidneys. Gingerol conjugation is carried out by UGT1A1, 1A3, and 2B7 isoforms [21].

Additionally, biliary excretion and intestinal reabsorption result in enterohepatic circulation of these substances. In the small intestine, 6-gingerol glucuronide diffuses from the liver into the bile, where it is excreted. Enterocytes in the gut hydrolyze it, allowing it to enter the bloodstream once again. All of these occurrences are linked to a longer plasma half-life and a longer duration of action (Figure 1).

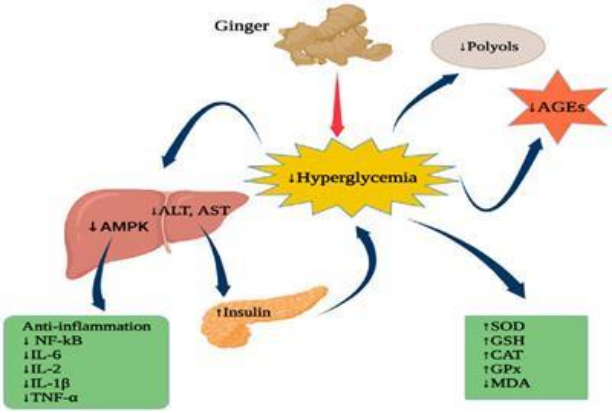

Figure 1: Bioavailability of Ginger

Biological properties of Zingiber officinale

Perennial herb Zingiber officinale is a member of the Zingiberaceae family, and its thick tuberous rhizomes are much sought after in therapeutic applications. There is a reference to this plant in the ancient Sanskrit literature. It is also frequently mentioned in ancient Buddhist, Arabic, Greek, and Roman texts for its medicinal properties. For this reason, it is known as "Singabera" in Sanskrit, and as "Zingiber" in Latin because of the resemblance of its roots to antlers on a deer [22]. Ginger officinale is a spice and flavouring agent that may be found all over the world, as well as a medical ingredient. No one knows for sure where it came from, although it's most likely from India or Southeast Asia. It is grown in China, the West Indies, Mexico, and other nations for commercial purposes.In traditional Chinese medicine, Ayurvedic, and Unani-Tibb treatment systems, ginger was used to treat a wide range of ailments, including dyspepsia, constipation, indigestion, nausea, catarrh, diabetes, nervous system disorders, gingivitis toothache, sore throats, fever, sprain, and muscular aches, infectious diseases, helminthiasis, and strokes. Because of its digestive stimulant and carminative effects, it was particularly valuable [23].

To cure infantile colic, ginger is combined with milk or water in the Ayurvedic system; ginger combined with honey is used for asthmatic bronchitis, cough, other respiratory illnesses, and hiccups.

Digestive issues can be alleviated by using ginger in Western medicine. Ginger is a common ingredient in Greek bread and is often taken as a digestive aid. Aphrodisiac and sexual stimulant benefits of ginger, as well as blood cleansing capabilities, anti-nausea, anti-vomiting, and appetiser effects [24] are other traditional applications of ginger.

A variety of ailments can be relieved with fresh ginger, including colds, nausea, rheumatic conditions like gout and rheumatism, as well as respiratory ailments like asthma and bronchitis. Cough and asthma sufferers in India used a 19th-century remedy that combined fresh garlic juice with honey and fresh ginger juice. Headaches were eased with the use of powdered dry ginger. Cure for coughs in India are ginger juice and honey [25], according to modern health professionals.

As part of the Yin-Yang theory, Ginger is supposed to counteract the negative effects of Yin while also providing the body with essential nutrients. Ginger, sometimes referred to as "hot character" in Chinese medicine, is believed to treat the body as a whole as well as cold extremities. Additionally, it has been shown to enhance a weak pulse and bolster the body following blood loss. In addition, the plant's anti-heart disease properties have been touted. Ginger's antiemetic properties have long been recognised in Chinese and Iranian medicine [26]. It has also been used traditionally in Iran to improve male sexuality, control the menstrual cycle and soothe women's painful period.

Several investigations in vitro and in vivo have shown ginger to have antioxidant properties. It also has anti-inflammatory and apoptotic properties. As a result, in vitro testing has shown that ginger components replicate the pharmacological features and side effects of dual-acting non-steroidal anti-inflammatory medications (NSAIDs). The prostaglandin-suppressing properties of gingerols are well-known. The molecular pathways involved in chronic inflammation can be modulated by ginger and some of its components, which decrease cytokine synthesis and release. Inflammation response genes, cytokines, chemokines, and COX-inducing enzymes are all inhibited by them[27]. It also inhibits the expression of beta-amyloid peptides generated by chemokines and cytokines. Ginger has been proven to be anti-inflammatory, anti-nociceptive, and anti-fever in preclinical investigations. In preclinical trials, it has also been shown to lower serum levels of prostaglandin E2. Furthermore, 6-gingerol and its metabolites suppress iNOS and macrophage expression.

Ginger and its bioactive components have been the subject of extensive research in recent years. It has been established that 6-gingerol has anti-inflammatory, analgesic, and antipyretic activities, making it the most bioactive component in ginger. A number of

physiological events, including cholesterol and glucose levels, blood pressure, blood coagulation, body temperature, gastrointestinal tract function and intracellular calcium concentration have been demonstrated to have significant effects on the body [28].

Ginger essential oil has been shown in many studies to raise liver levels of SOD, GPx, and GST. To counteract the damaging effects of free radicals, ginger essential oil can boost antioxidant enzyme activity in cells [29]. Antioxidants, such as ginger extract, can help treat oxidative stress-related conditions. Many phenolic chemicals, including gingerols and sogaols, have been found to relieve pain and to protect neurons from the damaging effects of ageing and memory loss [30].

Studies in the last few years have indicated that lipid peroxidation of neurons' cell membranes is a significant factor in the development of neurodegenerative illnesses like Alzheimer's [31]. Ginger root extracts contain polyphenols, secondary metabolites with significant antioxidant activity. Dietary antioxidants counteract reactive oxygen species (ROS), which are responsible for DNA damage, heart disease, and other age-related health issues [32]. Because of its anti-inflammatory and analgesic properties, IBS is viewed as an effective therapeutic approach for colic or muscular pain, and plant essential oil is utilised in the treatment of gastrointestinal system diseases. Antimicrobial properties of ginger make it an efficient treatment for bacterial illnesses. Ginger essential oils have been shown to have antibacterial properties against Gram-positive bacteria, but not Gram-negative bacteria, in tests. Ginger volatile oil contains many antibacterial compounds, including -zingiberene, -curcumene, -farnesene, -bisabolene, -sesquiphellandrene, and geranial. Despite this, Shigella flexneri, Salmonella typhimurium, and Escherichia coli were found to be resistant to the essential oil of ginger [33].

Ginger has been shown to reduce the risk of cardiovascular disease and diabetes by controlling the body weight and lowering serum glucose and cholesterol levels. As a result of ginger's anti-diabetic effects in diabetic rats' serum, glucose, triglycerides, free fatty acids, LDL and VLDL levels were dramatically lowered, while high-density lipoprotein (HDL) levels increased (HDL). Zingerone and shogaols are less responsible for this impact.

IV. ANTI-INFLAMMATORY ACTIVITY

Ginger and its active ingredients have been shown to have anti-inflammatory properties, which could protect against inflammation-related disorders such as colitis. PI3K, Akt, and the nuclear factor kappa light chain-enhancer of activated B cells (NF-B) were found to have the most anti-inflammatory effects. The protective benefits of 6-shogaol against TNF—induced intestinal barrier disruption in human intestinal cell cultures were also demonstrated. By inhibiting PI3K/Akt and NF-B signalling pathways, it also blocked Claudin-2 overexpression and Claudin-1 disassembly [34]. Dehydroshogaol was more effective than 6-shogaol in lowering the synthesis of proinflammatory mediators such as nitric oxide (NO) and prostaglandin E2 (PGE2) in murine macrophage RAW 264.7 cells. Zingerone and ginger extract also suppressed NF-B activation and reduced IL-1 levels in the colons of mice, alleviating the colitis caused by 2, 4, 6-trinitrobenzene sulfonic acid. Ginger has also been shown to protect mice against enteritis caused by anti-CD3 antibodies, and ginger can lower the generation of TNF- and the activation of Akt and NF-B [35]. Nanoparticle-derived ginger (GDNPs 2) might also decrease intestinal inflammation by boosting the levels of anti-inflammatory cytokines such as interleukin-10 (IL-10) and IL-22, while decreasing the levels of proinflammatory cytokines such as TNF- and IL-6 in mice with acute colitis [36]. Colitis symptoms were reduced and wound healing was improved in mice with dextran sulphate sodium-induced colitis when 6-shogaol nanoparticles were administered. Ginger exosome-like nanoparticle microRNAs (GELN) also improved mice colitis by increasing the production of IL-22, an anti-inflammatory cytokine. In addition, rats treated with chlorpyrifos had their inflammatory markers such as myeloperoxidase, NO, and TNF- reduced by a fraction rich in 6-gingerol [37]. In addition, 28 male endurance runners took ginger powder capsules of 500 mg. A number of cytokines that cause inflammation, including plasma IL-1, IL-6, and TNF- were shown to be reduced by the therapy.

Antioxidant properties

Ginger's antioxidant activity remains strong even after alcohol extraction, making it an excellent antioxidant supplement to include in your diet. Ethanol and methanol extracts have been shown in experiments to have higher levels of anti-free radical and anti-oxidant action than water-based extracts. A previous study demonstrated that ginger extract had superior DPPH radical scavenging and FRAP activity versus turmeric extract[38]. While ginger extract has less antioxidant activity than kesum extract, the reverse is true for ginger flavonoids. At 60 degrees Celsius, another study found 10-gingerol and 6-shogaol to be more potent antioxidants than 6-gingerol and 8-gegerol. These antioxidant effects were predicted due to the active compound's hydroxyl groups and solubilizing side chains. A study by Yusof and Abdul-Aziz discovered that ginger extract had the same ability to eliminate free radicals (superoxide radicals and hydrogen peroxide) from cancer cell lines as superoxide dismutase (SOD) and other antioxidant proteins like glutathione peroxide and catalase (CAT). In a hepatoma cell line, ginger extract at a concentration of 200–500 g/ml decreased the activity of SOD, GPx, and CAT[39]. For diabetics, ginger has been found to ease insulin resistance by enhancing glucose transport activity and improving

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blood sugar tolerance. Another study found that ginger can assist persons with type 2 diabetes lower their cholesterol, blood glucose, and triacylglycerol. The effects of ginger on blood sugar, cholesterol, and triglycerides have been studied in diabetic rats[40].

Ginger and Alzheimer's disease

Many ailments of the nervous system can be helped using ginger's therapeutic capabilities, including brain tumours and stroke, as well as neurological conditions such as neurosis and depression. According to the Food and Drug Administration (FDA), ginger is "Generally Recognized as Safe" (GRAS). If you're suffering from Alzheimer's or any other neurological disease, ginger is an excellent supplement[41]. The absence of adverse effects from therapeutic amounts of ginger, combined with the herb's multiple health benefits, makes it an intriguing candidate for treatment of neurodegenerative illnesses and memory problems. Zingiber officinale roots have been used in traditional Persian medicine to treat memory loss and Alzheimer's disease (AD). TPM polyherbal preparations included ginger and other medicinal plants [43,44]. A research of traditional oriental medicines (TOMs) confirmed ZO's ability to treat AD [45]. According to the application of ginger in traditional Chinese medicine (TCM), ginger with presence of antioxidant and anti-inflammatory characteristics may feasibly be effective in AD [42]. Antioxidant effect, anti-amyloidogenic potential, cholinesterase inhibition, and neuroprotective qualities are only some of ZO's many uses in Unani medicine. An Ayurvedic investigation found that ZO had a nootropic effect [43]. Also, the traditional usage of Z. officinale in dementia treatment in South Asia supports this therapeutic potential (Lim et al., 2014b) (Lim et al., 2014b). The plant's methods of action and the active compounds that give it these properties have been the focus of research. Many research, both in vivo and in vitro, have been carried out to this end. Due to the retrieved data in this study, alteration and amelioration were noticed in animal and human cognition tests. Regarding animals; MWM, Y-Maze, Foraging Maze, T-Maze, EPM, 8-arm Radical Maze, Rotarod test, NORT, and PAT were explored [44]. MMSE-J, ADAS-cog, CDR-SOB, and RBANS-J scores have all been examined in human investigations [45]. Neuronal growth factor (NGF) has been shown to play a role in medicinal plants' memory-enhancing properties, according to a number of studies (NGF). Memory improvement, hippocampus long-term potentiation (LTP) simplicity, and neurite outgrowth excursion have all been facilitated by NGF (Lim et al., 2014b). When tested on middle-aged women, ginger was given orally and its use was shown to improve scores for digit vigilance, word recognition, choice reaction, spatial working memory and arithmetic working memory [46]. An additional research in mice showed that ginger treatment improved memory function by increasing hippocampal NGF levels, which in turn activated extracellular signal-regulated kinases (ERK) and chronologically cAMP response element-binding protein (CREB), resulting in increased synaptogenesis [47]. In the early stages of dementia, ginger has been shown to be able to regain cognitive function. By controlling A plaque-induced neuronal cell death and memory deficits, narcotics-induced memory dysfunction, ACh dependency, and pathological changes, plant metabolites improve cognitive function [48]. The development of neurotoxicity and synaptic toxicity by A oligomers is relevant to the pathogenesis of Alzheimer's disease. Ginger inhibits the expression of pro-inflammatory cytokines and chemokines in human monocytic THP-1 cells, which protects against LPS, A, and cytokine neurotoxicity. As a consequence, ginger strongly suppressed LPS, TNF-, IL-1, COX-2, MIP-1, MCP-1, and IP-10 mRNA expression and levels [49]. After the MWM and PAT behavioural studies, ginger was found to lessen escape latency and improve step-through latency, distance taken to identify the platform, crossing platform timings, and spatial memory capacities in a study of A-induced AD in mice Additional findings include anti-inflammatory, anti-oxidant, and anti-aggregation of A characteristics[50]. Corticosterone-induced stress damage in primary hippocampal neurons (PHN) cells and in vivo was reduced by ginger in a complex. Caveolin-1, GR, BDNF, TrkB, and FKBP4 mRNA and protein expression levels have increased [51]. Lipid peroxidation, the quantity and duration of escape latency, and oxidised protein concentrations in rat brain homogenates were all reduced by the addition of ginger in a complex. Ginger oil and extract dramatically enhanced the levels of AchE, NF-kB, caspase3, and p53 in the brains of AD rats, according to Ahmed et al. In rats, Ghayur et al. found that dried ginger has Ca2+ antagonist, muscarinic, and BuChE inhibitory activities, demonstrating the herb's potential in Alzheimer's disease (AD) through the potency of 6-gingerol [52]. Ginger methanolic extract was studied by Ali et al. to see if it may lower AChE and COX-1 levels. DPPH free radical scavenging activity of ginger has also been shown to support its antioxidative effects. Six-shogaol and eight-shogaol have been shown to reduce AchE activity, while 6-gingerol, methoxy-6-gingerol, methoxy-10-gingerol, and diacetoxy-6-gingerol have shown good antioxidant properties [53]. Cleaved caspase-1, NLRP-3, interleukin-1, interleukin-8, and pyroptotic cell death were all reduced by ginger exosome-like nanoparticles in the study by Chen et al. By decreasing AChE and improving cognitive activities in fish, ginger and its nanoparticles added to fish feed improved fish Cyprinus carpio cognition [54]. Methanolic extracts of ginger and n-hexane, as well as EtOAc, have all demonstrated their ability to ablate -secretase. Using the A1-42 plaque-induced AD mouse model, ginger fermented with Schizosaccharomyces pombe has been examined. Ginger components have been made more bioavailable through fermentation. In the Y-Maze and NORT cognition-

related trials, ginger reduced the amount of time spent exploring the novel object and the percentage of spontaneous changes. SYN expression in the CA3 area has also increased, as has PSD95 expression [55]. SOD and CAT, as well as the inflammatory markers NF-B and IL-1, can be increased in the presence of ginger in order to attenuate A1–40 plaque-induced behavioural impairment and neuronal cell death. In rats with A25-35-induced AD, treatment with ginger in a complex resulted in an increase in memory deficits. Amyloid plaques and MDA, NO and AChEbuildup were also relieved. BDNF, SOD, GSH, CAT, NE, DA, 5-HT, and CAT levels have all been increased as well. PC12 cells have increased cell proliferation and viability as well as MMP and decreased ATP levels when treated with 6-Gingerol, a Nrf2 activator [56]. Zeng et al. tested the effects of 6-gingerol on A1–42-treated PC12 cells to see if it may improve cognitive performance. 6-gingerol has been shown to boost cell survival, SOD levels, Akt activation, and GSK-3 expression. Additionally, 6-gingerol lowered the synthesis of ROS and other reactive oxygen species (ROS), as well as the production of NO, LDH, and MDA [57]. Administration of 6-gingerol in scopolamine-induced amnesia in C57BL/6 mice repaired memory deficits. BDNF expression, stimulation of the Akt-CREB signalling pathway, and p-CREB rise were important improvements. In C6 cells, 6-gingerol reduced IL-6, TNF-, NO, and NOS2 protein expression, as well as IL-6, TNF-, and NO production. 6-gingerol also prevented ROS production in C6 cells figure 2. A drop in EL and an increase in TSTQ were seen in the behavioural trials. With the abrogation of the MAPK/NF-B pathway, Zingerone was able to reduce oxidative stress and age-related inflammation. In order to protect SH-SY5Y cells against A, Hur et al. found that borneol reduced ROS generation, increased nuclear Nrf2 expression, and increased Bcl2 expression [58]. Ginger pharmacopuncture was studied by Jittiwat et al. to see if it may help with oxidative stress and cognitive decline caused by cerebral ischemia. When administered to C57BL/6 mice using the 6-shogaol HFSD paradigm, behavioural abnormalities were reversed. Pal et al. reported that ginger acetone extract improved spatial working memory and long-term working memory in scopolamine-rats [59]. 6 shogaol has been shown to have anti-neuroinflammatory actions by reducing glial cell activation and the production of pro-inflammatory molecule in both LPS-treated astrocytes and animal models of diverse pathological conditions. This compound also greatly inhibited A1–42-induced microglial and astrocyte activation. 6-Shogaol therapy also increased brain NGF and synaptic molecule expression considerably. It appears that 6-shogaol may lessen AD-related cognitive problems by reducing inflammatory reactions, positively modulating NGF levels, and improving synaptic genesis. BDNF (brain-derived neurotrophic factor) and neural cell protection have also been shown to be linked to ginger consumption [60]. 6-Shogaol was found to be a potent inhibitor of IL-1 excretion mediated by the canonical NLRP3 inflammasome by Ho et al. In H2O2-treated HT22 cells, 6-Shogaol decreased ROS production and increased ChAT, ChTp, and BDNF RNA and protein [61]. APP/PS1 and HT22 cells treated with 6-shogaol showed increased SORL1 and decreased BACE, APP, and A in brain slices, as demonstrated by Na et al. Shogaol-huprine hybrids have been linked to a decrease in AChE, BuChE, A42, tau aggregation, and free radical scavenging capacities [62]. Focus on Alzheimer's disease (AD) has shown ZO's key function in the amelioration of cognitive and memory deficits.

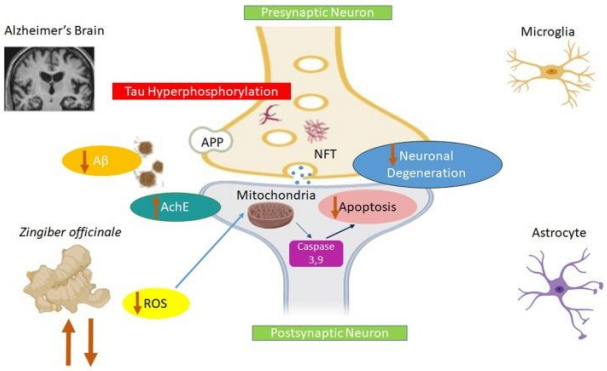

Figure 2: Zingiber officinale role in Alzheimers disease and cognitive impairments

Vascular Dementia

VD is second only to Alzheimer's disease as the most common kind of dementia. The term "Mild Cognitive Impairment" (MCI) has been coined to describe patients who have mild to moderate signs of Alzheimer's disease (AD) but have not yet reached the stage of dementia [63]. Vascular mild cognitive impairment (VaMCI) is a group of patients with cognitive deficits following cerebrovascular illness. For the most part, Vascular Cognitive Impairment (VCI) is a broad term for all of the diseases in which there is evidence of cognitive impairment after vascular brain injury. As a result, it is vital to note that VD and AD are not two independent illnesses, but rather, the BBB breakdown plays an important role in the most common forms of dementia [64]. The vascular system has long been recognised as an important component in the onset of dementia [65] since dementias were once thought to be caused by the "hardening of arteries." The BBB, a complex combination of endothelial cells, pericytes, and astrocytes, protects the brain against the entry of undesired molecules, substances, or creatures, is an important characteristic of the brain vascular system. More specifically, only ions and infections and toxins have access to the brain. Drug distribution is hampered because water-soluble compounds cannot traverse the BBB [66]. At various levels, the barrier's effectiveness is

guaranteed. Endothelial cell adhesions impede the movement of molecules between the interstitial space of the brain and the blood flow. Considering that the brain requires 20% of the body's total blood supply, it's no wonder that any vascular system malfunction might have serious repercussions, including cognitive impairment. Some basic generalisations can be drawn, even though it is difficult to pinpoint exactly how each illness contributes to VD. Even if this condition is reversible, the decreased blood supply to the brain region has a significant impact on the onset of dementia since it is associated with decreased brain activity and cognitive performance [67]. Due to the lack of oxygen and glucose, neuronal death occurs when blood flow is disrupted for an extended period of time. This situation cannot be reversed. It is also important to note that neurovascular dysfunction is linked to oxidative stress and inflammation. Because free radicals activate pro-inflammatory transcription factors and inflammation weaken cell antioxidant defences, the two are directly linked and mutually reinforcing. Oxidative stress causes endothelial cells to release prostanoid and growth factors for vascular leakage. These two factors are also implicated in the death of BBB cells, which inhibits the regeneration of injured white matter [68]. When the blood-brain barrier is disrupted, not only are blood cells and pathogens allowed to get into the brain but they can also get into the brains of people with intact BBBs [69]. While we work to slow its progression, there are no effective treatments for vascular dementia as of yet. To help cure VD, it is possible to employ phytocompounds like ginger on their own or in combination with other substances.

V. EFFECTS OF GINGER IN VD STUDIES

Ginger has been found to have neuroprotective properties in several trials, suggesting that it could be used to treat vascular dementia. As of now, there are no viable treatments for Alzheimer's disease in patients with metabolic syndrome (MetS). To this end, it is imperative that ischemic stroke patients in the MetS receive treatment that can slow the onset of dementia and memory loss. Mulberry fruit and ginger (PMG) encapsulated in a phytosome were examined by Wattanathorn et al. [70] in an in vivo experimental model of MetS. Male Wistar rats were fed a high-fat, high-carb diet for 16 weeks to induce MetS. The right middle cerebral artery (Rt. MCAO) was occluded using nylon to isolate the right external and internal carotid arteries and simulate an ischemic injury. PMG was administered orally to rats both before and after surgery. Researchers studied the levels of AChE, MDA, neuron density, SOD and glutathione peroxidase (GPx) in the cerebral cortex and hippocampus, as well as the possible underlying mechanisms of signal transduction via the ERK pathway, because inflammation and oxidative stress are linked to cognitive deficits. Taking PMG enhanced cognitive impairments and neuronal density in the cerebral cortex and hippocampus, according to the data[71]. The activity of AChE, MDA, and the expression level of IL-6 were also lowered by PMG administration, as well as SOD, catalase (CAT), GPx, and ERK phosphorylation in the cortex and hippocampus. By lowering the level of AChE, PMG may be able to ameliorate memory deficiencies by promoting ERK phosphorylation, which in turn can reduce inflammation. PMG, on the other hand, increases ACh availability and ERK activation by lowering AChE levels, regulating inflammation, and thereby relieving cognitive impairments fig 3. Neuroprotective benefits of PMG in MetS male Wistar rats fed a high-fat and carbohydrate diet were also explored by Palachai et al. [72]. After that, rats were subjected to ischemic brain injury and reperfusion by Rt. MCAO. PMG was delivered orally to test the neuroprotective effects of PMG on memory impairments. This study found that ischemia damage increased oxidative stress and inflammation in the brain, which in turn impaired ATPase pumps, particularly Na+ and K+, ATPase generates brain edoema and influences neurological impairments, as it did in the prior one.. Inflammation and oxidative stress were reduced by PMG delivery, as seen by lower levels of NF-B, TNF, and MDA. PPAR (Peroxisome proliferator-activated receptor) is upregulated in response to the therapy, as is the activity of SOD, CAT, and GPx. It is true that PPAR expression influences both oxidative stress and inflammation[73]. In this line, PPAR agonists have been demonstrated to decrease oxidative stress and inflammation, which could play a neuroprotective role against cerebral ischemia. There is a good chance that PMG could protect against brain injury and MCAO in MetS circumstances, according to the study data. Neuroprotective effects of Ginger were demonstrated in rats with localised cerebral ischemia by Wattanathorn et al. [74]. Before and after generating the Rt. MCAO model, ginger rhizome was fed orally to male Wistar rats in order to examine the impact on cognitive function. It was discovered through the Morris Water Maze test that ginger rhizome extract increased cognitive performance and decreased oxidative stress. Further studies have demonstrated that ginger can decrease the size of cerebral infarctions and increase the number of neurons in the brain. By boosting neuronal density in the hippocampus, enhancing spatial memory, and decreasing the extent of infarction in the cerebral cortex, ginger exerted its neuroprotective effects[75]. Ginger may be able to counter focal cerebral ischemia, but additional research is needed. The neuroprotective effects of Houshiheisan, a herbal blend composed by chrysanthemun flower, divaricate saposhnikovia root, Manchurian wild ginger, cassia twig, Szechwan lovage rhizome, platycodon root, ginseng, Chinese angelica, large-head atractylodes rhizome, Indian bread, and zingiber and used as classic prescription for stroke in

traditional Chinese medicine, were evaluated by Wang et al. [76] in a rat model of focal cerebral ischemia. The animals were gavaged with Houshiheisan both before and after surgery. Treating ischemia penumbras with Houshiheisan decreased damage to this critical region between the undamaged and damaged regions. To further enhance neurovascular unit stability and reduce injury, Houshiheisan therapy protected neurovascular units from aberrant A deposition. As a result, Houshiheisan may be effective in protecting neurovascular units following cerebral ischemia, according to the findings of the study. Gaire et al. [77] investigated 6-paradol's neuroprotective effects on focal cerebral ischemia and inflammation in vivo and in vitro. The substance with the strongest anti-inflammatory effect was 6-paradol, which was chosen from a group of five paradol derivatives, including 2-, 4-, 6-, 8-, and 10-paradol. There must be ways to minimise the neuroinflammatory responses of activated microglia, since this is one pathogenic feature of cerebral ischemia. After reperfusion, Gaire et al. [78] given 6-paradol orally into MCAO/reperfusion (M/R) mice, who were then studied for the effects of the drug. Results from the in vivo study suggest that 6-paradol reduces brain damage, improves neurological impairments, and also improves the lifespan of neurons. In addition, 6-paradol inhibited microglial activation by reducing TNF- and iNOS levels in the studied microglia. When LPS (100 ng/mL) was added to murine microglial BV-2 cells, it was found to reduce neuroinflammation, as seen by the lowering of iNOS and proinflammatory cytokines IL-6 and TNF-a [79-80].

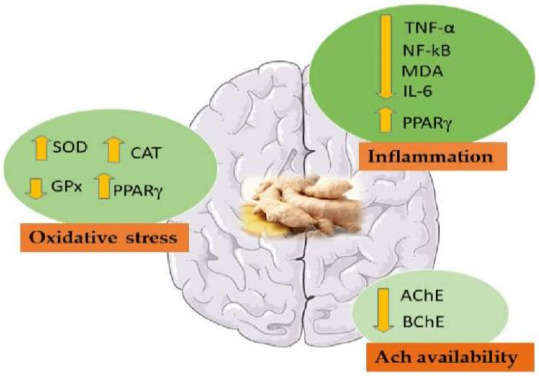

Figure 3: Effect of Ginger in Vascular Dementia

VI. CONCLUSIONS

The beneficial compounds found in ginger include gingerols and shogaols, among others. As an anti-inflammatory and anti-apoptosis agent in addition to being an antioxidant, ginger has a wide range of health benefits. Even more so, ginger has the possibility of being employed as a nutraceutical in order to combat Alzheimer's disease and other cognitive and memory problems. Indeed, clinical investigations using ginger and its various bioactive components in vitro can demonstrate its efficiency in preventing or reversing memory loss. There has been a resurgence in the scientific community's interest in natural substances in recent decades, as people seek alternatives to manufactured medications for reasons of safety and effectiveness. As a promising treatment for dementia, ginger has also shown promise as a preventative measure. Several studies have revealed ginger's ability to slow the progression of dementia in all of its stages, from neurodegeneration to neuroinflammation, while simultaneously maintaining the survival of neurons. A cure for advanced stages of dementia may never be found, but greater research into ginger's therapeutic characteristics and improvements to its dosage, administration route, and timing could provide solid support for existing treatments. Functional foods and nutraceuticals, as well as ginger's potential role in a wide range of health issues, include cancer prevention, cardiovascular disease management and prevention as well as nausea and vomiting management and prevention. Further research on the biological effects of ginger's bioactive chemicals and the methods by which they work is needed in the future. Ginger and its many bioactive components should be tested in clinical trials to prove their usefulness against these disorders in humans.

Functional foods and nutraceuticals, as well as ginger's potential role in a wide range of health issues, include cancer prevention, cardiovascular disease management and prevention as well as nausea and vomiting management and prevention. Biological activities and mechanisms of action associated to further ginger bioactive substances should be studied in the future. The efficacy of ginger and its numerous bioactive components against these disorders in humans must be demonstrated in carefully conducted clinical trials.

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