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A review on memory enhancing activity of ginger

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Abstract--Age-related ailments are on the rise as people live longer. Worldwide, there is an increasing need for dementia drugs, however the current medications do not meet those needs. Natural compounds, used in ancient medicine for their advantages and tolerance, have recently attracted scientific study. This analysis examines ginger's anti- and anti-vascular dementia (*Zingiber officinale*) properties, two of the most common and devastating dementias. Clinical trials on Alzheimer's and Vascular Dementia models have indicated therapeutic advantages from ginger compounds. This research reveals that ginger's components may help treat and prevent the disease. Alzheimer's disease is a neurological disorder that primarily affects the elderly and causes cognitive failure. Various cellular problems such as amyloid-beta buildup, hyperphosphorylation of tau protein, neurotransmitter imbalance, apoptosis, oxidative stress, and inflammatory reactions cause this disease. New Alzheimer's medicines should be able to tackle additional ailments, such as side effects and pharmacokinetic difficulties. Phytochemicals are powerful anti-disease agents that are widely used in humans. In vitro trials are included after eligibility screening. The most frequent interventive processes are oxidative stress and apoptosis. A recent study links Alzheimer's pathology with signalling pathways. In vivo studies and clinical trials assist clarify cognitive test results. Several classic AD ginger eating aspects are also explored in this review. More research is needed to analyse ginger's

pharmacological and therapeutic properties to improve and cure memory dysfunctions.

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

1. Introduction

Ginger (*Zingiber officinale* Roscoe) is a spice and medicinal herb from the Zingiberaceae family and genus. Ginger root can help heal common symptoms like a cold or a headache⁽¹⁾. Ginger includes phenolic and terpene compounds, among others. The gingerols and shogaols are phenolic compounds that are responsible for the bioactivities of ginger. Ginger has recently been found to have antioxidant, anti-inflammatory, antibacterial, and anticancer properties⁽²⁾. Ginger has been demonstrated to help prevent and treat diseases like Alzheimer's, heart disease, and obesity, as well as chemotherapy-induced nausea and emetic. Its bioactive components and bioactivities, as well as its mechanisms of action, are reviewed⁽³⁾. As seen in Figure 1, the active components of ginger are cyclic.

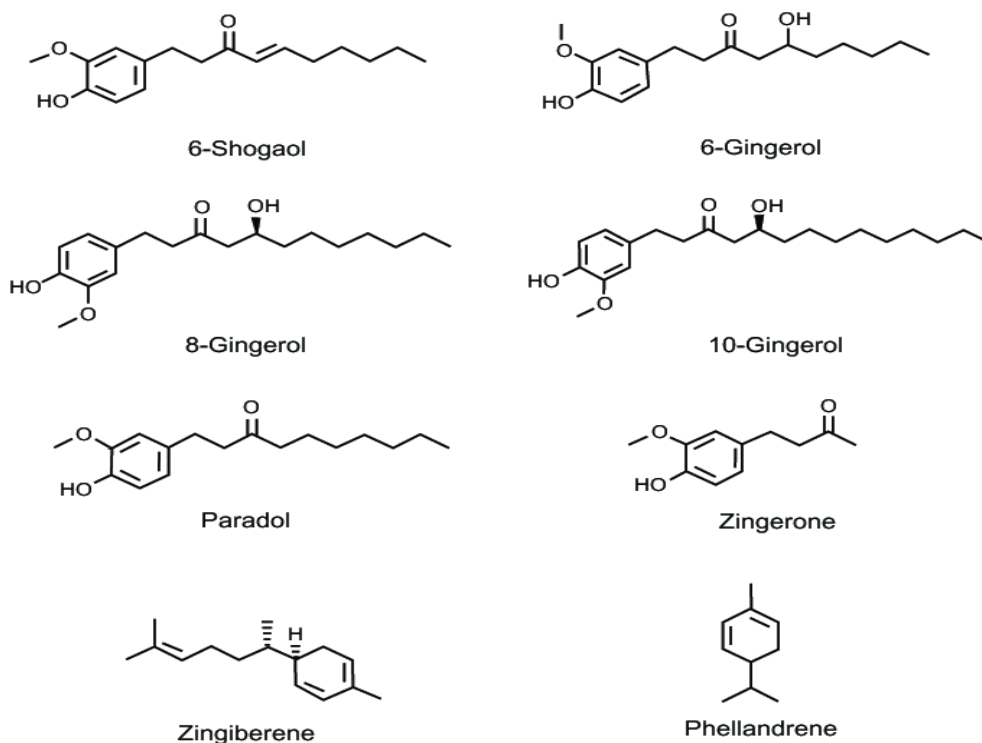


Fig. 1: Chemical structure of ginger, *zingiber officinale* roscoe

Ginger's bioactive components and compounds have been shown to have antibacterial, anticancer, anti-inflammatory, anti-diabetic, and gastroprotective properties⁽⁴⁾.

1.1 Antibacterial Properties

An earlier study found ginger extract to be antibacterial against Gram-positive bacteria such *Staphylococcus aureus* and *Streptococcus pyogenes*. Further testing revealed antibacterial activity of ethanolic ginger extract against *Escherichia coli* and *Salmonella typhi*. Ginger also had antibacterial effects against *Enterococcus faecalis*. Ginger oil outperformed *Orthosiphon stamineus* extract in preventing *E. faecalis* suspension adhesion⁽⁵⁾. A new study confirms ginger's antibacterial properties. Ginger effectively reduced *Pseudomonas aeruginosa*, a bacteria that can form biofilms in the human body. An ethanol extract of ginger root outperformed an ethanol extract of ginger leaf and a water extract of ginger root in antibacterial activity. Ginger extract's antibacterial activity is dose and extraction technique dependent⁽⁶⁻⁷⁾.

1.2 Antioxidant Properties

Ginger has strong antioxidant activity following alcohol extraction, making it a good antioxidant supplement. ethanol and methanol extracts had stronger anti-free radical and antioxidant activity than water-based extracts⁽⁸⁻¹⁰⁾. In a previous study, ginger outperformed turmeric extract in scavenging DPPH radicals and FRAP activity. Ginger extract, however, is less antioxidant than kesum extract⁽¹¹⁾. Another study found 10-gingerol and 6-shogaol to be more antioxidant than 6-gingerol and 8-gingerol at 60°C. The antioxidant properties of the active molecule were predicted⁽¹²⁾. Yusof and Abdul-Aziz observed that ginger extract had the same ability to eliminate free radicals (superoxide radicals and hydrogen peroxide) from cancer cell lines as SOD and other antioxidant proteins including glutathione peroxide and catalase (CAT). Ginger extract inhibited SOD, GPx, and CAT activity in a hepatoma cell line⁽¹³⁻¹⁴⁾. Sugar transport activity and glucose tolerance are both improved by ginger, aside from its antioxidant properties. Another study found that ginger reduces blood sugar, cholesterol, and triacylglycerol in persons with type 2 diabetes. Ginger decreases urine protein levels and lowers blood sugar, cholesterol, and triglycerides in diabetic rats⁽¹⁵⁾.

1.3 Anti-Inflammatory Properties

To reduce TNF and IL-1 production, COX-2 inhibitors diminish COX-2 activity, and ginger has been found to be anti-inflammatory⁽¹⁶⁾. Another study found that ginger reduces TNF and hs-CRP in diabetics. Ginger extract combined with antituberculosis therapy can lower TNF-, lipid peroxidation, and MDA levels in tuberculosis patients⁽¹⁷⁾.

1.4 Neuroprotective Properties

Polyphenolic compounds in ginger, which change neurotransmitter levels and limit the development of 8-hydroxy-2'-deoxyguanosine and amyloid (8-OHdg) and so reduce the neurotoxic effects of MSG, have been proven to be neuroprotective⁽¹⁸⁾. This study indicated that ginger benefited the brain's histological characteristics, citing its antioxidant properties. Ginger has been found to protect diabetic brains by reducing oxidative stress, inflammation, and apoptosis⁽¹⁹⁾. Ginger also reduced Ach expression, controlled astroglial injury response, and aided neurogenesis. In

another study, ginger lowered MDA levels and increased the brain's oxidative defence mechanism in diabetic rats. SOD, CAT, and GPx activities were elevated, indicating increased brain oxidant defense⁽²⁰⁻²³⁾.

1.5 Anticancer Properties

In animal investigations, 6-gingerol and 6-shogaol have been shown to reduce COX-2 expression, suppress NF-DNA binding, and increase BAX expression, indicating anticancer potential⁽²⁴⁾. Apoptosis and Bcl-2 reduction require ginger's capacity to inhibit oval cell development and caspase-8 synthesis. In another trial, ginger extract improved 5-FU's anti-colorectal cancer effects. Compared to 5-FU alone, ginger extract therapy increased apoptosis. Ginger extract and honey Gelam increased 5-FU's antitumor activity⁽²⁵⁾.

2. Ginger in the prevention and treatment of degenerative disease

Ginger has also been shown to prevent and treat degenerative diseases. Ginger's antioxidant and anti-acetylcholinesterase activities were examined in Alzheimer's patients⁽²⁶⁾. The ability of ginger extract to scavenge free radicals in the DPPH experiment confirmed its antioxidant and anti-acetyl cholinesterase activities. When ginger extract is introduced to a solution, α -amyloid inhibits butyrylcholinesterase and promotes cell viability. 6-gingerol reduces the expression of α -amyloid, which is activated by ROS and nitrogen species, increases antioxidant enzyme expression, and restores glutathione. However, gingerol, contained in ginger, increased learning and memory in an Alzheimer's rat model and reduced oxidative stress and inflammation⁽²⁷⁾. This study found that high doses of ginger extract increased Nissl bodies and neurons, activated SOD and CAT, and decreased MDA, NF-B, and IL-1 levels. Another study found ginger to be effective in preventing and treating Alzheimer's disease in rats. It boosted T-maze test results, and lowered acetylcholinesterase activity in AD rats given 108 or 216 mg/kg ginger⁽²⁸⁾. Histological evidence shows that ginger consumption reduced amyloid plaques in AD animals.

Six-shogaol decreased astrogliosis and microgliosis in the brains of Parkinson's disease mice and enhanced NGF and synaptic molecule expression. The active component in ginger may lower inflammation, NGF levels, and synaptic growth in Alzheimer's disease (AD), according to this study⁽²⁹⁾. It rescued dopaminergic neurons from MPTP and MPP⁺-induced degeneration in an in vitro and vivo PD model. The substantia nigra pars compacta and stratum corneum protect dopaminergic neurons from oxidative stress by inhibiting iNOS and TNF-. Another investigation came to the same conclusion⁽³⁰⁾.

Ginger has antioxidant and anti-diabetic effects, such as α -amylase inhibitory capabilities. α -amylase degrades complex dietary saccharides into oligosaccharides and disaccharides before glucosidase converts them to monosaccharides. Overexpression of these two enzymes can induce hyperglycemia. An earlier study found ginger to be antihypercholesteraemic in rats fed a high-cholesterol diet. Antihypercholesteraemic ginger's ability to inhibit ACE. Taking ginger pills for eight weeks reduced insulin levels and resistance while increasing triglycerides and low-density lipoproteins (LDL)⁽³¹⁾. Ginger may reduce insulin, TG, and LDL-C

levels in diabetics. In a second trial, ginger lowered TG and total cholesterol in diabetics but had no effect on LDL or HDL levels⁽³²⁾. Ginger increases hepatic cholesterol hydroxylase enzyme activity, which is required for cholesterol to bile acid conversion. Another study found that taking 3 g of ginger every day for three months reduced blood glucose, insulin resistance, MDA and CRP levels while increasing antioxidant capacity and paraoxonase 1 levels (PON-1). TAC showed that ginger can reduce oxidative stress and lipid peroxidation⁽³³⁾.

Ginger extract is also used to treat and prevent rheumatoid and osteoarthritic arthritis. Activating the LX pathway and increasing the iNOS2/cyclooxygenase-2 (COX-2) pathway can increase TNF and IL levels, whereas consuming one gramme of ginger per day reduced TNF and IL levels in a human osteoarthritis study⁽³⁴⁾. Another study found that consuming ginger pills for three months reduced NO and hs-CRP levels in osteoarthritis patients. This could be explained by an increase in the body's inflammatory response and decreased nitric oxide synthase activation. Inflammation, stiffness, discomfort, and difficulty in daily activities are all reduced by ginger's anti-inflammatory qualities. The VAS was used to quantify the decrease in discomfort⁽³⁵⁾.

Ginger extract has been shown to protect against cardiovascular diseases such coronary atherosclerosis and hypertension. A prior study found that ginger extract reduced infarct size in coronary atherosclerosis rabbits. Atherosclerotic vascular disease rabbits exhibited decreased total serum cholesterol⁽³⁶⁾. Ginger extract prevented the production of atherosclerotic plaques in rats. This discovery was connected to a decrease in plasma LDL cholesterol, atherogenic changes in LDL, and macrophage oxidative response. This study confirmed earlier findings that ginger extract can reduce atherosclerotic artery lesions, reverse inflammatory cytokine expression, and improve lipid profile in rats with atherosclerosis. Ginger crude extract has been found to relax endothelium-dependent pig coronary arteries. Ginger extract is vasoprotective in coronary arteries by reducing cyclooxygenase and nitric oxide synthase⁽³⁷⁾.

Table 1: Effects of ginger on degenerative disease

Related disease	Constituent	Effects
Alzheimer's disease	Ginger root extract	Showed antioxidant and antiacetyl cholinesterase activity, Inhibitory effects towards butyrylcholinesterase, Increased cell survival following β -amyloid expression.
	6-Gingerol	Suppressed the expression of β -amyloid, Increased the expression of antioxidant enzyme, Restored glutathione level.
Parkinson's disease	6-Shogaol	Protected dopaminergic neurons against MPTP- and MPP + induced neurotoxicity
	6-Shogaol	Inhibited the release of NO and the expression of inducible nitric oxide synthase

Type 2 diabetes mellitus	Ginger extract	Exhibited strong antioxidant activities
Cardiovascular disease	Ginger extract	Induced the relaxation of coronary arteries, Increased Vaso protection through the suppression of the cyclooxygenase pathway and nitric oxide synthetase

3. Alzheimer's Disease

Alzheimer's disease has two forms: sporadic late-onset (SAD) and familial early-onset (FAD), with SAD being the more common. Aging, gene abnormalities such as APOE 4 and PSEN 1, and risk factors including obesity and hypertension can all contribute to the disease⁽³⁸⁾. Alzheimer's disease is caused by oxidative stress, apoptosis, and inflammation. Senile plaques are made up of fibrillary A, and NFTs are made up of hyperphosphorylated Tau protein. Secretase abnormally proteolyzes the transmembrane protein APP, a component of brain homeostasis, yielding A peptides⁽³⁹⁾. A-peptide aggregates can impair neuroinflammation, apoptosis, and synaptic plasticity, leading to brain deterioration. Tau's phosphorylation and dephosphorylation balance regulates axonal transit and microtubule stabilisation. A putative relationship between tau hyperphosphorylation, GSK-3 activity, and A aggregates shows that the two basic hallmarks of Alzheimer's disease are linked⁽⁴⁰⁾.

A new study suggests that obesity may be one of the risk factors for dementia. Hyperinsulinism and obesity-related insulin resistance may impair the brain's ability to eliminate amyloid beta, raising the risk of dementia and Alzheimer's⁽⁴¹⁾. Obesity causes proteins and hormones that promote inflammation in brain tissue, pointing to insulin resistance as a contributor to brain abnormalities in Alzheimer's patients. Memory and learning areas of the brain have high levels of insulin, which is thought to be necessary for cognitive function maintenance. Because GSK3- and A peptide share a degradation enzyme with insulin, NFTs and A plaques are more prone to develop. Diabetes patients and obese people are more prone to dementia and cognitive impairment⁽⁴²⁻⁴³⁾.

Given the lack of approved dementia medications, natural compounds like ginger may be beneficial in treating Alzheimer's disease. Study after study has proved the benefits of ginger and its components⁽⁴⁴⁾. One of the key constituents, gingerols, has long been known to have pharmacological properties similar to non-steroidal anti-inflammatory medicines (NSAIDs). Thus, ginger reduces inflammation by inhibiting enzymes implicated in inflammation, such as COX-2 and 5-lipoxygenase (5-LOX), which produce leukotrienes (LTs)⁽⁴⁵⁻⁴⁶⁾.

3.1 Effects of ginger in alzheimer disease

Several studies have demonstrated that ginger and its components have anti-amyloidogenic, anti-cholinesterase, and neuroprotective properties. Only a few drugs are now approved to treat Alzheimer's. So researchers are turning to multi-target medicines to lessen side effects while improving therapeutic potential⁽⁴⁷⁾.

Many studies have been done on ginger and its components in the development of new Alzheimer's treatments.

4. Computational Studies

Researchers utilised molecular docking to examine the interactions of 12 ginger compounds with other molecules to see if they may be used to treat Alzheimer's disease⁽⁴⁸⁾. Several ginger compounds, including gingerol, shogaol, and zingerone, have been shown to interact with multiple molecular targets. The study identified TNF-converting enzyme, AChE and BChE, NOS, COX-1 and COX-2, c-jun N-terminal kinase, and N-methyl-D-aspartate as prospective targets or enzymes (NMDA). AChE is the most potential molecular target, while JNK is the least promising. In tests, BChE, TACE, COX-2, NOS, and NMDA were identified as the most likely targets for ginger bioactive chemicals⁽⁴⁹⁻⁵¹⁾.

Comparing ginger extracts to donepezil, an AChE inhibitor used to treat Alzheimer's disease, revealed that some active components block AChE. Mol1 and Mol2 are natural AChE inhibitors with similar efficacy to donepezil⁽⁵²⁾. Ginger chemicals have been shown to reduce AChE activity in the choline binding pocket (Trp86). Trp86 had hydrophobic interactions with all ginger compounds tested. Glu202 must be avoided at all costs when creating AChE inhibitors. Also, donepezil was compared to ginger components' effects on BChE. In particular, they discovered (E)-1.7 bis (4 hydroxy 3-methoxyphenyl) hept-4 en-3-one and (5 hydroxy 3-methoxyphenyl) hept-4 en-1 (2S,4R,6R) 4-[2-(4-methoxyphenyl)] oxan-2-yl] BChE inhibitors such -3-methoxybenzene-1,2-diol (G3) may help. Ginger compound binding to Trp82 and Tyr332 residues also limits BChE activity. BChE inhibitors must also avoid repulsive interactions with Glu197.

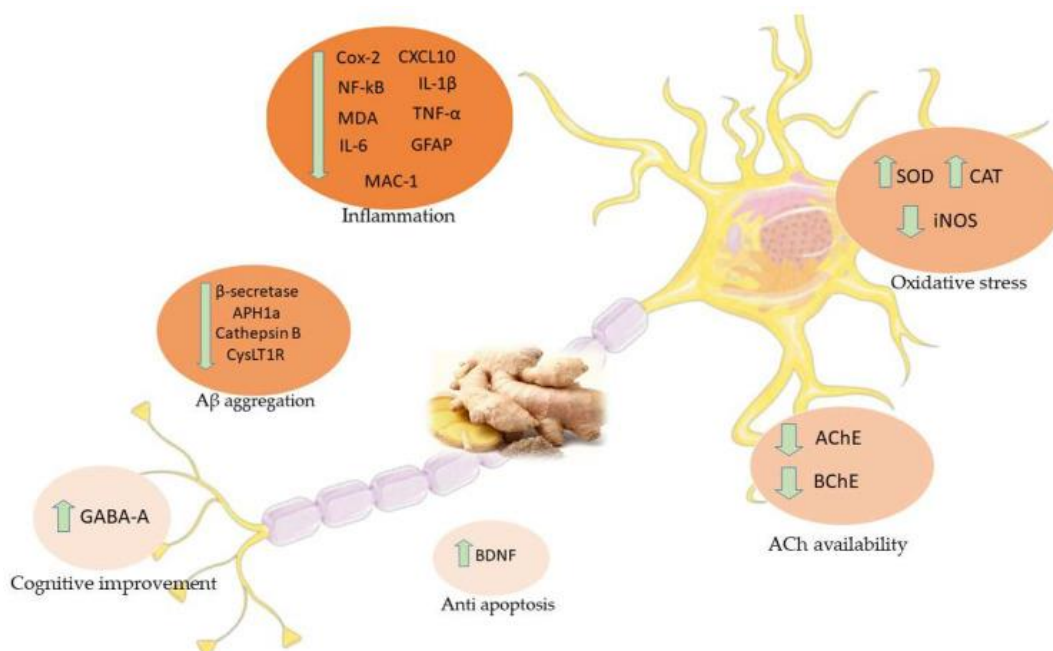


Fig. 2: Ginger impacts in alzheimer disease studies

5. Effects of ginger in vascular diseases

Several studies have revealed ginger's neuroprotective benefits as a potential VD therapy. Dementia caused by cerebral ischemia in metabolic syndrome is common and currently untreatable. Thus, decreasing dementia and memory problems caused by ischemic stroke in the MetS is required⁽⁵³⁾.

Phytosomes containing mulberry fruit and ginger (PMG) were studied in an *in vivo* MetS model. Male Wistar rats were fed a high-fat, high-carb diet for 16 weeks. The ischemic injury was mimicked by occluding the right middle cerebral artery (Rt. MCAO) using nylon. PMG was given to rats before and after surgery. AChE, MDA, neuronal density, SOD and glutathione peroxidase (GPx) levels in the cerebral cortex and hippocampus were investigated, as well as the possible underlying processes of signal transduction via the ERK pathway. The results demonstrated that PMG reduced cognitive impairments and neuronal density in the cortex and hippocampus. The PMG therapy also reduced AChE, MDA, and IL-6 expression while increasing SOD, CAT, GPx, and ERK phosphorylation in the cortex and hippocampus. PMG may help memory loss by lowering AChE levels, which in turn boosts ERK phosphorylation and reduces inflammation⁽⁵⁴⁾. PMG increases ACh availability and stimulates ERK by lowering AChE levels, regulating inflammation, and so alleviating cognitive impairments.

Also studied PMG's neuroprotective effects in MetS male Wistar rats fed a high-fat, high-carb diet. Rt. MCAO was used to cause ischemia damage/reperfusion in rats. Oral PMG was given to test its neuroprotective effect on memory impairments. ATPase pumps, especially Na⁺ and K⁺, cause brain edoema and influence neurological impairments. PMG reduced inflammation and oxidative stress as measured by NF-B, TNF, and MDA⁽⁵⁵⁾. The therapy also increases SOD, CAT, and GPx activities, as well as PPAR expression. PPAR expression can affect oxidative stress and inflammation. In this line, PPAR agonists have been demonstrated to protect against cerebral ischemia by reducing oxidative stress and inflammation. Overall, the study found that PMG may help protect against brain injury and MCAO in MetS patients.

Its neuroprotective effects on focal cerebral ischemia and inflammation have been examined *in vivo* and *in vitro* Among 5 paradol derivatives, 2-, 4-, 6-, 8-, and 10-paradol was chosen as the most anti-inflammatory. Because neuroinflammation caused by activated microglia is a pathogenic feature of cerebral ischemia, it is critical to identify effective therapeutic techniques to minimise neuroinflammation. MCAO/reperfusion (M/R) animals were given 6-paradol orally shortly after reperfusion. Acute 6-paradol treatment reduced brain injury, enhanced motor and sensory function, and increased neuronal survival *in vivo*. Furthermore, 6-paradol decreased microglial activation by reducing TNF and iNOS. The decrease of iNOS and proinflammatory cytokines IL-6 and TNF was seen in murine microglial BV-2 cells pretreated with 6-paradol and activated with LPS (100 ng/mL) for 24 hours.

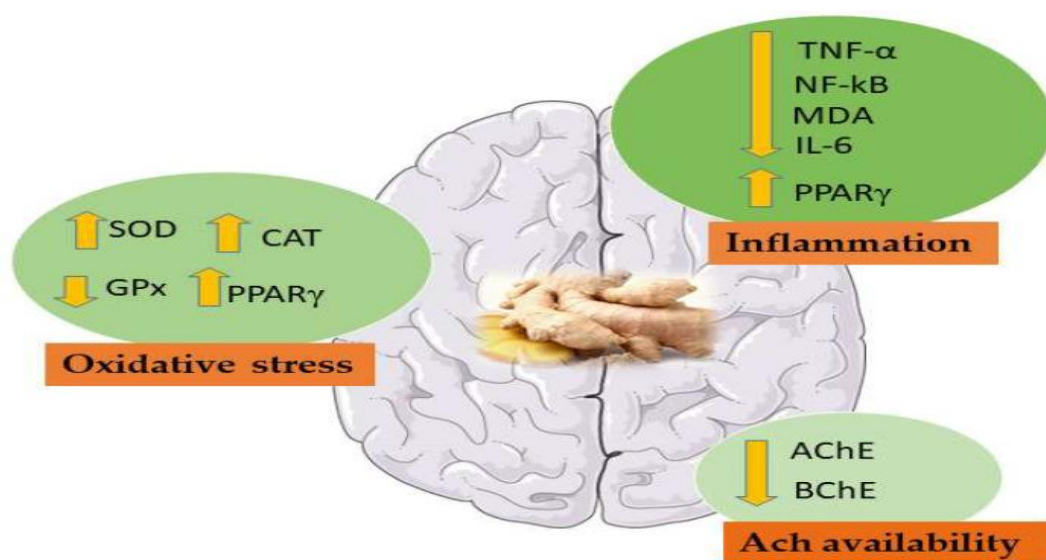


Fig. 3: Ginger effects in vascular diseases studies

Conclusion

Finally, ginger includes bioactive compounds including gingerols and shogaols. Ginger has antioxidant, anti-inflammatory, and anti-apoptotic properties. Ginger may also be used as a nutraceutical to prevent diseases like Alzheimer's, cognitive decline, and memory loss. Interestingly, *in vitro* studies of ginger and its bioactive components show promise in preventing memory loss. Natural substances have gained popularity in recent decades, as scientists seek to prevent or improve the adverse effects of synthetic medications. Ginger has shown promise in the treatment and prevention of dementia. Several studies revealed ginger's ability to slow the progression of dementia, from neurodegeneration to neuroinflammation, while boosting neuron survival. Even if ginger is not yet a treatment for severe dementia, further research may reveal more therapeutic characteristics, and improvement of dosage, method, and timing of administration may assist current therapy. Ginger may also be used to treat or prevent diseases such as cancer, cardiovascular disease, diabetes, obesity, neurodegenerative diseases, nausea, emesis, and respiratory ailments. More bioactive chemicals in ginger could be extracted and identified in the future, and their biological effects and related mechanisms of action studied. Human efficacy against these disorders requires well-designed clinical trials of ginger and its numerous bioactive components.

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