Original Article

Volatile Alkaloids And Brain Disorder Investigation Of The Cognitive And Mood Effects Of Zingiber Officinale Essential Oil With In Vitro Properties Relevant To Central Nervous System Function

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Abstract

As the human life expectancy increases, age-linked diseases have become more and more frequent. The worldwide increment of dementia cases demands medical solutions, but the current available drugs do not meet all the expectations. Recently the attention of the scientific community was attracted by natural compounds, used in ancient medicine, known for their beneficial effects and high tolerability. All these evidences suggest a potential role of the compounds of ginger not only in the treatment of the disease, but also in its prevention.. Ginger (Zingiber officinale Roscoe) is a common and widely used spice. It is rich in various chemical constituents, including phenolic compounds, terpenes, polysaccharides, lipids, organic acids, and raw fibers. The health benefits of ginger are mainly attributed to its phenolic compounds, such as gingerols and shogaols. This review is focused on Ginger (Zingiber officinale) and explore its properties against Alzheimer Disease and Vascular Dementia, two of the most common and devastating forms of dementia. This work resumes the beneficial effects of Ginger compounds, tested in computational in vitro and in vivo models of Alzheimer's Disease and Vascular Dementia, along with some human tests.

Keywords: Ginger, Neuro disease, Phytochemical, Antioxidant

Introduction

Alzheimer's disease (AD) is characterised by a gradual deterioration in cognitive abilities, including memory loss and amnesia. This condition is brought on by the buildup of amyloid plaques and tangled fibres in the brain (memory loss). Due to the limited and inefficient treatment options available, Alzheimer's disease (AD) is regarded to be the most frequent form of neurodegeneration. The majority of cases of AD are observed in persons who are 65 years of age or older. Significant symptoms of Alzheimer's disease include amnesia (memory loss), aphasia (expressive aphasia is the inability to find the right words, whereas receptive aphasia demonstrates an inability to understand), apraxia (loss of motor function), and agnosia. These symptoms can be better understood and diagnosed if their underlying pathophysiology is better understood (loss of functioning of 5 senses). Acetylcholinesterase inhibitors (AChEIs), N-methyl-D-aspartate (NMDA) receptor antagonists, Selegiline (used to treat Parkinson's disease), oestrogen therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and other medications have all been approved for the treatment of Alzheimer's disease by the Food and Drug Administration (FDA) (Non-Steroids Anti-Inflammatory Drugs). Alzheimer's disease (AD), sometimes known as Alzheimer's, is a neurological ailment that is characterised by memory loss and cognitive impairment. This disease is severe regardless of whether or not the specific cause for the death of cholinergic neurons in particular parts of the brain is ever discovered. The present treatment for Alzheimer's disease seeks to slow the progression of the condition in patients by increasing their levels of acetylcholine, which is a chemical messenger that plays an important role in both memory and judgement. In light of the potentially hazardous side effects of these drugs, researchers have started looking into botanicals and dietary supplements in their pursuit of discovering fresh approaches to halt or halt the progression of Alzheimer's disease (AD). Ginger, also known scientifically as Zingiber officinale, is a well-known plant species that has its origins in Asia and is a part of the family Zingiberaceae. It is grown in a wide variety of tropical countries, including India, China, Australia, Brazil, Jamaica, and numerous states in the United States. In traditional Chinese medicine, ginger's fresh rhizomes are used to treat colds, headaches, vomiting, and flatulence, while the dried rhizomes are used to treat stomach aches, lumbago, diarrhoea, and memory improvement. Ginger has been shown to be one of the most effective therapeutic herbs. It has been shown to be effective as an antiemetic (for motion sickness), an antioxidant, an anti-inflammatory, an anti-bacterial, an anti-tussive, an anti-hepatotoxic, an anti-mutagenic, a diuretic, a spasmolytic, and an immunological stimulant. Both ginger methanolic extract (GME) and ginger essential oil (GEO) were put through a series of tests to determine whether or not they had the ability to improve learning and memory in an in-vivo rat model of Alzheimer's disease and to reduce the amount of acetyl cholinesterase (AChE) activity in both the laboratory and in the wild. Both of these abilities were found to be present. In addition, the antioxidant capabilities of these components and the compounds that were isolated from them were investigated. Alzheimer's disease (AD) is a neurodegenerative disorder that is characterised by the gradual degradation of hippocampal and cortical neurons. This gradual degradation results in an impairment of memory and cognitive capacity and is one of the most economically costly diseases to society. The first visible symptom of dementia is a decline in short-term memory; long-term memory retention and recall, on the other hand, seem to hold up pretty well. As the disease advances, people lose the capacity to accomplish tasks like compute and operate ordinary household objects and equipment. One of the pathological characteristics of Alzheimer's disease is senile plaques, which are spherical accumulations of the protein ß-amyloid. Neurofibrillary tangles, which are made up of connected helical filaments and other proteins, are another pathological hallmark of Alzheimer's disease. This is consistent with the clinical picture of severely diminished memory and abstract reasoning alongside preserved eyesight and motor function.

The specific insufficiency of acetylcholine in Alzheimer's disease served as the impetus for the development of the "cholinergic theory," which postulates that a lack of acetylcholine is essential in the development of the symptoms of Alzheimer's disease. As a result, one of the key focuses of Alzheimer's disease treatment has been on boosting the activity of cholinergic receptors in the brain. For this reason, acetyl cholinesterase inhibitors such as tacrine, donepezil, rivastigmine, and galantamine are utilised. According to a number of hypotheses, inflammation plays a crucial role in

the progression of Alzheimer's disease (AD). In addition to this, research has demonstrated a correlation between increased levels of reactive oxygen species (ROS) and the progression of Alzheimer's disease.

The pharmacological and therapeutic characteristics of medicinal plants, which have been used for a long time for the treatment of a variety of human maladies, have been traced to a wide diversity of chemical compounds recovered from the crude extracts of the medicinal plants themselves. Plants contain significant quantities of chemical compounds that have antioxidant activity. It is possible that these chemicals are responsible for the preventive effects of plants against a wide variety of degenerative diseases, such as cancer, neurological disorders, and cardiovascular disease. Therefore, the antioxidant capacities of plants offer a wide variety of applications that could be used in human treatment.

Ginger is included on the permissible ingredient list that can be found in the document named "Generally Recognized as Safe" (GRAS) that is published by the FDA (FDA). It is possible to consider ginger to be a hypolipidemic factor due to the fact that ginger extract reduces the risk of atherosclerosis in mice that were fed a diet high in cholesterol. Ginger also performs exceptionally well in the process of platelet aggregation. Because it has a high concentration of the polyphenolic component gingerol, it possesses anti-oxidative properties and has the ability to scavenge both superoxide anion and hydroxyl radicals. Ginger possesses anti-inflammatory properties in addition to gingerols and diarylhepatanoids, which prevent the synthesis of prostaglandin and leukotriene, respectively.

This research was conducted with the intention of determining whether or not an aqueous infusion of ginger (Zingiber officinale) is effective in the prevention and treatment of Alzheimer's disease, which was artificially created in rats by administering $AlCl_3$.

Material & Methods

All the information finding from different source like Google Scholar, Science direct, Pubmed, NCBI, Scopus, Keywords: Alzheimer disease, Neurodegenration, Zingiberaceae.

Bioactive present in Zingiber officinale

There are 69 volatile chemicals in the rhizome of Zingiber officinale, which account for 97% of the essential oils' overall makeup. The most abundant compounds are -Zingiberene (28.52%), Camphene (9.32%), Ar-curcumene (9.09%), β-Phellandrene (7.97%), E-α-Farnesene (5.52%), β-Bisabolene (5.54%), and -Pinene (2.57%). Their antibacterial, antioxidant, cytotoxic, insecticidal, and anti-inflammatory actions, in addition to their value in maintaining food qualities, have all been well-documented.

The majority of the bioactive compounds that are found in the rhizome of Zingiber officinale are derived from non-volatile molecules (oleoresins). Gingerols (1-(4-hydroxy-3-methoxyphenyl)-5-hydroxyalcan-3-one), Shogaols (1-(4-hydroxy-3-methoxy-phenyl)-4-decen-3-one), and Paradols (1-(4-hydroxy-3-methoxy-phenyl)-5-hydroxyalcan-3-one) are the three most major types of oleoresins currently known.

It is the shogaols, which are generated when gingerol analogues undergo dehydration processes to make the equivalent shogaols, which are more stable and have larger pharmacological effects than their antecedents, that give dried ginger its distinctively pungent flavour. During the processes of drying and ageing, rhizomes go through this change in terms of their chemical composition. In bacteria, 6-shogaol goes through a metabolic change and is converted into 6-paradol (Figure 1).

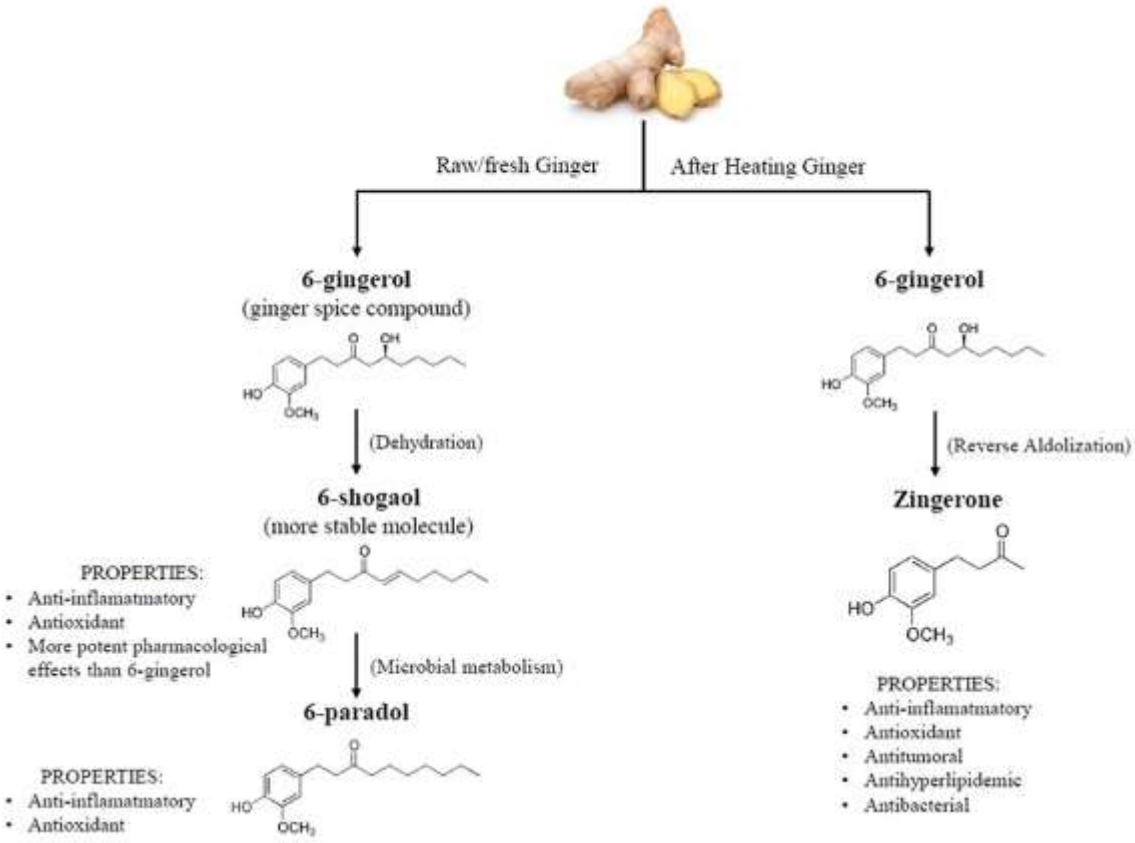

Fig: 1 Chemical Structure and bioactive compound of Ginger

There is evidence that T cells may play a part in the aetiology of certain autoimmune diseases as well as other chronic inflammatory conditions. The primary focus of this research was on examining the effector effects that 6-gingerol, 8-gingerol, and 10-gingerol have on T cells. In addition to that, an investigation into the signalling and production of cytokines via the IL-2 receptor was carried out. Although all three gingerols have the ability to inhibit T-lymphocyte DNA and the production of IL-1, only 8- and 10-gingerol have the ability to suppress CD25 and CD69 expression as well as the production of IL-2. In the presence of 8- or 10-gingerol, exogenous IL-2 did not increase the rate of T-lymphocyte proliferation; however, it did increase the rate of proliferation in the presence of 6-gingerol. The expression of CD25 was unaffected by either 8-gingerol or 10-gingerol; however, both of these gingerols were able to decrease the proliferation of IL-2-stimulated CTLL-2 cells. The inhibition of T cells was found to be at its highest for 10- and 8-gingerol, but this compound still had a lower degree of activity than 6-gingerol.

The cooperation of immune effector cells, local fibroblasts, and tissue macrophages is what determines liver damage and the link between chronic inflammation and fibrosis. Both of these conditions are linked to cirrhosis. It has been discovered that six-gingerol can lessen the severity of liver fibrosis in rats. This effect is mediated in part by a reduction in the expression of nuclear factor kappa B, tumour necrosis factor alpha, intercellular adhesion molecule (ICAM), toll-like receptor (TLR4), and vascular cell adhesion molecule (VCAM). In an in vitro model of hepatic inflammation, HuH7 cells were given S-6-gingerol treatment and then subjected to IL1 stimulation. S-6-gingerol was shown to raise levels of 24-dehydrocholesterol reductase mRNA, which in turn decreased levels of oxidative stress, inflammation,

and serum amyloid A1 (SAA1) mRNA. S-6-gingerol was also found to reduce levels of IL-6 and IL-8 (DHCR24). This medication proved successful in inhibiting both the activity of NF-κB as well as the elevation of COX2 that was caused by IL1β.

The effectiveness of immunomodulators as cancer treatments can be attributed, in part, to their anti-inflammatory, anti-oxidant, apoptotic, angiogenesis-inhibiting, and metastasis-preventing effects. According to recent findings, 6-gingerol may be beneficial in the treatment of cancer by targeting molecular signalling pathways. The suppression of epidermal growth factor-induced activated activator protein 1 (AP-1) by 6-gingerol has significant impact on the promotion of tumours. The cell migration and motility of breast cancer (MDA-MB-231) cells that were treated with escalating dosages of 6-gingerol exhibited a dramatic reduction in both of these properties. The administration of this chemical was proven to have no effect on the protein levels of matrix metalloproteinase-9 (MMP-9), but it did have the opposite effect on the protein levels of matrix metalloproteinase-2 (MMP-2), which were observed to decrease. 6-gingerol inhibits the adhesion, invasion, and motility of MDA-MB-231 cells. This is shown by the fact that 6-gingerol has an effect on matrix metalloproteinases (6-gingerol), which are a class of proteins that may play a role in cancer cell invasion and metastasis. 6-gingerol has been shown to suppress MMP-2 expression by lowering both the cytoplasmic and nuclear levels of yes-associated protein (YAP), which is a promoter in tumour metastasis for a variety of cancers. According to the findings of another study, 6-gingerol reduces the viability of human promyelocytic leukaemia (HL-60) cells by inhibiting the process of DNA synthesis and leading to apoptotic cell death. It has been postulated that the inhibition of B-cell lymphoma 2 (Bcl-2) expression, which results in DNA fragmentation in HL-60 cells, is the mechanism by which 6-gingerol induces apoptosis. 6-gingerol was discovered to inhibit autophagy flux and accelerate TRAIL-induced cell death in human lung cancer (A549) cells in a separate study. This was accomplished by increasing the accumulation of microtubule-associated protein light chain 3-II and p62 in the cells. In a study done by, they discovered that 6-gingerol increased the rate of mitochondrial biogenesis in CTLL-2 (cytotoxic T cells) cells, which in turn increased the rate of CD8+T cell cytotoxicity against tumour cells.

In H9c2 cells that had been chemically stimulated by CoCl2 to imitate hypoxia-related cellular damage, we evaluated the possible effect of 6-gingerol in activating the endogenous primary antioxidant, the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, and the p38/NF-B signalling pathways. Their findings revealed that the cytoprotective effect of 6-gingerol may be linked to its ability to activate the Nrf2 pathway and decrease the p38/NF-KB pathways, hence controlling oxidative stress and apoptosis. This was suggested by the fact that 6-gingerol was able to do both of these things. The same group of researchers recently shown in vitro that 10-gingerol can protect H9c2 cardiomyocytes from damage caused by hypoxia and reoxygenation. In order to determine whether or not 10-gingerol protects against myocardial ischemia damage and the potential mechanisms of action, they examined histopathological lesions, cardiac enzyme expression levels, in vivo oxidative stress and apoptosis, and proteins involved in the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signalling pathway. In the end, their research demonstrated that 10-gingerol has the potential to be employed as a treatment for cardiovascular disease. Because persistent inflammation can trigger carcinogenesis, tumours and therapy-induced inflammation both contribute to the spread of colorectal cancer (CRC). CRC is an abbreviation for colorectal cancer. The significance of the T-cell response in either limiting or driving the growth of tumour cells has been demonstrated by the correlation between T helper 1 (TH1)-cell-mediated immune responses and IFN levels in CRC tumours and a better prognosis, and between TH17-cell-mediated immune responses and a worse prognosis. This correlation has shown that TH1-cell-mediated immune responses are associated with a better prognosis. Gingerols have demonstrated considerable potential as a chemopreventive treatment for colorectal cancer due to the anti-inflammatory properties that they possess. 6-gingerol was discovered to block cyclin D1, cyclin A, and cyclin B1, which resulted in significant G2/M cell cycle arrest as well as mortality in colorectal cancer cell lines LoVo and HCT116. Ginger extract led to a dose-dependent increase in apoptosis, cell cycle arrest in G0/G1 and G2/M phases, and a reduction in S-phase DNA synthesis when it was used

to treat HCT116 and HT29 colon cancer cells. Following treatment with fresh ginger extract containing gingerols, HT29 colon cancer cells were found to exhibit both an increase in the expression of caspase 9, which is a gene that promotes apoptosis, and a decrease in the expression of Bcl-xL, which is a gene that inhibits apoptosis. An association between the inhibitory gene IB and the downregulation of genes in the cancer pathway was discovered. These genes include Kirsten rat sarcoma virus (KRAS), extracellular signal-regulated kinase (ERK), and Akt, as well as nuclear factor kappa B (p65). Through the phosphorylation of downregulated PMA, ERK1/2, and c-Jun N-terminal kinase (JNK), mitogen-activated protein kinases (MAPKs), and the activation of the AP-1 transcription factor, 6-gingerol promotes death in SW-480 (colon cancer) cells. Targeting the epidermal growth factor receptor (EGFR)/signal transducer and activator of transcription/extracellular signal-regulated kinase pathway, 8-gingerol was able to suppress the proliferation and migration of CRC (HCT116 and DLD1cell lines) cells. Due to the significance of leukotrienes in human cancer and chronic inflammation, as well as the overexpression of leukotriene A4 hydrolase in colorectal cancer, research on the effects of 6-gingerol was carried out. According to the findings, 6-gingerol was able to reduce the activity of leukotriene A4 hydrolase (LTA4H), which in turn was able to suppress the proliferation of anchorage-independent cancer cells in HCT116 colorectal cancer cells. The cytotoxic effects of 10-gingerol have been demonstrated in a wide variety of tumour cells, including A549, HCT15, SK-MEL-2, and SK-OV-3. At concentrations of 50 M or higher, 10-gingerol is responsible for the concentration-dependent death of cells; however, no cytotoxic effect was observed at lower dosages. 10-gingerol was tested on human colorectal cancer cells line SW480 and shown to have an effect. It has been demonstrated that 10-gingerol can promote protein kinase C-independent Ca2+ release from the endoplasmic reticulum as well as Ca2+ inflow through non-L-type Ca2+ channels. This can result in an increase in [Ca2+]. In a second experiment, 10-gingerol was evaluated on three different cell lines derived from ovarian cancer: SKOV-3, OVCAR3, and HEY. Ovarian cancer cell lines that were treated with 10-gingerol displayed a dose- and time-dependent decrease in cell number. However, this was not the result of cytotoxicity but rather a slowdown in the rate at which the cells were growing. The explanation for the decreased proliferation was found in an increased number of cells that were in the G2 phase of the cell cycle, as well as a concerning decrease in the percentage of cells that were in the G1 phase. Ovarian cancer cells that were treated with 10-gingerol showed a reduction in their production of cyclins A, B1, and D3. Following treatment with 10-gingerol, the apoptotic markers poly-ADP-ribose polymerase, caspase-3, and caspase-9 were all activated in the human colon cancer (HCT116) cell line. Another pathway that happens in concert with apoptosis is phosphorylation of the MAPKs family, which includes JNK, p38 MAPK (p38), and ER

Animal trail study on bioavailability of Gingerols

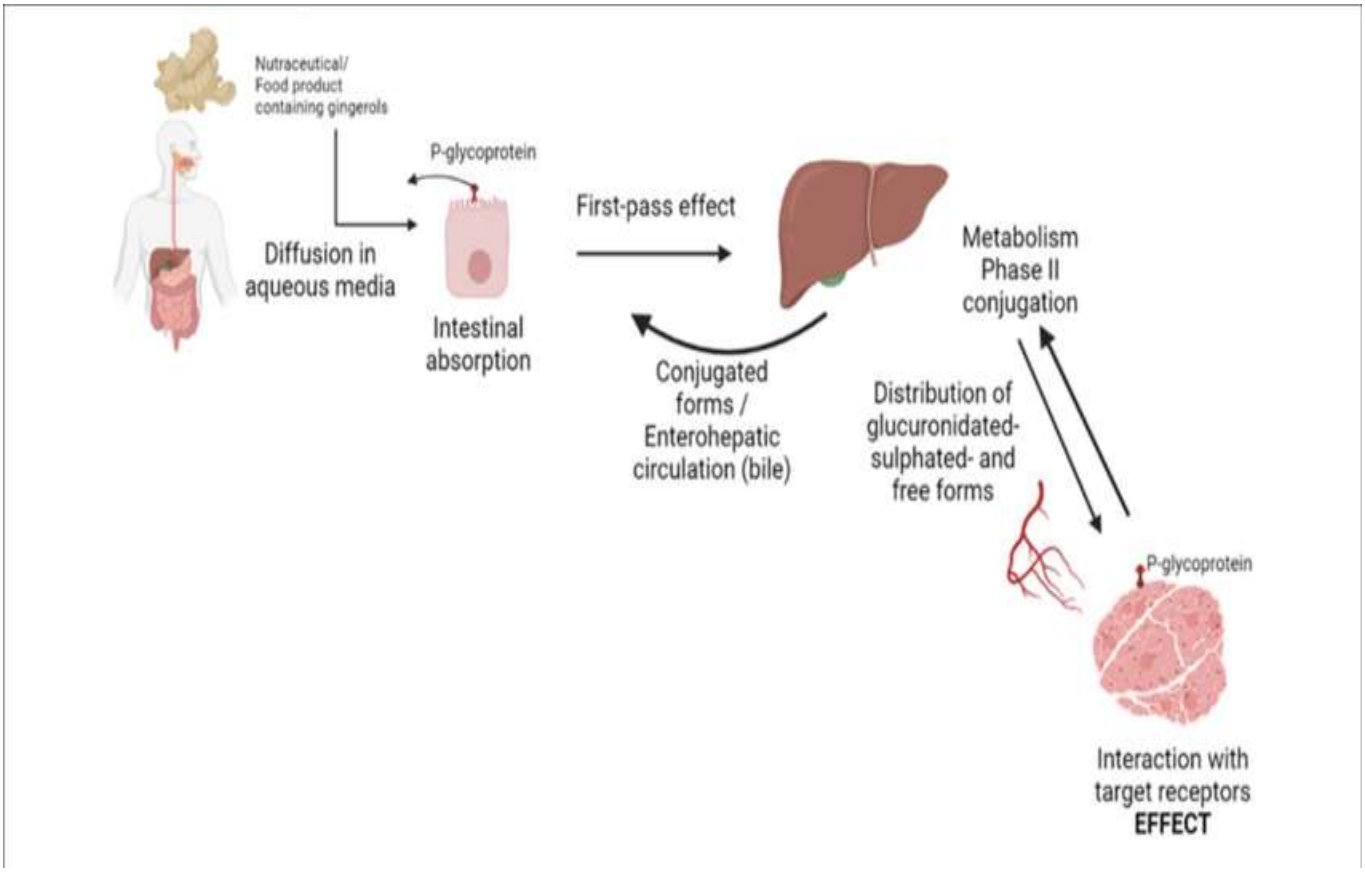

Fig: 2 Scheme of bioaccessibility and bioavailability routes of gingerols in the organism.

CUR is the most active component of the curcuminoids, as was described in the previous sentence. According to the Biopharmaceutics Classification System, CUR is placed in the fourth (and least effective) medicine class, which is known as Class IV. This placement is due to CUR's low water solubility and limited epithelial permeability in the digestive tract. Due to the fact that CUR is also a P-glycoprotein substrate, the P-glycoprotein substrate ATP-dependent drug efflux pump is responsible for removing CUR from the intestinal membrane. Several different approaches have been proposed as possible answers to the difficulties associated with the bioavailability of CUR. Increasing its solubility can be accomplished by a variety of different approaches, some of which include the use of solid self-emulsifying drug-delivery systems, solid dispersions, and cyclodextrin inclusion complexes. Other strategies include the manufacture of prodrugs, the alteration of crystal structures while the drug is in a solid state, and the micronization of the drug in order to increase the surface area available for solubilization. Because CUR is a substrate for P-glycoprotein, increasing its bioavailability can be accomplished by inhibiting P-glycoprotein using substances like piperine and quercetin. Nanoformulations have proven to be an effective and desirable alternative for the administration of drugs with low bioavailability. The ease with which a drug load can be transported through the gastrointestinal mucosal barrier; the possibility of obtaining controlled and sustained release formulations; a pathway for drug localization and cell-specific uptake Many various nanoformulation processes have been developed in order to address bioavailability concerns and maximise the numerous therapeutic advantages offered by curcuminoids, in particular CUR. Nanosuspensions, microemulsions, self-microemulsifying drug-delivery systems, nanoemulsions, and polymeric nanoparticles are only a few examples of the broad categories that these technologies may be classified

as belonging to. Each of these many kinds of nanoformulations for curcuminoids comes with their own set of benefits as well as drawbacks. When heated, the CUR molecule becomes 12 times more soluble than it was before. In addition to this, CUR is hydrophobic. Consuming turmeric in the form of curries and other oil-based dishes that are cooked at high temperatures is the optimal way to take use of the bioactive compounds it contains.

In this study, a mouse model of Parkinson's disease was utilised to demonstrate that 6-shogaol protects against MPTP- or MPP+-induced neuronal injury and motor dysfunction through regulating microglial activation and downstream proinflammatory factors. The investigation was carried out in mice.

In order to investigate the neuroprotective effects of 6-shogaol against the neurotoxicity caused by MPP+ or MPTP, studies were conducted on the mobility impairments and alterations that occurred in dopaminergic neurons. The neurotoxin MPTP is utilised frequently in the production of Parkinson's disease symptoms in animal models. In order for MPTP to access dopaminergic neurons in the brain, it must first undergo a transformation into the active metabolite MPP+ through the action of monoamine oxidase B in cells that are not dopaminergic. Dopaminergic neurons in the SNpc are especially susceptible to toxic damage and death when there is an accumulation of MPP+. This is because MPP+ inhibits complex I of the mitochondrial electron transport chain, making dopaminergic neurons particularly at risk. The rate of neuronal death correlates with the severity of motor dysfunction, which is caused by a decrease in the number of neurons that produce dopamine and is associated to the development of motor impairments. The findings of the current experiment revealed that treatment with 6-shogaol significantly improved the motor deficits and bradykinesia in the pole test that are brought on by MPTP. Dopaminergic neurons were significantly protected against this toxicity after being treated with 6-shogaol, as shown by histological tests. This treatment also increased the amount of TH-IR cells and retained the architecture of dopaminergic neurons in rat primary mesencephalic cells and mice. Recent studies have shown that 6-shogaol has a neuroprotective impact on neuronal cells, which means it can prevent neurotoxicity from occurring. In order to evaluate whether or not 6-shogaol could protect against the MPP+- or MPTP-induced activation of microglia and downstream proinflammatory factors, the levels of TNF- α, NO, iNOS, and COX-2 as well as the activation of MAC-1 were assessed. Although MPP+ and MPTP have been linked to the activation of glial and microglial cells as well as the production of inflammatory mediators, the exact functions that these two chemotherapeutic agents play in this process are still not completely understood16. Reactive gliosis is a common response to neuronal injury that occurs in the brain as a result of MPTP's effects. Neuroinflammation is the cellular expression of reactive gliosis. In reactive gliosis, microglia and astroglia are both activated. Microglia and astroglia are both capable of responding to injury and taking part in pathogenic events18. Microglial cells that have been activated can contribute to the degeneration of neurons by the release of a number of neurotoxic chemicals. These compounds include reactive oxygen and nitrogen species, as well as proinflammatory cytokines, chemokines, and prostaglandins. There is a possibility that crucial intracellular activities are related with microglial activation. These processes include the induction of TNF- and NO, as well as an increase in the production of COX-2 and iNOS. Due to the presence of the TNF receptor-1 on the cell surface of dopaminergic neurons, it is possible that these neurons are more susceptible to the cytotoxic effects of TNF α. This receptor is linked to a pathway that is involved in the demise of intracellular organelles. Activation of TNF receptor-1 causes signal transduction that ultimately results in increased COX-2 expression. In addition, the synthesis and activation of the low affinity receptor of immunoglobulin E24 in microglial cells may be stimulated by these cytokines, leading to an increase in the expression of iNOS. This may result in the production of toxic quantities of NO free radicals, which may subsequently trigger the formation and release of TNF- α by neighbouring microglial cells, so further magnifying the inflammatory response. They may be causing damage to neurons as they accumulate over time, particularly in those with Parkinson's disease. We discovered that 6-shogaol significantly decreased microglial activation brought on by MPP+ or MPTP, as well as the production of downstream proinflammatory factors such as tumour necrosis factor-alpha, nitric oxide synthase and cyclo-oxygenase-2. In addition, previous studies demonstrated that 6-shogaol inhibited the release of lipopolysaccharide-

induced nitric oxide (NO) as well as the expression of iNOS. In addition, 6-shogaol inhibited the production of COX-2, p38 mitogen-activated protein kinase, and nuclear factor kappa B, all of which contributed to the anti-inflammatory effects of the compound.

The current research shown that 6-shogaol, a pungent molecule produced from ginger, suppresses inflammatory pathways. This property enables 6-shogaol to protect dopaminergic neurons from the neurotoxicity induced by MPP+ and MPTP. It has been hypothesised that the naturally pungent chemicals produced by plants have a protective purpose as a result of the antioxidant, anti-inflammatory, and anti-carcinogenic qualities that these molecules possess. Capsaicin and piperine extracted from pepper fruits, paradol extracted from Amomum melegueta Roscoe, and allicin extracted from garlic have been found to possess some of the most potent neuroprotective and anti-inflammatory properties ever discovered in plant compounds. These findings were made possible by the fact that these compounds were isolated from pepper fruits. Even though further research is required, preliminary findings suggest that 6-shogaol may have a neuroprotective effect in PD via reducing neuro inflammation.

Effect of Ginger and Neuro protection disease

Ginger and the compounds derived from it have been the subject of a number of studies that have demonstrated their therapeutic promise for the improvement of cognitive impairments. These studies have focused on ginger's anti-amyloidogenic potential, inhibition of cholinesterase, and neuroprotective capabilities. At the moment, there are only a limited number of pharmaceuticals that have been proven to be effective in treating AD. Because there are a limited number of therapeutic targets and a wide variety of adverse effects, researchers are looking into multi-target medicines as a way to obtain a safer and larger therapeutic potential. On the basis of the therapeutic properties of ginger and the components that make it up, a number of studies have been conducted for the development of new Alzheimer's disease treatments. We show that 6-shogaol and its biotransformed metabolite, 6-paradol, are therapeutically efficacious for EAE by reducing EAE clinical symptoms and histological sequelae such as demyelination, cell accumulation, and astrogliosis in injured spinal cords of EAE mice. This was accomplished by demonstrating that 6-shogaol and 6-paradol are biotransformed from 6-shogaol. In addition, we demonstrated that the therapeutic effects of 6-shogaol and 6-paradol on EAE were linked to a reduction in microglial activation and TNF- α overexpression in the spinal cords of EAE animals that had been injured. These mice had the condition. According to these findings, 6-shogaol or 6-paradol may offer therapeutic promise for treating multiple sclerosis (MS) by lowering neuro inflammatory reactions. These reactions are one factor that contributes to the symptoms of the disease.

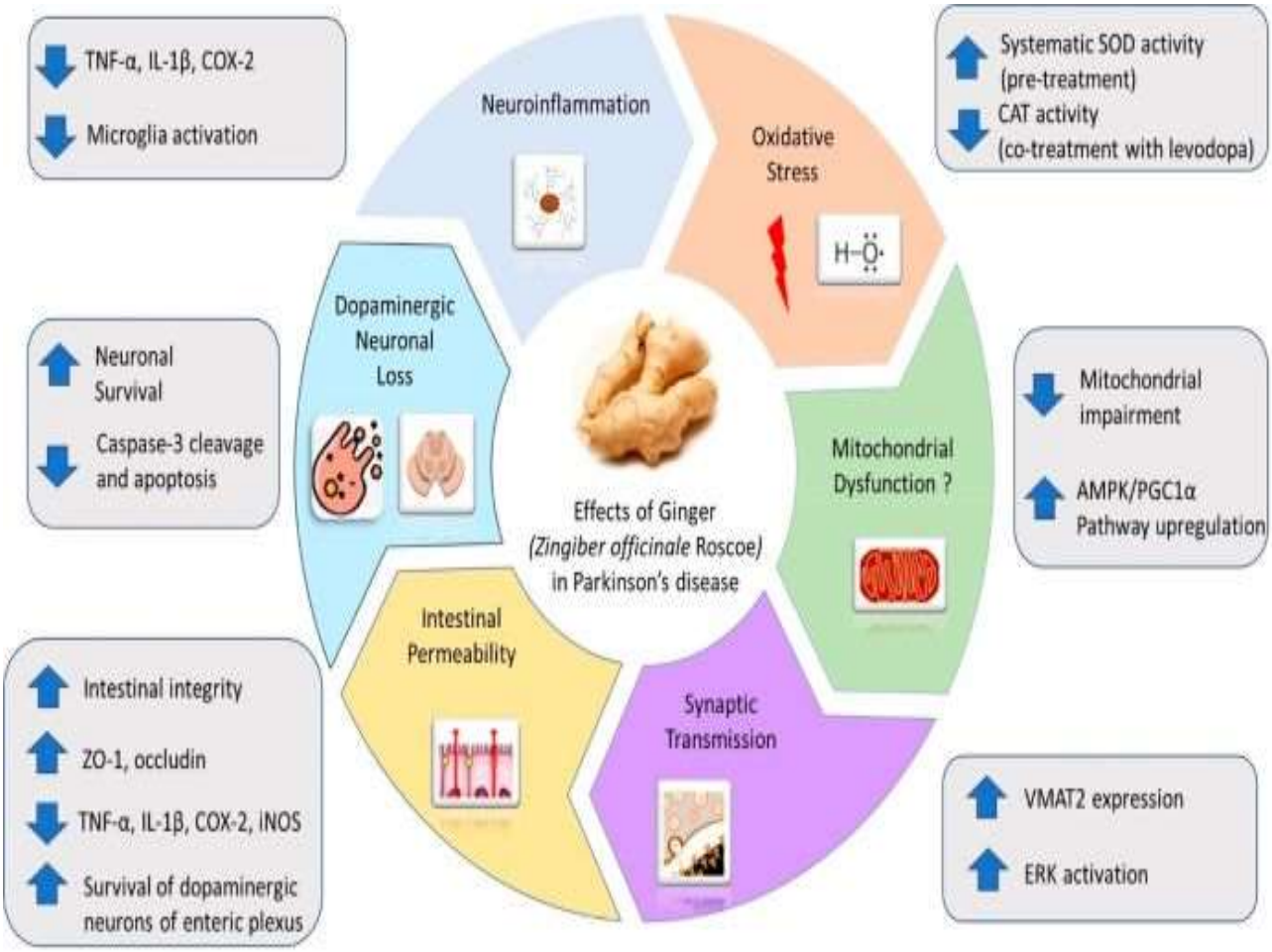

Fig: 3 Beneficial Effects of Ginger (Zingiber officinale Roscoe) in Parkinson's Disease

Ginger has been shown to have anti-inflammatory and neuroprotective effects on a variety of central nervous system (CNS) illnesses, such as experimental autoimmune encephalomyelitis, Alzheimer's disease, focal cerebral ischemia, and 3,4-methylenedioxymethamphetamine-induced neurotoxicity, amongst others (EAE). In addition, there have been many attempts made to separate the active components of ginger extract in the hopes of developing new medications to treat conditions that affect the central nervous system. Non-volatile molecules with a potent odour, such as gingerols, shogaols, and zingerone, as well as paradols, which are biotransformed metabolites of shogaols and have a more subdued odour, have been identified as the active components in ginger. These molecules are known as gingerols, shogaols, and zingerone. Dehydration of 6-gingerol results in 6-shogaol, which then undergoes hydrogenation to produce 6-paradol. 6-gingerol is the primary pungent component found in fresh ginger. Intriguingly, 6-shogaol and 6-paradol have more anti-inflammatory and anti-oxidative capabilities than 6-gingerol, which suggests that they may be active elements of ginger that demonstrate neuroprotective advantages on a number of conditions that affect the central nervous system (CNS). One research group discovered that giving ginger extract to inoculated mice was related with neuroprotective benefits in experimental autoimmune encephalomyelitis (EAE). This was discovered in the context of the experimental autoimmune encephalomyelitis (EAE) study (from day 3 post immunization). Because of this medication, the disease did not develop in the mice that had been immunised against it, and the expression of critical cytokines and chemokines that are involved in the immune response was reduced.

Both previous studies and our own findings point to the active components in ginger extract being 6-shogaol and 6-paradol, which are responsible for the ginger extract's alleged effectiveness. The clinical symptoms of EAE mice were relieved by treatment with these two compounds; as a result, the therapeutic efficacy of these substances is highlighted in this work. Demyelination, increased cell density, and astrogliosis are all symptoms that are seen in patients with multiple sclerosis as well as rat EAE models. During the course of this work, it was discovered that both 6-shogaol and 6-paradol can reduce the visibility of these histological indicators of EAE. It has been reported that astrogliosis can be found in EAE patients before the development of clinical symptoms. Furthermore, astrogliosis and the glial scarring that results from it can impair central healing pathways in multiple sclerosis, including as remyelination. Monosodium glutamate is an ingredient that can be found in a variety of foods all around the world (MSG). Due to its widespread accumulation throughout the brain and subsequent neurotoxicity, it causes synaptic dysfunction as well as neurodegeneration. Within the central nervous systems of animals, the excitatory neurotransmitter glutamate salt is involved in a wide variety of physiological and pathological activities. According to the findings of this study, the administration of MSG to our animal models resulted in a variety of toxicological consequences. In spite of this, the potential benefits of ginger and propolis aqueous extract in reversing these toxicological effects have been the subject of extensive research. The findings revealed that MDA, which is a biomarker for lipid peroxidation, 8-OHdG, which is a marker of DNA oxidation, and nitric oxide were considerably raised in the brain tissues of rats that were treated with MSG. This indicates that oxidative stress is present. It is consistent with increased NO production due to mitochondrial malfunction being the cause of increased NO in our results. This, in turn, increases cytokine production, which activates genes like inducible nitric oxide synthase (iNOS), which increases nitric oxide synthesis, which leads to more mitochondrial damage.

Our findings also revealed a reduction in the levels of the antioxidant enzymes glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT), all of which are found in the brain. These findings are in line with earlier reports that described an increase in oxidative stress in the liver and kidneys of rats following the administration of MSG. The level of GSH depletion is directly related to the amount of damage that has occurred in the tissues that are deteriorating. Following the administration of MSG for seven days, Shivasharan and colleagues discovered lower levels of GSH, GST, and CAT activity, in addition to MDA and nitrite, in brain tissues. The biomarker known as 8-hydroxy-2'-deoxyguanosine (OHdG) has also been applied to the problem of determining whether or not DNA has been damaged as a result of oxidative stress. The oxidative damage that is generated by the biochemical interactions between reactive oxygen species (ROS) and target biomolecules such as nucleic acids, lipids, and proteins has been linked to a large number of oncologic and neurological disorders.

Although what we discovered was that providing mice that had been treated with MSG ginger and propolis rejuvenated their antioxidant enzymes and lowered the oxidative stresses that they had. It has been hypothesised that the putative antioxidant properties of ginger are due to compounds known as shogaols, gingerols, and other phenolic-ketone derivatives that have been shown to be helpful in reducing the severity of ROS-induced damage to the CNS. It was found in an earlier study that gingerol reduced the amount of ascorbate/ferrous complex-induced lipid peroxidation (LPO) in rat liver microsomes. This finding lends credence to our primary finding, which was that ginger supplementation reduced the amount of LPO that occurred in brain tissue. The current experiment demonstrated that ginger supplementation inhibited nitric oxide in brain tissue beyond macrophages, which is consistent with the findings of an earlier study which reported that nitric oxide suppression occurred in activated macrophages. Because 6-shogaol is one of the most bioactive components of ginger rhizome, the level of iNOS can be decreased by using it. Because the brain contains a high concentration of polyunsaturated fatty acids (PUFA), such as archidonic acid and docosahexaenoic acid, the cell membranes of brain tissue are especially prone to lipid peroxidation. We discovered that MSG-induced oxidative stress resulted to an increase in free -amyloid peptides, which is quite similar to what Butterfield and Lauderback found. An earlier investigation showed results that were consistent with ours, indicating

an increase in free -amyloid peptides in the brain tissues of MSG-treated rats. This finding was connected with adverse effects on the cognitive neurotransmitters. However, ginger supplementation was more effective at preventing these occurrences than propolis supplementation was, and this difference may be due to the antioxidant properties of ginger, as discussed in the section on free radical scavenging activity in our in vitro study. Propolis supplementation was also effective at preventing these occurrences. In addition to this, it is possible that it is linked to 6-gingerol, an active component of ginger that was investigated in a separate study and found to play an important role in the decrease of beta-amyloid.

Unsaturated fatty acids found in membranes are susceptible to damage caused by free radicals, which can set off an autocatalytic process that inhibits the ability of AchE to perform its function. Our findings, which demonstrate that MSG dramatically lowers AchE activity in the brains of rats that were treated with MSG, are consistent with those of an earlier study. In the cerebral cortex of rats that had been drunk with MSG, researchers found that levels of the neurotransmitters serotonin, dopamine, and glutamate were considerably altered. This finding was supported by the fact that variations in serotonin levels were seen in the cortex, hippocampus, striatum, hypothalamus, the olfactory lobe, the cerebellum, and the brain stem of rats that had been exposed to MSG and aspartame. Ginger and propolis both have antioxidant properties, which may help explain why they were beneficial in reducing the frequency of these occurrences after they were administered. Glutamate is hypothesised to play an important part in the regulation of blood-brain barrier permeability. Destabilization of the blood-brain barrier can occur when glutamate receptors in cerebral capillaries are overstimulated. We found that exposure to MSG increased glutamate levels in the brains of rats. This finding is in line with previous research that established a connection between an overexpression of glutamate levels and the breakdown of the blood-brain barrier as well as neurotoxicity in the hippocampal and hypothalamic regions of the brain. Multiple studies have shown that the anti-5HT3-receptor effects of ginger fractions contribute to fast excitatory synaptic transmission in the central nervous system (CNS) upon stimulation. Additionally, it has been shown that these effects modulate the release of -aminobutyric acid, the exocytosis of which is facilitated by direct Ca2+ influx through the ionophore of presynaptic 5-HT3-receptors.

Because of the neurotoxicity of MSG, the levels of Na+ and Ca+2 in the brain tissue of rats that had been treated with MSG were much greater than those found in the normal control group, although the levels of K+ were significantly lower. When compared to the group that was treated with MSG, the groups that were treated with ginger and propolis showed much lower amounts of sodium and calcium in the brain tissue, and significantly higher quantities of potassium. Ginger, which was taken as a supplement, was found to have a larger effect than propolis, which may be due to the powerful antioxidant capabilities of ginger as well as its other bioactive components.

Conclusion

The appeal of natural compounds has increased in the last decades and the scientific community seems to regain interest in them, in order to avoid the side effects of synthetic drugs or to increase their efficacy. Ginger has proven to be a valuable candidate for the treatment of dementia, with evidence also supporting its use in prevention. Several experiments have enlightened ginger's effect in hampering multiple phases of dementia developing, from neurodegeneration to neuro inflammation, supporting on the other hand the survival rate of neurons. Even if at present ginger does not represent a definitive cure for advanced stages of dementia, further studies could discover more beneficial properties, and the refinement of dosage, route, and timing of administration could represent a valid support for current therapies. Owing to this mechanism, ginger is a promising wide-spectrum analgesic, effective in various types of pain, including neuropathic and inflammatory pain, which are currently unmet medical needs. The data provided herein demonstrate that the key to an effective analgesic strategy is targeting multiple key elements regulating the nociceptive process. However, future systematically designed research, including sufficient sample size, should assess the extent of ginger's usefulness in specific types of pain in humans and the type of

extract with the best analgesic effect. Furthermore, its comparative efficacy reported in other alternative interventions should be also investigated.

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