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REVIEW ARTICLE

Pharmacological and therapeutic potential of ginger in the management of neurodegenerative disorders

Babatunde O. Adetuyi and Peace A. Olajide

Department of Natural Sciences, Faculty of Pure and Applied Sciences, Precious Cornerstone University, Ibadan, Nigeria

ABSTRACT

Ginger is rich in secondary metabolites such as 6-gingerol, 6-shogaol, 10-gingerol, gingerdiones, gingerdiols, paradols, 6-dehydrogingerols, 5-acetoxy-6-gingerol, 3,5-diacetoxy-6-gingerdiol, and 12-gingerol. These compounds are largely responsible for the evidenced pharmacological properties of ginger. Among them, 6-shogaol and 6-gingerol are considered the most crucial active ingredients. Research supports ginger's medicinal properties, particularly its antioxidant and anti-inflammatory activities. On the other hand, the neuroprotective benefits of ginger, while intriguing, remain relatively unexplored and understudied. Neurodegenerative disorders (NDs), characterized by increased oxidative stress, neuro-inflammation, and protein misfolding, are becoming increasingly prevalent as life expectancy rises. Ginger's phytochemicals show promise in treating NDs due to their ability to target specific ligand sites, as suggested by their structure-activity relationships. The bioactive compounds in ginger may alleviate neurological symptoms and pathological disorders by influencing markers associated with cell death or survival. Furthermore, ginger's potential to enhance cognitive clarity could be attributed to its impact on the monoamine and cholinergic systems in different brain regions. It also appears to decrease the incidence of inflammation-related components. This review aims to highlight how ginger could be leveraged to treat major neurological conditions such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease.

Keywords Alzheimer's disease, antioxidants, ginger, multiple sclerosis, neurodegenerative diseases, Parkinson's disease

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Corresponding Author
Peace A. Olajide
olajidepeace2019@gmail.com

Department of Natural Sciences, Faculty of Pure and Applied Sciences, Precious Cornerstone University, Ibadan, Nigeria

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Pages: 151-179

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INTRODUCTION

As the number of people in Western countries over the age of 65 has increased, age-related neurodegenerative disorders have become more prevalent. Alzheimer's disease is by far the most prevalent pathology, affecting more than 26 million people worldwide today.

It is anticipated that this number will have quadrupled by the year 2050. As people get older, their risk of developing neurodegenerative illnesses increases, and there currently are no viable treatments for these diseases despite their high personal and societal costs and rapid progression.[1] The primary difficulties of scientific inquiry are the avoidance of these illnesses and the discovery of new nutraceuticals and medications to counteract them. Some plant extracts have been shown to reduce the symptoms of cognitive impairment thanks to their beneficial anti-inflammatory and antioxidant properties.[2]

Bioactive chemicals in ginger have been studied for their potential medicinal effects in recent years (Ogunlana et al., 2021).The thick tuberous rhizomes of the perennial herb *Zingiber officinale* (Zingiberaceae) are widely used as a medicinal and culinary spice and flavoring agent (Mann, 2011).[3] There is less information about its history, although it probably originated in South or Southeast Asia or India.[3] *Zingiber officinale*'s bioactive component content changes depending on its growing environment and drying methods. *Zingiber officinale*'s rhizome contains trace amounts of plant oils, oleoresins, essential minerals, polysaccharides, mucilage, gums, and organic acids. Roughly 40-60% of the dry mass of Zingiber officinale rhizome is comprised of starch. Among the many bioactive compounds found in ginger, the most notable are 6-gingerol and 6-shogaol (Tanaka et al., 2015).[4] Ginger's biological properties as an antibacterial, anti-inflammatory, antioxidant, anticancer (by increasing expression levels of markers for colorectal cancer risk), and anti-allergic agent have been discovered in recent years (Semwal et al., 2015).[5] Numerous studies have shown that ginger can reduce the risk of many different diseases, including cardiovascular issues and their associated pathologies (diabetes, obesity, and metabolic syndrome), as well as chemo-induced nausea and vomiting, arthritic pain and inflammation, gastric dysfunction, chronic pain, and respiratory and neurodegenerative issues (Anh et al., 2020).[6] Increasing lipolysis and thermogenesis, inhibiting lipogenesis, reducing fat absorption, and controlling hunger are only few of the potential processes through which ginger could influence obesity. Hyperglycemia and high cholesterol levels are two conditions that ginger has been shown to improve. These beneficial effects are mediated by transcription factors like nuclear factor B, peroxisome proliferator-activated receptors, and adenosine monophosphate-activated protein kinase (Wang et al., 2017).[7] Therefore, Zhu et al. (2018) demonstrated that ginger improves plasma lipid profile, reduces glycosylated hemoglobin in type 2 diabetes, and increases insulin sensitivity.[8] Neurodegenerative diseases, which are characterized by neuroinflammation, oxidative stress, and protein misfolding, are characterized by brain damage, synaptic dysfunction, and neuronal apoptosis (Choi et al., 2018).[9] Mitochondrial failure, neurofibrillary tangles composed of hyperphosphorylated tau proteins, and the excessive accumulation of beta-amyloid plaques outside of cells all contribute to the oxidative stress that characterizes Alzheimer's disease. Antioxidant, amyloid-preventing, inflammation-reducing, and cholinesterase-blocking activities have all been seen in gingerols (Adeleke et al., 2022).[10] 6-gingerol, the main component isolated from Zingiber officinale, has been shown to have antioxidant, anti-inflammatory, and astrocyte overactivation-inhibiting properties. In microglia activated with lipopolysaccharide, 6-gingerol treatment reduced increases in intercellular nitric oxide concentrations and

iNOS enzyme activity, as well as inhibited the production of pro-inflammatory cytokines like IL-6 and IL-1 (Zhang et al., 2018).[11] After Alzheimer's sickness, Parkinson's illness is the most successive type of neurodegeneration (Olajide et al., 2022). This degenerative disorder is characterized by the accumulation of alpha-synuclein protein within neurons, including Lewy bodies and Lewy neurites, and its prevalence rising with age (Pimentel et al., 2012).The development of Parkinson's disease has been linked to both genetic and environmental factors, such as brain iron buildup and oxidative stress. According to the findings of a study conducted by Medeiros et al., (2016), Parkinson's disease patients had significantly elevated levels of inflammatory and oxidative stress markers. Theactive ingredient in ginger may help alleviate the cognitive dysfunction that frequently accompanies it by inhibiting the inflammatory response, increasing nerve growth factor levels, and encouraging the formation of synapse (Mohd et al., 2019).[12] Demyelination of neurons and axonal degeneration in the central nervous system are hallmarks of multiple sclerosis, both of which are triggered by a prolonged inflammatory response. The onset and course of multiple sclerosis are connected to inflammatory, oxidative, and immunopathological characteristics. Ginger and its bioactive components may be investigated as potential treatments for multiple sclerosis due to their anti-inflammatory, antioxidant, and immunomodulatory properties (Mohd et al., 2019).[12] Anti-inflammatory and antioxidant medications like ginger and its derivatives may be beneficial for neurodegenerative disorders due to the fact that oxidative stress and inflammation are major contributors to the onset of these conditions. As a result, the purpose of this review is to provide a summary of the ways that ginger can prevent major neurodegenerative diseases like Alzheimer's, Parkinson's, and multiple sclerosis.

NUTRITIONAL COMPOSITION OF GINGER

Ginger is a popular spice that has long been utilized in both culinary and alternative medical applications. The plant Zingiber officinale, or common ginger, is from the Zingiberaceae family. Initially, it was a spice used for medical purposes, as stated in Confucius' Analects (475-221 BC) (Pickersgill, 2005).[13] As a result of its antiviral and antioxidant characteristics, ginger has been studied for its impact on a wide range of ailments, including asthma, stroke, diabetes, constipation, mental disorders, etc (Mashhadi, et al., 2013).[14] When ginger is at its peak of freshness, it contains roughly 81% water, 2% protein, 1% fat, 1% minerals, 3% fiber, and 75% carbs (more than twelve percent). Ginger contains a number of essential micronutrients, such as phosphorus, calcium, and iron. It's also a great source of vitamins like thiamine, riboflavin, vitamin C, and niacin. Different types of ginger have different nutritional profiles (Zadeh & Kor, 2014).[15]

BIOACTIVE COMPOUNDS

Ninety-seven percent of a Zingiber officinale rhizome's chemical make-up is made up of essential oils, and these volatile chemicals are all present in the plant's pungency.

Table 1. Prevalent molecules and their composition in *Zingiber officinale*.[16]

No.	Molecules	Composition
1.	E-α-Farnesene	5.52%
2.	β-Bisabolene	5.54%
3.	α-Pinene	2.57%
4.	Camphene	9.32%
5.	Arcurcumene	9.09%
6.	α-Zingiberene	28.62%

Over time, proof of their effectiveness in preserving food characteristics as well as their antimicrobial, antioxidant, cytotoxic, insecticidal, and anti-inflammatory effects has collected (Didunyemi et al., 2019). [17] Bioactive chemicals in Zingiber officinale rhizomeare primarily derived from non-volatile molecules (oleoresins). Gingerols, Shogaols, and Paradols are the three most major classes of oleoresins currently known, together accounting for 88.6% of the overall composition (Asadi-Samani et al., 2013). [16] Shogaols are more abundant in dried ginger, whereas gingerols are more abundant in fresh ginger (Kiran et al., 2013). [18] Shogaols, which are created when gingerol analogs go through dehydration processes to produce the identical shogaols, that are both more stable and have stronger therapeutic action than their antecedents, give dried ginger its distinctively pungent flavor. Rhizomes undergo this chemical transformation during the thermal drying process and prolonged storage. Bacterial metabolism changes 6-shogaol into 6-paradol (Mohd, 2016). [19] Some of the additional phenolic compounds discovered in ginger include quercetin, zingerone, gingerenone-A, and 6-dehydrogingerdione. The maturity state, varietal, habitat, and processing techniques have a major impact on the biosynthesis and quantity of biologically active compounds in ginger. Methoxyflavones are what give black ginger its distinctive flavor; ordinary ginger contains phenolic acids similar to gingerol (Asamenew et al., 2019). [20]

PHARMACEUTICAL POTENTIAL

Whether the rhizomes are fresh or dried also affects the composition of ginger, which can be quite different depending on both factors (Mbaveng and Kuete, 2017). [6,21,22] The compounds gingerol, shogaols, zingiberene, zingerone, paradols, etc., give ginger its medicinal and therapeutic reputation. Many of these bioactivities rely on gingerols, one of these phytocompounds (Kubra and Rao, 2012).[23] Many studies and clinical trials have been conducted on ginger because of its purported health advantages and effectiveness. The pharmacological effects of 6-gingerol were enhanced when it was converted to 6-shogaol in dried ginger. To add insult to injury, 6-shogaol was converted to 6-Paradol via biotransformation (Jafarzadeh et al., 2021).[24] Zingerone, the main phytochemical in ginger used for therapeutic purposes, is responsible for its spicy flavor. Due to its aromatic and spicy properties, ginger is also a common food addition (Srinivasan, 2017). [25]

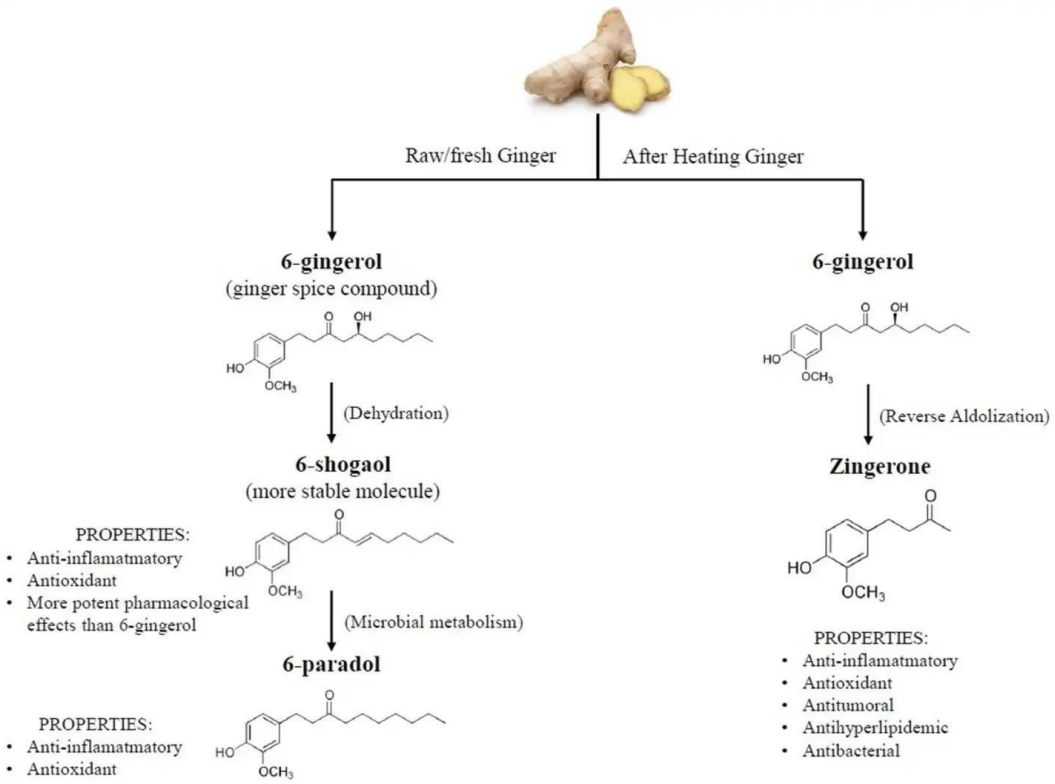

Figure 1 Chemical structure and properties of ginger bioactive compounds.

Gingerols

Polyphenols known as gingerols have been successfully extracted from ginger's fresh root. The rhizomes of the ginger plant are particularly abundant in the bioactive compounds that are unique to ginger. 6-Gingerol has a moiety of 5-hydroxydecan-3-one (Fig. 2), which is hypothesized to prevent adipogenesis because of the presence of a 4-hydroxy-3-methoxyphenyl group at position 1 (Kumara et al., 2017). [26] This particular beta-hydroxy ketone is a member of the guaiacol family of plant metabolites. This substance inhibits the growth of tumors. Including the antioxidant [8]-gingerol, it is also high in cardiotonic and heart-protective properties (Xue, et al., 2021b). [27]

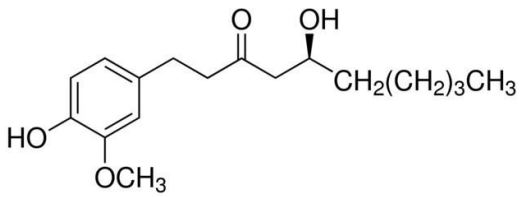

Figure 2 6-Gingerol.

Shogaol

Ginger contains bioactive compounds called shogaols, which have been found to have gastroprotective and neuroprotective properties. Monomethoxybenzenes like [6]-shogaol are a subclass of phenols and enones. Ionic liquid dimethylammonium dimethylcarbamate was used in a Mannich process to produce shogaol by Mase and coworkers (Mase et al., 2010). [28] Edema can be reduced by using 6-shogaol because it prevents leukocytes from entering inflamed tissue. 6-Shogaol modulates the cytoprotective HO-1 in both vitro and in vivo (Bischoff-Kont and Fürst, 2021).[29] In addition to having outstanding anti-proliferative effects against human lung cancer cell lines, the 6-, 8-, and 10-shogaols also neutralize free radicals (Sang et al., 2009). [30] According to earlier studies, 6-shogaol contains antioxidant properties that protect against neurological disorders and inhibit glial cell stimulation.

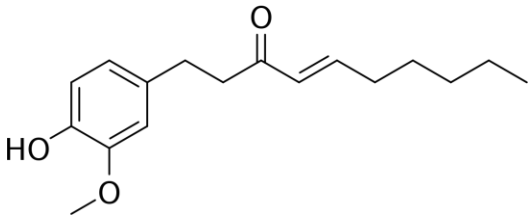

Figure 3 Shogaol.

Paradols

[6]-paradol is a ketone, monomethoxybenzene, and phenol (Fig. 4). Without activating AMPK, it regulates a number of genes implicated in obesity. In just two weeks, 6-paradol stops the development of fatty tissue in the visceral and subcutaneous fat regions of mice. Liver cholesterol, triglyceride production, lipogenesis, and lipid distribution were all reduced. Adipocyte distinction in the adipose and liver tissues was also repressed (Hattori, et al., 2021). [31] Though 6-paradol is only a tiny component of ginger, mostly produced from 6-gingerol, 6-shogaol is converted into 6-paradol almost entirely (Chen et al, 2012). [32] 6-Paradol inhibits lipid synthesis in 3T3-L1 cells, which results in an intensity decline in membrane lipids buildup and a comparable reduction in insulin-induced lipid accumulation, according to a study examining the effects of 6-Paradol at various ratios on glucose absorption (Wei et al, 2017). [33]

Zingerone

There are methoxy and hydroxy groups attached to the phenyl ring at positions 3 and 4, respectively, in zignerone, which classifies it as a 4-phenylbutan-2-one (Fig. 5). It's what gives ginger its distinctive bite, and it also has antioxidant, anti-inflammatory, antiemetic, flavoring, aroma, and plant metabolite applications (Baliga, et al., 2011). [34] Antioxidant

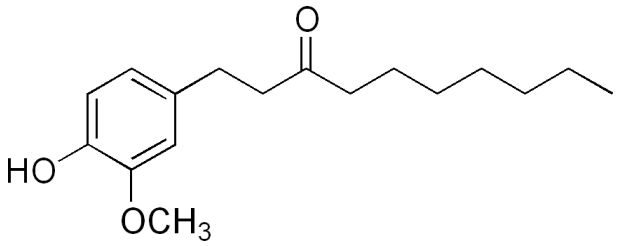

Figure 4 **Paradols**

Enzyme levels and inflammation were both improved by zingerone. It was proposed that RA be treated by taking the medication orally. It dramatically increased IL-10 and decreased NF-κB, TGF-α, TNF-β, IL-1β, IL-6, and Hs-CRP (Bashir et al., 2021).[35] Inflammation, Oxidative stress, and apoptosis in the liver are all avoided thanks to Gingerone's ability to control the AMPK pathway (Mohammed, 2022). [36]

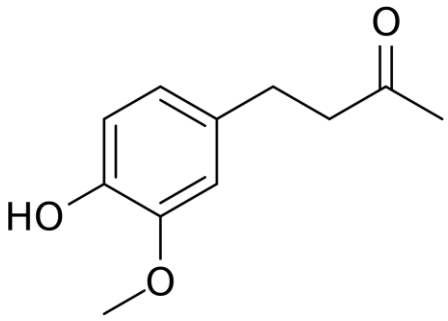

Figure 5 **Zingerone.**

Zingiberene

It is a sesquiterpene and a cyclohexadiene that has a proton at the 5 position that is substituted by a 6-methyl-hept-5-en2-yl group (R configuration) (Fig. 6). Zingiber officinale, or ginger, has it in its dried rhizomes (indonesian ginger). Scientists found terpenes like zingiberene in ginger rhizomes, which blocked MAO-A enzymes (Kukula-Koch et al., 2018).[37] Research indicates that zingiberene may be used as a novel, all-natural treatment for neurological conditions to prevent cell stress (Togar et al., 2015a).[38] Testing the cytotoxic, genotoxic, and antioxidant effects of zingiberene on a population of rat brain cells in vitro has been done to learn more about its possibility as a chemotherapeutic medication (Togar et al., 2015b).[39]

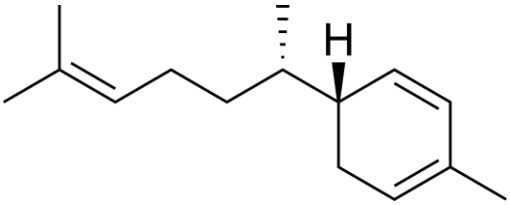

Figure 6 **Zingiberene**

Zerumbone

Steam distillation of Southeast Asian ginger yields zerumbone, a sesquiterpene and cyclic ketone produced from (1E,4E,8E)-alpha-humulene (Fig. 7). It functions as a blocker of some oncogenes and as an anti-inflammatory drug for gliomas as a botanical compound (Rahman, et al., 2013).[40] Scientists have shown that zerumbone can lessen Zearalenone-induced liver damage and haverevealed the molecular basis for zerumbone's potentialapplications in managing Zearalenone-induced liver lesions (AbuZahra et al., 2021).[41] Studies conducted in the recent past have shown indicated that Zerumbone reduces inflammation by blocking NF-κB and TLR. The use of zerumbone has been proposed for the management of diabetes and its consequences (Kim et al., 2022).[42] In response to paclitaxel and proapoptotic proteins, zerumbone was found to boost expression of BAX, caspase-7, and caspase-9 while decreasing expression of BCL-2. Increased ROS-mediated oxidative stress within the cell is how zerumbone makes breast cancer cells more sensitive to PTX again (Li et al., 2022).[43]

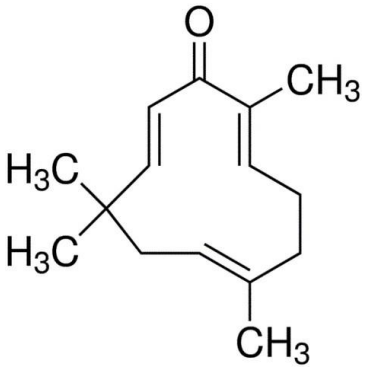

Figure 7 **Zerumbone.**

BIOAVAILABILITY AND PHARMACOKINETICS

For gingerols from food to have an effect on the body, they must first circulate through the blood and into the tissues. The dissolution rate of a substance in gastrointestinal fluid

and potential gastrointestinal tract breakdown, the penetrability of the enterocytes' cell wall, protein-mediated intestinal effiux, and pre-systemic gut and/or hepatocellular metabolism all have an impact on the amount of a substancethat attains the tissues in which it can exhibit its impact (He et al., 2011).[44] Because of its low bioavailability, ginger has only a limited role in nutraceuticals and enriched food items. Because gingerols and their derivatives are fat-soluble, they should be easily absorbed by the intestinal epithelium via passive diffusion. They are assimilated in brush border cells, but before that can happen, they must first be dissolved in an aqueous medium due to their chemical makeup, which renders them less hydrophilic. The term "bioaccessibility," which refers to the amount of an ingested nutrient that can be absorbed, is related to this phenomenon. Nevertheless, the concept of "bioavailability," which describes the portion of a compound's administered dose that circulates in the blood and the precise locations in which it can perform its activity, marks a development. When considering whether or not a molecule can have an effect on an organism, bioaccessibility is the first and most important limiting factor. Gingerols, unlike other types of compounds like flavonoids, are not often present in a glycosylated condition to prevent being absorbed by the glycosidase enzymes of the intestinal brush barrier. Gingerols, however, are P-glycoprotein substrates. This protein is highly expressed in the cell surface of the liver, brain, kidney, and enterocytes in the intestinal tract. It is a significant defense mechanism against toxins that prevents the absorption of many medications by the intestines (Gessner et al., 2019).[45] Gingerols, once ingested, are transported to the liver via the hepatic portal vein and metabolized there (this process is known as the "first-pass effect"). Phase II conjugative activities shorten the half-life of these substances by converting them into more polar molecules for biliary or kidney tubular secretion, such as glucuronidation facilitated by UDP-glucuronosyl-transferases (UGTs) and sulphation facilitated by sulphotransferases (SULTs). The UGT isozymes 1A1, 1A3, and 2B7 facilitate gingerol conjugation (Pfeiffer et al., 2006).[46] Additionally, these chemicals undergo enterohepatic circulation via biliary excretion and intestinal reabsorption. A water soluble compound called 6-gingerol gluuronide diffuses from hepatocytes and is discharged in bile into the small intestine. There, -glucuronidases in the intestine can break it down so that it can re-enter the bloodstream via the enterocyte (Adetuyi et al., 2021).[47] These events are linked to pharmacological effects that last longer than their half-lives in plasma.

Antioxidant and anti-inflammatory

The generation of free radicals like reactive oxygen species (ROS) or nitrogen reactive species is the root cause of many oxidative-related illnesses, which include the most prevalent neurological disorders (Poprac et al., 2017).[48] We can only hope that antioxidant bioactive chemicals are abundant throughout many different dietary matrices, such as fruits, vegetables, cereal grains, edible flowers, and medicinal plants (Deng et al., 2013).[49] Additionally, recent studies have focused on the potent antioxidant and anti-inflammatory properties of ginger (Abolaji et al., 2017).[50] Antioxidant, antibacterial, anticancer, anti-inflammatory, anti-allergic, and neurodegenerative disease prevention are only some of the many bio-

logical properties attributed to gingerols and shogaols. Dried ginger outperformed fresh, stir-fried, and carbonized forms of the spice in tests measuring its antioxidant properties. This is because the polyphenol content is higher in dried ginger, whereas the gingerols in fresh ginger can be converted into the less potent shogaols during cooking processes like stir-frying and carbonization (Li et al., 2016). Further, ginger has been reported to be helpful for the protection of oxidative-related harm in the scientific literature (Akinyemi et al., 2013).[51] In a human chondrocyte cell culture, ginger root extract prevented the generation of reactive oxygen species (ROS) and decreased lipid peroxidation, indicating that it possessed antioxidant effects comparable to interleukin-1 (Hosseinzadeh et al., 2017). ROS production was also inhibited in human fibrosarcoma cells by ginger extract (Romero et al., 2018).[52] Malondialdehyde, another lipid peroxidation marker, was also decreased in rat cardiac homogenates treated with ginger extract. In particular, ginger's antioxidant properties have been seen through the Nrf2 signaling pathway (Peng et al., 2015). 6-shogaol upregulates Nrf2, metallothionein 1 (MT1), heme oxygenase-1 (HO1), ferritin light chain (FTL), aldo-keto reductase family 1 member B10 (AKR1B10), and -glutamyltransferase, which in turn enhances the intracellular glutathione/glutathione disulfide ratio (GSH/GSSG) in human colorectal cancer (GGTLA4). In vivo experiments on ginger extract have shown that powerful anti-inflammatory and antioxidant dosages range from 200 to 500 mg/kg/-day, while efficient immunomodulatory doses were shown to vary from 28 to 720 mg/kg/-day. Doses, routes of administration, and treatment duration can vary widely between studies (Jafarzadeh et al., 2018).[53] As much as four grams of ginger may be regularly consumed, according to safety reports (Nazir et al., 2022).[54] In both in vitro and in vivo studies, researchers have discovered that ginger and its supplementary biologically active compounds, particularly 6-shogaol, 6-gingerol, and oleoresin, show significant antioxidant properties by direct radical scavenging activity. The fundamental mechanisms involved also depend on the Nrf2 transcriptional activation being activated. Antioxidants are essential for warding off diseases like neurodegenerative disorders, which have been linked to an excessive ROS and NOS production (Dugasani et al., 2010).[55] Although studies have shown that ginger and its pharmacological ingredients have anti-inflammatory properties, the outcomes have been inconsistent (Arablou et al., 2014).[56] This discrepancy may be due to differences in study design, intervention time, subject characteristics, and dosages. Activation of Akt and nuclear factor-kappa B (NF-κB) can be blocked by ginger, which may explain its anti-inflammatory effects. Eukaryotic cells frequently employ the NF-κB pathway to regulate genes involved in cell proliferation and cell survival. NF-kappa B is an essential regulator of the inflammatory response because it promotes the production of inflammatory target genes like cytokines, chemokines, and COX2. This enzyme stimulates the manufacture of certain prostaglandins in response to inflammation, promoting the release of proinflammatory cytokines. Ginger decreases the production of cytokine genes and consequently the inflammatory response by blocking NF-kappa B (Wang et al., 2017).[7] In a meta-analysis from 2016, ginger treatment was demonstrated to lower C-reactive protein (CRP) as well as other extremely severe proteins (Mazidi et al., 2016).[57] In previous studies, Naderi et al. (2016) found that ginger powder administration at a daily dose of 1g was successful in lower-

ing plasma concentrations of CRP over a 12-week period (Munir et al., 2022). [58] Ginger has anti-inflammatory properties because, like turmeric, it has the capacity to block COX-2 and 5-lipoxygenase enzymes. This decreases amino acid metabolism. Pro-inflammatory thromboxanes and prostaglandins are also inhibited, and platelet aggregation is lowered (Azimi et al., 2014). [59] Ginger's anti-inflammatory properties are linked to its ability to inhibit COX-2 without impacting COX-1, which provides a potential benefit over conventional NSAIDs due to their associated negative effects (van Breemen et al., 2011). [60] Van Breemen et al. used pulsed ultra-filtration mass spectrometry to show that many compounds connected to gingerol were COX-2 ligands. Arachidonic acid cannot be turned into prostaglandin (PG) H2, which prevents it from being transformed into pro-inflammatory prostaglandins like prostaglandin D2 (PGD2) and E, unless cyclooxygenase-2 (COX-2) is inhibited. Nitric oxide, inflammatory cytokines, and prostaglandin synthase enzymatic activity have all been found to be inhibited, which may contribute to a reduced inflammatory response (Khan et al., 2019). [61] The therapeutic dose and dissolution rate characteristics of ginger forms, as well as the overall health, genetic predispositions, lifestyle choices, and nutritional status of consumers, may have an impact on the bioavailability, biodistribution, and finally the biological properties of ginger compounds. This may help to explain the contradictory or divergent results seen in in vitro and in vivo studies.

Table 2. The anti-inflammatory, antioxidant activities and immunomodulatory effects of ginger and its components.

Down-regulation of the	Immune reactions associated with Th1 cells Immune reactions involving Th17 cells Immune responses involving B cells The Cells That Display Antigens Mediators produced from arachidonic acid Chemokine and chemokine receptor expression is induced by oxidative stress. Proteins that bind together cells
Modulation of the	Responses of the immune system including Th2 cells Reactions of the immune system caused by Th9 cells Influence of Th22 cells on immunological responses Results from Macrophage Responses Secretion of Inflammatory and Anti-Inflammatory Cytokines
Up-regulation of the	Signaling pathways associated with Toll-like receptors Reactions involving inflammasomes Immune responses involving Treg cells

Antitumor and anticancer

In terms of the impact on the world's population, cancer is among the worst non-communicable diseases. Increases in aberrant cells in the human body over time can induce the development of malignant tumors (Greenwell & Rahman, 2015)[62] , some of which may spread to other parts of the body. These cells' ongoing proliferation is sometimes linked to how oxidative stress is affected. Alternative therapies are urgently needed as many of the available alternatives (such as cancer therapy, radiotherapy, synthetic drugs, etc.) have unfavorable adverse reactions (nausea, hair loss, etc.). In recent years, scientists have discovered the potential of many different plant species in the prevention and treatment of cancer, and the amount of work put into discovering and developing novel compounds is staggering. Ginger is a fantastic example of such MPs with excellent preventive and cura-

tive anticancer effects. Although these benefits are not yet known for all types of cancer, a study by Karna et al. in the United States found that ginger and its derivative (gingerol) had a wide range of effects on various different cancers, including lung, colon, ovarian, prostate, etc. According to Karna et al. (2012), a regular intake of ginger at a dosage of 100 mg/kg body weight reduced PC-3 xenograft growth, confirming its anti-prostate cancer effects both in vitro and in vivo. Interestingly, the same proportion in a different study reduced tumor necrosis factor-alpha (TNF-alpha) activity leading to the inhibition of rat liver cancer. Its effects on Panc-1 cells as well as other cell lines have been shown in vitro and in experimental animals, and it was successful over breast cancer when combined with several other spices like garlic and turmeric (Vemuri et al., 2017). [63] In terms of the impact indicated above, multiple studies have shown that ginger derivatives, such as 6-shogaol, 8-shogaol, 10-shogaols, 6-gingerol, 6-paradol, and zingerone, have anti-cancer properties against several cancer types, such as pulmonary, colorectal, gastrointestinal, cervical, and prostate cancer (Ogunlana et al. 2021). The anti-tumor influences of ginger have been related to a variety of molecular basis, including the upregulation of repressors, the initiation of programmed cell death, and the inhibition of vascular endothelial growth factor (VEGF), a tumor angiogenic component that stimulate the development and advancement of tumors.

Antihyperglycemic

Diabetes mellitus (DM) is one of the degenerative illnesses that is most widespread throughout the world. An hormonal disorder or metabolic disorder characterized by hyperglycemia (extremely high blood sugar levels) is triggered by insulin resistance or insulin deficiency in relation to carbohydrate intake, fat, or protein. For the treatment or control of diabetes mellitus, oral antidiabetic drugs, such as sulphonyl ureas, biguanides, and others, may be combined alongside non-pharmacological techniques (exercise, diet plan). There is an urgent need for an alternate method of treatment that has no or minimal side effects because of the risks associated with the use of these chemicals or synthetic agents (such as obesity), as well as their lack of accessibility and high cost. These days, even medical plants have these surprising characteristics. The World Health Organization has endorsed the use of MPs for diabetes management and control in multiple technical publications. It's fascinating to learn that a group of MPs have discovered a use as a treatment for diabetes and its problems (Parmar & Rupasinghe, 2015).[64] Ginger is one such conventional MP that helps diabetes. Indeed, numerous studies have been done to demonstrate the effectiveness of this spice in both in vitro and in vivo investigations (Mele, 2019). [65] Additional evidence may well be provided in Ojewole's (2006) paper, which was previously cited. In vitro and in animal models, its aqueous extract lowers blood sugar levels after streptozotocin administration. Ginger and its metabolites have indeed been investigated for their capacity to cure these disorders since oxidative stress has been associated with type 2 diabetes and its complications, such as hyperlipidemia, hypercholesterolemia, myopia, and nerve damage. [66]

Antihypertensive

High blood pressure in the arteries is the hallmark of hypertension, also known as the ”silent killer” due to the lack of symptoms it typically causes in its victims. This condition manifests itself when both the systolic and diastolic blood pressures are greater than 140/90 mmHg. Hypertension was found to be associated with several risk factors for cardiovascular disease, including excessive salt intake, smoking, alcohol consumption, renal vasculature narrowing, and the use of hormonal birth control. Diuretics, beta-blockers (atenolol), angiotensin-converting enzyme inhibitor (Lisinopril), calcium channel blockers, and other synthetic compounds may be used for treatment (Adetuyi et al., 2020). Non-pharmacological methods (such as changing one’s lifestyle) are also an option. But unfortunately, all these antihypertensive medicines cause terrible side effects including angioedema, dry cough, weakness, headaches, etc.; hence, there is a need for an alternative method of therapy for people with high blood pressure (HBP). Ginger is a well-known example of a herb that has shown useful in the fight against HBP treatment using herbal products from MPs. Ginger extracts at concentrations between 0.3 and 3 mg/kg were found to reduce arterial blood pressure in rats and guinea pigs. Another study with human subjects confirmed ginger’s antihypertensive action by showing that taking 10 grams of the spice twice daily resulted in a decrease in arterial blood pressure to 94.80 mmHg after 2 months (Didunyemi et al., 2020).[67] To be clear, the activity of this spice was previously proven to occur via muscarinic receptor stimulation and calcium channel blocking.

Anticholesterolemic

Cholesterol is a sterol found in eukaryotic (higher) plasma membranes and essential for proper cellular function and development. Suffice it to state that there is good (high-density lipoprotein cholesterol, or HDL-c) and bad (low-density lipoprotein cholesterol, or LDL-c) cholesterol, and that hypercholesterolemia develops when there is an elevated level of cholesterol (Kuppusamy et al., 2015).[68] There are reports of high levels of cholesterol in the blood on the influence of excessive production of FRs (Balogun & Ashafa, 2018),[69] and hypercholesterolemia is a risk factor to many disorders including cardiovascular disease, atherosclerosis, myocardial infarction (MI), etc. In order to treat, cure, or prevent illness, herbal medicines (also known as MPs) have been used for centuries (Duke, 2002).[70] For example, ginger is one herbal remedy that has been shown to reduce cholesterol levels. Oral administration of 500 mg/kg bw of aqueous extract reduced high cholesterol in Wistar rats (Thomson et al., 2002). Cholesterol and other lipid profiles were reduced by 29% in a mouse research after receiving 250 mg/kg of the ethanolic extract examined in rabbits and rats (100, 400 mg/kg bw) fed a high-fat diet (Nammi et al., 2009).[71] In keeping with this, a study on humans discovered that low-dose concurrent administration of atorvastatin and ginger lowered blood cholesterol levels, particularly in those with hepatic lesion or inflammation (Adetuyi et al., 2022).

Antimicrobial

Worldwide, infectious diseases are rapidly overtaking all others as the leading cause of death. Multiple bacterial etiological factors contribute to infectious disease, and antibiotics have become the silver bullet against their debilitating effects. But it's vital to remember that antimicrobial resistance is currently on the increase, making even prudent use of these medications pointless. Antibiotic resistance is a growing concern, and as a result, MPs are increasingly being used to treat infectious diseases. Many plants, including ginger, have been shown to have antimicrobial effects in a variety of in vitro, in vivo, and preclinical studies, including those conducted with ethanol, ethyl acetate, and hexane. Ginger compounds have been found to possess antimicrobial properties against a variety of microbes and mycobacteria, including Acinetobacter baumannii, Helicobacter pylori, Mycobacterium avium, and Mycobacteriumtuberculosis. These compounds include 6-dehydrogingerdione, 6-gingerol, 10-gingerol, and 6-shogaol. Intriguingly, reports of ginger and/or its derivatives being more effective than conventional synthetic antibiotics against infectious disorders are cited as evidence of their efficacy (Sebiomo et al., 2011). [72]

Antiulcer (gastroprotective)

The imbalance between protective and aggressive components is the root cause of gastric and duodenal ulcers, a disease that has affected the majority of the world's population for over ten (10) decades (Asnaashari et al., 2018).[73] Ulcer development and/or worsening can be affected by a wide variety of factors, some of which are etiologic (Helicobacter pylori) and others not (such as a sedentary lifestyle, food, medicine (NSAIDs), smoking, bacterial infection, free radicals, etc.). Antimicrobial drugs (such as metronidazole, tetracycline, amoxicillin, etc.) are used in the therapies to eradicate H. pylori, along with anti - secretory medications (such as omeprazole), H2 receptor antagonists (such as cimetidine, ranitidine, etc.), as well as other medications that aim to damage the bacteria's cellular membrane (bismuth salt). However, these sequences of therapies result in toxicities, which has led to a demand for a less toxic alternative, such as that which can be found in medicinal plants like ginger. Ginger's antiulcerative effects come about because of its ability to increase mucin synthesis and inhibit an enzyme (thromboxane synthase) (Mele, 2019). [65]

Antiemetic

Ginger was reported to exhibit an anti-serotonin and 5-HT3 receptor antagonist impact in an animal study, which caused the animals to feel queasy and puke following surgery (Vutyavanich et al., 2001). [74] It was also found that gingerol, shogaols, galanolactone, and diterpenoid, all of which are derived from ginger, were effective in reducing nausea and vomiting (Olajide et al., 2022). Others found descriptions of cancer patients' experiences with nausea and vomiting treatment (Revol et al., 2019). [75]

Hepatoprotective

The liver is responsible for the metabolism of medicines and chemicals and is the second biggest organ in the body (after the skin). For this reason, maintaining a healthy body requires paying close attention to this organ. Liver illnesses are a serious public health issue in the world today, usually brought on by exposure to or consumption of hazardous toxins, and conventional treatments for them are inefficient and have adverse effects. Yet MPs like ginger have shown helpful in alleviating these symptoms. Researchers found that either 100 mg/kg bw of ginger alone or 100 mg/kg bw of ginger with curcumin were able to alleviate the liver impairment caused by carbon tetrachloride in rats with cirrhosis (Abd-Allah et al., 2016).[76] In response to acetaminophen-induced hepatic injury, ginger substantially decreases the levels of liver function enzymes (alanine transaminase and aspartate aminotransferase) and boosts the antioxidant enzyme activities (superoxide dismutase, catalase, and glutathione peroxidase), according to various researches (Rahmani et al., 2014). [77]

Neuroprotective

The procedure of shielding the central nervous system (CNS) from nerve cell damages brought on by acute and/or chronic neurological diseases (such as brain haemorrhage, Alzheimer's, Huntington's, and Parkinson's diseases), which result in the degeneration of CNS neurons and, in turn, a deterioration of the patients' intellectual capacity or capacity for logical reasoning, is referred to as "neuroprotection" (Elufioye et al., 2017). [78] It's worth noting that age raises the likelihood of having neurological diseases (Ogunlana et al., 2020). Inherent phenolic and flavonoid components in medicinal plants like ginger are responsible for their beneficial effects in illness management and therapy, including that of NDD. The toxicity caused by monosodium glutamate is reduced in rats given a root extract of ginger at 100 mg/kg body weight. Since neuropathy is a common consequence of diabetes mellitus, it stands to reason that there is an association between FR, NDD, and diabetes. In fact, ginger has been shown in multiple studies to boost the brain's antioxidant defense mechanism after streptozotocin induction (El-Akabawy & El-Kholy, 2014). [79] The effects of 6-shogaol on microglia in transient global ischemia were also investigated (Ha et al., 2012).[22]

Alzheimer's disease

The neurodegenerative disease Alzheimer's disease (AD) is associated with severe memory loss and cognitive decline. The accumulation of -amyloid protein, hyperphosphorylation of tau protein, fluctuations in neurotransmitters, oxidative stress, apoptosis, and inflammatory responses, and other cellular damage are all implicated in its development (Melo et al., 2011). [80] Current research indicates that ethnomedicinal plants, like Zingiber officinale, may be beneficial in the management and treatment of a wide diverse array of dysfunctions as well, offering an unusual chance for their assessment in the treatment of impaired memory. Ethnomedicinal plants, like Zingiber officinale, have been utilized for

centuries to treat a broad range of conditions (Karam et al., 2014).[81]

Due to its anti-inflammatory and antioxidant qualities, Zingiber officinale is a therapeutic target for neurodegenerative disorders like Alzheimer's. In particular, ginger has been proven to boost the expression of nerve growth factor (NGF), which is essential for better memory performance, easier long-term hippocampus augmentation, and faster neurite outgrowth, all of which have been demonstrated in clinical investigations. Preclinical investigations in mice have demonstrated a relationship between increased synaptogenesis and the stimulation of cAMP response element binding protein (CREBs) and extracellular signal-regulating kinases (ERKs) (Moon et al., 2014).[82] The expression of inflammatory cytokines and chemokines in THP-1 cells has also been found to be suppressed by ginger. Researchers found that ginger dramatically reduced the mRNA levels of several pro-inflammatory cytokines and endothelium adhesion activating proteins in experimental animals (Grzanna et al., 2004).[83] Several bioactive compounds of Zingiber officinale have been shown to cross the blood-brain barrier in in vitro and animal studies, leading us to speculate that the plant's beneficial properties, as observed in a wide range of pathologies, may have utility in the treatment of neurodegenerative diseases like Alzheimer's (Simon et al., 2020).[84] Brain tumors, cardiovascular accidents, neurosis, sadness, insomnia, and psychiatric disorders are only some of the diseases that Zingiber officinale may be able to treat. It is considered a safe nutraceutical that has the potential to be utilized in the treatment of neurodegenerative illnesses, and it is on the "Generally Recognized as Safe" (GRAS) list of the US Food and Drug Administration (FDA) (Karam et al., 2014).[81] Human clinical trials, however, are scant, and those that do exist sometimes mention Davaie Loban or Kihito, two supplements containing a blend of herbs used in traditional Oriental medicine that may or may not contain ginger. The dietary supplement Cognitex, which includes sage, blueberry, and Zingiber officinale, has been shown to increase cognitive capacities, according to the works of other authors. The results of Saenhong et al (2012) analysis of ginger's individual effects are notable. A placebo-controlled study using standardized ginger extracts showed an improvement in participants' ability to comprehend information, with the greatest results shown at doses of 800 mg daily.[85]

Parkinson's disease

In adults, Parkinson's disease (PD) manifests itself as a complex neurodegenerative process, and it is the second most frequent form of neurodegeneration after Alzheimer's dementia. Dopaminergic neuron loss in the midbrain substantia nigra pars compacta (SNpc) and insoluble masses of improperly folded alpha-synuclein protein (Lewy bodies) are the pathogenic underpinnings of this disorder. This neurodegeneration leads to a loss of dopaminergic neurons in the SNpc's projections to the striatum, which disrupts the normal functioning of the basal ganglia (Obeso et al., 2017).[86] These events cause a deficiency in dopamine (DA), which in turn causes the hallmark symptoms of the condition, such as resting tremor, bradykinesia, postural rigidity, and instability, to manifest. Non-motor symptoms, such as apathy or depression, sleep difficulties, autonomic dysfunction, or sensory

abnormalities, can also appear and are more common as the disease advances (Valadez-Barba et al., 2021). [87] Oxidative stress and iron accumulation in the brain are two environmental factors that have been linked to the development of PD, together with genetic predisposition. It is now well established that neuroinflammation plays a critical role in the etiology, pathogenesis, and progression of PD and other neurodegenerative disorders (Adetuyi et al., 2015). Parkinson's disease (PD) is associated with oxidative stress due to mitochondrial dysfunction and chronic inflammation, both of which generate reactive oxygen species (ROS) and reactive nitrogen species (RNS). Dopaminergic neurons in the substantia nigra die as a result of these reactive species combining with the deposited iron in the brain and damaging brain structures. This mechanism initiates a feedback loop comprising cell injury, neuroinflammation, and the formation of reactive oxygen and nitrogen species (ROS/RNS), ultimately leading to the death of neurons (Perfeito et al., 2012). [88] Damage to the brain's structure and the loss of dopaminergic neurons in the substantia nigra are the results of oxidative stress and elevated levels of tissular iron. Therefore, the increasing motor impairment seen in PD is attributable to the death of these substantia nigra dopaminergic neurons. In fact, people with PD have considerably elevated levels of oxidative stress and inflammatory markers. As it stands, the only effect that the current treatments have is symptomatic. Among medications for PD, levodopa has proven to be the most successful in reducing the disease's motor symptoms. To yet, there is no medication that can stop the neurodegeneration that causes PD, and the treatments available only ameliorate the symptoms. The potential therapeutic effect of natural items like ginger on the onset and course of PD has garnered more attention in recent years. Using a PD model, Park et al. (2013) found that 6-shogaol protected dopaminergic cells from MPP+ - and MPTP-induced neurotoxicity by reducing microglial neuroinflammatory responses. [89] The findings of Moon et al. (2014) imply that 6-shogaol may help alleviate memory loss and prevent glial cell activation in dementia animal models. [22,82] Specifically, Kongsui et al. (2020) hypothesized that ginger crude extract may be used as a neuroprotective agent against the neurodegenerative disorders brought on by lipopolysaccharide. [90] The polyphenolic components in ginger may be responsible for its therapeutic benefits on MSG-induced neurodegenerative diseases, as demonstrated in a separate study conducted by Hussein et al. (2017). [91]

Table 3. Parkinson's disease and ginger.

Effects	Reference
Inhibiting Astrocytic Hyperactivation suppressed GFAP and IL-1ß expression in the hippocampus, hence limiting LPS-induced neuronal cell death.	90
Parkinson's disease (PD) neurodegeneration is caused by low levels of antioxidants that are unable to control free radical and ROS/RNS production, which leads to inflammation and further neurodegeneration.	92
TNF-α, nitric oxide, cyclooxygenase-2, and inducible nitric oxide synthase are all inflammatory pathway components that have been inhibited (iNOS)	89
In animal models of dementia, 6-shogaol has been found to decrease glial cell activation and improve memory.	82

Multiple sclerosis

Early symptoms of multiple sclerosis (MS) include inflammation, demyelination of neurons, and axonal degeneration. MS is a chronic inflammatory disease of the central nervous system (CNS). Multiple sclerosis (MS) is one of the most common causes of neurological dysfunction in young individuals (Awoyelu et al., 2020),[93] most often affecting women between the ages of 25 and 30 (Perez-Carmona et al., 2019).[94] Multiple sclerosis is currently understood to be a chronic, inflammatory illness with neurodegenerative symptoms (Rio & Montalban, 2014).[95] Some people have a higher predisposition than others to develop an aberrant autoimmune response, and environmental factors play a role in both the onset and the course of the disease. The major histocompatibility complex plays a pivotal role in mediating inherited susceptibility. Epstein-Barr virus infection, overweight in adolescence, low vitamin D levels, and smoking are all linked to an increased risk (Perez-Carmona et al., 2019).[94] An estimated 2.5 million people worldwide are affiicted with MS, with about 700,000 of those people residing in Europe. This number has been steadily rising over the past few decades (Browne et al., 2014).[96] Damage to the myelin sheath and disruption of myelinated tracts in the central nervous system are thought to be the root causes of MS symptoms, although the specific etiology of the disease is still unknown despite decades of research (Dworsky-Fried et al., 2021).[97] Generally speaking, patients will experience cognitive, sensory, motor, and autonomic abnormalities as part of the disease's hallmark clinical manifestations. Coordination and balance issues, eyesight problems, difficulties with executive functioning, chronic pain, and emotional instability are all indications of this condition. Unfortunately, there is presently no surefire way to get rid of MS. While there is no cure for MS, several pharmaceutical and rehabilitation therapy exist to treat acute attacks, ameliorate symptoms, and alter the disease's progression (Gilmour et al., 2018).[98] Herbal therapy and other forms of complementary and alternative medicine have recently shown promise as a treatment for multiple sclerosis (Yadav et al., 2015).[99] Such therapies, of which ginger is one example, have the potential to be useful in the treatment of MS by, among other things, inhibiting demyelination, promoting remyelination, and, most importantly, suppressing or lowering inflammatory processes. Reducing inflammatory processes happens when inflammatory cell infiltration into the central nervous system is blocked, which in turn decreases production of proinflammatory cytokines. Inflammation plays a crucial role in multiple sclerosis and is linked to demyelination and neurodegeneration, both of which are magnified during the disease's acute and recurrent phases (Yadav et al., 2015).[99] Neutrophils, dendritic cells, macrophages, CD4+ T cells, and CD8+ T cells are just few of the leukocytes that infiltrate the central nervous system (CNS), with CD4+ T cells having the most significant effect on demyelination of neurons and axonal damage (Glatigny & Bettelli, 2018).[100] To polarize myelin-specific T-lymphocytes into Th1, Th2, Th9, Th17, Th22, and Treg cells, DCs must traverse the compromised blood-brain barrier. Treg and Th2 cells have a protective effect against autoimmune disorders, but Th1 and Th17 cells have a harmful role in the immunopathological process of MS (Jafarzadeh et al., 2014).[101] The proinflammatory cytokines secreted by astrocytes and microglia are also involved in the development of multiple sclerosis (Jafarzadeh & Nemati, 2018).[53] Today, more than a dozen different med-

ications are available for the management of multiple sclerosis. But their mild effectiveness and potential for harm cast doubt on their use. There are plant-based components with anti-inflammatory and immunomodulatory characteristics and low side effects, which raises the prospect that ginger can be used to alleviate MS symptoms (Jafarzadeh & Nemati, 2018).[53] In the treatment of multiple sclerosis, ginger consumption is risk-free and there is no possible danger of clinically meaningful interactions, according to a recent systematic study on the contemporaneous consumption of ginger extract and other medications (Petersen et al., 2021).[102] Due to ginger's anticoagulant characteristics, coadministration with other anticoagulants was shown to be the only contraindication. The autoimmune disease known as experimental autoimmune encephalomyelitis (EAE) is a model of human multiple sclerosis that can be induced in susceptible animals. It is commonly produced in mice because they provide a robust model in which to investigate the causes of MS and to evaluate potential treatments (Lassmann & Bradl, 2017).[103] Clinical symptoms of EAE were delayed and illness severity scores were reduced in several investigations involving ginger extract and EAE in mice compared to placebo (Jafarzadeh et al., 2017). Primary demyelination of axons is the hallmark of multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE), leading to signal blockage or impaired conduction at the demyelinated location.[104] Clinical symptoms of EAE appear to be mitigated by pre-treatment with ginger extract, perhaps due to the up-regulation of inflammatory cytokines and chemokines (IL-23, IL-33, IFN-, CCL20, and CCL22).[105,106] Both 6-shogaol and 6-paradol appear to alleviate clinical symptoms in mice with EAE, according to a recent study. Also, they were linked to reduced neuroinflammatory responses like astrogliosis, microglial activation, and TNF-α expression. Since this is the case, it is possible that 6-shogaol and 6-paradol are the effective components of ginger extract.[104] The similarities between EAE in mice and MS in humans make this model a useful one for studying the disease and developing therapies.[107] Therefore, even if additional study is required, we see it as a promising and crucial first step in assessing the efficacy before human investigations.

CONCLUSIONS

The antioxidant and anti-inflammatory characteristics of ginger's many bioactive compounds—including gingerols, shogaols, and paradols—may be useful in treating neurological illnesses. Unfortunately, the medications used to treat these conditions have limited efficacy and might cause unwanted side effects because of their involvement of multiple inflammatory, oxidative, and immune-pathological characteristics in their etiology. Based on its antioxidant, immune-modulatory, and anti-inflammatory properties, ginger appears to be able to thwart the progression of multiple sclerosis and reduce the impact of other neurological illnesses like Parkinson's, Alzheimer's, migraine, and epilepsy. However, more research is needed to see if greater doses and/or longer delivery methods are more beneficial without creating undesirable side effects. Nutraceutical formulations including ginger or ginger extracts may offer protection against neurodegenerative disorders. New

pharmaceutical formulations for delivering ginger's therapeutic components are being developed to overcome the low bioavailability and substantial phase II metabolism that have hampered its usage in neurodegenerative diseases. There is promising evidence for the therapeutic potential of ginger in neurodegenerative illnesses, but further toxicological and pharmacokinetic investigations of these novel formulations are required before they can be applied in human trials.

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REFERENCES

1. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, et al. Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol. 2019;15(10):565–581. 10.1038/s41582-019-0244-7.
2. Reddy PH, Manczak M, Yin X, Grady MC, Mitchell A, Tonk S, et al. Protective effects of indian spice curcumin against amyloid-β in Alzheimer's disease. J Alzheimers Dis. 2018;61(3):843–866. 10.3233/JAD-170512.
3. Mann A. Biopotency role of culinary spices and herbs and their chemical constituents in health and commonly used spices in Nigerian dishes and snacks. African J Food Sci. 2011;5:111–135.
4. Tanaka K, Arita M, Sakurai H, Ono N, Tezuka Y, et al. Analysis of chemical properties of edible and medicinal ginger by metabolomics approach. Biomed Res Int. 2015;p. 671058–671058. 10.1155/2015/671058.
5. Semwal RB, Semwal DK, Combrinck S, Viljoen AM, et al. Gingerols and shogaols: Important nutraceutical principles from ginger. Phytochemistry. 2015;117:554–568. 10.1016/j.phytochem.2015.07.012.
6. Anh NH, Kim SJ, Long NP, Min JE, Yoon YC, Lee EG, et al. Ginger on human health: a comprehensive systematic review of 109 randomized controlled trials. Nutrients. 2020;12(1):157–157. 10.3390/nu12010157.
7. Wang J, Ke W, Bao R, Hu X, Chen F, et al. Beneficial effects of ginger Zingiber officinale roscoe on obesity and metabolic syndrome: a review. Ann N Y Acad Sci. 2017;1398(1):83–98. 10.1111/nyas.13375.
8. Zhu J, Chen H, Song Z, Wang X, Sun Z, et al. Effects of ginger (Zingiber officinale Roscoe) on Type 2 diabetes mellitus and components of the metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2018;p. 5692962–5692962. 10.1155/2018/5692962.
9. Choi JG, Kim SY, Jeong M, Oh MS, et al. Pharmacotherapeutic potential of ginger and its compounds in age-related neurological disorders. Pharmacol Ther. 2018;182:56–69. 10.1016/j.pharmthera.2017.08.010.
10. Adeleke DA, Olajide PA, Omowumi OS, Okunlola DD, Taiwo AM, Adetuyi BO, et al. Effect of Monosodium Glutamate on the Body System. World News of Natural Sciences. 2022;44:1–23. 10.17179/excli2018-1092.
11. Zhang F, Zhang JG, Yang W, Xu P, Xiao YL, Zhang HT, et al. 6-Gingerol attenuates LPS-induced neuroinflammation and cognitive impairment partially via suppressing astrocyte overactivation. Biomed Pharmacother. 2018;107:1523–1532. 10.1016/j.biopha.2018.08.136.
12. Sahardi M, Nfn, Ginger MS. Zingiber (officinale Roscoe) in the prevention of ageing and degenerative diseases: review of current evidence. Evid Based Complement Alternat Med. 2019;p. 5054395–5054395. 10.1155/2019/5054395.
13. Pickersgill B. The Cultural History of Plants. Routledge. G P, M N, editors; 2005.

14. Mashhadi NS, Ghiasvand R, Askari G, Hariri M, Darvishi L, Mofid MR, et al. Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: review of current evidence. Int J Prev Med. 2013;4(1):36–42.
15. Zadeh JB, Kor NM. Physiological and pharmaceutical effects of Ginger (Zingiber officinale Roscoe) as a valuable medicinal plant. Eur J Exp Biol. 2014;4(1):87–90.
16. Asadi-Samani M, Rafieian-Kopaei M, Azimi N. Gundelia: a systematic review of medicinal and molecular perspective. Pakistan J Biol Sci PJBS. 2013;16(21):1238–1285. 10.3923/pjbs.2013.1238.1247.
17. Didunyemi MO, Adetuyi BO, Oyebanjo OO. Morinda lucida attenuates acetaminophen-induced oxidative damage and hepatotoxicity in rats. J Biomed Sci. 2019;8(2):0–0.
18. Kiran CR, Chakka AK, Amma K, Menon AN, Kumar M, Venugopalan VV, et al. Influence of cultivar and maturity at harvest on the essential oil composition, oleo-resin and [6]-gingerol contents in fresh ginger from northeast India. J Agric Food Chem. 2013;61(17):4145–4154. 10.1021/jf400095y.
19. Yusof M, A Y. Gingerol and its role in chronic diseases. Adv Exp Med Biol. 2016;929:177–207. 10.1007/978-3-319-41342-6$_8$.
20. Asamenew G, Kim HW, Lee MK, Lee SH, Kim YJ, Cha YS, et al. Characterization of phenolic compounds from normal ginger (Zingiber officinale Rosc) and black ginger (kaempferia parviflora wall) using UPLC-DAD-QToF-MS. Eur Food Res Technol. 2019;245(1):653–665. 10.1007/s00217-018-3188-z.
21. Mbaveng AT, Kuete V. Zingiber officinale. Medicinal Spices and Vegetables from Africa. Academic Press; 2017.
22. Ha SK, Moon E, Ju MS, Kim DH, Ryu JH, Oh MS, et al. 6-Shogaol, a ginger product, modulates neuroinflammation: A new approach to neuroprotection. Neuropharmacology. 2012;63(2):211–223. 10.1016/j.neuropharm.2012.03.016.
23. Kubra IR, Rao LJM. An impression on current developments in the technology, chemistry, and biological activities of ginger (Zingiber officinale Roscoe). Crit Rev Food Sci Nutr. 2012;52(8):651–688. 10.1080/10408398.2010.505689.
24. Jafarzadeh A, Jafarzadeh S, Nemati M. Therapeutic potential of ginger against COVID-19: Is there enough evidence? J Tradit Chin Med Sci. 2021;8(4):267–279. 10.1016/j.jtcms.2021.10.001.
25. Srinivasan K. Ginger rhizomes (Zingiber officinale): A spice with multiple health beneficial potentials. PharmaNutrition. 2017;5(1):18–28. 10.1016/j.phanu.2017.01.001.
26. Kumara M, Shylajab MR, Nazeemc PA, Babu T, et al. 6-Gingerol is the most potent anticancerous compound in ginger. Zingiber officinale Rosc) J Dev Drugs. 2017;6(1):1–6. 10.4172/2329-6631.1000167.
27. Xue Y, Zhang M, Liu M, Liu Y, Li L, Han X, et al. 8-Gingerol Ameliorates Myocardial Fibrosis by Attenuating Reactive Oxygen Species, Apoptosis, and Autophagy via the PI3K/Akt/mTOR Signaling Pathway. Front Pharmacol. 2021;12:711701–711701. 10.3389/fphar.2021.711701.

28. Mase N, Kitagawa N, Takabe K. Protection-, Salt-, and Metal-Free Syntheses of [n]-Shogaols by Use of Dimethylammonium Dimethyl Carbamate (DIMCARB) without Protecting Groups. Synlett. 2010;2010(01):93–96. 10.1055/s-0029-1218389.
29. Bischoff-Kont I, Fürst R. Benefits of ginger and its constituent 6-shogaol in inhibiting inflammatory processes. Pharmaceuticals. 2021;14(6):571–571. 10.3390/ph14060571.
30. Sang S, Hong J, Wu H, Liu J, Yang CS, Pan MH, et al. Increased growth inhibitory effects on human cancer cells and anti-inflammatory potency of shogaols from Zingiber officinale relative to gingerols. J Agric Food Chem. 2009;57(22):10645–10650. 10.1021/jf9027443.
31. Hattori H, Mori T, Shibata T, Kita M, Mitsunaga T, et al. 6-Paradol Acts as a Potential Anti-obesity Vanilloid from Grains of Paradise. Mol Nutr Food Res. 2021;65(16):2100185–2100185. 10.1002/mnfr.202100185.
32. Chen H, Lv L, Soroka D, Warin RF, Parks TA, Hu Y, et al. Metabolism of [6]-shogaol in mice and in cancer cells. Drug Metab Dispos. 2012;40(4):742–753. 10.1124/dmd.111.043331.
33. Wei CK, Tsai YH, Korinek M, Hung PH, El-Shazly M, Cheng YB, et al. 6-Paradol and 6-Shogaol, the Pungent Compounds of Ginger, Promote Glucose Utilization in Adipocytes and Myotubes, and 6-Paradol Reduces Blood Glucose in High-Fat Diet-Fed Mice. Int J Mol Sci. 2017;18(1):168–168. 10.3390/ijms18010168.
34. Baliga MS, Haniadka R, Pereira MM, Souza JJ, Pallaty PL, Bhat HP, et al. Update on the chemopreventive effects of ginger and its phytochemicals. Crit Rev Food Sci Nutr. 2011;51(6):499–523. 10.1080/10408391003698669.
35. Bashir N, Ahmad SB, Rehman MU, Muzamil S, Bhat RR, Mir MUR, et al. Zingerone (4-(four-hydroxy-3-methylphenyl) butane-two-1) modulates adjuvant-induced rheumatoid arthritis by regulating inflammatory cytokines and antioxidants. Redox Rep. 2021;26(1):62–69. 10.1080/13510002.2021.1907518.
36. Mohammed HM. Zingerone ameliorates non-alcoholic fatty liver disease in rats by activating AMPK. J Food Biochem. 2022;46(7):14149–14149. 10.1111/jbc.14149.
37. Kukula-Koch W, Koch W, Czernicka L, Glowniak K, Asakawa Y, Umeyama A, et al. MAO-A Inhibitory Potential of Terpene Constituents from Ginger Rhizomes-A Bioactivity Guided Fractionation. Molecules. 2018;23(6):1301–1301. 10.3390/molecules23061301.
38. Togar B, Turkez H, Tatar A, Hacimuftuoglu A, Geyikoglu F, et al. Cytotoxicity and genotoxicity of zingiberene on different neuron cell lines in vitro. Cytotechnology. 2015;67(6):939–946. 10.1007/s10616-014-9729-9.
39. Togar BASAK, Türkez H, Stefano AD, Tatar A, Cetin DAMLA, et al. Zingiberene attenuates hydrogen peroxide-induced toxicity in neuronal cells. Hum Exp Toxicol. 2015;34(2):135–144. 10.1177/0960327114538987.
40. Rahman HS, Abdullah R, Abdul AB, Allaudin ZN, Namvar F, Othman HH, et al.. Zerumbone, a Natural Dietary Sesquiterpene from Zingiber Zerumbet for Leukaemia Therapy In Vitro.; 2013. 10.2174/2210289201304010067.

41. Abuzahra HM, Rajendran P, Ismail MB. Zerumbone Exhibit Protective Effect against Zearalenone In-Duced Toxicity via Ameliorating Inflammation and Oxidative Stress Induced Apoptosis. Antioxidants. 2021;10(10):1593–1593. 10.3390/antiox10101593.

42. Kim A, Gwon MH, Lee W, Moon HR, Yun, M J, et al. Zerumbone suppresses high glucose and LPS-induced inflammation in THP1-derived macrophages by inhibiting the NF-κB/TLR signaling pathway. Nutr Res. 2022;100:58–69. 10.1016/j.nutres.2022.01.002.

43. Li J, Wang L, Sun Y, Wang Z, Qian Y, Duraisamy V, et al. Zerumbone-induced reactive oxygen species-mediated oxidative stress re-sensitizes breast cancer cells to paclitaxel. Biotechnol Appl Biochem. 2022;70(1):28–37. 10.1002/bab.2326.

44. He SM, Zhou CE, F S, Adme, et al. ADME properties of herbal medicines in humans: evidence, challenges and strategies. Curr Pharm Des. 2011;17(4):357–407. 10.2174/138161211795164194.

45. Gessner A, König J, Fromm MF. Clinical aspects of transportermediated drug-drug interactions. Clin Pharmacol Ther. 2019;105(6):1386–94. 10.1002/cpt.1360.

46. Pfeiffer E, Heuschmid FF, Kranz S, Metzler M, et al. Microsomal hydroxylation and glucuronidation of [6]-gingerol. J Agric Food Chem. 2006;54(23):8769–74. 10.1021/jf062235l.

47. Adetuyi BO, Toloyai PEY, Ojugbeli ET, Oyebanjo OT, Adetuyi OA, Uche CZ, et al. Neurorestorative Roles of Microgliosis and Astrogliosis in Neuroinflammation and Neurodegeneration. J Medical Biomed Sci . 2021;1(1):1–5. 10.54117/sjmams.v1i1.1.

48. Poprac P, Jomova K, Simunkova M, Kollar V, Rhodes CJ, Valko M, et al. Targeting free radicals in oxidative stress-related human diseases. Trends Pharmacol Sci. 2017;38(7):592–607. 10.1016/j.tips.2017.04.005.

49. Deng GF, Lin X, Xu XR, Gao LL, Xie JF, Li HB, et al. Antioxidant capacities and total phenolic contents of 56 vegetables. J Funct Foods. 2013;5(1):260–266. 10.1016/j.jff.2012.10.015.

50. Abolaji AO, Ojo M, Afolabi TT, Arowoogun MD, Nwawolor D, Farombi EO, et al. Protective properties of 6-gingerol-rich fraction from Zingiber officinale (Ginger) on chlorpyrifos-induced oxidative damage and inflammation in the brain, ovary and uterus of rats. Chem Biol Interact. 2017;270:15–23. 10.1016/j.cbi.2017.03.017.

51. Akinyemi AJ, Ademiluyi AO, Oboh G. Aqueous extracts of two varieties of ginger (Zingiber officinale) inhibit angiotensin I-converting enzyme, iron(II), and sodium nitroprusside-induced lipid peroxidation in the rat heart in vitro. J Med Food. 2013;16(7):641–647. 10.1089/jmf.2012.0022.

52. Romero A, Forero M, Sequeda-Castañeda LG, Grismaldo A, Iglesias J, Celiszambrano CA, et al. Effect of ginger extract on membrane potential changes and AKT activation on a peroxide-induced oxidative stress cell model. J King Saud Univ. 2018;30(2):263–272. 10.1016/j.jksus.2017.09.015.

53. Jafarzadeh A, Nemati M. Therapeutic potentials of ginger for treatment of Multiple sclerosis: a review with emphasis on its immunomodulatory, anti-

inflammatory and anti-oxidative properties. J Neuroimmunol. 2018;324:54–75. 10.1016/j.jneuroim.2018.09.003.

54. Nazir A, Itrat N, Shahid A, Mushtaq Z, Abdulrahman SA, Egbuna C, et al. Orange Peel as Source of Nutraceuticals. In: Food and Agricultural Byproducts as Important Source of Valuable Nutraceuticals. Springer; 2022. p. 97–106.
55. Dugasani S, Pichika MR, Nadarajah VD, Balijepalli MK, Tandra S, Korlakunta JN. Comparative antioxidant and anti-inflammatory effects of [6]-gingerol. J Ethnopharmacol. 2010;127:515–535.
56. Arablou T, Aryaeian N, Valizadeh M, Sharifi F, Hosseini A, Djalali M, et al. The effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus. Int J Food Sci Nutr. 2014;65(4):515–535. 10.3109/09637486.2014.880671.
57. Mazidi M, Gao HK, Rezaie P, Ferns GA. The effect of ginger supplementation on serum C-reactive protein, lipid profile and glycaemia: a systematic review and meta-analysis. Food Nutr Res. 2016;60:32613–32613.
58. Munir N, Hasnain M, Waqif H, Adetuyi BO, Egbuna C, Olisah MC, et al. Gelling Agents, Micro and Nanogels in Food System Applications. In: Application of Nanotechnology in Food Science, Processing and Packaging. Springer; 2022. p. 153–167.
59. Azimi P, Ghiasvand R, Feizi A, Hariri M, Abbasi B, et al. Effects of cinnamon, cardamom, saffron, and ginger consumption on markers of glycemic control, lipid profile, oxidative stress, and inflammation in type 2 diabetes patients. Rev Diabet Stud. 2014;11(3-4):258–66. 10.1900/RDS.2014.11.258.
60. Van Breemen RB, Tao Y, Li W. Cyclooxygenase-2 inhibitors in ginger (Zingiber officinale). Fitoterapia. 2011;82(1):38–43. 10.1016/j.fitote.2010.09.004.
61. Khan M, Ullah N, Azhar M, Komal W, Muhammad W. A mini-review on the therapeutic potential of Zingiber officinale (ginger). Nat Prod An Indian J. 2019;15:125–125.
62. Greenwell M, Rahman P. Medicinal plants: Their use in anticancer treatment. International Journal of Pharmaceutical Sciences and Research. 2015;6(10):4103–4115. 10.13040/IJPSR.0975-8232.6(10).4103-12.
63. Vemuri SK, Banala RR, Subbaiah G, Srivastava SK, Reddy AG, Malarvili T, et al. Anti-cancer potential of a mix of natural extracts of turmeric, ginger and garlic: A cell-based study. Egypt j basic appl sci. 2017;4(4):332–344. 10.1016/j.ejbas.2017.07.005.
64. Parmar I, Rupasinghe H. Antioxidant capacity and anti-diabetic activity of wild berry stem infusions. J Medicinal Plants . 2015;8(1):11–28. 10.9734/EJMP/2015/17115.
65. Mele MA. Bioactive compounds and biological activity of ginger. J Multidiscip Res. 2019;1(1):1–7. 10.33888/jms.2019.111.
66. Ojewole JA. Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of Zingiber officinale (Roscoe) rhizomes (Zingiberaceae) in mice and rats.

Phytother Res. 2006;20(9):764–772. 10.1002/ptr.1952.
67. Didunyemi M, Adetuyi B, Oyewale I. Inhibition Of Lipid Peroxidation And In-Vitro Antioxidant Capacity Of Aqueous, Acetone And Methanol Leaf Extracts Of Green And Red Acalypha wilkesiana Muell Arg. Int J Biol Med Res. 2020;11(3):7089–7094.
68. Kuppusamy P, David RS, Raj P, Ilavenil S, Kaleeswaran B, Govindan N, et al. Evaluation of antihypercholesterolemic effect using Memecylon edule Roxb. ethanolic extract in cholesterol-induced Swiss albino mice. J Acute Med. 2015;5(4):85–91. 10.1016/j.jacme.2015.09.001.
69. Balogun FO, Ashafa A. Protective action of aqueous leaf extract of Gazania krebsiana (Less.) 'Asteraceae' antagonizes isoproterenol-triggered myocardial infarction in Rattus norvegicus. Comp Clin Path. 2018;27(6):461–470. 10.1007/s00580-017-2614-0.
70. Duke JA. Handbook of Medicinal Herbs. Maryland, USA, CRC Press; 2002.
71. Nammi S, Sreemantula S, Roufogalis BD. Protective effects of ethanolic extract of Zingiber officinale rhizome on the development of metabolic syndrome in high-fat diet-fed rats. Basic Clin Pharmacol Toxicol. 2009;104(5):366–373. 10.1111/j.1742-7843.2008.00362.x.
72. Sebiomo A, Awofodu AD, Awosanya AO, Awotona FE, Ajayi AJ, et al. Comparative studies of antibacterial effect of some antibiotics and ginger (Zingiber officinale) on two pathogenic bacteria. J Microbiol. 2011;3(1):18–22.
73. Asnaashari S, Dastmalchi S, Javadzadeh Y. Gastroprotective effects of herbal medicines (roots). Int J Food Prop. 2018;21(1):902–920. 10.1080/10942912.2018.1473876.
74. Vutyavanich T, Kraisarin T, Ruangsri RA. Ginger for nausea and vomiting in pregnancy: Randomized, double-masked, placebo-controlled trial. Obstet Gynecol. 2001;97(4):577–582. 10.1016/s0029-7844(00)01228-x.
75. Revol B, Gautier-Veyret E, Arrivé C, Sam-Laï F, Mcleer-Florin N, Pluchart A, et al. Pharmacokinetic herb-drug interaction between ginger and crizotinib. Br J Clin Pharmacol. 2019;86(1):1–2. 10.1111/bcp.13862.
76. Abd-Allah GA, El-Bakry KA, Bahnasawy MH, El-Khodary ER, et al. Protective effects of curcumin and ginger on liver cirrhosis induced by carbon tetrachloride in rats. Int J Pharmacol. 2016;12(4):361–369. 10.3923/ijp.2016.361.369.
77. Rahmani AH, Shabrmi FM, Aly SM. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. Physiol Int. 2014;6(2):125–136.
78. Elufioye TO, Berida TI, Habtemariam S. lants-derived neuroprotective agents: Cutting the cycle of cell death through multiple mechanisms. ; 2017.
79. El-Akabawy G, El-Kholy W. Neuroprotective effect of ginger in the brain of streptozotocin-induced diabetic rats. Ann Anat. 2014;196(2-3):119–128. 10.1016/j.fct.2010.12.013.
80. Melo A, Monteiro L, Lima R, Dmde O, Mdde C, Elbachá RS, et al. Oxidativestress in neurodegenerative diseases: mechanisms and therapeutic perspectives. Oxid Med

Cell Longev. 2011;p. 467180–467180. 10.1155/2011/467180.

81. Karam A, Nadia A, Abd EF, Nemat A, Siham M, et al. Protective effect of ginger (Zingiber officinale) on Alzheimer's disease induced in rats. J Neuroinfect Dis. 2014;5(2):159–159.

82. Moon M, Kim HG, Choi JG, et al. 6-Shogaol, an active constituent of ginger, attenuates neuroinflammation and cognitive deficits in animal models of dementia. Biochem Biophys Res Commun. 2014;449(1):8–13. 10.1016/j.bbrc.2014.04.121.

83. Grzanna R, Phan P, Polotsky A, Lindmark L, Frondoza CG, et al. Ginger extract inhibits beta-amyloid peptide-induced cytokine and chemokine expression in cultured THP-1 monocytes. J Altern Complement Med. 2004;10(6):1009–1022. 10.1089/acm.2004.10.1009.

84. Simon A, Darcsi A, Kéry A, Riethmüller E, et al. Blood-brain barrier permeability study of ginger constituents. J Pharm Biomed Anal. 2020;177:112820–112820. 10.1016/j.jpba.2019.112820.

85. Saenghong N, Wattanathorn J, Muchimapura S, Tongun T, Piyavhatkul N, Banchonglikitkul C, et al. Zingiber officinale improves cognitive function of the middle-aged healthy women. Evid Based Complement Alternat Med. 2012;p. 383062–383062.

86. Obeso JA, Stamelou M, Goetz CG, Poewe W, Lang AE, Weintraub D, et al. Past, present, and future of Parkinson's disease: a special essay on the 200th anniversary of the shaking palsy. Mov Disord. 2017;32(9):1264–1310. 10.1002/mds.27115.

87. Valadez-Barba V, Juárez-Navarro K, Padilla-Camberos E, Díaz NF, Guerramora JR, Ne DM, et al. Parkinson's disease: an update on preclinical studies of induced pluripotent stem cells. Neurologia. 2021;4853(21). 10.1016/j.nrl.2021.01.005.

88. Perfeito R, Cunha-Oliveira T, Rego AC. Revisiting oxidative stress and mitochondrial dysfunction in the pathogenesis of Parkinson disease- resemblance to the effect of amphetamine drugs of abuse. Free Radic Biol Med. 2012;53(9):1791–806. 10.1016/j.freeradbiomed.2012.08.569.

89. Park G, Kim HG, Ju MS, et al. 6-Shogaol, an active compound of ginger, protects dopaminergic neurons in Parkinson's disease models via anti-neuroinflammation. Acta Pharmacol Sin. 2013;34:1131–1140. 10.1038/aps.2013.57.

90. Kongsui R, Sriraksa N, Thongrong S. The neuroprotective effect of zingiber cassumunar roxb. extract on LPS-induced neuronal cell loss and astroglial activation within the hippocampus. Biomed Res Int. 2020;2020:4259316–4259316. 10.1155/2020/4259316.

91. Hussein UK, Hassan NH, Elhalwagy M, Zaki AR, Abubakr HO, Venkata N, et al. Ginger and Propolis Exert Neuroprotective Effects against Monosodium Glutamate-Induced Neurotoxicity in Rats. . Molecules. 2017;22(11):1928–1928. 10.3390/molecules22111928.

92. Medeiros MS, Schumacher-Schuh A, Cardoso AM, et al. Iron and oxidative stress in parkinson's disease: an observational study of injury biomarkers. PLoS ONE. 2016;11.

93. Awoyelu EH, Oladipo EK, Adetuyi BO, Senbadejo TY, Oyawoye OM, Oloke JK, et al. Phyloevolutionary analysis of SARS-CoV-2 in Nigeria. . New Microbes and New Infections. 2020;36:100717–100717. 10.1016/j.nmni.2020.100717.
94. Perez-Carmona N, Fernandez-Jover E, Sempere AP. Rev Neurol. 2019;69:32–40.
95. Río J, Montalbán X. Med Clin. 2014;143:3–6.
96. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, et al. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. Neurology. 2014;83(11):1022–1026. 10.1212/WNL.0000000000000768.
97. Dworsky-Fried Z, Chadwick CI, Kerr BJ, Taylor A, et al. Multiple sclerosis and the endogenous opioid system. Front Neurosci. 2021;15:741503–741503. 10.3389/fnins.2021.741503.
98. Gilmour H, Ramage-Morin PL, Wong SL. Multiple sclerosis: PREVALENCE and impact. Heal reports. 2018;29(1):3–8.
99. Yadav SK, Mindur JE, Ito K, Dhib-Jalbut S, et al. Advances in the immunopathogenesis of multiple sclerosis. Curr Opin Neurol. 2015;28(3):206–225. 10.1097/WCO.0000000000000205.
100. Glatigny S, Bettelli E. Cold Spring Harbor perspectives in medicine,Experimental Autoimmune Encephalomyelitis (EAE) as Animal Models of Multiple Sclerosis (MS). Cold Spring Harb. 2018;8(11):28977–28977. 10.1101/cshperspect.a028977.
101. Jafarzadeh A, Ebrahimi HA, Bagherzadeh S, Zarkesh F, Iranmanesh F, Najafzadeh A, et al. Lower serum levels of Th2-related chemokine CCL22 in women patients with multiple sclerosis: a comparison between patients and healthy women. Inflammation. 2014;37(2):604–614. 10.1007/s10753-013-9775-z.
102. Petersen MJ, Bergien SO, Staerk D. A systematic review of possible interactions for herbal medicines and dietary supplements used concomitantly with disease-modifying or symptom-alleviating multiple sclerosis drugs. Phytother Res. 2021;35(7):3610–3641. 10.1002/ptr.7050.
103. Lassmann H, Bradl M. Multiple sclerosis: experimental models and reality. Acta Neuropathol. 2017;133(2):223–267. 10.1007/s00401-016-1631-4.
104. Sapkota A, Park SJ, Choi JW. Neuroprotective effects of 6-shogaol and its metabolite, 6-paradol, in a mouse model of multiple sclerosis. Biomol Ther. 2019;27:152–161. 10.4062/biomolther.2018.089.
105. Jafarzadeh A, Arabi Z, Ahangar-Parvin R, et al. Ginger extract modulates the expression of chemokines CCL20 and CCL22 and their receptors (CCR6 and CCR4) in the central nervous system of mice with experimental autoimmune encephalomyelitis. Drug Res. 2017;67:632–641. 10.1055/s-0043-113455.
106. Jafarzadeh A, Ahangar-Parvin R, Nemat M, et al. Ginger extract modulates the expression of IL-12 and TGFβ in the central nervous system and serum of mice with experimental autoimmune encephalomyelitis. Avicenna J Phytomedicine. 2017;7(1):54–65.
107. Olajide PA, Adetuyi OA, Omowumi OS, Adetuyi BO. Anticancer and antioxidant phytochemicals as speed breakers in inflammatory signaling. World News Nat Sci.

2022;44:231–259.