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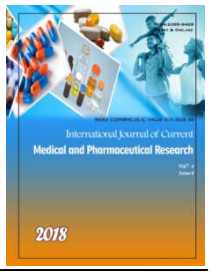

POTENTIAL OF GINGER [ZINGIBER OFFICINALE] IN THE TREAMENT OF EPILEPSY

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ABSTRACT

Epilepsy is one of the most common brain disorder which compromises the patient's quality of life. Even many old and new antiepileptic drugs are available, treatment of epilepsy is far away from achieving optimum results. In the etiopathogenesis of epilepsy recently, the role of oxidative stress and inflammation is highlighted. Certain antiepileptic drugs like sodium valproate, phenytoin sodium and carbamazepine were found to either initiate or enhance the oxidative stress and weaken the antioxidant defense mechanism. They also have serious adverse reactions including teratogenicity. Hence there is a serious need of searching newer drugs which will address the problems of the inflammation and oxidative stress efficiently. Ginger was proved to overcome these problems effectively and adequately. Ginger is devoid of any serious adverse effects of antiepileptic drugs including teratogenicity and fills the void of safe and effective adjunct in the treatment of epilepsy. After conducting extensive clinical trials, it's regular use can be encouraged in the treatment of epilepsy to achieve the satisfactory control of epilepsy.

INTRODUCTION

Epilepsy was probably first described around 2000BC in Egyptian writings. In modern era it is found in the writings of Jackson in late 1870s.[1] Electroencephalography was introduced in 1930 which helped to understand the epilepsy better.[2] Despite the availability of many antiepileptic drugs, more than 30% of cases of epilepsy are found to be intractable, with temporal lobe epilepsy being the most difficult to control.[3] The currently available antiepileptic drugs have serious adverse effects including teratogenicity. Certain antiepileptic drugs like valproic acid, phenytoin sodium and carbamazepine were found to increase the oxidative stress on the brain cells which may be the reason for not getting their optimum antiepileptic effects.[4]

This necessitates the need for developing alternate therapeutic approach for the treatment of epilepsy which will help to reduce the seizure threshold as well as reduce the oxidative stress and also will be devoid of serious adverse effects including teratogenicity. Ginger [Zingiber officinale] possibly addresses all these problems and fulfils these requirements. Ginger and it's constituents were studied for their antiepileptic potential and were found to be promising.[5]

Ginger is a medicinal plant that has been widely used in Chinese, Ayurvedic and Tibbe-Unani herbal medicines all over the world, since antiquity, for various ailments like arthritis, rheumatism, muscular aches, sore throats, cramps, constipation, indigestion, vomiting, hypertension, hyperglycemia, dementia, fever, infectious diseases and helminthiasis.[6]

Ginger, is a popular spice used globally especially in most of the Asian countries.[7] Chemical analysis of ginger shows that it contains more than 400 different compounds. The major constituents in ginger rhizomes are carbohydrates, lipids, terpenes, and phenolic compounds. They bear properties like anti-inflammatory, antioxidant, antimicrobial, anti-angiogenesis, anti-atherosclerotic and antineoplastic.[8]

Terpene compounds of ginger constitute zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene. Phenolic compounds include gingerol, paradols, and shogaol. These gingerols and shogaol are major contents of ginger .It also contains amino acids, raw fiber, ash, protein, phytosterols, vitamins like nicotinic acid and vitamin A, minerals and trace elements.[9,10] The aromatic constituents include zingiberene and bisabolene. The pungent constituents are gingerols and shogaols.[11] Other gingerol or shogaol-related compounds in ginger rhizome, are 6-paradol, 1-dehydrogingerdione, 6- gingerdione and 10-gingerdione, 4-gingerdiol, 6-gingerdiol, 8- gingerdiol, and 10-gingerdiol, and diarylheptanoids. [6,12] Volatile oils like shogaols and gingerols impart the characteristic flavor and odor to the ginger.[13]

Enhanced oxidative stress and rise in inflammatory mediators in the brain locally decrease the seizure threshold and initiates the episode of epilepsy which also in turn increase oxidative stress and inflammatory mediators in brain tissue. This becomes vicious cycle which needs to be interrupted. Thus

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unbalanced oxidative stress and increased inflammatory mediators play a crucial role in the process of epileptogenesis. Hence by reducing the oxidative stress and concentration of inflammatory mediators in the brain, the seizure threshold can be raised to control epilepsy.[14]

Epilepsy and Oxidative Stress

Brain utilizes highest amount of oxygen as compared to other body organs hence becomes more susceptible for oxidative stress. Brain has high concentrations of polyunsaturated fatty acids which are prone for lipid peroxidation. Rich contents of iron in the brain catalyze the formation of hydroxyl radicals. Brain has low catalase [CAT] activity.[15] Brain enzymatic antioxidant defense mechanism can metabolize superoxide radicals effectively but finds difficulty in eliminating hydrogen peroxide molecules which is a major concern, as the rich contents of iron and copper in the brain enhance the formation of hydroxyl radicals and these are prone to induce lipid peroxidation.[16]

Oxidative stress is the result of the imbalance between the generation and elimination of the reactive oxygen species [ROS] and Reactive nitrogen species.[17] Oxidative stress results into the oxidation of biomolecules like lipids, proteins and nucleotides and cause cellular dysfunction, damage and death.[18] Protein oxidation causes dysfunction of various enzymes[19] and lipid peroxidation results in to the alteration in membrane structure affecting membrane fluidity, permeability and membrane protein activity.[20] Seizure generation can be a result of prolonged and excessive oxidative stress and ROS induced mitochondrial damage. These also have an important role in the other neurodegenerative disorders like parkinson's disease and Alzheimers's disease.[21,22]

Epileptic seizure initiates marked influx of Ca^{++} through voltage gated and N-methyl D-aspartate [NMDA] dependent ion channels. This high level of intracellular Ca^{++} can induce generation of ROS.[23] ROS including superoxide radicals, hydrogen peroxide, hydroxyl radicals and singlet oxygen are scavenged by certain enzymes like superoxide dismutase [SOD], catalase [CAT] glutathione reductase [GR] and peroxidase [GPx] and by peroxiredoxins [Prxs] and also through non enzymes like vitamin E and C and reduced form of glutathione (GSH). Excessive ROS further reacts with nitric oxide and generates active nitrogen species [RNS] like peroxinitite.[24] Antioxidant therapies reduce oxidative stress and can ameliorate the process of epileptogenesis.

Epilepsy and Inflammation

Age related neurological dysfunction, reduced seizure threshold and spontaneous seizure activity can arise due to the over expression of cytokines like interleukin- 6 [IL-6] and tumor necrosis factor–α [TNF-α] in the astrocytes.[25] Inflammatory cytokine IL-6 activate IL-1 receptor type 1 and high mobility group box 1 activate Toll like receptor-4 and can regulate neuronal excitability and their signaling, inhibit outward efflux of ca++ and alter the synaptic transmission and decrease GABA production.[26]

Inflammatory process may occur prior to the onset of epilepsy in humans which potentially contribute to the etiopathogenesis of spontaneous seizures. This inflammatory response is also observed to be taking place in the glia when seizure is induced by chemoconvulsant or electric stimulation. [27]

Effects of Antiepileptic Drugs on Antioxidant Defense Mechanism of the Patient

Evidence shows that antiepileptic drugs either induce or exacerbate the oxidant stress in the patients who are receiving the antiepileptic drugs like valproic acid, phenytoin sodium, carbamazepine and phenobarbital and they increase the lipid peroxidation and nucleic acid oxidation of blood cells.[28] One possible mechanism for the effects of antiepileptic drugs on antioxidant defense mechanism is that these drugs get metabolized to the reactive epoxide intermediates which bind to biomolecules covalently and induce structural and functional damages and disturb the antioxidant defense system.[29]

Antioxidant Effects of Ginger

Generation of free radicals or reactive oxygen species [ROS]during the metabolism of the tissue, beyond it's antioxidant capacity results in to the oxidative stress which play an important role in the development of neurodegenerative disorders, atherosclerosis and ageing.[30,31] The bioactive constituents of ginger like gingerols have shown antioxidant effects.[32]

Evidence shows that the inclusion of nutritional antioxidants in diet can improve cognition and reduce or prevent brain damage.[33]

The rich phytochemical constituents of ginger scavenge free radicals produced in biological systems. The generation of some free radicals generated during the process of oxidation are essential for the purpose of energy production.[34] Increased production of free radicals leads to oxidative stress which can induce DNA damage.[35] Under such circumstances of imbalance between the oxidant stress and antioxidant capacity, antioxidant supplementation is essential for the viability and vitality of cells.[36] The anti-oxidative properties of ginger and its components have been explored in various in vitro and in vivo studies.[10] 6-Shogaol has exhibited the most potent antioxidant and anti-inflammatory properties in ginger, which can be attributed to the presence of alpha, beta-unsaturated ketone moiety.[32]

Animal studies have shown that ginger significantly decreased the lipid peroxidation and increased the levels of antioxidant enzymes, along with serum glutathione.[37] Ginger reduced the lipid peroxidation induced by malathion and lindane in animal studies. Concomitant dietary feeding of ginger [1%w/w] also improved the levels of glutathione (GSH), and the GSH-dependent enzymes glutathione peroxidase, glutathione reductase, and glutathione S-transferase.[38,39] Zingerone scavenged O^{2-} and OH and suppressed lipid peroxidation as observed in vitro studies. This property of ginger has significant role in the treatment of neurodegenerative disorders like parkinsonism and epilepsy.[40]

Dietary supplementation of ginger improved the decreased levels of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione in the ethanol induced hepatic damaged tissue.[41] Ginger showed renoprotective effects in renal failure which is attributed to their anti-inflammatory properties like the reduced serum C-reactive protein levels and antioxidant effects like the reduction in lipid peroxidation marker, malondialdehyde levels, and increasing renal superoxide dismutase activity.[42]

Various types of ginger extracts were studied for their antioxidant effects. Fresh ginger has better antioxidant potential. Antioxidant capacity was better with the methanolic extract of ginger than that of hexanic. Good correlation was found between the total phenolic content and antioxidant activities of the non-volatile extracts.[43]

Ginger was found to have an equal antioxidant effect to that of ascorbic acid in animal studies.[38]

Anti-inflammatory effects of ginger

Gingerol, shogaol, and other structurally-related substances in ginger inhibit prostaglandins and leukotriene biosynthesis through the suppression of the enzymes like 5-lipoxygenase or prostaglandin synthetase. They also inhibit synthesis of pro-inflammatory cytokines like IL-1, TNF-α, and IL-8.[44,45]Shogaol was found to down-regulate inflammatory iNOS and COX-2 gene expression in macropahges.[46]Hexanic extract of ginger was observed to inhibit the excessive production of NO, PGE,TNF-alpha, and IL-1beta.[10,47]

Ginger extract could reduce the elevated expression of Nf-κB and TNF-α in rat liver cancer cells. Nf-kB plays an important role in the chronic inflammatory disorders.[48]Gingerols were found to inhibit LPS-induced COX-2 expression and the production of PGE-2.[49]

Neuritogenesis Potential of Ginger Constituent-6-Shogaol

6-shogaol, a constituent of ginger has an antioxidant, anti inflammatory,[32] anti neuroinflammatory[50] activities. When 6-shogaol was tested for neuritogenic activities in animal studies, was found to have protective effect in rat pheochromocytoma (PC-12) and humans neuroblastoma cells obtained from beta amyloid insult.[51]

6-shogaol protected cholinergic neurons from reactive oxygen species,[52] and improved memory in memory impaired and normal mice as well.[53] 6-shogaol was found to have anti oxidant and cytoprotective effect.[54] Neuritogenesis is an important process in the development of brain and neuronal differentiation, sprouting and the extension of neurons. Neurotrophins like nerve growth factor [NGF] regulates this process of their development and maintenance. Study done by Seow S *et al* showed that low concentration of 6-shogaol induced neuritogenesis in PC-12 cells. This effect may be due to the induction of biosynthesis of NGF in PC 12 cells and also as 6-shogaol has NGF mimetic activity. This neuritogenesis was thought to be through activation of both TrkA- dependent and TrkA independent initiated NGF responsive signaling pathways, MEK/ERK1/2 and PI3K/AKT pathways.[55]

Antiepileptic Potential of Ginger

Chronic administration of ginger extract in pentynyltetrazole [PTZ] induced epilepsy animal model reduced the threshold of seizure induction in both the generalized clonic and myoclonic seizures. Proconvulsant activity of PTZ is partially mediated through interaction with chloride channel in the GABA-chloride channel complex.[56]

When the anticonvulsant effects of ginger in intravenous PTZ-induced seizure mice model were studied, it showed that different doses of ginger extracts significantly increased the threshold for the myoclonic seizures and forelimb tonic extension as compared with control groups. Higher dose of ginger was required to increase the threshold for the generalized clonic seizures significantly. The possible mechanisms thought for the anticonvulsant effects of ginger were the antioxidant mechanisms, oxidative stress inhibition. The antioxidant ingredients in ginger include gingerols, shogaols and some phenolic ketone derivatives.[57] The other mechanisms were calcium channels blockade, inhibition of NO production and reduction of iNOS as found in lipopolysaccharide-stimulated mouse macrophages, rise in intracellular cGMP level, and inhibition of chloride ion channel in the complex of GABA-A receptors.[57-60] However,theprecise molecular mechanism of anticonvulsant effects of ginger needs further exploration.

Antioxidant trace elements such as zinc, selenium and copper were found to be low in the blood of epileptic patients indicating the role of these trace elements in the etiopathogenesis of epilepsy. Selenium with or without Topiramate when administered in human and animal reduced the seizure activity.[4] Fresh ginger contains significant amounts of selenium [7.5mcgm/100gm of ginger].Hence regular dietary use of fresh ginger might help in reducing seizure episodes which needs to be confirmed by clinical studies after evaluating the blood selenium levels in the patients of epilepsy before and after the ginger supplementation in the diet.[61]

CONCLUSION

Despite the availability of the plethora of antiepileptic drugs, the treatment of epilepsy remains unsatisfactory as they do not address the problem of oxidative stress, a factor contributing for the etiopathogenesis of epilepsy and on the contrary they enhance it. Ginger having strong antioxidant and anti-inflammatory potential can be considered as an adjunct in the treatment of epilepsy. Ginger also has neuritogenic property which helps to improve brain function. It is safe and is devoid of adverse effects of currently available antiepileptic drugs. Hence to substantiate its potency and regular use in the treatment of epilepsy, as an adjunct extensive clinical trials should be conducted

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