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Review Article

Garlic and Neurodegenerative Disorders: A Review

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ABSTRACT
Incidence of neurodegenerative disorders is increasing at alarming high rate. Oxidative stress, neuroinflammation and associated disorders like diabetes mellitus hypertension, hyperlipidemia and hyperhomocysteinemia aggravate the underlying pathology. Though treatments for alzheimers disease, parkinsonism, Huntingtons disease and cerebrovascular stroke have witnessed enormous developments, still all the underlying etiopathologies are not adequately addressed by them. Contents of garlic like aged garlic extract [AGE] and S-allyl cysteine [SAC] fill this void by their pleiotropic actions. Their antioxidant property constitute scavenging of free radicals and induction of antioxidant enzymes with inhibition of pro oxidant enzymes. Activation of factor Nrf2, a master regulator of cellular redox state and chelation of metals contribute for neuroprotection. Increased insulin contents in the brain, inhibition of aldose reductase, anti platelet, anti hypertensive, NO and H2S generating properties play a vital role in amelioration of neurodenerative disorders.

Keywords: Garlic, Antioxidant, Neurodegenerative Disorders, Nrf2

INTRODUCTION

Life expectancy is increasing as result of better health care. This invites increased incidence of age related neurodegenerative disorders[1] causing many social challenges and imposing huge economical burden. The impressive gain in life expectancy is unfortunately gets overshadowed by loss of mental functions in old age. Common neurodegerative disorders comprise of dementias like Alzheimers disease [AD]. Parkinsons disease, Huntingtons disease and cerebrovascular stroke[2]. Available therapies for these disorders are not very satisfactory. Increased oxidative stress is the major underlying cause for neurovascular damage. Other contributing factors for these disorders include diabetes mellitus, hypertension, hyperlipidemia, enhanced platelet aggregation and coagulation activity, ischaemic heart disease, atherosclerosis, endothelial dysfunction and hyperhomocysteinemia[3]. With various studies garlic has been proved to be potent antioxidant[4-10]. It has antiaging effect also[11]. Botanically garlic is known as Allium Sativum, and it contains organosulphur compounds. It has been tried for many ailments like heart disease, tumors, cerebrovascular disorders which have been mentioned in 3500yrs old document Egyptian codex ebers[12], in ancient Vedas[13] and also in Hippocrates documents[14]. Garlic is known to possess antioxidant[15,16], antithrombotic[17,18], hypolipidemic[19], hypoglycemic[20], antihypertensive[21-25] and homocysteine lowering properties[26], Garlic preparations which have been investigated for their therapeutic potential are raw garlic, garlic powder or tablet, oil of garlic and aged garlic extract [AGE]. S-allyl cysteine[SAC] is the major constituent of AGE which is extensively studied. The various actions of garlic, mainly those of AGE and SAC which contribute to the amelioration of neurodegenerative disorders are as follows.

Antiplatelet action of garlic

Shrivastava K C found that garlic inhibited platelet aggregation induced by ADP, collagen, arachidonate [AA], epinephrine and calcium inophore 23187.It also reduced the formation of thromboxane, incorporation of AA in platelet phospholipids and mobilization of calcium leading to decreased platelet aggregation[17]. Rahman K found that garlic reduced cyclooxygenase activity and thromboxane A2 generation. Increased intraplatelet cAMP and cGMP and reduced calcium mobilization with fall in intracytosolic calcium contributes for antiplatelet activity. Antioxidant property of garlic enhances nitric oxide synthase [NOS] resulting in to rise in intraplatelet nitric oxide [NO] which is a known platelet antiaggregator. Garlic also interacts with glycoprotein IIb and IIIa receptors and inhibits binding of platelets to fibrinogen[18]. Rehman also found enhanced fibrinolytic activity along with inhibition of platelet aggregation by garlic[27]. Increased fibrinolytic activity was observed with garlic in healthy persons and also in patients of myocardial infarction[28,29]. Steiner M observed that garlic reduced platelet aggregation and their adhesion to collagen and von Willebrand factor[30]. Antioxidant property of garlic[31] and its capacity to generate NO and hydrogen sulfide [H2S] in endothelial cells is also responsible for its antiplatelet action[32].

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Hypolipidemic effect of garlic

Garlic is known to reduce cholesterol synthesis due to inhibition of cholesterol synthesizing enzyme HMG Co A reductase[33,34]. Various clinical trials[35,36] and meta-analysis done by Zeng et al[19] also confirmed the hypolipidemic effect of garlic.

Antioxidant property of garlic-AGE and SAC

AGE is extensively studied garlic preparation.SAC is the major organosulphur compound abundantly present in AGE along with other minor compounds. AGE and SAC scavange reactive oxygen species [ROS]. Thiol group in the SAC is responsible for its antioxidant property.SAC scavenges superoxide anion[9,37,38], hydrogen peroxide [H_2O_2][4,9,39], hydroxyl radical [OH][31,39] and peroxinitrite anion [$ONOO^-$][10,39]. SAC prevents lipid peroxidation[4], protein oxidation and also nitration[9]. AGE is known to scavenge O_2[40] and H_2O_2[4]. Though SAC is the major compound in the AGE exhibiting antioxidant property its other constituent compound like S-allyl mercaptocysteine also have antioxidant property which scavenges O_2 and OH[41]. Alliin scavenges O_2[31], OH[42] and H_2O_2[4]. Alliin also inhibits lipid peroxidation[4]. Tetrahydro beta carbolines scavenges H_2O_2 significantly. It also inhibits lipid peroxidation and liposaccharide induced nitrite production[43,44]. N alpha-L-arginine scavenges H2O2[45,46] and also inhibits copper induced oxidation of LDL and peroxide release. Garlic restores glutathione reductase, peroxidase and superoxide dismutase47.AGE and SAC induce antioxidant enzymes and transcription factor Nrf2 [nuclear factor- ER 2 related factor 2]. Nrf2 regulates redox homeostasis and also basal and inducible expression of antioxidant and cytoprotective genes which provide protection against various oxidative stress induced diseases like cerebrovascular ischemia[48,49]. Nrf 2 is highly expressed in detoxifying organs like liver and kidney[50]. SAC present in AGE is rich in organosulfides and possesses neuroprotective action against stroke. Studies suggest that SAC attenuates ischemic neuronal injury by activating `Nrf 2 dependent antioxidant mechanism both in vitro and in vivo. SAC provides the protection to the primary neuron against oxygen and glucose deprivation induced oxidative insults.SAC attenuated neural damage arising out of middle cerebral artery occlusion in wild type [Nrf 2 +/+] which was not observed in Nrf 2 knockout mice. This suggests that SAC activates Nrf 2 related antioxidant response and offers neuroprotective effect in stroke. Shi H et al provided the evidence that SAC protects the brain against ischemic injury by activating Nrf 2 signaling pathway, antioxidant responsive element [ARE], glutathione cysteine ligase regulated subunit [GCLC], glutathione cysteine ligase modulatory subunit [GCLM], haemoxygenase-1 [HO-1], C-jun N–terminal kinase [JNK], and kel ch–like ECH–associated protein 1[Keap 1]. SAC is known to induce endogenous Nrf2 target genes like haem oxygenase-1 [HO-1], GCLC and GCLM in primary cortical neurons. JNK/p38 MAPK is the main signaling pathway for ischemic neuronal death. SAC was shown to inhibit phosphorylation of both JNK and p38 and subsequent activation of pro-apoptotic caspase-3 in experimental conditions[51]. SAC can readily cross blood brain barrier and is much less toxic than other antioxidants[52]. Thus potency of SAC and lack of its toxicity makes it a promising tool for neuroprotection. Along with offering neuroprotection in stroke it also protects against parkinsons disease[53-56]. It has shown protection in alzhemier disease[57-60] and also in huntingtons' disease[61]. Nrf 2 is a master transcription factor which governs phase two enzyme expression. Antioxidant action is related to its ability to activate Nrf2. Under quiescent condition Nrf2 is not active as it is bound to and is sequestrated by Keap l resulting in to its degradation and low transcriptional activity[62,63]. Studies have shown that SAC dissociates Keap 1 from Nrf 2 as it interacts with thiol groups on cysteine residues of Keap l[56]. Nrf2 is ubiquitously present[64]. In the brain it acts as important defense mechanism against oxidative stress[65-69]. It protects the astrocytes[70] and neurons[71] against toxic insults by upregulating antioxidant enzymes[72,73]. Nrf2 plays a protective role in neurodegenerative disorders like parkinsons disease[74] Alzheimers disease[75]and huntingtons disease[76]. Increasing evidence suggests the protective role of Nrf2 in ischemic cerebral diseases[77]. Ameliorating effect of SAC on oxidative damage in experimental stroke was shown by several studies[78,79]. Nrf2 may improve cerebral vascular function in larger vessels and in areas of blood brain barrier. It also improves nerve blood flow[80]. The expression and activity of Nrf2 is reduced in aging mice[81,82] and also in patients[83]. SAC is proved to potentiate the brain levels of protective Nrf2. AGE and SAC inhibit some pro oxidant enzymes like xanthine oxidase[84], cycloxygenase[85], NADPH oxidase[86,87] and iNOS[88]. Enzyme NADPH catalyses the formation of O_2. NADPH over activity has been implicated in the pathophysiology of renal injury[86], hypertension, atherosclerosis and ischemia reperfusion injury[89]. In experimental conditions SAC was found to have antioxidant property probably by inhibiting NADPH[87]. Cycloxygenase-2 [COX-2] plays an important role in the inflammation, oxidative stress and in production of O_2. AGE decreases the production of COX-2[85]. AGE and SAC are useful in diseases where oxidative stress induced dysfunction of NO is the underlying etiology. NOS produce NO. NOS are either constitutive like eNOS and nNOS or inducible like iNOS. Constitutive NO plays physiological roles in neurotransmission, vascular relaxation, blood pressure regulation and immune modulation[90]. iNOS plays role in inflammation.SAC inhibits its action and suppresses nuclear factor kappa beta activation[91,92] SAC also inhibits iNOS gene expression[88]. iNOS generate NO in disproportionate amount which is degenerative as against eNOS induces NO in appropriate quantity to carry only physiological functions. SAC stimulates eNOS and inhibits iNOS[93]. Chelating effect of AGE and SAC-Divalent metals like iron and copper are involved in the generation of reactive oxygen radicals, increase in oxidative stress and mitochondrial damage resulting into neuronal death[94]. Through Fenton and Haber-Weiss reactions free iron or copper produce reactive oxygen species like OH leading to oxidative degradation of lipids, proteins and DNA[95-97]. The brains of Alzheimers patients have increased levels of iron, zinc and copper as

compared to normal population[97-99]. Similarly marked rise in iron and Zinc levels were found in brains of parkinsons patients[97]. In experimental studies SAC was found to possess the property of chelating Fe^{++} and Fe^{+++}.[100] Inhibition of Cu induced LDL oxidation was shown by AGE[40] and SAC[101] due to their Cu chelating property.

Anti diabetic action of garlic

The beneficial effect of garlic in diabetes mellitus is attributed to the presence of sulphur compounds like Alliin, Allicin, Diallyl di sulphide [DADS], Di allyl tri sulphide [DATS] and SAC. Kumar et al in 2013 confirmed the hypoglycemic effect of garlic in patients of DM[20]. In experimental studies Thompson M et al proved the role of garlic in glucose lowering and in prevention of atherosclerosis and diabetic nephropathy[102]. S. Mirunalini et al in 2011 studied the effect of garlic in diabetic patients and observed the glucose and lipid lowering effects[103]. Glucose lowering effect of garlic may be attributed to increase in insulin release, enhanced insulin sensitivity and release of bound insulin[104]. Allicin in garlic can prevent insulin inactivation[105].

Antihypertensive effect of garlic

Hypertension is a modifiable risk factor for both cardiovascular and neurodegenerative disorders. Garlic was found to reduce blood pressure in hypertensive patients and not in normotensives[21-23,25]. SAC modulates oxidative stress, increases the bioavailability of NO and H_2S and thus reduces blood pressure. Inhibition of angiotensin converting enzyme [ACE], decreased expression of nuclear factor kappa beta and proliferation of vascular smooth muscles also contributes for its antihypertensive action[106]. The gama-glutamyl cysteines compounds in garlic have been shown to reduce blood pressure by inhibiting enzyme ACE in vitro studies[107]. NO relaxes vascular smooth muscle cells via guanylyl cyclase dependent mechanism[108]. H_2S reduces blood pressure through sulfhydration of ATP sensitive potassium [kATP] channels resulting in to opening of voltage sensitive channels and relaxation of the vascular smooth muscles[109].

Hyperhomocysteinemia and garlic

Hyperhomocysteinemia is known to cause endothelial dysfunction and cardiovascular diseases[110]. Decreased endothelial production of H_2S may lead to hyperhomocysteinemia[111]. Budoff M J studied the effect of garlic in atherosclerosis patients and found the potential of garlic in reduction of homocysteine levels[26]. Increased homocysteine levels were found in people with low dietary intake of suphur containing amino acids[112]. SAC corrects this sulphur deficiency and counteract hyperhomocysteinemia[113].

Garlic and cardiovascular health

Garlic maintains cardiovascular health by anti platelet, hypolipidemic, fibrinolytic, antioxidant and antihypertensive actions as discussed earlier. Generation of NO, H_2S and homocysteine lowering also contributes for this effect.

Neuroprotective effect of garlic - SAC and AGE in neurodegenerative disorders

Garlic-SAC and Alzheimers disease- Alzheimers disease [AD] is a neurodegenerative disorder causing progressive loss of memory and cognitive ability. Accumulation of amyloid beta [AB] deposits in the brain is the diagnostic feature of AD. AB peptide is generated from amyloid precursor protein [APP] as result of sequential enzymatic cleavage by beta secretase [BACE-1] and gama secretase to produce AB peptide[114]. Phosphorylation of Tau proteins follows AB deposition and then form neurofibrillary tangles. AB deposition activates microglia and produce cytochemokines like TNF alpha and interleukins [ILs] resulting into neuroinflammation. Reactive oxygen species, nuclear factor kappa beta and peroxisome proliferator activated receptor gama [PPAR gama] also play an important role in neuroinflammation of AD[115]. Oxidative stress plays an important role in its pathogenesis. Hence treatment with an agent which possesses antioxidant and anti amyloidogenic properties is promising. SAC can prevent progression of AD by various mechanisms. SAC acts both as an antioxidant and a neurotrophic.

Antioxidant mechanism

SAC has both direct and indirect antioxidant activity. Direct antioxidant mechanism constitutes scavenging of free radicals and reactive oxygen species. Restoration of glutathione reductase and peroxidase and also superoxide dismutase activity constitute the indirect antioxidant mechanism of SAC[47]. As a result of antioxidant mechanism there is decreased lipid peroxidation[5-7] and DNA fragmentation[47,57,116]. It also reduces protein oxidation[9] and nitration[10]. Decreased endoplasmic reticulum [ER] stress due to SAC[58] results in diminished Ca2+ release, attenuation of caplain[117] and caspase 3 and 12 dependent pathway which all together decrease cell death[58,117-119,120].

Inhibition of amyloidogenesis

SAC decreases AB formation and increases its clearance by reducing APP and decreasing expression of mRNA and BACE-1. SAC restores PKC activity and expression of PKC alpha and gama causing APP cleavage and decreases formation of AB[121]. SAC not only inhibits AB fibrillation, it also destabilizes preformed AB fibrils[122]. SAC reduces activity and phosphorylation of Tau 2 which involves GSK-3 beta protein and has anti amyloidogenic, anti-inflammatory and anti tangle activity[123].

Inhibition of aldose reductase

Activity and mRNA expression of aldose reductase is inhibited by SAC resulting into decreased production of sorbitol and advanced glycation end products and decreased glycative stress[121].

Anti inflammatory activity

TNF alpha, IL 1 beta and IL 1 beta positive plaque associated microglia are reduced by SAC[123]. Thus SAC can prevent progression of AD by various mechanisms like antioxidant, anti glycative, anti-inflammatory, anti amyloidogenic and anti tangle activity in experimental models.

Diabetes mellitus-role of garlic

Positive correlation has been observed between diabetes mellitus and AD. Diabetes mellitus is either due to decreased production of insulin or as result of enhanced insulin resistance which can lead to development of AD.

In the brain insulin carries growth factor like function[124]. Insulin degrading enzyme which catalyses insulin also breaks down AB peptide in the brain[125]. Garlic acts like insulin secretogogue and enhances release of Insulin from beta cells of pancreas[126]. This increases brain levels of insulin and insulin like growth factor [IGF] leading to decreased brain AB burden and inhibition of GSK-3 beta activation. This also prevents Tau phosphorylation[123,127]. Insulin also enhances the expression of choline acetyl tranferase in the basal forebrain cholinergic neurons[128].

Hyperlipidemia-Alzheimers disease-garlic

Hyperlipidemia is a common culprit for cardiovascular diseases and for accumulation of AB peptide in AD[129]. Hyperlipidemia can potentiate hyperphosphorylation of Tau proteins[130]. Garlic and its various compounds have hypolipidemic properties. By inhibiting enzyme HMG COA reductase and by decreasing synthesis of cholesterol it helps in amelioration of AB formation[131,132]. Role of peroxisome proliferators activated receptors gama [PPAR gama] in AD-PPAR gama, a subtype of PPAR family is involved in microglial inflammation. Activation of PPAR gama in microglia and macrophages alleviates inflammation by reducing the production of pro inflammatory cytochemokines[133]. Activation of PPAR gama is also involved in clearance of AB[134]. In experimental studies a garlic compound DADS which is a component of AGE has been shown to increase expression of PPAR gama in cell culture. Thus garlic can ameliorate the neuroinflammation in AD through PPAR gama mechanism[135,136].

Pro cholinergic properties of garlic

Neuronal degeneration and synaptic loss arising out of neuroinflammation in cholinergic neurons in the basal forebrain is a feature of AD. The drugs which enhance choline uptake by cholinergic neurons and / or preserve the enzyme choline acetyl transferase [ChAT], a rate limiting enzyme in choline synthesis can prevent or reverse depletion of acetyl choline in the neurons in AD.AGE by increasing high affinity cholione uptake[HACO] and ChAT was suggested to have pro cholinergic activity[60]. Garlic being insulin secretogogue enhances insulin secretion and increases the expression of ChAT in the basal forebrain cholinergic neurons in AD[128].

SAC in parkinsonism

Parkinsons disease is characterized by progressive degeneration of dopaminergic neurons in substantia nigra pars compacta with the formation Lewy bodies. Its pathogenesis also constitutes oxidative tissue damage and bioenergetic deficits[137]. In experimental models of parkinsonism, 1-methyl-4-phenyl pyridinium [MPP] and 6-hydroxy dopamine [6-OHDA] are used to induce nigrostriatal dopaminergic neurotoxicity. MPP is a stable metabolite of -1methyl-4-phenyl-1,2,3, 6-tetrahydropyridine [MPTP] and causes nigrostriatal dopaminergic neurotoxicity. In these models SAC protected dopamine levels, decreased RAS production, oxidative damage and lipid peroxidation. In MPP model, levels of Cu and Zn superoxide dismutase were increased. Thus protection provided by SAC is due to its antioxidant property[55]. SAC in Huntingtons disease-3-nitro propionic acid and quinolinic acid are used to induce Huntingtons disease in animal models. Administration of SAC in these models decreased lipid peroxidation and mitochondrial dysfunction. It also increased Mn and Cu/Zn superoxide dismutase activity and prevented behavioral changes[138,139]. Quinolinic acid induced lipid peroxidation was reduced by binding of SAC to Fe^{++} and Fe^{+++} and by preventing redox cycling of iron. Ability of SAC to preserve cell redox status is through its antioxidant property and possibly its iron binding capacity also contributes to its neuroprotective effect[100]. Anti ischemic property of SAC-Garlic preparations like AGE and SAC can protect the brain against ischemic episodes due to their antiplatelet, hypolipidemic, antioxidant, fibrinolytic and antiatherogenic properties. Antidiabetic, antihypertensive properties and generation of NO and H2S and lowering of homocysteine also contributes for this effect.

SAC provided neuroprotection in animal models of middle cerebral artery occlusion. This was due to decrease in mitochondrial lipid peroxidation, cytochrome C release, protein carbonyl levels and intracellular H2O2 levels. SAC restored mitochondrial glutathione and glucose 6 phosphate dehydrogenase, ATP content and mitochondrial respiratory complex activity[140]. Thus, SAC by decreasing oxidative stress and modulating mitochondrial dysfunction results into protection against ischemic brain damage.

Neuroprotective effect of AGE

Thioallyl group of garlic including SAC is essential for its neuroprotective activity[141]. In experimental conditions AGE increases survival and axonal branching of neurons[142]. AGE directly and indirectly activates expression of important genes needed for neuronal survival[143]. In experimental designs of middle cerebral artery occlusion induced brain damage AGE significantly decreased mitochondrial lipid peroxidation and maintained the levels of antioxidant enzymes like glutathione peroxidase and superoxide dismutase[144]. AGE also decreased infarct size and levels of TNF alpha and COX-2[85]. AGE also has anti aging effect. Oxidative stress and immune dysfunction are the important causes of aging[145,146]. Abnormal immune reaction play an important role in age related dementias like AD[147]. AGE may also improve age related decline in immune system. In experimental studies AGE reduced TNF alpha, IL 1 beta and exerted anti-inflammatory effect[148]. Expression and activity of Nrf 2 are decreased in aging mice[81,82] and also in patients[149]. SAC is known to enhance activation of protective Nrf2.

Role of Fru Arg in neurodegerative disorders

Along with organosulfide compounds AGE also contains carbohydrate derivatives like N-alpha-[1-deoxy-D-fructos-1-yl]-L-arginine [Fru Arg]. Both AGE and Fru Arg inhibit nitric oxide production induced by lipo polysaccharides. They are also involved in inflammatory responses and Nrf2 mediated oxidative stress response. AGE has been proved as potent superoxide scavenger and chelator of transition metals[150]. Fru Arg is the major bioactive component of AGE[151-153]. It is a product of Maillard reaction taking place during the processing of AGE. It has both anti inflammatory and antioxidant

effects[154]. By its antioxidant property it scavenges hydrogen peroxide, protects macrophages and endothelial cells from damage induced by oxidized LDL[154,46]. In vivo studies Fru Arg was known to suppress norepinephrine induced rise in blood pressure. It also reduced levels of blood sugar[153]. Microglia are the immune modulating cells in the CNS. They defend against oxidative and inflammatory responses by stimulating antioxidant products[155]. Disproportionately generated NO by inducing nitrosative stress in the cells can cause neurovascular injuries and initiate neurodegenerative diseases like Parkinsons disese, Alzheimers disease and cerebral ischemia[155-159]. Nrf2 mediated pathway forms a major antioxidant mechanism for neuroprotection against oxidative stress[160]. Both AGE and Fru Arg modulate the Nrf2 mediated signaling pathway which forms an important mechanism for cellular defense against oxidative stress[161]. AGE and Fru Arg may also modulate Toll-like receptors[TLRs] which activate and help nuclear translocation of pro inflammatory transcription factors required for gene regulation[162,163].

CONCLUSION

Many ingredients like AGE and SAC of garlic and their properties possess neurotrophic activities which have been tried in neurodegenerative disorders and in the prevention of cerebral ischemia. Garlic is also known to prevent or delay age related morphological changes. Considering these advantages, garlic needs further identification, isolation, purification of its specific ingredients to substantiate the experimental claims and their mechanism of actions. This will help in its regular use in clinical conditions.

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