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INVITED REVIEW

The potential role of S-allylcysteine as antioxidant against various disorders in animal models

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ABSTRACT

Successful regulation of cellular equilibrium among oxidation and anti-oxidation is significant for cellular function and DNA integrity as well as gene expression for signal transduction. Numerous pathological processes, such as cancer, diabetes, heart and/or kidney diseases, Parkinson's and Alzheimer's diseases, have been revealed to be associated to the redox state of cells.

In a challenge to curtail the onset of oxidative stress, administration with diverse recognized antioxidants has been recommended. Glutathione (GSH) is accepted for its capability to reduce oxidative stress and downstream the harmful effects such as lipid peroxidation. Antioxidants thus play a significant part in protecting the human body against the damage caused by reactive oxygen species. S-Allylcysteine (SAC), a sulfur containing amino acid derived from garlic, has been experimentally demonstrated to possess antioxidant and other beneficial activities.

In the present review, we addressed the therapeutic effects of SAC as a potential antioxidant on various disorders by increasing GSH and other antioxidants. Authenticated with a number of in *vivo*, *in vitro*, animal experiments and some human clinical trials, beneficial effects of SAC were reported in cancer, neurodegeneration, nephrotoxicity, ischemic stroke, myocardial infarction and other heart diseases, Alzheimer's disease, Parkinson's disease, preeclampsia and diabetes mellitus. On the other hand, there is no scientific evidence against SAC for having adverse effects.

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INTRODUCTION

Oxidative damage replicates discrimination between the ability of biological systems and the systemic manifestation of reactive oxygen species (ROS) to restore the resultant damage or to voluntarily detoxify the reactive intermediate. Enhanced oxidative stress and destabilized antioxidant protection system are essential aspects of the progression and pathogenesis of diseases related to oxidants. Oxidative trauma can be related to improved rate of ROS formation, a decline of antioxidant defense or a mixture of both. ROS dependent modifications comprise cell damages, organs or tissues, and are projected as key features in the numerous disease mechanisms [1].

Superoxide radicals ($O_2^{\bullet -}$) generate other kinds of cell destructive oxidizing agents and free radicals. The detrimental action of the hydroxyl radical ($OH^{\bullet}$) is the strongest bounded by free radicals. Hydroxyl radicals are chiefly prone to initiate the multistage carcinogenesis development starting with DNA damage, cellular manifestation, degenerative cell growth and ultimately resulting in carcinoma. Cellular antioxidant enzymes and the free radical scavengers usually protect the cell from toxic effects of the ROS. However, if production of ROS overtakes antioxidant protection of the cells, they can lead to oxidative damage of the cellular macromolecules [2].

Antioxidants produced from a plant source draw additional attention as free radical protectors because they are protective against ROS-induced oxidative damage. S-Allylcysteine (SAC), the largely abundant organosulfur compound derived from garlic (*Allium sativum*, Liliaceae), has numerous beneficial effects, such as cholesterol lowering action, antioxidant function and radical scavenging [3]. SAC is derived from the amino acid cysteine in which an allyl group has been added to the sulfur atom. SAC is an extremely constant compound: in aged garlic extracts, it remains unchanged for up to 2 years. It is a white crystalline powder with a distinguishing odor, it has no hygroscopic capacity, and it melts at 223.7°C. Stored crystal samples demonstrate a minor change into a yellowish color, but no alteration or decay is noticed. SAC is engrossed in the gastrointestinal tract after oral supplementation without any modifications. The antioxidant properties of SAC have been accounted in a number of experiments. SAC is capable to scavenge hydroxyl radical, hydrogen peroxide (H_2O_2), superoxide and even peroxynitrite ($ONOO^-$) anion [4].

Garlic, a constituent of *Allium* vegetables, has been used for remedial profit since ancient times. *Allium*-derived organosulfur compounds (OSC) are constituted to prospective control and are curative agents against various disorders. Various studies have demonstrated that SAC is an antitumor mediator allied with diverse cancers. Antidiabetic, anti-obesity and other plentiful beneficial effects were also reported [5]. The present review has been designed to demonstrate the antioxidant activity of SAC in animal models and endeavor to be aware of the mechanism of its therapeutic efficacy with reference to biochemical and oxidative markers.

S-ALLYLCYSTEINE AS ANTIOXIDANT IN VARIOUS DISORDERS

S-allylcysteine in cancer

Chemoprevention by nutritional components has been materialized as a cost-effective move towards handling incidences of gastric cancer, the second most general malignancy worldwide, and a main cause of death in India [6]. Gastric cancer induced by the administration of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in Wistar rats illustrates resemblance to human gastric tumor [7]. Cell proliferation, which plays a major role in cancer progression, is linked with modifications in free radical-induced lipid peroxidation and the status of antioxidants that utilize glutathione (GSH) as a substrate [8].

SAC has come under widespread review in the light of its anticancer effects both *in vitro* and *in vivo* [9]. Some researchers established a positive connection between the antioxidant properties of SAC and its chemo-preventive efficiency against DMBA (7,12-dimethylbenz[a]anthracene)-induced hamster buccal pouch carcinogenesis [10]. Chemo-preventive prospective of SAC may be due to lowering the level of lipid peroxidation and increasing the antioxidant status with respect to the GSH redox cycle in the liver, stomach tissue and venous blood during the MNNG-induced gastric carcinogenesis. SAC reverses the receptiveness of gastric tumors to lipid peroxidation and also concurrently raises the antioxidant status with subsequent suppression of cell propagation in the target organ. These conclusions are in line with other workers who report that chemo-preventive agents exert an electrophilic counterattack response which is due to the enhancement of phase II enzymes that employ GSH as substrate [11].

In the blood and liver, SAC enhances the antioxidant status and condenses the amount of lipid peroxidation. Chemo-preventive mediators are identified to upregulate the capability of the liver to induce antioxidant enzymes and metabolize carcinogens, and even alter the tumor progress at extra-hepatic sites [12]. SAC has been reported to protect hepatocytes via radical scavenging activity against oxidative damage [13]. SAC has been found to inhibit free radical-induced formation of 8-oxodeoxyguanosine in DNA as well as commencement of nuclear factor-kappa B (NFκB) in human T-cells [14]. SAC ameliorated MNNG-induced vulnerability of the gastric mucosa while concurrently mounting the antioxidant status. According to this, SAC exercises its chemo-preventive efficacy by enhancing GSH-dependent antioxidants and altering the lipid peroxidation level in the target organ as well as in the blood and liver [15].

S-Allylcysteine against nephrotoxicity

Nephrotoxicity has been related with the augmented production of ROS [16] and inhibition of antioxidant enzymes, such as glutathione reductase (GR), superoxide dismutase (SOD), glutathione-S-transferase (GST), glutathione peroxidase (GPx) and catalase (CAT) [17]. Due to its antioxidant properties, SAC has been used in several *in vitro* and *in vivo* models of oxidative stress to reduce lipoperoxidation and to scavenge ROS. Its main effect was the attenuation of protein oxidation and lipoperoxidation, which were notably reduced, perhaps due to the capability of SAC to scavenge free radicals like H_2O_2, $O_2\bullet^-$, OH• and singlet oxygen ($^1O_2$) [18].

Oxidative damage to proteins and lipids was totally prohibited in distal tubules whereas this damage was only attenuated in proximal tubules by the administration of SAC. This might be due to the sensitive nature of proximal tubules towards the toxicity of copper (Cu). In addition, it has been exposed that lesser concentrations (9-12 μM) of Cu are necessary for an outcome of 50% cell mortality in proximal tubules than those (17 μM) required to provoke the same result in distal tubules [19]. Copper treatment suppressed Nrf2 expression which is connected to oxidative stress [20]. Furthermore, the Cu-induced diminishment in Nrf2 expression was prohibited by SAC treatment. Fascinatingly, it has been established that SAC is able to activate Nrf2 in kidneys [21] by increasing the activity of GPx, GR and CAT enzymes and scavenges ROS.

S-Allylcysteine in heart diseases

The parallel between high levels of oxidized low density lipoproteins (ox-LDL) and improved frequency of heart disease has been recognized. Native LDL particles are harmless and possess lipophilic antioxidants (β-carotene and α-tocopherol) to defend against oxidative damage. Nevertheless, a similarity point is achieved when oxidant load devastates these defenses and the LDL particle begins its pathogenic alteration into ox-LDL [22]. *In vitro* LDL oxidation upon incubation with activated endothelial cells or with metal ions has been established [23]. Once oxidative conversion has occurred, the ox-LDL particle can show innumerable pathogenic effects in the atherosclerotic development. With its native LDL receptor domain cleaved during oxidative modification, ox-LDL moves across the cell membrane via an alternate scavenger receptor on the cell surfaces of endothelial cells and macrophages [24]. The dependence of the atherogenic process on ROS generation and oxidative pathways makes antioxidant involvement a viable therapeutic measure. Earlier, probucol has been employed as a therapeutic adjunct along with other anti-arteriosclerotic drugs with great success. The lipophilic properties of probucol allow it to integrate equally into cellular membranes in a fashion similar to many of the tocopherol antioxidants [25].

Consequently, hydrophilic antioxidants such as SAC turn out to be ever more considerable oxidant scavengers like lipophilic antioxidants. The hydrophilic nature of SAC allows countering the oxidant molecules imbedded in cellular membranes (*i.e.* lipid peroxides) and also foraging the extracellular medium for more hydrophilic ROS such as hydroxyl radicals and superoxide anions

[14]. So, SAC wields a synergistic result in decreasing oxidant load by scavenging membrane bound and extracellular oxidants, while concurrently regenerating lipid-soluble antioxidants. The systemic distribution and absorption of SAC [26] advises that there is no addition of metabolic by-products. In addition, SAC exerts the capability to restrain peroxide release from ox-LDL activated macrophages and human umbilical vein endothelial cells [27, 28].

Myocardial infarction

Myocardial infarction (MI) is the severe state of necrosis of the myocardium that happens as a consequence of disparity between myocardial demand and coronary blood supply [29]. Loper *et al* [30] have stated that there is improved production of lipid peroxidation and a momentary inhibition of protective enzymes such as SOD in both unstable angina and MI. Catecholamines endure auto-oxidation and it has been put that the oxidative products of catecholamines are accountable for the alterations in the myocardium. It is well recognized that the rat model of isoproterenol (ISO) infused myocardial necrosis has been regularly used to estimate the use of cardio-protective drugs and to revise myocardial consequences of ischemic disorders [31]. Oxidative stress can spoil various biological molecules and, certainly, DNA and proteins are frequently more important targets of injury than lipids; lipid peroxidation often occurs late in the injury process [32].

ISO supplementation leads to damage in the myocardium, which might be due to the induction of free radical-mediated lipid peroxidation. So, therapeutic involvement with antioxidants may be helpful in preventing these harmful changes as a consequence of ISO administration. Lipid peroxides play an imperative function in the myocardial cell damage. Massive amounts of ROS like H_2O_2, hydroxyl radicals and superoxide are formed during MI. Reports from *in vitro* and *in vivo* experiments, as well as epidemiological studies advised that there is an opposite association between levels of antioxidants and severities of oxidative stress induced diseases. SOD reduces superoxide radical to hydrogen peroxide and oxygen; two other enzymes, CAT and GPx are considered biologically essential in the reduction of hydrogen peroxide [33].

GPx and GR are crucial for preserving a stable ratio of GSH to oxidized glutathione (GSSG) in the cell. Suppressed GSH levels in ISO-stressed rats increased consumption in protecting thiol/sulfhydryl (SH) groups that contained proteins from free radicals. Reduced accessibility of GSH also decreases the activity of GST and GPx in MI. Inactivation of GR in the heart causes the accretion of GSSG. GSSG inhibits protein synthesis and inactivates enzymes containing SH groups. Oral supplementation with SAC is shown to boost the concentration of GSH and the activities of GR, GPx and GST in rats. During myocardial necrosis, the levels of GSH and ascorbic acid also reduced drastically, leading to improved free radical production. Due to the reduced levels of antioxidants, the free radicals are not neutralized and the myocardium exhibits improved propensity to the peroxidation in the existence of lipid peroxidation promoters. SAC administration prohibited the reduction in ascorbic acid and GSH in the MI rat model, which may be due to its antioxidant efficacy [34].

S-Allylcysteine in neurologic disorders

The mechanisms by which antioxidants work are thought to be mediated by substitution or even reinforcement of the endogenous antioxidant capacity to preserve tissue integrity and resist toxic endogenous pathways at molecular and biochemical levels to commence lasting defensive signals [35]. The practical protection of nerve endings since the early stages of toxicity in a given damaging insult, either chronic or acute, by means of neuroprotective and antioxidant agents, is a prime need to intend for the therapeutic approach in neurodegenerative disorders, with meticulous emphasis on those diseases which display depleted and excitotoxic energy metabolism components. SAC was examined as a post-treatment antioxidant agent in different *in vivo* and *in vitro* neurotoxic models. Many reports demonstrated that SAC is able to apply some fortification in mitochondrial function and biochemical markers of redox activity compromised by the toxic actions of mediators inducing excitotoxicity and depleting energy metabolism. In fact, for the specific case of the 3-nitropropionic acid (3-NPA)-induced toxic model, SAC protection was connected with the protection of key physiological functions evidenced by behavioral evaluation. In addition, the statement that SAC protected more markers linked to 3-NPA-induced toxicity than those from the quinolinic acid (QUIN)-toxic model suggested that this antioxidant may be more effective as a post-treatment on oxidative stress depending on the leakage of ROS at a mitochondrial level, since 3-NPA is more associated to this toxic pattern. In this regard, SAC was most likely less helpful to defend against QUIN-induced toxicity under *in vivo* circumstances [3].

Taken together, SAC ameliorated some markers of mitochondrial dysfunction, oxidative stress and abnormal behavior in the toxic models evoked by QUIN and 3-NPA. The outline of defense wield by SAC is, in general terms, diverse to that exhibited by levocarnitine, which was tested in the same models and the same conditions in a previous study [36]; thus representing that, even though both agents can be considered typical antioxidants, they may be acting through different mechanisms, probably involving diverse signaling pathways [37, 38]. However, SAC is a capable tool in designing and exploring pharmacological remedies to control depleted energy metabolism components and neurodegenerative disorders with excitotoxicity, once initiated. The issue whether the positive actions of SAC might also involve other functions in synaptosomes, such as neurotransmitter release and calcium homeostasis, remains to be elucidated in further studies [39].

Ischemic stroke

Oxidative damage has been concerned in a variety of models of chronic neurodegeneration and severe brain damage as well as focal ischemic stroke [40]. The brain is extremely disposed to the damage caused by oxidative stress because of high polyunsaturated fatty acids (PUFA) content and inadequate neuronal cell repair activity. Improved levels of ROS are the key reason of tissue injury after cerebral ischemia, which leads to the inactivation of antioxidant enzymes and utilization of antioxidants. [41]. The brain has several sources of ROS [42] and a large oxidative capacity, but its ability to fight against oxidative stress is partial [43]. Oxidative stress has an imperative part in the pathogenesis of ischemic brain damage. Ischemia induces a disparity of antioxidants and overproduction of toxic free radicals. Reperfusion also comes with healthy fabrication of ROS and reactive nitrogen species (RNS) that potentiate early brain damage caused by ischemia. Many reports have shown that the large generation of ROS and $ONOO^-$, a major RNS, caused protein oxidation, DNA damage and lipid peroxidation [44].

There is some information about the modulatory effect of SAC on GSH, lipid peroxidation and antioxidant enzymes after brain injury [45]. In according with these verdicts, SAC considerably condensed the thiobarbituric acid reactive substances (TBARS) levels, a main marker for the amount of lipid peroxidation, along with improved activities of antioxidant enzymes and GSH level. The H_2O_2 created by SOD and by other processes is scavenged by CAT and GPx, an omnipresent protein that catalyzes the dismutation of H_2O_2 into water and molecular oxygen. Supplementation of SAC decreases the development of ischemic damage throughout anti-inflammatory and antioxidant properties. All of these findings provide great convenience in exploring the possible benefit of SAC in humans [46].

Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disarray which is distinguished by the progressive corrosion of cognitive and memory function. It influences great numbers of people and has become a main social and medical burden, particularly for developing countries. The development of extracellular deposits of amyloid-β-peptide [47] principal to the formation of neurofibrillary tangles and neurotic plaques in the brain is a well-known pathological characteristic of AD. The brain is extremely predisposed to the damage caused by oxidative stress, due to its quick oxidative metabolic activity, elevated polyunsaturated fatty acid content, inadequate neuronal cell repair activity and relatively low antioxidant capacity [48]. Oxidative damage to proteins (protein carbonyl formation) and lipids (lipid peroxidation) can lead to functional and structural damage of the cell membrane, inactivation of enzymes, and eventually cell death. Oxidative stress resulting from ROS production is also concerned in apoptosis. Free radical-induced damage to macromolecules plays a vital part in the hastening of aging and age interrelated neurodegenerative disorders such as AD [49].

Lipid peroxidation points out neuronal membrane degeneration. It is accounted that lipid peroxidation in the brain happens in early AD [50]. Aging also amplifies lipid peroxidation in the brain of a senescence accelerated mouse [51]. In addition, results from the many reports showed a decrease in the level of GSH and its dependent enzymes GR and GPx, and a noteworthy increase in the TBARS content, in the brains of a non-transgenic mouse model, namely the icv-streptozotocin (STZ) mouse, of Alzheimer's disease. Throughout free radical content, oxyradicals are reduced by GPx at the cost of GSH to appearance of GSSG. GSH is further formed by redox recycling, in which GSSG is reduced to GSH by GR with an outflow of one nicotinamide adenine dinucleotide phosphate (NADPH) molecule. Condensed level of GSH vitiates endorsed formation of OH• and H_2O_2 clearance, leading to more oxidative stress and free radical level [52].

There is some information about the modulatory effects of SAC on antioxidant enzymes and lipid peroxidation following pathologies like brain injuries and ischemia/hypoxia. In agreement with these reports, SAC increased considerably in the activity of antioxidant enzymes and condensed the TBARS level in hippocampus following the STZ induction. This retort of SAC could be endorsed to its impending antioxidant property [53]. Changes found in oxidative stress parameters with cognitive dysfunction in the STZ-induced model of dementia in mice [54] signify that STZ-induced memory and learning destruction is related to oxidative stress. The valuable effects of SAC in spatial memory processing may be based on its capability to defend the cholinergic function and avert neuronal damage, perhaps through its antioxidant capabilities. These results recommend that SAC is a potential substitute for treating the cognitive impairment. Additional research into the neuro-protective prospective and action mechanisms of SAC is necessary to find out whether it can be an effectual cure for cognitive impairment [45].

Parkinson's disease

Parkinson's disease (PD) is a neurological disorder categorized by deterioration and decease of the dopaminergic neurons of the nigrostriatal pathway in the brain. Death of these neurons creates diminishment in striatal dopamine (DA) content. The reason of this neuronal loss is uncertain, but there is mounting proof signifying that oxidative stress, via free radical production, plays a vital role in the process [55]. Free radicals are formed constitutively in usual physiological environment. Organisms have developed diverse defense mechanisms to defend themselves against damage from free radicals. Such defense mechanisms comprise free radical scavengers, metal chelating agents and antioxidant enzymes. In general, there is equilibrium between the antioxidant defense system and generation of free radicals activity *in vivo* [56].

Oxidative stress leads to damage of PUFA by lipid peroxidation, a chain reaction that results in several deprivation products such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). Anatomical studies on

patients with PD have reported modifications such as increased iron levels, increased lipid peroxidation and loss of glutathione in the substantia nigra. The neuroprotective efficacy of SAC against neurotoxicity induced by MPP^+ (1-methyl-4-phenylpyridinium) in the striatum has been demonstrated previously: SAC exerts defensive effect in the whole striatal tissue, which comprises the neurons synaptic cleft and glia. It was reported that SAC can provide valuable fortification against the damage to midbrain DA neurons arising from the neurotoxic effects of MPP^+ *in vivo*; this is evidently revealed by the fact that the direction of SAC to MPP^+-injected animals resulted in extensively attenuated MPP^+-induced loss of striatal DA levels [57].

A number of studies in the central nervous system have explained that the defensive activities of SAC are connected to its antioxidant properties by reduction of edema development in an ischemic rat brain through the neuro-protection against excitotoxicity, inhibition of lipid peroxidation and oxidative damage induced by QUIN [58]. It is also clear that one more contributing feature to the defensive actions exerted by SAC on MPP^+-induced neurotoxicity is the protection of Cu/Zn-SOD activity, the enzyme responsible for competent superoxide radical removal. Modifications in Cu/Zn-SOD activity are due to structural alterations of this enzyme, but not to a diminution in the amount of the enzyme, as revealed by the lack of changes in the Western blot analysis. This kind of adaptations in proteins may be due to the toxic action of ROS [59].

One of the significant considerations in drug development therapies for patients with PD is to avoid the potential side effects during or after long term management. There is universal awareness about the discovery of new and safe antioxidants from natural resources to avoid oxidative damage of living cells. The use of synthetic antioxidants has declined due to their alleged activity as carcinogenesis promoters, together with a general consumer refusal of synthetic food additives. Furthermore, SAC administration has an incredibly notable clinical safety record and it rapidly crosses the blood-brain barrier, making it an apparently brilliant source for additional research of its worth in the treatment of PD [60].

Huntington's disease

Huntington's disease (HD) is a neurodegenerative hereditary muddle that influences muscle dexterity and leads to cerebral turndown and behavioral symptoms. 3-NPA is a familiar fungal poison causing neurotoxicity in humans and animals. The brain abrasions created by the general organization of 3-NPA to animals demonstrated that elevated specificity for the striatal tissue, hypothalamus, cortex and hippocampus are also exaggerated. This feature has served to fabricate an investigational model of Huntington's disease when the toxin is supplemented to non-human primates and rodents [61, 62]. As a key consequence, the oxidative pattern formed by 3-NPA in the brain comprises the subsequent characteristics: changes in endogenous antioxidants, augmented levels of 3-nitrotyrosine (3-NT), a biomarker of $ONOO^-$ formation, ROS development and the oxidative commotion of the mitochondrial respiratory chain [63].

In this view, some results on the association of oxidative damage caused by 3-NPA represent that the employment of diverse antioxidants, such as nicotine, vitamin E and melatonin, results in incomplete or absolute preclusion of 3-NPA-induced neurotoxicity. An additional possible cause of 3-NPA-toxicity has been formulated [64] depending on an inhibitory exploit of this toxin on glutamate uptake by synaptic vesicles, a state associated to secondary excitotoxicity and cell death. In addition, SAC is recognized to scavenge several ROS, and has been revealed to put forth neuroprotective effects in diverse neurotoxic paradigms as well as HD [65].

Furthermore, the defensive possessions of SAC on the markers of toxicity exercised by 3-NPA are evocative of its prospective use for additional research. SAC might be a substitute as a free radical scavenger in 3-NPA-induced toxicity [66].

S-Allylcysteine in preeclampsia

The placenta plays an essential role in controlling the local circulatory system that arbitrates fetal growth and maternal condition. Its purposes are resolute by its blood flow, differentiation of the trophoblast and vascular development [67]. Modern clinical statistics discover a reduction/oxidation disparity with rise in oxidative stress attached to a reduced capability of antioxidant systems in preeclampsia (PE). Experiments showed a contrary connection between nitric oxide (NO) and H_2O_2 at early stages in maternal transmission and at term in placenta in preeclamptic women [68]. Improved ROS production could escort the containment of endothelial NO synthase (eNOS) function and expression [69], and consequently, it can lead to reduced bioactivity of NO which is usually connected with vasoconstriction, reduced trophoblast invasion and endothelial dysfunction. This could effectively induce permanent systemic vasoconstriction and endothelial dysfunction observed in PE [70].

Several researchers advise that PE must be categorized by a distraction of general vascular dilatation, which is chiefly mediated by disturbance of ROS and NO. Based on the characteristics of SAC, researchers intended study to perceive whether SAC could play a role in regulating NO signaling and oxidative damage within the placenta, which would signify a possible treatment for PE. Some researchers explained that H_2O_2 acts as an inhibitor of NO synthesis in the trophoblast cell line TEV-1. Conclusions are reliable with their findings of a reduced NO level in H_2O_2-treated TEV-1 cells. In addition, H_2O_2 treatment also suppressed eNOS and cyclic guanosine monophosphate (cGMP) levels in TEV-1 cells, which causes oxidative damage to almost all main molecules of the NO/cGMP pathway. Additional Cu treatment considerably amplified the level of NO, cGMP and eNOS in contrast to H_2O_2 alone; SAC was able to reverse the decreased cGMP and NO levels close to control values. These findings explain a possible defensive effect of SAC on oxidative stress-induced damage to placenta existing in PE. The efficacy of SAC on NO level appear

to be cell-specific, which boost NO in human umbilical vein endothelial cells (HUVEC) while inhibiting in macrophages [71].

As noticed in other research, SAC is capable to increase NO level in TEV-1 cells and placenta explants at non-oxidative stress position, which could add to amplify the placental perfusion. Many researchers also found that SAC exhibits protective effects on multisystem disorders, such as cardio-protective, nephro-protective, neuro-protective and hepato-protective activities [72]. In addition, SAC can be transformed into hydrogen sulphide (H_2S), an endogenous vascular cell signaling molecule, which can also influence NO signaling [73].

S-Allylcysteine in diabetes mellitus

Diabetes mellitus (DM) involves a cluster of persistent disorders characterized by diminished insulin secretion or hyperglycemia, or both together. DM rivets high level of blood glucose, which boosts free radical production [1]. Decreases in the activity of free radical scavenger systems and amplified formation of oxygen-derived free radicals have been documented in DM [74]. It has also been projected that rise in oxidative stress could be related to tissue damage in DM. Nowadays, there is much more attention toward oxidative stress and its role in the progress of DM complications. Thus, apart from the conventional antidiabetic treatment, antioxidant treatment may be suitable in DM. Throughout diabetic state, augmented generation of ROS occurs and causes a disproportion between the antioxidant and oxidant status [75]. Increased levels of free radicals noticed in diabetic rats are recognized for chronic hyperglycemia [76].

SAC may wield antioxidant activities and defend the tissues from lipid peroxidation. Loven *et al* [77] had recommended that diminishment in tissue GSH level could be the effect of increased degradation or decreased synthesis of GSH by oxidative stress in DM. The altitude of GSH levels in kidneys and liver was noticed in the SAC treated diabetic rats: This points out that SAC can amplify the biosynthesis of GSH or decrease the oxidative stress principal to less deprivation of GSH. GSSG and GSH levels are normally used markers for oxidative stress. GSSG appears to be released from most cells as an important marker of oxidative stress, reflecting oxidation of the cellular GSH pool. In other words, a low GSH/GSSG ratio suggests increased oxidative stress [78].

Any drug that replenishes GSH may be competent to reverse the oxidative damage caused in DM and stop the allied disorders. SAC is able to strengthen the antioxidant status by supporting the GSH levels. The histopathological assessment of the liver and kidneys of diabetic rats demonstrated mononuclear cellular infiltration and vascular congestion of the hepatocytes, as well as areas of mononuclear cellular infiltration and inter-tubular hemorrhage. This response is aggravated by the improved production of highly reactive intermediates by STZ, which are usually detoxified by endogenous GSH. The pathological changes were condensed in diabetic rats which were treated with SAC. According to this, supplementation of SAC has an antioxidant efficacy and it also defends lipid peroxidation and improves its consequence on cellular antioxidant defense. This action contributes to the fortification against oxidative damage in STZ-induced DM [81].

CONCLUDING REMARK

This review concludes that S-allylcysteine has the potential to act as an antioxidant against metabolic disorders, which was substantiated with a number of *in vivo*, *in vitro*, animal studies and some clinical trials. SAC also presents beneficial effects on various disorders like cancer, myocardial infarction, neurological disorders, ischemic stroke, Alzheimer's disease, Parkinson disease, Huntington's disease, preeclampsia and diabetes mellitus by acting as a prominent antioxidant. Taken together, these studies emphasize the prospective favorable effects of this nutraceutical derived from garlic.

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