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ORIGINAL ARTTICLE

Evaluation of the Antioxidant Potency of *Allium sativum* L. on Acrylamide – Induced Neurotoxicity in Male Wistar Rats

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KEYWORDS

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ABSTRACT: Acrylamide (ACR), a common toxic byproduct formed in thermally processed foods, is known to cause neurotoxicity in humans, resulting in damage to peripheral nerves. This investigation assessed the neuroprotective efficacy of graded doses of *Allium sativum* L. (garlic) against ACR-induced neurotoxicity in the cerebral cortex of male Wistar rats, with a specific focus on the attenuation of glutathione (GSH) depletion and the reduction of elevated malondialdehyde (MDA) levels. A total of forty-two male Wistar rats were randomly allocated into seven experimental groups (n=6 per group). Group 1 received normal saline (control). Group 2 was administered 50 mg kg^{-1} ACR. Groups 3, 4, and 5 were administered ACR at a dose of 50 mg kg^{-1}, followed 30 minutes later by oral gavage of garlic at 100, 200, and 400 mg kg^{-1}, respectively. Group 6 received a daily dose of 200 mg kg^{-1} garlic only. Group 7 was co-administered 50 mg kg^{-1} ACR daily and 200 mg kg^{-1} vitamin E every other day, with the vitamin E delivered via oral gavage 30 minutes post-ACR administration. At the conclusion of the treatment protocol, we evaluated motor coordination through a standardized gait score assessment. ACR exposure significantly impaired gait, increased cortical MDA levels, and reduced GSH content ($p<0.001$ for both). Administration of garlic at doses of 100, 200, and 400 mg kg^{-1} resulted in a significant attenuation of cortical MDA levels ($p < 0.05$) and a concomitant elevation of reduced GSH content ($p < 0.05$), indicating a mitigation of ACR-induced oxidative stress. Gait abnormalities were also ameliorated in treated groups. The administration of garlic proved effective in alleviating gait disorders and neurotoxicity triggered by ACR in Wistar rats. The reduction of oxidative stress, evidenced by decreased MDA and increased GSH levels, likely contributes to the neuroprotective effects of garlic against ACR toxicity.

INTRODUCTION

Acrylamide (ACR), with the chemical formula C3H5NO, is a reactive, colorless crystalline compound with high water solubility. It is widely used in industrial processes to produce polymers for cosmetics, water treatment, and paper and pipe manufacturing. Notably, ACR forms at elevated levels in heat-processed carbohydrate-rich foods like potatoes and cereals [1]. Numerous reviews have examined its safety, highlighting significant concerns regarding neurotoxic and reproductive effects [2]. The chief toxicological concern of ACR is its impact on the nervous system. The neurotoxic profile of ACR is characterized by clinical manifestations such as ataxia, muscular weakness, reduced body weight, and peripheral edema. Histopathological assessment revealed that ACR

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intoxication induces axonal degeneration in the central and peripheral nervous systems, characterized by structural alterations in neurofilaments, demyelination, and apoptosis of neurons and astrocytes [3, 4]. The estimated average daily intake of ACR for the general population is approximately 34.03 μg per person, which corresponds to 0.57 μg kg^{-1} of body weight [5, 6].

Research in animal models has validated the neurotoxic nature of ACR, which presents as deficits in sensory, motor, and autonomic functions associated with disruptions in neurotransmitter activity. Oxidative stress is a principal pathway through which ACR causes neurodegeneration [7]. ACR exposure promotes lipid peroxidation, measured by increased malondialdehyde (MDA), and depletes the critical antioxidant glutathione (GSH), thereby compromising the nervous system's antioxidant defense [8]. This assertion is further substantiated by evidence demonstrating that ACR elevates reactive oxygen species (ROS) and induces oxidative DNA damage in hepatic cells [9]. Rodent models consistently show that ACR-induced ROS generation leads to lipid peroxidation, GSH depletion, and altered apoptosis markers [8, 10-12]. Consequently, compounds with antioxidant properties represent a promising therapeutic strategy for neurodegenerative conditions in both animal models and humans [13-16].

Allium sativum L. (garlic), a member of the Alliaceae family, is a plant with a well-documented history of dual use as a culinary staple and a therapeutic agent [17]. The therapeutic profile of garlic is attributed to its diverse array of bioactive compounds, including allicin, alliin, ajoenes, and allyl sulfides. These constituents are responsible for a broad spectrum of pharmacological activities, such as antioxidant, anti-inflammatory, cardioprotective, antimicrobial, and anticancer effects [18, 19]. The pharmacological applications of garlic encompass neuroprotection [20], blood pressure and cholesterol reduction [21] [22], immune system enhancement [23], hepatoprotection [24], and antioxidant action [25]. Garlic's efficacy is partly attributed to its ability to modulate ROS, which are central to the oxidative stress pathway implicated in various pathologies [26]. For instance, garlic extract has been shown to reduce plasma and erythrocyte MDA levels in patients, independent of changes in antioxidant enzyme activities [27].

Given the well-documented neurotoxicity of ACR and the established antioxidant properties of garlic, this study aimed to explore the neuroprotective potential of various garlic doses against ACR-induced neurotoxicity. The findings of this study demonstrate that garlic confers protection against ACR-induced neurotoxicity via the amelioration of key oxidative stress biomarkers.

MATERIALS AND METHODS

Chemicals and reagents

ACR, thiobarbituric acid (TBA; Catalog No. 108180), and trichloroacetic acid (TCA; Catalog No. 100807) were obtained from Merck (Darmstadt, Germany). 5,5'-Dithiobis (2-nitrobenzoic acid) (DTNB; Catalog No. D8130-5G) was sourced from Sigma-Aldrich (St. Louis, MO, USA). Vitamin E (100 IU/mL) ampules were procured from Daropakhsh, and garlic tablets were obtained from Dineh Company.

Animals

This study utilized forty two adult male Wistar rats (weighing 230–250 g), procured from the Pasteur Institute of Iran. Rats were housed under standard laboratory conditions with a 12-hour light/dark cycle, an ambient temperature of 23 ± 2 °C, and *ad libitum* access to standard rodent diet and water.

Experimental groups and treatments

The rats were randomly allocated into seven experimental groups (n=6 per group) as follows:

-Negative Control Group: Administered an equivalent volume of normal saline.

-ACR Group: Received ACR at a dose of 50 mg kg^{-1} day^{-1} via intraperitoneal (i.p.) injection for a period of 11 days [28].

-ACR + Garlic (100 mg kg^{-1}) Group: Treated with ACR (50 mg kg^{-1} day^{-1}, i.p.) followed 30 minutes later by garlic (100 mg kg^{-1}) via oral gavage for 10 days [28].

-ACR + Garlic (200 mg kg^{-1}) Group: Treated with ACR (50 mg kg^{-1} day^{-1}, i.p.) followed 30 minutes later by garlic (200 mg kg^{-1}) via oral gavage for 10 days [28].

-ACR + Garlic (400 mg kg^{-1}) Group: Treated with ACR (50 mg kg^{-1} day^{-1}, i.p.) followed 30 minutes later by garlic (400 mg kg^{-1}) via oral gavage for 10 days [28].

-Garlic Group: Administered garlic (200 mg kg^{-1} day^{-1}) via gavage for 10 days.

-Positive Control Group: Administered ACR (50 mg kg^{-1} day^{-1}, i.p.) followed 30 minutes later by vitamin E (200 mg kg^{-1}, oral gavage) every other day [28].

Behavioral assessment (Gait score evaluation)

At the end of the treatment regimen, motor coordination was evaluated using a gait score test as per LoPachin et al. [29]. Each rat was observed for 3 minutes in a transparent Plexiglas chamber (90×90 cm). Gait scores were assigned based on the following criteria:

Score 1: Normal, unaffected gait.

Score 2: Slight impairment, including foot splay and mild hind limb weakness.

Score 3: Moderate impairment, with noticeable foot splay, hind limb weakness, and limb spread during movement.

Score 4: Severe impairment, characterized by significant foot splay, profound hind limb weakness, limb dragging, and inability to rear.

Tissue preparation and biochemical assays

Upon completion of behavioral assessments, the rats were deeply anesthetized using a ketamine/xylazine cocktail and subsequently euthanized via decapitation. The cerebral cortex was subsequently dissected, immediately snap-frozen in liquid nitrogen, and stored at -80°C pending further biochemical analysis.

Cortical GSH levels were quantified according to established methods. Briefly, tissue samples were weighed and homogenized on ice in a chilled phosphate buffer (0.0001 mol L^{-1} Tris-HCl, 0.01 mol L^{-1} EDTA-2Na, 0.8% saline, pH 7.4) to generate a 10% (w/v) homogenate, utilizing a mechanical homogenizer. The resultant homogenates were subjected to centrifugation at 4°C (4000 × g for 30 minutes). The ensuing supernatant was carefully collected and subsequently analyzed for GSH content [30, 31].

The extent of lipid peroxidation was quantified by measuring MDA concentrations via the TBA assay. For this purpose, a 10% (w/v) tissue homogenate was prepared in ice-cold 1.15% KCl solution. A 0.5 mL aliquot of the homogenate was then combined with 3 mL of 1% phosphoric acid (H_3 PO_4) and 1 mL of 0.6% TBA. The reaction mixture was incubated in a boiling water bath for 45 minutes. After cooling to room temperature, the chromogen was extracted into 4 mL of n-butanol. The solution was vortexed vigorously and centrifuged at 5000 × g for 20 minutes. The absorbance of the resulting organic (n-butanol) phase was measured spectrophotometrically at 532 nm [12, 32].

Statistical analysis

All statistical analyses were conducted using GraphPad Prism (version 9.4.1). For parametric biochemical data, inter-group differences were assessed using a one-way analysis of variance (ANOVA), with post-hoc comparisons conducted via Tukey's honestly significant difference test. The non-parametric Kruskal-Wallis test was employed for the ordinal gait score data. Data are presented as mean ± standard deviation (SD). A probability (p) value of less than 0.05 was defined as the threshold for statistical significance.

RESULTS

Effect of ACR on MDA and Neuroprotective effect of garlic

Our findings indicate that ACR administration resulted in a significant rise in cortical MDA levels ($p<0.001$), a marker of heightened lipid peroxidation. Treatment with garlic significantly reduced MDA levels at doses of 100 mg kg^{-1}

($p<0.01$), 200 mg kg^{-1} ($p<0.001$), and 400 mg kg^{-1} ($p<0.001$), with the greatest neuroprotective effect observed at 400 mg kg^{-1}. Similarly, vitamin E (200 mg kg^{-1}, every other day) significantly attenuated ACR-induced lipid peroxidation ($p<0.001$). These findings demonstrate that garlic and vitamin E effectively mitigate ACR-induced oxidative stress in the rat cortex (Figure 1).

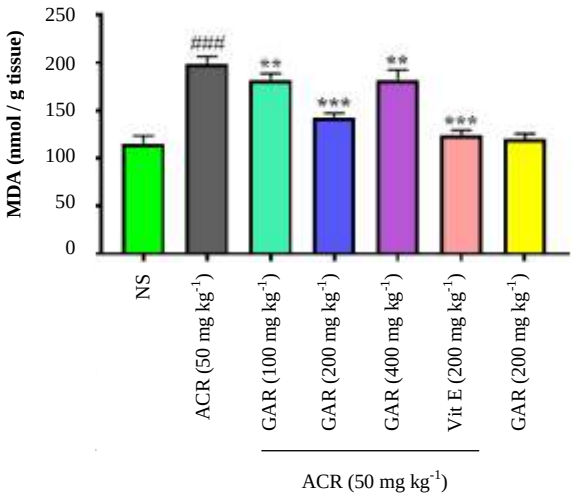

Figure 1. Effect of garlic co-treatment on cortical MDA levels in a rat model of ACR-induced neurotoxicity. Data are presented as the median with range (n=6 animals per group). ###p<0.001 vs. NS; ***p<0.001 and **p<0.01 vs. ACR. MDA, malondialdehyde; VIT E, vitamin E; GAR, garlic; NS, normal saline; ACR, acrylamide.

Effect of ACR on GSH and Neuroprotective effect of garlic

Administration of ACR (50 mg kg^{-1} day^{-1}, i.p., 11 days) induced a significant depletion of cortical GSH in male Wistar rats ($p < 0.001$), indicative of pronounced oxidative stress. This depletion was significantly attenuated by concomitant treatment with garlic. GSH levels were restored in a dose-dependent manner, with statistical significance observed at doses of 100 ($p < 0.05$), 200 ($p < 0.001$), and 400 mg kg^{-1} ($p < 0.001$), the latter demonstrating the most robust restorative effect. Similarly, vitamin E (200 mg kg^{-1}, every other day) also significantly reversed the ACR-induced GSH deficit ($p < 0.001$). These results suggest that garlic and vitamin E effectively counteract ACR-induced oxidative stress by enhancing GSH levels in the rat cortex (Figure 2).

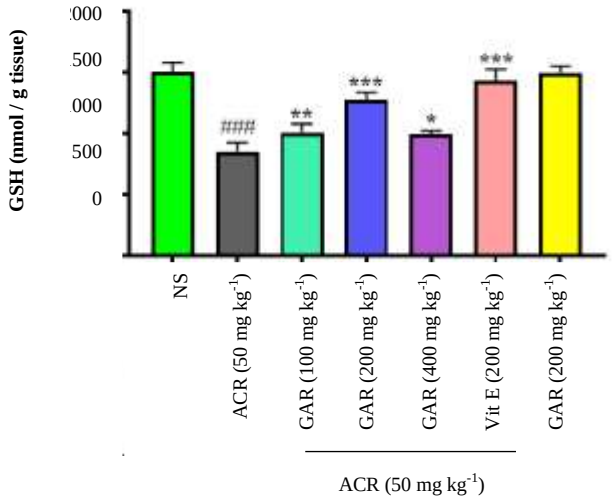

Figure 2. Effect of garlic co-treatment on cortical GSH content in a rat model of ACR-induced neurotoxicity. Data are presented as the median with range (n=6 animals per group). ###p<0.001 vs. NS; ***p<0.001, **p<0.01 and *p<0.05 vs. ACR. GSH, glutathione; VIT E, vitamin E; GAR, garlic; NS, normal saline; ACR, acrylamide.

Effect of ACR on Neurological Gait Scores and the

Attenuating Role of garlic

Intraperitoneal administration of ACR (50 mg kg^{-1} daily for 11 days) induced a progressive deterioration of gait function in male Wistar rats, as assessed by a standardized gait scoring system. A significant impairment in motor coordination and balance was observed in the ACR-treated group compared to controls ($p < 0.01$). Concomitant administration of Allium sativum L. extract (100-400 mg kg^{-1}, oral gavage, 10 days) significantly and dose-dependently attenuated these

ACR-induced neuromotor deficits, with the 400 mg kg^{-1} dose demonstrating the most potent neuroprotective effect. Administration of the positive control, vitamin E (200 mg kg^{-1} every other day), resulted in a significant amelioration of ACR-induced gait impairment ($p < 0.01$). These findings indicate that garlic and vitamin E effectively mitigate ACR-induced motor coordination deficits in rats (Figure 3).

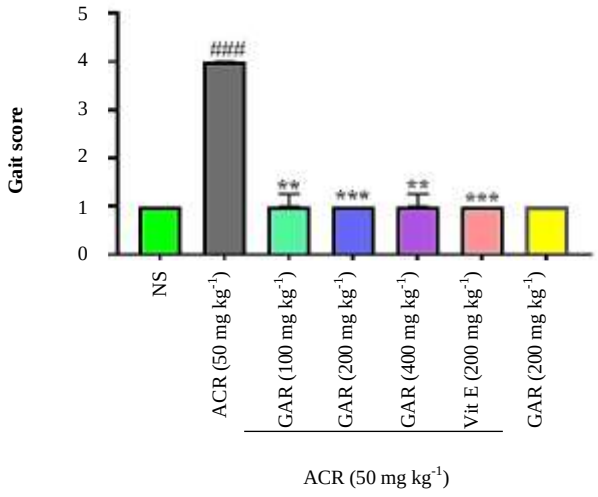

Figure 3. Effect of garlic on behavioral index (gait scores) in rats during treatment with ACR. Data are presented as the median with range (n=6 animals per group). ###p<0.001 vs. NS; ***p<0.001 and **p<0.01 vs. ACR. VIT E, vitamin E; GAR, garlic; NS, normal saline; ACR, acrylamide.

DISCUSSION

It is well known that ACR exerts cumulative neurotoxic effects in both humans and rodent models [33]. While low-level chronic exposure may not produce immediate symptoms, higher doses over a shorter period elicit significant neurotoxic effects, highlighting its cumulative nature [34]. Classified as a Group 2A carcinogen [35], ACR's toxicity extends to the liver, genes, and development. Our study demonstrates that garlic co-administration significantly inhibited ACR-induced neurotoxicity in Wistar rats, with the 400 mg kg^{-1} dose being particularly effective in reducing gait abnormalities.

The neurotoxic sequelae of ACR intoxication, including clinical manifestations of ataxia and skeletal muscle weakness, are mechanistically linked to degenerative pathology within both central and peripheral nervous systems [36, 37]. Proposed mechanisms include axonal degeneration, induction of apoptosis and autophagy, oxidative stress, and neuroinflammation [8, 12, 38]. Several hypotheses attempt to explain its action, including alterations in neurotransmitter release, impairment of kinesin-mediated axonal transport, and disruption of synaptic vesicle fusion [33]. Furthermore, ACR can cross the placental barrier, posing a potential risk for developmental neurotoxicity [39].

One of the body's main defense mechanisms against ACR involves its conjugation with glutathione (GSH), facilitating the neutralization of free radicals and supporting the antioxidant system [3]. Therefore, antioxidant agents are a logical therapeutic approach. Garlic is rich in sulfur compounds (e.g., allicin, alliin), vitamins, minerals, and flavonoids, which collectively contribute to its potent antioxidant capacity. Previous research supports the neuroprotective role of garlic and its constituents [25-27]. For example, allicin combined with melatonin has been shown to protect against ACR-induced neuronal damage by reducing DNA damage and modulating neurotransmitters [25].

Our investigation demonstrated that garlic, at the administered doses, provided neuroprotection against ACR in a dose-dependent manner, an effect most probably attributable to its antioxidant properties. As anticipated, vitamin E, employed as a positive control, conferred significant protection against ACR-induced neurotoxicity, an effect consistent with its well-characterized antioxidant profile and emerging evidence of anti-apoptotic activity (38, 40). Notably, the efficacy of garlic (200 mg kg^{-1}) was not statistically different from that of vitamin E (200 mg kg^{-1}) in mitigating both lipid peroxidation and gait abnormalities. This finding positions garlic as a potent neuroprotective agent with comparable efficacy to a known standard.

The outcomes of our study align with the earlier work of Ghareeb and colleagues (2010) [40]. Both investigations confirm that ACR triggers oxidative stress and neurotoxicity in rats, evidenced by increased MDA, decreased GSH, and motor impairments, with garlic and vitamin E effectively mitigating these effects by reducing MDA, restoring GSH, and improving motor coordination. The present study demonstrates a dose-dependent neuroprotective effect of garlic (100–400 mg kg^{-1}) in the cerebral cortex, with maximal efficacy observed at 400 mg kg^{-1}. This was corroborated by significant improvements in neuromotor function (gait scores, $p < 0.01$–0.001), an effect mirrored by vitamin E (200 mg kg^{-1}). These findings are complemented by the work of Ghareeb et al., who employed a subchronic model (20 mg kg^{-1} ACR for 4 weeks) and reported congruent antioxidant effects for a single dose of garlic (250 mg kg^{-1}) and vitamin E. While the latter study provides confirmation of efficacy in a longer-term model, it offers less resolution on dose-dependency and specific motor outcomes. Collectively, these investigations provide complementary evidence from acute and subchronic exposure paradigms.

The combined therapeutic application of allicin and melatonin has demonstrated efficacy in promoting neuronal recovery following ACR-induced damage, potentially through mechanisms involving the regulation of DNA damage repair and the upregulation of neurotransmitter levels [20]. The observed neuroprotective effects of garlic against ACR-induced neurotoxicity are likely mediated by

its antioxidant properties. This is supported by the significant protection afforded by the positive control, vitamin E, a known antioxidant. The comparable efficacy of garlic and vitamin E in ameliorating ACR-induced gait abnormalities further substantiates that the neuroprotection conferred by garlic is, at least in part, attributable to its potent antioxidant activity. The neuroprotective properties of vitamin E, extensively documented in the scientific literature, are primarily mediated through its robust antioxidant mechanisms [38]. Recent evidence indicates that vitamin E also exhibits anti-apoptotic properties [41]. Vitamin E, a compound with established neuroprotective efficacy, was utilized as a positive control to quantitatively benchmark the neuroprotective effects of garlic against ACR-induced neurotoxicity. The results demonstrated that the efficacy of garlic (200 mg kg^{-1}) in inhibiting lipid peroxidation was statistically equivalent to that of vitamin E. This finding substantiates the classification of garlic as a potent neuroprotective agent.

CONCLUSIONS

In conclusion, the present study demonstrates that an 11-day regimen of ACR (50 mg kg^{-1}, i.p.) induces significant neuromotor deficits, including impaired gait and coordination, concurrent with elevated cortical lipid peroxidation and depletion of reduced GSH. These manifestations of neurotoxicity were significantly and dose-dependently ameliorated by concomitant administration of garlic (100-400 mg kg^{-1}), with efficacy comparable to the reference antioxidant vitamin E (200 mg kg^{-1}). Garlic reduced ACR-induced neurotoxicity by suppressing lipid peroxidation and elevating GSH levels, highlighting its antioxidant-mediated neuroprotective potential. The present findings indicate that garlic exhibits significant potential as a therapeutic intervention for ameliorating ACR-induced neurotoxicity. The observed neuroprotective efficacy was comparable to that of vitamin E, an established positive control.

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ETHICAL CONSIDERATION

This experimental study investigated the antioxidant effects of garlic on ACR-induced neurotoxicity in the cortex of male Wistar rats. All procedures were conducted in compliance with the guidelines of the Iranian Biomedical Research and Ethics Committee (IR.IAU.DAMGHAN.REC.1403.023).

Conflicts of interests

The authors declare that there is no conflict of interest.

Author contributions

Nadia Touzandehjani: Investigation, Methodology, Writing- Original draft preparation, Resources. Azadeh Serri: Software, Data curation, Validation. Jamshid Tabeshpour: Conceptualization, Supervision, Methodology, Validation, Project administration, funding acquisition.

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Date availability

Data will be made available on request.

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