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### Original Paper

## Selenium nanoparticles coated with resveratrol ameliorates the neurobiochemical abnormalities by attenuating oxidative stress and improving neurotransmissions in AlCl<sub>3</sub>-induced Alzheimer's model of rats

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### ABSTRACT

The present study aimed to investigate whether long-term administration of resveratrol coated with Selenium nanoparticles (RSV-Nano selenium) could shield rats from aluminum-induced AD pathogenesis and oxidative injury. Thirty male albino wistar rats were orally administered with aluminum chloride (300 mg/kg b. wt.) once daily for 30 days for induction of AD. The rats of induced model of AD were orally administrated with RSV-Nano selenium (200 mg/kg, b. wt.) once daily for 3 weeks. The rats were scarified on the 52nd and brain tissue of each rat was dissected and frozen at  $-80^{\circ}\text{C}$ . Biochemical research was conducted to determine the degree of oxidative injury through measuring Catalase, Glutathione (GSH), Malondialdehyde (MDA),  $\gamma$ -Secretase and Calcium levels in brain tissue. Aluminum chloride administration caused neurotoxicity and severe memory loss, as well as significant oxidative harm. It also resulted in substantial rise in  $\gamma$ -secretase and a significant decrease in calcium levels. RSV-Nano selenium administration increased neuronal transmission by reducing oxidative stress and metal chelation in AD model of rats ( $P < 0.05$ ). In conclusion, RSV-Nano selenium protects against AD and oxidative harm caused by aluminum.

## 1. INTRODUCTION

The general name for a gradual and cumulative loss of both structure and activity of neurons in the brain and nervous system is "neurodegeneration" the prevalence of age-related disorders like Alzheimer's, Parkinson's, Huntington's, and Amyotrophic lateral sclerosis (ALS) was predicted to rise in parallel with age and human population density. With early dementia, people struggle to retain previously learned information; in later phases, they are unable to speak, to learn new things, and to think rationally. Amyloid- $\beta$  ( $A\beta$ ) hyperphosphorylation and accumulation of neurofibrillary tangles are the two observable manifestations of AD (Mattson, 2000). Excess free radicals and oxidants can play a part in the disease. Due to our limited understanding of the actual causes of such illnesses, treatments have not yet been effective in combatting them. It should also be noted that there are other barriers to its care, namely the blood-spinal cord barrier (BSB) and blood-cerebrospinal fluid (BSF) (Mendes et al., 2018). In some circumstances, some of the antineoplastics are used as pharmaceuticals. It was recorded that over thirty million individuals globally actually suffer from the various forms of neurodegenerative disorder, of which Alzheimer's disease is the most devastating to the patient and their families (Maqbool et al., 2016). Around 80% of the older population have dementia due to AD. Much more striking is the global decline in size and no glucose absorption in patients with AD than the traits, indicating a drop in neuronal function. According to the data of the ageing global population in the world, the number of older adults

with AD and other dementias will rise from 46.8 million to 131.9 million to 89.6 million in the year 2050s (Ibáñez et al., 2012).

Oxidative stress is described as an increase in the release of reactive oxygen species (ROS) and/or a degradation of the antioxidant defense mechanism in cells and tissues, resulting in a prooxidant-antioxidant imbalance that can cause damage. ROS can attack polyunsaturated fatty acids in the bio-membrane, allowing lipid peroxidation and free radical chain reactions to increase (Omayma et al., 2017a). A set of disorders, including AD, Parkinson's disease (PD), atherosclerosis, stroke, and diabetes, have been related to oxidative stress (Omayma et al., 2017b).

The potential uses of nanomaterials include neuroprotective in AD, as well as the ability to support neuronal health, and smart distribution. Thus, metal ions can trigger oxidative stress, which makes degeneration of the brain more likely in Alzheimer's patients. Most of the applications are due to the fact that matter at the nanometer scale has different properties as compared with the bulk state. Using plant extract is one of the most recent used methods for synthesizing nanoparticle. Nanoparticles of many metals have been produced this way (Nunes et al., 2012). Biogenic synthesis is useful not only because of its reduced environmental impact compared with some of the physicochemical production methods, but also because it can be used to produce large quantities of nanoparticles that are free of contamination and have a well-defined size and morphology. Moreover, biosynthetic routes can actually provide nanoparticles of a better-defined size and morphology than some of the physicochemical methods of production (Omayma et al, 2015)

Resveratrol is a polyphenol attracting widespread attention due to its therapeutic potential in AD. It has been shown to reduce A $\beta$  production and suppress the progression of AD via various mechanisms including inhibiting inflammation and (Drygalski et al., 2018). Resveratrol (RSV) is primarily present in grape skin, peanut, and pomegranate seed skin. RSV is by far the greatest dietary source of the wine. RSV has been shown to prevent and ameliorate certain degenerative diseases in animal studies, such as cancer, cerebrovascular disease, and depression, as well as neurodegenerative disorders, among other things. Neuroprotection helps, as it crosses the blood-cereine barrier and is water-soluble, works in the brain as well several investigations have shown that RSV can protect neurons from toxicity. RSV has demonstrated immunity from the effects of central nervous system diseases, such as stroke, spinal cord inflammation, and hemorrhage in animal and human and clinical trials, demonstrating promise for the treatment of AD, and a possible benefit in preventing the formation of new ones in patients with AD (Ahmed et al., 2017). It has been shown to be anti-inflammatory, anitoxemic, anaesthetic, and astringent in several tests. Studies suggest that RSV inhibits the development of  $\beta$ -amyloid plaques and reduces the progression of AD. Recent studies indicate that RSV protection is related to presence of mitochondria. Any research claims that it acts on SIRT1, a protein with beneficial impact on cAMP behavior following transcription. RSV supplementation can help reduce the synthesis of amyloid- $\beta$  even through inhibition of GSK-3 $\beta$  (Kumar et al., 2011). This study aimed to identify the potential action of resveratrol carried on nano selenium particles against aluminum chloride-induced Alzheimer model rats through evaluating biochemical and neurochemical alterations

## 2. MATERIAL AND METHODS

Selenium dioxide (Na<sub>2</sub>SeO<sub>3</sub>), NaBH<sub>4</sub>, and resveratrol were purchased from Sigma-Aldrich-Co (Saint Louis, USA). AlCl<sub>3</sub> Was purchased from Algomhoria-Co (Cairo, Egypt).

### 2.1. Preparation and characterization of RSV-SeNPs

A 200  $\mu$ L aliquot of 0.1 M Na<sub>2</sub>SeO<sub>3</sub> solution was mixed with 3.2 mL 25 mM RSV. After that, 160  $\mu$ L of 0.1 M NaBH<sub>4</sub> was added and stirred for 30 min until the color of solution was change to red. The excess of RSV and Na<sub>2</sub>SeO<sub>3</sub> were removed by dialysis (Yang et al., 2018).

### 2.2. Experimental animals

Thirty male Wistar albino rats weighing 180–200 g aged 6–8 weeks were obtained from animal house of Animal Health Research Institute (Giza, Egypt). Animals were acclimatized to the laboratory conditions a week prior to experimentation and were maintained at standard laboratory conditions such as 25  $\pm$  2  $^{\circ}$ C, humidity of 50  $\pm$  5% and natural 12:12 hrs light and dark cycle along the experiment.

Animals were cared in accordance with the standards outlined in Guide for the Care and Use of Laboratory Animals and ethics committee of Veterinary Medicine (Benha, Egypt)

### 2.3. Experimental design

The experimental animals were randomly assigned to three different groups of ten animals each. Group I received 0.5% sodium carboxy methyl cellulose (CMC) orally as a vehicle for 30 days and considered as control. Group II (AD model) orally administrated with AlCl<sub>3</sub> (300 mg/kg/day) once daily for 30 days and Group III (RSV-Nano-selenium treatment) orally administrated with AlCl<sub>3</sub>(300 mg/kg/day) once daily for 30 consecutive days then, treated with 200 mg/kg of RSV-Nano-selenium for 3 weeks.

### 2.4. Sampling:

Animals (n = 10/group) were decapitated 1 h after the last injection of the drugs or their vehicles. The brain of each animal was removed quickly, and the PFC and hippocampus were carefully dissected on ice and rapidly frozen at  $-80^{\circ}$  C. The hippocampus and PFC were homogenized with tissue protein extraction reagent (Pierce Biotechnology, Rockford, USA) containing protease inhibitors, centrifuged at 12,000  $\times$  g for 10min and the supernatant was used for subsequent analyses of oxidative stress and biochemical parameters (liu et al., 2016).

### 2.5. Biochemical Parameters

The levels of non-enzymatic antioxidants GSH were estimated in the brain tissue of control and experimental groups of rats (Habig et al., 1974). Then, the levels of lipid peroxidation MDA determined in the brain tissue of control and experimental groups of rats (Draper and Hadley 1990). The activities of enzymatic antioxidants, catalase were measured in brain tissue of control and experimental groups of rats (Palsamy and Subramanian, 2011). Calcium levels in the brain tissue of control and experimental groups of rats were measured by calcium assay colorimetric kit purchased from abcam-co (Cambridge, U.K) according to Jones and Keep (1988). Norepinephrine was measure according to Barakat method by ELISA (a sandwich enzyme Immunoassay) (Barakat, 1996).  $\gamma$ -secretase activity was measured according to method of Haass and De Strooper (1999).

### 2.6. Statistical analysis

Data were analyzed using computer software, Statistical Package for the Social Sciences (SPSS) version 16 (SPSS Inc. Released 2007, SPSS for Mac, and Version 16.0. Chicago, SPSS Inc.). Results were presented as mean  $\pm$  SEM. P  $\leq$  0.05 was considered statistically significant (Borai et al., 2017)

## 3. RESULTS

Results summarizes the biochemical changes in the brain tissues with AlCl<sub>3</sub>-induced AD with and without RSV treatment (Fig. 1-6). Resveratrol partially normalized these oxidative biomarkers as GSH and Catalase suggesting that it has strong antioxidant properties to increase the antioxidant potential in the brain tissues. Results indicated that treatment with RSV-Nano-selenium significantly elevated neuronal calcium levels. The levels of NE were significantly decreased in AlCl<sub>3</sub> group as compared to control group, while the levels of NE were significantly increased in AlCl<sub>3</sub> + RSV-Nano-selenium group compared with the AlCl<sub>3</sub> group ( $p < 0.05$ ).

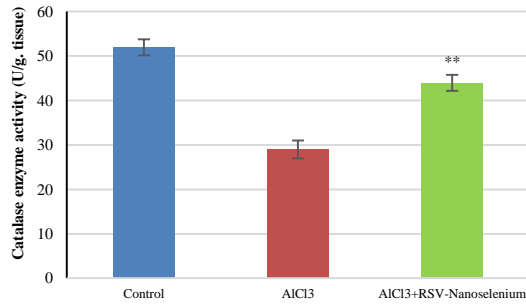


Fig.1 Catalase enzyme activity in brain tissue (U/g. tissue). Data were given as mean ± SEM. P value < 0.05 compared to control

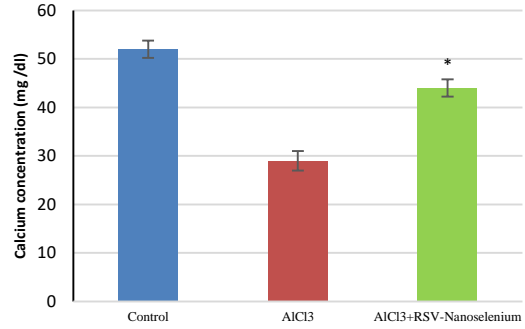


Fig.5 Calcium level in brain tissue(mg /dl).Data were given as mean ± SEM. Pvalue< 0.05 compared to control

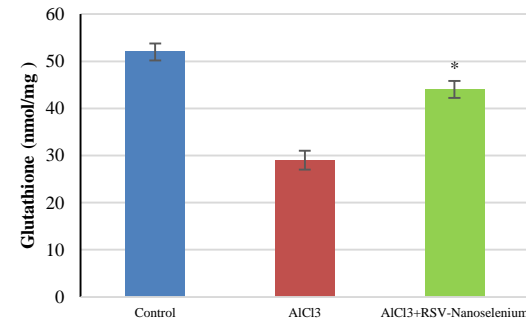


Fig.2 GSH level in brain tissue (nmol/mg protein).Data were given as mean ± SEM. P value < 0.05 compared to control

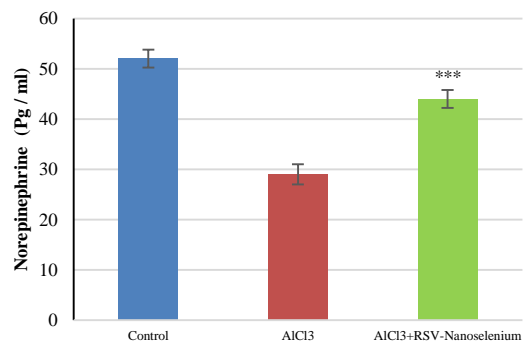


Fig.6 Norepinephrine level in brain tissue(Pg / ml).Data were given as mean ± SEM. P value< 0.05 compared to control.

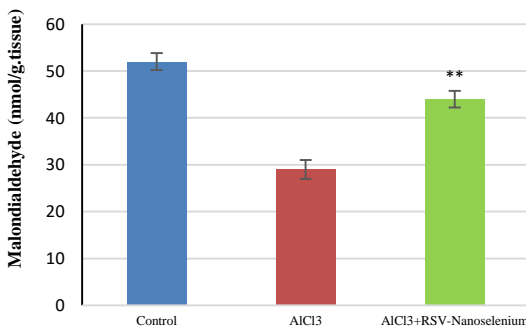


Fig. 3 MDA level in brain tissue (nmol/g. tissue). Data were given as mean ± SEM. P value< 0.05 compared to control.

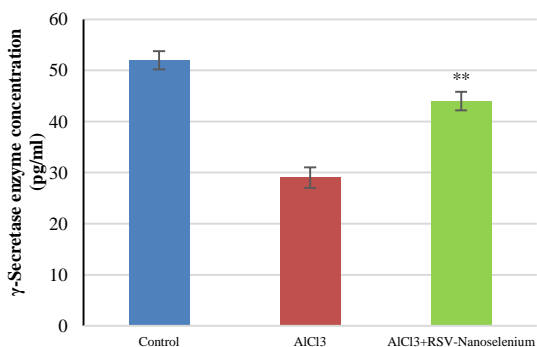


Fig.4 Gamma Secretase enzyme level in brain tissue(pg/ml). Data were given as mean ± SEM. P value< 0.05 compared to control

#### 4. DISCUSSION

Brain is the main organ for the memory function and cognition. Memory formation is considered to stem from neural or synaptic plasticity whose continuance is of importance for the normal mental cognition. Many studies demonstrated a significant beneficial effects of polyphenolic and flavonoids compounds on AD through its protecting effects against mitochondrial oxidative stress induced apoptosis (Bakhtiari et al., 2017). The purpose of the present study was to determine the therapeutic efficiency of resveratrol which might be effective against oxidative stress and enhance the antioxidant systems to protect brain tissues from AD.

Since it modifies the cholinergic, dopaminergic, and noradreny transmitter release, AICl<sub>3</sub> has the ability to decrease both the amount of choline and the production and release of neurotransmitters. Secondly, it is both impalpalsynetic and galvanic. The first explanation is related to a reduction in the release of acetylcholine, the second is related to choline deficiency, which results in reduced acetylcholinesterase function. Second, elevated ACh activity levels contribute to usable ACh decomposition. Since animals who are subjected to aluminum show altered brain transmitters (i.e., Alzheimer's, Parkinson's, etc.) may produce more reactive forms of oxygen, this may contribute to the development of neurodegenerative illnesses. oxide is greater in Al-exposed animals, and the development of quinones, which intermingle with cysteine-cysteine residues of glutathione (Cys) proteins to result in the inhibition of its antioxidant effect (Borai et al., 2017).

P-Tau is a microtubule-associated protein; tau-associated proteins are involved with neuron organization and microtubule formation. In AD, this tau serves as an ATP molecule that gets hyperphosphorylated and combines with

pNFT to create NFT Aluminum has previously been identified as a powerful pro-oxidant believed to improve lipid peroxides in cortex and hippocampus. It also resulted in free iron ions that underwent the Fenton reaction, resulting in oxidation, and in neural harm. It also attacks mitochondria triggering cytochrome c releases and the activation of pro-apoptotic protein such as bax and caspase-3, which cause apoptotic neuronal death. As peroxidation is mediated by free radicals, it was critical to check on the levels of these naturally occurring protective mechanisms (antioxidant) enzymes: catalase, superoxide dismutase, and glutathione. As was associated with increased lipid peroxidation and decreased enzymatic (catalase, glutathione S-transferase, and superoxide dismutase) accumulation in brain tissue. It is possible that the axonal mitochondria membrane turnover was slowed down, as a consequence of the interference on the golgi, and peroxynitrite and enzyme release, and this could trigger a buildup of malondialdehyde and peroxynitrite in the cells. Superoxide dismutase into water and oxygen under oxidative conditions. The catalase in solution converts hydrogen peroxide to water and oxygen (Kumar et al., 2009).

Catalase is found in the peroxisomes of mammalian cells and is believed to be associated with H<sub>2</sub>O<sub>2</sub>-oxidizing agents contained in these organelles, possibly to provide fast degradation of H<sub>2</sub>O. Because of the connection between oxidative stress and cognitive impairment, agents and dementia, medications that affect the activity of reactive oxygen species could be a possible neuroprotectants for the treatment of AD disease (Kumar et al., 2011).

Our results revealed an improvement in oxidative stress condition in group treated with RSV-Nanoselenium, it increased Catalase and GSH and decreased MDA. Reduced glutathione serves as the most abundant internal antioxidant and also acts as a substrate for the glutathione peroxidase enzyme, which participates in the hydrogen peroxide detoxification system of the cell. It is also recognised that catalase serves as an antioxidant, and this fact is supported by evidence that it combines with reactive free radicals in catalysis. In our study, we demonstrated that RSV-Nanoselenium restored reduced glutathione and increased catalase in aluminium treated rats (Kumar et al., 2011).

RSV-Nanoselenium also inhibited a formation by activating cells' anti-oxidative defenses and influencing APP cleavage, according to our findings. The fact that RSV is a powerful antioxidant and SIRT1 inducer seems to play the most influential part in the first process (Chiang et al., 2018). RSV improves antioxidant potential in AD neurons by increasing HO-1 and GSH levels through the AMPK-SIRT1-Nrf-2 pathway and decreasing A synthesis through GSK-3 inhibition (Huang et al., 2011). Research indicates that RSV treatment can alter the permeability of the blood-brain barrier (BBP) and the decline of the inflammatory mediators' in addition, antiviral antibodies reduce A $\beta$  polymerization in the brain. New findings indicate that CSF levels of A $\beta$ 40 and A $\beta$  have decreased following the intake of RSV. It has been postulated that RSV impedes the progression of AD pathology and is seen as an effect on A $\beta$  deposition in the brain and on A $\beta$  synthesis via the BBB. This confirms that previous preclinical research, which has found that RSV reduces BACE1 expression, while increasing the synthesis and clearance of A $\beta$  (Moussa et al., 2017).

Our study showed an improvement in norepinephrine level in brain tissue of Alzheimer model rats treated with RSV-Nanoselenium. RSV has antioxidant properties the ability

to scavenge both O<sub>2</sub><sup>-</sup> and OH<sup>-</sup> radicals both in vivo and in vitro. In addition to scavenging ROS, exogenously administered resveratrol modulates the expression and activity of antioxidant enzymes, such as SOD, glutathione peroxidase, and catalase. Resveratrol ability to improve neural response through increasing norepinephrine level mediated by the regulation of the central serotonin and noradrenaline levels and the related monoamine oxidase-A activities, as well as the activation of hippocampal brain-derived neurotrophic factor (BDNF). In addition, resveratrol exerts its neuroprotective actions against activated microglia by scavenging ROS through increasing GSH and catalase levels (liu et al., 2016).

Deficiency of the monoaminergic neurotransmitters, NE in brain biogenic systems in the hippocampus accelerates the cognitive impairment and plays a crucial role in early pathological processes of AD. The present results indicating an improvement in the level of NE in group treated with RSV-Nano-selenium suggesting that it has ability to modulate neurotransmissions (Sarubbo et al., 2015).

Elevation of neuronal calcium levels in group of rats treated with RSV-Nano-selenium also leads to calcium-dependent increase in glucose utilization by the neuronal cells then improving neurotransmission and cognitive function (Ahmed et al., 2017)

## 5. CONCLUSION

Results from the current study revealed that treatment with RSV-Nanoselenium might aid to improve NA neurotransmission that modulated normally as an outcome of neurotoxicity of AlCl<sub>3</sub>. RSV-Nanoselenium exhibited beneficial effect as antioxidant and anti-inflammatory. This study recommends usage of RSV-Nanoselenium as a new therapeutic option in patients with AD.

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest for current data

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