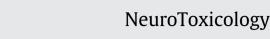
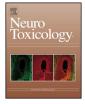
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# Neuroprotective role of hydroalcoholic extract of *Vitis vinifera* against aluminium-induced oxidative stress in rat brain



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#### ABSTRACT

The present study was designed to examine the protective potential of hydroalcoholic extract of Vitis vinifera in ameliorating the alterations induced by aluminium (Al) on behavioural and neurochemical indices. Al was given orally (100 mg/kg b.wt./day) whereas V. vinifera extract was administered through diet (400 mg/kg, p.o.) to rats for a total duration of 45 days. Passive avoidance and open field tests revealed significant alterations in the short-term memory and cognitive behaviour in rats treated with Al. Further, locomotor as well as muscular activities were also found to be significantly affected. Coadministration of V. vinifera extract with Al caused significant improvement in the short-term memory, cognition, anxiety, locomotion and muscular activity. Al exposure led to a significant decrease in the acetylcholinesterase activity in the brain, increase in serum glucose, TG, TC, ALP and ALT. Anti-oxidant parameters-reduced glutathione, catalase and glutathione reductase levels were also found to be significantly decreased but the levels of lipid peroxidation was significantly increased in brain following Al treatment. V. vinifera extract supplementation to Al treated animals caused a significant improvement in the activity of enzyme acetylcholinesterase which was altered by Al. Serum glucose, TG, TC, ALP and ALT were brought back to normal levels. Further, V. vinifera extract when given along with Al was also able to regulate the levels of Anti-oxidant parameters in brain and the values were found close to the normal controls. Histopathological studies revealed neurodegeneration and vacuolated cytoplasm after Al treatment. Therefore, the study strengthens the hypothesis that V. vinifera extract can be used as a neuroprotectant during Al induced neurotoxicity.

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#### 1. Introduction

Aluminium exposure causes adverse health effects, some neurodegenerative diseases like Alzheimer's disease (AD) (Pratico et al., 2002). Aluminium widely distributed metallic element in the earth's crust and it acts as a neurotoxin. Aluminium contain high levels in diet led to increase risk of central nervous system and similar to Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and parkinsonism dementia complex (Zatta et al., 2002). It promotes aggregation of synthetic  $\beta$ -amyloid protein (Kuroda and Kawahara, 1994). It activates neurotoxicity in central nervous, skeletal and haematopoietic systems (Sethi et al., 2008). The extensive damage of nervous system caused learning and memory impairment of animals. Yokel (2000) reported that potentially damaged brain in animals and humans induced by Al toxicity (Walton et al., 1995). Aluminium-containing chemicals are widely used in medicine, food additives, and cosmetics and are added to tap water in some areas as a flocculating agent during the water purification process, it is important to study factors that might increase the absorption of aluminium across the gastrointestinal barrier (Cunat et al., 2000).

Black grapes (*Vitis vinifera*) is one of the most widely grown fruit crops in the world. Grape juice jams and raisins are also important commodities in the market of the whole world. Numerous studies focused on the health-promoting and antioxidant effects of grapes. Interest in the health benefits of Black grapes has increased due to their high phenolics contents. Most phenolics in Black grapes are located in the seeds (Poudel et al., 2008). Gallic acid, catechin and epicatechin are the main phenolics found in Black grapes seeds,

*Abbreviations:* Fig., figure; i.p., intra-peritoneal; kg, kilogram; mg, milligram; ml, millilitre; p.o., per oral; w/w, weight/weight; w/v, weight/volume; LD<sub>50</sub>, lethal dose; rpm, rotations per minute; VVE, *Vitis vinifera* extract; rpm, rotations per minute; GSH, glutathione; CAT, catalase; LPO, lipid peroxidation; MDA, mal-ondialdehyde; ALP, alkaline phosphatase; TC, total cholesterol; TG, triglycerides; ALT, alanine transaminase.

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while ellagic acid and myricetin are the major ones in the skins. Black grapes well known for their high levels of antioxidants and polyphenols, have also shown promise as novel antimicrobial agents (Brown et al., 2009), anti-cancer properties (Mertens-Talcott et al., 2006), anti-inflammatory activity (Greenspan et al., 2005), antimicrobial activity against *Escherichia coli* 0157:H7 (Kim et al., 2009), nootropic activity, antiulcerative, antiarthritic, anti-viral prevent skin ageing, inhibit UV-radiation induced peroxidation activity (Bagachi et al., 1997; Dragsted, 1998) and scavenge free radicals (Lakshmi et al., 2013). Resveratrol, Quercetin, Catechin, Flavone, Flavonols, Procyanidin, Anthocyanin, gallic acid, Epicatechin are the phenolic compounds isolated from the black grapes.

Little information is available on protective effect of *V. vinifera* against aluminium-induced neurotoxicity. In view of these facts the present study was designed to test the hypothesis whether a nutritional strategy like chronic administration of hydroalcoholic extract of *V. vinifera* could prevent aluminium-induced neurotoxicity in terms of oxidative stress in rat brain.

#### 2. Materials and methods

#### 2.1. Collection of plant material

The Black grapes were collected from the local market in Ranga Reddy District and the botanical authentication was done by Dr. Ram Chandra Reddy, Head of Botany Department, Osmania University, Hyderabad.

#### 2.2. Preparation of the hydroalcoholic extract

The fresh fruits were sliced using a home slicer and the slices obtained were shade-dried, pulverized and passed through a 20-mesh sieve. The dried, coarsely powdered plant material was extracted with hydroalcoholic solvent (60 ml water and 40 ml methanol) using Soxhlet apparatus at a temperature below 60 °C for 24 h. The solvent was evaporated under vacuum, which gave semisolid mass (yield: 57%, w/w) with respect to the dried powder. Oral suspensions containing 400 mg/ml of the hydroalcoholic extract of *V. vinifera* were prepared and used for the evaluation of oxidative stress in liver and kidneys of rats.

#### 2.3. Chemicals

Aluminium chloride (Al) was purchased from Merck, Chennai, India. All chemicals were pure with an efficiency of greater than 99%. The Tritonx-100 solution was purchased from Sigma–Aldrich Pvt. Ltd, Bangalore, India. All chemicals for sensitive biochemical assays were obtained from Sigma Chemicals Co. India and Hi media Chemicals, Mumbai, India. Distilled water was used for biochemical assays. All kits were obtained from Span Diagnostics Ltd., Surat, India.

#### 2.4. Animals

Adult male Sprague-Dawley rats ( $150 \pm 10$  g body weight) were obtained from the departmental animal facility where they were housed under standard husbandry conditions ( $25 \pm 2$  °C temperature, 60–70% relative humidity and 12 h photoperiod) with standard rat feed and water *ad libitum*. Experiments were conducted in accordance with the guidelines set by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India and experimental protocols were approved by the Institutional Animal Ethics Committee (CPCSEA/1217/2008/a).

#### 2.5. Experimental design

Twenty-four male Sprague-Dawley rats of weight  $150 \pm 10$  g were selected for this study. Animals were divided into four groups of six animals each.

Group 1: Control group (distilled water 1 ml).

Group 2: *V. vinifera* hydroalcoholic extract 400 mg/kg body weight/day, orally.

Group 3: Aluminium chloride 100 mg/kg body weight/day, orally.

Group 4: *V. vinifera* hydroalcoholic extract 400 mg/kg body weight/day, orally + aluminium chloride 100 mg/kg body weight/day, orally.

All the groups were treated once daily for a period of 45 days. The animals were weighed and behavioural observations were recorded before and at the end of the experiment. After the administration of last dose, the animals were given rest overnight and then on the next day, they were sacrificed under light ether anaesthesia. The organs were removed, cleaned, washed with phosphate buffer saline (pH 7.4) for various studies (Bhalla et al., 2010).

#### 2.6. Blood biochemical analysis

At the end of experimental period, animals were sacrificed using light ether anaesthesia and the blood samples were collected into blood collecting tubes by cardiac puncture from all animals. The blood samples were allowed to clot for 60 min at room temperature. Serum was separated by centrifugation using cool centrifuge (REMI) at 2000 g for 15 min and stored at -20 °C which was later used for estimation of various serum parameters like TG, TC, ALP, ALT and glucose according to the standard procedures.

#### 2.7. Tissue sample preparation

Animals were sacrificed with light ether anaesthesia and the brain of each rat was removed and washed well with ice-cold saline to remove blood and stored at -80 °C. Later the brain was taken and minced into small pieces and a total of 10% (w/v) homogenate was prepared using phosphate buffer (0.1 M, pH 7.4) containing 1 mmol ethylene diamine-tetra-acetic acid (EDTA), 0.25 M sucrose, 10 mM potassium chloride (KCL) and 1 mM phenyl methyl sulfonyl fluoride (PMSF) with a homogenizer (REMI) fitted with a Teflon plunger, which was centrifuged at 2000 g for 30 min at 4 °C to yield the supernatant. Later the supernatant was used for the estimation of acetyl cholinesterase (AChE) and antioxidant parameters (MDA, CAT, GSH and glutathione reductase).

#### 2.7.1. Lipid peroxidation (LPO)

LPO was estimated colorimetrically by measuring malondialdehyde (MDA) formation as described by Nwanjo and Ojiako, 2005. In brief, 0.1 ml of homogenate was treated with 2 ml of a 1:1:1 ratio of TBA–TCA–HCl (TBA 0.37%, TCA 15%, HCl 0.25 N) and placed in water bath at 65 °C for 15 min, cooled, and centrifuged at 5000 g for 10 min at room temperature. The optical density of the clear supernatant was measured at 535 nm against a reference blank. The MDA formed was calculated by using the molar extinction coefficient of thiobarbituric acid reactants (TBARS;  $1.56 \times 10^5$  l/ mole cm<sup>-1</sup>). The product of LPO was expressed as nmol of MDA formed per g of tissue.

#### 2.7.2. Catalase (CAT)

Catalase (CAT) activity was estimated following the method of Aebi, 1993. The homogenate  $(100 \ \mu l)$  was treated with ethanol

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