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Pomegranate from Oman Alleviates the Brain Oxidative Damage in Transgenic Mouse Model of Alzheimer's Disease

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ABSTRACT

Oxidative stress may play a key role in Alzheimer's disease (AD) neuropathology. Pomegranates (石榴 Shí Liú) contain very high levels of antioxidant polyphenolic substances, as compared to other fruits and vegetables. Polyphenols have been shown to be neuroprotective in different model systems. Here, the effects of the antioxidant-rich pomegranate fruit grown in Oman on brain oxidative stress status were tested in the AD transgenic mouse. The 4-month-old mice with double Swedish APP mutation (APPsw/Tg2576) were purchased from Taconic Farm, NY, USA. Four-month-old Tg2576 mice were fed with 4% pomegranate or control diet for 15 months and then assessed for the influence of diet on oxidative stress. Significant increase in oxidative stress was found in terms of enhanced levels of lipid peroxidation (LPO) and protein carbonyls. Concomitantly, decrease in the activities of antioxidant enzymes was observed in Tg2576 mice treated with control diet. Supplementation with 4% pomegranate attenuated oxidative damage, as evidenced by decreased LPO and protein carbonyl levels and restoration in the activities of the antioxidant enzymes [superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione (GSH), and Glutathione S transferase (GST)]. The activities of membrane-bound enzymes [Na^+ K^+-ATPase and acetylcholinesterase (AChE)] were altered in the brain regions of Tg2576 mouse treated with control diet, and 4% pomegranate supplementation was able to restore the activities of enzymes to comparable values observed in controls. The results suggest that the therapeutic potential of 4% pomegranate in the treatment of AD might be associated with counteracting the oxidative stress by the presence of active phytochemicals in it.

Key words: Alzheimer's disease, antioxidant, Oman, Oxidative stress, Pomegranate, Tg2576 mouse

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most prevalent form of dementia characterized by a progressive decline in memory, behavior, and cognitive functions in the elderly population.[1] It affects millions of people and has become a major medical and social burden in developed and developing countries.[2] The disease has been the sixth lead-

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ing cause of death across all ages and the fifth leading cause of death in those aged 65 and above. The neuropathology of AD is characterized at first by the deposition of senile plaques mainly composed of amyloid beta protein (Aβ) and neurofibrillary tangles containing hyperphosphorylated tau protein in the brain and later by the loss of neurons and their processes.[3,4] Cognitive impairment appears to be most closely correlated in time with the loss of neurons and neuronal processes.[5] At present, the etiology of AD is still not well understood. Accumulation of Aβ peptide causes an increase in intracellular reactive free radicals and reactive oxygen species (ROS). The generation of free radicals (ROS) due to the Aβ peptide can induce functional and structural damage to cell membranes through lipid peroxidation (LPO) and protein carbonyl formation which may be involved in the pathogenesis of AD.[6] These abnormal events in cells lead to oxidative neuronal cell death and cognitive decline in patients with AD.[7] However, the relationship between plaque and tangle deposition and the neuronal degeneration that follows it is not clearly understood.

More recently, the interest in the role of dietary antioxidants in human health has prompted research in the field of AD. Fruits are good sources of these bioactives, and there are a number of commercial polyphenol-rich beverages which base their marketing strategies on antioxidant potency. Naturally occurring compounds from plants have been shown to have therapeutic potential f or AD.[8-10] Curcumin and *Ginkgo biloba* extract are such natural compounds that have been shown to be protective against the progression of AD pathology in AD murine models.[11,12] Mediterranean and Middle East countries are the main regions where pomegranate (石榴 Shí Liú) is cultivated and produced.[13,14] Pomegranates (*Punica granatum* Linn.) contain very high levels of polyphenols, as compared to other fruits and vegetables. They have been extensively used in Unani, Ayurvedic, and Chinese systems of medicine.[15] Different parts of the fruit have been successfully evaluated for various diseases, including peptic ulcer, hepatic damage, and snakebite. The ripe fruit is a tonic, astringent to the bowels, aphrodisiac, and alleged panacea for a myriad of conditions, including biliousness, fever, heart diseases, sore throat, and stomatitis. The rind of the fruit is antihelminthic and useful in diarrhea, dysentery, and ulcer (Ayurveda).[16] Recently, we have reported that the four different pomegranate varieties grown in Oman offer protection to Parkinson's disease like neurotoxicity in human primary neurons.[17] Dietary supplementation of pregnant mice with pomegranate juice was shown to protect against neurodegeneration in neonatal mice subjected to hypoxic–ischemic brain injury.[18] A recent study suggested that 3 months of supplementation with pomegranate may attenuate AD progression by offering the brain anti-inflammatory effects in amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice.[19] But till now, there are no studies conducted to find out the effect of long-term dietary supplementation of pomegranate on oxidative stress status in APPSw/Tg2576 transgenic mouse model. To fill the information gap, we designed this study to find out whether long-term dietary supplementation (15 months) with pomegranate would influence AD-like oxidative stress in an APPsw/Tg2576 mouse model of AD.

MATERIALS AND METHODS

Collection and preparation

Fresh pomegranate (石榴 Shí Liú) "Helow" (literally, sweet) variety of Oman fruits were purchased from a local farm in Al-Jabal Al-Akhdar, Oman. The fruits were transported to our laboratory in an electric cooler box maintained at 9°C. Then the edible parts were separated and freeze dried at −40°C for 5 days. The samples were then grinded into fine powder by using a KMF grinder (KIKA Werke, Wilmington, Delaware USA) at 6000 rpm. Powders were kept in air-tight plastic containers and stored at −40°C until they were sent for the diet preparation. Before sending, we analyzed the samples for the qualitative presence of polyphenols. Phytochemicals such as anthocyanin, hydroxycinnamic acid derivatives (e.g. caffeic acid, etc.), hydrolyzable tannins (e.g. ellagic acid, quercetin-3-*O*-glucoside, punicalin, etc.), hydroxybenzoic acids (gallic acid, protocatechuic acid, etc.), hydroxycyclohexane carboxylic acids (quinic acid), and hydroxyphenyls (kaempferol, catechin, etc.) have been reported to be present in pomegranate. This was confirmed by qualitative analysis by high performance liquid chromatography (HPLC; data not included).

Diet preparation for the animals

The ground pomegranate samples were sent to USA to prepare the diet for the mice. Based on the our primary dose-dependent study (2, 4, 6, 8 and 10% on the amyloid beta 1-42 induced AD like status in mice) results, we have chosen the 4% (data not shown). The diet was prepared by mixing the pomegranate (4%) with regular diet as per National Institute Health, USA protocol by Research Diet, Inc, NJ, New Brunswick USA. The constituents of the diet are given in Table 1.

Animals and treatment

Twelve transgenic females (APPsw/Tg2576) and six wild control (non-transgenic) mice (Taconic Farm, Hudson St, Manhattan NY, USA) were used. Animals were quarantined for 7 days after shipping and individually housed in plastic cages in an animal room which was maintained at a temperature of 22 ± 2°C, a relative humidity of 50 ± 10%, and a 12-h light/dark automatic light cycle (0800-2000 h). Tap water was offered *ad libitum* throughout the study. The study was approved by the Animal Care and Use Committee of the Sultan Qaboos University, Oman (SQU/AEC/2010-11/3).

All these animals were free from pathogens and viruses. Experimental period commenced from the age of 4 months. The animals were divided into three groups as follows: Group 1: Wild type (non-transgenic) control of the APPsw mice fed with regular diet; Group 2: AD transgenic mice also fed with regular diet; and Group 3: AD mice fed with 4% pomegranate fruit diet. Dose of pomegranate was designed based on the preliminary study done with different percentages of fruits and 4% showed better effects. These experimental and control mice were examined at the age of 15 months, and oxidative stress, antioxidants and membrane bound enzymes were investigated. All animal experiments in the present study were conducted in compliance with the Animal Care and Use Committee of the Sultan Qaboos University, Oman.

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