



Review Article

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A COMPREHENSIVE REVIEW ON NEUROPROTECTIVE EFFECTS OF POMEGRANATE

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ABSTRACT

Pomegranate is one of the oldest, edible fruit with high nutritional values and has been a part of Mediterranean diet since ancient times. The fruit, bark, roots and leaves of pomegranate are reported to have medicinal benefits. Pomegranate is very rich in various poly-phenols, which are probably responsible for most of the beneficial properties of the fruit. The medicinal properties include, anti-ageing, anti-cancer, anti-diabetic, cardio protective, lipid-lowering, gastro protective, hepatoprotective, anti-trichomonal, anti-nociceptive, anti-diarrheal, anti-viral effects and beneficial effects against neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Neuroprotective effects of Pomegranate extract are reducing accumulation of amyloid plaques in hippocampus, preventing neuronal tissue loss, modulating GABA and glutamate levels, inhibiting acetylcholine esterase and inhibiting lipid peroxidation in brain. Here we review the possible mechanisms by which pomegranate may affect neuro-degeneration, and suggest necessary translational research in this area, for the benefit of neurodegenerative patients and the society in general.

Keywords: Pomegranate, neuro-degeneration, poly-phenols.

INTRODUCTION

Pomegranate is a highly nutritious fruit and has been widely consumed in various cultures since ancient times and several reports of its therapeutic qualities have echoed throughout millennia. Pomegranates belongs to the family *Punicaceae* and are widely cultivated in Iran, India and the Mediterranean countries¹. All parts of the fruit, especially arils, seeds and peel contains greatest medicinal value, including its leaves and husk, which are used to treat various diseases. Pomegranates are very rich in various poly-phenols, which are likely responsible for most of the beneficial properties of the fruit. The medicinal properties of various parts of Pomegranate include anti-ageing, anti-cancer, anti-diabetic, cardio protective, lipid-lowering, gastro-protective, hepato-protective, anti-trichomonal, anti-nociceptive, anti-diarrheal, anti-viral effects and beneficial effects against neurodegenerative diseases like Alzheimer's and Parkinson's disease^{2,3,4}. In addition, it is widely used in therapeutic formulas, cosmetics and food seasonings. Several preclinical and epidemiological studies have reported association between antioxidant consumption and cognitive protection⁵. The emerging data on pomegranate and their inherent poly-phenols suggest benefits of pomegranate consumption ranging from neuro-protective effects⁶ to staving off effects of senescent neuro-degeneration in preclinical models of Alzheimer's disease^{7,8}. It is hypothesized that several cellular and molecular events are involved, including increase in oxidative stress, impaired mitochondrial function, activation of neuronal apoptosis, deposition of aggregated protein and neuronal excitotoxicity. Mitochondrial dysfunction characterized by decreased oxidative phosphorylation and increased free radical and reactive oxygen species generation was reported to be associated with certain neurodegenerative diseases including Alzheimer's and Parkinson's disease. Most of

available drugs for the treatments of neurodegenerative disorders are unable to prevent degeneration of neurons and associated with side effects. Hence there is a need for development of alternative therapies to prevent the neuro-degeneration with little or no side effects^{9, 10 and 11}. Several studies have explored the antioxidant strategies to combat neuronal damage. Indeed, neuro-protective effects of a group of plant secondary metabolites known as poly-phenols, which are powerful antioxidants, has generated potential drug discovery interests^{12,13}. Hence we review here the research reports related to pomegranate consumption and its neuroprotective effects, with the intent of highlighting the present knowledge, and indicate the potential future research directions to validate the health benefits of pomegranate consumption.

Pomegranate's inhibitory effect on neuro-degeneration and neuro-inflammation

Neuro-degeneration observed in Parkinson's, Alzheimer's, and other neurodegenerative diseases are multifactorial, i.e., a complex set of toxic reactions, including inflammation, glutamatergic neurotoxicity, increase in iron and nitric oxide, depletion of endogenous antioxidants, reduced expression of trophic factors, dysfunction of the ubiquitin-proteasome system, and expression of proapoptotic proteins leading to the degeneration of neurons. Pomegranate is an important source of poly-phenols including phenolic acids, ellagic tannins (punicalin, punicalagin, gallagic, and ellagic acid), flavanoid (anthocyanins, catechins, rutin, epigallocatechin-3-gallate), and anthocyanins (delphinidin, cyaniding, and pelargonidin), which possess potent antioxidant and radical scavenger properties¹⁴. Pomegranate juice extract was shown to be neuroprotective in a mice model¹⁵ due to its significant antioxidant capacity¹⁶. Neonatal brain protection against a hypoxic-ischemic insult was

also observed after maternal dietary supplementation with pomegranate juice and this neuroprotection was effective even 7 days' post birth. Interestingly, this lasting neuroprotection transferred from mother to neonates is attributed to whole-fruit pomegranate poly-phenols¹⁷. Methanolic Extract of pomegranate peel also protects brain through decreasing the aluminum accumulation and stimulating antioxidant activities and anti-apoptotic proteins such as Bcl-2.

Pomegranate's inhibitory effect on lipid peroxidation

Lipid peroxidation is one of the major outcomes of free radical-mediated injury, which directly damages cell membranes and generates several secondary radical products, both from fission and endocyclization of neurotoxic oxygenated fatty acids. Numerous studies have demonstrated increased lipid peroxidation in brain of patients with Alzheimer's disease (AD) compared with age-matched controls¹⁸. Thus, maintaining an oxidative balance state is necessary for a healthy brain and it is in maintaining this balance pomegranate phytochemical may be effective. Pomegranate also reduces free radical induced lipid peroxidation¹⁹. Pomegranate poly-phenols increase serum paraoxonase activity, resulting in the hydrolysis of lipid peroxides in oxidized lipoproteins and in atherosclerotic lesions. Dietary supplementation of polyphenol-rich pomegranate juice to atherosclerotic mice was reported to significantly inhibit the development of atherosclerotic lesions by protecting LDL against oxidation²⁰. Inhibition of lipid peroxidation contributes to the attenuation of macrophage cholesterol accumulation, foam-cell formation and atherosclerosis. Pomegranate juice consumption is also reported to reduce macrophage Ox-LDL uptake and cholesterol esterification²¹.

pomegranate's modulatory effect on Gamma(γ)-aminobutyric acid (GABA) and glutamate

Pomegranate extract is reported to have anxiolytic, antidepressant, and anti-nociceptive properties. Effects of pomegranate poly-phenols on CNS are due to influence on two of the most important neurotransmitters i.e., GABA and Glutamate. Phytochemicals can modulate the neurotransmitter activity. Indeed, anxiolytic activity of pomegranate extracts was related to GABA-mediated transmission via a possible binding of phenolic bioactives to GABA benzodiazepines complex and antidepressant-like effects were similar to CNS stimulant drugs, which are related to a glutamate increment. Thus, pomegranate constituents may modify the levels of two of the most important neurotransmitter in CNS: GABA and glutamate. Catechins (another component of pomegranate) also modulate tyrosine kinase and protein kinase C signal transduction pathways in vitro. Protein kinase C is demonstrated to play a role in microglial release of glutamate. Other study suggests that, the combination medication of *Punica granatum* and either magnesium or buspirone offered better effects on anxiolytic-like effect, which was dependent on interactions with both GABAergic (related to Mg) and serotonergic (5-HT1A) systems. Ellagic acid also showed significant antiepileptic activity in mice, probably through increase of GABAergic transmission in brain^{22,23}.

Pomegranate's inhibitory effect on acetylcholine esterase (AChE)

Various parts of pomegranate plant and fruit have anticholinesterase activity. Ethanolic extract of pomegranate bark and leaves inhibit acetylcholinesterase in several neuronal tissue^{24, 25}. Recent study has shown that phytochemicals derived

from pomegranate have high AChE inhibitory activity²⁶. Methanolic extracts of dry fruits of *Punica granatum* inhibit AChE, which support the efficacy of this fruit in enhancing cognitive skills. Thus, the potential biological effects of pomegranate bioactives on both CNS and PNS neurotransmitters, necessitates further investigations to develop these bioactives as therapeutics. This observation collaborates with previous reports whereby intracerebroventricular (i.c.v.) administration of streptozotocin at sub-diabetogenic dose was shown to induce memory deficits, along with an increase in oxidative stress and AChE activity^{27, 28}. Koladiya *et al*²⁹ have reported that AChE activity was significantly increased in the hippocampus in L-methionine-induced model of vascular dementia. Amyloid beta peptides can induce Ca²⁺ influx that leads to increased activity of AChE which is attributed to Ca²⁺-mediated oxidative stress. It remains to be tested if the pomegranate bioactives would be therapeutically active in these models of neuronal disorders, which may facilitate further therapeutic development of pomegranate extracts.

Pomegranate effect on improving mitochondrial dysfunction in brain

Decay of mitochondria in brain neurons are a primary cause of all neurodegenerative disorders from dementia to Parkinsonism³⁰. Oxidative mitochondrial decay is now recognized as a major contributor to neurodegeneration³¹. Studies have also reported brain as the primary target of mitochondrial aging and several studies have reported the potential of flavonoids rich diet in delaying brain aging and lowering the incidence of neurodegenerative disease. Flavonoids in fruits improve mitochondrial dysfunction and may have therapeutic benefits in long term treatment of age related cognitive impairment in animals and humans³². The significant reduction of risk in developing Alzheimer's disease by Mediterranean diet is likely due to the high daily intake of flavonoids³³. Inclusion of flavonoids in diet, leads to raise in cAMP levels in the brain, which may have additional benefit by reducing the production of proinflammatory mediators and stimulating the transcriptional machinery necessary for mitochondrial biosynthesis^{34,35}. Additionally pomegranate supplementation is reported to promote mitochondrial function and eliminate oxidative stress and inflammation, this nutraceutical property of pomegranate is used for the treatment of Non alcoholic fatty liver disease³⁶.

Anti-oxidative related properties of Pomegranate in brain

Oxidative stress is principally associated with deposition of amyloid in brain³⁷. The anti-oxidant properties of pomegranate poly-phenols may have beneficial effect by reducing oxidative stress. Pomegranate also has the capacity to restore the activities of various anti-oxidant enzymes (super oxide dismutase, catalase, glutathione peroxidase, glutathione and glutathione S transferase). Indeed, pomegranate supplementation was reported to reduce the accumulation of soluble amyloid beta and amyloid deposition in hippocampus in transgenic mouse model of Alzheimer's and consequently delaying development of cognitive impairment. Hence pomegranate can also help enhance learning and memory^{38,39,40}. Ellagic acid, an important component of pomegranate extract was reported to inhibit beta-secretase activity⁴¹, hence supporting the potential of pomegranate extract to prevent the formation of amyloid beta proteins from precursors Amyloid Precursor Protein (APP). Additionally, ellagic acid also suppresses the pro-inflammatory nuclear transcription factor-kB activation pathway and positively modulates its cell signaling pathways⁴². It was

suggested that the sugar fraction of pomegranate juice, which consists of conjugated sucroses, fructoses and glucose may have significant anti-oxidant properties independent of phenolic compounds. Pomegranate juice also inhibited the activation of oxidation-sensitive genes in response to cellular stress⁴³ and the modulation of endothelial nitric oxide synthase expression⁴⁴. Hence several studies support the antioxidant potential of pomegranate, which may be valuable in preventing aging associated brain disorders.

CONCLUSION

As pomegranate is being effective in preventing neurodegenerative changes through different mechanisms, therefore pomegranate may be effective in reducing aging induced changes in the brain. Hence we do recommend regular consumption of pomegranate as a goal to maintain a healthy lifestyle with aging; however, our recommendation does need rigorous scientific validations in future.

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