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A LIGHT ON THE EFFECT OF POMEGRANATE ON NEUROLOGICAL EVIDENCES OF PARKINSON'S DISEASE: A REVIEW

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Review Article

ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disease, in which the dopamine containing neurons gets degenerated in the SN region of ventral mid-brain. Various herbal or plant components have been tested in rodent models of Parkinson's disease to understand its therapeutic effect. Recent progresses in therapeutic interventions against neurodegenerative disorders have shown the potential role of Pomegranate juice (PJ) as a promising neuroprotective agent. The fruit of pomegranate is a highly consumed all over the world and has proven its efficacy in many health beneficial aspects. PJ contains active ingredients mainly, 'polyphenols' which are found to be protective against the disease pathology of Alzheimer's disease. A recent study demonstrated that PJ potentiate parkinsonian pathology in rodent. Meanwhile, PJ had shown neuroprotective effect in parkinsonian toxin induced cellular model. Thus, from the available literatures, no conclusion can be made whether PJ possess neuroprotective or neurodegenerative potential towards dopamine containing neurons in PD.As pomegranate juice has been recommended to possess medical benefit and is being used in daily diet, studying its potential benefits or side effect are of immense importance. Amending altogether, the therapeutic potency of pomegranate has been well evaluated and reported and the review had been forwarded to evaluate the diversified effects of pomegranate juice in Parkinson's disease.

Keywords: Parkinson's disease; neurodegeneration; neuroprotection; pomegranate; phytocomponents.

ABBREVIATIONS

AChE : Acetyl cholinesterase
AD : Alzheimer's disease
ALS : Amyptrophic lateral sclerosis
BChE : Butyryl cholinesterase
COX : Cyclo oxygenase
DA : Dopamine
DAergic : Dopaminergic
GSH : Reduced glutathione
GSSG : Glutathione disulphide
Iba : Ionised calcium binding adaptor molecule
IL : Interleukin
iNOS : Inducible nitric oxide synthase
MAO : Monoamine oxidase
MAPK : Mitogen activated protein kinase
MMP : Matrix metallo peptidase
NFkB : Nuclear factor kappa of beta cell
NO : Nitric oxide
8-OHDG : 8-Hydroxy 2-deoxy guanosine
PD : Parkinson's disease
PJ : Pomegranate juice
ROS : Reactive oxygen species
SN : Substantia nigra
TNF-α : Tumor necrosis factor alpha

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1. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that progresses with age and is characterized clinically by the degradation of dopamine containing neurons in substantia nigra pars compacta (SNpC) of the brain. The disease pathology is confined to the known classical symptoms of the disease viz. bradykinesia, akinesia, tremor, rigidity and postural instability. Limited evidences have shown the effectiveness of herbal remedies against the pathogenic progression of PD. Use of pomegranate in daily diet has been shown to be promising in neurological relevance. Neuroprotective attribution of pomegranate has been reported mainly on Alzheimer's disease (AD) and PD emphasizing on the improvement in cognitive as well as memory function [1-5].

Although no single underlying cause has been established for beta-amyloid plagues associated with AD, metabolic imbalances have been found in AD patients and are likely to contribute to the symptoms of the disease [3,6]. Due to these properties, Pomegranate has been shown to address several of those imbalances in a positive way [7-9]. These activities include cholesterol reduction [10], inhibition of MAO-B activity, and defence against damage from ROS, inhibition of acetylcholinesterase (AChE), butyrylcholinesterase (BChE) activity, and beta-secretase, and reduction in the amyloid-beta genesis [11]. Due to this, a reduction in the aggregation of amyloid-beta plaque and phenotypic pathology is found in mouse model of AD. Although the pathology of PD has been pinned to the formation of Lewy body protein aggregation and loss of dopaminergic neurons in the brain, the causes that lead up to the pathology are largely unknown [12]. Due to our lack of understanding of the true cause of this disease, effective treatment strategies are yet to be developed. Thus, therapies against PD gains much interest which can ameliorate the disease pathology and retards the loss of dopamine. There has been substantially lower rate of research against the potentiality of pomegranate against the disease and therefore, much evaluation is needed to gather knowledge on the medicinal and therapeutic values of pomegranate for treatment against Parkinson's disease [13-17].

2. COMPONENTS OF POMEGRANATE AND ITS HEALTH BENEFICIAL ROLE

Phytotherapy is a traditional approach, practiced for the prevention and treatment of diseases, although it lacks scientific affirmation. Much work has been done and aimed to clinically examine the bioavailability of some potent plants concerned with the disease pathology, which also includes *Punica granatum* L. (Pomegranate). Besides its historical exploitation, pomegranate is being used in a vast field of medicine as herbal remedy. Recent reviews reported the chemical constituents of different parts of pomegranate as well as their potency in preventing and treating different neurological disorders. Fruit, leaves, flowers, peel and roots of the plant have been reported to be highly effective [18-21] and active in amelioration of diseases. Pomegranate has been reported to possess a high level of antioxidant capacity with contents of phenolic compounds [22,23], whose antimicrobial [24], anticancer and anti-arteriosclerotic effects have been confirmed [25-29]. Prior to this, many phytocomponents of the plant have been screened, out of which six anthocyanins are identified in the peel and aril pigment viz. delphinidin 3-glucoside, 3,5-diglucoside, cyanidin 3-glucoside, 3,5-diglucoside, pelargonidin 3-glucoside and 3,5-diglucoside [30-32]. The antioxidant capacity along with the presence of phenolic compound is highly significant in evaluating the fruit for its potential health beneficial effects [29,33,34].

Extensive research work has been carried out in pomegranate cultivating regions, concerning the pomegranate traits, cultivar variability regarding the nature of soil, climatic condition, cultivation culture and genotype [35,36]. Pomegranate juice is found to possess nutritive sources like glucose, sucrose and fructose along with some simple organic acids such as malic acid, ascorbic acid, fumaric acid and citric acid [37-40]. It also contains small amounts of amino acids, specifically proline, methionine, and valine [3,27,29]. Among these bioactive molecules, tannins and flavanoids are found in large amounts and possess pharmacological potentiality as it contains high antioxidant and preservative properties [9,37,41]. Ellagitannin, that breaks down to form hydroxybenzoic acid viz. ellagic acid [40,42,43,44] is widely used in plastic surgeries, which prevents skin flap's death due to its antioxidant activity [45-48]. Two other ellagitannins viz. punicalagin and punicalin are found in Pomegranate juice as well as peel [37,40,49]. Several flavonoids have also been reported that include anthocyanins, flavan 3-ols, and flavonols [29,33,34], besides catechins with a high antioxidant activity [47,50] which are essential compounds of anthocyanin's production. The red color of juice is due to the presence of Anthocyanins, which is a high source of antioxidant, and is not found in the peel [51-53]. Flavanoids show antioxidant activity during the pathological alteration of the disease with reversed inhibition of inflammatory markers like TNF- α [10,54,55]. The bark and roots of Pomegranate contains rich source of alkaloids [19,37,56] and are used to treat worms in

gastrointestinal tract of human in traditional medicine [7].

Pomegranate has been examined in most of the diseases including cardiovascular disease, stress, neurological disorders like AD and PD etc [23,57,58]. Mingling together all the documentations of the research work on pomegranate, the present review highlights the potency of pomegranate juice on Parkinson's disease and can be assumed that pomegranate juice will be an effective therapeutic agent against Parkinson's disease besides being aware of the proceedings of treatment with caution, as slight species-dependent difference in pomegranate metabolism may account for different potentiality of the agent.

2.1 Pomegranate and Parkinson's Disease: Gain at a Cost

Although the pathology of PD has been confined to the formation of lewy body protein aggregates and loss of DAergic neurons in the brain, the causes that lead up to the pathology are yet to be exposed. Due to our lack of understanding of the true cause of this disease, effective treatment strategies remain to be developed. There has been substantially less research done on the therapeutic potential of Pomegranate against PD. However, there are at least two documented effects that merit Pomegranate or at least some derivative or metabolite in consideration for continued studies to further address the possibility of its use as an anti-PD agent. In 2014, Kim et al.elaborated a chemically-induced parkinsonian mouse model to test the neuro-protective effect of Pomegranate and reported that, at 50 mg kg−1, Pomegranate significantly prevented both memory and balance loss in the experimental mice as compared to their untreated counterparts. They found that the DA containing neuronal damage was lacking in SN with corresponding loss of DAergic neuron and reduces apoptosis in the hippocampus of the treated group as compared with the control. This recent study showed a very promising outlook for Pomegranate for consideration as a selected compound for treatment against PD. However, the results of *Kim et al*. Contradicted to the findings of the *Lee group* in South Korea, where they reported that in chemical induced rat model of PD, pomegranate exhibited neurotoxic effect. In these studies, first, a PC12 cell model of PD showed that when treated with Pomegranate, DAergic loss was elevated as compared to the untreated controls. It is important to note that the differences in findings between the *Lee group* and Kim et al. could possibly be partially attributed to their differences in animal models (mouse vs. rat) and the species-dependent rates of Pomegranate metabolism. MAO-A and MAO-B are natural dopamine- degrading agents and are found effective in therapeutic treatment against PD. However, due to the toxic side-effects of MAO inhibitors, it has usually been chartered as a final effort in patients with advancing PD. To validate the method of treatment with MAO-B inhibiting agents in treatment of PD, *Castillo* et al. used LED fluorescence to detect changes in the levels of MAO-B. Although it was previously known that, Pomegranate could inhibit the activity of MAO with

Table 1. Effect of pomegranate on PD models

Disease model	Toxin/Causative entity	Effect of PJ	Target for PJ	References
PC12 Neuroblastoma cell culture	3-nitropropionic acid	Neuroprotection	lipid peroxidation,	Rojanathammanee et al. [90]
			Reactive oxygen species,	
			Extracellular nitric oxide	Choi et al. [28]
			Neuroinflammation	Choi et al. [28]
Human Primary Neurons	MPTP	Neuroprotection	Mitochondrial dysfunction	Braidy et al. [20]
			Neuroinflammation	Essa et al. [34]
			Oxidative stress	
Mice model of Alzheimer's disease	Transgenic mutation	Neuroprotection	lipid oxidation	Essa et al. [34]
			Neuronal loss	Mizrahi et al. [77]
			Oxidative stress	
Rat model of Parkinson's disease	Rotenone	Neurodegeneration	Oxidative stress	Tapias et al. [92]
			Dopaminergic neuron loss	Tapias et al. [92]
			Reduction of TH-positive cells	Tapias et al. [92]
			Mitochondrial dysfunction	Tapias et al. [92]
			Neuroinflammation	Tapias et al. [92]

an IC50 of 126 µmol L−1 for MAO-A and 98.4 µmol L−1 for MAO-B, the results of this study framed a reference to the usefulness of Pomegranate as a MAO-inhibitor in PD treatment. It was also discovered that in pomegranate prevented cell death by defending against ROS damages in human-derived SH-SY5Y cells as an in vitro model of PD. The mechanism revealed the activation of heme oxygenase-1 and inhibition of caspase-3 activation to deflect neuronal apoptosis. However, the results of Choi et al. [2] contrasted to the findings of the *Tapias group* in USA, which published the neurotoxic effects of Pomegranate when used to treat chemically-induced rat models of PD. In their studies, as shown in Table 1 rotenone induced rat model of PD showed neurodegeneration when treated with Pomegranate, DAergic loss was elevated as compared to the untreated controls. Treatment of a PD rat model with Pomegranate aggravated depletion of DA as well as degeneration of tyrosine hydroxylase-immunopositive cells *in vivo* [5]. The animal models of PD are being described in Table 1.

2.2 Neuroprotection of PJ: Its Evidences

Pomegranate possesses various metabolites which are beneficial to many health issues. The antioxidant potency of the plant contains high polyphenol compounds viz. Ellagitannins and hydrolysable tannins. PJ exhibits the property to inhibit COX-1 and COX-2 enzymes (member of heme peroxidise) along with the activity of IL-1 β.It has also been reported that Pomegranate can alienate the stimulation of mRNA of MMP-9 in THP-1/monocytes [59] as the fruit and phytocompounds of the plant can inhibit promoter activity of TNF- induced MMP-9. Human intestinal microflora metabolizes certain metabolites like Urolithins that decreased TNF induced MMP-9 secretion and mRNA levels. Ellagitannins has been reported to control excessive production of MMP-9, which could result in reduced noxious cytokine TNF production. While inducing transcription of several genes like MMP-9, TNF cytokines promote binding of NFκB to target sequences. However, ellagitannins are reported to degrade the activity of NFκB promoter as it blocks NFκB- driven transcription and thereby affecting cytokine cascade. Ellagitannins can also inhibit the activation of inflammatory pathways such as MAPK. In addition, Pomegranate compounds, in cancer [24,60,61], could inhibit the process of angiogenesis through the down regulation of vascular endothelial growth factor [62]. Consumption of PJ therefore does not affect the bioavailability of drugs as described in a study on human liver microsomes which showed that pomegranate in rats inhibits CYP2CP and increases bioavailability of tolbutamide (substrate for CYP2CP) [53].

Some of the mechanisms of neuroprotection of PJ on the action of physiological degradation during neurodegenerative diseases are summarised below:

2.3 PJ and Oxidative Stress

Oxidative stress has been strongly implicated in the pathophysiology of PD. In many researches antioxidants are being suggested as an effective and potent antioxidant in amelioration and treatment of the disease and pomegranate is reported to own the highest antioxidant ability.

Two important biological phenomena were reported that increases ROS generation in SN: (1) iron level elevation and (2) reduction in the level of antioxidant defence. In the SNpc of parkinsonian brain and DA neurons, iron level was increased [47,50,63] in contrast to a reduction in cellular ferritin and an elevation in lactoferrin receptor expression [43,64]. Due to the presence of neuromelanin, increase in iron level may lead to escalated ROS generation [63]. But during the phase of degeneration, decrease in reduced and oxidized glutathione (GSH/GSSG) correlation may enhance toxic hydroxyl radical formation, which represents one of the earliest biochemical defects in PD [12,65,66]. Again, due to increased DA turnover, GSH-dependent detoxification impairment may occurs which in turn increases and deplete basal hydrogen peroxide production and GSH stocks respectively [5,67,68]. Additionally, relative depletion in GSH is accompanied by catalase reduction [65] and expression of GSH-peroxidase [68,69]. All these aforesaid phenomena increase the level of ROS and deteriorate cellular macromolecules and their subsequent peroxidation. Indeed, the level of polyunsaturated fatty acid decreases in parkinsonian brain and in contrast increased the level of thiobarbituric acid-reactive compounds and 8-hydroxy- 2_deoxy-guanosine (8-OHDG) [2]. Due to activated microglial cells, free radicals may elevate in degenerating DA neuronal region [4,70], which generates NO and cytokines, which subsequently elevates the expression of iNOS in PD brain [71]. This, however, elevates NO levels and can initiate harmful peroxynitrite radical. Moreover, the level of cytokines (such as TNF) and ROS may also be increased through glial cell activation or may directly lead to apoptosis [2,65,72]. Eventually, high ROS levels could instigate secondary agitation in toxicity by raising free cellular calcium and in turn increase the levels of intracellular NO.

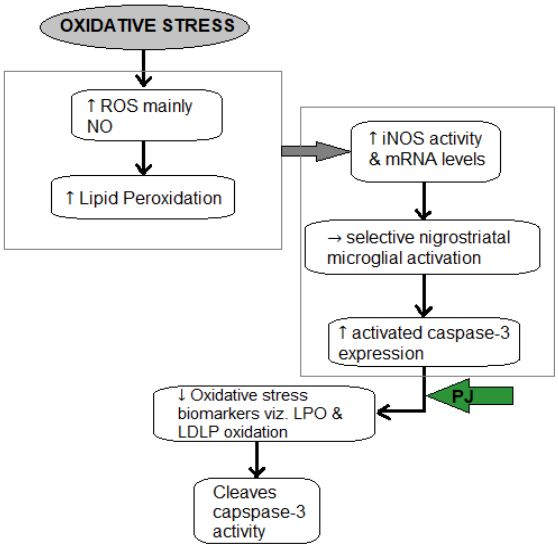

Fig. 1. Effect of PJ on oxidative stress in PD

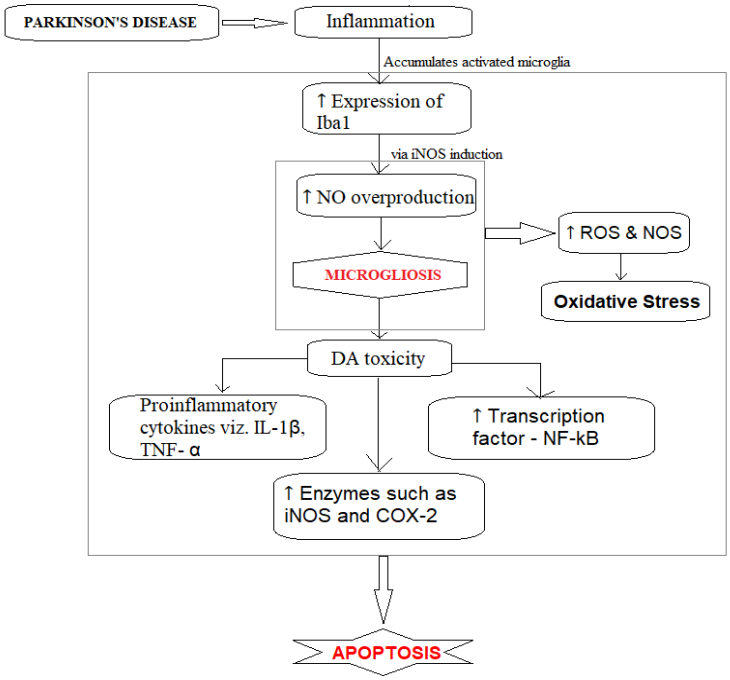

Fig. 2. Inflammation leading to oxidative stress and apoptosis in PD

2.4 PJ and Apoptosis

Apoptosis is generally defined as cell death. Macrophages or the microglial cells phagocytise the apoptotic cells, preventing inflammations occurring during cellular necrosis [47,50,73]. Pathogenesis of PD involves strong oxidative stress, reduced antioxidant levels and mitochondrial dysfunction all known to induce apoptosis in several cellular systems [74,75]. Studies have highlighted active involvement of cell death in PD and the first study was performed by Mochizuki et al. [72] by staining the 3_-end terminal of DNA and observed the DNA fragmentation in-situ in the SNof parkinsonian patients [76,77]. Apoptosis was suggested in SNpc of parkinsonian patient, although no TUNEL positive

staining was observed in younger patients. Some of the authors showed that 6% of the observed melanised neurons exhibit ultra-structural hallmarks of apoptosis, such as chromatin condensation, convolution of nuclear envelope, cell shrinkage and presence of apoptotic bodies. These reports marked a controversy on the apoptosis existence in SN of PD. Since in-situ end-labelling method also stains non-apoptotic cells in the assessment of apoptosis, it is suggested to be handled with caution [65,72]. Therefore, only morphological studies can reliably explain whether SNpc degeneration in PD is apoptotic or not. Indeed, it cannot be justified with certainty whether the degeneration in PD involves an 'event' or a 'process' [78]. Clarke et al. (2000), in the 'one-hit model for inherited degeneration' hypothesized some of the indigenous factors may lead to successive DAergic neuronal loss followed by ageing [79]. In PD, active cell death proved inhibition of this phenomenon which is capable of delaying or preventing the progression of the disease pathology. Considering the interpreting data obtained from human samples, neurotoxic compounds in animal models of PD mimic the degeneration of DA which may provide a convenient way to expose the type of cell death that occur in human SNpc [80].

2.5 PJ and Inflammation

Inflammation leads to certain alterations in PD that includes infection, traumatic brain injury, toxic metabolites or autoimmunity. Neuroinflammation is considred to be a leading hypothesis in PD progression with the growing interest to determine whether reduction in inflammation will overrule the process of neurodegeneration. Phytotherapeutic treatments reduced the loss of neuron and inflammation to a large extent. Due to the presence of various antioxidants in PJ, multiple sclerosis has been recovered which may include interferon-B, Glatiramer actitate and Mitoxantrone, which function by reducing or inhibiting T-cell activation (but may have side-effects of systemic immuno-suppression) [81]. In certain neurological disorders, the use of PJ decreased the risk of disease progression like the work done by Braidy et al. [1] and Rojanathammanee et al. [4]. Support to evidences explains the involvement of inflammation in PD, and is typically typified by an accumulation of activated microglia. Upon activation of microglia, upregulation of Iba1 expression takes place. Activation of Microglial cells causes overproduction of NO• via the induction of iNOS [4]. Examination of PD brains resulted in microgliosis [82] and the presence of high levels of iNOS expression in SN [50]. In DA toxicity of cerebrospinal fluid and brain tissue of PD patients, proinflammatory cytokines viz. IL-1β and TNF-α involves the activity of enzymes such as iNOS and COX-2 and transcription factors like NF-kB [2,50,65,83].

2.6 PJ and Mitochondrial Dysfunction

Mitochondria are regarded as the prime mediators in cell death; especially in neurodegeneration. In neurodegeneration, mutations in mitochondrial DNA and oxidative stress play a great role in ageing and progressive neurological disorders. By far the greatest risk factor for neurodegenerative diseases such as AD, PD and ALS is ageing, and mitochondria have been thought to contribute to ageing through the accumulation of mitochondrial DNA (mtDNA) mutations and net production of ROS [84-86]. Mitochondria consume oxygen and contain various redox enzymes that are capable of transferring electrons to oxygen, which in turn generates ROS superoxide (O2 –) [87]. Enzymes of mitochondria are known to generate ROS that include aconitase (ACO) and α-ketoglutarate dehydrogenase (KGDH) of tricarboxylic acid (TCA) cycle; complex I, II and III of electron-transport chain (ETC); pyruvate dehydrogenase (PDH) and glycerol-3-phosphate dehydrogenase (GPDH); dihydroorotate dehydrogenase (DHOH); the monoamine oxidases (MAO) A and B and cytochrome *b*5 reductase (B5R) [65,86,88]. Superoxide generation through transfer of electrons to oxygen provoke redox carriers with electrons and with high potential energy, as reflected by high mitochondrial membrane potential [89]. When the available electrons are less in number, generation of ROS is decreased which eventually lowers the potential energy for the transfer of electrons [84,89]. Nonenzymatic components of the system include α-tocopherol (aTCP), coenzyme Q10 (Q), cytochrome *c* (C) and glutathione (GSH) and some enzymatic components viz. catalase (Cat), manganese superoxide dismutase (MnSOD), phospholipid hydro peroxide glutathione peroxidase (PGPX), glutathione peroxidase (GPX), glutathione reductase (GR); peroxiredoxins (PRX3/5), glutaredoxin (GRX2), thioredoxin (TRX2) and thioredoxinreductase (TRXR2) [86,90]. The GSH and reduced TRX2, depending on NADPH can be regenerated and are derived from substrates like isocitrate dehydrogenase (IDH), malic enzyme (ME) or membrane potential like nicotinamide nucleotide transhydrogenase (NNTH) [86]. So, like the generation of ROS, antioxidant defence mechanisms are also bound to the redox and energetic state of mitochondria [2,78]. The antioxidant defence ability of mitochondria balances the generation of ROS and a minimum net ROS is produced. Mitochondrial damage with less ROS generation establish further

damage to mitochondria that may lead to extensive generation of free-radical and loss or consumption of antioxidant capacity [65].

3. FACTOR OF DISCUSSION

Pomegranate has proved to be a competent source in the field of health science. Although pomegranate has shown a positive effect in most of the life threatening diseases, it proved to be a potent source of anti-oxidant in cardio-vascular diseases, skin diseases, neurological disorders, etc. Among all the related collection of research database majority of therapeutic efficacy of pomegranate has documented on its anti-cancer effect [24,25,44,56,72,91]. The benefits of consuming pomegranates have been attributed to the consistence of high antioxidant capacity that strongly correlates with the high concentration and chemical composition of polyphenolic compounds [41,91,92], whose antimicrobial [66], anticancer and anti-arteriosclerotic effects have been remarked [1,39,60,91]. With a collection of recorded data on the neuroprotective effect of PJ, the results of Choi et al. in [2] in comparison with Rojanathamanee in 2014 is in stark contrast to the findings of the *Tapias group* in USA, which published the neurotoxic effects of Pomegranate when used to treat chemically-induced rat models of PD. As PJ exacerbated the pathological progression of PD, the faith on the use of PJ on daily diet has increased. As published in 2011, Choi et al. [2] respectively have experimented the use of PJ on PC-12 neuronal cell lines in 3-nitropropionic acid induced PD model where PJ proved to have a positive impact in protecting the neuronal degeneration. Again, Rojanathamanee in 2014 followed by Choiet al. [2] used the administration of PJ on a transgenic mice model of AD, where PJ again have shown to be neuroprotective [93]. But the studies of Victor Tapias et al. [5] have altered the concept of PJ in neuroscience. They have reported that oral administration of PJ in a rotenone induced rat model of PD did not mitigate or prevent experimental PD but instead increased nigrostriatal terminal depletion, dopaminergic neuron loss together with inflammatory response and activation of caspase-3 expression in nigral dopaminergic neurons, thereby have shown signs of neurodegeneration in consistent with its potential pro-oxidant activity. In their studies, rotenone induced rat model of PD showed neurodegeneration when treated with Pomegranate, DAergic loss was elevated as compared to the untreated controls. Treatment of a PD rat model with Pomegranate aggravated depletion of DA as well as degeneration of tyrosine hydroxylase-immuno positive cells *in vivo*. It is important to note that the differences in the findings between *Tapias group* and Choi et al. [2] could possibly be partially attributed to their differences in animal models (mouse vs. rat) and the species-dependent rates of Pomegranate metabolism and also could be a result of time point (PJ gavages) dependent effect of neurotoxin administration. However, the results show the possibilities of Pomegranate as a therapeutic agent against PD, and also suggest proceeding with caution, as slight species-dependent differences in Pomegranate metabolism could account for different efficacy or even effect of Pomegranate.

4. CONCLUSION

Pomegranate has shown great therapeutic potential against neurodegenerative diseases including AD and PD as well as stroke. It has the ability to cross the blood-brain barrier and allows for the remarkably extraordinary ability to act on a number of molecular targets, which proves to be an anti-neurodegenerative agent. Because of the extensive range of effects, Pomegranate is likely to treat diseases in a positive way. One possibility is that Pomegranate may help clear toxic products or unfolded proteins to achieve multi-faceted benefits in reducing cellular toxicity. However, Pomegranate is unlikely to have a very strong effect on any single one of these aspects, which may prevent harmful levels of imbalance and side effects. These facts coupled with its overall favourable effects on brain function suggest a potential myriad of other undiscovered applications on neurodegenerative diseases. Finally, the therapeutic potential of Pomegranate shows promising potency and gains much interest and research investment for future development and exploration into the possibilities of this non-toxic herbal compound.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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