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Garcinol, a multifaceted sword for the treatment of Parkinson's disease

Satarupa Deb[a,1], Banashree Chetia Phukan[a,1], Muhammed Khairujjaman Mazumder[a], Ankumoni Dutta[a], Rajib Paul[b], Pallab Bhattacharya[c], Rajat Sandhir[d], Anupom Borah[a,*]

[a] Cellular and Molecular Neurobiology Laboratory, Department of Life Science and Bioinformatics, Assam University, Silchar, 788011, Assam, India
[b] Department of Zoology, Pandit Deendayal Upadhyaya Adarsha Mahavidyalaya (PDUAM), Eraligool, 788723, Karimganj, Assam, India
[c] Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Ahmedabad, 382355, Gandhinagar, Gujarat, India
[d] Department of Biochemistry, Panjab University, Chandigarh, 160014, India

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ABSTRACT

Garcinol, the principal phytoconstituent of plants belonging to the genus *Garcinia*, is known for its anti-oxidant as well as anti-inflammatory properties, which can be extended to its possible neuroprotective role. Recent reports disseminate the capacity of garcinol to influence neuronal growth and survival, alter the neurochemical status in brain, as well as regulate memory and cognition. The concomitant neuro-rescue property of garcinol may render it as an effective compound in Parkinson's disease (PD) therapeutics since it is capable of ameliorating the related pathophysiological changes. Emerging pieces of evidence linking histone acetylation defects to the progression of neurodegenerative diseases provide an effective basis for targeting PD. Hyperacetylation of histones has been reported in Parkinsonian brain, which demands the use of pharmacological inhibitors of histone acetyltransferases (HAT). Garcinol serves as a potent natural HAT inhibitor and has unveiled promising results in molecular interaction studies against Monoamine oxidase B (MAO-B) and Catechol-O-Methyltransferase (COMT), as well as in L-DOPA induced dyskinesia. This review highlights the prospective implications of garcinol as a novel anti-Parkinsonian agent, and establishes a bridge between histone acetylation defects and the pathological aspects of PD.

1. Introduction

Parkinson's disease (PD) arises due to the loss of dopaminergic neurons in the midbrain substantia nigra pars compacta (SNpc) region, and the resultant depletion of dopamine from their terminals in corpus striatum (Beitz, 2014; Emamzadeh and Surguchov, 2018; Jankovic, 2008; Dexter and Jenner, 2013; Quinn, 1997; Schapira, 2009). Decline in this neurotransmission leads to the characteristic motor behavioral abnormalities of PD, which include resting tremor, bradykinesia, rigidity and postural instability (Mazzoni et al., 2012; Kalia and Lang, 2015; Emamzadeh and Surguchov, 2018). Despite several research and discoveries, the exact cause of PD is still obscure, and thus the treatment options are limited. So far, dopamine replenishment therapy using its precursor, L-DOPA (L-3,4-dihydroxyphenylalanine), has been the therapeutic gold standard for symptomatic relief (Cotzias et al., 1967), albeit its prospective side-effects of prolonged use have extensively been reported, which includes exaggeration of PD itself (Borah and Mohanakumar, 2007, 2010(a,b), 2012; Olanow et al., 2004; Yuan et al., 2010).

Naturally occurring antioxidants and anti-inflammatory compounds such as epigallocatechin-3-gallate, ginkgolides, baicalein, silymarin, lycopene, curcuminoids, etc. have been widely tested in PD, and more effective components are still being searched (Borah et al., 2013a,b; Ríos et al., 2016; Sengupta et al., 2016). One such emerging compound is garcinol, a polyisoprenylated benzophenone derivative of *Garcinia* sp., belonging to the Clusiaceae family (Ramachandran, 2014). Pure garcinol, bearing molecular weight of 602.812 g/mol, was first obtained as a yellow crystal from hexane extract of *Garcinia* fruit rind (Krishnamurthy et al., 1981; Padhye et al., 2009). The compound has been reported as a potent antioxidant and anti-inflammatory agent since multiple studies have proved its free radical scavenging property, and its ability to prevent inflammatory cascade (Liao et al., 2005; Liu et al., 2015; Yamaguchi et al., 2000a).

Attempts are being made to investigate the effect of garcinol in neurological disorders. Garcinol can effectively restore the balance between the neurotransmitters glutamate and γ-aminobutyric acid (GABA), rescue neural precursor cells as well as promote their rapid growth (Hao et al., 2016; Weng et al., 2011). It also serves as a strong

* Corresponding author.
E-mail address: anupomborahh@gmail.com (A. Borah).
[1] Authors contributed equally to this manuscript.

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inhibitor of histone acetyltransferases (HAT) (Balasubramanyam et al., 2004). The disturbance in histone acetylation status contributes to rapid neurodegeneration in parkinsonian brain, which has been pharmacologically targeted by inhibitors of both histone acetylases and deacetylases (Hegarty et al., 2016). But a large number of emerging reports advocate the promising role of HAT inhibition over Histone deacetylase (HDAC) inhibition (Park et al., 2016; Song et al., 2011, 2010; Wang et al., 2009). Dopamine restorative potency of garcinol, its homocysteine lowering ability as reported *in silico* (Mazumder et al., 2018, 2016), as well as the countering of L-DOPA-induced dyskinesia in PD model by garcinol (Ryu et al., 2018), demonstrate its worthiness as a potential drug candidate against PD (Mazumder et al., 2018, 2016; Ryu et al., 2018).

Taking into account the numerous beneficial potentials of garcinol, this review highlights its overall mechanism of action and suggests its application as a novel medication in the treatment of PD. The HAT inhibitory property of garcinol, which is discussed here in detail, may be regarded crucial for it being a forerunner among the natural neuroprotective agents against PD.

2. Dysregulated histone acetylation in neurodegenerative disorders

Alterations in the architecture of chromatin allow or inhibit the transcriptional machinery to control gene expression (Mirabella et al., 2016). These customizations are carried out by specific enzymes involved in modifications of histones, thereby maintaining a proper balance (Berson et al., 2018). Acetylation and deacetylation of histones form two essential steps in this regard, which are typically driven by HAT and HDAC respectively. Through these processes, functional acetyl groups are alternately added and withdrawn from the lysine residues in the N-termini of histone core (Fass et al., 2012). Acetylation eliminates the positive charge on histones which would otherwise form close association with the negatively charged DNA, thereby unwinding the chromatin packaging and facilitating gene transcription. Deacetylation reverses this relaxed state and limits DNA accessibility (Grunstein, 1997). Thus, despite having identical genome in every cell of our body, a highly regulated unique expression pattern is maintained. Dysregulation of chromatin remodeling leads to the development of various diseases. Extensive research on the etiology of neurodegenerative diseases has shed light on the involvement of dysregulated epigenetic mechanisms (Urdinguio et al., 2009).

In Alzheimer's disease (AD), the presence of C-terminal fragments of amyloid precursor protein (AICD) has been examined, which bears the ability to induce neuronal death and cognitive decline (Müller et al., 2008). Over-expression of AICD increases acetylation of histones H3K14 and H4K5, contributing to severity of the disease (Kim et al., 2004). However, it has been reported that acetylation of histone H4 is necessary for the correct repair of DNA. This process may be affected in AD patients, since the accumulation of phospho-H2AX (an indicator of DNA strand breaks) is prominent (Stante et al., 2009). Again, in R6/2 and 82Q mice models of Huntington's disease, detailed epigenetic research has revealed that the acetylation of histones H3 and H4 is reduced by the expression of a mutant huntingtin protein (Steffan et al., 2000). RNA-binding FUS protein, which is characteristic to amyotropic lateral sclerosis (ALS), strongly inhibits HAT activity. Simultaneously, there is an alteration in HDAC levels in brain and spinal cord of ALS patients with decreased HDAC1 and increased HDAC2 mRNA levels (Mirabella et al., 2016).

In PD, a pathological disparity in histone acetylation and deacetylation has been demonstrated. Hyperacetylation increases the loss of dopaminergic neurons through autophagy (Park et al., 2016). Therefore, specific HATs are required to be targeted by inhibitors for the effective treatment of PD (Milano et al., 2017). Midbrain dopaminergic neurons of PD patients display an increased level of histone acetylation (Park et al., 2016). Conversely, cytoplasmic aggregates of α-synuclein, the pathological hallmark of PD, possess strong binding affinity for histones, thereby reducing the levels of acetylated histone H3 and inhibiting HAT-mediated acetyltransferase activity (Kontopoulos et al., 2006). Thus, there is a dichotomy on histone hypo- and hyperacetylation in PD. On the one hand, studies in cell cultures reported hypoacetylation (Kontopoulos et al., 2006), while studies in human brain as well as in animal models revealed that activation of microglia and their infiltration, which are absent in cell culture systems, are key factors in inducing histone hyperacetylation *in vivo* (Harrison et al., 2018; Park et al., 2016). The study by Kontopoulos et al. (2006) made use of a homogenous dopaminergic cell line (SH-SY5Y) without glia and with over-expression of α-synuclein. Here, it was demonstrated that α-synuclein masks acetylation sites of histones, which hence leads to histone hypoacetylation. It can be argued that while the degenerating dopaminergic neurons exhibit hypoacetylation, the activated glia promote hyperacetylation, and thus there is a resultant net disease-dependent increase in the overall level of histone acetylation.

Significant epigenetic modifications in dopaminergic neurons have been demonstrated in toxin-induced parkinsonian models. Exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a widely used toxin for induction of hemiparkinsonism, leads to hyperacetylation of histone H3. Further, administration of L-DOPA was found to restore acetylation status (Nicholas et al., 2008). Lowered α-synuclein mediated toxicity has been observed in cells receiving Sirt2 HDACs (Outeiro et al., 2007). Thus, aberrant modulation of histones in favour of hyperacetylated state contributes to the rapid progression of neurodegeneration (Landgrave-Gómez et al., 2015).

2.1. Histone acetylation defects and its relevance to the pathophysiology of PD

Fairly large number of reports support that oxidative stress (OS) is involved in increased acetylation of histone H3 (Choudhury et al., 2010; Kreuz and Fischle, 2016; Niu et al., 2015). In epithelial cell lines, OS enhances the acetylation of histone H4, thus increasing the release of inflammatory cytokines like IL-8 (Rahman et al., 2002; Tomita et al., 2003). These molecules eventually activate transcription factor NF-κB, an important mediator of inflammatory response. Further, OS intensifies the binding tendency between p65 component of NF-κB and the histone acetyltransferase CBP (Rahman et al., 2004). Inflammatory genes can be switched off by HAT inhibitors or HDAC activators (Barnes et al., 2005).

As neuronal growth and survivability are controlled by chromatin remodeling through post-translational histone modifications, alterations in these processes often result in loss of cellular integrity and initiation of apoptotic pathways, eventually amplifying the disease symptoms. Harrison and his group recently demonstrated a step-wise increase in acetylation of histone H3, specifically in lysine 9 residue, from early to late stage PD (Harrison et al., 2018). In addition to this, the action of multiple HDACs are simultaneously diminished in MPP + -treated cells and MPTP-treated mouse brains, as well as in midbrain tissues of human PD patients, resulting in an increased level of acetylated histones (Harrison et al., 2018; Park et al., 2016).

Among several reasons suggested for accumulation of α-synuclein in PD, malfunction of ubiquitin-proteasomal system is a significant one (Kumar et al., 2018). Proteasomes are responsible for degrading unnecessary or damaged cytoplasmic as well as nuclear proteins (Tanaka, 2009). Environmental neurotoxins such as dieldrin, have been shown to increase histone acetylation in dopaminergic neurons and upregulate the level of cAMP response element-binding protein by inhibiting ubiquitin proteasomal activity (Song et al., 2010). This provides a basis for relating high levels of acetylated histones with proteasomal impairment, leading to the aggregation of α-synuclein (Fig. 1).

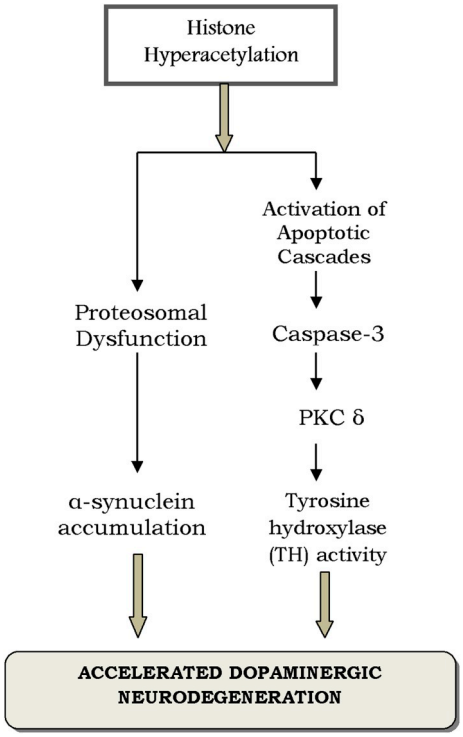

Fig. 1. Increase in histone acetylation leads to enhanced dopaminergic neurodegeneration in PD. Histone hyperacetylation initiates several downstream cellular apoptotic processes, including caspase-3 and PKCδ (Protein Kinase C delta) activation, which is an oxidative stress-sensitive kinase. PKCδ, in turn, inhibits tyrosine hydroxylase (TH) activity, thereby reducing dopamine synthesis. Again, environmental neurotoxins lead to Parkinsonian symptoms by means of proteosomal dysfunction due to histone hyperacetylation. Since one of the major causes of α-synuclein aggregation involves impairment of proteosomal activity, we hypothesize that hyperacetylation of histone may be a cause behind aggregation of α-synuclein.

2.2. HAT inhibition as a promising approach in PD

The chemical modifications of the histones can be used as biomarkers, as well as therapeutic targets by the use of epigenetic modulators of HAT and HDAC. Inhibitors of both the processes have proven to be effective in reducing the overall neurotoxicity (Chen et al., 2015; Song et al., 2010). Whether HAT or HDAC is more functional in neurodegenerative disease is still debated. A wide range of natural as well as synthetic HDAC inhibitors, including vironostat, AK7, sodium butyrate, and valproate, have been demonstrated to confer protective effects in animal models of neurodegenerative disorders (Chen et al., 2015; Didonna and Opal, 2015; Harrison et al., 2018; St. Laurent et al., 2013). However, accumulating evidences in favor of HAT inhibition and obscure knowledge on the mechanism of neuroprotection offered by HDAC inhibitors have paved the ways towards unleashing the role of HAT inhibition in PD (Didonna and Opal, 2015). Here, we describe the accumulating reports that reinforce the idea of employing inhibitors of HAT as a strategy for the treatment of PD.

Naturally occurring HAT inhibitors can mediate the survival of neurons by preventing their apoptotic death caused by exposure to environmental toxins (Song et al., 2011, 2010). For example, garcinol can effectively protect against 1-methyl-4-phenylpyridinium (MPP+) – induced cytotoxicity whereas, anacardic acid (another naturally occurring HAT inhibitor) has been demonstrated to exert neuroprotection against dieldrin-induced apoptosis, independent of its antioxidant effects (Park et al., 2016; Song et al., 2010). Besides, increase in histone acetylation initiates downstream cellular apoptotic processes, including activation of caspase-3 and Protein Kinase C delta (PKCδ) which is an oxidative stress-sensitive kinase (Jin et al., 2014; Song et al., 2010). PKCδ, in turn, inhibits tyrosine hydroxylase (TH) activity, thereby reducing dopamine synthesis (Zhang et al., 2007). In simple words, hyperacetylation-induced upregulation in PKCδ leads to depletion of dopamine as well as accelerates degeneration of dopaminergic neurons (Jin et al., 2014) (Fig. 1). Likewise in AD model, the increase in Tip60 HAT activity was reported to exacerbate amyloid precursor protein – mediated neurodegeneration (Pirooznia et al., 2012).

In addition to this, treatment of dopaminergic neuronal cell lines like rat N27, mouse MN9D and human SH-SY5Y with the HDAC inhibitor, trichostatin A (TSA), has been found to induce neuronal apoptosis (Wang et al., 2009). HDAC inhibitors facilitate hyperacetylation of histones, thereby arresting growth and differentiation, and leading to cell death (Somech et al., 2004). Also, the expression of HDAC Sirt2 has been found to be relatively stable throughout the progression of PD. Furthermore, administration of HDAC inhibitors has elicited similar effects as that of dopaminergic toxins like amphetamine (Shen et al., 2008). A higher risk of developing PD is reported with increasing exposure to amphetamine, which potentiates the psychomotor behavioral abnormalities (Christine et al., 2010). Reduced levels of HDACs has been related to changes in histone acetylation in PD, and the balance can be restored by employing HAT inhibitors (Park et al., 2016).

3. Pivotal neuroprotective role of garcinol against PD pathology

Since time immemorial, plants of the genus *Garcinia* have been extensively used in Ayurvedic medicinal practices for treating a wide range of diseases and ailments (Liu et al., 2015). Garcinol (Fig. 2), the bioactive compound of *Garcinia*, has been annotated for these multiple beneficial effects (Sang et al., 2001; Liu et al., 2015; Padhye et al., 2009). Considerably high dose of garcinol, up to 2000 mg/kg, exhibited no abnormal clinical responses, including hematological, reproductive or developmental defects in rodents (Majeed et al., 2018). Evidences on garcinol-mediated amelioration of neurological conditions, its lipophilicity and average molecular weight, suggest that it can extravasate into brain by traversing the blood-brain barrier (Fasolo et al., 2016; Hao et al., 2016; Tang et al., 2013). In this section, we have compiled the reports in support of the effectiveness of garcinol in ameliorating the pathophysiological changes of PD.

3.1. HAT inhibitory potential of garcinol

Garcinol is reported to be an excellent inhibitor of p300 histone acetyltransferase activity [IC_{50} = 7 μM] and p300/CBP-associated factor (PCAF) [IC_{50} = 5 μM]. Thus, the compound effectively reduces the transcription of genes induced by increased HAT activity (Balasubramanyam et al., 2004) (Table 1). In *Cryptococcus neoformans*, an environmental fungus, garcinol has been found to inhibit histone acetylase Gcn5, which otherwise regulates the expression of genes

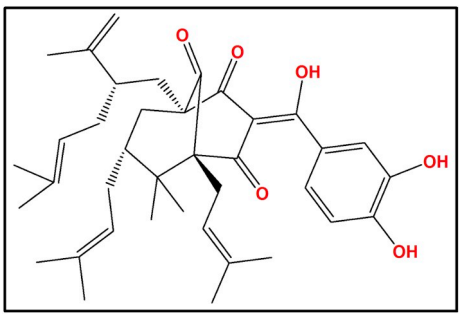

Fig. 2. The chemical structure of garcinol. The structure is obtained from NCBI PubChem compounds database (https://pubchem.ncbi.nlm.nih.gov/) (Compound ID 5490884) and re-drawn using ChemDraw Ultra software.

Table 1
Studies relevant to the neuroprotection by Garcinol and/or *Garcinia* extracts. While there are two studies in PD models involving garcinol and *Garcinia*, others studies are also relevant to the pathophysiologies of PD as listed above.

Sl. No.	Relevant studies	Reference	Findings of the studies
1	Studies in Parkinson's disease model	Antala et al. (2012)	In 6-OHDA rat model of PD, methanolic extract of *Garcinia indica* (100, 200, and 400 mg/kg body) ameliorated motor behavior, elevated the levels of dopamine and its metabolites in nigro-striatum.
2		Ryu et al. (2018)	In mice model of 6-OHDA induced parkinsonism and L-DOPA-induced dyskinesia, garcinol (5 mg/kg) reduced the dyskinetic behavior, suppressed the over-expression of c-Fos, Fra-2, and Arc, and ERK cascade induced by chronic L-DOPA treatment.
		Park et al. (2016)	HAT inhibition by garcinol significantly reduces MPP + -induced cell death and reduction in ATP content in SH-SY5Y neuroblastoma cells.
3	Computational studies on neuroprotection by Garcinol	Mazumder et al. (2016)	Garcinol was found to inhibit catechol-O-methyltransferase (COMT), and thus it was suggested to prevent dopamine depletion as well as production of COMT-mediated reactive oxygen species.
4		Mazumder et al. (2018)	Garcinol was found to inhibit monoamine oxidase-B (MAO-B), and is thereby hypothesized to prevent depletion of dopamine through MAO-B mediated catalysis, and prevent generation of its toxic metabolites.
5	Garcinol in other neurological disorders and neuronal cell lines	Hao et al. (2016)	In rat model of epilepsy, Garcinol (50, 100 or 200 mg/kg) ameliorated pentylenetetrazole-induced loss of cognition, prevented apoptosis and neurodegeneration. The mechanism was found to be due to suppression of caspase-3 expression, pro-apoptotic proteins Bax and Bad, and inhibition of BDNF-TrkB – mediated excitotoxicity. Further, garcinol enhanced expression of GAD65 and $GABA_A$ receptors, and thus stimulated the production of inhibitory neurotransmitter, GABA. Moreover, garcinol reduced the level of the excitatory neurotransmitter glutamate.
6		Liao et al. (2005)	In primary astrocytes, garcinol (5 μM) was found to inhibit generation of NO.
7		Weng et al. (2011)	In primary cortical cell cultures containing glial cells, garcinol (at 5 μM) enhanced neuronal survival and neurite outgrowth, induces neuronal differentiation by significantly elevating glial fibrillary acidic protein, and microtubule associated protein 2, modulates ERK pathway. Further, garcinol reduced growth factor deprivation-mediated cell death.
8	Garcinol in PD related pathologies	Ahmad et al. (2010)	Garcinol (25 μmol/L) significantly inhibits NF-κB and was found to prevent inflammation.
9		Hong et al. (2006)	In LPS-treated cell lines, garcinol and its metabolites (at 1 μM) inhibited expression of iNOS, PLA2, COX-2, NF-κB activation, and STAT1 phosphorylation.
10		Liao et al. (2004)	In LPS-treated macrophages, garcinol inhibits expression of cPLA2 and iNOS activity through down-regulation of NF-κB.
11		Yamaguchi et al. (2000a)	In free radical generation system, garcinol was found to scavenge both hydrophilic and hydrophobic free radicals, including superoxide anion, hydroxyl radical and methyl radical.
12		Yamaguchi et al. (2000b)	Garcinol showed chelation activity, scavenged superoxide anion, and suppressed protein glycation.
13		Sang et al. (2001)	In HL-60 cell lines, garcinol (10–20 μM) inhibited generation of NO and H_2O_2, activities of MMPs and expression of iNOS.
14		Kolodziejczyk et al. (2009)	Garcinol (0.1–25 μg/ml) inhibited oxidative and nitrosative stress by decreasing the levels of TBARS, formation of carbonyl groups in plasma and platelet proteins caused by peroxynitrite.
15		Hong et al. (2006)	In cell lines, garcinol (1 μM) and its derivatives modulated ERK½ and AKT pathways.
16	Garcinol as a HAT inhibitor, and the ameliorative effects	Maddox et al. (2013)	When infused into lateral amygdale of brain (at 10 mg/kg), garcinol inhibited acetylation of histone H3, and thus impaired reconsolidation of older fear memory.
17		Balasubramanyam et al. (2004)	Garcinol (10 μM) inhibited HATs – p300 and PCAF in both *in vitro* and *in vivo*.
18	Oral toxicity study	Majeed et al. (2018)	Garcinol given by oral gavation at the acute single dose of 2000 mg/kg b.w., and in sub-acute and sub-chronic repeat dose of 100 mg/kg b.w. at 28 days and 90 days interval respectively. No hematological, histological, or developmental toxicity could be found. There was no alteration of body weight, food intake or mortality.

relating to varying environmental conditions (O'Meara et al., 2010). This clinically significant property of garcinol is also extended to its possible use in radio-sensitization because of its effects on DNA damage responses (Oike et al., 2012). Thus, it is suggested that the hyper-acetylation of histones, as evident in PD patients and animal models of the disease, can be regulated and effectively controlled by garcinol, and therefore confer neuroprotection to dopaminergic neurons (Fig. 3).

3.2. Inhibition of cellular oxidative stress by garcinol

Oxidative stress is one of the major contributors to dopaminergic neurodegeneration in PD (Beal, 2005; Leszek et al., 2016; Jenner, 2003; Chinta et al., 2007; Dexter and Jenner, 2013; Quinn, 1997, Schapira, 2009), and several antioxidants have been reported to confer significant neuroprotection in animal models of the disease (Borah and Mohanakumar 2009, 2010(a,b); Fujisawa et al., 2004; Grunstein, 1997; Tapias et al., 2009; Yuan et al., 2010). Garcinol causes a favorable downshift in reactive oxygen species (ROS) by quenching hydroxyl as well as methyl radicals, and preventing their interruption in normal functioning of cellular biomolecules at an inhibitory concentration of 0.32 μM (Padhye et al., 2009; Liu et al., 2015; Yamaguchi et al., 2000b) (Table 1). Because of its phenolic hydroxyl groups and β-diketone moiety, the potential of garcinol to elicit strong anti-oxidant activity is comparable to that of curcumin, one of the most potent antioxidant compounds ever discovered (Pan et al., 2001). The superoxide radical scavenging activity of garcinol has experimentally revealed to be as potent as gallic acid and stronger than that of tea catechins (Liu et al., 2015). Furthermore, in aqueous ethanol solution, garcinol can reduce the levels of the free radical DPPH (1,1-diphenyl-2-picrylhydrazyl) with three times higher efficiency compared to α-tocopherol, another lipid soluble anti-oxidant. Its presence favorably decreases thiobarbituric acid reactive substance (TBARS) formed by peroxynitrite (Kolodziejczyk et al., 2009). The prevention of free radicals and lipid peroxidation by garcinol provides a basis for its possible use in neuro-degenerative diseases, since the plethora of cellular oxidative burden remains the main reason in neuronal death in PD (Bhattacharjee and Borah, 2016; Beal, 2005; Leszek et al., 2016; Jenner, 2003; Chinta et al., 2007). Since garcinol effectively scavenges both hydrophilic as well as

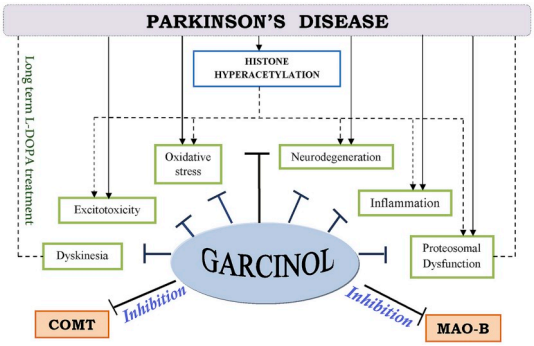

Fig. 3. Histone hyperacetylation in PD pathology: A schematic representation of the possible neuroprotective role of Garcinol. Out of the multiple hypotheses framed to explain the pathophysiology of PD, oxidative stress, neuroinflammation, neuronal excitotoxicity and proteosomal dysfunction are the primary ones. Based on the findings, we speculate that histone hyperacetylation may be indirectly responsible in causing PD, since it bears a potential relevance to the principal pathophysiological changes observed. Garcinol can function against the *primae faciae* mechanisms of dopaminergic cell death in PD, and can also attenuate the activity of monoamine oxidase-B (MAO-B) and catechol-O methyltransferase (COMT) enzymes, thereby improving the availability of the neurotransmitter dopamine by antagonizing its metabolism.

hydrophobic radicals, it is expected to be a more potent antioxidant (Yamaguchi et al., 2000a) (Table 1).

3.3. Garcinol displays anti-inflammatory activity

In both idiopathic and genetic cases of PD, neuroinflammation is an underlying mechanism that leads to cellular dysfunction and death (Leszek et al., 2016). Impaired elimination of NO radicals and metabolism of arachidonic acid are reported to be involved in the activation of glial cells, leading to inflammatory responses (DiSabato et al., 2016). In a remarkable study designed to understand the neuroprotective property of garcinol, Liao et al. (2004) demonstrated that 5 μM of garcinol can prevent the accumulation of nitric oxide in lipopolysaccharide-treated astrocytes. Simultaneously, it minimizes the expression of inflammatory mediators, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (Liao et al., 2005) (Table 1). Lowering of iNOS level is mediated *via* inhibition of Signal transducer and activator of transcription 1 (STAT-1). Garcinol terminates the phosphorylation of cytosolic phospholipase A2 (cPLA2), thereby directly regulating arachidonic acid metabolism. More specifically, cPLA2 phosphorylation is diminished through suppression of extracellular signal-regulated kinase 1/2 (ERK1/2) and NF-κB activity (Hong et al., 2006) (Table 1).

3.4. Evidences on neuroprotective ability of garcinol

Garcinol, with its emanating importance in the management of OS and inflammation, has also been optimistically employed in several neurological conditions. Change in the levels of extracellular glutamate and GABA causes hyperactivation of N-methyl-D-aspartate (NMDA) glutamate receptors which trigger several signaling cascades to initiate neuronal degeneration through excitotoxicity (Ambrosi et al., 2014). Garcinol effectively normalizes the glutamate: GABA ratio by up-regulating the expressions of glutamic acid decarboxylase 65 and $GABA_A$ receptors, thereby preventing hyperactivation of NMDA receptor and the resultant excitotoxicity. It enhances memory and cognition in C57BL/6 mice, significantly lowers epileptic seizure scores and has been proposed to control neuronal loss (Hao et al., 2016). Garcinol also exhibits desirable anti-cholinesterase properties by inhibiting the enzyme acetylcholinesterase with an IC_{50} value of 0.66 μM, which is comparable to that of the widely used cholinesterase inhibitor, galantamine (IC_{50} = 0.50 μM) (Lenta et al., 2007). Again, garcinol may systematically control traumatic memories, depicting its advantage in the management of anxiety in post-traumatic stress disorder (Maddox et al., 2013) (Table 1). It can be employed to understand the intricate relationship between acetylation machinery and memory formation (Merschbaecher et al., 2012; Zhao et al., 2012).

Although the ability of garcinol to arrest cell differentiation and inhibit the growth of cancerous cells have been demonstrated in a number of experiments, there is no report on decreased viability of normal cells with its exposure. Cambogin, another isoprenylated benzophenone of *Garcinia* exhibiting highly similar physical properties as garcinol, is cytotoxic only to cells that particularly express platelet-derived growth factor receptors (Tian et al., 2011). Besides, garcinol improves the neuronal count in hippocampal regions following administration of pentylenetetrazole (PTZ). A marked upregulation in the expression of anti-apoptotic factors Bcl-2 and Bcl-xL, and the simultaneous decrease in pro-apoptotic factors Bax and BAD along with caspase 3-positive cells were observed (Hao et al., 2016). In cultured rat cortical progenitor cells, garcinol can reduce cell death associated with growth factor deprivation. It also promotes neurite outgrowth in epidermal growth factor-responsive neural precursor cells and supports the survival of neurons (Weng et al., 2011) (Table 1).

3.5. Rationale for utilizing garcinol in PD therapeutics

L-DOPA is considered as the 'gold standard treatment' for PD, despite the fact that its long term administration leads to numerous side-effects, a significant one being abnormal involuntary movement called dyskinesia (Dorszewska et al., 2014; Pandey and Srivanitchapoom, 2017). In unilaterally 6-hydroxydopamine (6-OHDA)-lesioned hemiparkinsonian mice, 5 mg/kg of garcinol co-treatment with L-DOPA effectively controlled the axial, limb, and orofacial (ALO) score for dyskinesia analysis. Following the administration of garcinol, a decreased expression of c-Fos, FRA-2, and ARC genes have been visualized (Ryu et al., 2018) (Table 1), which are usually over-activated in L-DOPA induced dyskinesia (Bastide et al., 2014). Moreover, methanolic extract of *Garcinia indica,* which is known to contain garcinol, effectively elevates dopamine level in the striatum and confer neuroprotection to dopaminergic neurons in 6-OHDA lesioned experimental rats (Antala et al., 2012) (Table 1). Even pharmacological inhibition of HATs by garcinol can notably suppress MPP^+-induced cell death due to reduction in ATP content (Park et al., 2016).

Dopamine is chiefly metabolized by monoamine oxidase B (MAO-B) and catechol-o-methyltransferase (COMT) enzymes, for which inhibitors of these enzymes are typically used in the treatment of PD (Männistö, 2010; Riederer and Laux, 2011). *In silico* studies on the molecular interaction between garcinol and the active sites of COMT and MAO-B revealed that garcinol can potentially inhibit the activity of the two enzymes, similar to their known inhibitors (Mazumder et al., 2018, 2016) (Table 1). Since inhibition of MAO-B and COMT can be correlated to increase in availability of dopamine as well as prevent generation of toxic dopamine metabolites including homocysteine, 3-o-methyldopa, 3-methoxytyramine, 3,4-dihydroxyphenylacetaldehyde, etc., garcinol may prove to be a dependable remedial measure in PD therapeutics.

4. Conclusion and future perspective

Stagnant scenario of PD therapeutics persuades the researchers to think beyond restoration of dopamine level due to the fact that their long-term application has decreased efficacy and displays numerous complications. Therefore, compounds which can cure the defects in epigenetic mechanisms associated with PD exhibit a high significance as therapeutics. The multitudes of parameters including oxidative stress, inflammation, excitotoxicity and protein aggregation are the *prima facie* mechanisms in the causation of PD. Based on the reports

discussed in this review, it may be concluded that the compound garcinol displays its positive effects towards neuroprotection by circumventing all the major pathophysiologies that are held responsible for PD. HAT inhibitory role of garcinol might be the upstream event and the other favorable neuroprotective effects might be its consequences. Thus, the current requirement is to understand the extended role of garcinol in varieties of Parkinsonian models through effective research techniques. For the early recruitment of garcinol in PD therapeutics, its toxicological profiles, safe dosage as well as its bioavailability improving strategies stand in the need of being elucidated. This will allow the implementation of garcinol as a promising compound in the clinical research and treatment of PD.

Conflicts of interest

The authors declare no conflict of interest in publishing the article.

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Appendix A. Supplementary data

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