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Review

Lycopene - A pleiotropic neuroprotective nutraceutical: Deciphering its therapeutic potentials in broad spectrum neurological disorders

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ABSTRACT

Lycopene is a naturally occurring carotenoid found abundantly in red fruits and vegetables. Myriads of literature documented potential health benefits of lycopene, owing to its sublime capacity of suppressing oxidative stress, inflammation, and modulation of various cell survival pathways. Due to its lipophilic nature, lycopene can reach brain adequately by traversing the blood-brain barrier thereby extending it's promising therapeutic benefits in neurological disorders. Lycopene efficiently assists in restoring the characteristic behavioural and pathophysiological changes associated with neurodegenerative disorders, epileptic conditions, aging, subarachnoid hemorrhage, spinal cord injury, and neuropathy. The detrimental impacts of environmental neurotoxins on brain and neuropathological consequences of consumption of high-lipid diet can also be mitigated by lycopene. Apart from its high antioxidant potency, lycopene confers neuroprotection by preventing proteinopathies, neuroinflammation, apoptosis, cerebral edema, and synaptic dysfunction. This review provides a lucid idea on the potential multi-faceted benefits of lycopene in disorders of the central nervous system and elucidates the molecular mechanisms and pathways of its action.

1. Introduction

Lycopene is nature's one of the most versatile red carotenoids owing to its health benefits in diverse groups of diseases or disorders of systemic and central origin (Story et al., 2010; Senkus et al., 2019; Saini et al., 2020). This carotenoid is found most abundantly in tomatoes and other red-coloured fruits, like guava, grapefruit, watermelon and papaya (Story et al., 2010). It is a potent antioxidant carotenoid with many folds higher free radical scavenging potential than the other known antioxidants, such as glutathione (GSH) and vitamin E (Mortensen et al., 1997; Böhm et al., 2001; Shi et al., 2004). Therefore, since its discovery, numerous scientific literature have persuasively registered the effectiveness of lycopene against several diseases, including metabolic disorders, cancer, and infertility where oxidative stress plays a pivotal role (Elgawish et al., 2020; Senkus et al., 2019; Story et al., 2010; Pakrashi and Oehninger, 2014). Most importantly, lycopene can traverse blood-brain barrier (BBB) and reach brain (Khachik et al., 2002; Johnson et al., 2013) which prompted scientists to evaluate its therapeutic efficacy in neurological disorders. Accordingly, lycopene has been found to confer promising neuroprotection against central nervous system (CNS) disorders caused due to neurodegeneration (Saini et al., 2020; Sandhir et al., 2010; Zhao et al., 2018a), epileptic conditions (Kumar et al., 2016), aging (Zhao et al., 2018b), spinal cord injury (Hua et al., 2019), neuropathy (Icel et al., 2019), environmental toxins (Hedayati et al., 2019), metabolic disorders (Yin et al., 2014), and high-lipid diets (HLD; Yang et al., 2018). Lycopene's potency to ameliorate oxidative stress is the *prima facie* mechanism of neuroprotection (Klebanov et al., 1998; Shi et al., 2004; Guest and Grant. 2012); besides its ability to

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counter neuroinflammation (Hazewindus et al., 2012; Wang et al., 2019a), proteinopathies (Wang et al., 2018a; Liu et al., 2013), apoptosis (Huang et al., 2017), cerebral edema (Zhao et al., 2018a), and synaptic dysfunction (Wang et al., 2019a). These neuroprotective attributes of lycopene cumulatively ameliorate behavioural abnormalities, including cognitive deficits, locomotor impairments, dementia, seizures, anxiety and depression-like behaviour associated with neurological disorders (Kumar et al., 2016; Crowe-White et al., 2019; Zhu et al., 2020).

The present review summarizes all the investigations and experimental evidences on the pharmacological benefits of lycopene in managing neurological disorders. The possible mechanism of its action is also discussed, along with a detailed exposition of the metabolic pathways influenced by lycopene which can lead to a promising therapeutic intervention in CNS disorders.

2. Lycopene: chemistry and pharmacokinetics

Lycopene is a lipophilic compound, with an aliphatic unsaturated hydrocarbon chain, having chemical formula $C_{40}H_{56}$ and molecular weight 536.87 g/mol. It is a symmetrical tetraterpenoids assembled from eight isoprenoid units (octaprene) joined by regular head-tail bindings except one tail-tail binding in the middle of the molecule (Kiokias et al., 2016). The all-*trans* configuration of lycopene is the most predominant isomer among its extensive isomers (Story et al., 2010), however, compared to the all-*trans* configuration, *cis* isomers are thermodynamically more stable as well as have higher absorption and bioavailability in human (Srivastava and Srivastava, 2015).

As a lipophilic compound, lycopene passively diffuses through the duodenal mucosal cells and follows the same absorption route of dietary fat (Williams et al., 1998). Only about 7–10% of the total lycopene intake is absorbed through the intestine while half of the significant remaining portion is excreted and another half is retained by the body (Boileau et al., 2002; Cámara et al., 2013). The bioavailability of lycopene is impaired by aging (Cardinault et al., 2003), high fibers diets (Riedl et al., 1999), and factors that generally decrease fat absorption (Koonsvitsky et al., 1997). In a single-dose phase I pharmacokinetic and toxicity study, the maximum plasma concentration of total lycopene has been reported to be 4.03–11.27 μg/dl after 15.6–32.6 h with an oral gavage of 10–120 mg/day (Gustin et al., 2004). Studies show wide variation in the persistence of lycopene in the body with a half-life of 12–33 days (Rock et al., 1992), 2–3 days (Stahl and Sies, 1992), 28.1–61.6 h (Gustin et al., 2004) and 5 days (Ross et al., 2011) in human, 36 h in dogs (Korytko et al., 2003) and about 12–20 h in cell lines (Levy et al., 1995). Apart from liver, which is it's primary accumulating and mobilization site, a significant amount of lycopene is widely parceled and stored in lipid enriched tissues and organs such as adipose tissues, adrenal glands, testes, kidney, prostate gland, lungs and ovary (Story et al., 2010; Srivastava and Srivastava, 2015). Acute, subchronic, and chronic toxicity studies of lycopene have been extensively reviewed (Trumbo et al., 2005). A study suggested that required daily intake of lycopene is 5–10 mg (Rao and Shen, 2002), and interestingly no known adverse health effects of either dietary or formulated lycopene consumption with an intake of as high as 3 g/kg/day have been observed (Gustin et al., 2004; Trumbo et al., 2005). Toxicity studies also revealed that lycopene has no unexpected or significant adverse effects in rat and dog (Trumbo et al., 2005).

Lycopene is likely to be undergoing chemical and enzymatic oxidation during its biotransformation pathway (Ross et al., 2011; Cichon et al., 2018). Lycopene oxidation with m-chloroperbenzoic acid produces lycopene-1, 2-epoxide and lycopene-5, 6-epoxide as the main metabolites, and other minor metabolites. This is followed by ring opening and rearrangement (Khachik et al., 1998). Lycopene metabolism products 5, 6-dihydroxy-5, 6-dihydrolycopene (Khachik et al., 1995) and epimeric 2, 6-cyclolycopene-1, 5-diols (Khachik et al., 1997) were detected in human serum. Both cleavage and oxidation products were identified in a study using post-mitochondrial fraction of rat mucosa with lipoxigenase (Ferreira et al., 2003). Similarly, 8 carbonyl compounds were detected in an *in vitro* study on cleavage products formed by lycopene autoxidation (Kim et al., 2001). In connection with the excretion pathways, lycopene is excreted mainly through feces (Zaripheh et al., 2003), and in much lower amounts through urine (Ross et al., 2011) and sebaceous glands (Camara et al., 2013).

3. Neuroprotective and therapeutic potentials of lycopene in CNS disorders

3.1. Lycopene in Alzheimer's disease

Alzheimer's disease (AD) is the most common progressive neurodegenerative disorder with cognitive impairments and it is the leading cause of dementia (Ewers et al., 2012; Sharma et al., 2019). Pathological hallmarks of AD brain are deposition of beta-amyloid peptides (Aβ) as senile plaques outside neurons (Glenner and Wong, 1984) and neurofibrillary tangles with hyperphosphorylated tau proteins inside neurons (Wood et al., 1986; Chen and Mobley, 2019). Cognitive decline in AD is correlated with cholinergic deficit, including loss of cholinergic neurons and decrease level of the neurotransmitter acetylcholine (Reinikainen et al., 1988; Mega et al., 2000; Karran et al., 2011; Hampel et al., 2018). Thus, inhibition of acetylcholinesterase (AChE) is one of the prime therapeutic strategies for the amelioration of cognitive decline and dementia in AD (Terry and Buccafusco, 2003; Hampel et al., 2018).

Administration of lycopene enhances cognitive functions and ameliorates memory deficit in animal models of AD (Prakash and Kumar 2014; Sachdeva and Chopra, 2015; Yu et al., 2017). It reduces Aβ-induced paralysis in *C. elegans* (Chen et al., 2015). The underlying neuroprotective mechanisms have been reported to be multi-faceted. Lycopene prevents loss of cell viability, mitochondrial fragmentation, and decreases the expression of pro-apoptotic markers (Prakash and Kumar 2014; Qu et al., 2011a; Hwang et al., 2017). Further, it is found to ameliorate AChE activity in cortex and hippocampus in animal models of AD (Sachdeva and Chopra, 2015). Studies on the molecular pathophysiologies revealed that the compound reduces secretion of Aβ, downregulates amyloid precursor protein (APP) level, and decreases tau hyperphosphorylation in brain (Yu et al., 2017). It is therefore suggested that lycopene may inhibit the activities of the secretases responsible for the processing of APP, as well as inhibit glycogen synthase kinase 3 beta (GSK-3β), and thereby confer neuroprotection in AD. Although the potential of the compound in inhibiting these enzymes needs to be explored, its role in ameliorating oxidative stress, inflammation, and apoptosis in brain of animal models of AD is well-established (Prakash and Kumar, 2014; Sachdeva and Chopra, 2015). Shred of evidence strongly implicated the mitochondrial restorative potentials of lycopene in AD models. It ameliorates mitochondrial complexes dysfunctions, restores mitochondrial redox homeostasis, improves mitochondrial membrane potential, and reduces generation of reactive oxygen species (ROS) (Prakash and Kumar 2014; Sachdeva and Chopra, 2015; Chen et al. 2015; Qu et al., 2011a, 2016; Hwang et al., 2017). The antioxidant potential of lycopene is further exemplified by the fact that it ameliorates the levels and expressions of superoxide dismutase (SOD), catalase (CAT) and GSH in brain (Sachdeva and Chopra, 2015). In addition, lycopene is an established anti-inflammatory molecule and has been reported to decrease the levels of inflammatory cytokines in hippocampus in rat model of AD (Sachdeva and Chopra, 2015). These processes are hereby considered to be the underlying mechanisms of neuroprotection in AD. The details of the neuroprotective potentials of lycopene, as revealed from cellular and animal models of AD, are summarized in Table 1.

Thus, the neuroprotective potential of lycopene in AD may be attributed to its disease-modifying capabilities by way of preventing apoptosis, reducing amyloidogenesis and preventing hyperphosphorylation of tau protein (Fig. 1). In addition, the compound is a potent anti-oxidant and anti-inflammatory molecule that ameliorates

Table 1
Neuroprotective effects of lycopene on neurodegenerative disorders.

Disorder	Model System	Lycopene's effective doses, dosing route, Time	Neuroprotective attributes
Alzheimer's disease (AD)	$A\beta_{25-35}$-challenged primary cultured cortical neurons of rat	2 μM; In culture medium; 4 h prior to Aβ exposure	i. Prevents Aβ-induced loss of cell viability, and apoptosis by reducing Bax/Bcl-2 ratio. ii. Decreases intracellular ROS generation. iii. Improves mitochondrial membrane potential. iv Reduces Aβ-induced increase in the expression of caspase-3. (Qu et al., 2011a)
	Aβ exposed rat	2.5 and 5 mg/kg b.w; Orally; 21 days	i. Enhances cognitive function and increases BDNF level. ii. Attenuates Aβ-induced reduction in activity of mitochondrial complex-I, II, III, IV in hippocampus. iii. Decreases OS by ameliorating the levels of MDA, nitrite, CAT, SOD, GSH in hippocampus. iv. Ameliorates IS by reducing the levels of TNF-α and IL-6 in hippocampus. v Reduces caspase-3 level in hippocampus. (Prakash and Kumar, 2014)
	SH-SY5Y cells expressing human APPsw	1 μM; In culture medium; 2 h	i. Reduces secretion of $A\beta_{1-42}$ and down-regulates APP level. iii Rescues from H_2O_2- and $CuCl_2$-induced loss of cell viability. (Chen et al., 2015)
	$A\beta_{1-42}$ (ICV) exposed rat	4 mg/kg; Orally; 14 days	i. Ameliorates cognitive impairment and increase in AChE activity in cortex and hippocampus. ii. Ameliorates OS in cortex and hippocampus by reducing the level of MDA and nitrite, and by increasing the level of GSH, SOD and CAT. iii. Ameliorates IS by reducing the level of TNF-α, TGF-β and IL-1β in cortex and hippocampus. iv. Prevents apoptosis by decreasing the level of caspase-3 and NF-κB p65 subunit. v Restores activity of mitochondrial complex-I, –II and –IV in cerebral cortex and hippocampus, and mitochondrial redox activity. (Sachdeva and Chopra, 2015)
	$A\beta_{1-42}$-transgenic *C. elegans*	1 and 4.1 μM; In culture medium; 7 days	Decreases Aβ-induced paralysis rate of the worm. (Chen et al., 2015)
	$A\beta_{1-42}$-challenged primary cultured cortical neurons of rat	2 μM; In culture medium; 4 h prior to Aβ exposure	i. Attenuates Aβ-induced intracellular and mitochondrial ROS generation and hence protects the integrity of mitochondrial DNA from oxidative damage. ii. Prevents mitochondrial fragmentation and opening of mPTP. iii. Ameliorates mitochondrial complexes-I, –II, –III and –IV activity and hence improves mitochondrial energy metabolism. iv Reduces release of cytochrome *c* from mitochondrial to cytoplasm. (Qu et al., 2016)
	Tau transgenic mice with P301L mutation	5 mg/kg b.w.; Orally; 8 weeks	Ameliorates memory deficits and decreases tau hyperphosphorylation in brain. (Yu et al., 2017)
	Aβ-challenged human neuroblastoma SH-SY5Y cells	0.2 and 0.5 μM; In culture medium	i. Prevents Aβ-induced loss of cells, and apoptosis by decreasing p53, Bax/Bcl-2 ratio, caspase-3 and Nucling. ii. Decreases intracellular and mitochondrial ROS production. iii. Ameliorates mitochondrial dysfunction by improving MMP and oxygen consumption ratio. iv Reduces level of phosphorylated IκBα and prevents NF-κB activation. (Hwang et al., 2017)
Parkinson's disease (PD)	MPTP exposed C57BL/6NCrj mice	20% (w/w) lyophilized tomato powders; With feed; 28 days pretreated	Replenishes DA levels in NCP. (Suganuma et al., 2002)
	6-OHDA-infused in left SN in Fischer344 rats	5% w/w lyophilized wild/GM tomato; With feed; 14 days	i. Lycopene (4.7 ± 0.2 ng/ml) detected in serum only in wild type tomato fed group. ii Replenishes DA and 3,4-dihydroxyphenylacetic acid level in NCP of wild type fed with tomato. (di Matteo et al., 2009)
	Rotenone exposed Wistar rat	10 mg/kg b.w.; Oral; 30 days	i. Ameliorates motor and cognitive impairments, and increases AChE activity. ii. Ameliorates OS by reducing the level of MDA, and by increasing the level of GSH and SOD in NCP. iii Improves mitochondrial complex-I activity. (Kaur et al., 2011)
	Rotenone exposed C57BL/6 mice	10 mg/kg b.w.; Orally; 35 days	i. Alleviates cognitive and motor behavioural abnormalities. ii. Ameliorates OS by elevating the activities of SOD, GPx and CAT in NCP and SN. iii. Prevents TH-positive neuronal loss and microtubule-associated protein 3 light chain (LC3-B) positive neurons, and decreases α-synuclein level. Liu et al. (2013)
	MPP^+-challenged SH-SY5Y Cells	1.0, 2.0 or 4.0 μM; In culture medium; Pretreated 2 h prior MPP	i. Prevents MPP^+-induced loss of cell viability and apoptosis ii. Ameliorates OS by reducing MDA and intracellular ROS level, and mitochondria derive ROS production. iii. Prevents mitochondrial morphological changes and opening of mPTP. iv. Improves mitochondrial membrane potential and energy metabolism. v Maintains mtDNA copy numbers and mtRNA transcript levels. (Yi et al., 2013)
	MPTP exposed C57bL/6 mice	10 mg/kg b.w./day; Orally; 7 days	i. Ameliorates motor impairment and replenishes DA and homovanillic acid level in NCP. iii. Ameliorates OS in SN by reducing the level of MDA, SOD and CAT, and by increasing the level of GSH and GPx. iv Prevents apoptosis by ameliorating caspase 3, 8, 9, Bcl2 and cytochrome-c level in SN. (Prema et al., 2015)
	6-OHDA infused in right SN of rat		i. Ameliorates decrease in density of DA receptors (D1 and D2) in SN and hippocampus.

(*continued on next page*)

Table 1 (*continued*)

Disorder	Model System	Lycopene's effective doses, dosing route, Time	Neuroprotective attributes
		0.5 ml/100 g b.w; Orally; 60 days post-surgery	ii Ameliorates decrease in density of GABA receptor in SN and hippocampus. (Zabihollah and Mohammad, 2015)
	6-OHDA-challenged PC-12 cells	0.1 mM; In culture medium; 24 h	i. Ameliorates OS by elevating the activities of SOD, CAT, GST, GPx and GSH level, and depleting MDA level. ii. Scavenges free radicals and improves antioxidant potential of the cell. iii Rescues from cell death and apoptosis. (Srivastava and Dua, 2015)
	Haloperidol-induced orofacial dyskinesia in rats	5 and 10 mg/kg; Orally; 21 days	i. Attenuates haloperidol-induced impaired muscle co-ordination, motor activity, grip strength and orofacial dyskinetic movements. ii. Replenishes DA, 5-HT, 5-Hydroxyindoleacetic acid and nor-epinephrine levels in NCP. iii. Ameliorates OS by reducing MDA and nitrite level and by elevating GSH level in NCP. iv Ameliorates IS by reducing the levels of TNF-α, IL-1β and IL-6 in NCP. (Datta et al., 2016)
	Wistar rat	4 mg/kg; i.p.; Two dose	Reduces cerebral infarct size and volume. (Hsiao et al., 2004)
Huntington's disease (HD)	3-NP treated Wistar rats	5 and 10 mg/kg; Orally; 14 days	i. Alleviates 3-NP-induced cognitive impairment. ii Ameliorates redox potential in NCP and hippocampus by increasing the level of total GSH, reduced GSH and GST. (Kumar and Kumar, 2009)
	3-NP treated Wistar rats	2.5, 5 and 10 mg/kg; Orally; 14 days	i. Alleviates 3-NP-induced decrease in locomotor activity. ii. Ameliorates OS in cortex, NCP and hippocampus by reducing MDA and nitrite levels, and restoring SOD and CAT activity. iii Restores activity of mitochondrial complex-I, II and IV, and ameliorates mitochondrial redox activity in same regions. (Kumar et al., 2009)
	3-NP treated Wistar rats	10 mg/kg b.w.; Orally; 15 days	i. Ameliorates 3-NP-induced locomotor behaviour and memory deficits. ii. Restores activity of mitochondrial complex-II, -IV and –V impaired by 3-NP in NCP. iii. Ameliorates mitochondrial redox activity, increase in levels of ROS, nitrite and lipid peroxidation and reduction in activity of mitochondrial SOD in NCP. iv. Ameliorates reduction in mitochondrial total, low molecular weight thiols and protein thiols level in NCP. vi Prevents swelling of mitochondrial and attenuates cytosolic caspase-3 level in NCP. (Sandhir et al., 2010)
	3-NP treated Wistar rats	25 mg/kg; Orally; 14 days	i. Increases 3-NP-induced decrease in body weight. ii Ameliorates 3-NP-induced anxiolytic and depression-like behaviour. (Jain and Gangshettiwar, 2014)
Focal/Global Cerebral Ischemia (CI)	Sprague-Dawley rat	5 and 20 mg/kg b.w.; Orally; 15 days prior to surgery	24h after surgery: i Improves neurological behavioural deficits, reduces cerebral infarct size. ii. Ameliorates OS by reducing MDA level, NO level and activity of iNOS, and by elevating activity of SOD and CAT. iii Upregulates mRNA expression of HIF-1α and Bcl-2 in hippocampus. (Wei et al., 2010a,b)
	Mongolian gerbil	5 mg/100 g feed; 1.5–2.0 months (Treated till 1st/3rd/7th day post-surgery)	i. Increases Bcl-2 expressions in hippocampus in all treated groups. ii. Decreases caspase-3 activity after 7 days of surgery. iii Increases activity of SOD after 1 and 3 days of surgery. (Fujita et al., 2013)
	C57BL/6 mice	20 mg/kg; I.p.; 7 successive days prior to surgery	72h after surgery: i. Improves motor neurological score. ii. Increases number of viable neurons and prevents apoptosis in CA1 region of hippocampus. iii. Ameliorates OS by reducing ROS and increasing GSH level. iv Upregulates the expression of nuclear and total Nrf2, and cytoplasmic HO-1 protein. (Lei et al., 2016)
	Wistar rats	6 mg; Orally; 14 days prior to surgery	Compared to naked LYC, nano-liposome-LYC more efficiently: i Increases LYC level in brain and reduces cerebral infract size, and improves neurobehavioural deficits. iii. Ameliorates OS by decreasing the level of MDA, NOX-2 and HO-1, and increasing the level of SOD, CAT and GSH. iv. Ameliorates nitrosative stress by decreasing the level of NO, iNOS and nNOS. v. Ameliorates IS by reducing the expression of IL-6 and STAT3 phosphorylation. v Lowers accumulation of iron and ferritin due to increased expression of FPN1 by suppressing the expression of hepcidin, a regulator of FPN1. (Zhao et al., 2018a)

Abbreviations: Aβ, amyloid beta peptide; ROS, reactive oxygen species; BDNF, brain-derived neurotrophic factor; OS, oxidative stress; MDA, malondialdehyde; CAT, catalase; SOD, superoxide dismutase; GSH, glutathione; IS, inflammatory stress; TNF-α, tumour necrosis factor alpha; IL, interleukin; APP, amyloid precursor protein; APPsw, swedish mutant form of human - APP; H_2O_2, hydrogen peroxide; $CuCl_2$, cupric chloride; AChE, acetylcholinesterase; TGF-β, transforming growth factor beta; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; mPTP, mitochondrial permeability transition pore; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; MMP, mitochondrial membrane potential; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; OHDA, hydroxydopamine; DA, dopamine; NCP, striatum; GPx, glutathione peroxidase; TH, tyrosine hydroxylase; MPP+, 1-methyl-4-phenylpyridinium; mt, mitochondria; SN, substantia nigra; GABA, gamma-aminobutyric acid; PC-12, pheochromocytoma 12 cell line; GST, glutathione S-transferase; i.p., intraperitoneal; 3-NP, 3-Nitropropionic acid; NO, nitric oxide; iNOS, Nitric oxide synthases; hypoxia-inducible factor 1-alpha; CA-1, cornu ammonis; HIF-1α, hypoxia-inducible factor 1-alpha; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; NOX-2, NADPH oxidase 2; STAT3, signal transducer and activator of transcription 3; FPN1, Ferroportin 1.

mitochondrial dysfunctions (Fig. 1).

3.2. Lycopene in Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder with motor behavioral abnormalities resulting from depleted dopamine levels in the striatum due to the death of dopamine synthesizing neurons in substantia nigra (SN) region of midbrain (Dauer and Przedborski, 2003; Balestrino and Schapira, 2020). Oxidative stress (Saravanan et al., 2006; Paul et al., 2018), mitochondrial dysfunctions (Schapira et al., 1989; Chandra et al., 2019), and inflammation (McGeer et al., 1988) are among the unanimously reported pathophysiologies of PD.

Several studies in animal and cellular models have reported neuroprotective potential of lycopene in ameliorating the pathophysiological processes of PD. Administration of lyophilized tomato powder in mice model of PD ameliorates striatal levels of dopamine and its metabolites (Suganuma et al., 2002). As lycopene is the most abundant carotenoid of tomato, the observed neuroprotective role of dried tomato powder in PD mice is surmised to be due to its high lycopene content. Lycopene has been reported to ameliorate motor behavioural abnormalities as well as cognitive impairment in mice models (Kaur et al., 2011; Liu et al., 2013; Prema et al., 2015; Man and Bi, 2018). Accordingly, it is found that lycopene can replenish the levels of dopamine as well as its metabolites in SN and striatum of PD mice (Suganuma et al., 2002; di Matteo et al., 2009; Man and Bi, 2018) and ameliorate the density of dopamine receptors in SN (Zabihollah and Mohammad, 2015). Amelioration of the cognitive impairment in PD mice by lycopene (Kaur et al., 2011; Liu et al., 2013) has been identified to be due to an increase in the activity of AChE (Kaur et al., 2011). Studies in toxin-induced dyskinesia in rat model revealed promising neuroprotection by lycopene in improving motor abnormalities, replenishing the levels of several neurotransmitters, including dopamine, serotonin, 5-hydroxyindoleacetic acid, and nor-epinephrine in striatum. Further, lycopene elevates the level of the anti-oxidant molecule GSH, and reduces the levels of malondialdehyde, nitrite, and inflammatory markers including tumour necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 in striatum (Datta et al., 2016). Further molecular studies identify that the compound rescues cells from Parkinsonian toxin-induced cell death, enhances cell viability and prevents apoptosis (Prema et al., 2015; Yi et al., 2013; Srivastava and Dua, 2015), thereby prevents loss of tyrosine hydroxylase (TH)-positive neurons (Liu et al., 2013). Lycopene has also been reported to reduce α-synuclein level and attenuates loss of TH-positive dopaminergic neurons in mice brain (Liu et al., 2013). Since accumulation of Lewy bodies, which comprises of α-synuclein (Spillantini et al., 1997), and loss of TH-positive neurons are hallmark pathologies of PD, the anti-Parkinsonian potential of lycopene is promising. In addition, lycopene has been reported to reduce the levels of apoptotic markers, including caspase 3, 8 and 9, Bcl-2, and cytochrome *c* (Prema et al., 2015; Man and Bi, 2018).

The dopaminergic neuroprotection by lycopene may be attributed to amelioration of oxidative stress, inflammation, and mitochondrial functions, as reported in several studies (Prema et al., 2015; Srivastava and Dua, 2015; Kaur et al., 2011; Yi et al., 2013; Datta et al., 2016). It has been reported that lycopene ameliorates activities of the mitochondrial complexes, morphological aberrations, membrane potentials (Kaur et al., 2011; Yi et al., 2013), as well as maintains mitochondrial DNA copy number and transcript levels (Yi et al., 2013). The anti-inflammatory potential of lycopene has been investigated in rat model of dyskinesia (Datta et al., 2016). The growing evidence suggests that lycopene confers protection against oxidative stress in three ways: first, it has been found to be a potent free radical scavenger in cellular model of PD (Srivastava and Dua, 2015), second, it elevates the levels of GSH in striatum (Kaur et al., 2011), and third, it increases the activities of several cellular anti-oxidant enzymes, including SOD, CAT, and glutathione peroxidase in animal and cellular models of PD and dyskinesia (Kaur et al., 2011; Prema et al., 2015; Srivastava and Dua, 2015; Datta et al., 2016).

Thus, the neuroprotective role of lycopene in animal and cellular models of PD and dyskinesia are promising, and the compound has multi-faceted roles (Table 1; Fig. 2). These include anti-oxidant, anti-inflammatory and anti-apoptotic potentials, and amelioration of mitochondrial structure and functions. Thus, lycopene confers protection to dopaminergic neurons, maintains neurotransmitter homeostasis, which ultimately ameliorates motor and non-motor behavioural abnormalities in PD (Fig. 2).

3.3. Lycopene in Huntington's disease

Huntington's disease (HD), also called Huntington's chorea, is an autosomal dominant genetic neurodegenerative disorder, and is classically associated with progressive emotional, psychiatric, and cognitive impairments (Pandey et al., 2009; Bates et al., 2015). As revealed from studies in animal models, lycopene has neuroprotective potentials in HD, and ameliorates several of the pathophysiological processes involved in the disease. Oral administration of lycopene in HD models ameliorates cognitive impairments and memory deficit, psycho-motor impairments and loss of weight (Kumar and Kumar 2009; Kumar et al., 2009; Sandhir et al., 2010; Jain and Gangshettiwar, 2014). Lycopene has been found to prevent mitochondrial swelling and reduce caspase-3 level in striatum (Sandhir et al., 2010), and is thereby suggested that the observed amelioration of behavioural abnormalities by lycopene may be due to its potential in preventing mitochondrial dysfunctions and apoptosis. Further investigations on the molecular pathophysiologies reveal that lycopene ameliorates oxidative stress in different brain regions including striatum and hippocampus (Kumar and Kumar, 2009; Kumar et al., 2009; Sandhir et al., 2010). These include amelioration of redox homeostasis, increasing GSH levels, and decreasing ROS, protein thiol and nitrite levels (Kumar and Kumar, 2009; Kumar et al., 2009; Sandhir et al., 2010). Importantly, lycopene has been reported to restore activities of mitochondrial complexes in the striatum (Kumar et al., 2009; Sandhir et al., 2010). Thus, studies in animal models reveal that lycopene prevents oxidative stress, mitochondrial dysfunctions and maintains cellular redox homeostasis, and thereby prevents apoptosis and neurodegeneration in HD (Fig. 3a). This ameliorates cognitive functions, memory deficits, and psycho-motor behavioural abnormalities (Table 1). Further, the established anti-inflammatory potential of lycopene may also confer neuroprotection in HD, although no study has been undertaken to elucidate the same.

3.4. Lycopene in Cerebral Ischemia

Brain ischemia or Cerebral Ischemia (CI) refers to the condition when there is an insufficient flow of blood to the brain, causing oxygen-glucose deprivation which leads to cerebral hypoxia culminating to the death of brain tissue, cerebral infarction and stroke (Flynn et al., 2008; Lee et al., 2018). The pathophysiologies associated with neurodegeneration in CI include apoptosis, oxidative and nitrosative stress, excitotoxicity and inflammation (Borah et al., 2013; Mazumder et al., 2014; Veenith et al., 2016; Lee et al., 2018). Lycopene has been reported to ameliorate behavioural abnormalities and improve motor behavioural performance (Wei et al., 2010a, b; Lei et al., 2016; Zhao et al., 2018a). Administration of the compound through oral and intra-peritoneal routes reduces infarct size and volume (Hsiao et al., 2004; Wei et al., 2010 a, b). Several studies reported that lycopene increases the number of viable neurons (Lei et al., 2016) and prevents apoptosis (Wei et al., 2010a, b; Fujita et al., 2013; Lei et al., 2016) in brain. The observed neuroprotective role of lycopene has been investigated further, and the compound was found to prevent oxidative stress and inflammation in brain of animal models of CI (Wei et al., 2010a, b; Fujita et al., 2013; Lei et al., 2016; Zhao et al., 2018a). Lycopene prevents both oxidative and nitrosative stress by reducing levels of nitric

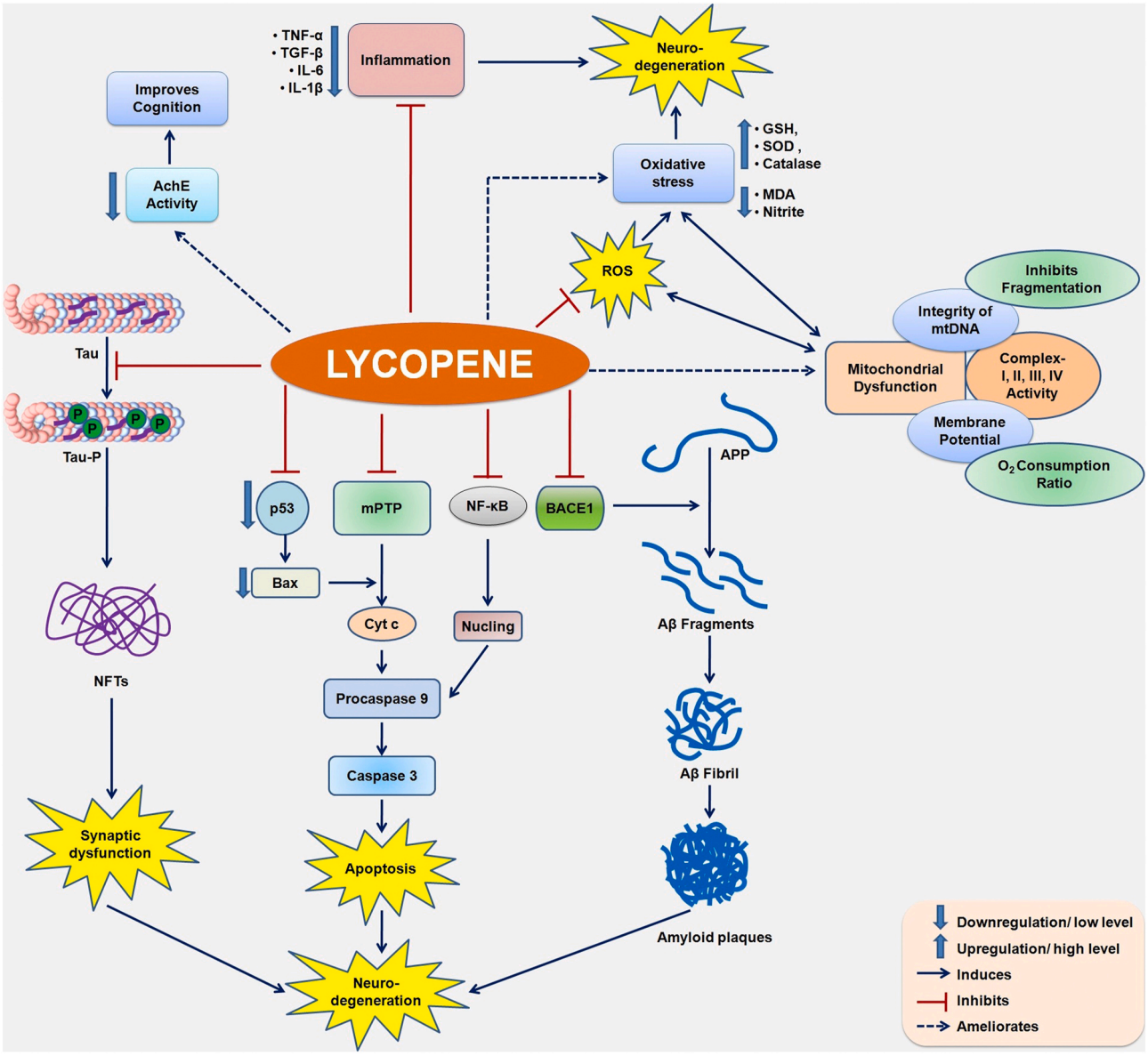

Fig. 1. Schematic illustration of the mechanisms of neuroprotection by lycopene in Alzheimer's disease (AD): Lycopene confers neuroprotection in AD by (i) ameliorating cognitive impairments by decreasing AChE activity, (ii) attenuating oxidative stress by inhibiting lipid peroxidation, scavenging ROS, and increasing the levels of SOD, CAT, and GSH, (iii) improving mitochondrial structure and function by inhibiting its fragmentation and swelling, ameliorating MMP, protecting mtDNA, and preventing inhibition of complex-I, –II, –II and -IV, (iv) attenuating neuroinflammation by inhibiting production of inflammatory mediators, including NF-κB, TNF-α, TGF-β, IL-1β, and IL-6, (v) preventing mitochondria-dependent apoptotic cell death by inhibiting the production of apoptotic proteins (p53, Bax) and reducing the release of cytochrome *c* from mitochondria, and most importantly, (vi) preventing amyloid plaques formation by inhibiting BACE1-mediated formation of Aβ, and (vii) inhibiting formation of NFTs by preventing Tau hyperphosphorylation. *Aβ, amyloid beta peptide; NFTs, neurofibrillary tangles; AChE, acetylcholinesterase; MDA, malondialdehyde; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GSH, glutathione; MMP, mitochondrial membrane potential; mPTP, mitochondrial permeability transition pore; mt, mitochondria; TNF-α, tumour necrosis factor alpha; TGF-β, transforming growth factor beta; IL, interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; Cyt c; cytochrome c; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; BDNF, brain-derived neurotrophic factor; APP; amyloid precursor protein; BACE, beta secretase.*

oxide (NO) through inhibiting inducible nitric oxide synthase (iNOS) and neuronal NOS (nNOS) activity (Wei et al., 2010a, b; Zhao et al., 2018a), increasing GSH level (Wei et al., 2010a, b; Lei et al., 2016), and elevating the activities of SOD and CAT (Wei et al., 2010a, b; Fujita et al., 2013; Lei et al., 2016; Zhao et al., 2018a). Lycopene suppresses the expression of hepcidin and ferroportin-1 (neuronal iron exporter) (Zhao et al., 2018a), thus prevents iron and ferritin accumulation, and the resultant neurodegeneration in CI models. In view of the mentioned attributes, it reveals that the neuroprotective potential of lycopene in CI is promising (Table 1; Fig. 3b).

3.5. Lycopene in epilepsy and seizure

Lycopene has been reported to have beneficial role in epilepsy in animal models. It ameliorates oxidative stress and mitochondrial dysfunctions in cortex and hippocampus, and thereby maintains levels of neurotransmitters and confers neuroprotection in mice model of kindling epilepsy induced by pentylenetetrazol (Bhardwaj and Kumar, 2016; Kumar et al., 2016). It has the potential to replenish the level of gamma-aminobutyric acid (GABA) in brain, and thereby increase seizure latency in mice with kindling epilepsy (Kumar et al., 2016). In addition, lycopene downregulates the expression of GABA receptors in

hippocampus, ameliorate seizures and reduces neuronal death in kainic acid-induced seizures in mice (Li et al., 2019).

3.6. Lycopene in age-related neurological disorders and amnesia

Prolonged supplementation of lycopene (50 mg; 60 days) to aged CD-1 mice ameliorates aging-related aspects not only at behavioural level but also at biochemical level (Zhao et al., 2018b). Oral administration of lycopene can arrest the toxic accumulation of $A\beta_{1-42}$ in brain by decreasing APP and beta-secretase 1 (BACE1) proteins and thereby prevents cognitive dysfunction. In addition, age-related neuronal damage in hippocampus and synaptic dysfunction are ameliorated by lycopene with increase in the level of brain-derived neurotrophic factors (BDNF). The compound protects mice models from these age-related brain damages by ameliorating oxidative as well as inflammatory stress (Zhao et al., 2018b).

Lycopene pretreatment (5 and 10 mg/kg) improves the symptoms in the scopolamine-induced mice model of amnesia, which was conspicuous through an exceptional improvement in learning ability and retention of learned memory, by ameliorating the increased level of AChE in brain. Moreover, inhibition of oxidative stress and neuronal damage in cortex and hippocampus can be attributed towards these neuroprotective potentials of lycopene (Bala et al., 2015).

3.7. Lycopene in spinal-cord injury and spinal neuropathic pain

In rodent models, lycopene recovered the affected animals from locomotor impairments by reducing edema and preventing apoptosis in the injured regions of spinal cord (Zhang et al., 2016a; Hu et al., 2017; Hua et al., 2019). Lycopene prevents apoptosis at injured spinal cord developed by dorsal laminectomy and contusion at T10 in rat by ameliorating decreased expression of anti-apoptotic factor (Bcl-2), and increased expression of pro-apoptotic factors, cytosolic cytochrome C, cleaved levels of caspases and Bax (Hu et al., 2017). The compound attenuates disruption of blood-spinal cord barrier by upregulating the expression of tight junction proteins, zonula occluden-1 and claudin-5 in

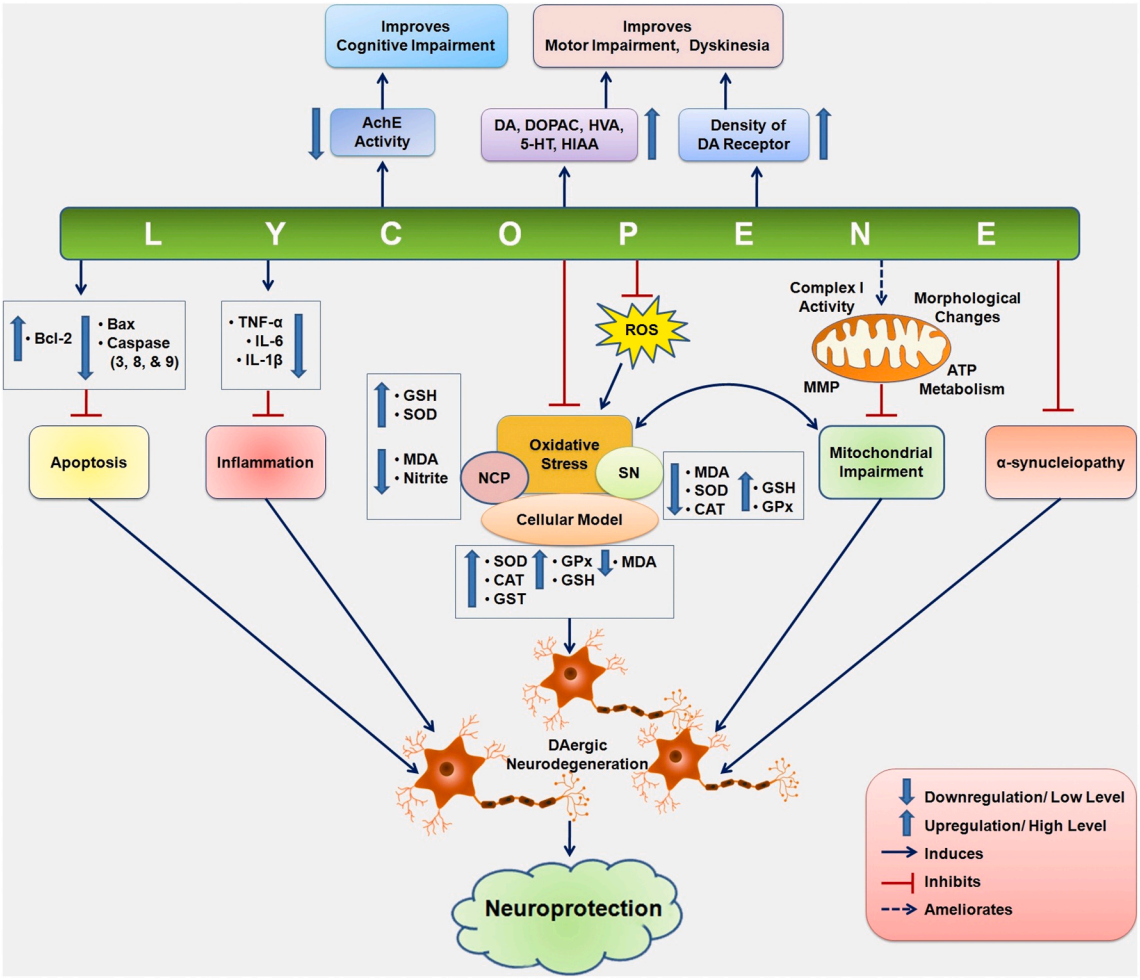

Fig. 2. Schematic illustration of the mechanisms of neuroprotection by lycopene in Parkinson's disease (PD): In PD models, lycopene (i) ameliorates motor impairment and dyskinesia by replenishing the levels of neurotransmitters and their metabolites (DA, DOPAC, HVA, 5-HT and 5-HIAA) and decrease in density of dopamine D1 and D2 receptors, (ii) improves cognitive impairments by decreasing AChE activity, (iii) attenuates oxidative stress by inhibiting lipid peroxidation, scavenging ROS and nitrate, and increasing the activity of antioxidant enzymes (SOD, CAT, GST, GPx) and the levels of antioxidant molecule (GSH), which results in functional improvement of mitochondria, (iv) attenuates neuroinflammation by inhibiting production of proinflammatory cytokines (TNF-α, IL-1β, IL-6), (v) shows anti-apoptotic property by reducing the production of pro-apoptotic (Bax, caspase 3, 8 and 9) and increasing production of anti-apoptotic factor (Bcl-2), and most importantly, (vi) prevents aggregation of the hallmark pathogenic protein of PD pathology, α-synuclein, and (vii) prevents loss of DA-ergic neurons in SN. Thus, lycopene confers DAergic neuroprotection in PD by virtue of its anti-oxidant, anti-inflammatory, anti-apoptotic properties. *DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid, AChE, acetylcholinesterase; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; MDA, malondialdehyde; GPx, glutathione peroxidase; GST, glutathione S-transferase; GSH, glutathione; SN, substantia nigra; MMP, mitochondrial membrane potential; Cyt c; cytochrome c; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; TNF-α, tumour necrosis factor alpha; IL, interleukin.*

a mice model of spinal cord injury developed by weight-dry method (Zhang et al., 2016a). Inflammatory stress is controlled by reducing the levels of inflammatory cytokines, TNF-α, IL-1β, IL-6, and IL-8, and down-regulating the expression of cyclooxygenase 2 (COX-2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and activator protein 1 (AP-1), and improving the expression of heme oxygenase-1 (HO-1) (ZZhang et al., 2016c; Hua et al., 2019). Furthermore, lycopene prevents oxidative stress in spinal cord injury models by preventing lipid peroxidation and elevating activities of SOD and CAT. Lycopene also enhances mitochondrial function at injured spinal cord by increasing mitochondrial membrane potential as well as mitochondrial biogenesis by upregulating the expression of mitochondrial transcription factor A (MTFA; Hu et al., 2017).

Partial sciatic nerve ligation model of neuropathic pain in mice shows an increased mechanical hypersensitivity. Intrathecal injection of lycopene between L5 and L6 vertebrae regulates expression of connexin 43 protein in the spinal dorsal horn and efficiently helps in proper motor coordination (Zhang et al., 2016b).

3.8. Lycopene in subarachnoid hemorrhage

In rat model of subarachnoid hemorrhage, administration of a single dose of lycopene (40 mg/kg) along with tetrahydrofuran after 2 h of surgery improves the neurological deficits in sensory-motor assessment. It attenuates cerebral edema by reducing water content in brain and prevents the disruption of BBB, which may be mediated through acid-sensing ion channels. Apoptosis of brain cells is also slowed down by reducing the level of cleaved caspase. Lycopene further ameliorates inflammatory stress by reducing the level of proinflammatory cytokines, like TNF-α, IL-1β, and intercellular adhesion molecule 1 (Wu et al., 2015).

4. Neuroprotective attributes of lycopene on organic compound-induced neurotoxicity

Owing to its potency to elicit inflammatory response, lipopolysaccharide (LPS) is used as a toxin to generate models of neuroinflammation (Batista et al., 2019). Lycopene shows promising neuroprotective effects in LPS-stimulated neuroinflammation and associated pathologies in cellular (Shyu et al., 2008; Lin et al., 2014; Wang et al., 2018a) and animal models (Lin et al., 2014; Zhang et al., 2016c; Wang et al., 2018a, 2019a), as summarized in Table 2.

In mice model, lycopene ameliorates LPS-induced motor and cognitive impairment, and depression-like behaviour (Lin et al., 2014; Zhang et al., 2016c; Wang et al., 2018a). Lycopene attenuated LPS-induced activation of microglia (microgliosis) and the resultant neuroinflammation in discrete brain regions, including cortex, striatum, and hippocampus (Lin et al., 2014; Wang et al., 2018a). Reduced

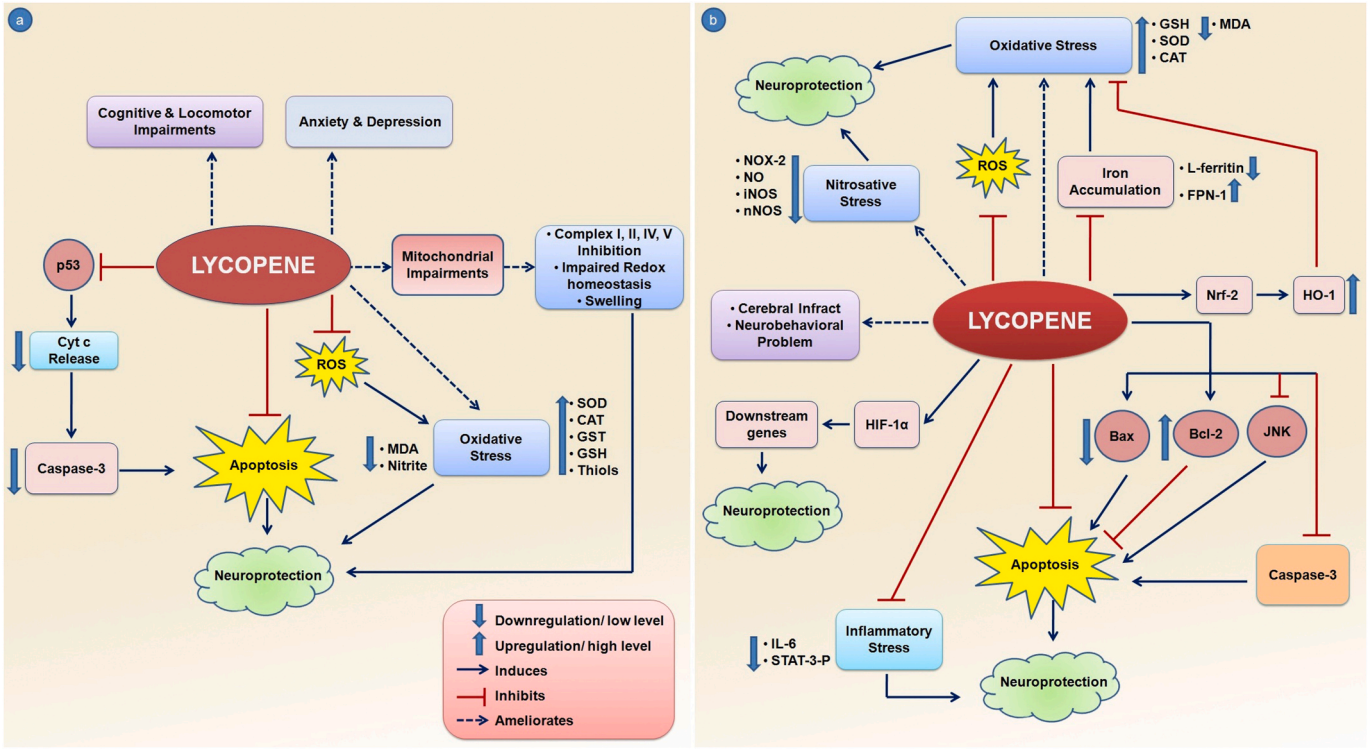

Fig. 3. Schematic illustration of the mechanisms of neuroprotection by lycopene in (a) Huntington's disease (HD) and (b) Cerebral Ischemia (CI):
In HD, lycopene confers neuroprotection by (i) ameliorating oxidative stress by scavenging ROS and nitrite, inhibiting lipid peroxidation, and increasing levels of antioxidant mediators (SOD, CAT, GST, GSH, and thiols), (ii) improving mitochondrial function by preventing swelling and inhibition of complexes (I, II, III, IV) activity, (iii) inhibiting apoptosis by preventing p53 mediated release of proapoptotic signals (Cyt *c* and caspase 3).
Lycopene confers neuroprotection in CI by (i) reducing cerebral infract size and thus ameliorates neurobehavioural deficits, (ii) ameliorating oxidative stress by scavenging ROS, inhibiting lipid peroxidation, increasing levels of antioxidant enzymes (HO-1, SOD, CAT, GSH), and preventing iron accumulation regulated by FPN1 (iii) ameliorating nitrosative stress by preventing NOS-mediated production of NO, (iv) attenuating inflammation by preventing STAT-3 phosphorylation-mediated production of IL-6, (v) inhibiting apoptosis by modulating pro-apoptotic (Bax, JNK, and cleaved caspase 3) and anti-apoptotic (Bcl-2) signals, and (vi) downstream genes of neuroprotection mediated by HIF-1α.
ROS, reactive oxygen species, MDA, malondialdehyde; Nrf-2, nuclear factor erythroid 2–related factor 2; HO-1, heme oxygenase-1; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GST, glutathione S-transferase; GSH, glutathione; Cyt c; cytochrome c; IL, interleukin; NOX 2, NADPH oxidase 2; NO, nitric oxide; iNOS, inducible nitric oxide synthase; nNOS, neuronal NOS; FPN1, ferroportin-1; HIF1α, hypoxia-inducible factor 1-alpha; STAT3, signal transducer and activator of transcription 3; JNK, c-Jun N-terminal kinases; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2.

Table 2
Protective effects of lycopene on toxins and high-lipid diet induced anomalies in brain.

Factor	Model system	Lycopene's effective doses, dosing route, Time	Neuroprotective attributes
Lipopolysaccharides (LPS)	Primary cultured microglia	10 and 20 μM; In culture medium; 30 min prior to 24 h on LPS	Ameliorates increased production of IL-1β, TNF-α and NO by Inhibiting of ERK1/2. (Shyu et al., 2008)
	Primary cultured microglia of mice/rat; murine BV2 microglial cell	5, 10 or 20 μM; In culture medium; 30 min prior to 24 h on LPS	Mitigates inflammation in microglia by: i Reducing the expression COX-2, iNOS and IL-6, and reducing production of NO. ii. Attenuating DNA binding capacity of NF-κB and AP-1. iii. Inducing the expression of HO-1 protein. iv. Increasing phosphorylation of AMPKα (Thr^{172}) and its upstream molecular regulators, LKB1 (Ser^{428}) and CaMKII (Thr^{286}) and translocated from cytoplasm to nucleus. Lin et al. (2014)
	ICR mice	10 mg/kg; i.p.; 3 days	i. Ameliorates LPS-induced motor impairment. ii Attenuates LPS-induced activation of microglia in striatum, cortex and hippocampus. (Lin et al., 2014)
	ICR mice	60 mg/kg; Orally; 7 days	i. Ameliorates depression-like behaviour. ii. Ameliorates inflammatory stress by decreasing the expression of IL-6, IL-1β and TNF-α in the hippocampus. iii Reduces expression of HO-1 in hippocampus. (Zhang et al., 2016c)
	C57BL/6J mice	0.03% (w/w); With rodent chow; 35 days pretreated	i. Suppresses LPS-induced accumulation of $A\beta_{1\text{-}42}$ peptide in cortex and hippocampus by down-regulating the expression of APP and BACE1, and by upregulating ADAM10, and thus ameliorates cognitive impairments. ii. Prevents microgliosis by down-regulating expression of IBA-1 in cortex. iii. Ameliorates OS by elevating GSH level, and increasing SOD and CAT activity in hippocampus. v Ameliorates inflammatory stress in hippocampus by down-regulating the expression of iNOS, COX-2, IL-1β and MMP9, and elevating expression of IL-10. (Wang et al., 2018a)
	BV2 microglial cells	50 μM; In culture medium; 8 h prior to 12 h on LPS	i. Down-regulates the expression of IBA-1 and COX-2, nuclear/cytoplasmic NF-kB and pIκB/IκB. ii. Increases the expression of pJNK/JNK, pERK1/2/ERK1/2, p38/p38 and pAKT/AKT ratios, and nuclear/cytoplasmic Nrf2 ratio. iii Reduces intracellular ROS generation, and upregulates expression of HO-1 and NQO1. (Wang et al., 2018a)
	C57BL/6J mice	0.03% (w/w); Orally; 35 days	i. Reduces the number of degenerated neurons in cortex and hippocampus. ii. Elevates mRNA expression of neurotrophic factors, BDNF, NGF, NT-3 and NT-4 in cortex and hippocampus. iii. Suppresses hippocampal synaptic dysfunction by upregulating the expression of synaptic proteins, SNAP-25 and PSD-95. iv. Ameliorates insulin resistance by activating AKT and GSK3β, elevating expression of Gluts (*Glut1*, *Glut3*, and *Glut4)*, and restoring expression of PTP1B in hippocampus. v. Ameliorates mitochondrial dysfunction through elevating the decreased expressions of complex I, II, III and IV. vi. Ameliorates OS in brain by up-regulating the expressions of HO-1 and NQO1. vii Ameliorates neuroinflammation by down-regulating the expression of TNF-α, IL-1β, IL-6, p-IκB, p-NFκB, iNOS and COX-2. (Wang et al., 2019a)
Trimethyltin (TMT)	Primary cultured rat hippocampal neurons	1 μM; In culture medium; 2 h prior to 24 h on TMT	i. Rescues from TMT-induced loss of cell viability. ii. Prevents apoptosis by inhibiting release of cytochrome *c* and activation of caspase 3. iii. Ameliorates OS by reducing production of intracellular and mitochondria derived ROS. iv Prevents opening of mPTP, and improves MMP. (Qu et al., 2011b)
Colchicine	Wistar rats	5 mg/kg; Orally; 21 days post-surgery	i. Ameliorates memory impairment, and increases AChE activity in cortex and hippocampus. ii. Ameliorates OS by reducing MDA and nitrite levels, elevating GSH, and activity of SOD, CAT in cortex and hippocampus. iii. Restores activities of mitochondrial complex-I, –II, –III and -IV in cortex and hippocampus iv. Ameliorates inflammatory stress by reducing the level TNF-α and IL-6 in cortex and hippocampus. v Attenuates the increased activity of caspase-3 in cortex and hippocampus. (Prakash and Kumar, 2013)
Ethanol	Primary cultured human astroglial cells	1 μM; In culture medium; 3.5 h	Ameliorates ethanol-induced depletion in the level of NAD(H). (Guest et al., 2015)
Monosodium glutamate	Albino Wistar rats	10 mg/kg bw/day; Orally; 28 days	i. Ameliorates OS by reducing the level of MDA and activities of GST, CAT and SOD, and increasing level of GSH in brain. ii. Ameliorates increase in activity of AChE in brain. iii Down-regulates expression of Bax and upregulates Bcl-2. (Sadek et al., 2016)
Formaldehyde	Wister rat		i. Ameliorates OS in brain by reducing MDA level and SOD activity, and by elevating CAT activity and GPx level.

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Table 2 (*continued*)

Factor	Model system	Lycopene's effective doses, dosing route, Time	Neuroprotective attributes
		10 mg/kg b.w; Orally; 84 days	ii. Elevates BDNF level, and prevents neurodegeneration in cortex and hippocampus. iii Replenishes levels of dopamine, noradrenaline and adrenaline in brain. (Ahmed et al., 2016)
Hydrogen peroxide (H_2O_2)	Human SH-SY5Y neuroblastoma cells	2.0 and 4.0 μmol/L; In culture medium; 2 h prior to 24 h on H_2O_2	i. Ameliorates OS by decreasing levels of intracellular ROS, and increasing activities of SOD and CAT. ii. Prevents depolarization of the MMP, and opening of mPTP. iii. Rescues loss of cell viability, down-regulates cleaved caspase 3 activity, and prevents neuronal apoptosis. iv. Upregulates expression of Bcl-2 and down-regulates Bax in mitochondrial fraction. v. Expression of cytochrome *c* is downregulated in cytoplasmic fraction and upregulated in mitochondrial fraction. vi Suppresses the translocation of AIF from mitochondria to nucleus as the expression of AIF is upregulated in mitochondria and downregulated in nucleus. (Feng et al., 2016)
D-galactose	CD-1 mice	50 mg/kg bw/day; With feed; 56 days	i. Reduces accumulation of $A\beta_{1\text{-}42}$ in brain by decreasing APP and BACE1 proteins, and thus ameliorates cognitive impairments. ii. Rescues D-galactose-induced neuronal damage in hippocampus. iii. Increases the level of BDNF in hippocampus. iv. Ameliorates OS by restoring GSH, SOD and GPx activities, and upregulates expression of antioxidant enzymes (HO-1 and NQO1), and reduces MDA level, in hippocampus. v. Ameliorates inflammatory stress by suppressing the expression of IL-1β, TNF-α, and COX-2 in hippocampus. vi Inhibits astrogliosis and microgliosis by suppressing over expression of GFAP and IBA-1 respectively in hippocampus. (Zhao et al., 2017)
Tert-butyl hydroperoxide (t-BHP)	Primary cultured mouse cerebral cortical neurons	2 and 4 μM; In culture medium; 4 h prior to 24 h on t-BHP	i. Prevents loss of cell viability, and promotes expression of NGF, EGF, BDNF, and VEGF in neural stem cells. ii. Rescues loss of cell viability and prevents neurite damage by increasing the expression of synaptic proteins, synaptophysin and PSD-95. iii. Ameliorates OS by decreasing intracellular ROS generation, increasing reduced GSH level and GSH/GSSG ratio. iv. Prevents t-BHP-induced loss of MMP. v. Inhibited mitochondria-mediated apoptotic pathway by decreasing expression of cleaved caspase 3, Bax and cytochrome *c*, while increasing Bcl2. vi Stimulates anti-apoptotic pathway by increasing the level of phosphorylated PI3K and expression of Akt proteins. (Huang et al., 2018, 2019)
Bisphenol A	Albino rats	10 mg/kg/b.w.; Orally; 42 days	i. Ameliorates cognitive impairment and increases AChE activity in hippocampus. ii. Ameliorates OS in hippocampus by increasing the level of GSH and decreasing MDA. iii. Prevents apoptosis in hippocampus by ameliorates upregulated expression of Bax and caspase-3, and dwnregulated Bcl-2 in hippocampus. iv. Elevates the level of BDNF in hippocampus by upregulating TrKB, MAPK, ERK1/2, CREB. (El Morsy and Ahmed, 2020)
Dextran sulfate sodium (DSS)	C57BL/6 mice	50 mg/kg b.w/day; With feed; 40 days	i. Alleviates anxiety and depression-like behaviour, and elevates BDNF level in cortex and CA3 region of brain. ii. Inhibits DSS-induced degeneration of neurons in cortex and CA3 region of brain. iii. Reduces IS by ameliorating overexpression of IBA-1, TNF-α, IL-1β, TLR-4, and iNOS in cortex and CA3 region of brain. iv Ameliorates structural impairments at synapse by elevating the expression of PSD-95 in cortex and hippocampus. (Zhao et al., 2020)
Manganese	Sprague-Dawley rats	10 mg/kg bw/day; Orally; 20 days	i. Ameliorates OS by reducing MDA, and increasing GST and GSH levels ii Attenuates increase in AChE activity, and morphological changes in astrocytes. (Lebda et al., 2012)
Methylmercury (MeHg)	MeHg-challenged cultured rat cerebellar granule neurons	10 μM; In culture medium; 2 h prior to 12 h on MeHg	i. Rescues from MeHg-induced loss of cell viability. ii. Ameliorates OS by reducing production of intracellular and mitochondria derived ROS. iii. Prevents opening of mPTP. iv. Improves MMP, and intracellular ATP level. v. Ameliorates dysfunctions of mitochondrial complex –III and -IV. vi Maintains mtDNA copy numbers and mtRNA transcript levels. (Qu et al., 2013)
Cadmium (Cd)	Kunming mice	5 mg/kg; Orally; 21 days	i. Abrogates Cd-induced upregulated transcription of autophagy-related genes (ATG) in hippocampus (ATG3, ATG4B, ATG5, ATG7, ATG9A, ATG9B, ATG13, ATG14, ATG16-2 and beclin1). ii. Abrogates Cd-induced increased transcription of Akt1, MAPK1 and PRKAs. iii. Inhibition of same ATGs were consistent with TH22 hippocampal cell lines. iv. Prevents Cd-induced disruption of Ca-homeostasis in hippocampus by increasing Ca^{2+}-ATP_{ase} activity and decreasing release of $Ca2^{+}$ from ER. Similar finding also observed in TH22 hippocampal cell lines. v. Ameliorates OS by upregulating activities of GPx, SOD, T-AOC and CAT, and decreasing levels of GSH, MDA and H_2O_2 in hippocampus. vi Rescues TH22 hippocampal cell lines from Cd-induced loss of cell viability. (Zhang et al., 2017)

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Table 2 (*continued*)

Factor	Model system	Lycopene's effective doses, dosing route, Time	Neuroprotective attributes
Aluminum	Wistar rat	4 mg/kg/day; Orally; 90 days	i. Increases hippocampal co-efficient, and ameliorates cognitive impairment. ii. Improves neuronal count in hippocampal CA1 and CA3 regions. iii. Ameliorates OS by decreasing levels of ROS, MDA, 8OHdG, and by increasing activity of SOD and elevating GSH level in hippocampus. iv. Prevents apoptosis in hippocampal neurons by down-regulating the expression of p53, Bax, cytosolic cytochrome *c* and cleaved caspase 3, and by upregulating expression of Bcl-2. v. Ameliorates inflammatory stress by down-regulating expression of IL-1β, IL-6 and TNF-α in hippocampus. vi. Upregulates the expression of HO-1, NQO1, GCLC and SOD1 in hippocampus. vii Prevents transport of Nf-κB p65 from cytoplasm to nucleus. Increases expression of nuclear Nrf2. (Cao et al., 2019)
Diet-induced anomalies in neurons	Sprague Dawley rat	11, 22, 44 mg/kg bw/day; Orally; 21 days	i. Ameliorates serum lipid profile. ii. Reduces expression of APP and Bax, and upregulates Bcl-2 in CA1 region of hippocampus. iii Restores the number and morphological anomalies of pyramidal cells in hippocampus. (Zeng et al., 2009)
	High-fat diet fed Sprague-Dawley rats	4 mg/kg/day; Orally; 21 days	i. Ameliorates serum lipid profile. ii. Improves cognitive impairments. iii Prevents the reduction in dendritic spine density in hippocampal CA1 neurons. (Wang et al., 2016)
	Sprague-Dawley rats	25, 45, 65, 85 mg/kg/day; Orally (1 ml/day); 28 days	Ameliorates hyperlipidemia-induced: i Abnormal lipid profile of brain by decreasing the level of total cholesterol, LDL-C and triglyceride, and the level of cerebral LDL-receptor and NGF. ii. OS and inflammation by reducing the levels of oxidized LDL, and proinflammatory cytokines, including IL-1, TNF-α in brain. iii. Anomalous neurochemical status by increasing the level of GABA and serotonin, and decreasing the levels of glutamic acid, dopamine and ratio of glutamic acid/GABA. v. Increase in the expression of NMDA1R and dopamine D1 receptor, and decrease in the expression of $GABA_A$ and 5-HT_1 receptors. vi. Increase in the expression of pro-apoptotic factors, caspase 3 and Bax, and decrease in the expression of Bcl-2. vii Decrease in the number of neurons in CA1 and CA3 regions of hippocampus. (Yang et al., 2018)
	High cholesterol diet fed Sprague-Dawley rats	25, 45, 65, 85 mg/kg/bw/day; Orally; 28 days	i. Ameliorates serum lipid profile, and cerebral lipid profile by restoring the levels of total cholesterol, triglyceride, LDL-C and free fatty acids. ii. Ameliorates cerebral inflammation by reducing the levels of inflammatory mediators, including IL-1, IL-6, TNF-α, as well as oxidized-LDL. iv. Reduces the levels of VEGF and VCAM-1, while elevates Claudin-5, in hippocampus. v Prevents morphological changes and apoptosis of neurons in the CA1 and CA3 regions. (Wang et al., 2018b)
	Western diet fed C57BL/6J mice	0.03% (w/w); Along with feed; 70 days	i. Lowers body weight and ameliorates serum lipid profile. ii. Improves lipid profile of brain by decreasing expression of FAS and PPARγ, increasing phosphorylation of ACC, increases expression of lipid transport proteins, ApoE and LDLr. iii. Attenuates insulin resistance in brain by decreasing the phosphorylation of IRS-1 (Ser_{307}) and increasing the phosphorylation of IRS-1 (Tyr_{612}). iv. Improves cognitive impairment. v. Improves expression of BDNF, NGF, NT-3 and NT-4 in hippocampus. vi. Improves length and width of the postsynaptic density in the hippocampus by upregulating the expression of SNAP-25 and PSD-95. vii. Increases expression of Glut4 and suppresses PTP1b in brain. viii. Ameliorates inflammatory stress by reducing microgliosis (IBA-1), down-regulating expression of inflammatory mediators, Cox-2, iNos and IL-6 in hippocampus. Wang et al. (2019b)

Abbreviations: IL, interleukin; TNF, tumor necrosis factor; NO, nitric oxide; ERK, extracellular signal-regulated kinase; COX; cyclooxygenase; iNOS, nitric oxide synthases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; AP, activator protein; HO, heme oxygenase; NQO1, NAD(P)H dehydrogenase [quinine] 1; AMPK, 5′ adenosine monophosphate-activated protein kinase; CaAMKII; Ca^{2+}/calmodulin-dependent protein kinase II; ICR, institute of Cancer research; i. p. intraperitoneal; Aβ, amyloid beta peptide; APP, amyloid precursor protein; BACE, beta-secretase; ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; OS, oxidative stress; GSH, glutathione; SOD, superoxide dismutase; CAT, catalase; IBA1, ionized calcium binding adaptor molecule; MMP9, matrix metallopeptidase 9; JNK, c-jun N-terminal kinase; NRF2, nuclear factor erythroid 2; ROS, reactive oxygen species; BDNF, brain-derived neurotrophic factor; NT, neurotrophin; NGF, nerve growth factor; SNAP, synaptosomal-associated Protein; PSD, postsynaptic density; GSK3β, glycogen synthase kinase 3 beta; Glut, glucose transporters; AChE, acetylcholinesterase; MMP, mitochondrial membrane potential; mPTP, mitochondrial permeability transition pore; MDA, malondialdehyde; NAD, nicotinamide adenine dinucleotide; GST; glutathione S-transferases; GPx, glutathione peroxidise; AIF, apoptosis inducing factor; GFAP; glial fibrillary acidic protein; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor; CREB, cAMP response element-binding protein; IS, inflammatory stress; TLR, toll like receptor; mt, mitochondria; H_2O_2, hydrogen peroxide; T-AOC, total antioxidant capacity; 8OHdG, 8-Oxo-2′-deoxyguanosine; GCLC, glutamate cysteine ligase.

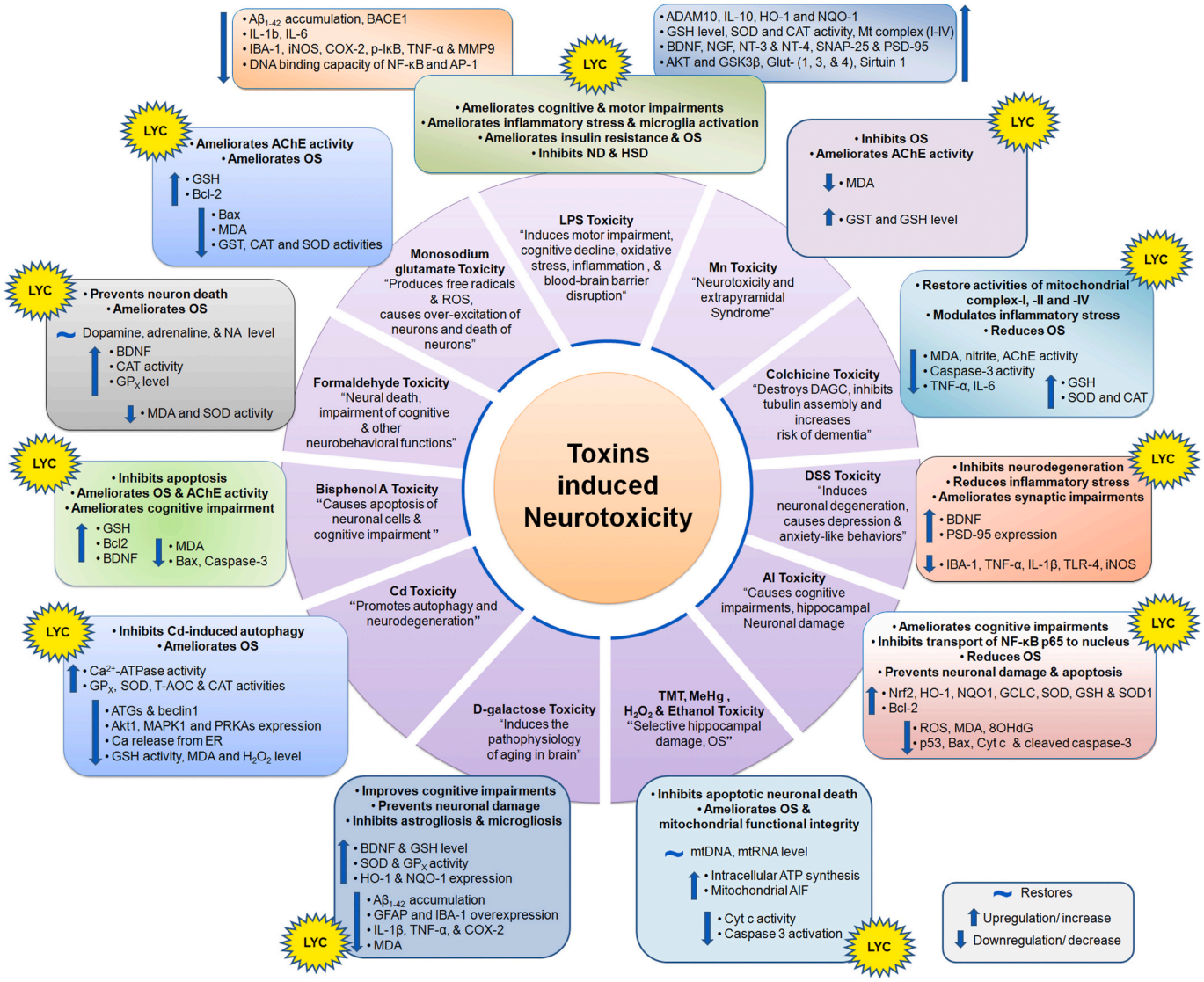

Fig. 4. Therapeutic attributes of lycopene in different toxin-induced neurotoxicity. Up arrow and down arrow indicate upregulation or increase level and downregulation or decreased level, respectively. The ~ symbol indicates restoration or amelioration of different molecules or activity as neuroprotective response. *LYC, lycopene; ND; neurodegeneration; HSD, hippocampal synaptic dysfunction, mtDNA, mitochondrial DNA; TMT, trimethyltin; AIF, apoptosis inducing factor; BDNF, brain-derived neurotrophic factor; ER, endoplasmic reticulum; GFAP, glial fibrillary acidic protein; Iba1, Ionized calcium binding adaptor molecule 1; MAPK1, mitogen-activated protein kinase 1; PRKAs, protein kinase AMP-activated catalytic subunits; Nrf2, nuclear factor erythroid 2–related factor 2; HO-1, heme oxygenase-1; NQO1, NAD(P)H dehydrogenase [quinone] 1; GCLC, glutamate-cysteine ligase catalytic subunit; 80HdG, 8-Hydroxydeoxyguanosine; APP; amyloid precursor protein; BACE1; beta-secretase 1; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; MMP-9, matrix metallopeptidase 9, TNF-α, tumor necrosis factor-α; AP-1, activator protein 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; NT-3/4, Neurotrophin-3/4; SNAP-25, synaptosomal associated protein 25; PSD-95, post-synaptic density protein 95; GSK3β, glycogen synthase kinase 3 β; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; SOD, superoxide dismutase; CAT, catalase; MDA, malondialdehyde; GPx, glutathione peroxidase.*

expression of microglia activation marker (IBA-1) and associated proinflammatory mediators such as IL-6, IL-1β, TNF-α, iNOS, COX-2 and matrix metallopeptidase 9, and elevated expression of anti-inflammatory markers (IL-4, IL-10, IL-13) are the underlying mechanisms of lycopene-mediated attenuation of microgliosis and neuroinflammation (Shyu et al., 2008; Lin et al., 2014; Wang et al., 2018a, 2019a). Lycopene mediated regulated expression of proinflammatory cytokines might be linked with the induction of HO-1 through activation of AMP-activated protein kinase (AMPK) pathway (Lin et al., 2014; Zhang et al., 2016c). Studies reported that lycopene reduces LPS-stimulated formation of toxic $A\beta_{1-42}$ peptide in cortex and hippocampus regions of mice brain by suppressing the expression of APP and BACE1, and elevating ADAM10 expression and thus ameliorates cognitive impairments (Wang et al., 2018a). ADAM10 is an α-secretase which influences APP processing in the non-amyloidogenic pathway resulting in the formation of soluble APP which is non-toxic to neurons (Karran et al., 2011). Neuroinflammation is often associated with oxidative stress and mitochondrial dysfunction and *vice versa*, which is consistent with LPS-mediated toxicity. Lycopene significantly ameliorates LPS-induced oxidative stress by increasing the level of enzymatic and non-enzymatic antioxidant markers, and by reducing the level of lipid peroxidation in discrete brain regions (Lin et al., 2014; Zhang et al., 2016c; Wang et al., 2018a, 2019a). Also, lycopene scavenges intracellular ROS and restores the expression of respiratory chain complexes in mitochondria which are impaired upon LPS exposure in mice brain (Wang et al., 2019a). Furthermore, the compound prevents LPS-induced neuronal damage as well as synaptic dysfunction by increasing the expression of neurotrophic factors and synaptic proteins in hippocampus

(Wang et al., 2019a).

Apart from LPS, lycopene also confers protection against other organic compounds, including trimethyltin (TMT), colchicine, glutamate, dextran sulfate sodium (DSS), D-galactose, tert-butyl hydroperoxide (t-BHP), bisphenol A, formaldehyde, hydrogen peroxide, and ethanol-induced neurotoxicity (Table 2, Fig. 4). These compounds display a wide array of neurological complications, including behavioural abnormalities (cognitive and psychomotor), proteinopathy (Aβ accumulation), mitochondrial dysfunction, synaptic dysfunction, and neurodegeneration, mainly by influencing the expression and/or activity of several oxidative and inflammatory stress markers, and apoptotic markers (Prakash and Kumar, 2013; Zhao et al., 2017; El Morsy and Ahmed, 2020).

Cognitive impairment induced in rodents by colchicine, D-galactose and bisphenol A is reported to be ameliorated upon lycopene treatment which is linked to its ability either to restore AChE activity (Prakash and Kumar, 2013; El Morsy and Ahmed, 2020) or reduced accumulation of toxic Aβ (Zhao et al., 2017). Lycopene also ameliorates psychometric behaviour (anxiety and depression) in DSS-exposed mice possibly by elevating the level of BDNF in cortex and hippocampus (Zhao et al., 2020).

Thus, it is revealed that lycopene efficiently shields neurons from insults of all these compounds by i) scavenging intracellular and mitochondrial ROS, ii) reducing lipid peroxidation level, iii) increasing the level of GSH, iv) ameliorating activities of SOD and CAT, and v) influencing the expression of antioxidant enzymes. These perhaps result in restoration of mitochondrial functional parameters in discrete brain regions (Prakash and Kumar, 2013; Feng et al., 2016; Huang et al., 2018, 2019).

By reducing the expression of proinflammatory mediators (IL-6, IL-1β, TNF-α, and COX-2), lycopene ameliorates inflammatory stress induced in colchicine and D-galactose challenged rodents (Prakash and Kumar, 2013; Zhao et al., 2017). The compound also prevents D-galactose-induced astrogliosis- and microgliosis-mediated neurotoxicity in hippocampus by suppressing the over-expression of glia-activation markers (Zhao et al., 2017).

Lycopene prevents apoptosis of neuronal cells induced by bisphenol A, TMT, hydrogen peroxide, t-BHP and monosodium glutamate by decreasing the expression of pro-apoptotic factor (Bax), increasing the expression of anti-apoptotic factor (Bcl-2), and by inhibiting the release of cytochrome *c* and preventing activation of caspase-3 (Qu et al., 2011b; Sadek et al., 2016; Feng et al., 2016; Huang et al., 2018, 2019; El Morsy and Ahmed, 2020).

Most significantly, lycopene attenuates neuronal degeneration in cortex and hippocampus of rodents induced by formaldehyde (Ahmed et al., 2016) and DSS (Zhao et al., 2020), which is attributed to its efficient antioxidant and anti-inflammatory properties.

5. Neuroprotective attributes of lycopene on metal-induced neurotoxicity

Lycopene exerts neuroprotective effects from neurotoxic insults induced by metals, such as mercury, cadmium, and aluminium in cellular and animal models (Fig. 4; Qu et al., 2013; Zhang et al., 2017; Chao et al., 2019) by ameliorating oxidative stress (Fig. 4; Lebda et al., 2012; Qu et al., 2013; Zhang et al., 2017; Chao et al., 2019).

Occupational exposure to aluminium has been implicated in neurological diseases (Yokel, 2000). In rat model, lycopene attenuates aluminium chloride-induced cognitive impairments and lesions in hippocampus by ameliorating the levels of oxidative as well as inflammatory stress markers (Chao et al., 2019). Aluminum-induced loss of neurons in the cornu Ammonis 1 (CA1) and CA3 regions of hippocampus is prevented by lycopene through inhibiting caspase-mediated apoptosis (Chao et al., 2019).

Zhang et al. (2017) reported that lycopene prevented cadmium-induced hippocampal dysfunction by inhibiting autophagy and oxidative stress, and by improving neuronal calcium signaling in animal as well as cellular models (Table 2).

Neurotoxic potency of methylmercury is linked to its ability to hamper mitochondrial function (Qu et al., 2013). Owing to its antioxidant potential, lycopene prevented methylmercury-induced toxicity to cerebellar granule neurons by improving membrane potential and complexes activity of mitochondria, and by preventing the opening of mitochondrial permeability transition pore (Qu et al., 2013).

Although manganese is an essential nutrient and a cofactor of several enzymes, its elevated level in brain is associated with serious neurotoxicity (Zhang et al., 2011). Lycopene protected neurons in rat brain from toxic insults of manganese by ameliorating oxidative stress and AChE activity (Lebda et al., 2012). Furthermore, manganese-induced morphological changes in astrocytes of cerebral cortex, which are of typical Alzheimer type II pattern (Hazell et al., 2006), are ameliorated by lycopene treatment (Lebda et al., 2012).

6. Neuroprotective effect of lycopene on diet-induced anomalies in neurons

Our group convincingly demonstrated that chronic exposure to high-cholesterol diet caused AD as well as PD-like pathologies in mice not only at behavioural level but also at the biochemical level (Paul et al., 2015, 2017a, 2017b; Paul and Borah, 2017). Consumption of HLD is associated with an abnormal increase in lipids (hyperlipidemia), including total cholesterol, low density lipoprotein cholesterol (LDL-C) and triglyceride and other fatty acids, in serum and brain (Yang et al., 2018; Wang et al., 2018b, 2019b). Lycopene treatment significantly restores hyperlipidemia-induced abnormal lipid profile in the brain (Zeng et al., 2009; Yang et al., 2018; Wang et al., 2018b, 2019b). In HLD-fed mice, lycopene restores brain lipid profiles by AMPK activation mediated inactivation of acetyl-CoA carboxylase (ACC1; Wang et al., 2019b), the enzyme which catalyzes the rate-limiting step of fatty acid synthesis (Abuelheiga et al., 2001).

Studies reported that HLD-stimulated hyperlipidemia is linked with altered neurochemical homeostasis in brain at the level of neurotransmitter (Paul et al., 2017a, 2017b; Yang et al., 2018) which might lead to behavioural abnormalities. Yang et al. (2018) reported that lycopene ameliorated the levels of dopamine, serotonin, GABA, and glutamic acid by regulating the expression of their corresponding receptors in brain of HLD-fed animals (Yang et al., 2018). HLD is reported to cause cognitive impairments possibly by mediating insulin resistance or synaptic dysfunction in discrete brain regions (Wang et al., 2016, 2019b). By stimulating IRS/AKT activation and inactivating the negative regulator of insulin signaling (PTP1B), along with an increased expression of the glucose transporter (GLUT4) in brain cells, lycopene attenuates insulin resistance in HLD-fed rodents (Wang et al., 2019b). HLD-stimulated synaptic dysfunction and altered neurite outgrowths in hippocampus are prevented upon lycopene treatment, along with the elevated expression of neurotrophic factors (Zeng et al., 2009; Wang et al., 2016, 2019b). These attributes of lycopene might lead to amelioration of cognitive impairments stimulated by HLD in rodents (Wang et al., 2016, 2019b).

Furthermore, lycopene protects the brain cells from hyperlipidemia-induced inflammatory stress by reducing the levels of proinflammatory cytokines (IL-1, IL-6, TNF-α) and other inflammatory mediators (Cox-2, iNOS, and oxidized-LDL), and thereby inhibiting microgliosis (Yang et al., 2018; Wang et al., 2018b, 2019b). Lycopene supplementation prevents apoptosis by decreasing the expression of pro-apoptotic factors (Bax, caspase 3) and increasing the expression of anti-apoptotic factor (Bcl-2) which might prevent HLD-induced reduction in the number of cells in hippocampus (Table 2; Zeng et al., 2009; Yang et al., 2018; Wang et al., 2018b).

7. Concluding remarks

Treatment of neurodegenerative diseases is a global health challenge, perhaps because of the complexity of the diseases, many paradoxes, mostly practiced symptomatic therapies and lack of effective drugs. Efforts are being devoted to present new concepts on nutraceuticals owing to their pleiotropic therapeutic benefits. Based on their disease-modifying potency and limited side-effects, natural products are recruited to substitute synthetic drugs, of late. Lycopene is one such pleiotropic natural compound having ample potency to be used as a pharmaceutical alternative or as an adjunctive therapy. Due to its effective antioxidant potential, lycopene shows beneficial effects in several human diseases, including those pertaining to the nervous system. Preclinical evidences strongly supports the excellent neuroprotective potentials of lycopene which are primarily attributed to its antioxidant, anti-inflammatory, anti-apoptotic, anti-amyloidogenic, and mitochondrial boosting properties. Thus, the future of lycopene as a multifunctional neuroprotective molecule is promising since it ameliorates multiple pathways that are generally dysregulated in CNS disorders, including neurodegenerative disorders. Additionally, it exhibits a potent neuroprotective role in neurotoxic insults induced by various toxins and HLD. The promising preclinical results and limited toxicity of the molecule warrant systematic clinical trials to impose these results in human beings and to consider lycopene in curing diverse CNS diseases including neurodegenerative disorders.

Authors contribution

First three authors contributed equally.

Declaration of competing interest

None declared.

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