Neuroprotective role of Beta-asarone: A review

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INTRODUCTION

Acorus calamus (Acoraceae) also known as sweet flag in Indian traditional medicine is generally used for treatment of various ailments like cough, fever, bronchitis, inflammation, depression, tumours, haemorrhoids, skin diseases, insomnia, hysteria, epilepsy, and loss of memory (Raja et al., 2009). Asarone is a chemical compound of the phenylpropanoid class found in plants such as Acorus and Asarum. There are two isomers, α (trans) and β (cis). Alpha-asarone is potentially toxic compared to beta-asarone and hence pharmacological elucidation of beta-asarone is wide. Beta-asarone due to its blood brain barrier crossing property it is well elucidated for potential neuroprotective effect. The beneficial properties of beta-asarone are attributed to molecular pathways of endoplasmic reticulum stress, autophagy and synaptogenesis through IRE1/XBP1 ER stress pathway, mitochondrial ASK1/MKK7/JNK pathway, CaMKII/CREB/Bcl-2 expression and PERK/CHOP/Bcl-2/Beclin-1 pathways. The memory enhancing property of beta-asarone is said to be due to beclin dependent autophagy by PI3K/AKT/mTOR pathway. The aim of this review is to highlight the neuroprotective role of beta asarone in terms of neuroinflammation, apoptosis, neurogenesis and autophagy with special emphasis on two neurodegenerative disorders Parkinson’s disease and Alzheimer’s disease along with its beneficial property in elucidating synaptic plasticity and neurogenesis. Further research on toxicity and pharmacokinetics of beta-asarone are much needed to bring this potential compound into therapeutic use.

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Many studies have investigated the potential of beta-asarone in regulating ER stress and autophagy in PD rats. Beta-asarone improved HVA, Dopac-l and 5-HIAA levels and no effect was seen on DA and 5-HT levels in the striatum of the 6-OHDA induced PD rat brain. It also increased TH levels while reducing alpha-synuclein levels. Expression levels of LC3-II was down-regulated and p62 was upregulated in SN4741 cells. It was also demonstrated that beta-asarone firstly reduced expressions of pJNK and p-JNK, with incremental increase in the expression of Bcl-2 thus inhibiting becline-1, which is said to be the major reason for inhibition of autophagy activation (Zhang et al., 2016b). Many recent studies revealed the endoplasmic reticulum (ER) stress, also a contributor for the pathogenesis of PD. A study investigated the beneficial role of beta-asarone in mitigating the PD symptoms through inhibition of transcription/mRNA levels of glucose regulated protein 78 (GRP78) and C/EBP homologus binding protein (CHOP), while decline in the expression of phosphorylated inositol-requiring enzyme 1 (p-IRE1) and X-box binding protein (XBP1) in 6-OHDA induced PD rats. This study suggested the possible anti-parkinsons effect of beta-asarone via IRE1/XBP1 ER stress pathway (Ning et al., 2016). In continuation with this another study explored protective effects of beta-asarone against ER stress and autophagy induced PD. ER stress and protein kinase RNA-like endoplasmic reticulum kinase (PERK) are seen in DA neurons of substantia nigra pars compacta (SnpC) of 6-OHDA induced PD rats. Beta-asarone and PERK inhibitor groups down-regulated GRP78, p-PERK, CHOP and Beclin-1, while up-regulated Bcl-2, strongly suggests the ability of beta-asarone in regulating ER stress-autophagy through inhibition of PERK/CHOP/Bcl-2/Beclin-1 pathway in protecting the 6-OHDA induced PD rats (Ning et al., 2019b). This protective effect of beta-asarone inhibiting autophagy was seen to be improved when co-administered with l-dopa. Decreased expression of beclin-1 and LC3B and increased expression of p62 was seen along with the decreased formation of autophagosomes in beta-asarone and the co-administered groups compared to 6-OHDA group. These data indicates the autophagy-inhibiting capacity of beta-asarone is said to potentiate when co-administered with l-dopa (Huang et al., 2015b). Further beta-asarone and l-dopa co-administration increased L-dopa, DA, DOPAC, HVA and 5-HT levels. Improvement in the MAO-B, COMT, TH and DAT levels suggested enhancement in the behavioural abilities of PD rats (Huang et al., 2017). Inactive myocyte enhancer factor 2D (MEF2D) and alpha-synuclein degradation has established asso-
ciation with macroautophagy, chaperone-mediated autophagy (CMA) and heat-shock protein 70 (HSP 70). Beta-asarone treatment down regulated alpha-synuclein, beclin-1 and LC3B, while upregulated HSP70, TH, MEF2D, HSC70, LAMP-2A and p62 levels in the mesencephalon of the PD rat brains. The protective action of beta-asarone is said to be mediated through HSP70/MAPK/MEF2D/Beclin-1 pathway (Huang et al., 2016a). Another study demonstrated the enhanced L-dopa, DA, DOPAC in striatum, reduced neuron-specific enolase (NSE), P-glycoprotein (P-gp), Zonula occludens-1 (Z-1), occluding, actin and claudin-5 in cortex of the co-administered group. Also small precrevices were seen in between the capillary endothelial cells at the intracellular tight junctions indicates that the treatment improved the BBB permeability of L-dopa, thus reducing the brain injury (Huang et al., 2016b). Co-administration also accelerated the conversion of L-dopa to DA through modulating COMT activity and DA metabolism (Huang et al., 2014). Co-administration also promotes DA generation through Aromatic amino acid decarboxylase (AADC) and also prevents DA metabolism via COMT (Huang et al., 2015a).

Alzheimer’s disease

Aβ(1-42) administration results in impairment of cognitive functions (Geerts et al., 2018) and neuronal apoptosis (Han et al., 2017; Takada et al., 2020). Aβ (1-42) induces c-Jun N-terminal Kinase (JNK), resulting in the phosphorylation, and down-regulation of Bcl-2, Bcl-w, JNK and caspase-3 activation, indicating the neuronal apoptosis. Which was significantly reversed with the treatment of beta-asarone in Aβ (1-42) induced neuronal apoptosis in rats (Li et al., 2010) thereby improving cognitive functions (Geng et al., 2010). Beta-asarone treatment in hippocampus of APP/presenilin-1 (PS1) transgenic mice decreased number of senile plaques, autophagosomes. Expression of A beta-40, A beta-42, APP, LC3A/B and beclin-1 was reduced along with upregulation of p62. Reports showed that the neuroprotective effects of beta-asarone is due to inhibition of autophagy in APP/PS1 transgenic mice (Deng et al., 2020). Many reports confirm the close association of autophagy in the metabolism of A beta and Tau proteins, while the autophagy dysfunction resulting in the impaired clearance of these proteins. Beta-asarone treatment has reduced cytotoxicity and improved cell proliferation in a dose dependent manner. Further inhibited Sp1 DER-beta Gal improving the cell senescence. APP, PS1, Abeta, BACE1 and P62 expression downregulated and SYN1, BECN1 and LC3 were upregulated followed by beta-asarone treatment in PC12 cell AD model. The protective action is by inhibiting the amyloid-beta and improving autophagy mechanism (Wang et al., 2020). Dementia or impairment in learning and memory is a major hallmark of Alzheimer’s disease. Beta-asarone treatment significantly improved the learning and memory abilities in the APP/PS1 transgenic mice. The treated mice also showed reduction in Ache and Amyloid beta levels while p-mTOR and p62 got up-regulated and AKT, Berlin-1 and LC3B got downregulated, along with decrease in the number of autophagosomes indicating the ability of beta-asarone in improving learning and memory via beclin dependent autophagy by PI3K/AKT/mTOR pathway (Deng et al., 2016) in Aβ1-42 treated PC12 cells (Xue et al., 2014). In APP/PS1 double transgenic mice and in NG108 cells, beta asarone-treatment improved learning and memory through upregulation of SYP and GluR1 expression hence antagonized the neurotoxic effects of amyloid beta (Liu et al., 2016).

Receptor of advanced glycation end products (RAGE) is a cell surface receptor, also referred to as pattern recognition receptor because of the heterogeneity of its diversified ligands reported to magnify the deleterious effects of the amyloid-beta peptide (Yan et al., 2009). In the pathogenesis of amyloid beta induced Alzheimer’s disease, RAGE acts as co-factor, interacting with the amyloid-beta peptide in the neurons, neuroglial cells like microglia and some vascular cells fastening and worsening the deleterious effects on neurons and synapses (Yan et al., 2012). The interaction of amyloid beta and RAGE expression follows positive feedback system (Lue et al., 2005). Beta-asarone treatment significantly improved survival of APP/PS1 mice neurons, by reducing A beta deposition, down-regulating A beta 1-42 levels in cortex and hippocampus further it also down regulated RAGE, indicating the A beta mitigating activity of beta-asarone via RAGE downregulation (Yang et al., 2016a).

Calcium/calmodulin-dependent protein kinase II (CaMkII), also termed as tau Kinase proved to be involved in memory formation (Oka et al., 2017). Dysregulation of CaMkII leads to impaired calcium signalling, loss of neurons, loss of neurons at synapses and diminished memory, which are also the characteristics of dementia associated Alzheimer’s disease (Ghosh and Giese, 2015). Interestingly an increase in the CaMkII/CREB/Bcl-2 expression was observed after beta-asarone treatment in the AβPP/PS1 mice, eventually reduced neuronal apoptosis and improved cognitive functions (Wei et al., 2013). PC12 cells on beta-asarone treatment improved the survival rates of the cells.
along with upregulation of the transcription of anti-apoptotic protein Bcl and down-regulation of the transcription of pro-apoptotic protein Bax (Liang et al., 2015).

Neurometabolic modulations like microgliosis apparently worsen the pathogenesis of AD by provoking the expression of cytokines like IL-1β, IL-6 and TNF-α (Kinney et al., 2018; Wang et al., 2015). Investigations have reported inhibition of these inflammatory cytokines, decreased expression of beclin-1, Lc3B and increased expression of Bcl-2 on beta-asarone treatment in Aβ25-35 induced cells. Suggesting the neuroprotective effect of beta-asarone elicited through ameliorating inflammation and autophagy by Bcl-2/Beclin-1 pathway (Chang and Teng, 2015).

Apoptosis signal-regulating kinase 1 (ASK1), member of MAP3K family Mitochondria-mediated cell death process and mitochondrial pathway ASK1/MKK7/JNK is also elucidated in the neuro-protective effect of beta-asarone against A beta induced neurotoxicity. P-ASK1, p-MKK7, p-JNK, Bax, Bad expressions were downregulated on beta-asarone treatment, these activities are enhanced by ASK1 si RNA (Zou et al., 2011).

A recent clinical interventional study treated a two groups of AD patients one with memantine, the other group with memantine, beta-asarone and tenuigenin. Before and after treatment assessments of Mini-mental state examination (MMSE) showed higher average nad Activities of daily living (ADL) and Clinical dementia rating scale (CDR) showed lesser averages compared to memantine group. The results were indicative of the efficacy of beta-asarone in overcoming cognitive impairment along with memantine and tenuigenin (Dong et al., 2018). Beta asarone inhibits TNF-alpha, IL-1beta, down-regulates AQP4 expression thus protects astrocytes and mitigate the symptoms of AD (Yang et al., 2017).

**Synaptic plasticity and neurogenesis**

Alpha and Beta-asarone are the major constituents of the AC plant, are investigated for their neuroprotective properties at molecular level by many researchers. Dizocilpine (MK-801) treated mice showed increased pro-inflammatory markers release including IL-6, IL-1beta, i-Nos, COX-2 which was mitigated by beta-asarone including the alleviation of expression of hippocampal synaptophysin (SYP) (Liu et al., 2016) and postsynaptic density protein 95 (PSD95) suggesting the improvement in cognitive functions via modulating the excess release of pro-inflammatory cytokines and microglial activation (Xiao et al., 2019). While beta-asarone from Acorus tatarinowii schott, increased lead induced reduction in the spine density in CA1 region of hippocampus and dentate gyrus, also increased the expression of NR2B, Arc and Wnt7a suggesting the neuroprotective effect through Arc/Arg 3.1 and Wnt pathways by regulating synaptogenesis (Yang et al., 2016b). Intragastric administration of beta-asarone in the asenescence-accelerated prone 8 (SAMP8) mice reduced the upregulation of ROCK expression and autophagy in hippocampus, followed by restoration of synaptic loss and cognitive functions. Further ROCK2 downregulation by SiRNA suppressed the beneficial effects of beta-asarone on autophagy and synaptic proteins expression in PC12 cells damage induced by Abeta1-42. It is concluded that the prevention of synaptic loss by beta-asarone is through suppression of ROCK expression in SAMP8 mice (Chen et al., 2014).

**CONCLUSION**

Beta asarone exhibits protective role against Parkinson’s and Alzheimer’s disease via regulation of ER stress, autophagy and synaptogenesis through IRE1/XBP1 ER stress pathway, mitochondrial ASK1/MKK7/JNK pathway, CaMKII/CREB/Bcl-2 expression and PERK/CHOP/Bcl-2/Beclin-1 pathways. The memory enhancing property of beta-asarone is attributed to beclin dependent autophagy by PI3K/akt/mTOR pathway.

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**Competing / Conflict of Interest**

The authors declare that there are no conflicts of / or competing interests.

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