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# Neuroprotective role of Beta-asarone: A review

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ABSTRACT

*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. Asarone is a chemical compound of the phenylpropanoid class found in plants such as Acorus and Asarum. There are two isomers, $\alpha$ (trans) and $\beta$ (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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## 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 certain plants such as Acorus and Asarum. There are two isomers, $\alpha$ (*trans*) and $\beta$ (*cis*). Alpha-asarone is potentially toxic compared to beta-asarone and hence pharmacological elucidation of beta-asarone is wide. Beta-asarone,(2,4,5-trimethoxy-(*Z*)-1-propenylbenzene)extracted from Acorus tatarinowii Schott, has significant pharmacological effects on the central nervous system (CNS) (Sinha *et al.*, 2003). Beta-asarone can pass through the Blood brain barrier (BBB) and then enter into the

brain. The absorption, distribution, and elimination of beta-asarone are rapid and it is found in low concentrations in the body. Brain is an important organ of distribution for beta asarone (Chellian *et al.*, 2017). It is quickly excreted in urine, faeces, and bile, but the excretion efficiency in urine is the highest (Lim *et al.*, 2014).

Many researchers have elucidated the neuroprotective effects of beta-asarone targeting various pathways, while mechanistic role of the compound is wider. A study reported attenuation of neuronal apoptosis in rat hippocampus (Liu *et al.*, 2016). Some researchers opine that $\beta$-asarone could prevent A$\beta$25–35-induced inflammatory responses and autophagy and thereby produce neuroprotection (Chang and Teng, 2015; Xue *et al.*, 2014). 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 neuro degenerative disorders Parkinson's disease and Alzheimer's disease.

**Parkinson's disease**

Various Long non-coding RNAs (LncRNA) are said to play major roles in the pathogenesis of neurodegenerative disorders including Parkinson's disease (Zhang *et al.*, 2017). Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) or nuclear enriched abundant transcript 2 (NEAT2) is overexpressed along with alpha-synuclein in the neurons. MALAT1 gets upregulated in the MPTP induced PD mice and MPP+ induced SH-SY5Y cells. While MALAT1 knockdown resulted in the mitigation of MPTP induced apoptosis of DA neurons in the PD mice (Liu *et al.*, 2017). A study demonstrated Beta-asarone induced increase in the tyrosine hydroxylase cells (TH+ cells) in MPTP treated PD mice along with the number of viable cells in MPP+ treated SH-SY5Y cells. The study also showed decrease in the alpha-synuclein and MALAT1 expression in the beta- asarone treated PD mice and MPP+ induced SH-SY5Y cell lines. While MALTA1 overexpression is said to reverse these effects of beta-asarone (Zhang *et al.*, 2016a).

Both ER stress and autophagy were investigated in many studies to explore their potential devastating effects in the pathogenesis of PD. 6-OHDA induced PD rats have shown increased expression of glucose regulated protein 78 (GRP78), C/EBP homologus binding protein (CHOP) and beclin-1 and decreased expression of p62. These observations led to conclude the involvement of ER stress and ER stress induced autophagy in PD (Ning *et al.*, 2019a). In many studies' beta-asarone was investigated for its potential in combating the 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 JNK 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 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 crevices 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**

A$\beta$(1-42) administration results in impairment of cognitive functions (Geerts *et al.*, 2018) and neuronal apoptosis (Han *et al.*, 2017; Takada *et al.*, 2020). A$\beta$ (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 A$\beta$ (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 SPiDER-beta Gal improving the cell senescence. APP, PS1, Abeta, BACE1 and P62 expression down-regulated 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 A$\beta$1-42 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 heterogenicity 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 A$\beta$PP/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).

Neuroinflammatory modulations like microgliosis apparently worsen the pathogenesis of AD by provoking the expression of cytokines like IL-1$\beta$, IL-6 and TNF-$\alpha$ (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 A$\beta$25-35 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 neuroprotective 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-alfa, 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 $B$eta -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 bata-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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