INTRODUCTION

1.1. Need for the study

Huntington disease (HD) is an incurable, adult-onset, autosomal dominant inherited disorder associated with cell loss within a specific subset of neurons in the basal ganglia and cortex. HD is named after George Huntington, the physician who described it as hereditary chorea in 1872 (Huntington G., 1872). Characteristic features of HD include involuntary movements, dementia, and behavioural changes (Folstein SE., 1989).

HD is a devastating inherited neurodegenerative disorder which is characterized by weight loss, impairment of motor function, cognitive dysfunction, and neuropsychiatric disturbances. (Gupta S, Sharma B et al., 2014). HD predominantly affects striatum, cerebral cortex and other areas of the brain controlling motor coordination and memory storage (Kumar P, Kumar A et al., 2009). HD affects most commonly the basal ganglia which are a group of nerve cells at the base of the brain. The main components of the basal ganglia are the dorsal striatum comprising of caudate nucleus and putamen, ventral striatum comprising of nucleus accumbens and olfactory tubercle, globus pallidus, ventral pallidum, substantia nigra, and subthalamic nucleus (Stephanie Liou., 2010). It has been demonstrated that mitochondria are the key factors in cell survival by controlling energy metabolism, apoptosis pathways and Ca2+ homeostasis (Chan DC et al., 2006; Green DR, Kroemer G., 2004). However, along with oxidative phosphorylation mitochondria also generates reactive oxygen species that plays a dual role, harmful and beneficial to the biological systems. Beneficial in cellular signaling and intended to defend against infectious agents at low or moderate levels, and toxic at higher concentrations. When the natural anti-oxidant defensive system fails to neutralize the production of reactive oxygen species leads to oxidative stress, mitochondrial dysfunction and neuronal death (M. Valko et al., 2007).

3- Nitropropionic acid (3-NP) is an irreversible inhibitor of succinate dehydrogenase that inhibits both the Tricarboxylic acid cycle (TCA cycle) and complex II activity. Selective lesioning of the striatum occurs after administration of 3-NPA in animal models.
Pharmacological intervention in the treatment of the movement disorder of HD is aimed at restoring the balance of neurotransmitters in the basal ganglia (Bonelli RM, et al., 1990). This mitochondrial toxic agent has been reported for its spontaneous generation of bilateral striatal lesions in the brain and Huntington's disease (HD) like symptoms in the subjects. The 3-NP model has been extensively using as an experimental model for the induction of HD like symptoms in the animal studies (J. Chakraborty et al., 2014). Whereas, the management of behavioral and psychological symptoms, administrations of mood stabilizing drugs were also reported as efficacious, but there is no particular management strategy to address the cognitive dysfunction of HD patients (S. Frank 2014). So, there is a need for an alternative therapy with fewer side effects to address the symptoms of the HD.

Flavonoids (or bio-flavonoids) are the class of plant secondary metabolites, which have been found to be of substantial significance as antioxidants (Katrin S.et al., 2014). More than 4000 flavonoids have been discovered and Naringenin is one of them. Naringenin is present in citrus fruits like grapes as “naringin” in inactive form and is broken down into an active aglycone form “Naringenin” by the action of intestinal bacterial enzymes. Chemically, it is 4, 5, 7-trihydroxyflavanone. Renowned for its diverse biologic effects on animal as well as well-being, Naringenin has been found to exhibit the properties and characteristics of being used as hepatoprotective (Renugadevi J, Prabu SM., 2009) anticarcinogenic, (Ekambaram G et al., 2008) anti-oxidant, (Santos KF et al., 1999) antidiabetic, (Rayidi S, Pari L.,2011) anti-atherogenic, (Goldwasser J et al., 2011) and anti-inflammatory (Pinho-Ribeiro FA et al., 2016). Further, neuroprotective effect of Naringenin has also been reported previously in animal model of amnesia, Alzheimer's disease (Khan MB et al., 2012) and 6-OHDA model of Parkinson's disease (Zbarsky V et al .,2005) also, Naringenin supplementation has shown to restore expression of choline acetyl transferase and improvement in learning and memory.(Khan MB et al., 2012, Muthaiah VK et al., 2013) Cytokine regulation and inflammation control by Naringenin in brain via TNF-α and IL-1β have also been reported. (Hunot S et al.,1999). Naringenin treatment effectively reduced the ROS level induced by carbaryl and maintained the mitochondrial membrane potential and also increased cell survival due to Naringenin treatment.
References


