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Impact of *Emblica officinalis* Fruit Extract on ATPases System under AD-induced conditions in Albino Rat

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ABSTRACT: Alzheimer's disease (AD) is the most common neurodegenerative disease, characterized by memory loss, cognitive impairment and personality disorders. There is presently no treatment for this illness despite substantial investigation. However, recent studies have shown therapeutic qualities in *Emblica officinalis*, natural extract. The aim of this study was to evaluate the efficacy of *Emblica officinalis* fruit methanolic extract on ATPase activity in the Cerebral Cortex and Hippocampus regions of AD-induced rat brain. Male albino rats which are, 3 months old disease free and experimental animals weighing between 150±25 grams were utilized in the study. They were divided into three groups as described in the materials and methods section. Rats from different groups were sacrificed by cervical dislocation. Cerebral Cortex and Hippocampus regions were isolated and used for estimation of 3 constituents of the ATPase system at selected time intervals. The results demonstrated that the ATPase levels in both brain regions of the AD-induced rats were inhibited while they were brought back to near control levels upon continuous oral administration of *Emblica officinalis* extract on 60th day of treatment thus demonstrating that EoFM extract had reversal effects on AD induced changes in ATPae system.

Keywords: *Emblica officinalis*, Male Albino rat, D-Galactose, ATPases, Cerebral Cortex and Hippocampus.

INTRODUCTION

Neurodegenerative Disorders (NDDs) result from the specific degeneration of brain neurons, impairing their structure and function, these are, progressive nerve cell degeneration renders NDDs incurable, posing a major global health concern for aging populations. Specific NDD traits, including Alzheimer's, Amyotrophic Lateral Sclerosis, Huntington's, and Parkinson's, hinge on affected neuronal types and regions, defining each disease uniquely. Conditions like spinocerebellar ataxia and spinal muscular atrophy, characterized by neuron loss and diverse pathologies (Cunnane, 2020), contribute to the staggering reality that 60-70% of the world's population is affected (WHO, 2022). The "Alzheimer's Association in India" study forecasts 4.1 million cases in India, set to double by 2035, with over 5,000 patients expected in Maharashtra and Uttar Pradesh by 2026. WHO foresees a near-doubling of cases every 20 years. Each year, around 10 million new dementia cases are diagnosed, 60% in low- and middle-income countries, affecting 5–8% of those over 60 globally. The Alzheimer's Association estimates Alzheimer's Disease, affecting the elderly, gradually impairs memory and behaviour and 82 million people will have dementia by 2030 and 152 million by 2050, incurring $300 billion in medical care costs (Alzheimer's disease International Report, 2022).

Mitochondrial dynamics are affected in a number of serious neurological disorders such as Parkinson's, Alzheimer's, and Huntington's disease. ATPases play a major role in these Neurological diseases (Song *et al.*, 2020). They use the energy released by the phosphate bond breakage to execute other biological activities. ATPases are enzymes that play critical roles in energy conservation, active transport and pH homeostasis in all known forms of life**.** Thus, ATPase is a charge-transferring complex that catalyses ATP creation by transporting ions across the membrane. Adenosine triphosphate or ATP is commonly referred to as the cell's energy currency because it plays an important role in metabolism, notably in energy transmission within cells. The molecule couples energy of exergonic and endergonic processes, allowing chemical reactions that are energetically unfavorable to occur. The role of ATP in different pathways of cellular metabolism such as Glycolysis, Krebs cycle and electron transport chain are well established. ATP is continuously recycled inside the nervous system to supply energy for the active movement of Sodium and Potassium ions, resulting in differential electrical charge between the inside and outside of neurons. Apart from the aforesaid qualities, ATP serves three important functions: It is released as an excitatory neurotransmitter between inter neurons and from the inter neurons to the motor neurons.

Finally, ATP may operate as a sensory mediator, from epithelial sources to the intrinsic sensory nerve terminals in the peripheral nervous system. ATPases are enzymes that catalyse the breakdown of ATP into ADP and a free phosphate ion and this dephosphorylation event generates energy, which the enzyme uses to drive additional chemical reactions that would not have occurred otherwise. During diseased conditions, this ATPase system is much effected which would result in several behavioral changes.

In view of the significance and multiple roles of ATPases, the present study was focused to test the reversal potential of Experimentally AD-induced pathological conditions in Albino rat model since the ATPase system plays important role in AD progression and up regulation of Na^+/K^+, Mg^{2+} and Ca^{2+} signaling distorts learning and memory systems.

MATERIAL AND METHODS

A. Preparation of Emblica officinalis Fruit Methanolic (EOFM) Extract

The Methanolic extract was prepared by immersing 500 grams of the crude powder in 2 liters of 80% methanol for 24 hours. Afterward, the resulting filtrate was separated and used for extraction in a Soxhlet apparatus, which was repeated three times with the remaining residue. The mixture was then filtered to separate the filtrate and residues. The total filtrate was concentrated using a Soxhlet, while the complete residues were collected and lyophilized following the method described by Mathew and Subramanian (2014) to obtain a powder. The extract underwent further freeze-drying and was stored at -20°C until needed, with a yield of 30% w/w.

B. Procurement and Maintenance of Experimental Animals

In this study, male Albino rats of the Wister Strain, approximately 3 months old and free from disease, were utilized as experimental subjects. These rats, weighing around 150±25 grams, were procured from Sri Venkateswara Traders Pvt. Limited, Bangalore. They were housed in polypropylene cages within the department's animal facility, where environmental conditions were maintained at a temperature of 28±2°C, with a 12-hour light and 12-hour dark photoperiod, along with a relative humidity of 75%. The rats had access to standard pellet diet (Hindustan Lever Ltd., Mumbai) and water ad libitum. The various rat groups, excluding the control group, received treatment with D-Gal and EoFM extract as outlined below. All doses were administered in the morning, specifically between 8 to 9 A.M., taking into consideration the rats' altered activity patterns between night and daytime. Ethical guidelines for animal protection and welfare, as outlined in CPCSEA438/01/a/cpcsea/dt.17.07.2001 (resolution No.09/(i)/a/CPCSEA /IAEC/ SVU/ ZOO/ KY/Dt.19-04-2012), were strictly adhered to throughout the study. Prior to experimentation, the rats were allowed to acclimatize to the laboratory conditions for a period of 10 days. Subsequently, the rats were randomly divided into three groups, each consisting of twelve individuals. The various rat groups, excluding the control group, received treatment with D-Gal and EoFM extract as outlined below. All doses were administered in the morning, specifically between 8 to 9 A.M., taking into consideration the rats' altered activity patterns between night and daytime.

C. Grouping of Animals

Rats received an intraperitoneal injection of D-Galactose at a dosage of 120 mg per kilogram of body weight.

D. Induction of Alzheimer's Disease to Rat

The use of D-Gal is seen to be a very successful way for developing AD symptoms in animal models in the current work despite the fact that researchers have established a number of alternative methods to generate AD in animal models. According to a technique developed by Zhang *et al.* (2005) and refined by Peera and Yellamma (2015); Alzheimer's Disease was induced in rats. D-Gal administered intraperitoneally to rats causes symptoms such abnormal biochemical marker changes, retrograde neural modifications and memory problems that are quite similar to those of Alzheimer's Disease.

Group -I	**Control Rat.**
Group -II (AD-I)	Rats received an intraperitoneal injection of D-Galactose (120 mg/ kg body weight) up to 60th day of experiment (Zhang *et al.*, 2005; Peera and Yellamma 2015).
Group-III (AD-I + EoFME-T)	AD-Induced rats, simultaneously administered (oral) with EoFM extract (200 mg/kg body weight) up to 60th day (Vasudevan and Parle 2007).

RESULTS AND DISCUSSION

ATPase SYSTEM. In the present study, changes in the levels of different biochemical parameters related to energy metabolism, such as Na^+/K^+ATPase, Mg^{2+} ATPase and Ca^{2+} ATPase enzyme activity were measured in Cerebral Cortex and Hippocampus regions of control and experimental rat brain.

Na^+ and K^+-ATPases:

EFFECT ON 30th DAY: On the 30th Day of the experiment, the activity levels of Na^+ and K^+-ATPases in control group of rats were higher in the Hippocampus (29.88mol/mg protein/h) than in the Cerebral Cortex (28.90 mol/mg protein/h). On the other hand, the Hippocampus experienced the greatest decrease in Na^+ and K^+-ATPase levels (-37.69%) in AD-induced rats, followed by the Cerebral Cortex (-32.072%). Oral administration of EoFM extract to AD-induced rats showed significant elevation in both

selected brain regions, including the Hippocampus (22.23%) and Cerebral Cortex (19.903%) when compared to AD-Induced rat.

EFFECT ON 60th DAY: A similar trend was observed on the 60th Day of experimentation, with rats recording elevations in Na^+ and K^+ ATPases in the Hippocampal (33.1 moles of Pi formed/mg protein/h) region, followed by the Cerebral Cortex (31.9 moles of Pi formed/mg protein/h). The AD-induced group, on the other hand, demonstrated a significant decrease in Na^+ and K^+-ATPase levels in both regions, with maximum decrease in Hippocampus (-56.283%) than Cerebral Cortex (-48.209 percent). The administration of EoFM extract to rats with induced Alzheimer's disease effectively reversed the cognitive impairment caused by AD in the brain. Notably, there was a significant increase in Na+ and K+-ATPase levels, with a rise of 46.077% in the HP region and 39.001% in the CC region.

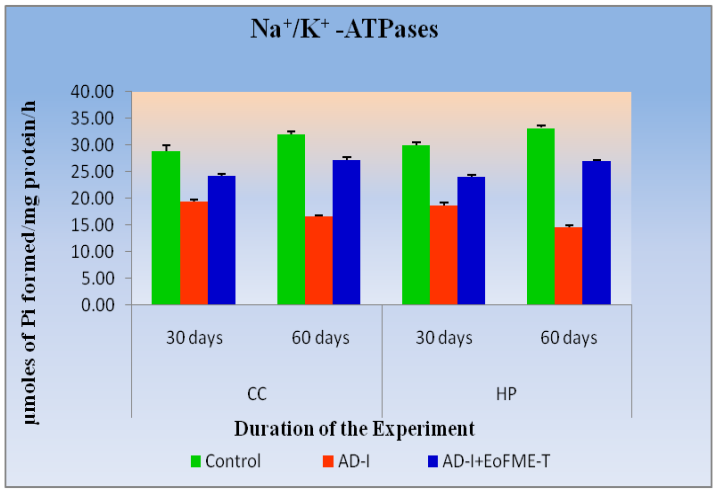

Fig. 1. Graph showing changes in Na^+/K^+ ATPase content (µ moles of inorganic phosphate formed/mg protein/hr) in selected brain regions on particular experimentation days.

Mg^{2+}-ATPases:

Effect on 30th Day: On the 30th Day of the experiment, the results on Mg^{2+}-ATPase levels in control rats, revealed that maximum activity levels in CC region (30.74 moles of Pi formed/mg protein/h) than in HC region (29.73 moles of Pi formed/mg protein/h). Contrary to this, there was drastic drop in Mg^{2+}-ATPase levels by 47.531% in the HP region and by 29.65% in the CC region of AD-Induced rat brain. Surprisingly, oral administration of EoFM extract to AD-induced rats revealed elevated levels in both regions, again the Hippocampus showing the greater increase (45.13%), followed by the Cerebral Cortex (14.281%).

Effect on 60th Day: On the 60th Day, both the control and experimental groups showed very similar patterns to that of the 30th Day where Cerebral Cortex of control rats had registered higher levels of Mg^{2+}-ATPases i.e. 33.93 (moles of Pi formed per mg of protein/h) and the Hippocampal with 30.48 (moles of Pi formed per mg of protein/h). However, in the AD-Induced rat group, even though both the regions showed lowered levels of Mg^{2+}- ATPases, the Hippocampus regions showed more lower levels (-52.001%) than the Cerebral Cortex region (-47.531%). Again, rats treated with EoFM extract, on the other hand, had higher levels of Mg^{2+}-ATP ases in the Hippocampus (53.911%) than in the cerebellum (27.317%), which were noticed to be close to that of the control levels.

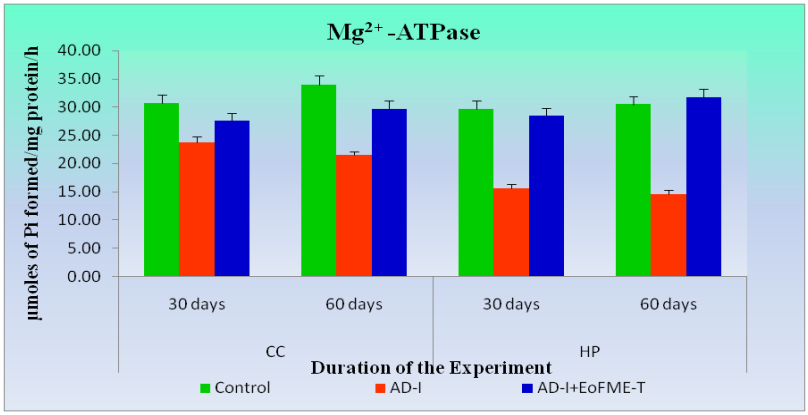

Fig. 2. Graph showing changes in Mg2+ATPases (moles of inorganic phosphate formed/mg protein/hr) in selected regions of brain from the Control and Experimental groups on specific experimentation days.

Ca^{2+}-ATPases:

Effect on 30th Day: The Ca^{2+}-ATPase activity levels were highest in the HP region (19.66 moles of Pi

formed/mg protein/h) than in the Cerebral Cortex (16.61 moles of Pi formed/mg protein/h) in the Control group of rats. Contrary to the Control group, AD-induced rats recorded a substantial decline in Ca^{2+}-ATPase levels, as follows: Hippocampus (- 31.272%) and CC region (-30.210%). When Alzheimer's disease-induced rats were subjected to EoFM treatment, notable increases of 25.89% in the CC region and 22.634% in the HP region were observed.

Effect on 60th Day: A quite similar trend was observed on the 60th Day, on par with the 30th Day of experimentation in all groups of rats, where the Control rats exhibited maximum levels of Ca^{2+}-ATPases in the Hippocampus (17.95) when compared to the Cerebral Cortex (19.51). However, Ca^{2+}-ATPase decline was greatest in the HP (-39.98%) region of AD- induced rats, followed by the Cerebral Cortex (-42.713%). Conversely, the group with induced Alzheimer's disease that received EoFM extract exhibited significantly elevated levels of Ca^{2+}-ATPases in HP region (37.735%) compared with CC region (35.668%). From these results, it was observed that the EoFM extract-Treated group of rats showed significantly elevated levels of Ca^{2+}-ATPases in the Hippocampal region when compared to the other brain regions.

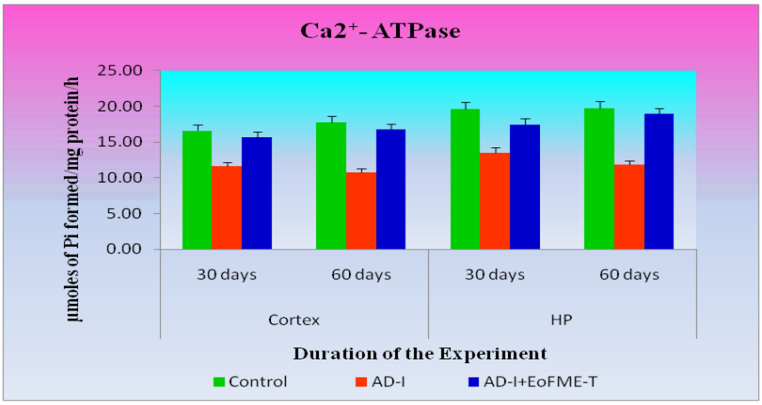

Fig. 3. Graph showing changes in Ca^{2+}ATPases (µ moles of inorganic phosphate formed/mg protein/hr) in selected brain regions from Control and Experimental groups of rats on selected days of experimentation.

DISCUSSION

The impact of *Emblica officinalis* Fruit Methanolic Extract (EoFME) on the enzymes associated with membrane transport metabolism and functions, such as Na^+/K^+, Ca^{2+} and Mg^{2+} -ATPases activity levels in specific brain regions, such as the CC and HP regions of control and experimental rats was analyzed and assessed (Pinz *et al.*, 2021). The results clearly showed that i.p. injection of D-Galactose inhibited the levels of all the 3 ATPases in both brain regions of the AD-induced rat, which could be restored to normal by continuous oral administration of EoFME to AD-Induced rats for 60 days.

By connecting ATP hydrolysis with energy release, ATPases serve a vital role in the maintenance of the ionic gradient. ATP, as a neurotransmitter and neuromodulator may have a direct influence on the release of other neurotransmitters by modifying the activities of relevant receptors (Ebanks *et al.*, 2020). Several prior evidences point to neurotransmitter release and cerebral bioenergetics as intertwined processes essential for appropriate brain function and as such Seizures, Parkinson's Disease, Alzheimer's Disease, Schizophrenia and other CNS illnesses have been linked to mitochondrial malfunction, excitotoxicity, formation of reactive oxygen species and energy crisis.

Na^+/K^+-ATPases: The observations in the present study derive strong support from several previous research reports. To name few: **1.** In ketamine-induced Schizophrenia, impaired energy metabolism, as exemplified by considerable decrease in Na^+/K^+-ATPase activity was noticed, implying an altered sodium gradient essential for the uptake of a number of neurotransmitters. **2.** A number of neurodegenerative disorders appear to have the common trait of decreased Na+/K+-ATPase function and mental illnesses (Ramalho *et al.*, 2018). **3.** Abnormalities in Na^+/K^+-ATPase activity have also been linked to Alzheimer's Disease, Seizures (Kurauchi *et al.*, 2018), Bipolar disorders (Valvassori, *et al.*, 2019), Spongiform encephalopathy and other Neuropsychiatric illnesses. Further, NKA dysfunction down-regulates the synaptic AMPA receptor, which contributes to synaptic transmission abnormalities and as a result, cognitive decline, the characteristics ageing and neurodegenerative Diseases (Vegh *et al.*, 2012).

A number of neurodegenerative disorders appear to share the common trait of decreased Na+/K+-ATPase function. It was well established that Na^+/K^+-ATPase is a membrane-bound enzyme that creates membrane potential in the CNS by active transport of sodium and potassium ions. The Na^+/K^+-ATPase maintains electrochemical gradients across the plasma membrane, which is required for signaling, secondary active transport, glutamate re-uptake and neuron excitability in animal cells. The Na^+ and K^+ ATPase which is widely expressed, has a high level of expression in the neuromuscular system and is a substantial consumer of cellular energy.

Another well-documented pathology of Alzheimer's Disease is the **Cholinergic-induced modulation of Na^+-K^+-ATPase which occurs due to** loss of cholinergic neurons. For instance, citicoline can be recovered by Acetylcholinesterase (AChE) and

Na+/K+-ATPase activity in the brain (Grimm *et al*., 2017), potentially improving memory performance and showing clinical efficacy in elderly patients with cognitive deficits, inefficient memory and early-stage AD (Kim *et al.,* 2017). Another example was that Rivastigmine, a cholinesterase inhibitor and AD medication lowers AChE activity, enhances Na^+/K^+-ATPase and Mg^{2+}-ATPase activity and improves cognitive performance in the aged rat brain (Carageorgiou *et al*., 2008). As a result, Na+/K+-ATPase is essential for AD caused by acetylcholinergic dysfunction.

Mg^{2+}-ATPases: In the present study, it was also observed that AD-Induced rats, when treated with EoFME recorded higher levels of Mg^{2+}-ATPases and that their concentration rose from the 30th Day to 60th Day and were higher than the control rats. Surprisingly, when compared to the other brain regions, the protective group (AD-I+ EoFME) rats had considerably higher levels of Mg^{2+}-ATPases in the CC region than Hippocampus. Previous studies suggested that Mg^{2+}-ATPase is a critical enzyme in phosphorylation activities and maintenance of high intracellular Mg^{2+} levels in the brains of elderly rats is essential.

In addition to this, Mg^{2+} is the most significant cofactor for Na+, K+ ATPase action. To name a few: Magnesium (Mg) is the fourth most abundant element in the body and the second most prevalent intracellular action (Volpe, 2015). Mg is a cofactor for over 300 enzymes and a critical dietary mineral that affects many metabolic reactions. As a result, this element is essential for a variety of physiological, cellular and metabolic processes. Furthermore, Mg magnesium has a neuroprotective effect on synaptic function (Wenwen *et al*., 2019). As a result, magnesium shortage has been linked to a variety of clinical illnesses ranging from indifference to insanity.

MAGNESIUM DEFICIENCY AND ALZHEIMER'S DISEASE

Previous experiments have provided substantial evidence to the effect that increasing concentration of Mg^{2+} in extracellular fluid (Mg^{2+}) causes a permanent improvement in synaptic plasticity in an in-vitro cultured hippocampus neuronal network eventually leading to improved learning and memory in experimental rats (Veronese *et al*., 2016). Thus the amount of magnesium in the diet is crucial for maintaining synaptic plasticity and declined levels, particularly in hippocampal synaptic connections have been linked to memory loss (Fan *et al*., 2017). This was further supported by recent findings in animal research which are intriguing and provide unique insights into magnesium's neuroprotective benefits such as intake of magnesium at an early stage may reduce the likelihood of cognitive decline in Alzheimer's Disease (Xu *et al*., 2014).

Furthermore, serum Mg^{2+} levels were found to be inversely related to the Global Deterioration Scale (GDS) and the Clinical Dementia Rating (CDR) in Alzheimer's patients (Cilliler *et al*., 2007). A causal relationship between decreased Mg^{2+} in Hippocampal neurons and learning impairment was also reported in old rats. Because ATP-Mg is the enzyme's true substrate, a reduction in Mg^{2+} inhibits Na^+/K^+-ATPase much more. Mg^{2+} enzyme inhibition can interfere with Mg^{2+} cellular microenvironment management as well as Mg^{2+}-dependent enzyme function (Ben Zaken *et al.,* 2020). These findings provide conclusive evidences to the current investigation where AD-induced rats were treated with *Emblica officinalis* caused substantial elevation in brain Na^+, K^+ and Mg^{2+}-ATPase activity due to its richness in bioactive constitution.

Ca^{2+}ATPase: According to the findings of the current investigation on Ca^{2+}ATPase, it was evident that when compared to the control group, Ca^{2+}-ATPases in EoFM extract-treated rats were considerably higher in all selected brain locations on both selected days. It was also worth noting that chronic D-galactose injections significantly reduced Ca^{2+}- ATPase function in AD-induced rats. The decreased activity of Ca^{2+}-ATPase shows that it was involved in Ca^{2+}-dependent quanta release of neurotransmitters, particularly in cholinergic and adrenergic neurons (Bussiere *et al.,* 2019).

In this connection, it was appropriate to cite the multifactorial biological functions of calcium such as: for healthy bones, teeth and blood: absorption of dietary vitamin B ; creation of the neurotransmitter, Acetylcholine, activation of enzymes such as pancreatic lipase; to regulate the activity of skeletal muscle, heart and many other tissues; a key signaling molecule in many physiological functions, such as synaptic transmission, production of energy, gene control, cell proliferation, membrane excitability, and plasticity.

Previous study has shown that in Alzheimer's Disease (AD), aberrant ER metabolism of proteins such as amyloid and tau increases neuronal calcium demand, resulting in ER stress (Hajieva *et al.,* 2018). Ca^{2+}-ATPase controls Ca^{2+} pump activity and intracellular calcium, which acts as a second messenger in the modulation of cellular processes and is essential for neurosecretion and release. Ca^{2+} ATPase inhibition can cause a rise in intracellular Ca^{2+} content as well as alterations in signalling pathways and cellular fluidity, which can lead to cell death. Neuronal dysfunction arises as a result of this abnormal Ca^{2+} regulation, which is a precursor to the onset and progression of severe neurodegenerative disorders such as Alzheimer's and multiple sclerosis (Mattson, 2007).

In this connection, it is worth mentioning about AD causing protein, beta- amyloid which raises cytosolic Ca^{2+}, inhibits synaptic plasticity and speeds up cell death via an L-channel-dependent mechanism. A new Ca^{2+}channel polymorphism has been linked to late-onset Alzheimer's Disease (Vingtdeux *et al*., 2008). This gene is highly expressed in brain locations such as the hippocampus, where cell death occurs early and extensively. These findings imply that Ca^{2+} channels act as a link between age-related Ca^{2+} dysregulation and signaling in neurodegenerative diseases, resulting in cell loss selectivity. The effect of changed calcium homeostasis on APP processing demonstrated that Extracellular calcium influx was found to reduce the APP/homer interaction (Vander Kant and Goldstein 2015).

Despite the fact that a vast majority of AD cases are sporadic (with no evident genetic link), 5% of all AD patients exhibit a Mendelian pattern of "Familial AD" (FAD) inheritance. FAD is connected to three genes: APP, presenilin-1 (PS1), and presenilin-2 (PS2). Presenilins are ER transmembrane proteins that have been demonstrated to influence ER Ca^{2+} dynamics via activating the SERCA pump which in turn can reduce ER stress (Krajnak and Dahl 2018). As previously stated, SERCA activation causes various PMCA isoforms and splice variants mediate the exact temporal and spatial processing of Ca^{2+} signals, as well as the re-establishment of resting Ca^{2+} levels in the nervous system. In neurons, PMCA failure is frequently under compensated, resulting in alterations in synaptic transmission, decreased excitability and eventually cell death. As people age, functional loss and decrease of PMCAs are hallmarks of dementia and mutations in PMCAs, in particular, cause neuronal damage and accelerated neurodegeneration in a variety of sensory and cognitive problems (Brini and Carafoli 2017).

Finally, the role of these ATP-ases was summarized as: Cation transport across the neuronal membrane influences the electron transport chain, biological oxidation in the mitochondria and antioxidant enzyme activities is mediated by ATPases (Jomova *et al*., 2022**)**. As such, inactivation of ATPases alters cell ionic homeostasis, which is regarded to be one of the primary culprits in the pathophysiology of various neurological disorders. Added to this, mitochondrial dysfunction causes tissue degeneration and may play a role in the etiology of the neurodegenerative disease including Alzheimer's. This implies that regular maintenance of membrane-bound enzymes in the brain requires a significant amount of energy. The ability of mitochondria to produce ATP declines with age as evidenced by previous observations where Mitochondria from old brain cells were shown to be more prone to free radical damage (Rehman *et al.*, 2022).

CONCLUSIONS

According to the findings of this study, it was evident that EoFME administration to AD-Induced rats normalized the activities of Na^+/K^+, Mg^{2+} and Ca^{2+} - ATPases indicating that EoFM has the potential to maintain ion gradients across biological membranes. They were founded on the concept that adding EoFME to the rat diet boosts membrane-bound transport ATPase activity, which is linked to its anti-oxidative effects. Furthermore, *Emblica officinalis* fruit extract may produce a variety of beneficial secondary metabolites that are engaged in a number of brain biochemical processes and so protect neurons by stabilizing the structural and functional integrity of the biological membrane.

FUTURE SCOPE

Although the role of these channels in AD pathogenesis is not fully understood, it opens up novel avenues for discovering new therapeutic targets for better understanding of the pathogenic mechanisms that occur during AD (Trombetta *et al*., 2020). More investigation and experimentation on higher mammalian models are required to determine the potential therapeutic aspects of *Emblica officinalis* in connection with the neurodegeneration process during pathological conditions.

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Conflict of Interest. None.

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