

## SYNERGISTIC EFFECT OF GALANTAMINE CARRIED ON A NOVEL NANO-DRUG DELIVERY SYSTEM ON INDUCED LUNG DISORDERS IN ALZHEIMER'S DISEASE

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### ABSTRACT

Alzheimer's disease AD, the most common form of dementia, usually presents with lung disorders including lung fibrosis. The aim of the present study was to verify that the curative role of Galantamine (the major therapeutic drug for AD) coated with Ce/Ca-HAp (nano-drug delivery particle) on brain tissue is capable of inducing similar therapeutic capabilities in lung disorders besides its role in AD therapy. Presentation of multiple biomarkers (CYP1A1, CYP2E1, TGF- $\beta$ 1, TAC and TOC) for pulmonary disorders and also brain Markers (5-OH tryptamine, TNF- $\alpha$  & IL- $\beta$ 1) measured in brain tissue may induce early detection thus adding to the efficacy of the curative competence. 64 adult female albino Wistar rats (189- 200 gm) were allotted into 4 groups: a) Control: Gonad intact rats (10). b)

Alzheimer (Alz): Ovariectomized rats (22) treated orally with AlCl<sub>3</sub> (17 mg/kg b.wt) daily for 2 months following one month surgery. c) Alz + Gal rats (16) d) Alz + Gal. + Ce/Ca-HAp rats (16). Results verified marked increases in levels of TNF- $\alpha$  & IL- $\beta$ 1, TOC, TGF- $\beta$ 1 while serum TAC and 5-OH tryptamine levels and tissue CYP<sub>1</sub>A<sub>1</sub>, CYP<sub>2</sub>E<sub>1</sub> were significantly decreased in AD rats. Histologically, thickening wall of blood vessels and lymphocytes inflammatory infiltration and degenerative alterations were viewed in lung tissue. Patent enhancements were more asserted following nano-therapy than GAL alone. In conclusion, as lung dysfunction highly presents with AD thus early detection using different biomarkers as lung profile (CYP<sub>1</sub>A<sub>1</sub>, CYP<sub>2</sub>E<sub>1</sub>, TGF- $\beta$ 1) antioxidant and oxidative status (TAC, TOC) and brain markers profile (5-OH tryptamine, TNF- $\alpha$  & IL- $\beta$ 1) is vital for curative competence.

Again as Ce/Ca-HAp nanoparticle presented as coating for GAL drug therapy, more promising ameliorative measures could be achieved.

**KEYWORDS:** Alzheimer, lung dysfunction, Galantamine, nanotherapy.

## INTRODUCTION

Dementia is a gradual decline of mental ability that affects intellectual and social skills to the point where daily life becomes difficult. Alzheimer's disease, the most common form of dementia affects about 5% of people over age 65.<sup>[1]</sup> It occurs more often with advancing age, affecting 20% to 25% of people over the age of 80. Mild cognitive impairment (MCI) is associated with a 5 to 10% annual conversion rate to dementia.<sup>[1,2]</sup> However, MCI is considered a potentially reversible state and not all of those with MCI go on to develop dementia. At least 10% of cases of dementia are due to a combination of Alzheimer's disease and multiple strokes. There is increasing evidence that cognitive impairment is more frequent in those with chronic lung disease than those without. Chronic obstructive pulmonary disease affects 210 million people, with cognitive impairment present in 60% of certain populations.<sup>[2]</sup> So, lung disease is one such medical co-morbidity with increasing evidence of an association with cognitive dysfunction and brain pathology.

Individuals with chronic lung disease are thought to be at an increased cognitive decline hazard. These risk features occur more commonly in those with lung disease (are known to negatively impact on cognition, as smoking and hypertension) and/or as a direct result of respiratory limitations (as hypoxaemia).<sup>[3]</sup>

Cytochrome P450 (P450 enzymes) belong to heme proteins superfamily performs vital roles in the exogenous and endogenous chemicals metabolism.<sup>[4]</sup> P450 enzymes, comprising CYP1A1, is also involved in the ROS formation and further reactions.<sup>[5]</sup> Several studies have proposed that CYP1A and CYP2B1 enzymes are induced by hyperoxia in rodents, and play a role in pulmonary oxygenotoxicity.<sup>[6]</sup> Several molecules are being recognized as oxidant-induced injury biomarkers throughout the body. They are also cellular injury mediators.<sup>[7,8]</sup> Cytochrome P450 2E1 (CYP2E1) is an N-nitrosodimethyl-amine demethylase is expressed primarily in the liver. It participates in the metabolism of drugs, moreover activates many pre-carcinogens and pre-toxins.<sup>[9]</sup> CYP2E1 activity is accompanied by active oxygen form generation, which damages cell membranes and macromolecules and leads to formation of DNA adducts. The cytokine TGF- $\beta$  plays a critical role in the tissue injury resolution in

multiple organs, including the lung.<sup>[10]</sup> Following acute lung injury (ALI), TGF- $\beta$  has been evaluated during the late tissue repair phases. It plays a critical role in the pulmonary fibrosis development.<sup>[11]</sup> In the lungs, TGF- $\beta_1$  is produced by different cell types, including alveolar macrophages, neutrophils, activated alveolar epithelial cells, endothelial cells, fibroblasts, and myofibroblasts. TGF- $\beta_1$  induces macrophage and fibroblast recruitment and fibroblast proliferation via platelet-derived growth factor (PDGF) expression. In these cells, TGF- $\beta_1$  stimulates a number of proinflammatory and fibrogenic cytokines, as TNF- $\alpha$ , PDGF, IL-1 $\beta$ , or IL-13, so enhancing and perpetuating the fibrotic response.<sup>[12]</sup>

Total antioxidant capacity or status (TAC) is used to measure the antioxidant capacity of all antioxidants in a biological sample.<sup>[13]</sup> Total oxidative capacity (TOC) is caused by an imbalance between the reactive oxygen production and detoxification resulting damage. Oxidative stress is involved in many diseases as chronic obstructive pulmonary, Alzheimer's.<sup>[3,14,15]</sup>

During the past 20 years, the 5-HT<sub>6</sub> receptor has received increasing attention and become a promising target for improving cognition. Several studies have shown that 5-OH tryptamine has helped clarify their specific roles in learning and memory.<sup>[16]</sup>

The major therapeutic pathway is Galantamine. It is an acetylcholinesterase inhibitor used for AD treatment and related dementias. Galantamine reduced circulating TNF- $\alpha$ . Galantamine enhanced cholinergic function by increasing the concentration of acetylcholine in the brain and enhancing cholinergic neuro-transmission in the brain.<sup>[17]</sup> Nevertheless, side effects from the drug have been reported in different tissues including lung as higher doses and therapeutic time durations are gradually required.

Hydroxyapatite (HAp) (HAp, Ca<sub>10</sub>(PO<sub>4</sub>)<sub>6</sub>(OH)<sub>2</sub>) has been used in medicine and suggested to be one of the most promising drug delivery systems owing to its biocompatibility, bioactivity, elevated hydrophilic character, chemical stability against oxidative conditions and non-toxicity nature.<sup>[18]</sup> Implementation of new species in the HAp lattice offer fundamentally new possibilities and areas of their practical applications in biology and medicine.<sup>[19]</sup> Ceria (CeO<sub>2</sub>) nanoparticles exhibit high catalytic activity and a regenerative capacity to neutralize ROS. Ceria was found to protect cells against oxidative stress, inflammation, or damage caused by radiation. The particles are small and can cross the blood brain barrier.<sup>[20]</sup>

Several drug delivery systems for Galantamine therapy have been examined, yet Galantamine coated with Cerium/ Calcium hydroxyapatite (Ce/Ca-HAp) has been recorded to be the most efficient to incur curative majors in brain of AD.<sup>[18,19]</sup>

Thus the aim of the presented study was to elucidate whether the curative role of Galantamine coated with (Ce/Ca-HAp) on brain tissue is capable of inducing similar therapeutic capabilities in lung disorders besides its role in AD therapy. Again the presentation of multiple biomarkers for lung disorders may induce early detection thus adding to the efficacy of the curative competence.

## MATERIALS AND METHODS

Adult female albino Wistar rats weighing 180- 200 gm (n=70) were obtained from the Medical Research Centre Ain Shams University. Experimental protocols followed the Guidelines for the Care and Use of Laboratory Animals approved by the Institutional Ethics Committee of Ain Shams University. Rats were housed in standard conditions of temperature (22–24°C), humidity (60%) and a 12-h light/dark cycle, with food and water offered ad lib. Following a one week adaptation period rats were randomly assigned to their experimental groups. AD was induced to ovariectomized rats by Aluminium chloride (17mg/kg b.wt.)<sup>[21]</sup> daily for 2 months after one month post-operative procedure. Both Galantamine<sup>[22]</sup> and Galantamine coated with Cerium/ Calcium hydroxyapatite (Ce/Ca-HAp) were i.p. injected at 2.5 mg/kg b.wt. for 2 and 4 weeks. Grouping was done according to.

Control: Gonad intact rats (10). b) Alzheimer (Alz): Ovariectomized rats (22) treated orally with AlCl<sub>3</sub> (17 mg/kg b.wt) daily for 2 months following one month surgery. c) Alz + Gal rats (16) d) Alz + Gal. + Ce/Ca-HAp rats.(16)

Following 4 weeks rats were anaesthetized by ether inhalation, lungs carefully excised, where part was washed in ice cold saline, and 10% homogenate of the washed tissue were prepared in 0.1 Tris-HCl (pH 7.4). After centrifugation at 3000rpm at 4°C the supernatant (10%) was separated for biochemical estimations. These included

lung profile: CYP<sub>1A1</sub><sup>[23]</sup>; CYP<sub>2E1</sub><sup>[24]</sup> and TGF-β<sub>1</sub><sup>[25]</sup>; antioxidant and oxidative status: TAC<sup>[26]</sup>; TOC<sup>[27]</sup> and brain markers profile: (5-OH tryptamine<sup>[28]</sup>, TNF-α<sup>[29]</sup> & IL-β<sub>1</sub><sup>[30]</sup>).

The second part was washed in sterile phosphate buffered saline fixed with 10% formaldehyde and paraffin embedded for histology analysis by standard methods. Embedded tissues were sliced into 5  $\mu\text{m}$  thin sections stained with hematoxylin and eosin<sup>[31]</sup> mounted on slides and examined for histological changes.

## RESULTS

### A-Biochemical investigations

#### 1- Pulmonary cytochrome enzymes & antioxidant and oxidative status

**Table (1): Pulmonary cytochrome enzymes and TGF- $\beta$ 1 levels in control, Alz, Gal., Alz +Gal and Alz +Gal coated by Ce/Ca-HAp treated rats.**

Groups	Control	ALZ	Alz+GAL	Alz+Gal+Ce/Ca-HAP
<b>Parameters</b>				
<b>CYP<sub>1A1</sub></b> (Pmol/min/mg protein)	13.72 $\pm$ 0.34 <sup>A</sup>	7.91 $\pm$ 0.11 <sup>B</sup>	11.14 $\pm$ 0.29 <sup>C</sup>	12.27 $\pm$ 0.31 <sup>D</sup>
<b>CYP<sub>2E1</sub></b> (Pmol/min/mg protein)	1.51 $\pm$ 0.079 <sup>A</sup>	0.81 $\pm$ 0.044 <sup>B</sup>	1.38 $\pm$ 0.075 <sup>C</sup>	1.46 $\pm$ 0.079 <sup>D</sup>
<b>TGF-<math>\beta</math>1</b> (pg/mg protein)	57.86 $\pm$ 1.54 <sup>A</sup>	276.59 $\pm$ 3.89 <sup>B</sup>	87.67 $\pm$ 2.18 <sup>C</sup>	85.17 $\pm$ 2.08 <sup>D</sup>

Values are expressed as mean  $\pm$  S.E.

- n = number of rats.

- A, B, C, D Means with a common superscript within a row are significantly different ( $P < 0.05$ ).

In the present study, marked increases in levels of TGF- $\beta$ 1, while marked decrease in lung tissue CYP<sub>1A1</sub>; CYP<sub>2E1</sub> were recorded as a result of AD. These were more or less ameliorated by Gal therapy and yet more improved as Gal was coated with Ce/Ca-HAp.

#### 2-Antioxidant and oxidative status.

**Table 2: Antioxidant and oxidative status in control levels in control, Alz, Gal., Alz +Gal and Alz +Gal coated by Ce/Ca-HAp treated rats.**

Groups	Control	ALZ	Alz+GAL	Alz+Gal+Ce/Ca-HAP
<b>Parameters</b>				
<b>TAC</b> (nmol/mg protein)	1.255 <sup>A</sup> $\pm$ 0.90	0.771 <sup>B</sup> $\pm$ 0.63	0.794 <sup>C</sup> $\pm$ 0.64	0.864 <sup>D</sup> $\pm$ 0.14
<b>TOC</b> (nmol/mg protein)	0.470 <sup>A</sup> $\pm$ 0.70	1.080 <sup>B</sup> $\pm$ 0.50	0.930 <sup>C</sup> $\pm$ 0.20	0.870 <sup>D</sup> $\pm$ 0.40

Values are expressed as mean  $\pm$  S.E.

- n = number of rats.

- A, B, C, D Means with a common superscript within a row are significantly different ( $P < 0.05$ ).

Presently while TAC levels were significantly decreased in Alz-induced rats as compared to normal ones yet such figures retreated greatly after treatment especially as Gal was coated with Ce/Ca-HAp. On the other hand, marked increases were evidenced in TOC that again were partially improved following Gal treatment especially visualized with Gal coated with Ce/Ca-HAp.

## 2- Brain markers profile

**Table (3): 5-OH tryptamine, TNF- $\alpha$  & IL- $\beta_1$  levels in control and Alz, Gal., Alz +Gal, Alz +Gal coated by Ce/Ca-HAp treated rats.**

Groups	Control	ALZ	Alz+GAL	Alz+Gal+Ce/Ca-HAP
<b>Parameters</b>				
5-OH tryptamine ( $\mu\text{mol/mg protein}$ )	101.42 $\pm$ 3.32 <sup>A</sup>	67.55 $\pm$ 2.16 <sup>B</sup>	87.49 $\pm$ 2.86 <sup>C</sup>	91.07 $\pm$ 2.93 <sup>D</sup>
TNF- $\alpha$ (pg/mg protein)	601.44 $\pm$ 7.23 <sup>A</sup>	1572.09 $\pm$ 22.54 <sup>B</sup>	827.44 $\pm$ 10.52 <sup>C</sup>	677.52 $\pm$ 11.49 <sup>D</sup>
IL- $\beta_1$ (pg/mg protein)	127.06 $\pm$ 0.771 <sup>A</sup>	338.44 $\pm$ 2.28 <sup>B</sup>	167.12 $\pm$ 1.49 <sup>C</sup>	159.11 $\pm$ 1.35 <sup>D</sup>

Values are expressed as mean  $\pm$  S.E.

- n= number of rats.

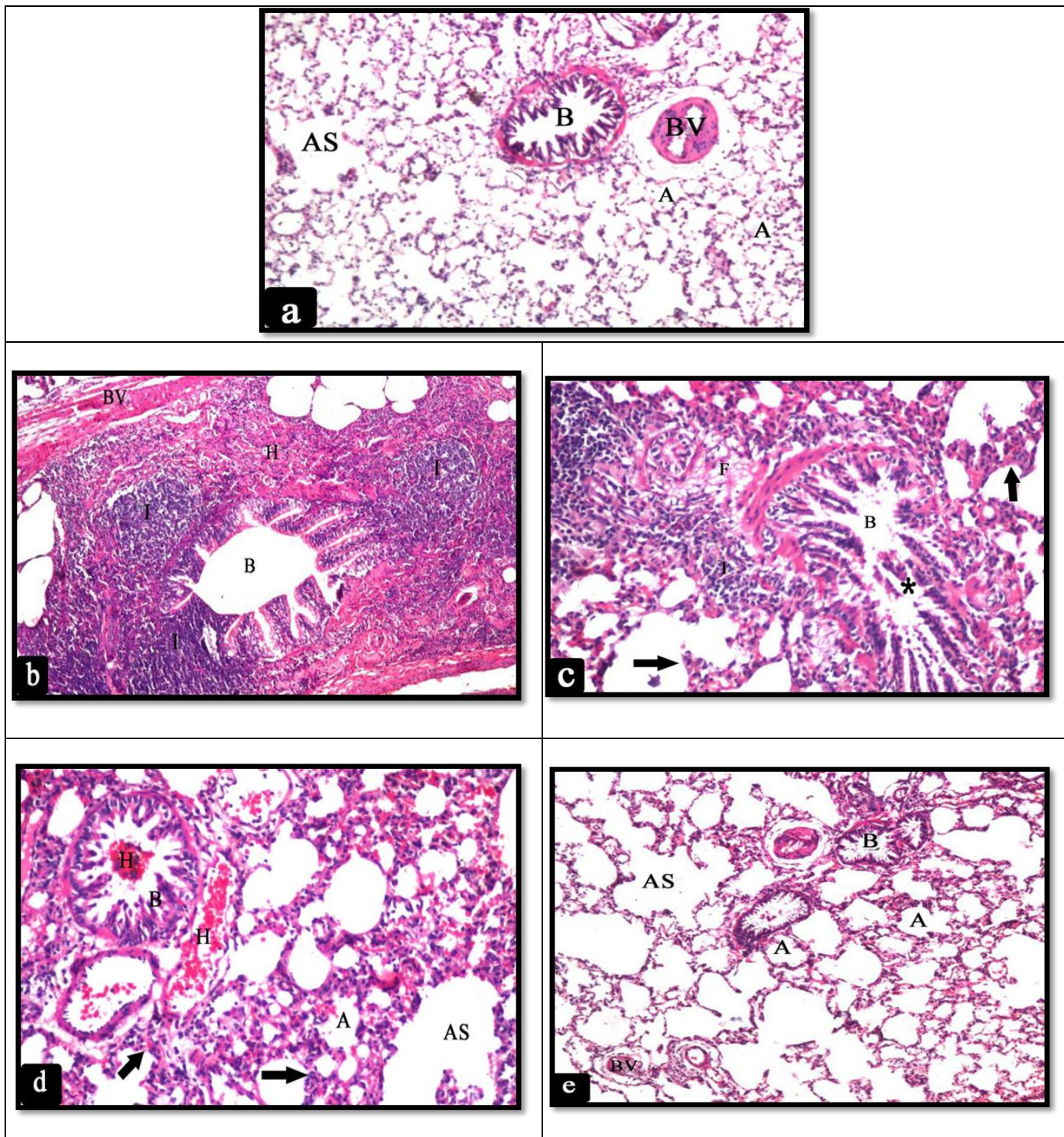
- A, B, C, D Means with a common superscript within a row are significantly different ( $P < 0.05$ ).

On presenting Brain markers profile in the current study, results manifested significant upregulated records of both TNF- $\alpha$  and IL- $\beta_1$  in Alz-induced rats. Contrary to that 5-OH tryptamine were significantly attenuated in the same group of animals. Marked improvements were more pronounced following GAL therapy coated with Ce/Ca-HAp than GAL alone.

## B- Histological investigations

Histopathological study of lung tissue in normal control group bared the alveolar sac and bronchioles with normal epithelium. (Fig.1a). In a section from lung of Alz-induced rats, thickening of interalveolar septa, focal hemorrhage, mononuclear cell infiltration in interstitial space, detached epithelial cells and interstitial necrosis (Fig. 1 b& c). Also viewed is an increase in inflammatory cells mainly monocytes and lymphocytes accompanied by degenerative alterations and thickening in the interalveolar septa. Such alterations persisted in sections obtained from Alz-induced rats treated with GAL (Fig. 1d) although with lower profiles. Lung sections of Alz-induced rats treated with GAL coated with Ce/Ca-HAp

designated ameliorated figures where hemorrhage and thickening of interalveolar wall regressed (Fig. 1e). Bronchiole appeared more or less near to normal in pattern.



**Figure 1:** Cross sections of lung in experimental groups stained with H&E, 40×. (a): normal control showing normal lung architecture with polygonal alveoli (A) having thin interalveolar septa, alveolar sacs (AS), a bronchiole(B) and blood vessels (BV); (b& c): Alz group

showing the accumulation of inflammatory cells and lymphoid nodules around the interalveolar septa (I), Dilated congested blood vessels (BV), thickened wall of alveolar septa (arrow), fibrotic area (F) and detached epithelium (\*). (d) Alz+ Gal group showing moderate restoration with mild hemorrhage (H) in bronchiole and thickened alveolar wall (arrow). (e):Alz+Gal+Ce/Ca-HAP group showing almost uniform structure of pulmonary tissue with some areas of congested blood vessels and peri-bronchiolar infiltration (I).

## DISCUSSION

In a recent study<sup>[31]</sup> emphasized on the efficacy of coating GAL (effective remedy for AD) with drug delivery nano-particles (Ce/Ca-HAP) in incurring therapeutic measures for AD. Accordingly, in the present study different biochemical tests were utilized to enhance early diagnostic measures for pulmonary disorders namely cytochrome profile, TGF- $\beta$ , antioxidant and oxidative status and Brain markers profile. Currently, marked increases in level of TGF- $\beta$  were recorded as a result of AD. As limited therapeutic levels were encountered with GAL therapy yet it was more improved as Gal was coated with Ce/Ca-HAP. Similar records were reported by.<sup>[32]</sup> Increase in TGF- $\beta$  levels could be used as a reliable biomarker for pulmonary disorders especially fibrosis.<sup>[33,34,35]</sup> TGF- $\beta$ 1 is the major profibrotic growth factor which stimulates fibroblast collagen production and deposition. As a result of previous studies, TGF- $\beta$ 1 is believed to be a high mediator of fibrotic, and remodeling responses in the lung and other organs, and these responses are believed to be mediated by the ability of TGF- $\beta$ 1 to activate fibrogenic and apoptotic “injury” pathways.<sup>[36]</sup>

Additional biochemical markers for pulmonary disorders and AD were TAC and TOC. Presently TAC level was significantly decreased in Alz-induced rats while TOC levels markedly increased as compared to normal ones. Similar records were demonstrated by several workers.<sup>[3,14,15]</sup> There is an inverse association between TAC and the number of damaged vessels in brain or other tissues.<sup>[35]</sup> Also, reports by<sup>[15]</sup> stated that the oxidant production due to chronic inflammation, as evidenced by the increased (oxidative stress index) OSI levels and decreased level of TAC might contribute to persistent lung injury. As oxidative stress is a significant element in AD pathogenesis thus attenuated protection against ROS production in elder patients might trigger and add to the onset of AD and its progression. Several studies have shown that oxidative stress is able to transform lung epithelium into mesenchymal cells via generation of intracellular (mitochondrial) ROS and up-regulation of TGF-  $\beta$ 1 expression.<sup>[36]</sup>



Currently, marked increases in levels of TNF- $\alpha$ , and IL- $\beta$ 1 and decrease in 5-OH tryptamine were recorded as a result of AD. As limited therapeutic levels were encountered with GAL therapy yet it was more improved as Gal was coated with Ce/Ca-HAp. The cytokine tumor necrosis factor (TNF-alpha) is a pleiotropic polypeptide that plays a significant role in brain immune and inflammatory activities. TNF-alpha is produced in the brain in response to various pathological processes such as infectious, ischemia, and trauma.

Several studies demonstrated the role for TNF alpha in the pathophysiology of AD is suggested by findings of over expression of TNF alpha in AD brains.<sup>[37]</sup>

Activation of the TNF receptor 1 is required for neuronal cell death as a toxic consequence of beta amyloid protein. TNF alpha inhibits learning by inhibiting long term potentiation, a process critical for memory.<sup>[38]</sup> Inhibition of TNF alpha has been shown to decrease amyloid plaques and tau phosphorylation in the mouse brain, processes associated with dementia.<sup>[37,39]</sup>

Several studies indicate that a neuroimmune reaction, associated with inflammatory mechanisms, can contribute in Alzheimer's disease (AD) to cell damage and neurodegeneration,<sup>[38]</sup> These results clearly demonstrate that dementia patients show a generalized increment of IL $\beta$ -1 production in the CNS, with maximum response in those brain regions where AD neuropathology is most prominent. This overall increase in cytokine production might represent an early event in the activation of a neuroimmune cascade leading to cell death and neurodegeneration in brain regions where a primary cause (e.g., genetic, toxic, vascular) facilitates the induction of resting microglia for firing brain immune function.<sup>[37,38,40,41]</sup>

5-OH tryptamine performance as a tissue hormone, neurotransmitter and neuromodulator.<sup>[42,43]</sup> It is one of the most important neurotransmitters in the central nervous system (CNS) regulating multiple physiological functions such as body temperature, appetite, sleep, mood and pain.<sup>[44]</sup>

Several studies reported that pathological change in 5-HT level have been associated with AD, anxiety and Depression.<sup>[45,46]</sup> The decrease in the level of tissue 5-HT may be attributed to amyloid depositions in the projection sites of serotonergic neurons lead to the degeneration of 5-HT axons followed by the degeneration of the corresponding neuronal cell bodies.<sup>[47]</sup> On the other hand, several AD-associated abnormalities like hyper-phosphorylation of tau

become primarily evident in the dorsal raphe nucleus, which subsequently leads to the 5-HT neuron demise.<sup>[48]</sup> Sheline et al<sup>[49]</sup> demonstrated that disorder in 5-HT receptors of AD increase the production of toxic amyloid proteins and amyloid plaques.<sup>[49,50]</sup>

Frequencies of CYP1A1, CYP2E1 were associated with cystic fibrosis, chronic obstructive lung disease, bronchiectatic disease, chronic non obstructive bronchitis, and recurring bronchitis. As lung tissue is injured in pulmonary disorders the enzymes and proteins leak out of damaged lung tissue, and their levels rise in tissue and in the bloodstream. A high CYP1A1, CYP2E1 level often indicates high amounts of tissue damage and lysed cells and thus is a general indicator of both cellular and tissue disease.<sup>[51]</sup>

In the current study all the above mentioned biochemical biomarkers of pulmonary profile (CYP1A1, CYP2E1 and TGF- $\beta$ ) and antioxidant and oxidative status (TAC and TOC) were partially improved following Gal treatment where near to normal levels were specially visualized with Gal nanodrug. Among different therapeutic trials, cholinesterase inhibitors (ChEIs) as Galantamine are the first group of compounds that have produced considerable improvements in AD patients.<sup>[52]</sup> Thus it remains to be the major therapeutic drug of choice.

Cerium oxide nanoparticles have neuroprotective effects.<sup>[53]</sup> CeO<sub>2</sub> doped calcium hydroxyapatite powder has been previously synthesized and used for its bioactivity towards AD by<sup>[18]</sup> and has been proved to induce ameliorated measures in AD therapy on brain.

Histological assessment was followed to validate previously mentioned biochemical results. Lung sections from AD rats manifested, thickening of interalveolar walls, focal hemorrhage, and inflammatory infiltration in interstitial space, detached epithelial cells and degenerative alterations. Although limited studies have discussed histological features in lung tissue of AD patients yet the present study have to suff with that of<sup>[2]</sup> reported that the impaired lung function is chronic obstructive pulmonary disease (COPD), a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways. Inspiring factors for asthma is correlated to the accumulation of inflammatory cells in airways.<sup>[41]</sup> It has been verified that airway's neutrophils are increased in asthma. IL-17 may be concerned with the infiltration of neutrophils into the lung tissue.<sup>[56]</sup> Neutrophils secrete elastase, which is a neutrophil serine protease that causes degeneration of lung elastin. The production of reactive oxygen is motivated and airway inflammation is increased.<sup>[57]</sup> Furthermore, the glycoprotein

compounds accumulate in airways so as to compensate for these alterations, the thickness of epithelium in the alveoli was enhanced. Therefore, various centers full of blood in the connective tissue between alveoli and hemorrhage in some alveolar sacs were observed as suggested by.<sup>[58]</sup> In AD increase in free radical occurs circulating with blood flow and thus attacking several organs, in this case lung tissue causing disturbances in pulmonary architecture. Additional risk factors would be the inadequate blood flow from AD that can damage and eventually kill different cell lines. As AD rats were administered GAL therapy alterations persisted although with lower profiles, whereas therapy with GAL coated with Ce/Ca-HAp evidenced regression in Aaggregates and near to normal patterns for lung tissue.

Among most of the metallic species, ceria (CeO<sub>2</sub>) nanoparticles exhibit high catalytic activity and a regenerative capacity to neutralize ROS. Ceria was found to protect cells against oxidative stress, inflammation and other cellular damage.<sup>[20]</sup> The particles are small and can cross the blood brain barrier enhancing the drug targeted release in infected areas

## CONCLUSION

Accordingly, evidences may be drawn that pulmonary disease may greatly increase one's risk of developing AD and vice-versa. GAL therapy or other line of treatments cannot act alone to induce obvious remedies. In contrast, a more promising method is the initiation of drug delivery systems as Ce/Ca-HAp that may increase the efficacy of the drug and induce a curative role in lung tissue.

## REFERENCES

1. Dubois, B.; Feldman, H.H.; Jacova, C. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol*, 2010; 9(11): 1118–1127.
2. Dodd, J.W. Lung disease as a determinant of cognitive decline and dementia. *Alzheimer's Res & Ther*, 2015; 7-32.
3. Dodd, J.W.; Getov, S.V. and Jones, P.W. Cognitive function in COPD. *EurRespir J*, 2010; 35: 913–22.
4. Guengerich, F.P. Enzymatic oxidation of xenobiotic chemicals. *Crit. Rev. Biochem. Mol. Biol*, 1990; 25: 97–153.
5. Morel, Y.; Waziers, I.D. and Barouki, R. A repressive cross-regulation between catalytic and promoter activities of the CYP1A1 and CYP2E1 genes: role of H<sub>2</sub>O<sub>2</sub>. *Mol Pharmacol*, 2000; 57: 1158–1164.

6. Moorthy, B.; Parker, K.M.; Smith, C.V.; Bend, J.R. & Welty, S.E. Potentiation of oxygen-induced lung injury in rats by the mechanism-based cytochrome P450 inhibitor, 1-aminobenzotriazole. *J Pharmacol Exp Ther*, 2000; 292: 553–560.
7. Fessel, J. P.; Porter, N. A.; Moore, K. P.; Sheller, J. R. & Roberts, L. J. Discovery of lipid peroxidation products formed in vivo with a substituted tetrahydrofuran ring (isofurans) that are favored by increased oxygen tension. *Proc. Natl. Acad. Sci*, 2002; 99: 16713–16718.
8. Morrow, J. D. and Roberts, L. J. The isoprostanes: Their role as an index of oxidant stress status in human pulmonary disease. *Am. J. Respir. Crit. Care Med*, 2002; 166: S25–S30.
9. Ramaiah, S.K.; Apte, U. and Mehendale, H.M. Cytochrome P450<sub>2E1</sub> induction increases thioacetamide liver injury in diet-restricted rats. *Drug Metab. Dispos*, 2001; 29: 1088–1095.
10. Shull, M.M.; Ormsby, I.; Kier, A.B.; Pawlowskr, S.; Diebold, R.J.; Yin, M.; Allen, R.; Sidman, C.; Proetzel, G.; Calvint, D.; Annunziata, N. and Doetschman, T. Targeted disruption of the mouse transforming growth factor-beta 1 gene results in multifocal inflammatory disease. *Nature*, 1992; 359: 693–699.
11. Giri, S.N.; Hyde, D.M. & Hollinger, M.A. Effect of antibody to transforming growth factor beta on bleomycin induced accumulation of lung collagen in mice. *Thorax*, 1993; 48: 959–966.
12. Fernandez, I.E. & Eickelberg, O. The Impact of TGF-b on Lung fibrosis from Targeting to Biomarkers. *Proc. Am. Thorac. Soc*, 2015; 9(3): 111–116.
13. Kusano, C. & Ferrari, B. Total Antioxidant Capacity: a biomarker in biomedical and nutritional studies. *J Cell Biol. Mol. Sci*, 2008; 7(1): 1-15.
14. Dodd, J.W.; Charlton, R.A.; van den Broek, M.D. & Jones, P.W. Cognitive dysfunction in patients hospitalized with acute exacerbation of COPD. *Chest J*, 2013; 144: 119–27.
15. Hanedan, B.; Akin Kirbas, F.; Kandemir, M.; Ozkaraca, M.; Kilic, K. and Benzer, F. (2015): Arginase activity and total oxidant/antioxidant capacity in cows with lung cystic echinococcosis. *Med. Weter*, 2015; 71(3): 167-170.
16. Butzlaff ,M.; Ponimaskin, E. The role of Serotonin Receptors in Alzheimer’s disease. *.Opera Medica & Physiologica*, 2016; 1: 91-100.
17. Kihara, T.; Sawada, H.; Nakamizo, T.; Kanki, R.; Yamashita. H.; Maelicka, A.& Shimohama S. Galanamine modulates nicotinic receptor and blocks Abeta-enhanced glutamate toxicity., 2004; *Biochem.Biophys. Res. Commun*, 2004; 325: 976-982.

18. Wahba, S.M.R, Darwish, A.F. and Kamel, S. M. Ceria-containing uncoated and coated hydroxyapatite-based Galantamine nanocomposites for formidable treatment of Alzheimer's disease in ovariectomized albino-rat model. *Mater. Sci. Eng. C*, 2016; 65: 151-163.
19. Mostapha, W.A. & El-Bakry, S.T. Developed Galantamine Therapy for Alzheimer's Disease by Introducing Nano-Drug Delivery Systems. *Int. J Clin. Psychiatry. Ment. Health*, 2016; 4: 19-29.
20. Estevez, A.Y.& Erlichman J.S. Cerium Oxide nanoparticles for the treatment of neurological oxidative stress diseases. *Am. Chem. Soc*, 2011; 1083: 255-288.
21. Krasovskii, G. N.; Vasukovich, L. Y. & Chariev, O. G. Experimental study of biological effects of lead and aluminium following oral administration. *Environ. Health Perspect*, 1979; 30: 47-51.
22. Iliev, A. I.; Traykov, V. B.; Mantchev, G. T.; Stoykov, I.; Prodanov, D. & Yakimova, K. S. A post-ischemic single administration of galantamine, a cholinesterase inhibitor, improves learning ability in rats. *J. Pharm. Pharmacol*, 2000; 52:1151 - 1156.
23. Kalow, W & Tang, B. K. Use of caffeine metabolite ratios to explore CYP1A2 and xanthine oxidase activities. *Cline. Pharmacol. Ther*, 1991; 50: 508-519.
24. Zerilli, A.; Ratanasavanh, D.; Lucas, D.; Goasduff, T.; Dréano, Y.; Menard, C.; Picart, D. & Berthou, F. Both cytochromes P450 2E1 and 3A are involved in the O-hydroxylation of p-nitrophenol, a catalytic activity known to be specific for P450 2E1. *Chem. Res. Toxicol*, 1997; 10(10): 1205-12.
25. Shaukat, A. ; Joyce, J & Tsuda, T. Quantification of active and total transforming growth factor- $\beta$  levels in serum and solid organ tissues by bioassay. *BMC Research Notes*, 2012; 5: 636.
26. Benzie. I. F. & Strain, J. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay. *Anal. Biochem*, 1996; 239: 70-6.
27. Schimke, I. P.; Mouller, J.; Priem, F.; Kruse, I.; Schon, B.; Stein, J.; Kunze, R.; Wallukat, J. & Hetzer, R. Decreased oxidative stress in patients with idiopathic dilated cardiomyopathy one year after immunoglobulin adsorption. *J. Am. Coll. Cardiol*, 2001; 38: 178-83.
28. Benhamú, B., Martín-Fontecha, M; Vázquez-Villa, H.; Pardo, L. & María L. Serotonin 5-HT<sub>6</sub> Receptor Antagonists for the Treatment of Cognitive Deficiency in Alzheimer's Disease. *J. Med. Chem*, 2014; 57(17): 7160–7181.
29. Juhasz, K. *Expert. Rev. Clin. Immunol*, 2013; 9: 335.

30. Ospina, J.A.; Brevig, H.N.; Krause, D.N. & Duckles, S.P. Estrogen suppresses IL-1 $\beta$ -mediated induction of COX-2 pathway in rat cerebral blood vessels. *Am. J. Physiol. Heart Circ. Physiol*, 2004; 286.
31. Harris, H.F. & Bruce Casselman, W.G. *Histopathological Technique*. Methuen and Co. Ltd 1959.
32. Li, G.; Zhou, C.L.; Zhou, Q.S. & Zou, H.D. Galantamine protects against lipopolysaccharide-induced acute lung injury in rats. *Brazilian J. Med. and Biol. Res*, 2016; 49(2): 5008.
33. Cutroneo, K.R.; White, S.L.; Phan, S.H. & Ehrlich, H.P. Therapies for bleomycin induced lung fibrosis through regulation of TGF- $\beta$ 1 induced collagen gene expression. *J. Cell. Physiol*, 2007; 211: 585–589.
34. Yamada, M.; Kuwano, K.; Maeyama, T.; Hamada, N.; Yoshimi, M.; Nakanishi, Y. and Kasper, M. Dual-immunohistochemistry provides little evidence for epithelial-mesenchymal transition in pulmonary fibrosis. *Histochem. Cell Biol*, 2008; 129: 453–462.
35. Nojiri, S.; Daida, H.; Mokuno, H.; Iwama, Y.; Mae, K.; Ushio, F. & Ueki, T. Association of serum antioxidant capacity with coronary artery disease in middle-aged men. *Jpn Heart J*, 2001; 42: 677–690.
36. Gorowiec, M.R.; Borthwick, L.A.; Parker, S.M.; Kirby, J.A. Saretzki, G.C. & Fisher, A.J. Free radical generation induces epithelial-to-mesenchymal transition in lung epithelium via a TGF- $\beta$ 1-dependent mechanism. *Free Rad. Biol. & Med*, 2012; 52: 1024–1032.
37. Sharma, V.; Thakur, V.; Singh, S. & Guleria, R. Tumor necrosis factor and Alzheimer's disease: a cause and consequence relationship. *Bulletin of Clinical Psychopharmacology*, 2012; 22(1): 86–89.
38. Li, R.; Yang, L. Lindholm, K. Tumor necrosis factor death receptor signaling cascade is required for amyloid- $\beta$  protein-induced neuron death. *The Journal of Neuroscience*, 2004; 24(7): 1760–1771.
39. Pickering, L.; Cumiskey, M. & O' Connor, J. Actions of TNF- $\alpha$  on glutamatergic synaptic transmission in the central nervous system. *Experimental Physiology*, 2005; 90(5): 663–670.
40. Aloe, L.; Fiore, L.; Probert, P.; Turrini, and Tirassa, P. Overexpression of tumour necrosis factor  $\alpha$  in the brain of transgenic mice differentially alters nerve growth factor levels and choline acetyltransferase activity. *Cytokine*, 1999; 11(1): 45–54.

41. Wang, W.; Tan., M.S. & Yu, J. T. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann Transl Med*, 2015; 3(10): 136.
42. Fidalgo, S.; Ivanov, D.K.; Wood, S.H. Serotonin: from top to bottom. *Biogerontology*, 2013; 14: 21–45.
43. Ramakrishna, A.; Giridhar, P.& Ravishankar, G.A. Phytoserotonin. *Plant Signal. Behav*, 2011; 6: 800–809.
44. Arreola r.; Becerril-villanueva, E.; Cruz-fuentes, C.; Velasco-velázquez, M.A.; Garcés-alvarez, M.E.; Hurtado-alvarado, G.; Quintero-fabian, S.& Pavón, L. Immunomodulatory Effects Mediated by Serotonin. *J.Immunol. Res*, 2015; 22-36.
45. Bantick, R.A.; Deakin, J.F. & Grasby, P.M. The5-HT1A receptor in schizophrenia: a promising target for novel atypical neuroleptics? *J. Psychopharmacol. Oxf. Engl*, 2001; 15: 37–46.
46. Lai, M.K.; Tsang, S.W.; Francis P.T.; Esiri M.M.; Keene J.; Hope T.& Chen C.P. Reduced serotonin 5-HT1A receptor binding in the temporal cortex correlates with aggressive behavior in Alzheimer disease. *Brain Res*, 2003; 974: 82–87.
47. Liu, Y.; Yoo, M.; Savonenko, A.; Stirling, W.; Price, D.L.; Borchelt, D.R.; Mamounas, L.; Lyons, W.E.; Blue, M.E. & Lee, M.K. Amyloid Pathology Is Associated with Progressive Monoaminergic Neurodegeneration in a Transgenic Mouse Model of Alzheimer's Disease. *J. Neurosci*, 2008; 28: 13805–13814.
48. Hendricksen, M.; Thomas, A.J.; Ferrier, I.N.; Ince P. & O' brien J.T. Neuropathological Study of the Dorsal Raphe Nuclei in Late-Life Depression and Alzheimer's Disease With and Without Depression. *Am. J. Psychiatry*, 2004; 161: 1096–1102.
49. Sheline Y.I.; West T.; Yarasheski, K.; Swarm, R.; Jasielc, M.S.; Fisher J.R.; Ficker W.D.; Xiong, C.& Frederiksen, C. An Antidepressant Decreases CSF A $\beta$  Production in Healthy Individuals and in Transgenic AD Mice. *Sci. Transl. Med*, 2014; 6: 236re4–re236re4.
50. Cirrito J.R.; Disabato, B.M.; Restivo, J.L.; Verges, D.K.; Goebel, W.D.; Sathyan, A.; Hayreh, D.; D'angelo G.; Benzinger T. & Yoon, H. Serotonin signaling is associated with lower amyloid- $\beta$  levels and plaques in transgenic mice and humans. *Proc. Natl. Acad. Sci*, 2011; 108: 14968–14973.
51. Korytina, G.; Yanbaeva, D.; Viktorova, T. Polymorphisms of the Cytochrome P450 (*CYP1A1*, *CYP2E1*) and Microsomal Epoxide Hydrolase (*mEPHX*) Genes in Cystic Fibrosis and Chronic Respiratory Disease. *Molecular Biology*, 2003; 37(5): 663-670.

52. Zhang, X.; Shao, J.; Wei, Y. & Zhang, H. Efficacy of galantamine in treatment of Alzheimer's disease: an update meta-analysis. *Int. J. Clin. Exp. Med*, 2016; 9(4): 7423-7430.
53. Hosseini, A.; Sharifi, A.M.; Abdollahi, M.; Najafi, R.; Baeeri, M.; Rayegan, S.; Cheshmehnoor, J.; Hassani, S.; Bayrami, Z. & Safa, M. Cerium and Yttrium Oxide Nanoparticles against Lead-induced oxidative stress and apoptosis in rat hippocampus. *Biol. Trace Elem. Res*, 2014; 164(1): 80-89.
54. Makhloogh, E.; Mohseni, A.; Bagheri, B. & Fatahian, E. The investigation of the effect of theophylline on the contrast of nephropathy results from the angiography of corner vessels. *Med. Sci. Mazandaran*, 2006; 16: 27-34.
55. Zhou, Y.; McLane, M. & Levitt, R.C. The cytokines and asthma. Interleukin-9 as atherapeutic target for asthma. *Respir, Res*, 2001; 2: 80-84.
56. Sergejeva, S.; Ivanov, S.; Lotvall, J. & Lidn, A. Interlukin-17 as a recruitment and survival factor for airway macrophages in allergic airway inflammation. *Am. J. Respir. Cell Mol. Biol*, 2005; 33: 248-53.
57. Khosrou, A. & Sarvghadi, F. The investigation of Hypogonadism and the level of the serum of free testosterone in chemical injures who suffer from asthma which is the result of sulfur dioxide. *Military J. Med. Sci*, 2006; 4: 975-979.
58. Farokhi, F. & Khaneshi, F. Histopathologic changes of lung in asthmatic male rats treated with hydroalcoholic extract of *Plantago major* and theophylline. *AJP*, 2013; 3(2): 143-151.