Series of Clinical and Medical Case Reports and Reviews

Review Article

Relationship between Neurodegenerative Diseases and Proton Pump Inhibitors Using Bioinformatics

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Abstract

Proton pump inhibitors (PPIs) are a class of drugs used for the treatment of acid-related diseases by inhibiting gastric acid secretion. Although PPIs are considered safe and clinically beneficial in the short term, mounting evidence raises safety concerns about the long-term use of PPIs. Alzheimer's disease (AD) is the most common form and cause of dementia and one of the biggest public health challenges among neurodegenerative diseases in the elderly, with no effective treatment to date. In recent years, there have been conflicting studies in patients receiving long-term PPIs regarding the risk of dementia, and in particular, AD. Some studies showed a strong positive relationship between PPIs and their impact on dementia and AD. We performed an in-depth review and analysis of existing studies and performed some docking to investigate the interaction between PPIs and dementia, AD-associated proteins, enzymes, and receptors. This study aims to provide possible new insights about the long-term safety of PPI employment and eventual cognitive impairment leading to dementia and later AD.

Keywords: proton pump inhibitors, dementia, Alzheimer's disease, $GABA_A$ receptor, M1 muscarinic acetylcholine receptor, AMP-activated protein kinase

Abbreviations: PPIs: proton pump inhibitors, AD: Alzheimer's disease, AMPK: AMP-activated protein kinase, M1 mAChR: M1 muscarinic acetylcholine receptor, CNS: central nervous system, CKD: chronic kidney disease, AIN: acute interstitial nephritis, AKI: acute kidney injury, H2RA: H2 receptor antagonist, eGFR: estimated glomerular filtration rate, ESRD: end-stage renal disease, BBB: blood-brain barrier, APP: amyloid precursor protein, BACE1: ß-site APP-cleaving enzyme 1, AICD: APP intracellular domain, iGSMs: inverse γ-secretase modulators, VPP: vacuolar proton pumps, tTG: tissue transglutaminase, NFTs: neurofibrillary tangles, PHFs: paired helical filaments, PP2A: protein phosphatase 2A, AChE: acetylcholinesterase, ChAT: choline acetyltransferase, PKC: protein kinase C, ACh: acetylcholine

1. Introduction

One of the most studied potential adverse effects of the long-term use of proton pump inhibitors (PPIs) is dementia [1]. An early and large epidemiological study based on the German ageing, cognition, and dementia databases showed a significantly elevated risk of developing dementia in patients exposed to long-term PPI therapy [2]. A subsequent study conducted on a longitudinal sample of elderly patients from the largest German statutory health insurer also showed an increased risk of developing dementia compared with patients not exposed to PPIs [3].

A weak but significantly increased risk of non-AD dementia was observed among PPI users in a community-based retrospective cohort study conducted in the Catalan Health Service (CatSalut) system from 1st January 2002 to 31st December 2015. Although a higher dose of PPIs was not associated with an increased risk of either Alzheimer's disease (AD) or non-AD dementias, an increased risk of both AD and non-AD dementias was observed in users of two types of PPI in the above-mentioned 13 years of community-based data compared with those who employed only one type [4].

Conversely, a few recent meta-analyses and systematic reviews have concluded that there was no statistically significant association between PPI use and risk of dementia or AD (P >.05) [106–108].

However, these controversial findings claimed that distinct PPIs may have a potential role in the progression of cognitive disorders.

Despite these studies, the bioinformatics-based evidence from our current study led us to explore the relationship between PPIs and AD as well as non-AD dementias. In particular, we aimed to review the relationship between PPI use and the basic mechanisms of neuronal dysfunction. In this regard, we discuss whether PPI utilization is associated with greater susceptibility to developing dementia, focusing on the neurobiological basis of AD. Consequently, we propose a novel hypothesis regarding the physio-pathological mechanisms of cognitive impairment induced by acute and chronic PPI use and examine some associated factors that can increase dementia susceptibility after PPI exposure.

1.1 Limitations

Our review has certain limitations, such as the study being confined only to bioinformatics. These bioinformatic analyses were performed based on earlier evidence, and therefore, it is reliable to conduct some wet lab experiments as per our current findings. Some earlier studies that contradict facts can be better proven with wet lab experiments. This study has limitations because it shows the silico interactions between the drug and protein, but whether it's truly possible in vivo needs further studies, keeping this information as the base.

2. Methodology for Docking Study

The structures of proteins and ligands were downloaded from websites https://www.rcsb.org/ and https://pubchem.ncbi.nlm.nih.gov/. AutoDock Tool (ATD) 1.5.6 was utilized for this study. The AutoDock Vina 1.0 software automatically computed Gasteiger charges, merged non-polar hydrogens, and autodock type to each atom. Then torsions were defined, which showed rotatable and non-rotatable bonds in the ligand. Finally, results were saved in the pdbqt file format **(Figures 1 and 2)**. AutoDock Vina software was run using the Windows command prompt. All the program files, ligand [.pdbqt], protein [.pdbqt], and configuration files [.conf] were saved in the same folder. The computation was performed in the same folder as log.txt and ligand_out.pdbqt. Log.txt file showed the binding energy of the ligand to the protein and ligand_out.pdbqt file revealed sites on the proteins with binding energy. The output [.pdbqt] files obtained from the docking study were used to evaluate the hydrophobic interaction of the ligand with the protein. The results were then processed with Chimaera software version 1.8 for the creation of copies of the protein as well as the ligand. This was followed by an assessment of interactions between protein and ligand by using LigPlot+ version 1.4.5 [5–8].

3. Determination of Grid Box Size

The grid box should enclose the known binding site. It should be large enough to accommodate the largest ligand under consideration. It should provide enough room for flexible residues to manoeuvre. If the binding site on the receptor is known, then a smaller grid box will help in the reduction of docking time and increase the accuracy. The figure explains the procedure we adapted to fix the grid box size and to note the values. These values were used to run AutoDock Vina **(Figure 3)**.

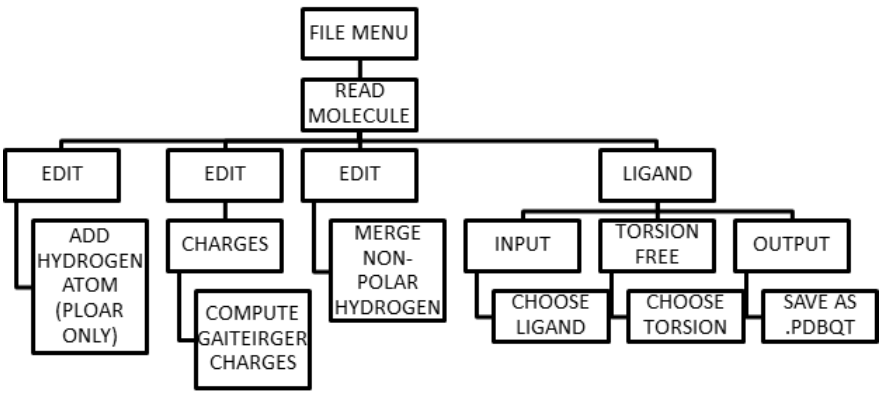


Figure 1: Detailed procedure for preparation of the .pdbqt file is shown.

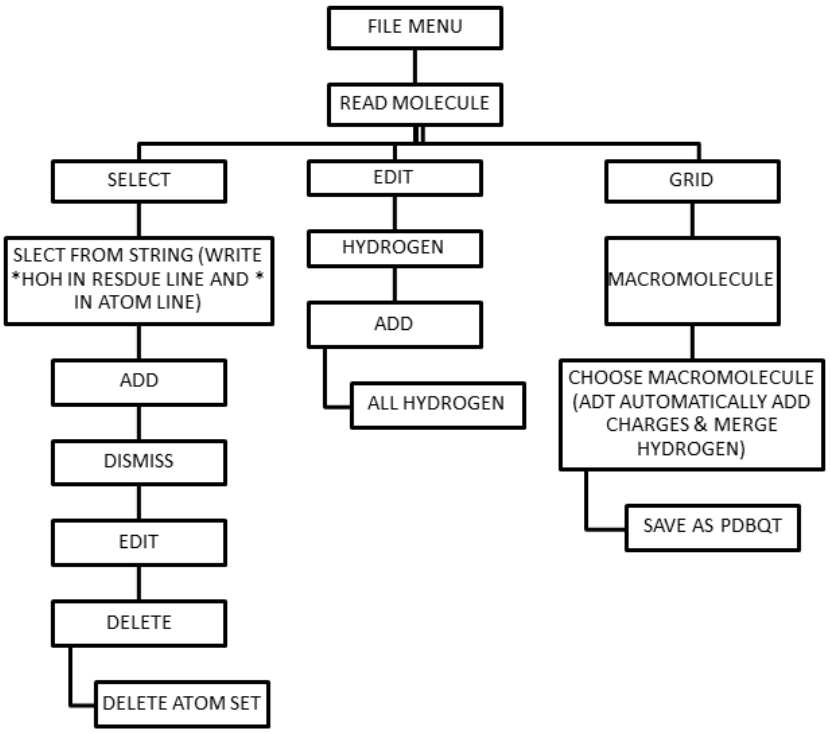


Figure 2: Detailed procedure for preparation of the .pdbqt file is shown.

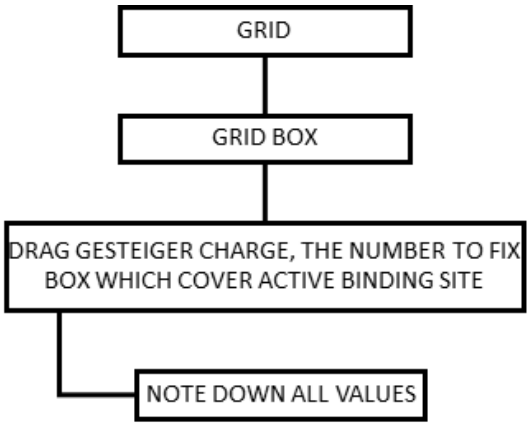


Figure 3: Determination of grid box size.

4. Results

4.1 PPI interaction with $GABA_A$ receptor

Comparative analysis of the binding ability of benzodiazepines and PPI to $GABA_A$ R showed that PPI binds to $GABA_A$ R in an almost similar fashion with high affinity and lower binding energy compared to benzodiazepines, and more hydrophobic interactions that increase the chances of easy binding. Therefore, it can be assumed that PPI may activate $GABA_A$ R, similar to benzodiazepines. Consequently, PPI may lead to neuronal degeneration, possibly causing dementia or AD **(Table 1 and Figure 4)**.

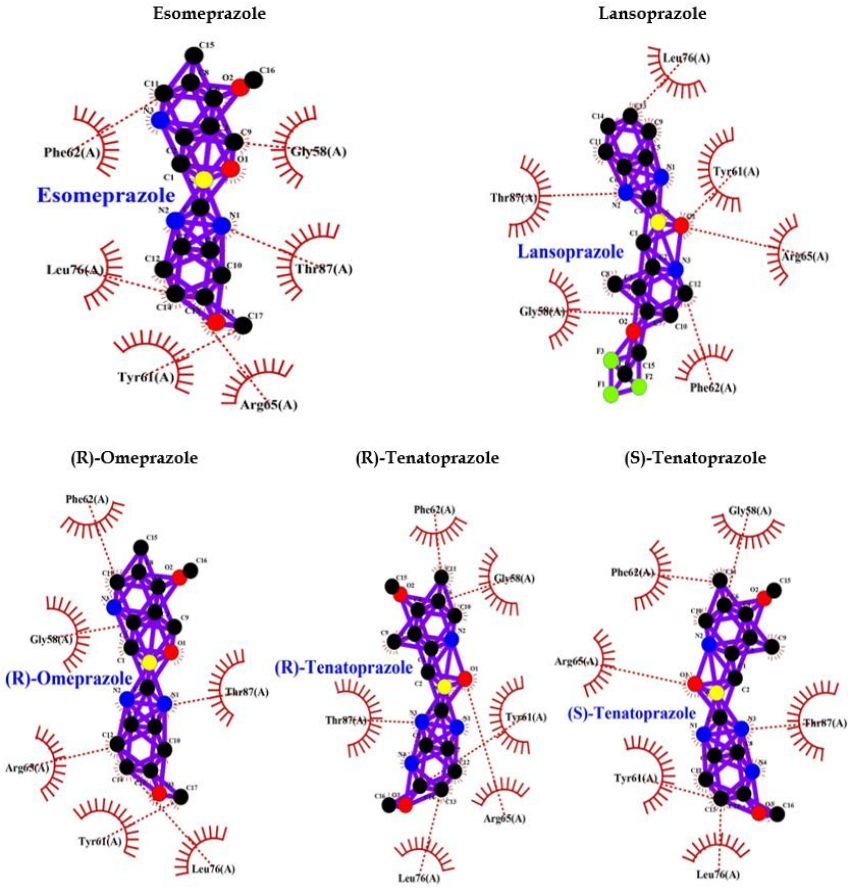
4.2 PPI interaction with AMP-activated protein kinase

PPIs such as (R)-(+)-pantoprazole, esomeprazole, lansoprazole, (R)-omeprazole, (R)-tenatoprazole, and (S)-tenatoprazole bind to AMP-activated protein kinase (AMPK) with less energy compared to the known inhibitor (dorsomorphin) of AMPK. Interaction bonds contain the number of amino acids with hydrogen bonding and hydrophobic bonding. The data have shown the lowest level of energy in the binding site. Thus, PPI can be a potential inhibitor of AMPK, and its long-term use may keep inhibiting AMPK for

the long term and thus may allow AD or dementia development **(Table 2 and Figure 5)**.

Complex with GABA(A) receptor	Energy (Kcal/mol)	Interaction bonds	
		Hydrogen bonding	Hydrophobic bonding
(R)-(+)-Pantoprazole	-8.1	--	Thr87, Phe77, Arg65, Leu76, Tyr61, Phe62, Gly58
Esomeprazole	-8.5	--	Gly58, Thr87, Arg65, Tyr61, Leu76, Phe62
Lansoprazole	-8.8	--	Leu76, Tyr61, Arg65, Phe62, Gly58, Thr87
(R)-Omeprazole	-8.5	--	Phe62, Thr87, Leu76, Tyr61, Arg65, Gly58
(R)-Tenatoprazole	-8.6	--	Phe62, Gly58, Tyr61, Arg65, Leu76, Thr87
(S)-Tenatoprazole	-8.6	--	Gly58, Thr87, Leu76, Tyr61, Arg65, Phe62
Benzodiazepine	-6.6	Leu76 (2.91 A° & 2.88 A°)	Phe77, Thr87, Arg65, Tyr61

Table 1: Protein ligand interactions for 1GNU.



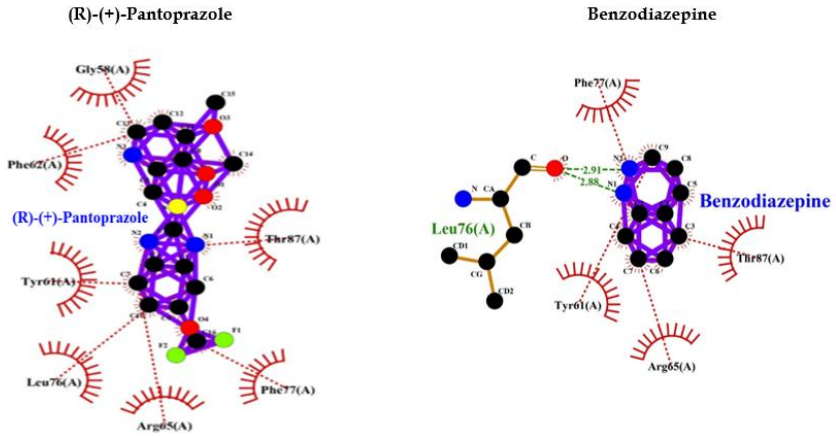
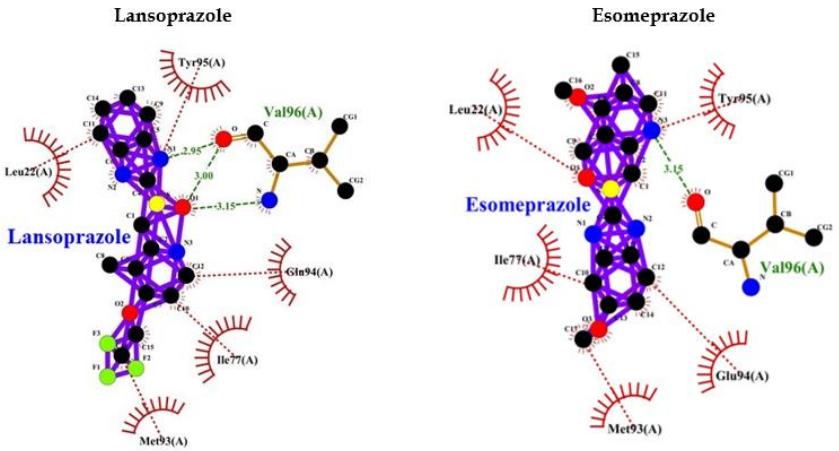


Figure 4: PPI Interaction with $GABA_A$ receptor.

Complex with AMPK	Energy (Kcal/mol)	Interaction bonds	
		Hydrogen bonding	Hydrophobic bonding
(R)-(+)-Pantoprazole	-8.1	Val96 (3.12 A°)	Tyr95, Leu146, Glu94, Met93, Ile77, Leu22
Esomeprazole	-8.1	Val96 (3.15 A°)	Tyr95, Glu94, Met93, Ile77, Leu22
Lansoprazole	-9.5	Val96 (2.95 A°, 3.00 A°, 3.15 A°)	Tyr95, Glu94, Ile77, Met93, Leu22
(R)-Omeprazole	-8.2	--	Leu146, Val96, Leu22, Gly25, Ser161, Asn162, Lys45, Val30, Ala43, Ile77, Tyr95, Glu94
(R)-Tenatoprazole	-8.3	Val96 (3.17 A°)	Gly23, Asn162, Val30, Lys45, Glu94, Tyr95, Ile77, Gly25, Val24
(S)-Tenatoprazole	-8.3	Val96 (3.18 A°)	Gly25, Asn162, Lys45, Glu94, Ile77, Tyr95, Val30, Gly23, Val24
Dorsomorphin	-1.1	--	Pro213, Phe214, Val202

Table 2: Protein ligand interactions for 6BX6.



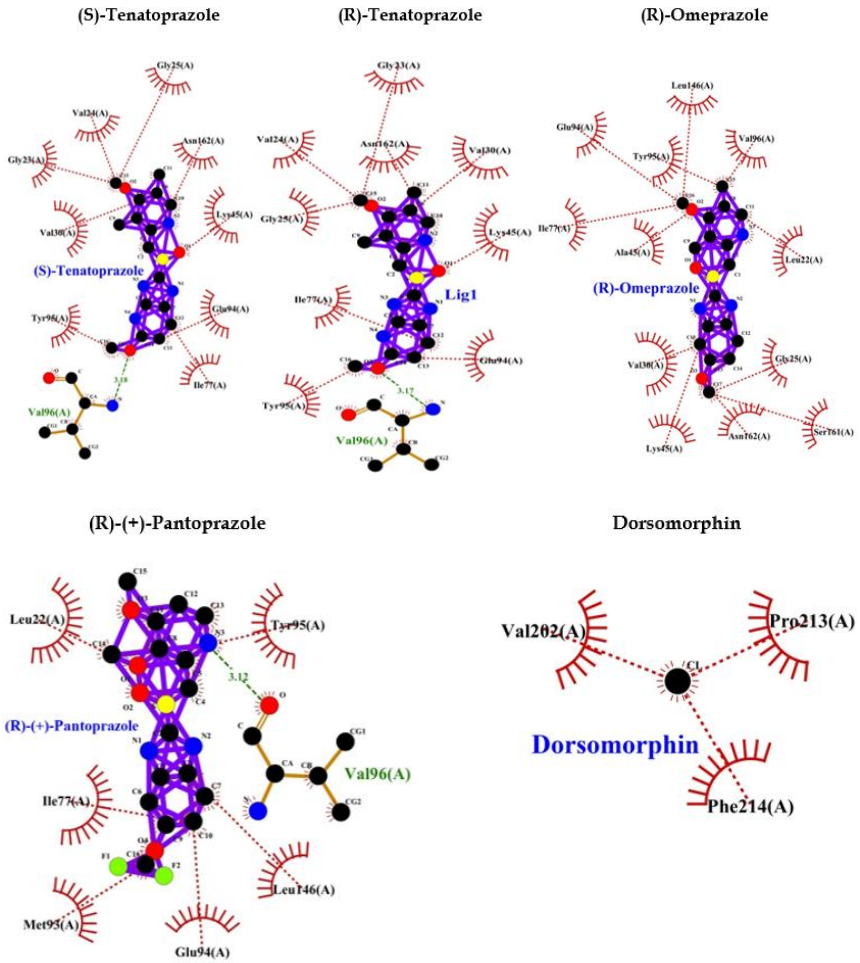


Figure 5: PPI interaction with AMPK.

4.3 PPI interaction with M1 muscarinic acetylcholine receptor

Benztropine is a known inhibitor of M1 muscarinic acetylcholine receptor (M1 mAChR). It shows a binding energy of -9.0 and a few hydrophobic bonds with no hydrogen bonds. Whereas, PPI shows interaction bonds of amino acids with hydrogen bonding and hydrophobic bonding, along with a binding energy lower than benztropine. These data indicate the lowest level of energy in the binding site, and thus, PPI can efficiently bind to M1 mAChR and inhibit it as benztropine **(Table 3 and Figure 6)**.

Complex with M1 muscarinic acetylcholine receptor	Energy (Kcal/mol)	Interaction bonds	
		Hydrogen bonding	Hydrophobic bonding
(R)-(+)-Pantoprazole	-9.5	--	Thr192, Trp157, Tyr106, Tyr404, Ser109, Asp105, Cys407, Tyr408, Trp378, Asn382, Ala196, Phe197, Ala193
Esomeprazole	-10.2	--	Asn382, Phe197, Ala193, Ser109, Trp378, Tyr408, Cys407, Tyr404, Tyr106, Tyr381, Ala196, Thr192
Lansoprazole	-10.6	Tyr106 (3.11 A°)	Asn382, Tyr381, Trp378, Ser109, Cys407, Tyr408, Tyr404, Asp105
(R)-Omeprazole	-9.6	--	Asn422, Thr366, Asn60, Phe63, Ile119, Leu64, Ala363, Lys362
(R)-Tenatoprazole	-9.5	Asp122 (3.00 A°& 3.10 A°)	Glu360, Arg123, Phe63, Ile119, Asn60, Leu64, Val127, Ser126

(S)-Tenatoprazole	-9.5	Asp122 (2.99 A° & 3.10 A°)	Glu360, Arg123, Leu64, Phe63, Asn60, Ile119, Val127, Ser126
Benztropine	-9.0	--	Tyr404, Tyr85, Leu86, Glu401, Tyr82, Trp400

Table 3: Protein ligand interactions for 5CXV.

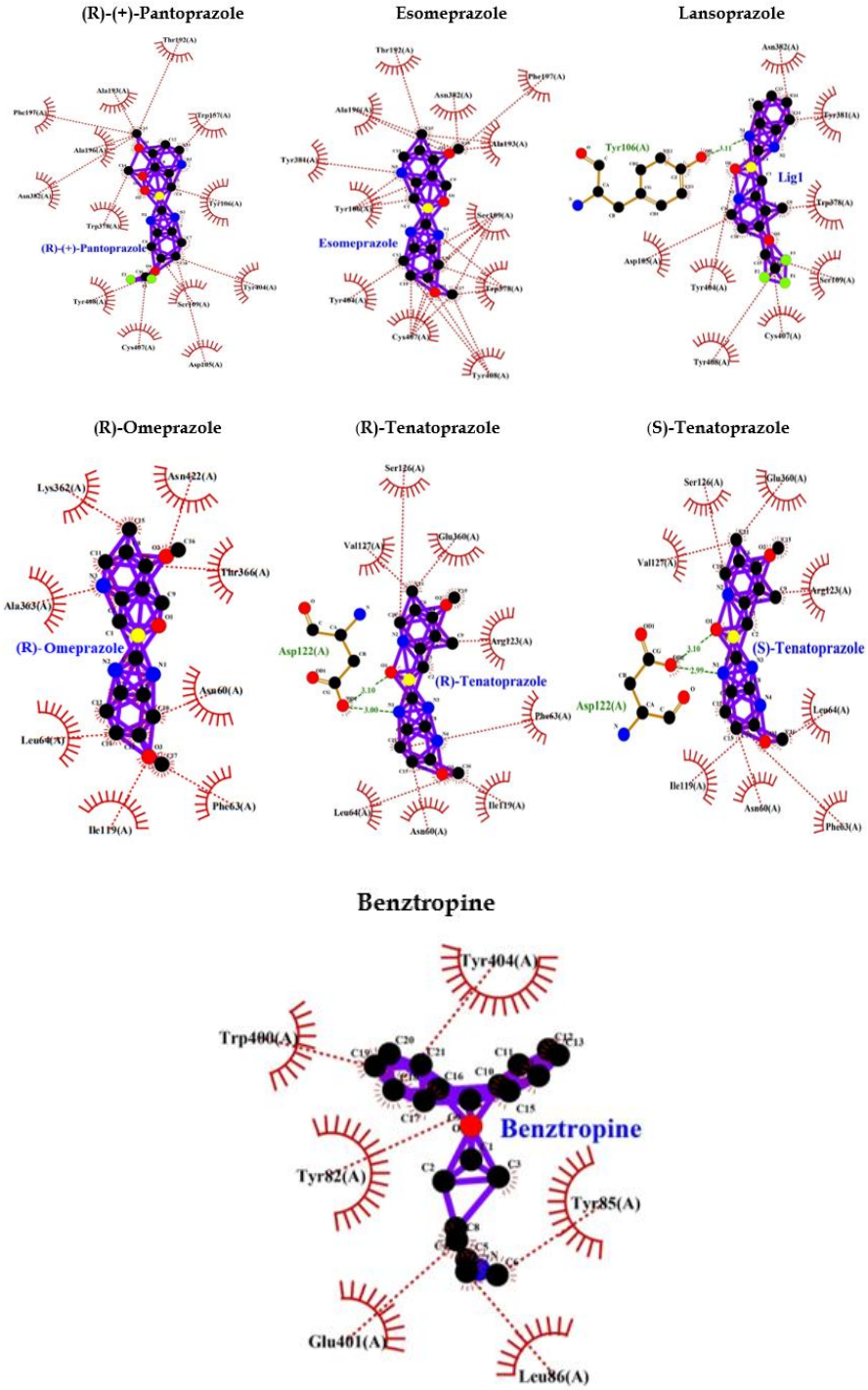


Figure 6: PPI Interaction with M1 muscarinic acetylcholine receptor (5CXV).

4.4 Postulated mechanism linking dementia and PPI use

The buildup of beta-amyloid has been implicated in the progression and pathogenesis of dementia

syndromes such as AD in humans. Central nervous system (CNS) microglial cells use enzymes such as V-ATPase to degrade and scavenge beta-amyloid [2].

Murine models suggest that PPIs interfere with the activity of scavenger enzymes such as V-ATPase, can lead to the accumulation of beta-amyloid [9]. PPIs have also been associated with certain chronic kidney disease (CKD) that may also lead to cognitive impairment, dementia, or AD. Further studies are needed to elucidate the mechanisms linking PPIs with dementia in humans. In the current study, we have considered various CNS-associated proteins by previous studies, such as tau aggregation and beta-amyloid accumulation, to find what type of effects PPI may have on the CNS.

4.5 Effect of PPI on chronic kidney disease and eventually dementia

Kidney disease case reports have linked PPIs to acute interstitial nephritis (AIN) and acute kidney injury (AKI) since 1992. In 2016, two studies received widespread attention because they connected PPIs to an excess risk for CKD [10, 11]. Data retrieved retrospectively from a cohort of 10,482 patients who were actively followed and another larger cohort of 249,751 patients, it was found that PPIs were associated with a 50% increased risk in the smaller cohort and a 17% increased risk for CKD in the larger cohort.

Another study compared 173,321 PPI users with 20,270 H2 receptor antagonist (H2RA) users in a VA dataset [11]. They included patients who had a normal estimated glomerular filtration rate (eGFR) at baseline and followed patients for up to 5 years, and found a 1.8% absolute annual excess risk for CKD in PPI users compared to H2RA users.

These studies are thought-provoking since PPIs' effect on the kidney may vary with the degree of severity within important comorbidity categories such as diabetes [9].

Evidence also exists that CKD is a risk factor for cognitive decline. Earlier studies explain that kidney disorder may be an important mechanism leading to cognitive impairment [12]. Cognitive dysfunction is a well-known complication of CKD [13]. AKI patients have a 3-fold higher risk of developing dementia compared with those without AKI. The association of AKI with dementia or death is valid in several studies and shows an increased risk of 60% [14].

How AKI may lead to cognitive dysfunction is unclear, but increased inflammation, oxidative stress, and endothelial dysfunction are all described complications of AKI [15–17]. In mouse models, ischemic AKI resulted in inflammation and functional changes in the brain. Specifically, compared with sham mice, those with AKI showed increased neuronal pyknosis and microgliosis in the brain [17]. In addition, the mice with AKI had significant microvascular dysfunction in the brain. Whether these changes occur in humans has not been determined, and further study is required. AKI is associated with long-term adverse outcomes. A significantly increased risk of dementia following AKI has been reported in patients without a previous history of cognitive dysfunction [13]. In a previous study conducted in Taiwan involving 2,905 patients, those with AKI had a greater risk of subsequently developing dementia than those without AKI, independent of cardiovascular risk factors [18]. PPI use is associated with an increased risk of AKI, incident CKD, and progression to end-stage renal disease (ESRD), ultimately leading to cognitive impairment [19].

4.6 The effect of PPIs on the central nervous system

AD or dementia is caused by the deposit of beta-amyloid and hyperphosphorylated tau protein in the brain of the patients, while in frontotemporal lobar degeneration, deposits of tau or TDP-43 can be characterized as Lewy body dementia, which is characterized by the presence of alpha-synuclein deposits [20–23].

Symptoms may be similar across different cognitive disorders in both the very early and late stages of the disease, making differential diagnosis challenging. However, the underlying causes of neurodegeneration differ in each condition. Evaluating the risk of PPIs on dementia and AD as a whole may provide essential insights into the disease. In this review, we discuss how PPIs may affect the CNS and contribute to neurodegeneration through various mechanisms.

4.7 PPI may inhibit ATP12A/ATP1AL1 (alpha polypeptide) gene product

The ATP12A/ATP1AL1 genes encode H+/K+-ATPase, which is expressed in the brain, colon, and placenta, while the ATP4A gene encodes H+/K+-ATPase in gastric epithelial cells. RNA blot analysis revealed that the colon had the highest levels of expression, whereas the kidney, uterus, heart, and forestomach had the lowest levels [109]. Moreover, this study has also shown the interaction of H+/K+-ATPase in gastric epithelial cells with rabeprazole and omeprazole [24, 25]. A few other isoforms of the H+/K+-ATPase are expressed in the CNS, which maintains acid-base and potassium homeostasis in neurons [24, 26]. V-ATPases are involved in both exocytosis and endocytosis in nerve terminals and are needed for the packing of neurotransmitters into synaptic vesicles by generating a proton gradient [27, 28]. PPIs, including omeprazole, lansoprazole, dexlansoprazole, rabeprazole, pantoprazole, and esomeprazole, bind to H+/K+-ATPases efficiently on the parietal cell membrane's luminal surface and inhibit acid secretion [29, 30]. Most of the PPIs react with cysteine 813, though the site of reaction on the enzyme differs according to the type of PPI [30]. Due to the homology

properties of P-type ATPases, PPIs can plausibly inhibit even other ionic pumps in the CNS and elsewhere. Hence, PPI may reduce pH in the brain, cerebrospinal fluid, and blood by inducing metabolic alterations.

According to the measurement of PPI passage through the blood-brain barrier (BBB), up to 15% of a single intravenous dose of omeprazole will pass through the BBB and enter the CNS [31]. Repetitive long-term use and 15% of this drug at each dose can potentially become a risk for the brain and can cause cognitive dysfunction. Lansoprazole has also been shown (in vitro and in vivo) to penetrate the BBB [32]. Lansoprazole, esomeprazole, and pantoprazole have been associated with headaches, dizziness, nervousness, tremor, sleep disturbances, and depression [33–35]. There have also been reports of senso-perceptual abnormalities (i.e., hallucinations) [36] and delirium [37] in very rare cases. Although the exact mechanisms of action of PPI on brain circuits and neurological side effects are not fully understood [38]. PPI drugs can facilitate tau and Aß-induced neurotoxicity, which may increase AD progression and cognitive decline. Below, we discuss the most relevant physiopathological mechanisms.

4.8 PPIs and Aβ Plaques

Dementia build-up of ß-amyloid (Aß) protein predisposes to AD. Microglial cells use V-type ATPases to degrade amyloid-ß, and PPIs may block V-ATPases to increase isoforms of amyloid-ß in mice [39]. PPIs increase the development of Aß plaques, which are one of the most well-known factors in the case of dementia [39]. Extracellular aggregation of Aß plaques, which leads to oxidative and inflammatory damage in the brain, is one of the main hallmarks of AD. Aß is produced through the proteolytic processing of a transmembrane protein, amyloid precursor protein (APP), by ß-secretases (also known as ß-site APP-cleaving enzyme 1 [BACE1]) and γ-secretases.

Amyloidogenic processing of APP is carried out by the sequential action of membrane-bound ß- and γ-secretases. ß-secretase cleaves APP into the membrane-tethered C-terminal fragments ß (CTFß or C99) and N-terminal sAPPß. CTFß is subsequently cleaved by γ-secretases into the extracellular Aß and APP intracellular domain (AICD) [40]. Although the total number of Aß plaques does not correlate well with AD severity, there is a direct effect on cognition and cell death in APP/tau transgenic mice because of neuronal loss and the astrocyte inflammatory response investigated the effect of PPIs on Aß production using cell and animal models and suggested a novel hypothesis that considers PPIs as acting like inverse γ-secretase modulators (iGSMs), which change the γ-secretase cleavage site and thereby increase Aß42 levels and decrease Aß38 levels [39, 41]. PPIs also increase BACE1 activity, thereby increasing levels of Aß37 and Aß40. In AD, the major pathological species is thought to be Aß42, but the most produced is Aß40 [42]. PPIs and specifically lansoprazole was also noticed to alter the media pH responsible for amplifying the activity of other proteases, such as memprin-ß, and generating Aß2-37, Aß2-40, and Aß2-42 species. Moreover, Badiola et al. [39] were able to demonstrate that lansoprazole enhances Aß production using in vivo and in vitro models, supporting the theory that PPIs affect AD by boosting Aß production [39, 41]. PPIs inhibit vacuolar proton pumps (VPP) in microglia and macrophages, which acidifies lysosomes by pumping protons from the cytoplasm into the lumen of vacuoles [43, 44]. This acidic environment in lysosomes causes the degradation of fibrillary Aß. As PPIs can cross the BBB, they act on V-ATPases in an inhibitory way, causing less degradation of fibrillary Aß and hence a reduction in its clearance [31, 44]. To date, few studies have explained the relationship between the effects of PPIs and the presence of Aß plaques. It would be interesting if future studies determine why Aß plaque production increases or their clearance decreases with PPI use. Results from solid-state NMR measurements showed that amyloid fibril "cross ß" structures are of two patterns: parallel and antiparallel. Tissue transglutaminase (tTG) causes crosslinking of Aß peptides and indicates that the Aß fibril is a hydrogen-bonded, parallel ß-sheet with the propagation long axis of the Aß fibril [45]. Similar to human AD cases, tTG was related to Aß depositions in these AD models. Evidence for an early role of tTG in Aß pathology was given in an earlier study [46].

One of the oxidative modifications involved in mediating Aß toxicity through Aß aggregation is the formation of dityrosine cross-links. Several studies have shown that Aß can be converted to dityrosine through two different biochemical pathways. One method is peroxidase-catalyzed cross-linked tyrosine, and the second method is metal-catalyzed oxidative tyrosyl radical formation [47–50]. At certain concentrations, omeprazole induced HO-1, which also increased H2O2 levels [51, 52]. This increased hydrogen peroxide due to PPI use may cause the formation of dityrosine cross-links, which leads to the formation of Aß aggregation that ultimately leads to cognitive impairment or dementia, or AD.

4.9 Role of PPI on Tau protein

A definitive diagnosis can only be confirmed histopathologically by the extensive presence of Aß and neurofibrillary tangles (NFTs) in the neocortex of post-mortem brain tissue [53]. The main component of NFTs is paired helical filaments (PHFs) formed from hyperphosphorylated tau protein [54, 55]. Tau protein acts as a microtubule-associated protein in neuronal axons, stabilizing and inducing microtubule assembly [56]. When tau protein is hyperphosphorylated, it loses its ability to bind and stabilize microtubules, resulting in neuron degeneration [57]. According to the neuro-immunomodulation hypothesis of AD, the earliest CNS modifications before the clinical onset of AD are caused by a persistent inflammatory reaction,

which causes excessive tau phosphorylation and triggers the development of PHFs and tau protein aggregates, eventually leading to cytoskeletal changes [58]. As a result, these lesions exist before the onset of clinical signs of AD [59]. They looked at over 2000 compounds to find agents for PET and discovered that quinoline and benzimidazole are high-affinity components of NFTs, and not senile plaques [59]. A docking experiment discovered significant hydrogen bond interactions between the NH group of lansoprazole's benzimidazole ring and the tau core's C-terminal hexapeptide (386TDHGAE391) [58]; lansoprazole has high lipophilicity and can cross the BBB within 37 min and can reach the brain; therefore, it has also been used as a radiotracer for PET imaging [60]. Tau undergoes multiple post-translational changes resulting in conformational modifications in aggregates that alter binding affinities and binding sites of tau protein [60]. Lansoprazole, indeed, with its high affinity for tau protein, can be used to create noninvasive techniques for diagnosing AD in the early stages. This has been proven that the tau protein effectively binds to PPI such as lansoprazole. Thus, the effect of other PPIs on the tau protein and its affinity may also increase aggregation and stabilize tau aggregates. It's worth noting that TSP1 usually forms disulfide-linked trimers; it's unclear if proteins with a proclivity for multimerization are more sensitive to omeprazole, but direct towards further investigation [61].

The appearance of abnormal phosphorylation of the microtubule-associated protein tau in the brains of patients with AD is a key characteristic of the disease's development. Identification of the kinases involved in this mechanism, as well as the development of pharmacological agents to inhibit these molecules, has been a major focus of research. This analysis focuses on recent advances in tau phosphorylation's physiological and pathological effects, as well as the role of phosphorylation in tau toxicity and pathological progression in AD. Therapeutic research is being reshaped by the emerging understanding of tau's functions in cellular biology and the mechanisms by which phosphorylation controls tau activity [62].

The balance of tau kinase and phosphatase activities controls tau phosphorylation. This equilibrium has been proposed to be disrupted, which may lead to abnormal tau phosphorylation and hence, tau aggregation. Thus, identifying the potential causes of tau aggregate development and developing defense methods to deal with these lesions in AD necessitates a thorough understanding of tau dephosphorylating control modes. Stimulation of some tau phosphatases is one of the effective and reasonably precise treatments for reversing tau phosphorylation. We looked at tau protein phosphatases and analyzed their physiological functions and regulation, their function in tau phosphorylation, and their possible connection with AD in this article. We also reviewed the involvement of tau phosphatase, including protein phosphatase 2A (PP2A) [63].

4.10 Effect of PPI on $GABA_A$ receptor

Findings suggest that NR2A receptor activation is critical in limiting tau phosphorylation by the PKC/GSK3 pathway, and they support the concept that these receptors can function as a molecular device to prevent neuronal cell death and a variety of pathological conditions. After $GABA_A$ receptor (R) activation, tau phosphorylation at these residues was elicited by a pathway requiring cdk5, resulting in reduced PP2A interaction with tau [64]. A reduced PP2A will result in increased tau phosphorylation that may stabilize microtubules, leading to neuron degeneration. Thus, hyper-activation of $GABA_A$ R imbalances tau's phosphorylation state, which may ultimately enhance the chances of dementia or AD via neuronal degeneration. According to previous positive interactive studies of PPI with some proteins, we made an interaction of $GABA_A$ R with various PPI and compared the interaction with a well-known $GABA_A$ R activator.

The binding of diazepam (benzodiazepines) to a specific allosteric site on $GABA_A$ R at the interface between α and γ subunits facilitates the inhibitory actions of GABA and can lead to a rapid increase in chloride/bicarbonate channels gating [65], which results in cumulative enhancement of GABA-mediated transmission at inhibitory synapses in the brain. Comparative analysis of the binding ability of benzodiazepines and PPI to $GABA_A$ R showed that it binds to $GABA_A$ R in an almost similar fashion with high affinity, and lower binding energy compared to benzodiazepines **(Table 1 and Figure 4)** and more hydrophobic interactions that increase the chances of easy binding. Therefore, it can be concluded that PPI may activate $GABA_A$ R as benzodiazepines. Accordingly, PPI may lead to neuronal degeneration, causing dementia or AD.

4.11 PPI as a potential inhibitor of AMP-activated protein kinase

A study also indicated that AMPK activation reduces tau phosphorylation, which improves brain function by inhibiting GSK3β in the AD-like model. These findings proved that AMPK might be a novel target for AD treatment in the future. Thus, activation of AMPK can be useful for preventing AD occurrence, and inhibition of AMPK will be unfavorable and may be associated with the development of AD [66]. In the current study, we performed an interactive study between AMPK and various PPIs, and our bioinformatics results showed that PPIs can inhibit AMPK, which may accelerate tau phosphorylation. This can be unfavorable for neuronal development due to imbalanced phosphorylation of tau and activation of GSK3β, which phosphorylates tau. The PPIs, such as (R)-(+)-pantoprazole, esomeprazole, lansoprazole, (R)-omeprazole, (R)-tenatoprazole, (S)-tenatoprazole,

bind to AMPK with less energy compared to a known inhibitor (dorsomorphin) of AMPK [67]. Interaction bonds contain the number of amino acids with hydrogen bonding and hydrophobic bonding. The data has shown the lowest level of energy in the binding site. Thus, PPI can be a potential inhibitor of AMPK, and its chronic use may keep inhibiting AMPK for the long term and thus, may allow AD or dementia development **(Table 2 and Figure 5)**.

4.12 PPI and acetylcholinesterase and M1 muscarinic acetylcholine receptor

A study also suggests that acetylcholinesterase (AChE) and the A-beta peptide may be involved in physiologically relevant interactions associated with the pathogenesis of AD [68]. An advanced in silico docking analysis followed by enzymological assessments was performed on PPIs against the core-cholinergic enzyme that is choline acetyltransferase (ChAT), which synthesizes acetylcholine (ACh). PPIs acted as inhibitors of ChAT, with high selectivity. Given that cholinergic dysfunction is a major driving force in dementia disorders [110]. This study mechanistically explains how prolonged PPI use may increase the incidence of dementia. Thus, prolonged PPI use in the elderly and patients with dementia or amyotrophic lateral sclerosis should be restricted.

4.13 Role of M1 muscarinic acetylcholine receptor in dementia and Alzheimer's disease: PPI binds M1 mAChR in an inhibitory fashion

Aß is an important player in AD and is derived from ß-APP through sequential cleavages by ß and γ-secretases: APP is cleaved by ß-secretase to generate the large secreted derivative sAPPß and the membrane-bound APP C-terminal fragment-ß; the latter can be further cleaved by γ-secretase to generate Aß and AICD. Alternatively, APP can be cleaved by α-secretase within the Aß domain, which prevents Aß production and instead generates secreted sAPPα, a neuroprotective protein [69, 70]. Interestingly, stimulation of M1 mAChR by agonists has been found to enhance sAPPα generation and reduce Aß production [71, 72]. Stimulation of M1 mAChR is well-known to activate Protein kinase C (PKC). PKC is found to promote the activity of α-secretase [72] and the transfer of APP from the Golgi/trans-Golgi network to the cell surface [73]. M1 mAChR stimulation also activates ERK1/2, which modulates α-secretase activity and processing of APP [74], though some contradictory findings show opposite results [72]. In mouse AD models, M1 mAChR promotes brain Aß plaque pathology by increasing amyloidogenic APP processing in neurons and the brain. M1 mAChR also affects BACE1, the rate-limiting enzyme for Aß generation [75, 76]. APP/PS1/tau triple transgenic (3×Tg) AD mice were treated with AF267B, a selective M1 mAChR agonist. It reduces BACE1 endogenous level, accompanied by a decreased Aß level via an unclear mechanism, directly interacts with BACE1, and mediates its proteasomal degradation [77, 78]. However, another study found that stimulation of M1 mAChR upregulates BACE1 levels in SK-SH-SY5Y cells via the PKC and MAPK signaling cascades [79]. M1 mAChR was found to induce the Wnt signaling pathway to counteract Aß-induced neurotoxicity [80]. The involvement of M1 mAChR in AD is also manifested by its amelioration of tau pathology. Carbachol and AF102B (agonists) stimulate M1 mAChR in two time- and dose-dependent manners and decrease tau phosphorylation in PC12 cells [81]. AF267B (M1 mAChR agonist) lessens tau pathology by activating PKC and inhibiting GSK-3ß in 3×Tg AD mice [77, 82]. Activation of M1 mAChR protects against apoptotic factors (such as DNA damage, oxidative stress, caspase activation, and mitochondrial impairment) in human neuroblastoma (SH-SY5Y cells) [83]. M1 mAChR cascade counteracts decreased cerebral blood flow, which is a pathological characteristic in AD, ischemic brain injury, and cognitive dysfunction [84, 85]. Uncoupling of M1 mAChR from G-protein in the hippocampal area, which is the most affected by Aß, was reported in the postmortem brains of AD patients [86–90]. Aß causes the uncoupling of M1 mAChR from G-protein, which inhibits the function of M1 mAChR [91, 92].

Eventually, these studies depicted that a decreased M1 mAChR signal transduction will reduce levels of sAPPα, thereby increasing Aß, thus triggering the onset of pathological features of AD. Though the mechanism of Aß disrupting mAChR-G-protein coupling is unclear and is palliated, implicating antioxidants and reducing the involvement of free radicals [91]. Ultimately, we found that inhibition of M1 mAChR results in dementia and AD, and since PPI has a wide range of interactions with various proteins, we selected to analyze the interaction between PPI and M1 mAChR. Benztropine is a well-known inhibitor of ACh muscarinic M1 and M3 receptors (mAChR). The implication of benztropine promotes differentiation of oligodendrocyte precursor cells and allows greater axonal remyelination in comparison to other drugs or molecules employed for treating multiple sclerosis [93]. More hydrophobic interactions were noticed in the case of PPI in comparison to benztropine, which suggests better chances of binding. PPI showed lower binding energy and higher chances of binding; lansoprazole and tenatoprazole also showed a hydrogen bond, which requires less binding energy. Whereas benztropine showed no hydrogen bonding, and thus PPIs have higher chances of binding, or a similar fashion of binding as benztropine.

PPI may also similarly inhibit M1 mAChR or potentially as benztropine **(Table 3 and Figure 6)**.

4.14 PPIs and vitamin B12 deficiency

Gastric acidity is necessary for the absorption of vitamin B12, which is an essential water-soluble

vitamin, obtained from different dietary sources such as fish, meat, dairy products, and fortified cereal [94]. The risk of B12 deficiency increases with age [95]. B12 is firmly bound to salivary R proteins and consequently requires acid-activated proteolytic digestion. PPI causes hypochlorhydria, resulting in vitamin B12 malabsorption [96]. PPI treatment for 2 years or longer showed a statistically significant association with an increased risk of B12 deficiency [97]. Whereas another study, in contrast, reported that a 3-year or longer PPI use had no change in B12 levels [98].

In recent studies, dementia and cognitive impairment have been associated with vitamin B12 deficiency due to chronic use of PPI [99]. Vitamin B12 is required for the production of nucleotides, phospholipids, and certain monoamine neurotransmitters [100]. Usually, vitamin B12 is responsible for converting tetrahydrofolate into methylcobalamin, which presents its methyl group to homocysteine, which is acted upon by methionine synthase and finally turns into methionine [99]. Vitamin B12 deficiency results in hyperhomocysteinemia and is considered a risk factor for cognitive impairment, dementia, and brain atrophy [101]. PP2A plays a crucial role in brain-associated disorders as it is the key serine/threonine phosphatase and prevents tau hyperphosphorylation in the brain [102]. Reduced methylation reduces PP2A function and leads to hyperphosphorylation and tau aggregation [99]. Hyperhomocysteinemia also increases Aß production, while folate/vitamin B12 supplementation may attenuate these effects in animal models [103, 104].

According to these studies, elevated homocysteine levels are a strong risk factor for developing AD [105]. Alternatively, B12 can interact with thiol groups, i.e., cobalamin can directly bind to tau protein via cysteine, forming a B12/tau protein complex that prevents fibrillation of tau protein [99]. Vitamin B12 capping on cysteine also prevents tau aggregation. In summary, PPI causes vitamin B12 deficiency and hyperhomocysteinemia, leading to PP2A inactivation and tau hyperphosphorylation, which may result in cognitive impairment. The direct binding of vitamin B12 to tau protein, resulting in inhibited fibrillation and aggregation, is also one of the major causes [99].

5. Conclusion

There is currently no consensus on the role of PPIs and their associated risk in the development of dementia and AD. Dementia and AD are multifactorial in nature, and chronic PPI consumption may represent an additional risk factor for inducing neurodegeneration through various interactions with the CNS. Moreover, PPIs, as well as their possible interactions with other drugs, may act as γ-aminobutyric acid ($GABA_A$) agonists, leading to neurological adverse events.

Indeed, people with dementia are often prescribed two or more medications, including PPIs and benzodiazepines, for a long time. The FDA has indicated that adverse events could be associated with PPIs and benzodiazepine interactions. Long-term benzodiazepine use itself has an underlying dementia risk, which can be increased by PPI use. Considering that PPIs can strongly bind and may have an inhibitory action on the $GABA_A$ R, this may lead to neurological dysfunction, the pathophysiology of dementia and AD, and other cognitive dysfunctions.

Though the mechanisms by which PPIs may induce brain impairment are currently unknown, they may influence multimerization and stabilize tau aggregates or increase their susceptibility to form aggregates. Additionally, PPIs affect ionic pumps that control membrane potential in neurons, thereby altering electrochemical gradients.

In summary, our results indicate that chronic treatment with PPIs can significantly influence several biochemical targets, including Aß and tau protein formation, as well as M1 mAChR, AMPK, $GABA_A$ R, and endothelial function. The effects of PPIs on vitamin B12 levels and their ability to induce H_2O_2 production may have indirect impacts on brain health, particularly in older adults with moderate to severe malnutrition or other chronic conditions.

Therefore, before starting a PPI treatment, except in remarkably inevitable cases, it is necessary to assess the cognitive status of patients, as well as the potential pharmacokinetic drug interactions that may occur from the concurrent use of multiple medications and PPIs. Finally, it is necessary to evaluate the risk-benefit ratio of chronic PPI use in patients at risk of dementia and AD when prescribing such drugs.

Author Contributions

Ahmed F and Nazmeen A were the guarantor of the study; Ahmed F, Nazmeen A, Vekaria M contributed to study conception, design, and data acquisition; Ahmed F supervised the manuscript; Nazmeen A and Vekaria M created the figures and tables; Ahmed F, Nazmeen A, and Shahini E provided critical reviews to the manuscript; all authors assisted in formatting, editing and revising the manuscript; all authors interpreted the data and wrote the first and final draft of the manuscript; all authors revised the article critically for important intellectual content and they gave final approval of the article to be published.

Conflicts of Interest

The authors declare no conflict of interest for this article.

References

1. Jaynes M, Kumar AB. The risks of long-term use of proton pump inhibitors: a critical

review. Ther Adv Drug Saf. 2018;10:2042098618809927.

2. Haenisch B, von Holt K, Wiese B, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci. 2015;265(5):419-28.

3. Gomm W, von Holt K, Thomé F, et al. Association of Proton Pump Inhibitors With Risk of Dementia: A Pharmacoepidemiological Claims Data Analysis. JAMA Neurol. 2016;73(4):410-6.

4. Torres-Bondia F, Dakterzada F, Galván L, et al. Proton pump inhibitors and the risk of Alzheimer's disease and non-Alzheimer's dementias. Sci Rep. 2020;10(1):21046.

5. Parasuraman S, Raveendran R, Vijayakumar B, et al. Molecular docking and ex vivo pharmacological evaluation of constituents of the leaves of Cleistanthus collinus (Roxb.) (Euphorbiaceae). Indian J Pharmacol. 2012;44(2):197-203.

6. Thal DM, Sun B, Feng D, et al. Crystal structures of the M1 and M4 muscarinic acetylcholine receptors. Nature. 2016;531:335-40.

7. Knight D, Harris R, McAlister MS, et al. The X-ray crystal structure and putative ligand-derived peptide binding properties of gamma-aminobutyric acid receptor type A receptor-associated protein. J Biol Chem. 2002;277(7):5556-61.

8. Dite TA, Langendorf CG, Hoque A, et al. AMP-activated protein kinase selectively inhibited by the type II inhibitor SBI-0206965. J Biol Chem. 2018;293(23):8874-85.

9. Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology. 2017;152(4):706-15.

10. Lazarus B, Chen Y, Wilson FP, et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. JAMA Intern Med. 2016;176(2):238-46.

11. Xie Y, Bowe B, Li T, et al. Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD. J Am Soc Nephrol. 2016;27(10):3153-3163.

12. Khatri M, Ryan CM, Gao X, et al. CKD Associates with Cognitive Decline in Middle-Aged and Older Adults with Long-Standing Type 1 Diabetes. Kidney360. 2023;4(8):1058-71.

13. Davey A, Elias MF, Robbins MA, et al. Decline in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning and verbal memory. Nephrol Dial Transplant. 2013;28(7):1810-9.

14. Kendrick J, Holmen J, Srinivas T, et al. Acute Kidney Injury Is Associated With an Increased Risk of Dementia. Kidney Int Rep. 2019;4(10):1491-93.

15. Grams ME, Rabb H. The distant organ effects of acute kidney injury. Kidney Int. 2012;81(10):942-48.

16. Verma SK, Molitoris BA. Renal endothelial injury and microvascular dysfunction in acute kidney injury. Semin Nephrol. 2015;35(1):96-107.

17. Liu M, Liang Y, Chigurupati S, et al. Acute kidney injury leads to inflammation and functional changes in the brain. J Am Soc Nephrol. 2008;19(7):1360-70.

18. Kao CC, Wu CH, Lai CF, et al. Long-term risk of dementia following acute kidney injury: A population-based study. Tzu Chi Med J. 2017;29(4):201-7.

19. Xie Y, Bowe B, Li T, et al. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017;91(6):1482-94.

20. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263-9.

21. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134(Pt 9):2456-77.

22. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76(11):1006-14.

23. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with

Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88-100.

24. van Driel IR, Callaghan JM. Proton and potassium transport by H+/K(+)-ATPases. Clin Exp Pharmacol Physiol. 1995;22(12):952-60.

25. Singh V, Mani I, Chaudhary DK. ATP4A gene regulatory network for fine-tuning of proton pump and ion channels. Syst Synth Biol. 2013;7(1-2):23-32.

26. Modyanov NN, et al. The family of human Na,K-ATPase genes. ATP1AL1 gene is transcriptionally competent and probably encodes the related ion transport ATPase. FEBS Lett. 1991;278(1):91-4.

27. Wang D, Hiesinger PR. The vesicular ATPase: a missing link between acidification and exocytosis. J Cell Biol. 2013;203(2):171-3.

28. Tabares L, Betz B. Multiple functions of the vesicular proton pump in nerve terminals. Neuron. 2010;68(6):1020-2.

29. Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil. 2013;19(1):25-35.

30. Shin JM, Munson K, Vagin O, et al. The gastric HK-ATPase: structure, function, and inhibition. Pflugers Arch. 2009;457(3):609-22.

31. Cheng FC, Ho YF, Hung LC, et al. Determination and pharmacokinetic profile of omeprazole in rat blood, brain and bile by microdialysis and high-performance liquid chromatography. J Chromatogr A. 2002;949(1-2):35-42.

32. Rojo LE, Alzate-Morales J, Saavedra IN, et al. Selective interaction of lansoprazole and astemizole with tau polymers: potential new clinical use in diagnosis of Alzheimer's disease. J Alzheimers Dis. 2010;19(2):573-89.

33. Liang JF, Chen YT, Fuh JL, et al. Proton pump inhibitor-related headaches: a nationwide population-based case-crossover study in Taiwan. Cephalalgia. 2015;35(3):203-10.

34. Martin RM, Dunn NR, Freemantle S, et al. The rates of common adverse events reported during treatment with proton pump inhibitors used in general practice in England: cohort studies. Br J Clin Pharmacol. 2000;50(4):366-72.

35. Chimirri S, Aiello R, Mazzitello C, et al. Vertigo/dizziness as a Drugs' adverse reaction. J Pharmacol Pharmacother. 2013;4 Suppl 1:S104-9.

36. Hanneken AM, Babai N, Thoreson WB. Oral proton pump inhibitors disrupt horizontal cell-cone feedback and enhance visual hallucinations in macular degeneration patients. Invest Ophthalmol Vis Sci. 2013;54(2):1485-9.

37. Heckmann JG, Birklein F, Neundörfer B. Omeprazole-induced delirium. J Neurol. 2000;247(1):56-7.

38. de la Coba Ortiz C, Argüelles Arias F, Martín de Argila de Prados C, et al. Proton-pump inhibitors adverse effects: a review of the evidence and position statement by the Sociedad Española de Patología Digestiva. Rev Esp Enferm Dig. 2016;108(4):207-24.

39. Badiola N, Alcalde V, Pujol A, et al. The proton-pump inhibitor lansoprazole enhances amyloid beta production. PLoS One. 2013;8(3):e58837.

40. Chen GF, Xu TH, Yan Y, et al. Amyloid beta: structure, biology and structure-based therapeutic development. Acta Pharmacol Sin. 2017;38(9):1205-35.

41. DaRocha-Souto B, Scotton TC, Coma M, et al. Brain oligomeric ß-amyloid but not total amyloid plaque burden correlates with neuronal loss and astrocyte inflammatory response in amyloid precursor protein/tau transgenic mice. J Neuropathol Exp Neurol. 2011;70(5):360-76.

42. Steven GY, Rudolph ET. Presenilins and Alzehimer's Disease. Berlin: Springer-Verlag, Heidelberg, 1998.

43. Fallahzadeh MK, Borhani Haghighi A, Namazi MR. Proton pump inhibitors: predisposers to Alzheimer disease? J Clin Pharm Ther. 2010;35(2):125-6.

44. Namazi MR, Jowkar F. A succinct review of the general and immunological pharmacologic effects of proton pump inhibitors. J Clin Pharm Ther. 2008;33(3):215-7.

45. Benzinger TL, Gregory DM, Burkoth TS, et al. Propagating structure of Alzheimer's beta-amyloid(10-35) is parallel beta-sheet

with residues in exact register. Proc Natl Acad Sci U S A. 1998;95(23):13407-12.

46. Wilhelmus MM, de Jager M, Smit AB, et al. Catalytically active tissue transglutaminase colocalises with Aß pathology in Alzheimer's disease mouse models. Sci Rep. 2016;6:20569.

47. Atwood CS, Moir RD, Huang X, et al. Dramatic aggregation of Alzheimer abeta by Cu(II) is induced by conditions representing physiological acidosis. J Biol Chem. 1998;273(21):12817-26.

48. Souza JM, Giasson BI, Chen Q, et al. Dityrosine cross-linking promotes formation of stable alpha -synuclein polymers. Implication of nitrative and oxidative stress in the pathogenesis of neurodegenerative synucleinopathies. J Biol Chem. 2000;275(24):18344-9.

49. Yoburn JC, Tian W, Brower JO, et al. Dityrosine cross-linked Abeta peptides: fibrillar beta-structure in Abeta(1-40) is conducive to formation of dityrosine cross-links but a dityrosine cross-link in Abeta(8-14) does not induce beta-structure. Chem Res Toxicol. 2003;16(4):531-5.

50. Atwood CS, Perry G, Zeng H, et al. Copper mediates dityrosine cross-linking of Alzheimer's amyloid-beta. Biochemistry. 2004;43(2):560-8.

51. Patel A, Zhang S, Shrestha AK, et al. Omeprazole induces heme oxygenase-1 in fetal human pulmonary microvascular endothelial cells via hydrogen peroxide-independent Nrf2 signaling pathway. Toxicol Appl Pharmacol. 2016;311:26-33.

52. Al-Hilaly YK, Williams TL, Stewart-Parker M, et al. A central role for dityrosine crosslinking of Amyloid-ß in Alzheimer's disease. Acta Neuropathol Commun. 2013;1:83.

53. Dawbarn D, Allen SJ. Neurobiology of Alzheimer's Disease. BIOS Scientific Publishers, 1995.

54. Farías GA, Vial C, Maccioni RB. Specific macromolecular interactions between tau and the microtubule system. Mol Cell Biochem. 1992;112(1):81-8.

55. Kosik KS, Joachim CL, Selkoe DJ. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. Proc Natl Acad Sci U S A. 1986;83(11):4044-8.

56. Maccioni RB, Cambiazo V. Role of microtubule-associated proteins in the control of microtubule assembly. Physiol Rev. 1995;75(4):835-64.

57. Billingsley ML, Kincaid RL. Regulated phosphorylation and dephosphorylation of tau protein: effects on microtubule interaction, intracellular trafficking and neurodegeneration. Biochem J. 1997;323(Pt 3)(Pt 3):577-91.

58. Rojo LE, Fernández JA, Maccioni AA, et al. Neuroinflammation: implications for the pathogenesis and molecular diagnosis of Alzheimer's disease. Arch Med Res. 2008;39(1):1-16.

59. Okamura N, Suemoto T, Furumoto S, et al. Quinoline and benzimidazole derivatives: candidate probes for in vivo imaging of tau pathology in Alzheimer's disease. J Neurosci. 2005;25(47):10857-62.

60. Fawaz MV, Brooks AF, Rodnick ME, et al. High affinity radiopharmaceuticals based upon lansoprazole for PET imaging of aggregated tau in Alzheimer's disease and progressive supranuclear palsy: synthesis, preclinical evaluation, and lead selection. ACS Chem Neurosci. 2014;5(8):718-30.

61. Cartee NMP, Wang MM. Binding of omeprazole to protein targets identified by monoclonal antibodies. PLoS One. 2020;15(9):e0239464.

62. Dolan PJ, Johnson GV. The role of tau kinases in Alzheimer's disease. Curr Opin Drug Discov Devel. 2010;13(5):595-603.

63. Martin L, Latypova X, Wilson CM, et al. Tau protein phosphatases in Alzheimer's disease: the leading role of PP2A. Ageing Res Rev. 2013;12(1):39-49.

64. De Montigny A, Elhiri I, Allyson J, et al. NMDA reduces Tau phosphorylation in rat hippocampal slices by targeting NR2A receptors, GSK3ß, and PKC activities. Neural Plast. 2013;2013:261593.

65. Nicholson MW, Sweeney A, Pekle E, et al. Diazepam-induced loss of inhibitory synapses mediated by PLCδ/ Ca2+/calcineurin signalling downstream of GABAA receptors. Mol Psychiatry. 2018;23(9):1851-67.

66. Wang L, Li N, Shi FX, et al. Upregulation of AMPK Ameliorates Alzheimer's Disease-Like

Tau Pathology and Memory Impairment. Mol Neurobiol. 2020;57(8):3349-3361.

67. Liu X, Chhipa RR, Nakano I, et al. The AMPK inhibitor compound C is a potent AMPK-independent antiglioma agent. Mol Cancer Ther. 2014;13(3):596-605.

68. Opazo C, Inestrosa NC. Crosslinking of amyloid-beta peptide to brain acetylcholinesterase. Mol Chem Neuropathol. 1998;33(1):39-49.

69. Zheng H, Koo EH. Biology and pathophysiology of the amyloid precursor protein. Mol Neurodegener. 2011;6(1):27.

70. Zhang YW, Thompson R, Zhang H, et al. APP processing in Alzheimer's disease. Mol Brain. 2011;4:3.

71. Haring R, Gurwitz D, Barg J, et al. Amyloid precursor protein secretion via muscarinic receptors: reduced desensitization using the M1-selective agonist AF102B. Biochem Biophys Res Commun. 1994;203(1):652-8.

72. Wolf BA, Wertkin AM, Jolly YC, et al. Muscarinic regulation of Alzheimer's disease amyloid precursor protein secretion and amyloid beta-protein production in human neuronal NT2N cells. J Biol Chem. 1995;270(9):4916-22.

73. Xu H, Greengard P, Gandy S. Regulated formation of Golgi secretory vesicles containing Alzheimer beta-amyloid precursor protein. J Biol Chem. 1995;270(40):23243-5.

74. Bigl V, Rossner S. Amyloid precursor protein processing in vivo--insights from a chemically-induced constitutive overactivation of protein kinase C in Guinea pig brain. Curr Med Chem. 2003;10(10):871-82.

75. Chami L, Checler F. BACE1 is at the crossroad of a toxic vicious cycle involving cellular stress and ß-amyloid production in Alzheimer's disease. Mol Neurodegener. 2012;7:52.

76. Cole SL, Vassar R. The Alzheimer's disease beta-secretase enzyme, BACE1. Mol Neurodegener. 2007;2:22.

77. Caccamo A, Oddo S, Billings LM, et al. M1 receptors play a central role in modulating AD-like pathology in transgenic mice. Neuron. 2006;49(5):671-82.

78. Jiang S, Wang Y, Ma Q, et al. M1 muscarinic acetylcholine receptor interacts with BACE1 and regulates its proteosomal degradation. Neurosci Lett. 2012;515(2):125-30.

79. Züchner T, Perez-Polo JR, Schliebs R. Beta-secretase BACE1 is differentially controlled through muscarinic acetylcholine receptor signaling. J Neurosci Res. 2004;77(2):250-7.

80. Farías GG, Godoy JA, Hernández F, et al. M1 muscarinic receptor activation protects neurons from beta-amyloid toxicity. A role for Wnt signaling pathway. Neurobiol Dis. 2004;17(2):337-48.

81. Sadot E, Gurwitz D, Barg J, et al. Activation of m1 muscarinic acetylcholine receptor regulates tau phosphorylation in transfected PC12 cells. J Neurochem. 1996;66(2):877-80.

82. Forlenza OV, Spink JM, Dayanandan R, et al. Muscarinic agonists reduce tau phosphorylation in non-neuronal cells via GSK-3beta inhibition and in neurons. J Neural Transm (Vienna). 2000;107(10):1201-12.

83. De Sarno P, Shestopal SA, King TD, et al. Muscarinic receptor activation protects cells from apoptotic effects of DNA damage, oxidative stress, and mitochondrial inhibition. J Biol Chem. 2003;278(13):11086-93.

84. Hanyu H, Shimizu T, Tanaka Y, et al. Regional cerebral blood flow patterns and response to donepezil treatment in patients with Alzheimer's disease. Dement Geriatr Cogn Disord. 2003;15(4):177-82.

85. Bateman GA, Levi CR, Schofield P, et al. Quantitative measurement of cerebral haemodynamics in early vascular dementia and Alzheimer's disease. J Clin Neurosci. 2006;13(5):563-8.

86. Ferrari-DiLeo G, Mash DC, Flynn DD. Attenuation of muscarinic receptor-G-protein interaction in Alzheimer disease. Mol Chem Neuropathol. 1995;24(1):69-91.

87. Tsang SW, Lai MK, Kirvell S, et al. Impaired coupling of muscarinic M1 receptors to G-proteins in the neocortex is associated with severity of dementia in Alzheimer's disease. Neurobiol Aging. 2006;27(9):1216-23.

88. Potter PE, Rauschkolb PK, Pandya Y, et al. Pre- and post-synaptic cortical cholinergic deficits are proportional to amyloid plaque presence and density at preclinical stages of

Alzheimer's disease. Acta Neuropathol. 2011;122(1):49-60.

89. Ladner CJ, Lee JM. Reduced high-affinity agonist binding at the M(1) muscarinic receptor in Alzheimer's disease brain: differential sensitivity to agonists and divalent cations. Exp Neurol. 1999;158(2):451-8.

90. Shiozaki K, Iseki E. Decrease in GTP-sensitive high affinity agonist binding of muscarinic acetylcholine receptors in autopsied brains of dementia with Lewy bodies and Alzheimer's disease. J Neurol Sci. 2004;223(2):145-8.

91. Kelly JF, Furukawa K, Barger SW, Rengen MR, Mark RJ, Blanc EM, Roth GS, Mattson MP. Amyloid beta-peptide disrupts carbachol-induced muscarinic cholinergic signal transduction in cortical neurons. Proc Natl Acad Sci U S A. 1996 Jun 25;93(13):6753-8.

92. Janíčková H, Rudajev V, Zimčík P, et al. Uncoupling of M1 muscarinic receptor/G-protein interaction by amyloid ß(1-42). Neuropharmacology. 2013;67:272-83.

93. Deshmukh VA, Tardif V, Lyssiotis CA, et al. A regenerative approach to the treatment of multiple sclerosis. Nature. 2013;502(7471):327-32.

94. Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician. 2003;67(5):979-86.

95. Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. BMJ. 2014;349:g5226.

96. Savarino V, Dulbecco P, Savarino E. Are proton pump inhibitors really so dangerous? Dig Liver Dis. 2016;48(8):851-9.

97. Lam JR, Schneider JL, Zhao W, et al. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA. 2013;310(22):2435-42.

98. Lombardo L, Foti M, Ruggia O, et al. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatol. 2010;8(6):504-8.

99. Rafiee S, Asadollahi K, Riazi G, et al. Vitamin B12 Inhibits Tau Fibrillization via Binding to Cysteine Residues of Tau. ACS Chem Neurosci. 2017;8(12):2676-82.

100. Penninx BW, Guralnik JM, Ferrucci L, et al. Vitamin B(12) deficiency and depression in physically disabled older women: epidemiologic evidence from the Women's Health and Aging Study. Am J Psychiatry. 2000;157(5):715-21.

101. Ma F, Wu T, Zhao J, et al. Plasma Homocysteine and Serum Folate and Vitamin B12 Levels in Mild Cognitive Impairment and Alzheimer's Disease: A Case-Control Study. Nutrients. 2017;9(7):725.

102. Bottiglieri T, Arning E, Wasek B, et al. Acute administration of L-DOPA induces changes in methylation metabolites, reduced protein phosphatase 2A methylation, and hyperphosphorylation of Tau protein in mouse brain. J Neurosci. 2012;32(27):9173-81.

103. Wei W, Liu YH, Zhang CE, et al. Folate/vitamin-B12 prevents chronic hyperhomocysteinemia-induced tau hyperphosphorylation and memory deficits in aged rats. J Alzheimers Dis. 2011;27(3):639-50.

104. Zhang CE, Wei W, Liu YH, et al. Hyperhomocysteinemia increases beta-amyloid by enhancing expression of gamma-secretase and phosphorylation of amyloid precursor protein in rat brain. Am J Pathol. 2009;174(4):1481-91.

105. Ravaglia G, Forti P, Maioli F, et al. Homocysteine and folate as risk factors for dementia and Alzheimer disease. Am J Clin Nutr. 2005;82(3):636-43.

106. Li M, Luo Z, Yu S, et al. Proton pump inhibitor use and risk of dementia: Systematic review and meta-analysis. Medicine (Baltimore). 2019;98(7):e14422.

107. Song YQ, Li Y, Zhang SL, et al. Proton pump inhibitor use does not increase dementia and Alzheimer's disease risk: An updated meta-analysis of published studies involving 642305 patients. PLoS One. 2019;14(7):e0219213.

108. Khan MA, Yuan Y, Iqbal U, et al. No Association Linking Short-Term Proton Pump Inhibitor Use to Dementia: Systematic Review and Meta-analysis of Observational Studies. Am J Gastroenterol. 2020;115(5):671-78.

109. Crowson MS, Shull GE. Isolation and characterization of a cDNA encoding the

putative distal colon H+,K(+)-ATPase. Similarity of deduced amino acid sequence to gastric H+,K(+)-ATPase and Na+,K(+)-ATPase and mRNA expression in distal colon, kidney, and uterus. J Biol Chem. 1992;267(19):13740-8.

110. Kumar R, Kumar A, Nordberg A, et al. Proton pump inhibitors act with unprecedented potencies as inhibitors of the acetylcholine biosynthesizing enzyme-A plausible missing link for their association with incidence of dementia. Alzheimers Dement. 2020;16(7):1031-42.

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