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DEMENTIA: A NEURODEGENERATIVE DISORDER

Anant Srivastava * and Rishabh Singh

Department of Pharmacology, Hygia Institute of Pharmaceutical Education and Research, Faizullaganj, Lucknow - 226020, Uttar Pradesh, India.

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Correspondence to Author:
Anant Srivastava

Assistant Professor,
Department of Pharmacology,
Hygia Institute of Pharmaceutical Education and Research, Faizullaganj, Lucknow - 226020, Uttar Pradesh, India.

E-mail: anantsrivastava88@gmail.com

ABSTRACT: Dementia is a cognitive decline which interferes with normal psychological functioning and behavioral patterns. Dementia is as a group of neurodegenerative diseases, which affects about 1 to 4% of the world's population over 65 years old. Several aetiologies are involved in the pathogenesis of dementia. Patient suffering or suffered from cardiovascular diseases (like hypertension, hypercholesteremia, diabetes, cerebral ischemia, and stroke) and neurodegenerative disorders are more vulnerable to dementia. Other factors like alcohol consumption and smoking further exacerbate this neurodegenerative disorder. Most common forms of dementia are Alzheimer's dementia, vascular dementia, frontotemporal dementia, semantic dementia and dementia with Lewy body. Alzheimer's dementia and dementia with Lewy bodies are more common in the elderly. Vascular dementia (VaD) is the second most common form of dementia after Alzheimer's dementia (AD), which may precipitate as a result of long term CVS diseases. Semantic dementia involves a progressive decline in semantic memory (knowledge of objects, people, concepts and words). In Lewy body dementia (LBD), aggregation of α-synuclein inhibits the neuronal development and plays a major role in the disease pathogenesis. Frontotemporal dementia represents a positive family history and displays a distinctive model of early injury to anterior cingulate and frontoinsular cortex. This review, also signifies the detoxication role of glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidize (GPx), and catalase (Cat) during oxidative stress and discuss the association of mitochondrial dysfunctioning in the pathogenesis of different diseases, which eventually leads to dementia. The aim of this review is, to study types, risk factors involved, understand the underlying mechanisms in the pathogenesis of dementia and new therapeutic approaches, thus maximize opportunities for the search for new and effective therapeutic strategies.

INTRODUCTION: Dementia is a mental disorder characterized by impairment of memory and loss of intellectual ability, sufficiently severe as to interfere with one's occupational or social activities and its prevalence rate increases exponentially with age [1, 2]. The most common subtypes of dementia are Alzheimer's disease (AD) and vascular dementia (VaD) [3].

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If incidence rates of AD differ from those of VaD, differences in the composition of the cohort, in terms of dementia subtypes, may account for a few differences between studies as well [4]. It is interesting to observe that the occurrence rate of these dementia subtypes is similar to that of all-cause dementia.

However, a few insignificant differences in the occurrence rates may occur among AD, VaD, and all-cause dementia in elderly patients [5]. Other studies, however, reported higher incidence rates for AD, which continued to increase with age, as compared to VaD, which remained lower and fairly stable across age [6]. The reason for this discrepancy is unclear. One possibility is the dying-off of the

individuals who are predisposed to VaD. Those individuals are likely to be survivors of cardiovascular diseases and stroke, and therefore are less likely to reach extreme old age. Also, the proportion of men and women who suffer from AD is different from this proportion in VaD. With women at higher risk for AD and having a longer life expectancy than men, differences in incidence rates between AD and VaD may be more robust in specific subgroups [7, 8].

Vascular dementia (VaD) is the second leading cause of dementia after AD [9]. VaD is referred to as the "silent epidemic of the twenty-first century" [10]. It encompasses all dementia syndromes resulting from cerebrovascular disease and typically follows damage from multiple diffuse infarcts, strategic infarcts, subcortical microvascular disease, or hemorrhage [11]. VaD may present either as a stepwise deterioration resulting from new vascular insults or as a chronically worsening condition [12]. There are overlaps in the clinical and pathologic features of VaD and AD due to the frequent existence of cerebrovascular lesions in patients with AD and the potential involvement of cholinergic mechanisms in the pathogenesis of VaD [13]. VaD is a distinct type of dementia with a spectrum of specific clinical and pathophysiological features [14]. Oxidative stress and vascular endothelial are recognized as important contributing factors in the pathogenesis of AD and dementia of vascular origin [14, 15].

Though, their alternations are frequently observed in an already aged brain, characterized by a series of cellular and molecular events that led to the pathogenesis of neurodegenerative diseases. The cell signaling defects and molecular dyshomeostasis might lead to neuronal malfunction before the death of neurons and the alteration of neuronal networks [16]. Optimal treatment of cardiovascular risk factors prevents and slows down age-related cognitive disorders [17]. Further, it has been suggested that dementia prevention can become effective without delay if the vascular components of dementia are aggressively targeted through the treatment of vascular risk factors [18].

Epidemiology: About 1 to 4% of the world's population over 65 years old suffers from dementia [19]. There is a significant variation in the occurrence of dementia in the world. To some extent, it is attributed to the lack of methodological consistency among studies involving diagnostic criteria and different mean population ages. Though, even after considering these factors of bias, differences in age-related dementia is still predominant in various regions of the world [20]. Even with low population aging, the occurrence of dementia is more prevalent in Latin America [21].

This phenomenon involves the combination of low standard educational skill and high vascular risk profile among the locals. However, the prevalence of dementia is the lowest among developed countries like Japan. In the regions like the Middle East and Africa, the number of dementia cases will be significantly large by the year 2040. In other words, low educational background and other socioeconomic factors have been associated with the risk of VaD and AD [20]. Although some of these risk factors are modifiable, there is no study on the efficacy of prevention of VaD [22, 23]. Regulating these factors is critical to generating the commitment to make dementia a public health priority.

Types of Dementia: Dementia is not a single disease entity; rather, it includes disorders that negatively affect brain function, including aspects of cognition, behavior, impact, and social interaction. Dementia impairs a person's ability to manage activities of daily living and increases the annual risk of morbidity and mortality.

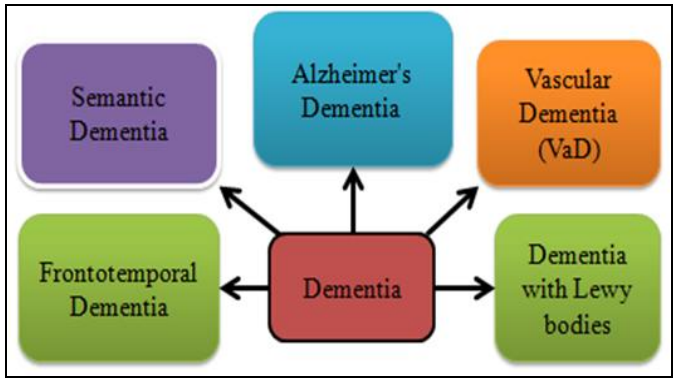

FIG. 1: TYPES OF DEMENTIA

Most common forms of dementia are Alzheimer's dementia, vascular dementia, frontotemporal dementia, semantic dementia and dementia with Lewy body. Alzheimer's dementia and vascular dementia together account for 85% to 90% of all

cases of dementia [27]. Dementias are a group of neurodegenerative disorders, which results in a progressive and irreversible loss of neurons and brain functioning.

Alzheimer's Dementia: Alzheimer's disease (AD) involves a progressive decline in the cognitive, learning and behavioral abilities of the elderly population. It is the sixth leading cause of all deaths and the fifth leading cause of death in persons aged ≥65 years [28]. It was first reported in 1907 by the German neurologist, Alois Alzheimer. The disease is generally classified into two types: sporadic AD (SAD) and familial AD (FAD). SAD accounts for more than 90% of all cases and occurs in patients aged 65 years or older. The å4 allele of the apolipoprotein E gene has been identified as the major risk factor for SAD. FAD is rare, and the age of onset is earlier than that of SAD, with symptoms appearing when patients are in their 40s or 50s. Three genes lead to FAD-amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin (PS2) [29]. Memory impairment in old age is a hallmark of the initial stage of Alzheimer's disease (AD), with dementia developing in the final stages.

According to the amyloid cascade hypothesis, the accumulation of amyloid β- peptide (Aβ) aggregates in the brain triggers a complex neurodegenerative cascade, which results in progressive cognitive impairment and dementia [30]. The neuropathology of AD is characterized by the deposition of Amyloid plaques in the cortex of AD patients. The major protein in neuritic plaques is amyloid β- peptide (Aβ), which is a 40-42 amino acid peptide derived from a membrane protein, the β-amyloid precursor protein (APP) after sequential cleavage by enzymes. APP encoded by a gene on chromosome 21. Genetic evidence implicates Aβ in the pathogenesis of Alzheimer's disease. Most of the patients with trisomy 21 (Down syndrome) develop pathologic changes which are similar to those observed in Alzheimer's disease, suggesting that having an increased copy of the APP gene increases the metabolism of APP to Aβ [31].

Presence of intracellular neurofibrillary tangles (NFTs) is another hallmark feature in the pathogenesis of Alzheimer's disease; these are intraneuronal aggregates of hyperphosphorylated and misfolded tau that become extraneuronal ("ghost" tangles) when tangle-bearing neuron dies. Tau protein is a microtube- associated protein, which is located in the axon, where it facilitates the axonal transport by binding and stabilizing the microtubules. In Alzheimer's disease, tau is translocated to the somatodendritic compartment, where it undergoes hyperphosphorylation, misfolding and aggregation, thus giving rise to neurofibrillary tangles and neuropil threads. The presence of senile plaques (SP) and neurofibrillary tangles (NFT) play a critical role in the pathogenesis of Alzheimer's dementia [32, 33].

Frontotemporal Dementia: Frontotemporal dementia is a focal form of dementia, which affects the personal and social conduct of an individual and is both clinically and pathologically distinct from other forms of dementia. It represents an essential model for understanding the basics functions of the frontotemporal lobes. After Alzheimer's dementia, which accounts for up to 20% of presenile dementia cases in the elderly population, frontotemporal dementia is considered as the most general form of primary degenerative dementia, which equally affects both men and women. Frontotemporal dementia represents a distinctive model of early injury to anterior cingulate and frontoinsular cortex. These regions, though often considered ancient in phylogeny, are the exclusive homes to the von Economo neuron (VEN), a large bipolar projection neuron found only in humans. VEN loss links FTD to its signature regional pattern [34]. Most of the cases with frontotemporal dementia (FTD) report a positive family history, which indicates the significance of genetic research in this disease.

In Parkinsonism, the gene responsible for frontotemporal dementia is linked to chromosome 17q21 has been known for 10 years, several families are found to be associated with the same chromosomal region. However, no particular mutation in the tau gene (MAPT) could be found. Few cases of frontotemporal dementia (FTD) displaying frontotemporal lobar dementia with ubiquitin-positive cytoplasmic and intranuclear inclusions (FTLD-U) were found to lack tau pathology. Mutations in the progranulin gene (PGRN) were found to be responsible for the occurrence of intranuclear inclusions (FTLD-U).

About 50-60% of familial cases of FTD are contributed to mutations in MAPT and PGRN [35].

FTD involves some marked features like early impairment in regulation of personal conduct, early emotional blunting, rapid loss of insight, the decline in personal hygiene, mental rigidity, mental inflexibility, distractibility, persistence, hyper-orality, dietary changes, perseverative behavior [36]. Emotional blunting includes Emotional blunting includes loss of the capacity to demonstrate both primary emotions such as happiness, sadness and fear, and social emotions such as embarrassment, sympathy, and empathy. Both cognitive and emotional awareness is affected, represented by the lack of expression of concern even when confronted by difficulties. The patient does a lot of overeating and usually has a preference for sweet foods.

Preservative and stereotyped behaviors include repetitive behaviors like humming, hand-rubbing, and foot-tapping, with complex behavioral routines. Various neuropathological changes are basically of three types. Around 60% cases of frontotemporal dementia involve degeneration of large cortical nerve cells, spongiform degeneration or microvacuolation of the superficial neuropil; however, gliosis is negligible, and there are no typical alternations like swellings or inclusions within the existing neurons. A second histological pattern accounts for approximately 25% of cases, is characterized by a loss of large cortical nerve cells with widespread and abundant gliosis but minimal or no spongiform change or microvacuolation. And the remaining 15% of cases includes both types of characteristics [37].

Semantic Dementia: Semantic dementia is a syndrome which involves progressive deterioration in semantic memory (knowledge of objects, people, concepts and words). Semantic dementia is a modified type of frontotemporal dementia, which involves progressive semantic decline, precipitation of anomia and preservation. The term ‘semantic dementia’ subsequently was introduced to convey the pattern of profound semantic deterioration which disrupts factual knowledge and object recognition/comprehension as well as semantic aspects of language [38]. In this degenerative disorder, patients present with a progressive loss of expressive and receptive vocabulary; they typically complain of difficulty in ‘remembering’ the names of people, places and things. The language impairment appears strikingly restricted to lexicosemantic processing: at least until late in the course of the disease, syntactic and phonological processes are largely uncompromised [39].

The occurrence of ubiquitin inclusions in the dentate gyrus and cerebral cortex of the postmortem brain is the characteristic feature of frontotemporal degeneration [40]. Semantic dementia involves asymmetrical temporal lobe atrophy (with larger left-sided damage). A severe neuronal degradation is observed in most of the structures associated with left anterior temporal lobe. Structures like entorhinal cortex, amygdala, middle and inferior temporal gyri, and fusiform gyrus are severely damaged. Asymmetrical, predominantly anterior hippocampal atrophy is also present [41].

Dementia with Lewy Bodies: Dementia with Lewy bodies (DLB) is one of the most prominent causes of neurodegenerative dementia in older people. The aggregation of α-synuclein inhibits the neuronal development and plays a significant role in the disease pathogenesis. DLB has many of the clinical and pathological characteristics of dementia that occurs during Parkinson's disease [42]. It is a broad term, which includes some disorders like diffuse dementia, senile dementia and Alzheimer's dementia [43]. DLB is a neurodegenerative disease, which results in slowly progressive and unrelenting dementia until death. Some clinical features like poor attention, frequent visual hallucinations and Parkinsonism are associated with DLB.

Other features associated with DLB include REM sleep disorders, severe neuroleptic sensitivity, and low dopamine transporter uptake in the basal ganglia. Other less frequent features associated with DLB includes repeated falls, syncope, transient or unexplained loss of consciousness, severe autonomic dysfunctioning, hallucinations, delusions, depression, relative preservation and reduced occipital activity [44]. Alpha-synuclein antibodies have exposed the extensive neuritic pathology involved in the DLB, thus signifying a link with other "synucleinopathies" including PD and multiple system atrophy (MSA). The most

significant correlates of cognitive failure in DLB appear to be with cortical LB and Lewy neurites (LNs) rather than Alzheimer type pathology [45].

Vascular Dementia: Vascular dementia (VaD) is believed to be the second most prevalent form of dementia accounting for 10–20% of all dementia case. Persons with VaD exhibit impaired attention, executive functioning, and psychomotor speed performance, but relatively preserved memory function when compared to AD patients. However, it is unclear whether this pattern holds when patients are followed longitudinally. Some researchers posit that VaD patients exhibit a progressive deterioration in cognition, with decline associated with exacerbation of cerebrovascular pathology. This notion is supported by the decline exhibited in some longitudinal studies in global cognitive abilities and domain-specific tasks, particularly in the oldest VaD patients.

However, support for progressive cognitive decline in VaD patients is far from universal; with many studies showing little or no decline over time [46]. Some etiopathogeneses are involved in the pathogenesis of VaD; cerebral ischemia is one of the most common pathologies and an evident proof, which indicates that stroke, plays a major role in the pathogenesis of VaD. VaD is known to increase exponentially with age [47]. Cardiovascular disorders are considered as main risk factors in the pathogenesis of VaD as well as AD [48]. Hyperhomocysteinemia or elevation of plasma total homocysteine is a significant risk factor for cardiovascular disorders, stroke and vascular dementia [49].

Increased levels of homocysteine have been documented to produce changes in the structure and function of cerebral blood vessels along with oxidative stress, which plays a key role in cerebral vascular endothelial dysfunction [50]. Oxidative stress and vascular endothelial dysfunction lead to structural deformities in the cerebral blood vessels that can impair cerebral perfusion with subsequent neuronal dysfunction and death.

These are recognized as important contributing factors in the pathogenesis of AD and other dementia of vascular origin [15, 47]. Other associated risk factors are advanced age, hypertension, diabetes, smoking, hyperhomocysteinemia, hyperfibrinogenaemia and other conditions that can cause brain hypoperfusion such as obstructive sleep apnoea, congestive heart failure, cardiac arrhythmias, and orthostatic hypotension [51]. Several aetiologies are responsible for producing different patterns of cerebral lesions, which result in varying clinical manifestations and psychological deficits.

The diagnostic criteria to characterize vascular dementia should be based on 2 factors: demonstration of the presence of a cognitive disorder by neuropsychological testing and history of clinical stroke or presence of vascular disease by neuroimaging that suggests a link between the cognitive dysfunction and vascular disease [52].

The frequency of VaD increases exponentially with age, and its occurrence vary from country to country. It affects most of the older adults above 65 years of age. The significant risk factors for VaD appear to be hypertension, diabetes, heart disease, stroke, *etc*. Although some of these risk factors are modifiable, there is no study on the efficacy of prevention of VaD. Research is going over VaD and many targets, which are not studied yet, can be explored in the near future. Thus further studies are warranted to find exact mechanisms and to appreciate the full potential of these agents in endothelial dysfunction and dementia of vascular origin.

Risk Factors Involved in the Precipitation of Dementia:

Cerebral Ischemia: The cerebral ischemia is a condition in which oxygen and glucose supply to the brain tissue gets reduced [53]. These pathophysiological mechanisms involve energy failure, which results in neuronal depolarization and causes activation of glutamate receptors, which in turn alters ionic gradients of Na^+, Ca^{++}, Cl^-, and K^+. As glutamate increases in the extracellular space, peri-infarct depolarization occurs [54]. Then, as water shifts occur, cells swell with resulting cerebral edema. The result of increasing intracellular Ca^{++} is an upregulation of a variety of enzyme systems such as lipases, proteases, and endonucleases.

As a result, free O_2 radicals are generated *via* a variety of biochemical pathways, and apoptotic cell

death occurs. Free radicals also induce the formation of a variety of inflammatory mediators such as platelet and endothelium selectins, a variety of molecules, platelet activating factor, tumor necrosis factor, and an assortment of interleukins [55]. Mitochondrial dysfunctioning affects calcium homeostasis in neurons, which plays an essential role in regulating the normal neuronal function. Elevated intracellular calcium level in mitochondrial matrix cause the opening of mitochondrial transition pore, facilitate the production of reactive oxygen species (ROS) and may eventually lead to cerebral ischemia [127].

Hypertension: Hypertension, currently defined as systolic blood pressure (SBP) above 140 mm Hg and diastolic blood pressure (DBP) above 90 mm Hg is a risk factor for many disorders, including AD, stroke, atherosclerosis, myocardial infarction, and cardiovascular disease [56]. Hypertension is estimated to affect 25% of the general population with 50% prevalence in people over 70 years of age [57]. But midlife (approximately 30 years of age) hypertension is mainly associated with an increased risk of developing both AD and VaD, whereas elevated blood pressure late in life does not appear to have the same associated risk [58].

Hypertension or elevated blood pressure, occurring in middle age or late in life, plays an important role in the development of cognitive dysfunction and is associated with an increase in the risk for VaD [59]. It is thought that hypertension causes vascular alterations that then lead to lacunar or cortical infarcts and leukoaraiosis and ultimately cognitive decline. Hypertension can have adverse effects on neuronal health and increase the production of Aβ and can thereby lead to neuronal dysfunction, synapse and neuronal loss, and dementia [60].

Hypotension, defined as having a DBP $\leq$ 70 mm Hg. Although it has been shown that increased blood pressure is a strong risk factor for AD and VaD, a decrease in blood pressure can also have adverse effects on cognition in old age [61]. Pathological changes, such as the development of Aβ plaques, can lead to a reduction of arterial pressure, which in turn may produce hypoxic-ischemic changes that would act synergistically with existing pathology to exacerbate the degree of dementia [62].

Hypercholesterolemia: Elevated level of cholesterol level is also a significant risk factor for induction of vascular cognitive impairment. Hyper-cholestremia leads to activation of the NF-κB pathway. NF-κB is widely known for its ubiquitous roles in inflammation and immune responses, as well as in control of cell division and apoptosis [63]. One of the major pathways to NF-κB activation involves the phosphorylation of IκB by IκB kinase (IKK). An iκb kinase (IKK) affects two catalytic subunits (IKK-α and IKK-β) and a regulatory subunit (IKK-γ). The NF-κB family of transcription factors plays a significant part in the induction of inflammation. Both classical and alternative pathways are involved in regulating the nuclear translocation of NF-κB. Classical NF-κB activation is usually a rapid and transient response to a wide range of stimuli whose main effector is RelA/p50. The nf-κb pathway is a delayed reaction to a smaller range of stimuli resulting in DNA binding of RelB/p52 complexes.

NF-κB activation is a central event of inflammation has been considered as a common feature of many neurodegenerative diseases including Huntington, Parkinson, stroke, and AD [64]. Also, cholesterol plays an essential role in regulating the enzyme activity that is involved in the production of Aβ protein and the metabolism of APP. The cleavage of APP occurs within the hydrophobic lipid bilayer and is catalyzed by the activity of the α-secretase, β-secretase, and γ-secretase enzymes. High levels of cholesterol affect α-secretase activity and result in a decrease in soluble APP levels and an increase in Aβ proteins which are neurotoxic [58].

Diabetes: Diabetes mellitus (DM) is a rapidly increasing global problem. DM is a metabolic disorder that is common in more than 10% of the elderly population and is associated with changes in mental cognition and flexibility. Type 1 DM is characterized by a deficit in the production of insulin by the pancreatic β cells. Type 2 DM is characterized by resistance to the effects of insulin. Hyperglycemia has toxic effects on neurons, which can, in turn, lead to functional or cellular brain deficits through oxidative stress and the accumulation of glycation end products [65]. Advanced glycation end products (AGEs) are sugar-derived substances formed by a non-enzymatic reaction between reducing sugars and

free amino groups of proteins, nucleic acids, and lipids. They are usually produced in the body; however, their formation is greatly increased in individuals with diabetes because of the increased glucose availability [66].

AGE formation causes abnormal interactions of modified extracellular matrix proteins with other matrix proteins and integrins, and this results in decreased elasticity of vessels. Moreover, plasma proteins modified by AGE precursors produce ligands that bind to AGE receptors on endothelial cells. Such binding to the AGE receptor induces the activation of a transcription factor known as NF-κB, which is considered to be a cause of many neurodegenerative diseases [58]. Alternations in the mitochondrial dynamics or mitochondrial dysfunctioning in the organs like pancreas, liver, skeletal muscle, and white adipose tissue are implicated in the development of insulin resistance, obesity, and diabetes. Mitochondrial dynamics play a major role in maintaining brain physiology and are also crucial for neuronal function, survival and development [125].

Oxidative Stress: Oxidative stress is a state in which oxidation exceeds the antioxidant systems in the body. Oxidative stress is detrimental since oxygen free radicals attack biological molecules such as lipids, proteins, and DNA. Oxidative stress affects some biological processes like apoptosis, viral proliferation, and inflammatory reactions. Some gene transcription factors like nuclear factor-B (NF-B) and activator protein-1 (AP-1) are recognized as biomarkers of oxidative stress as they undergo their oxidation and reduction cycling [133]. Low levels of free radicals play an important role in maintaining normal physiological processes, whereas high levels cause detrimental effects. Antioxidants donate their electron to stabiles these free radicals and make them non-reactive.

Oxidative stress, manifested by increased protein oxidation, lipid peroxidation, decreased poly-unsaturated fatty acids (PUFAs), and the presence of reactive oxygen species (ROS), is a major characteristic of dementia. ROS have long been implicated in the pathogenesis of dementia and occur in response to inflammation, injury, and exceedingly low cerebral blood flow, leading to cell injury and death. Mitochondria are considered as a principal site of ROS generation. Superoxide anion ($O_2^{\bullet-}$) is the most common oxygen free radical, which is produced as a result of the inefficient transfer of electrons along the enzymes of the mitochondrial respiratory chain. The leakage of electrons on to molecular oxygen from complexes I and III results in the formation of superoxide anion ($O_2^{\bullet-}$). The rate of $O_2^{\bullet-}$ generation is influenced by the number of electrons available on the mitochondrial respiratory chain. The production of superoxide anion ($O_2^{\bullet-}$) is increased under conditions of hyperoxia and of hyperglycemia, as in diabetes. However, in the case of hypoxia, superoxide anions ($O_2^{\bullet-}$) tend to accumulate as the final electron acceptor (O_2) is unavailable at complex IV [134]. Superoxide dismutase enzymes detoxify Superoxide anion ($O_2\bullet^-$) by converting it to hydrogen peroxide (H_2O_2). Since H_2O_2 is not a free radical and is less reactive than $O_2\bullet^-$; thus it is less detrimental [135].

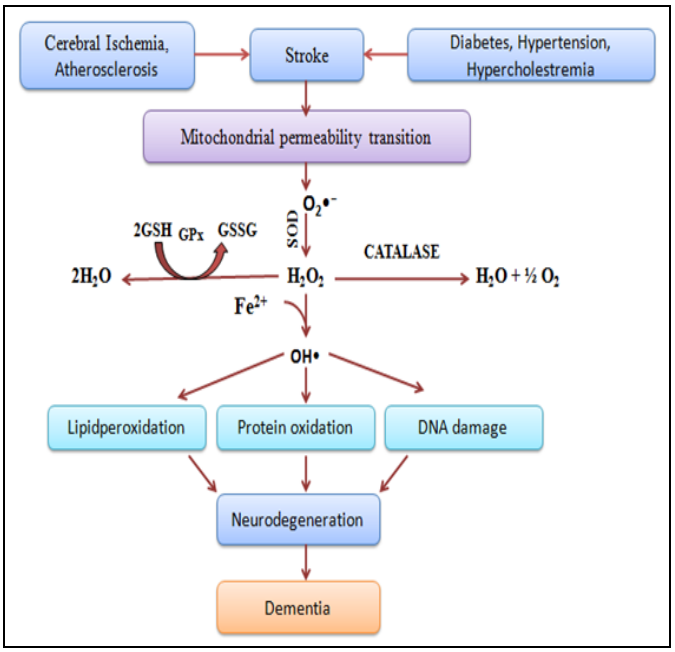

FIG. 2: SCHEMATIC DIAGRAM REPRESENTING THE DETOXIFICATION ROLE OF GLUTATHIONE (GSH), SUPEROXIDE DISMUTASE (SOD), GLUTATHIONE PEROXIDISE (GPX), AND CATALASE (CAT) DURING OXIDATIVE STRESS. Superoxide dismutase (SOD) enzymes detoxify superoxide anion ($O_2\bullet^-$) by converting it to hydrogen peroxide (H_2O_2). H_2O_2 is later detoxified by the enzymes catalase and glutathione peroxidase to H_2O. However, any disturbance in the equilibrium existing between the production of $O_2\bullet^-$ and H_2O_2 may result in the generation of more toxic hydroxyl ion (OH•). The later reaction is catalyzed by ferrous ions (Fe^{2+}) in the Fenton reaction. OH,• ion causes substantial damage and eventually leads to dementia through some pathogenic mechanisms (Lipid peroxidation, protein oxidation, DNA damage).

Since H_2O_2 is non-polar it is able to diffuse across cell membranes and may act as a secondary messenger in signal transduction mechanisms. H_2O_2 is later detoxified by the enzymes catalase and glutathione peroxidase to H_2O [136]. However, any disturbance in the equilibrium existing between the production of $O_2•^-$ and H_2O_2 may result in the generation of more toxic hydroxyl ion (OH•). The later reaction is catalyzed by ferrous ions (Fe^{2+}) in the Fenton reaction. Hydroxyl ion (OH•) is has a life span of 10^{-9} s; it does considerable damage within this time duration. Hydroxyl ion (OH•) is highly toxic and dangerous, and there is no known scavenger of OH• [134]. Reactive oxygen species (ROS) produced as a result of mitochondrial dysfunctioning is linked with the pathogenesis of CVS diseases like hypertension, cardiac hypertrophy, atherosclerosis, cerebral ischemia, and other endothelial diseases. Additionally, the overproduction of oxygen species, progressive respiratory chain dysfunction, and mitochondrial DNA damage further aggravate any existing CVS or neurodegenerative diseases [126].

Tobacco Smoking: There are roughly 1.3 billion tobacco smokers in the world, and this figure is estimated to become 1.7 billion by the year 2025. Long term tobacco smoking may result in the precipitation of CVS diseases in individuals. Chronic exposure to tobacco smoke may exacerbate mitochondrial dysfunctioning and gradually leads to oxidative stress through ROS production [130]. Chronic smoking is reported to show detrimental effects on complex IV and complex III activities in mitochondrial respiratory chain (MRC), which is considered as the underlying mechanism in the pathogenesis associated with tobacco consumption [131].

Mitochondrial dysfunctioning in neurons promote oxidative stress and may eventually lead to dementia [132]. Smoking causes many deleterious effects through vascular mechanisms, which result in atherosclerosis and thrombosis and increase the risk of cognitive decline. First, it has been established that exposure to tobacco can lead to the development of atherosclerosis, which in turn leads to an increased risk of ischemic stroke and hence dementia [70]. Second, nicotine has been shown to modulate the neurotoxic effects of Aβ, can exert potent neuroprotective effects, and may confer resistance to dementia. The presence of nicotine from cigarettes causes an up-regulation and activation of nicotinic acetylcholine receptors, which in turn protect against Aβ cytotoxicity [71].

Alcohol Consumption: Alcohol consumption is one of the health concerning issues worldwide. Alcohol consumption shows both positive and negative influence on the disease pathology. Different drinking patterns affect our body physiology in different ways; moderate use of alcohol is found to be beneficial (under certain conditions), whereas it's excessive consumption is dangerous to one's health [72]. The effects of heavy alcohol consumption and alcoholism are detrimental to memory function [73].

However, according to a recent study, the people who renounce alcohol in midlife or consumed more than 14 units per week are more prone to risks of dementia [74]. Alcohol is neurotoxic and long-term chronic ingestion of alcohol may precipitate neurodegenerative diseases like cerebellar degeneracy and alcoholic dementia. However, the mechanisms involved in the alcohol-induced neurotoxicity are still poorly understood. According to one of the hypotheses, activated microglial cells with elevated AGE-albumin levels may play an important role in promoting alcohol-induced neurodegeneration [75]. Ethanol facilitates the production of ROS and by hampering cellular defense mechanisms. These detrimental effects of ethanol are prominent in the liver, which is the major site of ethanol metabolism in the body [129].

Atherosclerosis: Atherosclerosis occurs as a result of chronic inflammation in which the artery wall thickens due to the accumulation of cholesterol, macrophages and smooth muscle cells (SMC), eventually restricting blood flow through the coronary artery and is considered as the major underlying pathologic condition that may ultimately lead to a number of cerebrovascular and cardiovascular diseases. Atherosclerosis is a cardiovascular disease that is known to affect both large and medium-sized arteries. In the brain, the circle of Willis is a part of the cerebral circulation. The blood vessels associated with the circle of Willis are more vulnerable to atherosclerosis and its severity increase with age [76]. Atherosclerotic plaques may rupture and result in thrombosis. The

thrombus may occlude the blood vessel and may result in an embolism. Embolism generally arises in the extracerebral regions of the vertebral artery the carotid arteries. An atherosclerotic aneurysm is a consequence of cerebral vessel wall destruction, rarely leading to subsequent rupture and hemorrhage [77]. Hence, vascular dysfunction in the brain acts as a contributing factor to the development of stroke and vascular dementia [78]. Reactive oxygen species (ROS) produced as a result of mitochondrial dysfunctioning is also linked with the pathogenesis of CVS diseases like hypertension, cardiac hypertrophy, atherosclerosis and other endothelial disorders [126]. Excessive production of mitochondrial reactive oxygen species promotes the destruction of pancreatic beta-cells, increased oxidation of LDL protein and dysfunction of endothelial cells-factors that promote atherosclerosis. Disturbances in mitochondrial dynamics may initiate apoptosis, thus facilitating plaque rupture. Subclinical episodes of plaque rupture may gradually lead to hemodynamically significant atherosclerotic lesions. Flow-limiting plaque rupture may further lead to myocardial infarction and stroke [128].

Stroke: Post-stroke patients frequently suffer from Cognitive Impairment and dementia. There is a close link existing between cerebrovascular disease and dementia. Generally, the onset of vascular dementia occurs with an incident of ischemic stroke. However, the underlying mechanisms involved in post-stroke cognitive impairment are still unknown [79]. Those at high risk of stroke may be at high risk of cognitive impairment and dementia after stroke [80]. Stroke is the most common risk factor for VaD, including the augmentation of β-amyloid production and tau protein phosphorylation.

Following the ischemic episode, the expression of the amyloid precursor protein (APP) upregulates β-amyloid oligomers in the brain's extracellular spaces and amyloid precursor protein production increases in astrocytes. The interaction between β-amyloid and factors like apolipoproteins, presenilins, tau protein, α-synuclein, inflammation factors, leads to ischemic brain degeneration, which involves degradation of the white matter and thus cell death. Except for necrotic cell death which happens within minutes, neuronal death (including apoptosis) commences several hours after ischemic stroke and lasts several days [81].

Blood-Brain Barrier Dysfunction: Another possible hypothesis that accounts for the pathogenesis of cognitive dysfunction is the impairment of blood-brain barrier. The BBB, found in all vertebrates, prevents the free diffusion of circulating molecules, leukocytes, and red blood cells into the brain interstitial space and is an essential regulator of the neuronal and glial cell environment. The barrier is formed by the presence of epithelial-like, high-resistance tight junctions that fuse brain capillary endothelial cells into a continuous cellular layer separating the blood and brain [82].

The disruption of tight junctions that are found in endothelial cells results in altered transport of molecules between the blood and brain and the brain and blood, aberrant angiogenesis, vessel regression, brain hypoperfusion, and inflammatory responses, and it can have detrimental effects on synaptic plasticity and neuronal survival. Indeed, reduced microvascular density, increased fragmentation of vessels, increased thickening of basement membranes, increased vessel diameter, and a reduced number of endothelial mitochondria [83]. Two main receptors are responsible for amyloid influx and efflux across the BBB.

The receptor for advanced glycation end products (RAGE), responsible for the influx of amyloid across the BBB, is a multi-ligand receptor in the immunoglobulin superfamily found in neurons, microglia, and cerebral endothelial cells. LRP, responsible for the efflux of Aβ across the BBB, is a member of the low-density lipoprotein receptor family and is a multifunctional scavenger and signaling receptor. Its ligands include biomolecules such as ApoE, APP, Aβ, α2-macroglobulin, tissue plasminogen activator, and lactoferrin [84, 85]. LRP is expressed in brain capillary endothelium, and exhibits reduced expression during normal aging [86].

Hyperhomocysteinemia: Homocysteine is one of the major markers of neurodegenerative diseases. Neurodegenerative diseases like Alzheimer's disease, vascular dementia, cognitive impairment or stroke are associated with increased levels of Homocysteine. Patients with severe hyper-

homocysteinemia (HHcy) are more prone to neurodegeneration [87]. Disturbance in the level of homocysteine is associated with atherosclerosis, stroke, and dementia.

Homocysteine causes extracellular matrix remodeling by the activation of matrix metalloproteinase-9 (MMP-9), in part by inducing redox signaling and modulating the intracellular calcium dynamics. Calpains are the calcium-dependent cysteine proteases, which are implicated in mitochondrial dysfunctioning by promoting oxidative injury. Mitochondrial abnormalities have been identified in hyperhomocysteinemia [88]. However, severe hyperhomocysteinemia (HHcy) is also an indicator of B vitamin deficiency, and the patient's clinical outcome can be improved by vitamin B supplementation [89].

Heavy Metal: Arsenic causes health concerns due to its significant toxicity and a worldwide presence in drinking water and groundwater [90]. Arsenic at high doses is a known neurotoxin with both neuro-developmental and neurocognitive consequences [91]. Arsenic exposure has been shown to cause morphologic and neurochemical alterations in the hippocampus, and other memory-related neuronal structures and expected learning and memory deficits have been noted [92]. Arsenic (As) is a toxic metalloid existing widely in the environment, and chronic exposure to it through contaminated drinking water has become a global problem of public health [93]. Arsenic is a well-known neurotoxin that leads to learning and memory impairment. The NMDA receptor complex and signaling proteins play important roles in synaptic plasticity, learning and memory and it has been studied that altered expression of NMDA receptor complex and postsynaptic signaling proteins explains arsenic-induced neurotoxicity and learning and memory impairment.

Some researchers also reported that arsenic exposure led to disturbance in biogenic amines (norepinephrine, serotonin, and dopamine) in the brain and resulted in impairment of learning and memory [94]. Some researchers have seen detrimental changes in neuronal synapses by arsenic exposure and hence contribute to impairment of spatial memory. Few scientists have demonstrated that arsenic exposure results in downregulation of Ca^{2+}/calmodulin-dependent protein kinase IV, an essential modulator of Long term depression (LTD) and induces learning and memory impairment [95]. It has also been reported that arsenic induces autophagy during the development of their toxicity on the brain. Although, autophagy if a cytoprotective reaction it causes a disturbance in cytoprotective autophagy and leads to cell/tissue injuries of the brain which further leads to learning and memory impairment [96].

Apart from brain damage oxidative stress is also associated with arsenic-induced learning and memory impairment. ROS produced by Nox proteins contributes to neurocognitive pathologies. Calcium regulation is significant in learning and memory [97], increase in calcium level by arsenic leads to impairment in learning and memory [98]. Therefore, arsenic leads to impairment in learning and memory through alteration in NMDA receptors, disturbances in biogenic amines, down-regulation of Ca^{2+}/calmodulin dependent protein kinase IV, oxidative stress, increase in calcium level and brain damage. Arsenic exposure plays a vital role in the pathogenesis of vascular endothelial dysfunction [99].

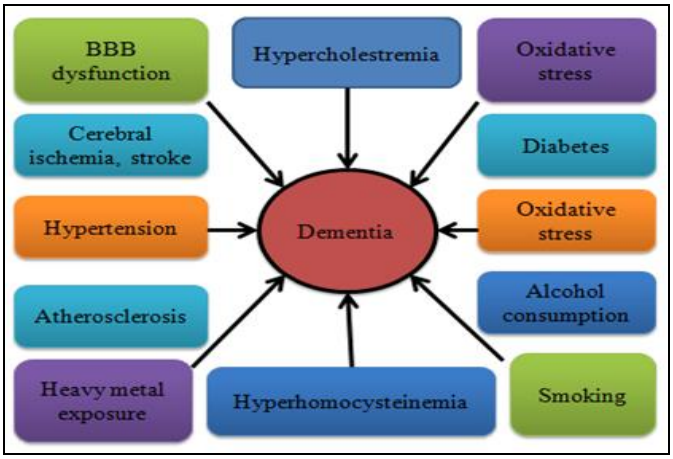

FIG. 3: DIFFERENT RISK FACTORS ASSOCIATED WITH THE DEMENTIA

Current Therapeutic Approaches in the Treatment of Dementia:

Nuclear Factor Kappa B-Receptors Antagonists: The nuclear factor kappa-B (NFκ-B) family of transcription factors regulates the induction and resolution of inflammation. NFκ-B is thought to promote cardiovascular disorder including endothelial dysfunction through its pro-inflammatory, pro-adhesion and pro-oxidant gene

transcription [100]. It has also been suggested that NFκ-B is involved in amyloid beta-42 induced neuronal cell death and subsequent memory impairment [101]. In aging-induced dementia, there is an activation of NFκ-B which results in the upregulation of genes of pro-inflammatory enzymes. Inhibition of NFk-B has been reported to exert a beneficial effect in experimental VaD [102].

NADPH Oxidase Inhibitor: NADPH oxidase is a multi-subunit enzyme complex, which plays a role in microbial activation and the production of both extracellular and intracellular ROS [103]. It is a multi-protein, electron transport system, which generates large amounts of superoxide *via* the reduction of molecular oxygen. NADPH oxidase is responsible for producing reactive oxygen species (ROS) and is also involved in several other physiological processes like host defense and signal transduction [104, 67]. NADPH is a superoxide-producing enzyme and has been implicated in several oxidative stress conditions including hypertension, and it is significantly activated in AD brains [68].

It has been shown that the presence of excess superoxide (O^{2-}) radicals in the brains of APP mice is due to the activity of NADPH oxidase, and the inhibition of NADPH activity by either pharmacological inhibitors or the inhibition of the NADPH oxidase complex assembly blocked the production of ROS and cerebrovascular dysfunction induced by Aβ and aging [69]. It has been found that there is an impairment of endothelium-dependent responses in the cerebral microcirculation through ROS generated in cerebrovascular cells by the enzyme NADPH oxidase that may cause increased susceptibility to cellular dysfunction, cellular death, and dementia. 4'hydroxy-3'-methoxyacetophenone (HMAP), an NADPH oxidase inhibitor has appreciably prevented induced endothelial dysfunction, memory impairment and biochemical changes in STZ induced diabetes in rats [105].

HMG-Co A Reductase Inhibitors: Statins are commonly known as HMG-Co A reductase inhibitors and are frequently used in the treatment of cardiovascular diseases. Statins are generally used to reduce serum cholesterol levels and thus to reduce the mortality associated with coronary heart disease. It has been reported that statins exert neuroprotective and antioxidant actions. Statins also improve learning and memory of animals. Statins have been shown to reduce the risk of ischemic stroke and related memory impairment by a variety of mechanisms [106]. It has also been reported that the ameliorative effect of statins in L-Methionine induced VaD [107, 108].

Angiotensin II Blockers: The local renin-angiotensin system (RAS) in the brain is a multitasking system. Aside from its vasoactive actions, brain angiotensin II (AT-II) has also been implicated in the pathogenesis of cognitive decline, and beneficial effects of angiotensin receptor blockers (ARBs) in AD are suggested [109]. AT-II type 1 receptor blockers (ARBs) have been demonstrated to reduce the onset of stroke, stroke severity, the incidence, and progression of dementia, as ARBs protect against ischemic brain damage and associated cognitive decline owing to an increase in cerebral blood flow and reduction in oxidative stress [110].

PPARγ Agonists: Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptors superfamily which are present in three isoforms as α, β/δ and γ [111]. PPAR-γ is present on vascular cells, exert a protective role in the vascular endothelial dysfunction [112]. PPAR-γ receptors are distributed broadly in central nervous system [113], and activation of these receptors prevents neuronal death by reduction of oxidative stress and inflammatory mechanisms [114]. Furthermore, PPAR-γ agonists have the potential to modulate various signaling molecules/pathways, including mitogen-activated protein kinases (MAPK), signal transducer and activator of transcription, amyloid precursor protein degradation, beta-site amyloid precursor protein cleaving enzyme 1 (BACE 1) [115] and Wnt signaling. Moreover, it has been recently reported that PPAR-γ is involved in the improvement of memory and cognitive function in AD [116].

Androgens: Testosterone is a gonadal sex steroid hormone, which affects some body tissues, including the brain. Beyond its reproductive function, this hormone is responsible for increased muscle mass, sexual function and libido, body hair and decreased risk of osteoporosis. Testosterone is

also known to induce neurogenesis [117]. Gender-specific morphological and behavioral patterns of the adult are determined by the presence or absence of this hormone during certain critical periods of the central nervous system (CNS) development [118].

Neuroprotective mechanism of androgens involves mitogen-activated protein kinase (MAPK) signaling in neurons. Testosterone and its metabolite dihydrotestosterone (DHT) are known to transiently activate MAPK in cultured hippocampal neurons, which involve the phosphorylation of extracellular signal-regulated kinase (ERK)-1 and ERK-2. Interestingly, the pharmacological suppression of MAPK/ERK signaling is known to mediate neuroprotection against beta-amyloid toxicity. Downstream of ERK phosphorylation suggested that DHT sequentially increases p90 kDa ribosomal S6 kinase (Rsk) phosphorylation and phosphorylation-dependent inactivation of BCl-2-associated death promoter protein (BAD). Prevention of androgen-induced phosphorylation of Rsk and bad blocked androgen neuroprotection [119]. Androgen deficiency is known to deteriorate endothelial functions since its lack leads to increased blood glucose levels, total cholesterol, low-density lipoprotein, levels of pro-inflammatory cytokines, and increased thickness of the arterial wall [120].

Inducible Nitric Oxide Synthase (iNOS): Nitric oxide (NO) is a crucial regulatory molecule, which plays an essential role in maintaining the homeostatic conditions associated with the cardiovascular, immune and nervous systems. NO is synthesized by the enzyme NO synthase (NOS), which is found in three isoforms classified as neuronal (nNOS), inducible (iNOS), and endothelial (eNOS). Inducible nitric oxide synthase (iNOS) plays an essential role in neuro-inflammation by generating high levels of brain nitric oxide (NO), a critical signaling and redox factor in the brain [121].

HDAC (Histone Deacetylase) Inhibitors: Histone deacetylase inhibitors (HDACis) are agents which inhibit histone deacetylases (HDACs) and facilitate posttranslational acetylation of lysine residues within nuclear and cytoplasmic proteins. HDAC inhibition has an intense effect on the acetylation status of histone proteins (within chromatin), resulting in the enhanced expression of genes related to protection from an ischemic insult. Recent researches have reported the neuroprotective role of histone deacetylase inhibitors like trichostatin A (TSA), sodium butyrate (SB), and vorinostator suberanilohydroxamic acid (SAHA) in the hypoxia-ischemia injury. Histone deacetylase inhibitors (HDACis) shows neuroprotection by preventing the serum levels of chemokine CXCL10, IL-1β, and COX-2 in the ipsilateral hemisphere [122]. Histone deacetylases (HDACs) play a key role in homeostasis of protein acetylation in histones and other proteins and also in regulating fundamental cellular activities such as transcription. Acetylation and deacetylation of histone proteins associated with chromatin play a pivotal role in the epigenetic regulation of transcription and other functions in cells, including neurons. HDAC inhibition has been reported to exert neuroprotective effects in both *in-vivo* and *in-vitro* models of brain disorders [123, 124].

DISCUSSION AND CONCLUSION: Dementia is the loss of cognitive function of sufficient severity to interfere with social and occupational functioning. There are different kinds of symptoms in dementia including – (i) impairment in activities of daily life, (ii) abnormal behavior and (iii) loss of cognitive functions [24]. Dementia most often occurs after 65 years of age, but it can also occur before 65 years of age and known as early onset of dementia [25]. There are many who will not receive a diagnosis of dementia until late in the course of the disease for a variety of reasons but have recognizable cognitive deficits. Mild cognitive impairment (MCI) involves measurable cognitive deficits but is considered to be at the high factor of progressive dementia [26]. Some medicines are currently available to treat dementia.

However, existing medications may provide moderate symptomatic benefits but are incapable of stopping disease progression. To prevent the progress of dementia, it is essential to interfere with the mechanism involved in the underlying disease pathogenesis. The search for novel therapeutic approaches targeting the underlying pathogenic mechanisms is essential to develop more novel medications with disease-modifying properties, which will provide more competent treatment

alternatives in the future. In this review, a brief information is provided with respect to few potential therapeutic novel agents like Nuclear factor kappa-B (NFκ-B) receptors antagonists, NADPH oxidase inhibitor, HMG-Co A reductase inhibitor, angiotensin II blockers, PPARγ agonists, androgen, inducible nitric oxide synthases (iNOS), HDAC (Histone Deacetylase) inhibitors, PPARγ agonists, androgen, which may provide new therapeutic strategies in further dementia oriented research.

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REFERENCES:

1. Skott KR and Barrett AM: Dementia syndromes: evaluation and treatment. Expert Rev Neurother 2007; 7(4): 407-22.
2. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D and Kawas CH: Dementia incidence continues to increase with age in the oldest old the 90+ study. Ann Neurol 2010; 67(1): 114-21.
3. Wallin A, Milos V, Sjögren M, Pantoni L and Erkinjuntti T: Classification and subtypes of vascular dementia. Int Psychogeriatr 2003; 15(S-1): 27-37.
4. Borenstein AR, Wu Y, Bowen JD, McCormick WM, Uomoto J, McCurry SM, Schellenberg G and Larson EB: Incidence rates of dementia, Alzheimer's disease and vascular dementia in the Japanese American Population in seattle, WA: The Kame Project. Alzheimer Dis Assoc Disord 2014; 28(1): 23-29.
5. Mejia-Arango S and Gutierrez LM: Prevalence and incidence rates of dementia and cognitive impairment no dementia in the Mexican population. J Aging Health 2011; 23(7): 1050-74.
6. Korczyn AD, Vakhapova V and Grinberg LT: Vascular dementia. J Neurol Sci 2012; 322(1-2): 2-10.
7. Podcasy JL and Epperson CN: Considering sex and gender in Alzheimer's disease and other dementias. Dialogues Clin Neurosci 2016; 18(4): 437-446.
8. Van der Flier WM and Scheltens P: Epidemiology and risk factors of dementia. J Neurol Neurosurg Psychiatry 2005; 76 (S-V): v2-v7.
9. Sharma B and Singh N: Defensive effect of natrium diethyldithiocarbamatetrihydrate (NDDCT) and lisinopril in DOCA-salt hypertension-induced vascular dementia in rats. Psychopharmacology 2012a; 223 (3): 307-17.
10. Battistin L and Cagnin A: Vascular cognitive disorder. A biological and clinical overview. Neurochem Res 2010; 35(12): 1933-8.
11. Raz L, Knoefel L and Bhaskar K: The neuropathology and cerebrovascular mechanisms of dementia. J Cereb Blood Flow Metab 2016; 36(1): 172-86.
12. Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW and Seshadri S: Vascular contributions to cognitive Impairment and Dementia. Stroke 2011; 42(9): 2672-13.
13. Attems J and Jellinger KA: The overlap between vascular disease and Alzheimer's disease - lessons from pathology. BMC Med 2014; 12: 206.
14. Sharma B and Singh N: Behavioral and biochemical investigations to explore the pharmacological potential of PPAR-gamma agonists in vascular dementia of diabetic rats. Pharmacol Biochem Behav 2011a; 100 (2): 320-9.
15. Kelleher RJ and Soiza RL: Evidence of endothelial dysfunction in the development of Alzheimer's disease: Is Alzheimer's a vascular disorder? Am J Cardiovasc Dis 2013; 3(4): 197-26.
16. Enciu AM, Constantinescu SN, Popescu LM, Mureşanu DF and Popescu BO: Neurobiology of vascular dementia. J Aging Res 2011; 2011: 401604.
17. Monsuez JJ, Gesquière-Dando A and Rivera S: Cardio-vascular prevention of cognitive decline. Cardiol Res Pract 2011; 2011: 250970.
18. Valenti R, Pantoni L and Markus HS: Treatment of vascular risk factors in patients with a diagnosis of Alzheimer's disease: a systematic review. BMC Med 2014; 12: 160.
19. McVeigh C and Passmore P: Vascular dementia: prevention and treatment. Clin Interv Aging 2006; 1(3): 229-35.
20. Rizzi L, Rosset I and Roriz-Cruz M: Global epidemiology of dementia: Alzheimer's and vascular types. Bio Med Research International 2014; 2014: 1-8.
21. Custodio N, Wheelock A, Thumala D and Slachevsky A: Dementia in Latin America: Epidemiological evidence and implications for public policy. Fro Agi Neur 2017; 9: 221.
22. Hébert R and Brayne C: Epidemiology of vascular dementia. Neuroepidemiology 1995; 14(5): 240-57.
23. Barnett JH, Hachinski V and Blackwell AD: Cognitive health begins at conception: addressing dementia as a life-long and preventable condition. BMC Med 2013; 11: 246.
24. Hoof JV, Kort HSM, Hensen JLM, Duijnstee MSH and Rutten PGS: Thermal comfort and the integrated design of homes for older people with dementia. Building and Environment 2010; 45(2): 358-70.
25. Fadil H, Borazanci A, Haddou EAB, Yahyaoui M, Korniychuk E, Jaffe SL and Minagar A: Early-onset dementia. International Review of Neurobiology 2009; 84: 245-62.
26. Drennan VM, Greenwood N, Cole L, Fader M, Grant R, Rait G and Iliffe S: Conservative interventions for incontinence in people with dementia or cognitive impairment, living at home: a systematic review. BMC Geriatr 2012; 12: 77.
27. Sheehan B: Assessment scales in dementia. Ther Adv Neurol Disord 2012; 5(6): 349-58.
28. Reitz C: Alzheimer's disease and the amyloid cascade hypothesis: A critical review. Int J Alzheimers Dis 2012; 2012: 369808.
29. Weggen S and Beher D: Molecular consequences of amyloid precursor protein and presenilin mutations causing autosomal-dominant Alzheimer's disease. Alzheimers Res Ther 2012; 4(2): 9.

30. Hardy J: Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. J Alzheimers Dis 2006; 9: 151-53.
31. O'Brien RJ and Wong PC: Amyloid precursor protein processing and Alzheimer's disease. Annu Rev Neurosci 2011; 34: 185-04.
32. Seo J, Kritskiy O, Watson LA, Barker SJ, Dey D, Raja WK, Lin YT, Ko T, Cho S, Penney J, Silva MC, Sheridan SD, Lucente D, Gusella JF, Dickerson BC, Haggarty SJ and Tsai LH: Inhibition of p25/Cdk5 attenuates tauopathy in mouse and iPSC models of frontotemporal dementia. J Neurosci 2017; 37(41): 9917-24.
33. Nelson PT, Braak H and Markesbery WR: Neuropathology and cognitive impairment in Alzheimer disease: A complex but coherent relationship. J Neuropathol Exp Neurol 2009; 68(1): 1-14.
34. Seeley WW, Carlin DA, Allman JM, Macedo MN, Bush C, Miller BL and Dearmond SJ: Early frontotemporal dementia targets neurons unique to apes and humans. Ann Neurol 2006; 60(6): 660-7.
35. Wider C and Wszolek ZK: Etiology and pathophysiology of frontotemporal dementia, Parkinson disease and Alzheimer disease: Lessons from genetic studies. Neurodegener Dis 2008; 5(3-4): 122-25.
36. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings L and Benson DF: Frontotemporal lobar degeneration. Neurology 1998; 51(6): 1546-1554.
37. Snowden JS, Neary D and Mann D: Frontotemporal dementia. Br J Psychiatry 2002; 180: 140-3.
38. Mummery CJ, Patterson K, Wise RJ, Vandenberghe R, Price CJ and Hodges JR: Disrupted temporal lobe connections in semantic dementia. Brain 1999; 122: 61-73.
39. Breeding SD, Saffran EM and Coslett HB: Reversal of the concreteness effect in a patient with semantic dementia. Cog Neuropsychol 1994; 11: 617-60.
40. Davies RR, Hodges JR, Kril JJ, Patterson K, Halliday GM and Xuereb JH: The pathological basis of semantic dementia. Brain 2005; 128(Pt 9): 1984-95.
41. Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, Leschziner G, Rossor AM, Stevens JM, Cipolotti L and Rossor MN: Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. Ann Neurol 2001; 49(4): 433-42.
42. McKeith I: Dementia with Lewy bodies. Dialogues Clin Neurosci 2004; 6(3): 333-41.
43. Kosaka K, Yoshimura M, Ikeda K and Budka H: Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree-a new disease? Cli Neuro 1984; 3: 185-92.
44. Weisman D and McKeith I: Dementia with Lewy bodies. Semin Neurol 2007; 27(1): 42-7.
45. McKeith IG, Burn DJ, Ballard CG, Collerton D, Jaros E, Morris CM, McLaren A, Perry EK, Perry R, Piggott MA and O'Brien JT: Dementia with Lewy bodies. Semin Clin Neuropsychiatry 2003; 8(1): 46-57.
46. Gunstad J, Brickman AM, Paul RH, Browndyke J, Moser DJ, Ott BR, Gordon N, Haque O and Cohen RA: Progressive morphometric and cognitive changes in vascular dementia. Archives of Clinical Neuropsychology 2005; 20(2): 229-41.
47. Wang J, Zhang H and Tang X: Cholinergic deficiency involved in vascular dementia: possible mechanism and strategy of treatment. Acta Pharma Sin 2009; 30: 879-88.
48. Justin BN, Turek M and Hakim AM: Heart disease as a risk factor for dementia. Clin Epidemiol 2013; 5: 135-45.
49. Ganguly P and Alam SF: Role of homocysteine in the development of cardiovascular disease. Nutr J 2015; 14: 6.
50. Škovierová H, Vidomanová E, Mahmood S, Sopková J, Drgová A, Červeňová T, Halašová E and Lehotský J: The molecular and cellular effect of homocysteine metabolism imbalance on human health. Int J Mol Sci 2016; 17(10): 1733.
51. Román GC, Erkinjuntti T, Wallin A, Pantoni L and Chui HC: Subcortical ischaemic vascular dementia. Lancet Neurol 2002; 1(7): 426-36.
52. Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, Blacker D, Blazer D, Chen C, Chui H, Ganguli M, Jellinger K, Jeste DV, Pasquier F, Paulsen J, NielsPrins N, Rockwood K, Roman GG and Scheltens PP: Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alz Dis Assoc Disor 2014; 28(3): 206-18.
53. Lee JM, Grabb MC, Zipfel GJ and Choi DW: Brain tissue responses to ischemia. J Clin Invest 2000; 106(6): 723-31.
54. Xing C, Arai K, Lo EH and Hommel M: Pathophysiologic cascades in ischemic stroke. Int J Stroke 2012; 7(5): 378-85.
55. Traystman RJ: Animal models of focal and global cerebral ischemia. ILAR J 2003; 44(2): 85-95.
56. Messerli FH, Williams B and Ritz E: Essential hypertension. Lancet 2007; 370: 591-03.
57. Skoog I and Gustafson D: Update on hypertension and Alzheimer's disease. Neurol Res 2006; 28 (6): 605-11.
58. Dickstein DL, Walsh J, Brautigam H, Stockton SD, Gandy S and Hof PR: Role of vascular risk factors and vascular dysfunction in Alzheimer's disease. Mt Sinai J Med 2010; 77 (1): 82-02.
59. Posner HB, Tang MX, Luchsinger J, Stern Y and Mayeux R: The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology 2002; 58 (8): 1175-81.
60. Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W, Nelson J, Davis DG, Hardman J, Foley DJ and Launer LJ: Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia Aging Study. Neurobiol Aging 2000; 21: 57-62.
61. Morris MC, Scherr PA, Hebert LE, Glynn RJ and Bennett DA: Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. Arch Neurol 2001; 58: 1640-46.
62. Iadecola C and Davisson RL: Hypertension and cerebrovascular dysfunction. Cell Metab 2008; 7: 476-484.
63. Mattson MP and Camandola S: NF-kappaB in neuronal plasticity and neurodegenerative disorders. J Clin Invest 2001; 107(3): 247-54.
64. Sharma B and Singh N: Defensive effect of natrium diethyldithiocarbamate trihydrate (NDDCT) and lisinopril in DOCA-salt hypertension-induced vascular dementia in rats. Psychopharmacology 2012a; 223(3): 307-17.
65. Gispen WH and Biessels GJ: Cognition and synaptic plasticity in diabetes mellitus. Trends Neuro 2000; 23: 542-49.
66. Brownlee M: Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414(6865): 813-20.
67. Burtenshaw D, Hakimjavadi R, Redmond EM and Cahill PM: Nox, reactive oxygen species and regulation of vascular cell fate. Antioxidants (Basel) 2017; 6(4): 90.
68. Shimohama S, Tanino H, Kawakami N, Okamura N, Kodama H, Yamaguchi T, Hayakawa T, Nunomura A, Chiba S, Perry G, Smith MA and Fujimoto S: Activation of NADPH oxidase in Alzheimer's disease brains. Biochem Biophys Res Commun 2000; 273(1): 5-9.

69. Hernandes MS and Britto LR: NADPH oxidase and neuro-degeneration. Curr Neuropharmacol 2012; 10(4): 321-27.
70. Shinton R and Beevers G: Meta-analysis of relation between cigarette smoking and stroke. BMJ 1989; 298: 789-94.
71. Moon JH, Kim SY, Lee HG, Kim SU and Lee YB: Activation of nicotinic acetylcholine receptor prevents the production of reactive oxygen species in the fibrillar beta-amyloid peptide (1-42)-stimulated microglia. Exp Mol Med 2008; 40 (1): 11-18.
72. Cahill PA and Redmond EM: Alcohol and cardiovascular disease--modulation of vascular cell function. Nutrients 2012; 4(4): 297-18.
73. Peters R, Peters J, Warner J, Beckett N and Bulpitt C: Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age Ageing 2008; 37(5): 505-12.
74. Sabia S, Fayosse A, Dumurgier J, Dugravot A, Akbaraly T, Britton A, Kivimäki M and Singh-Manoux A: Alcohol consumption and risk of dementia: 23-year follow-up of Whitehall II cohort study. BMJ 2018; 362: k2927.
75. Byun K, Bayarsaikhan D, Bayarsaikhan E, Son M, Oh S, Lee J, Son HI, Won MH, Kim SU, Song BJ and Lee B: Microglial AGE-albumin is critical in promoting alcohol-induced neurodegeneration in rats and humans. PLoS One 2014; 20; 9(8): e104699.
76. Iadecola C: Atherosclerosis and neurodegeneration: unexpected conspirators in Alzheimer's dementia. Arterioscler Thromb Vasc Biol. 2003; 23(11): 1951-3.
77. Grinberg LT and Thal DR: Vascular pathology in the aged human brain. Acta Neuropathol 2010; 119(3): 277-90.
78. Altman R and Rutledge JC: The vascular contribution to Alzheimer's disease. Cli Sc (Lond) 2010; 119(10): 407-21.
79. Caratozzolo S, Scalvini A, Cocchi S, Cassarino GS, Pelizzari S, Zanetti M, Rozzini L and Padovani A: Neurodegenerative and vascular involvement in post stroke dementia. J Alzheimers Dis Parkinsonism 2016; 6: 283.
80. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui, HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW and Seshadri S: Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42(9): 2672-13.
81. Pluta R, Jabłoński M, Ułamek-Kozioł M, Kocki J, Brzozowska J, Januszewski S, Furmaga-Jabłońska W, Bogucka-Kocka A, Maciejewski R and Czuczwar SJ: Sporadic Alzheimer's disease begins as episodes of brain ischemia and ischemically dysregulated Alzheimer's disease genes. Mol Neurobiol 2013; 48(3): 500-15.
82. Ballabh P, Braun A and Nedergaard M: The blood-brain barrier: an overview: Structure, regulation, and clinical implications. Neurobiol Dis 2004; 16(1): 1-13.
83. Zlokovic BV: The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron 2008; 57: 178-01.
84. Zhang W, Xiong H, Callaghan D, Liu H, Jones A, Pei K D, Brunette E and Stanimirovic D: Blood-brain barrier transport of amyloid beta peptides in efflux pump knock-out animals evaluated by *in-vivo* optical imaging. Fluids Barriers CNS 2013; 10: 13.
85. Deane R, Bell RD, Sagare A and Zlokovic BV: Clearance of amyloid-β peptide across the blood-brain barrier: Implication for therapies in Alzheimer's disease. CNS Neurol Disord Drug Targets 2009; 8(1): 16-30.
86. Ramanathan A, Nelson AR, Sagare AP, and Zlokovic BV: Impaired vascular-mediated clearance of brain amyloid beta in Alzheimer's disease: the role, regulation and restoration of LRP1. Front Aging Neurosci 2015; 7: 136.
87. Herrmann W and Obeid R: Homocysteine: a biomarker in neurodegenerative diseases. Clin Chem Lab Med 2011; 49(3): 435-41.
88. Moshal KS, Singh M, Sen U, Rosenberger DS, Henderson B, Tyagi N, Zhang H and Tyagi SC: Homocysteine-mediated activation and mitochondrial translocation of calpain regulate MMP-9 in MVEC. Am J Physiol Heart Circ Physiol 2006; 291(6): H2825-35.
89. Sharma M, Tiwari M and Tiwari RK: Hyper-homocysteinemia: Impact on neurodegenerative diseases. Basic Clin Pharmacol Toxicol 2015; 117(5): 287-96.
90. Jiang JQ, Ashekuzzaman SM, Jiang A, Sharifuzzaman SM and Chowdhury SR: Arsenic contaminated groundwater and its treatment options in Bangladesh. Int J Environ Res Public Health 2012; 10(1): 18-46.
91. O'Bryant SE, Edwards M, Menon CV, Gong G and Barber R: Long-term low-level arsenic exposure is associated with poorer neuropsychological functioning: a Project FRONTIER study. Int J Environ Res Public Health 2011; 8(3): 861-74.
92. Luo JH, Qiu ZQ, Shu WQ, Zhang YY, Zhang L and Chen JA: Effects of arsenic exposure from drinking water on spatial memory, ultra-structures and NMDAR gene expression of the hippocampus in rats. Toxicol Lett 2009; 184: 121-25.
93. Zhao X, Zhou W, Jian-Jun L, Chen C, Ping-Chuan Z, Lu D, Jing-Hong C, Qun C, Xiao-Tian Z and Zhi-Lun W: Protective effects of selenium on oxidative damage and oxidative stress-related gene expression in rat liver under chronic poisoning of arsenic. Food Chem Toxicol 2013; 58: 01-07.
94. Liu CH, Jiao H, Guo ZH, Peng Y and Wang WZ: Up-regulated GLT-1 resists glutamate toxicity and attenuates glutamate-induced calcium loading in cultured neurocytes. Basic Clin Pharmacol Toxicol 2013; 112(1): 19-24.
95. Wang Y, Li S, Piao F, Hong Y, Liu P and Zhao Y: Arsenic down-regulates the expression of Camk4, an important gene related to cerebellar LTD in mice. Neurotoxicol Teratol 2009; 31(5): 318-22.
96. Plaza-Zabala A, Sierra-Torre V and Sierra A: Autophagy and Microglia: Novel partners in neurodegeneration and aging. Int J Mol Sci 2017; 18(3): 598.
97. Giese KP and Mizuno K. The roles of protein kinases in learning and memory. Learn Mem 2013; 20(10): 540-52.
98. Assi MA, Hezmee MNM, Haron AW, Sabri MYM and Rajion MA: The detrimental effects of lead on human and animal health. Vet World 2016; 9(6): 660-71.
99. Balakumar P and Kaur J: Arsenic exposure and cardiovascular disorders: an overview. Cardiovasc Toxicol 2009; 9(4): 169-76.
100. Anthony JD, Gary LP, Lisa AL and Douglas RS: Role of NFκB in age-related vascular endothelial dysfunction in humans. Aging 2009; 1(8): 678-80.
101. Kim MK, Chung SW, Kim DH, Kim JM, Lee EK, Kim JY, Ha YM, Kim YH, No JK, Chung HS, Park KY, Rhee SH, Choi JS, Yu BP, Yokozawa T, Kim YJ and Chung HY: Modulation of age-related NF-kappaB activation by dietary zingerone *via* MAPK pathway. Exp Gerontol 2010; 45 (6): 419-26.
102. Jones SV and Kounatidis I: Nuclear Factor-Kappa B and Alzheimer Disease, Unifying Genetic and Environmental Risk Factors from Cell to Humans. Front Immunol 2017; 8: 1805.

103. Block ML: NADPH oxidase as a therapeutic target in Alzheimer's disease.BMC Neurosci 2008; 9 (S-2): S8.
104. Hernandes MS and Britto LRG: NADPH oxidase & neuro-degeneration. Curr Neuropharma 2012; 10(4): 321-27.
105. Sharma B and Singh N: Pitavastatin and 4'-Hydroxy-3'-methoxyacetophenone (HMAP) reduce cognitive dysfunction in vascular dementia during experimental diabetes. Current Neurovascular Res 2010; 7(3):189-191.
106. Schultz BG, Patten DK and Berlau DJ: The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms. Tran Neur 2018; 7: 5.
107. Sharma B and Singh N: Behavioral and biochemical investigations to explore the pharmacological potential of PPAR-gamma agonists in vascular dementia of diabetic rats. Pharmacol Biochem Behav 2011a; 100(2): 320-9
108. Koladiya BU, Jaggi AS, Singh N and Sharma BK: Ameliorative role of Atorvastatin and Pitavastatin in L-methionine induced vascular dementia in rats. BMC Pharmacol 2008; 8: 14.
109. Danielyan L, Klein R, Hanson LR, Buadze M, Schwab M, Gleiter CH and Frey WH: Protective effects of intranasal losartan in the APP/PS1 transgenic mouse model of Alzheimer disease. Rejuven Res 2010; 13 (2-3): 195-01.
110. Abraham HMA, White CM and White WB: The Comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases. Dr Saf 2015; 38(1): 33-54.
111. Tyagi S, Gupta P, Saini AS, Kaushal C and Sharma S: The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res 2011; 2(4): 236-40.
112. Mukohda M, Stump M, Ketsawatsomkron P, Hu C, Quelle FW and Sigmund CD: Endothelial PPAR-γ provides vascular protection from IL-1β-induced oxidative stress. Am J Physiol Heart Circ Physiol 2016; 310(1): H39-H48.
113. Warden A, Truitt J, Merriman M, Ponomareva O, Jameson K, Ferguson LB, Mayfield RD and Harris RD: Localization of PPAR isotypes in the adult mouse and human brain. Sci Rep 2016; 6: 27618.
114. Glatz T, Stock I, Nguyen-Ngoc M, Gohlke P, Herdegen T, Culman J and Zhao Y: Peroxisome proliferator-activated receptors gamma and peroxisome-proliferator-activated receptors beta/delta and the regulation of interleukin 1 receptors antagonist expression by pioglitazone in ischemic brain. J Hypertens 2010; 28(7): 1488-97.
115. Hampel H and Shen Y: Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) as a biological candidate marker of Alzheimer's disease. Scand J Clin Lab Invest 2009; 69(1): 8-12.
116. Nizzari M, Thellung S, Corsaro A, Villa V, Pagano A, Porcile C, Russo C and Florio T: Neurodegeneration in Alzheimer disease: Role of amyloid precursor protein and presenilin 1 intracellular signaling. Journal of Toxicology 2012; 2012: 1-14.
117. Chen Z, Ye R and Goldman SA: Testosterone modulation of angiogenesis and neurogenesis in the adult songbird brain. Neuroscience 2013; 239: 139-48.
118. Vigil P, Pablo del Río J, Carrera B, ArÁnguiz FC, Rioseco H and Cortés ME: Influence of sex steroid hormones on the adolescent brain and behavior: An update. Linacre Q 2016; 83(3): 308-29.
119. Nguyen TV, Yao M and Pike CJ: Androgens activate mitogen-activated protein kinase signaling: role in neuroprotection. J Neurochem 2005; 94: 1639-51.
120. Francomano D, Bruzziches R, Natali M, Aversa A and Spera G: Cardiovascular effect of testosterone replacement therapy in aging male. Acta Biomed 2010; 81: 101-6.
121. Sharma B and Singh N: Pharmacological inhibition of inducible nitric oxide synthase (iNOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, convalesce behavior and biochemistry of hypertension-induced vascular dementia in rats. Pharmacol Biochem Behav 2013; 103: 821-30.
122. Jaworska J, Ziemka-Nalecz MZ, Sypecka J and Teresa Zalewska T: The potential neuroprotective role of a histone deacetylase inhibitor, sodium butyrate, after neonatal hypoxia-ischemia. J Neuroinflam 2017; 14: 34.
123. Parbin S, Kar S, Shilpi A, Sengupta D, Deb M, Rath SK, and Kumar Patra SK: Histone Deacetylases: A saga of perturbed acetylation homeostasis in cancer. J Histochem Cytochem 2014; 62(1): 11-33.
124. Chuang DM, Leng Y, Marinova Z, Kim HJ and Chiu CT: Multiple roles of HDAC inhibition in neurodegenerative conditions. Trends Neurosci 2009; 32(11): 591-01.
125. Mary-Elizabeth P and Silvia C: The role of mitochondria in the pathogenesis of type 2 diabetes. Endocrine Reviews 2010; 31(3): 364-395.
126. Lahera V, de Las Heras N, López-Farré A, Manucha W and Ferder L: Role of mitochondrial dysfunction in hyper - -tension and obesity. Curr Hypertens Rep 2017; 19(2): 11.
127. Bakthavachalam P and Shanmugam PST: Mitochondrial dysfunction - Silent killer in cerebral ischemia J Neurol Sci 2017; 375: 417-23.
128. Madamanchi NR and Runge MS: Mitochondrial dys-function in atherosclerosis. Cir Res 2007; 100(4): 460-73.
129. Hoek JB, Cahill A and Pastorino JG: Alcohol and mitochondria: A dysfunctional relationship. Gastro-enterology 2002; 122(7): 2049-63.
130. Yang Z, Harrison CM, Chuang G and Ballinger SW: Effect of smoking cessation on mitochondrial respiratory chain function. J Toxicol Clin Toxicol 2003; 41(3): 223-8.
131. Cardellach F, Alonso JR, López S, Casademont J and Miró O: Effect of smoking cessation on mitochondrial respi-ratory chain function. J Tox Clin Tox 2003; 41(3): 223-8.
132. Moreira PI, Carvalho C, Zhu X, Smith MA and Perry G: Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. Biochimica et Biophysica Acta 2010; 1802(1): 2-10
133. Manisha, Hasan W, Rajak R and Jat D: Oxidative stress and antioxidants: An overview. International Journal of Advanced Research and Review 2010; 2(9): 110-119.
134. Burton GJ: Oxidative stress. Best Pract Res Clin Obstet Gynaecol 2011; 25(3): 287-99.
135. Sheng Y, Abreu IA, Cabelli DE, Maroney MJ, Miller AF, Teixeira M and Valentine JS: Superoxide dismutases and superoxide reductases. Chem Rev 2014; 114(7): 3854-18.
136. Day BJ: Catalase and glutathione peroxidase mimics. Biochem Pharmacol 2009; 77(3): 285-96.

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