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“Effect of inflammatory mediators and their inhibitors on Dementia”.

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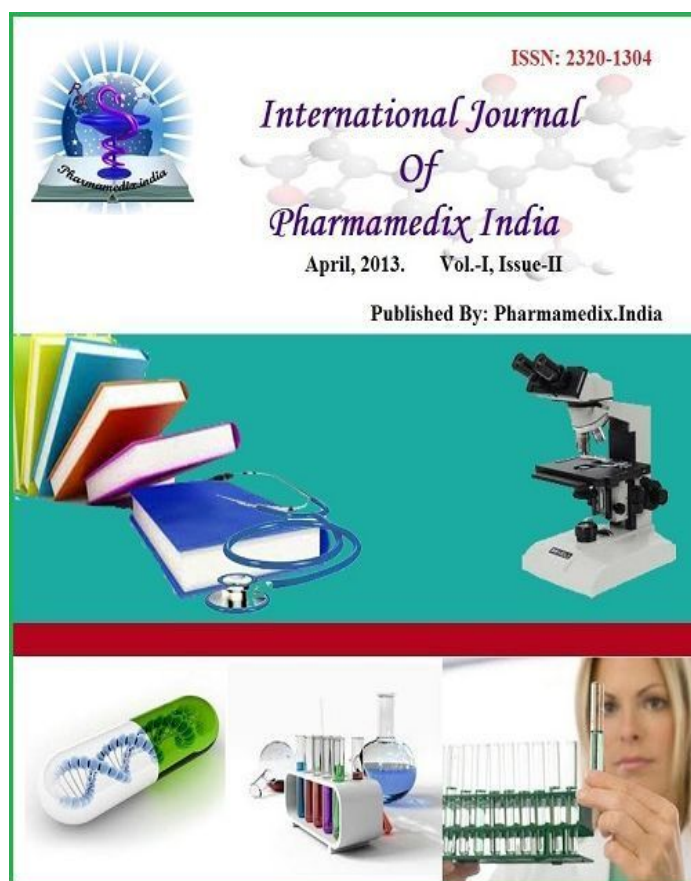
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Abstract:

Dementia is a decline of cognitive functions (reasoning, memory, and other mental disorders). It is caused by a damage in the brain tissue, causing disturbed brain functioning. Studies on Alzheimer's have led to major revaluation of concept such as 'Neuroinflammation'. Proinflammatory mediators released by activated glial cells during brain inflammation have been proposed to contribute to neuropathology underlying cognitive deficits. Glial- derived proinflammatory cytokines such as IL-1 β , IL-6, TNF- α , TGF- β set a spectrum of signalling events which influence in neurological disease and disorder. These proinflammatory cytokines induce nitric oxide synthase and COX-2 activity in astrocytes, leading to release of free radicals and oxidative stress causing neuronal death. NSAIDS have been reported to reduce the risk for AD, by decreasing neuroinflammation. Further double-blind clinical trial of COX-1 inhibitor showed arrest in the progression of disease, but due to serious side effects of NSAIDS their use in geriatric population is limited. As there are various inflammatory mediators involved in inflammation, they can be used as a new therapeutic approach in AD, such as TNF- α inhibitors, IL-1 inhibitors, new COX or Prostaglandins modulators. In this review we will discuss about the role of inflammatory mediators in Pathophysiology of neuroinflammation leading to dementia and role of their inhibitors in treatment of dementia.

Keywords: Inflammatory mediators, Neuroinflammation, Dementia.

Introduction:

Dementia is characterised by loss of or decline in memory and other cognitive abilities and reduces life span of affected people^[1,2]. Dementia patients have inability to generate Coherent speech or understand spoken or written languages, inability to recognise or identify objects, difficulties in executing motor activities etc. But the most

common problems associated with dementia are aphasia, apraxia and agnosia.

Neuroinflammation:

Neuroinflammation is a stimulus of various events such as infections, trauma, stroke, toxins; these are capable to initiate various types of inflammatory responses^[3, 4]. In acute phase inflammatory responses various type of

cytokines and chemokines are released due to the activation of microglia cells, in this condition there is an activation of oxidative and nitrosative stress^[5]. This kind of inflammatory response is beneficial for neurons it minimise injury and repair damage tissues. While in case of chronic inflammation is long lived and precipitate various neuroinflammatory processes such as sustain release of the various inflammatory mediators promoting their proliferation which leads to damaging effects to the brain cells^[6]. Many of neurodegenerative diseases are result of chronic inflammation. Inflammatory processes play an active role in the pathology of alzheimers disease leading to dementia. Various kinds of cytokines which triggers the vicious cycle are IL-1 β , IL-6, TNF- α leading to dysfunctioning of neuronal cell. Both on cellular and clinical levels neuroinflammation is seen to be a basic part of disease pathology. In this review we will summarise the complexity of the inflammatory mediators and their basic therapeutic approaches which can be beneficial in the future.

Various cells and cellular mediators involved in neuroinflammation: There are various types of cellular mediators involved in neuroinflammation such as Microglia, Astrocytes, Cytokines, Chemokines, Prostaglandins, Pentraxins, etc.

Cells:

Microglia:

These are cells that support and protect neurons. They are composed of mesodermally derived macrophages and they are able to express major histocapalibility complex type II (MHC II) proinflammatory cytokines, chemokines, and reactive oxygen species and complement proteins^[7]. It plays an important role in removing, presumably redundant, apoptotic neurons, such as they release a wide range of inflammatory factors such as reactive oxygen species, cytokines such as IL-1 β , IL-6, TNF- α and interferon γ (INF- γ), chemokines, complement complements etc^[8]. It also plays a central role in cellular response to pathological lesions such as A β and neuritic plaques. A β can attract and activate microglia leading to clustering of microglia around A β deposits sites in the brain. Along with phagocytosis, A β can induce expression of nitric oxide synthase in microglia leading to loss of neurons. Some of the A β laden microglias were found to migrate to vessels and to the ventricles in an attempt to rid the brain of the A β leading to deposition of A β on the vessels. Photon microscopy has justified the relationship of microglia to A β by showing microglial processes sample and react to A β deposits in transgenic mouse model^[9]. Many studies related to inflammatory factors and

receptors mediating microglial localisation and response to A β have been seen. A β activates various proinflammatory mediators and various immune responses leading to inflammatory responses^[10]. The peripheral application of antibodies to A β reduce the burden of amyloid plaques through receptor mediated phagocytosis and subsequent peptide degradation^[11]. Microglia is the critical convergence point for many diverse triggers that elicit in adaptive immune response. Pre-treatment of microglia with estrogen antagonist leads to the internalisation of the A β which is beneficial in the post menopausal women with AD^[12]. On the other hand release of insulin degrading enzyme (IDE) which tend to cleave small proteins such as insulin and glucagon and shown to degrade A β . Further studies revealed that insulin degrading enzyme (IDE) inhibitors block the degradation of A β ^[13]. The concept of microglia activation is profoundly seen in various diseases and role of microglia activation and neuroinflammation has more recently been considered as the main unifying factor of neurotoxicity.

Astrocytes:

Astrocytes also known collectively as astroglia are characteristic star-shaped glial cells in the brain and spinal cord. They perform many functions, including biochemical support of endothelial cells that

form the blood–brain barrier, provision of nutrients to the nervous tissue, maintenance of extracellular ion balance, and a role in the repair and scarring process of the brain and spinal cord following traumatic injuries. Astrocytes are also central to the maintenance of neuronal metabolism and neurotransmitter synthesis. There is a vast relationship between neurons, astrocytes and blood vessels which help astrocytes to modulate neuronal activity and cerebral blood flow. The role of astrocytes in the inflammation processes is difficult to express but they have been shown to secrete various interleukins, prostaglandins, leukotrienes, thromboxanes, coagulation factors, proteases etc^[14]. Various evidences show that astrocytes are involved in the synthesis and phagocytosis of A β . It is also accumulate neurons derived amyloid material resulting from local neurodegeneration, they itself undergo cell death and form amyloid plaques. It is also seen that dysfunction between the astrocytes and calcium signalling might contribute to disease state. The astrocytes propagate intracellular Ca²⁺ waves and release transmitters such as gliotransmitters and further leads to generation of signal and release of glutamate which is an excitatory neurotransmitter and plays an important role in pathology of AD^[15]. Various strategies such as astrocytes glutamate transporter EAAT₂ with paranexin 1 a molecule from spider venom have evolved, which reduce the excitotoxicity.

Grafting of various kind of healthy astrocytes cell in mouse model of ALS is reported to be beneficial.

Cytokines:

Cytokines are small cell-signalling protein molecules that are secreted by numerous cells and are a category of signalling molecules used extensively in intercellular communication. Cytokines can be classified as proteins, peptides, or glycoprotein; the term "cytokine" encompasses a large and diverse family of regulators produced throughout the body by cells of diverse embryological origin^[16]. A proinflammatory cytokine is a cytokine which promotes systemic inflammation. The most potent of these are interleukin (IL-1 β), IL-1, IL-6 and tumor necrosis factor- α (TNF- α). Each one of inflammatory mediators is associated with the neuroinflammation in the brain cells. Proinflammatory cytokines induce oxide synthase and COX-2 activity in astrocytes leading to an increase in free radical formation and oxidative stress in several neurodegenerative states. AD brain micro vessels release significantly higher levels of a number of inflammatory factors including nitric oxide (NO), thrombin, tumor necrosis factor- α (TNF- α), transforming growth factor- β (TGF- β), interleukin (IL) IL-1 β , IL-6, IL-8, and matrix metalloproteinase (MMPs).

- **IL-1:**

IL-1 is thought to be central to CNS inflammatory modulation response to CNS injury. The levels of IL-1 are found to increase after excitotoxicity injury, LPS challenge, mechanical damage and ischemia. IL-1 induces microglia proliferation and stimulates IL-6 leading to neuronal damage. Peripheral administration of IL-1 leads to behavioural and psychological changes such as lack of movement, decrease responding for food rewards, inhibition in sexual activity, anorexia and anxiety disorders^[17, 18]. IL-1 β also act as an major cytokines leading to damage the neuronal membrane an electrophysiological index of synaptic plasticity linked to memory and learning^[19]. IL-1 was the first cytokines identified and it has the ability to elicit fever and hence it was known as endogenous pyrogens. The IL-1 family of cytokines includes two agonist proteins IL-1 α and IL-1 β it also include IL-1ra which is a glucosylated secretory protein which counteracts the action of IL-1. In astrocytes IL-1 induces IL-6 production stimulate iNOS activity. It enhances neuronal acetylcholinesterase activity, microglial activation and astrocyte activation. Increase level of endogenous IL-1ra and IL-1RII are important in brain injury by leading to regulation of IL-1. Local expression of IL-1 caused impairment of hippocampal dependent memory processing. IL-1 β has showed blocking activity of hippocampal LTP. IL-1 β increases the

expression of pro-inflammatory cytokines, leukocytes, and chemotactic chemokines with in brain parenchyma. It is seen to be the potent mediator for the neuroinflammation. IL-1 is involved in the neuroinflammation and various studies have revealed presence of IL-1 in AD brain. IL-1 and IL-1 β are associated with neuronal and synaptic dysfunction and A β plaque accumulation. In many studies IL-1 β is seen to elevate the level of β -APP^[20]. IL-1 inhibitors can response in chronic neurodegenerative disease may provide new areas for therapeutic interventions.

- **IL-2:**

IL-2 enhances dopaminergic transmission^[21, 22]. IL-2 is deeply linked to the memory. Chronic peripheral administration of IL-2 leads to impairment of memory performance as it is associated with the hippocampal neurodegenerative further it leads to suppression of afferent sensory transmission in the primary somatosensory cortex leading to poor spatial learning^[23, 24, 25].

- **IL-6:**

IL-6 is secreted by T cells and macrophages to stimulate immune response plays an imp role in fighting infections. The CNS function of IL-6 are not fully established, it shows induction of acute phase proteins, increase in vascular permeability and lymphocytic activation^[26]. It causes astrocytes activation; long term treatment leads to enhance NMDA

further increase in excitotoxicity^[27]. It further facilitates neuroendocrine communication stimulation the hypothalamic-pituitary adrenal axis and causing adreno-corticotrophic hormone release. Systemic administration increases in noradrenergic and serotonergic neurotransmission^[28]. In mice it causes sensory impairment and impaired axonal degeneration such as ataxia, tremor, motor impairment and seizures^[29]. IL-6 is the chief stimulator of the production of most acute phase proteins. IL-6 elicits acute phase reactions as well as also the development of specific cellular and humoral immune responses, B cell differentiation, immunoglobulin secretion and T cell activation. IL-6 exhibits dual nature. In models of chronic inflammatory diseases, such as collagen-induced arthritis, murine colitis, or experimental autoimmune encephalomyelitis, IL-6 acts as proinflammatory mediator, whereas in models of acute inflammation IL-6 exhibits an anti-inflammatory profile. Circulating levels of IL-6 is seen in various models of chronic inflammation while IL-6 blockade can give a new approach to treatment of chronic inflammatory diseases.

- **TNF- α :**

It is a cytokine produced by microglia that is known to promote cell survival and death in the CNS. It leads to increase production of A β ^[30]. It is generated as a transmembrane 26-

kDa precursor molecule that is proteolytic and cleaves to yield a soluble TNF- α protein. It is essential in glutamatergic transmission, Microglial activation and control synaptic strength^[31]. An increased level is seen in neurodegenerative disorders such as Alzheimer and Parkinson^[32,33,34]. TNF- α -blocking agent etanercept cause reduction of TNF- α signalling. Other drugs with the use of small lipophilic molecules possessing the ability to inhibit TNF- α synthesis and penetrate the blood-brain barrier would be of significant ^[35, 36]. TNF- α receptor 1 and TNF receptor 2 are membrane glycoprotein receptors that specifically bind TNF and homotrimers of lymphotoxin A. TNFR1 is expressed in most of the cell while TNFR2 is expressed primarily by cells of the immune system and by endothelial cells. The potent evidence of TNF- α involved in the pathology of the AD is due to amyloidogenic plaques which are easily seen in the post mortem of AD patients. TNFR1 and TNFR2 present on chromosomes 1p and chromosomes 12p show genetic linkage with late onset AD^[37]. Brain undergoes oxidative stress which leads to generation of iNOS which damage neurons in AD brain. TNF and iNOS both are linked together in the cognitive deficits in the AD. Apoptosis is also a major component in the cell cycle and TNF also play a vital role in the apoptosis pathway. The activation of the programmed cell death is relying solely on the TNF-signalling pathway. TNFR1 contains a

cytoplasmic death domain which activates caspases causing apoptosis. Further neurotoxicity is also generated by TNF- α release which leads to activation of microglia via neuronal TNF-R1 and caspase 3 activation. It also acts as neurotoxic by causing over-excitation of glutamate an excitatory neurotransmitter leading to cell death. TNF- α mediates apoptosis, neurogenesis and other biological functions at the molecular and cellular levels.

- **IFN- α :**

Interferons (IFNs) are proteins made and released by host cells in response to the presence of pathogens such as viruses, bacteria, parasites or tumor cells. They allow for communication between cells to trigger the protective defences of the immune system that eradicate pathogens or tumors. It is having important neuroregulatory effect over behaviour, temperature regulation and feeding patterns^[38]. Higher doses showed reduced alertness further prolonged rise leads to memory loss, depression, and impaired motor activity. It is central dopamine agonist long term use leads to the down regulation of receptor as well as serotonin depletion leading to cognitive deficits ^[39,40]. Induction of cell death or apoptosis was not initially considered an action of IFNs. However in vitro IFN- α , IFN- β or IFN- γ has induced changes in morphology of cells such as rounding up and detachment of cells, characteristics of apoptotic cells, in multiple cell lines. Various

recent advances in genomics and proteomics are still trying to mitigate the effect of interferons which will be beneficial in neuronal disease as well as in cancer as it leads to alter apoptotic pathway.

- **Cyclooxygenase:**

It is an enzyme that is responsible for formation of important biological mediators called prostanoids, including prostaglandins, prostacyclin and thromboxane. COX is an integral membrane glycoprotein, consisting of a homodimer with an associated heme group involved in both enzymatic activities. Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain. Cyclooxygenase (COX) is an enzyme that plays an important role in the arachidonate cascade leading to prostaglandin synthesis. COX helps to mediate production of prostaglandin. Accumulating evidence indicates that COX-2 protein levels are increased in several areas of the dementia patients brain and may correlate with levels of A β and plaque density [41,42,43]. COX-1 and COX-2 are both involved in the inflammatory cascade but COX-2 expression is more prominent in AD. COX-2 expression is seen in the cell cycle by controlling G₀ and G₁ phase further leading to neuronal damage. COX-1 is appeared in microglial cells found in association with amyloid deposits. In moderate increase of COX-2 level are also associated with the

ischemia and excitotoxicity. Moreover, NSAIDS tend to show a protective effect in mild to moderate type of AD. So, specific COX-2 inhibition can be used as a potent therapy in future to treat neuronal damage.

- **Chemokines:**

Chemokines are small peptides that are potent activators and chemoattractants for leukocyte subpopulations and some non-hemopoietic cells. Chemokines bind to their respective chemokines receptors on the leukocyte cell surface, causes alteration of β 2 integrins, on the leukocyte cell surface. Then β 2 integrins bind to their Ig counterligands, such as ICAM-1, ICAM-2, and ICAM-3, which have been up-regulated on the endothelial cell surface by proinflammatory cytokines. The binding of chemokines to their respective leukocyte receptors also initiates a series of cellular events, such as changes in cell shape, secretion of lysosomal enzymes, and production of superoxide anions. In immune responses do not produce endothelial injury while in acute or chronic inflammation may occur in which the endothelium and surrounding tissues become damaged [44,45].

- **The Pentraxins:**

The Pentraxins are a family of acute phase protein that are involved in many pathological conditions in the body. They are involved in tissue injury and inflammation. The classical Pentraxins include amyloid P; they both are

involved in the innate immune defence system. AP is the component which have all amyloid deposits and key mediators associated with neurofibrillary tangles and amyloid plaques. It has a protective role in defence mechanism and in pathology of AD. It can be used as a mediator in neuroinflammation [46, 47].

Prostaglandins:

A prostaglandin is any member of a group of lipid compounds that are derived enzymatically from fatty acids and have important functions in the animal body. Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring. PGE₂ modulates the expression of inflammatory mediators by microglial cells. PGE₂ and its agonists inhibit the expression of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) and enhanced the expression of cyclooxygenase (COX)- 2 induced by lypopolysaccharide (LPS) in cultured microglia [48,49,50]. PGD₂ has also been shown to be important in neuroinflammatory conditions. It has been shown that PGD₂ produced by microglia acts on DP1 receptors of astrocytes, leading to astrogliosis. PGD₂ also induced apoptosis of mouse oligodendrocytes precursor (mOP) cells; interfere in the demyelination process that occurs in multiple sclerosis [51]. Patients with AD have higher cerebrospinal fluid (CSF) concentrations of PGE₂ than control subjects. PGE₂ increases amyloid precursor

protein (APP) gene expression and production in vitro. 15d-PGJ₂ induces neuronal apoptosis it was associated with neurodegeneration but it was elucidated that 15d- PGJ₂ reduces microglial production of NO, IL-6, and TNF- α induced by A β 40, having anti-inflammatory and having neuroprotective effect [52]. 15d-PGJ₂, and troglitazone and ciglitazone, other compounds known to activate PPAR γ and attenuate the A β -induced impairment of hippocampal LTP in vitro, have possible beneficial effect on AD progression [53].

Therapeutic approaches in dementia considering neuroinflammation as the key mediator:

As neuroinflammation is seen to be the indispensable part of Pathophysiology of disease, so the proper treatment of this condition can be done by using various kinds of antiinflammatories with minimum side effects. Drugs used so far for the treatment are NSAIDS and its synthetic analogs. But due to various limitations in the therapy of NSAIDS new therapeutic targets are need to be generated.

NSAIDS and dementia:

Chronic NSAIDS use reduces risk of dementia. One of the most popular the over the counter drug Ibuprofen is used in therapy. Various researches on ibuprofen have shown positive result on transgenic mice. Such as ibuprofen 375ppm in TG2576 mice reduced exterior cortex plaques and A β loads to 20-

25%^[54]. Other clinical trials on NSAIDS have satisfactory response in clinical trials such as celecoxib showed significant relief when given 400 or 200mg/day for 18 months, other drugs such as refecoxib showed positive result in 1457 students is appoint when given 25mg/kg dose to patients. Some other studies have achieved significant reduction in the pathological changes of AD^[55]. Various other COX-2 inhibitors are also examined, nimesulide is examined in the mouse model of amyotrophic lateral sclerosis (ALS) for its motor activity, there was a significant delay in the onset of motor impairment and reduced COX-2-mediated induction of proinflammatory prostaglandin in the cervical spinal cord. Nimesulide is a preferential COX-2 inhibitor with potent antioxidant properties it is well tolerated in geriatric patients for periods of more than 2 years. Low-dose aspirin may be associated with a reduced risk of cognitive decline and dementia. Aspirin against Alzheimer's disease comes from observational studies reporting an inverse relationship between risk of developing Alzheimer's disease and use of NSAIDs^[56]. It has been suggested that NSAIDs protect against Alzheimer's disease by reducing pro-inflammatory cytokine production by inhibiting COX. Elderly people on high-dose NSAIDs are more likely to have memory deterioration, possibly indicative of their increased susceptibility to the toxic effects of inhibiting physiological COX-2.

Further, COX-2 inhibition may fail to block other pathological cascades downstream of A β , like those involving tau, which could play significant roles in the pathogenesis of later stages of Alzheimer's disease. Persistent investigations on the effects of NSAIDs to involve synapse and brain function may renew interest in other potential protective mechanisms of NSAIDs, thus widening the possibilities for developing safe prophylactic medications for Alzheimer's. Recently Meloxicam (enolic derivative of Nsaids) and selegiline (MOA antagonist) have potential therapeutic effects on improving the anti-amnesic activity in mice through inhibiting lipid peroxidation augmenting endogenous anti-oxidant enzymes and decreasing acetylcholinesterase activity in the brain^[57]. Recently Meloxicam (enolic derivative of Nsaids) and selegiline (MOA antagonist) have potential therapeutic effects on improving the anti-amnesic activity in mice through inhibiting lipid peroxidation augmenting endogenous anti-oxidant enzymes and decreasing acetylcholinesterase activity in the brain .

Angiotensin II antagonists in dementia:

Angiotensin II antagonists are class of drugs acts in the axis of Renin Angiotensin and Aldosterone and used for the treatment of hypertension this may, in turn, facilitate nitric oxide generation that may contribute to an anti-inflammatory effect. It stimulates the

release of pro inflammatory cytokines, activates Nuclear factor kappa B (NF- κ B), increases oxidant stress, suppress nitric oxide synthesis and behave as an inflammatory molecule^[58,59]. Losartan 10 mg/kg possessed very significant activity whereas Irbesartan and Valsartan at 10 mg/kg possessed significant activity comparable to vehicle control in carageenin induced rat paw oedema. Ang II receptor antagonists could be benefit in atherosclerosis, diabetes mellitus, hypertension, myocardial infarction, Alzheimer's disease, dementia and schizophrenia, in which inflammation plays a significant role^[60].

Synthetic derivative as TNF- α Inhibitors in dementia:

Other studies done on 3,6-thiothalidomide a potent TNF- α inhibitors significantly reverse hippocampus dependent cognitive deficits induced by chronic neuroinflammation^[61]. 3,6'-dithiothalidomide (DT) is an isosteric analog of thalidomide (N- α -phthalimidoglutarimide), which has been reported to reduce the rate of TNF- α synthesis through enhanced degradation of its transcript^[62,63]. DT possesses a TNF- α lowering action that in LPS-stimulated RAW 264.7 cells^[64] and LPS-stimulated human peripheral blood mononuclear cells^[65,66]. This result suggests that by targeting TNF- α synthesis an effective therapeutic approach to severe human neurodegenerative disorder can be developed.

Statins and dementia:

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. These are the most common agents used in the treatment of hyperlipidemias. Currently available statins include atorvastatin, simvastatin, fluvastatin, lovastatin, pravastatin and rosuvastatin. They regulate the endothelial function by increasing endothelial nitric oxide synthetase and reducing endothelin-I thereby increasing cerebral blood flow (CBF). They act as antioxidants by decreasing free radical injury and reducing lipoprotein oxidation. They have anti-inflammatory properties by reducing pro-inflammatory cytokines such as tumor necrosis factor (TNF) - α , acute phase reactants and interleukin (IL)-6 in peripheral blood samples which in turn reduces cell damage^[67]. They stimulate alpha-secretase activity for APP processing, which helps in reduction of amyloid- β peptide generation and neuronal protection^[68].

Herbal plants with anti-inflammatory activity in dementia and neuroinflammation:

Turmeric (the common name for *Curcuma longa*) is an Indian spice derived from the rhizomes of the plant and has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase,

and inducible nitric oxide synthase (iNOS) enzymes; inhibits the production of the inflammatory cytokines tumor necrosis factor-alpha (TNF- α), interleukin (IL) -1, -2, -6, -8, and -12, monocytes chemoattractants protein (MCP), and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinases^[69,70]. Curcumin is thought to suppress NF- κ B activation and proinflammatory gene expression by blocking phosphorylation of inhibitory factor I-kappa B kinase (IkB). Curcumin induces cognitive improvement by inhibiting cholinergic system by suppressing the production of inflammatory cytokines such as IL- β and the inflammatory markers in astrocytes, reduced oxidative damage and plaque burden; compared with NSAIDs its side effects are very low. Neferine a major benzylisoquinoline alkaloids derived from *Nelumbo nucifera* having potent anti diabetic, anti arrhythmic and anti hypertensive activity showed significant improvement in cognitive impairment in scopolamine induced amnesic and moderate inhibitory activities in ChEs and BACE1 assays. It also possesses scavenging activity against DPPH, NO and O₂ free radicals⁷¹. Other plant includes the effects of *Glycyrrhiza glabra* Linn (popularly known as liquorice) on learning and memory in mice. Anti-inflammatory and antioxidant properties of liquorice may be contributing favourably to the memory enhancement effect. Since scopolamine-induced amnesia was reversed

by liquorice, it is possible that the beneficial effect on learning and memory was due to facilitation of cholinergic transmission in mouse brain^[72].

Conclusion:

There is evidence exhibiting the presence of neuroinflammation in AD patients which cannot be ignored. Drugs which are given to the patients to treat neuroinflammation are NSAIDs but they are not very much beneficial. There are various therapies for AD, such as IL-1 inhibitors, TNF- α inhibitors and various other inflammatory mediators which can lead to be a new ray of hope to treat the disease. Cellular players and the molecular pathways initiated by glial reactivity may provide more pharmacological intervention to resolve the harmful aspects of neuroinflammation. Various pharmacological strategies aimed at decreasing inflammation may be useful to restore neuronal function and reduce the cognitive deficits during neuroinflammation. This is the pathological condition which needs reconsidering in AD patients. Understanding of inflammation in AD brain will open more targets for its therapy. Detailed description of each element contributing in inflammation will give beneficial effect to AD patients. Focusing on the integrity of the cellular players and the molecular pathways which causes glial activation may provide more targeted treatments that specifically resolve the

harmful aspects of neuroinflammation while retaining its innate benefit. Finally, by reducing stress, reduction in inflammatory cytokines, by enhancing anti-oxidant properties and enhancement of the particular NSAIDs that impact COX-independent signalling we can get better potential to deal with the disease state and help the patient to live life without cognitive deficits and with extended life span.

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