IJPSR (2021), Volume 12, Issue 12 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 30 November 2020; received in revised form, 05 August 2021; accepted, 08 August 2021; published 01 December 2021

ALZHEIMER'S DISEASE AND PATHOLOGICAL ANGIOGENESIS

Mrunalini Devi Kotagiri [*1, 2] and Abhisek Pal [3]

Department of Pharmacology, GITAM Institute of Pharmacy [1], Gandhinagar, Rushikonda, Vishakapatnam - 530045, Andhra Pradesh, India.
Department of Pharmacology, CMR College of Pharmacy [2], Hyderabad - 501401, Telangana, India.
Department of Pharmacology, GITAM School of Pharmacy [3], Rudraram, Hyderabad - 502329, Telangana, India.

Keywords:

Alzheimer's disease, Amyloid beta, Bloodbrain barrier, Antiangiogenesis.

Correspondence to Author:
Ms. Mrunalini Devi Kotagiri

Research Scholar,
Department of Pharmacology,
GITAM Institute of Pharmacy,
Gandhinagar, Rushikonda,
Vishakapatnam - 530045, Andhra Pradesh, India.

E-mail: k.m.devikotagiri@gmail.com

ABSTRACT: In spite of huge investigations, the pathology of Alzheimer' sdisease (AD) is uncertain. Vessels dysfunction is a critical mark of AD. Research has stated like beta-amyloid (Aβ) results augmented vascular development in brains, a pathway observed in AD patients. In AD, cerebral endothelium releases pro substances for β-amyloid plaque and neurotoxins that kill cortical neurons. Vascular vulnerable features and neural, vascular dysfunction related through hypo or hypertension, hypercholesterolemia, diabetes mellitus, smoking, oxidative stress, and iron overload have been invented to play essential parts in the pathogenesis of stroke and AD. Antiangiogenic agents and small molecule kinase blockers are being examined and approved for anticancer therapy and showed normal blood vessel growth in the affected areas. Endothelial cells (EC) are triggered by the angiogenesis of cerebral ischemia and hypoxia. Outcomes of epidemiological research show that chronic administration of NSAIDs, statins, H_2 antihistamines, or calcium-channel blocker sappearstoavert AD. This is mainly due to the ability of the drugs to prevent angiogenesis. Many previous reviews on pathogenesis on AD have explained neuronal degeneration, but this review focuses on the effect of angiogenesis on the pathology of AD, which is believed to be the root cause for neuronal degeneration. This review attempts to launch a relation between vascular damage and AD pathology. If AD is anangiogenes is-related condition, then antiangiogenic drugs aiming at the abnormal cerebral EC will stop and treat the disease. Also, treating the disease from the root cause decreases the side effects of treatment.

INTRODUCTION: AD is one of the usual illnesses of current civilization. Disturbing 10% of the global people, this progressive neurodegenerative ailment results in expressible human misery and consumes US$ 100 billion annually in health inessca recharges. Though amyloid plaque has been recognized as a chief cause of AD, yet these plaques formed in cerebral region is uncertain.

In heritance, genetic polymorphism, reduced perfusion, endothelial inflammation, and lesions are recommended as possible pathways [1]. Still, a combined thoughtfulness of the illness and strong

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(12).6202-08

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(12).6202-08

references for interferences are absent. Subsequently, therapy is limited to amelioratethde signs of memory loss by growing cerebral concentration of acetylcholine by drug sliket acrine, donepezil, rivastigmine, or galantamine. In 1906, Dr. Alois Alzheimer [2] observed pathological neurological conclusions, categorized and additionally recognized as marks of AD; neural plaques, that are masses which are chiefly made of beta-amyloid (Aβ) peptides; [3, 4] and neurofibrillary tangles, that chief lycalmas intra neuronal hyperphosphorylated tau-masses [5].

Aβ, which is a 4 kDa peptide, a proteolytic destruction product of amyloid precursor protein (APP) by the function of α and γ secretase enzymes [6, 7]. Mutations in APP gene or in the secretase enzyme results in β secretase breakdown, making an abnormal Aβ mass (Aβ1-42). Such Aβ masses to produce oligomers, that multimerize to protofibrils by the creation of solid core amyloid plaques [8-10]. A barrier is present amidst the blood vessels in the cerebral area and other parts of the central nervous system, limiting fluid and particles from moving into the brain from the blood circulation called the blood-brain barrier (BBB) [11, 13]. Disfunction of this BBB was initially observed in animal experiments of AD 14 and was then recognized as the prime, yet the unclear path of AD [15, 20]. Hence, the pathway resulting to BBB disruption is a budding target for AD treatment.

Involvement of Angiogenesis and Not Apoptosis: Vascular hypothesis as specified presently guards that vessel disruption is a result of reduced perfusion to the brain, resulting in ischemia and hypoxia leading to BBB dysfunction [21, 25]. Succeeding amalgamation of Aβ, neuroinflammation, and final breakdown of neural vessels are observed, ending in vessel death [27, 28]. In the condition of hypoperfusion, the hypoxia-inducible features start angiogenesis by up-regulation of proangiogenic agents [29]. The key performers in angiogenesis is Vascular endothelial growth factor (VEGF), which encourages the division and multiplication of ECs from progenitor cells, hemangioblast, and angioblast. Further causes an incompetently formed primitive vessel plexus [30]. This vascular plexus experiences re-modeling, which is activated by angiopoietin-1 (Ang-1), to a matured vessel recognized through EC tubing and pericyte employment as in normal angiogenesis. Contritely to the above steps in AD, down-regulation of cell signalling factors to VEGF, angiopoietin-2 (Ang-2), weakens walls of established vessels [31, 32]. Dormant EC turns out to be subtle to VEGF, divide extensively, and move into small vessels that will not mature and then result in leaky vasculature [32]. This process is named pathological angiogenesis, a commonly seen step in the development of tumors. In accord with the present kind of vascular hypothesis, BBB damage is because of vessel death produced from programmed cell death and angiogenesis will safeguard tissue renewal and will be restricted in replacing injured tissue and confirm oxygenation of cerebral region.

Though, this function of apoptosis in BBB dysfunction is extremely is cussed. Current researches have exposed that EC proliferation in pathological angiogenesis leads to hypervascularity. AS an alternate path to the decreased blood circulation by leaky vessels, remodeling and structural variations occur in the anatomical plan of tight junctions (TJ), ensuing in conceded BBB veracity. The research of Biron *et al.* considered an association among amyloid generation and BBB integrity, although variations in the TJ anatomy in Tg2576 AD mouse. They noted Tg2576 AD mice show no superficial vessel apoptosis yet have significant TJ damage that was observed linking to pathological angiogenesis, ensuing in an important growth of blood vessel density in AD brain. So, this information supports that TJ disturbance outcomes raised vessel permeability which occurs in widespread angiogenesis [33, 40]. At least five imbricating paths initiate angiogenic in the cerebral region.

Is chemiainaged brain results in less oxygen supply, aprovocation that starts release of vaso-active elements like nitricoxide, hypoxia inducible factor 1a (HIF1a.) and VEGF, one of the ut most controlling pro angiogenic cyto kines. Amplified VEGF release is observed in active astrocytes and perivascular accumulation of AD people [41, 42]. Neurofibrillary tangles in AD, believed to be subordinate to β-amyloidgathering, comprise heparin sulphate proteoglycans, an agent which fixes keenly to rudimentary fibroblast growth factor (bFGF), other angiogenic cytokine [43, 44]. Thrombin in spires angiogenes is in areas of wounded vessel

endothelium [45]. Inflammatory inter media riespresent in brains of AD, like TNFa, interleukin 6, and monocyte chemoattra 00c tant protein-1, stimulate angiogenesis. Attacking macrophages and monocytes to secrets angiogenic growth factors VEGF, bFGF, and platelet-derived growth factor (PDGF). Gene expression of endogenicanti angiogenic agent, thrombo spond in, is condensed near by focal AD lesions, resulting in proangiogenic conditions such locations [46]. Such undesirable signals for angiogenesis are extra ordinarily similar to an excess of stimuli resulting in tumor angiogenesis [47]. Brain EC in AD owns unique genetic and phenotypic characters which are not seen in healthy brains. These EC heterogeneous are seen in contrast to abnormal with normal cell groups [48]. Subsequently, while angiogenesis happens in answer to brain-reduced oxygen supply, inflammation of AD and stroke patients, separate compulsive variations result in AD.

The hypothesis taken up in this review clarifies all puzzles stood by apparently unrelated therapeutic agents that discuss protection against AD. Anti-inflammatory agents, anti-H2-receptor, antihypertensive agents, and statins will cause antiangiogenesis [49, 50]. We endorse that an important decrease in hazard of AD stated in outcomes of population-based researches is primarily owing to antiangiogenic functions of the above medicines on EC. This pathway will not discard other significant paths of drugs, like NSAIDs and statins, which will straightly reduce the neuronal synthesis of β amyloids. Numerous of them may have moderate lyminor angiogenic inhibitory actions associated with strong and precise antiangiogenic drug sin studies for the tumor therapy, retinopathies, and psoriasis [51]. Though AD is a multifaceted ailment, cerebral neovascularisation will develop a new emphasis for clinical research. Even researchers rem aintountie pathways behind AD, patientsatriskmaygain from judicialutility of frequently used medicines that result in antiangiogenic process.

Angiogenesis: Inflammation and Vascular Stimulation: Growing proofs advocate vessel agitation seems like a character of AD pathology as its marks: amyloid and neurofibrillary tangles. Aβ in AD, as a consequence of reduced clearance from brain, is thought to be accountable for beginning of intellectual failure [52, 55]. Absurd to this hypothesis, accumulated Aβ can be broadly existing in brain in nonappearance of AD signs [55, 59]. Though Aβ theatres a vital character in AD, it is either essential or by itself adequate to result in complete AD pathology [60]. Another idea is that simple manufacture of Aβ, endorses wide spread compulsive angiogenesis, causing the rearrangement of TJs, that then result in disruption of BBB veracity, thus cumulative vascular penetrability, following hyper vascularization and ultimate AD pathology.

Hemostaticpathways In Relation To AD Angiogenesis: Conservation of flow of blood and restricting its harm on vessels is vital biological course called haemostasis [61]. It is likely wing to the being of a subtle equilibrium among procoagulation and anticoagulation along with many pathways [61, 62]. This process has three separate stages, firstly adhering platelets to spot of damage, making a platelet-plug [63]. Secondly includes the initiation of coagulation cascade, terminating in fibrin clot formation; the last phase is fibrinolysis, or dissolution of clot [64]. Escorted with vessel disfunction, a changed hemostatic situation is progressively concerned in AD.

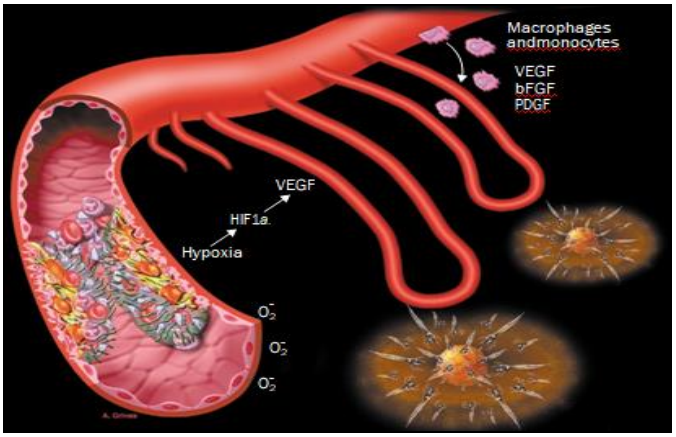

FIG. 1: ANGIOGENESIS IN THE ALZHEIMER'S BRAIN

Antiangiogenics: Small Molecule Tyrosine Kinase Blockers: Antiangiogenic agents and small molecule kinase blockers are being examined and approved for anticancer therapy and were showing normal blood vessel growth in the affected areas [65]. Sunitinib is a broad-spectrum tyrosine-kinase blocker. It inhibits the phosphorylation of numerous receptor tyrosine kinases and efficiently blocks VEGF and also platelet-derived growth factor (PDGF-β). Presently, sunitinib is in usage for

gastric tumors, cancers, and pancreas cancers. It was known to cut amyloid problem and converse intellectual weakening in AD mice, if researchers aim angiogenesis, they can relapserise in the gathering of Aβ and decrease intellectual weakening related to AD [63]. Drugs resulting in indirect antiangiogenesis in AD Consequences of epidemiologic trials propose that long time use of certain medicines meaning fully reductions risk of AD invulnerable people **Table 1.** These drugs contain NSAIDs, lipid-lowering drugs, H2 antihistamines and calcium-channel blockers. The clinical information is very convincing. Brain inflammation has developed in to a key emphasis for AD research.

Cerebral inflammation can not explain risk drop consulted by medicines that deficit considerable anti-inflammatory action. EC reply to reduced oxygen level and inflammation is by angiogenesis. Interceded by cytokine growth factors, angiogenesis includes initiating EC from existing vessels to form tube-like structures that supplement resident microcirculation by delivering oxygen and nutrients to tissues suffering from hypoxia. The EC also employs straight local actions by making a minimum of 20 paracrine agents which function on surrounding cells. Though most of these agents are anti-apoptotic survival signals, neovessels in injured cells release toxins like neurotoxins and amyloid precursors [60].

TABLE 1: DRUGS ASSOCIATED WITH DECREASED RISK OF ALZHEIMER'S DISEASE OR DECREASED FORMATION OF 13-AMYLOID PEPTIDE

Agent	Anti-inflammatory activity	Antiangiogenic activity
Lovastatin	-	+
Simvastatin	-	+
Pravastatin	-	+
Sulindac	+	+
Diclofenac	+	+
Indomethacin	+	+
Aspirin	+	+
H2blocker	-	+
Nitrendipine	-	+
Nimodipine	-	+

+and – denote the biological activity of each agent.

Testing the Hypothesis: The title role of vessel formation in AD could be examined in lab and clinical studies. The neovascular neurotoxin could be examined by studying EC develop menton tissue culture taken from AD brains. Gene studies of AD EC can recognize genes exclusively expressed in AD, which will be novel molecular marks for treatment.

Concluding Marks: AD characterizes an illness that can place the important problem on features of society. This problem chiefly plays on caretakers in a family and has projected billions in missing efficiency and healthcare pricing. Overages, incomplete development made with respect to the amyloid hypothesis in the therapy of AD, so new rationale towards AD pathogenesis is compulsory. Vascular vulnerable features and neural vasculard are related to hypo or hypertension, hypercholesterolemia, diabetes mellitus, smoking, oxidative stress, and iron overload have been invented to play essential parts in the pathogenesis of stroke and AD. Explanations present in augmented cerebral vascular ture penetrability former to the arrival of milestones of AD, sprouts new example in participating vessels modeling with the pathophysiology of the illness.

Based on this investigation engrossed on considering molecular pathways behind and pathophysiology of neovascularization resulting in AD. Clinical inhibition lessons should be undertaken in a high-risk population for AD by the usage of angiogenic blockers. Numerous oral angiogenic blockers are undertaking oncological studies, like thalidomide, AE-941, PTK787, endo stat in, and BMS275291. Patients getting antiangiogenic blockers will be predictable have ales ser frequency of AD, in comparison with placebo. Intervention studies can be made with predictable termination of illnesses tea diness. An agent can exist that gives defense against AD and also for cancer. Such studies will provide extensive and multifaceted management and so need strong, helpful preclinical results from lab experimentations. The sheer scale of AD in aging people encourages research investigators and industrial experts.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

ACKNOWLEDGEMENT: We thank the Management of CMR College of Pharmacy for their support in performing the literature review in the institution.

REFERENCES:

1. Shrivastava SR, Shrivastava PS and Ramasamy J: Letter to editor: dementia in middle-and low-income nations: a public health priority.
2. Siddappaji KK and Gopal S: Molecular mechanisms in Alzheimer's disease and the impact of physical exercise with advancements in therapeutic approaches. AIMS Neuroscience 2021; 8(3): 357-89.
3. Shi J, Sabbagh MN and Vellas B: Alzheimer's disease beyond amyloid: strategies for future therapeutic interventions. BMJ 2020; 371.
4. Kumar S, Kapadia A, Theil S, Joshi P, Riffel F, Heneka MT and Walter J: Novel phosphorylation-state specific antibodies reveal differential deposition of ser26 phosphorylated aβ species in a mouse model of alzheimer's disease. Frontiers in Molecular Neuroscience 2020; 13.
5. Mehta PD, Patrick BA, Barshatzky M, Mehta SP, Frackowiak J, Mazur-Kolecka B, Wegiel J, Wisniewski T and Miller DL: Generation and partial characterization of rabbit monoclonal antibody to pyroglutamate amyloid-β 3-42 (pe 3-aβ). Journal of Alzheimer's Disease. 2018; 62(4): 1635-49.
6. Daly T, Houot M, Barberousse A, Agid Y and Epelbaum S: Amyloid-β in alzheimer's disease: a study of citation practices of the amyloid cascade hypothesis between 1992 and 2019. Journal of Alzheimer's Disease 2020; 74(4): 1309-17.
7. Lee HN, Jeong MS and Jang SB: Molecular characteristics of amyloid precursor protein (app) and its effects in cancer. International Journal of Molecular Sciences 2021; 22(9): 4999.
8. Singh Y, Ormaza D, Massetti A, Minond D and Cudic M: Tyrosine o-galnac alters the conformation and proteolytic susceptibility of app model glycopeptides. ACS Chemical Neuroscience 2021; 29.
9. Bagyinszky E, Kang MJ, Van Giau V, Shim K, Pyun JM, Suh J, An SS and Kim S: Novel amyloid precursor protein mutation, Val669Leu ("Seoul APP"), in a Korean patient with early-onset Alzheimer's disease. Neurobiology of Aging 2019; 84: 236-e1.
10. Teixeira FB, Saito MT, Matheus FC, Prediger RD, Yamada ES, Maia CS and Lima RR: Periodontitis and alzheimer's disease: a possible comorbidity between oral chronic inflammatory condition and neuroinflammation. Frontiers in Aging Neuroscience 2017; 9: 327.
11. Chua XY, Chai YL, Chew WS, Chong JR, Ang HL, Xiang P, Camara K, Howell AR, Torta F, Wenk MR and Hilal S: Immunomodulatory sphingosine-1-phosphates as plasma biomarkers of Alzheimer's disease and vascular cognitive impairment. Alzheimer's Research & Therapy 2020; 12(1): 1-2.
12. Salmina AB, Komleva YK, Lopatina OL and Birbrair A: Pericytes in alzheimer's disease: novel clues to cerebral amyloid angiopathy pathogenesis. In Pericyte Biology in Disease 2019; 147-66.
13. Jefferies WA, Price KA, Biron KE, Fenninger F, Pfeifer CG and Dickstein DL: Adjusting thecompass: new insights into the role of angiogenesis in Alzheimer's disease. Alzheimers Res Ther 2013; 5: 64.
14. Deng F, Zhang Y, Zhang R, Tang Q, Guo Z, Lv Y, Wang Z and Yang Y: Compromised dynamic cerebral autoregulation in patients with central disorders of hypersomnolence. Frontiers in Neurology 2021; 12: 311.
15. Brodehl A, Ebbinghaus H, Deutsch MA, Gummert J, Gärtner A, Ratnavadivel S and Milting H: Human induced pluripotent stem-cell-derived cardiomyocytes as models for genetic cardiomyopathies. International Journal of Molecular Sciences 2019; 20(18): 4381.
16. Terada T, Yokokura M, Obi T, Bunai T, Yoshikawa E, Ando I, Shimada H, Suhara T, Higuchi M and Ouchi Y: *In-vivo* direct relation of tau pathology with neuroinflammation in early Alzheimer's disease. Journal of Neurology 2019; 266(9): 2186-96.
17. Ashraf A, Alepuz Guillen JA, Aljuhani M, Hubens C and So PW: Low cerebrospinal fluid levels of melanotransferrin are associated with conversion of mild cognitively impaired subjects to Alzheimer's disease. Frontiers in Neuroscience 2019; 13: 181.
18. Feldman H, Gabathuler R, Kennard M, Nurminen J, Levy D, Foti S, Foti D, Beattie BL and Jefferies WA: Serum p97 levels as an aid to identifying Alzheimer's disease. J Alzheim-ers Dis 2001; 3: 507-16.
19. Ashraf A, Alepuz Guillen JA, Aljuhani M, Hubens C and So PW: Low cerebrospinal fluid levels of melanotransferrin are associated with conversion of mild cognitively impaired subjects to Alzheimer's disease. Frontiers in Neuroscience 2019; 13: 181.
20. Singh C, Pfeifer CG and Jefferies WA: Pathogenic angiogenic mechanisms in alzheimer's. physiologic and pathologic angiogenesis. Signaling Mechanisms and Targeted Therapy 2017; 5: 93.
21. Yamada T, Yoshiyama Y, Kawaguchi N, Ichinose A, Iwaki T, Hirose S and Jefferies W: Possible roles of transglutaminases in Alzheimer's disease. Dementia Geriatr Cogn Disorder 1998; 9: 103-10.
22. Chakraborty A, Kamermans A, van Het Hof B, Castricum K, Aanhane E, van Horssen J, Thijssen VL, Scheltens P, Teunissen CE, Fontijn RD and van der Flier WM: Angiopoietin like-4 as a novel vascular mediator in capillary cerebral amyloid angiopathy. Brain 2018; 141(12): 3377-88.
23. Bennett HC and Kim Y: Pericytes across the lifetime in the central nervous system. Frontiers in Cellular Neuroscience 2021; 15: 71.
24. De Bem AF, Krolow R, Farias HR, De Rezende VL, Gelain DP, Moreira JC, Duarte JM and De Oliveira J: Animal models of metabolic disorders in the study of neurodegenerative diseases: an overview. Frontiers in Neuroscience 2021; 14: 1457.
25. Kook SY, Seok Hong H, Moon M and Mook-Jung I: Disruption of blood-brain barrier in Alzheimer disease pathogenesis. Tissue Barriers 2013; 23993.
26. Erickson MA and Banks WA: Blood-brain barrier dysfunction AS a cause and consequence of Alzheimer's disease. J Cereb Blood Flow Metab 2013; 33: 1500-13.
27. Muntsant A, Jiménez-Altayó F, Puertas-Umbert L, Jiménez-Xarrie E, Vila E and Giménez-Llort L: Sex-dependent end-of-life mental and vascular scenarios for compensatory mechanisms in mice with normal and AD-neurodegenerative aging. Biomedicines 2021; 9(2): 111.
28. Banks WA, Gray AM, Erickson MA, Salameh TS, Damodarasamy M, Sheibani N, Meabon JS, Wing EE, Morofuji Y, Cook DG and Reed MJ: Lipopolysaccharide-induced blood-brain barrier disruption: roles of cyclooxygenase, oxidative stress, neuroinflam- mation, and elements of the neurovascular unit. J Neuroinflamm 2015; 12: 223.
29. Zare D, Rajizadeh MA, Maneshian M, Jonaidi H, Sheibani V, Asadi-Shekaari M, Yousefi M and Esmaeilpour K: Inhibition of protease-activated receptor 1 (PAR1) ameliorates cognitive performance and synaptic plasticity

impairments in animal model of Alzheimer's diseases. Psychopharmacology 2021; 238(6): 1645-56.
30. Yamazaki Y and Kanekiyo T: Blood-brain barrier dysfunction and the pathogenesis of Alzheimer's disease. International Journal of Molecular Sciences 2017; 18(9): 1965.
31. Costa G, Tarannum N and Herbert SP: mRNA localization in endothelial cells regulates blood vessel sprouting. Bio Rxiv 2018; 374850.
32. Dal Prà I, Armato U and Chiarini A: Astrocytes' role in alzheimer's disease neurodegeneration. Astrocyte. Physiology and Pathology 2018; 21: 119.
33. Shalaby MA, Nounou HA and Deif MM: The potential value of capsaicin in modulating cognitive functions in a rat model of streptozotocin-induced Alzheimer's disease. The Egyptian Journal of Neurology Psychiatry and Neurosurgery 2019; 55(1): 1-3.
34. Xu X, Meng T, Wen Q, Tao M, Wang P, Zhong K and Shen Y: Dynamic changes in vascular size and density in transgenic mice with Alzheimer's disease. Aging Albany NY 2020; 12(17): 17224.
35. Ruffini N, Klingenberg S, Schweiger S and Gerber S: Common factors in neurodegeneration: a meta-study revealing shared patterns on a multi-omics scale. Cells 2020; 9(12): 2642.
36. Zhou R, Yang G and Shi Y: Dominant negative effect of the loss-of-function γ-secretase mutants on the wild-type enzyme through heterooligomerization. Proceedings of the National Academy of Sciences 2017; 114(48): 12731-6.
37. Hamada Y: Role of pyridines in medicinal chemistry and design of BACE1 inhibitors possessing a pyridine scaffold. London Intech Open 2018; 18.
38. Garg J, Lakhani A and Dave V: Effects of the involvement of calcium channels on neuronal hyperexcitability related to alzheimer's disease: a computational model. Neurophysiology 2020; 52(5): 334-47.
39. Ya L and Lu Z: Differences in ABCA1 R219K polymorphisms and serum indexes in Alzheimer and Parkinson Diseases in Northern China. Medical Science Monitor International Medical Journal of Experimental and Clinical Research 2017; 23: 4591.
40. Chen LY, Lin HJ, Wu WT, Chen YC, Chen CL, Kao J, You SL, Chou YC and Sun CA: Clinical use of acid suppressants and risk of dementia in the elderly: a pharmaco-epidemiological cohort study. International J of Environ Research and Public Health 2020; 17(21): 8271.
41. Bilen O and Wenger NK: Hypertension management in older adults. F1000 Research 2020; 9.
42. Cisbani G and Rivest S: Targeting innate immunity to protect and cure Alzheimer's disease: opportunities and pitfalls. Molecular Psychiatry 2021; 14: 1-2.
43. Villarejo-Galende A, González-Sánchez M, Blanco-Palmero VA, Llamas-Velasco S and Benito-León J: Non-steroidal anti-inflammatory drugs AS candidates for the prevention or treatment of alzheimer's disease: do they still have a role. Current Alzheimer Research 2020; 17(11): 1013-22.
44. Zhang C, Wang Y, Wang D, Zhang J and Zhang F: NSAID exposure and risk of Alzheimer's disease: an updated meta-analysis from cohort studies. Frontiers in Aging Neuroscience 2018; 28: 83.
45. Schultz BG, Patten DK and Berlau DJ: The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms. Translational Neurodegeneration 2018; 7(1): 1-1.
46. Poly TN, Islam MM, Walther BA, Yang HC, Wu CC, Lin MC and Li YC: Association between use of statin and risk of dementia: a meta-analysis of observational studies. Neuroepidemiology 2020; 54(3): 214-26.
47. Mészáros Á, Molnár K, Nógrádi B, Hernádi Z, Nyúl-Tóth Á, Wilhelm I and Krizbai IA: Neurovascular inflammaging in health and disease. Cells 2020; 9(7): 1614.
48. Rao HV, Bihaqi SW, Iannucci J, Sen A and Grammas P: Thrombin signaling contributes to high glucose-induced injury of human brain microvascular endothelial cells. Journal of Alzheimer's Disease 2021; 1-4.
49. Gameiro GR, Jiang H, Liu Y, Deng Y, Sun X, Nascentes B, Baumel B, Rundek T and Wang J: Retinal tissue hypoperfusion in patients with clinical Alzheimer's disease. Eye and Vision 2018; 5(1): 1-8.
50. Michalicova A, Majerova P and Kovac A: Tau protein and its role in blood–brain barrier dysfunction. Frontiers in Molecular Neuroscience 2020; 13: 178.
51. Howe MD, McCullough LD and Urayama A: The role of basement membranes in cerebral amyloid angiopathy. Frontiers in Physiology 2020; 11.
52. Sitohy B, Chang S, Sciuto TE, Masse E, Shen M, Kang PM, Jaminet SC, Benjamin LE, Bhatt RS, Dvorak AM and Nagy JA: Early actions of anti–vascular endothelial growth factor/vascular endothelial growth factor receptor drugs on angiogenic blood vessels. The American Journal of Pathology 2017; 187(10): 2337-47.
53. Govindpani K, McNamara LG, Smith NR, Vinnakota C, Waldvogel HJ, Faull RL and Kwakowsky A: Vascular dysfunction in Alzheimer's disease: a prelude to the pathological process or a consequence of it. Journal of Clinical Medicine 2019; 8(5): 651.
54. Strilchuk L: Nutraceuticals supporting cognitive function in mild cognitive impairment. nutraceuticals and cardiovascular disease. An Evidence-based Approach for Clinical Practice 2021; 12: 167.
55. Stokum JA, Cannarsa GJ, Wessell AP, Shea P, Wenger N and Simard JM: When the blood hits your brain: the neurotoxicity of extravasated blood. International Journal of Molecular Sciences 2021; 22(10): 5132.
56. Cao H, Seto SW, Bhuyan DJ, Chan HH and Song W: Effects of Thrombin on the Neurovascular Unit in Cerebral Ischemia. Cellular and Molecular Neurobiology 2021; 3: 1-2.
57. Chakraborty A: Vascular involvement in alzheimer's disease: from bench to bedside. May Be Reproduced, Stored or Transmitted In Any Form By Any 2020.
58. Jorda A, Campos-Campos J, Iradi A, Aldasoro M, Aldasoro C, Vila JM and Valles SL: The role of chemokines in alzheimer's disease. endocrine, metabolic & immune disorders-drug targets (formerly current drug targets-immune. Endocrine & Metabolic Disorders 2020; 20(9): 1383-90.
59. Isenberg JS and Roberts DD: Thrombospondin-1 in maladaptive aging responses: a concept whose time has come. American Journal of Physiology-Cell Physiology 2020; 319(1): 45-63.
60. Wei P, Cornel EJ and Du J: Ultrasound-responsive polymer-based drug delivery systems. Drug Delivery and Translational Research 2021; 24: 1-7.
61. Hooglugt A, van Der Stoel MM, Boon RA and Huveneers S: Endothelial YAP/TAZ signaling in angiogenesis and tumor vasculature. Frontiers in Oncology 2021; 10: 3162.
62. Lopez-Ramirez MA, Lai CC, Soliman SI, Hale P, Pham A, Estrada EJ, McCurdy S, Girard R, Verma R, Moore T and Lightle R: Astrocytes propel neurovascular dysfunction during cerebral cavernous malformation lesion formation. The Journal of Clinical Investigation 2021; 27.

63. Tijani AS, Farombi EO and Olaleye SB: Mechanisms underlying the healing potentials of the methanol extract of Chasmanthera dependens stem on the indomethacin-induced gastric ulcer. Egyptian Journal of Basic and Applied Sciences 2021; 8(1): 17-31.
64. Feleszko W, Balkowiec EZ and Sieberth E: Lovastatin and tumor necrosis factor-alpha exhibit potentiated antitumor effects against Ha-rast rans formed murinetumor *via* inhibition of tumor-induced angiogenesis. Int J Cancer 1999; 81: 560-67.
65. Cisbani G and Rivest S: Targeting innate immunity to protect and cure Alzheimer's disease: opportunities and pitfalls. Molecular Psychiatry 2021; 14: 1-2.

How to cite this article:
Kotagiri MD and Pal A: Alzheimer's disease and pathological angiogenesis. Int J Pharm Sci & Res 2021; 12(12):6202-08. doi: 10.13040/IJPSR.0975-8232.12(12).6202-08.