The Pharma Innovation Journal 2023; 12(1): 2430-2434

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(1): 2430-2434

www.thepharmajournal.com
Received: 01-10-2022
Accepted: 06-11-2022

Suryakant Ranjan
Ph.D. Scholar, Department of Biotechnology, School of Bioengineering and Biosciences, Lovely Professional University, Punjab, India

Himanshu Sekhar Behera
Ph.D. Scholar, Department of Soil Science and Agricultural Chemistry, School of Agriculture, Lovely Professional University, Punjab, India

Arun Kumar S
Ph.D. Scholar, Department of Soil Science and Agricultural Chemistry, School of Agriculture, Lovely Professional University, Punjab, India

Bitish Kumar Nayak
Department of Soil Science and Agricultural Chemistry, Palli-Siksha Bhavan, Visva-Bharati University, Sriniketan, West Bengal, India

Dr. Bijay Kumar Pany
Professor & EX-HOD, Department of Soil Science and Agricultural Chemistry, Institute of Agricultural Science, Siksha "O" Anusandhan University, Bhubaneswar, Odisha, India

Dr. Gour Hari Santra
Professor, Department of Soil Science and Agricultural Chemistry, Institute of Agricultural Science, Siksha "o" Anusandhan University, Bhubaneswar, Odisha, India

Dr. Awaneet Kumar
Associate Professor, Department of Genetics and Plant Breeding, Institute of Agricultural Science, Siksha "o" Anusandhan University, Bhubaneswar, Odisha, India

Suchismita Mohapatra
Assistant Professor, Department of Soil Science and Agricultural Chemistry Faculty of Agricultural Sciences, Siksha 'O' Anusandhan, Deemed to be University, Bhubaneswar, Odisha, India

Kawaljeet Kaur
Assistant Professor, Department of Soil Science and Agricultural Chemistry, CT Group of Institutions Jalandhar, Punjab, India

Himanshu Jangid
Ph.D. Scholar, Department of Microbiology, School of Bioengineering and Biosciences, Lovely Professional University, Punjab, India

Corresponding Author:
Suryakant Ranjan
Ph.D. Scholar, Department of Biotechnology, School of Bioengineering and Biosciences, Lovely Professional University, Punjab, India

Biomarker's of Alzheimer's disease: A review

Suryakant Ranjan, Himanshu Sekhar Behera, Arun Kumar S, Bitish Kumar Nayak, Dr. Bijay Kumar Pany, Dr. Gour Hari Santra, Dr. Awaneet Kumar, Suchismita Mohapatra, Kawaljeet Kaur and Himanshu Jangid

DOI: https://doi.org/10.22271/tpi.2023.v12.i1ab.18320

Abstract
There is a desperate requirement to identify non-invasive biomarkers which conceivably could delay development of the Alzheimer's disease. Biomarkers are a quantifiable signal of a certain biological condition. Biomarkers for Alzheimer can be recognized using Blood, Cerebrospinal fluid, Saliva, Urine sample has been an aim of numerous experimenter for several years. Aβ40, Aβ42, total tau, and p-tau in different body samples have characteristic use in AD. Assessment of CSF biomarker is helpful in the forecast the risk of progression from mild cognitive impairment to AD. This study is an outline of in progress joint efforts to set up biomarkers as a characteristic tool and carry out them in diagnostic procedures of the above-mentioned disease.

Keywords: Biomarker, CSF, plasma, neurofibrillary tangles (NFTs)

Introduction
AD was first distinguished by Alois Alzheimer in 1906. AD is a usual neurologic disorder is becoming a dire global health concern [1]. It is signalized by memory loss, a continuous decrease in thinking and by a continuous reduces of cognitive functions from (MCI) to the entire defeat of language, difficulties executing routine daily activity [2]. According to current figure (2019), nearly 50 million human beings suffer from AD or AD connected dementia global [3-4]. The incidence of dementia is forecast to spread by 68% in developing and developed countries by 2050 [5]. It is clinically diagnosed by the unusual accumulation of proteins in and all over the brain cells. Among them protein mixed up is called amyloid beta, accumulation of which build plaques all around brain cells. Another protein is tau protein deposits of which builds neurofibrillary tangles within brain cells [6], go along with induction of oxidative stress, inflammation and serious synaptic changes [7]. Aβ is produced by the consecutive breakup of the transmembrane amyloid-β progenitor protein (APP) by β-secretases and γ-secretases protease complex [8]. It is found that APP cleaning happens in lipid rafts [6, 9]. AD is caused by alternation in APP genes, presenilin-1, and presenilin-2 [10].
AD diagnose is not easy task. Changes in intracerebral region of the brain are recognized by assessing biochemical markers of different body fluid [11]. Biomarker is signal of pathogenesis mechanism, biochemical changes in body fluids to different medicinal treatment [12]. The sign of superior biomarker is that can recognize premature alternation of different illness and draw a distinction between AD and pseudo dementia and other changes [13]. AD cannot be easily detected in primary period when memory damage is light and may go unknown. At present, presence of AD is verified by investigate the CSF of spinal cord, Blood, Saliva, Urine containing markers such as Aβ protein, total tau protein and p-tau expression quantity [14, 15]. Cerebrospinal Fluid is an important origin of biomarkers, because it makes face to face association with intracerebral region and spinal cord and it fully supply various useful indicator profiles of the brain loss [16]. CSF draws by pierce in pale- mammalian cortex of victim which may be both injurious and unpleasant, which is difficult to diagnose the illness. There are numerous types of amyloid-β in which Aβ42 easily responsible for the formation of neuritis plaques in body fluids [17]. United estimation of decreased Aβ42 amount and raised p-tau amount in CSF is important biomarker of AD identification [18, 19].

AD-molecular mechanisms
Acetylcholine is a neurotransmitter and has foremost part in usual purpose in the brain region

Amyloid beta is a protein with conformation Aβ40 and Aβ42 and Aβ42. Aβ42 is the principal component for amyloid plaques obtained in individuals with AD in head region [22]. Aβ Peptide obtained by multi-step cleavage of APP which is 695 amino acid membrane proteins [23]. In the cerebral deposition of Aβ which leads to neuronal dysfunction and brain death [24-25].

The tau proteins are a protein manufactured by splicing from gene *MAPT*. It exists in group of six highly soluble protein isoforms [26]. Tau creates unsolvable fibre in Alzheimer's disease. It provides stability to microtubule [27]. In the AD tau proteins get Hyperphosphorylated through post translational modification into unsolvable neurofibrillary tangles and drop the tendency to attach to cytoskeleton of brain cells [28]. These NFTs disrupt neuronal plasticity and cause neurodegenration.

Excitotoxicity is the pathological process [29]. In excitotoxicity nerve cells are injured by excitement by neurotransmitters such as glutamate and others in adverse condition such as reduced levels of glucose, disease causing genetic mutation [30]. Glutamate is neurotransmitter in our body but due to hyper-excitation leads to excite-toxicity of brain cells which leads to death of brain cells [31].

An excess amount of free radicals plays an essential role in neurodegeneration [32]. Amyloid beta plays primary role in free radical production which ultimately leads to generate oxidative stress [33]. When body exposed to noise and carbon monoxide the basal metabolic rate of the body increase and this ultimately leads to generate oxidative stress conditions. There are many factors which produce oxidative stress like defective mitochondrial energy metabolism, excessive trace elements and metals [34].

There is so many genetic risk factors are involved in AD in which Ɛ4 allele of apolipoprotein E (APOE) is also one of them factor which is responsible for Alzheimer's disease progression [35]. It has various cellular functions such as carries cholesterol in different region of brain, neuronal signaling, neuro-inflammation. It has three isoforms. The E4 polymorphic form is related with progression of AD on the other side E2 diminish the risk [36].

Biomarkers

CSF biomarkers

The CSF may know as an important source for biomarkers in Alzheimer disease. CSF makes straight connection with intracellular region in brain, and any changes in composition of molecules of the CSF can through back biochemical alternation in brain region [37]. AD is caused by the aggregation of amyloid plaques and neurofibrillary tangles.in brain cells. Many types of biomarkers are found in CSF such as Aβ, p-tau and total tau [37-38]. After APP metabolism by beta and gamma secretes Aβ is released into CSF [39]. Aβ40 and Aβ42 are types of Aβ found in CSF of Alzheimer disease victims and these are main measure of that [40]. It was found that the amount of Aβ40 is rises and amount of Aβ42 reduces to 40-50% of control level in CSF of Alzheimer disease [37]. Low level value of Aβ42/ Aβ40 ratio of CSF in comparison to normal level is also found to be an important factor of diagnosis of AD [41].

Tau protein is important constituent of intra-neuronal NFTs and its level is increases in Alzheimer disease patient's CSF regularly and it is found that the AD patients CSF contains 300% or more total tau which is far more than normal value and ELISA method for quantification of total tau in CSF was used. The main reason for increase in tau is neuronal injury [37, 42].

As already mention different isoforms of tau proteins are found that is nitration, methylation and many in which p-tau is produced by phosphorylation of tau, NFT is also produced by phosphorylation of abnormal tau produced by different type of post translational modification and these are the sign of AD condition [43, 44]. It is found out through research that 85 phosphorylation positions are found in tau in region of brain [43].

Plasma biomarkers

Blood is body fluid in human and contains plasma as a fraction of 55% of whole blood with other component. This fluid is ideal for biomarker investigation. Through various studies it is found that the Aβ protein is present in plasma in different isoform and expressed in different proportion in comparision to normal [45] and form senile plaques in intracerebral region in AD.Among various technique used for detection of Aβ protein in AD which ELISA is one of them [46]. Like CSF association between Aβ40 and Aβ42 in quantity wise and ratio wise there is also same information found in plasma [47].

Platelet biomarkers

According to research it is found that Aβ is produced by different enzymatic processing of APP which shows increase regulation pathways in platelets of AD victims [48]. It is also found that the ratio of APP is also lessening and hence this is also an indicator of platelet biomarker of AD [49]. Glycogen synthase kinase 3 beta is a protein kinase shows phosphorylation of tau leading to the production of neurofibrillary tangles and also produce more Aβ in blood platelet [50]. Many isoforms of tau are present in platelet after APP cleavage with 3 or more enzymes like CSF biomarker [51]. Some biomarkers of platelet are coated platelet and platelet PLA2 enzyme. Patient with AD shows more amount of coated platelet in initial process [52] and low amount of platelet PLA2 enzyme in comparison to control in dementia [54].

Inflammatory Markers

Neuro-inflamation mechanism comprises with brain and it is directly related with AD [55]. If any patient suffering with AD faces over expression with cytokine, chemokine which is responsible for death of neuron Tumor necrosis factor receptor is an important biomarker which may be called inflammatory biomarker when overexpressed in comparison to normal level show death of so many neuron cells which leads to patient suffering with AD. According to research shown that blood serum contains different amount of ceramides. AD patient contains fewer amounts of NK cells [56].

Circulatory miRNAs

MiRNA is also considered as biomarker with biomarker as already mentioned above and this is non-coding part of RNA in cell [57]. Patients having AD many scientists relate AD with different proportion of miRNA in blood component and cerebrospinal fluid and are easily identified in that part with PCR [58]. It is also found the less regulation of miRNA in AD victims [59]. Besides this biomarker present in body liquid part it is also involved with genes such as amyloid precursor

protein, beta-site amyloid precursor protein cleaving enzyme 1 which is responsible for Alzheimer disease in human beings [60]. As now there is no treatment available for AD so these biomarkers will be important to initially identify the disease in patients and make early therapeutics [61].

Biomarkers for oxidative stress

Another important component which is used to detect early pathology in brain is oxidative stress as biomarker [62]. It is used to detect AD. After continuous research on brain it is found that AD victims contains high amount of reactive oxygen species [63] and hence show different alternation of proteins like nitration, oxidation and alter them [64]. It is also found that aldehydic lipid per-oxidation amount is also being high in dementing patients [65]. Oxidative stress levels are found in CSF also besides the blood of AD candidate other than amyloid beta and both show no co-relationship between them [66].

Saliva

There is need to identify biomarker in human which will no create pain so here saliva biomarker fitted perfectly because in this to identify marker simply take saliva from mouth and uses different analysis technique like ELIZA and identify [67]. Altered concentration of Aβ, tau proteins and lectoferrin are found which is used as saliva biomarker. These components easily transferred into saliva from blood. Both isoforms of Aβ such as Aβ42, Aβ40 are found and also tau with isoform p-tau and t-tau have also found after processing of APP with enzymes. Altered lectoferrin levels are also found as biomarker for AD patients [68].

Urine

Like so many biomarker in human body fluids urine is also a biomarker origin to identify early onset of AD. Although urine is far apart from region of brain but it shows some relationship. Urine biomarkers are identified using different analysis technique such as LC-MS/MS, ELIZA, NMR in human and mouse models [69]. AD victims show different concentration of APOC3 and in his urine. A study was done to analyse the urine of animals and it was found that urine contains altered amount of tyrosine in initial state of AD. A further study was done and found that urine sample with AD contain different concentration of L-arginine and allantonin whish is indicator of early AD disease [70].

Olfactory fluids

Olfactory fluid is body fluid of human being which is source for biomarker of AD victims [71] obtained with ELIZA and other analytical technique which detects the different concentration or altered concentration of Tau and Aβ in olfactory fluids of AD [72]. This fluid makes contact with brain region od AD [73]. Amyloid beta aggregates to form neurofibrillary tangles in olfactory fluids in comparison to control [74].

Ocular fluids

Our eye contains ocular fluids which is also directly related with brain and is non- invasive sample to isolate and detect the AD in diseased patients [75]. The Aβ deposits in ocular fluids of eye and aggregates to form NFT [76], tau is indicator of AD which is called biomarker to detect the AD in early stage which aggregates to form senile plaques [77].

Table 1: Biomarker in different fluids of human body for AD Diagnosis.

Sample	Biomarker
CSF	Aβ42
	t-Tau
	p-Tau
	Aβ42/ Aβ40 ratio
Plasma	Aβ40
	Aβ42
	Aβ42/ Aβ40 ratio
Platelet	Aβ
	BACE1
	Tau
Inflammatory	TNF-receptor 1
	TGF-β
	IFN-γ
	Interleukin
Oxidative stress	
Saliva	Aβ42
	t-Tau
	p-Tau
Urine	Apolipoprotein C3
Olfactory fluids	Aβ
	Tau
Ocular fluids	Aβ

Conclusion

Biomarkers play an important role in AD as it predicting Alzheimer disease. There are so many Biomarkers discussed for earlier diagnosis of AD but till now no particular drugs are available to treat the AD. Different types of biomarkers found in Saliva, CSF, Urine, Blood like Aβ, Tau, Aβ42/ Aβ40 ratio. Among these Urine, blood, saliva fluid is good source because can be collected easily in comparison to other without any pain.

References

1. Alzheimer's A. Alzheimer’s disease facts and figures. Alzheimers Dement. 2016;12(4):459–509.
2. Martha C, Rosales-Hernández, *et al*. Involvement of Free Radicals in the Development and Progression of Alzheimer’s Disease. INTECH, 2016, 248-275.
3. CP, World Alzheimer Report 2018. The state of the art of dementia research: new frontiers. London: Alzheimer’s Disease International; c2018.
4. Tiantian Guo, *et al*. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer’s disease. Molecular Neurodegeneration, 2020, 1-37.
5. Prince MJ, WA, *et al*. the global impact of dementia: an analysis of prevalence, Incidence, Cost and Trends; c2015.
6. Efthalia Angelopoulou, Yam Nath Paudel, Mohd. Farooq Shaikh, Christina Piperi. Flotillin: A Promising Biomarker for Alzheimer’s Disease. J. Pers. Med. 2020;10(2):2-13.
7. Leda Talib L, *et al*. Platelet biomarkers in Alzheimer’s disease. World J Psychiatr. 2012;2(6):1-7.
8. Janelle Nunan, *et al*. Federation of European Biochemical Societies. 2000;483(1):6-10.
9. Robert Ehehalt, *et al*. J Cell Biol. 2003;160(1):113-123.
10. Lynn Bekris M, *et al*. Genetics of Alzheimer’s Disease. J Geriatr Psychiatry Neurol. 2010;23:213-227.

11. Michael Weiner W, *et al*. Recent publications from the Alzheimer's Disease Neuroimaging Initiative: Reviewing progress toward improved AD clinical trials. Alzheimer's & Dementia. 2017;13(4):e1-e85.
12. Richard Mayeux, *et al*., Biomarkers: Potential uses and limitations. NeuroRx. 2004;1(2):182-188.
13. Silvia Mandel A, *et al*. Biomarkers for prediction and targeted prevention of Alzheimer's and Parkinson's diseases: evaluation of drug clinical efficacy. EPMA Journal. 2010;1(2):273–292.
14. Guy McKhanna M, *et al*. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263–269.
15. Ajay Prasad Hrishi, *et al*. Cerebrospinal Fluid (CSF) Analysis and Interpretation in Neurocritical Care for Acute Neurological Conditions. Indian Journol of Critical Care Medicine. 2019;23(Suppl 2):S115-S119.
16. Anoop A, *et al*. CSF Biomarkers for Alzheimer's Disease Diagnosis. International Journal of Alzheimer's Disease; c2010. p. 1-12.
17. Jinny Claire Lee, *et al*. Diagnosis of Alzheimer's disease utilizing amyloid and tau as fluid biomarkers. Experimental & molecular medicine. 2019;51(5):1-10.
18. Tero Tapiola, *et al*., Cerebrospinal Fluid -Amyloid 42 and Tau Proteins as Biomarkers of Alzheimer-Type Pathologic Changes in the Brain. Arch Neurol. 2009;66(3):382-389.
19. Paul Murphy M, *et al*., Alzheimer's Disease and the β-Amyloid Peptide. J Alzheimers Dis. 2010;9:1-17.
20. Marina Picciotto R, *et al*., Acetylcholine as a Neuromodulator: Cholinergic Signaling Shapes Nervous System Function and Behavior. Neuron. 2012;76(1):116-129.
21. Paul Francis T, *et al*., The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry. 1999;66(2):137–147.
22. Lieke Jäkel, *et al*., Aβ43 in human Alzheimer's disease: effects of active Aβ42 immunization. Jäkel *et al*. Acta Neuropathologica Communications, 2019, 1-11.
23. Richard O'Brien J, *et al*., Amyloid Precursor Protein Processing and Alzheimer's Disease. Annu Rev Neurosci. 2011;34:185-204.
24. Lujia Zhou, *et al*., Amyloid precursor protein mutation E682K at the alternative Beta-secretase cleavage beta'(-site increases Amyloid beta generation. EMBO Molecular Medicine. 2011;3(5):291–302.
25. Mako Takami, *et al*., Gama-Secretase: Successive Tripeptide and Tetrapeptide Release from the Transmembrane Domain of -Carboxyl Terminal Fragment. The Journal of Neuroscience. 2009;29(41):13042–13052.
26. Tiantian Guo, Denghong Zhang, Yuzhe Zeng, Timothy Huang Y, Huaxi Xu, Yingjun Zhao. Molecular Neurodegeneration. 2020;15(1):1-37.
27. Khalid Iqbal, *et al*., Tau in Alzheimer Disease and Related Tauopathies. Curr Alzheimer Res. 2010;7(8):656–664.
28. Alejandra Alonso D, *et al*. Hyperphosphorylation of Tau Associates with Changes in Its Function Beyond Microtubule Stability. Front Cell Neurosci. 2018**;**12:1-11.
29. Manuel Velasco, *et al*., Excitotoxicity: An Organized Crime at The Cellular Level. Journal of Neurology And Neuroscience. 2017;8:1-10.
30. Rui Wang, *et al*., Role of glutamate and NMDA receptors in Alzheimer's disease. J Alzheimers Dis. 2018;4:1-14.
31. Matthew Hynd R, *et al*., Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease. Neurochemistry International. 2004;45(5):583-595.
32. Lien Ai Pham-Huy, Hua He, Chuong Pham-Huy. Free Radicals, Antioxidants in Disease and Health. International journal of Biomedical science. 2008;4(2):89-96.
33. Paula Moreira I, *et al*., Alzheimer Disease and the Role of Free Radicals in the Pathogenesis of the Disease. CNS & Neurological Disorders - Drug Targets. 2008;7(1):3-10.
34. Piyoosh Sharma, *et al*., Comprehensive review of mechanisms of pathogenesis involved in Alzheimer's disease and potential therapeutic strategies. Progress in Neurobiology. 2019;174:53-89.
35. Chia-Chen Liu, *et al*., Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. Nat Rev Neurol. 2012;9(2):1-27.
36. Tosha Williams, *et al*., Therapeutic approaches targeting Apolipoprotein E function in Alzheimer's disease. Molecular Neurodegeneration. 2020;15(1):1-19.
37. Kaj Blennow, *et al*., csf biomarker for Alzheimer's disease: use in early diagnosis and evaluation of drug treatment. Expert review of molecular Diagnostics. 2014;5(5):661-672.
38. Sarah Kent A, *et al*., The physiological roles of tau and Aβ: implications for Alzheimer's disease pathology and therapeutics. Acta Neuropathologica. 2020;140(4):417–447.
39. Blennow K, *et al*., Biomarkers for Alzheimer's disease: current status and prospects for the future. Journal of Internal Medicine. 2018;284(6):643–663.
40. David Holtzman M, *et al*., CSF biomarkers for Alzheimer's disease: Current utility and potential future use. Neurobiol Aging. 2011;32:1-9.
41. Kurt Jellinger A, *et al*., Biomarkers for early diagnosis of Alzheimer disease: 'ALZheimer ASsociated gene' – a new blood biomarker?. J Cell. Mol. Med. 2008;12(4):1094-1117.
42. Tania Gendron F, *et al*., The role of tau in neurodegeneration. Molecular Neurodegeneration. 2009;4(1):1-19.
43. Tiantian Guo, *et al*., Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Molecular Neurodegeneration. 2020;15(1):1-37.
44. Michala Kolarova, *et al*., Structure and Pathology of Tau Protein in Alzheimer Disease. International Journal of Alzheimer's Disease, 2012, 1-13.
45. Christopher Aluise D, *et al*., Peptides and proteins in plasma and cerebrospinal fluid as biomarkers for the prediction, diagnosis, and monitoring of therapeutic efficacy of Alzheimer's disease. Biochimica et Biophysica Acta. 2008;1782(10):549-558.
46. Michael Irizarry C. Biomarkers of Alzheimer Disease in Plasma. American Society for Experimental Neuro Therapeutics. 2004;1(2):226–234.
47. Richard Mayeux, *et al*., Blood-based biomarkers for

Alzheimer's Disease: Plasma Aβ40 and Aβ42, and Genetic Variants. Neurobiol Aging. 2011;32:1-10.
48. Geneviève Evin, *et al*., Platelets and Alzheimer's disease: Potential of APP as a biomarker. World J Psychiatr. 2012;2(6):102-113.
49. Leda Talib L, *et al*., Platelet biomarkers in Alzheimer's disease. World J Psychiatr. 2012;2(6):1-7.
50. Balaraman Y, *et al*. Glycogen synthase kinase 3β and Alzheimer's disease: pathophysiological and therapeutic significance. Cell Mol Life Sci. 2017;63(11):1226-35.
51. Andrea Slachevsky, *et al*., Tau Platelets Correlate with Regional Brain Atrophy in Patients with Alzheimer's Disease. Journal of Alzheimer's Disease. 2017;55(4):1595-1603.
52. Calin Prodan I, *et al*., Coated-platelets are Higher in Amnestic Versus Nonamnestic Patient with Mild Cognitive Impairment. Alzheimer Dis Assoc Disord. 2007;21(3):259-261.
53. Calin Prodan I, *et al*., Rate of progression in Alzheimer's disease correlates with coated-platelet levels-a longitudinal study. Translational Research. 2008;152(3):99-102.
54. Cho HW, *et al*., Phospholipase A2 is involved in muscarinic receptor-mediated sAPPalpha release independently of cyclooxygenase or lypoxygenase activity in SH-SY5Y cells. Neuroscience Letters. 2005;397(3):214-218.
55. Sandra Amor, *et al*., Inflammation in neurodegenerative diseases. Immunology. 2010;129(2):154–169.
56. Weisman D, *et al*., Interleukins, inflammation, and mechanisms of Alzheimer's disease. Vitamins and Hormones. 2006;74:505-530.
57. Hirosha Geekiyanage, *et al*., Blood serum miRNA: Non-invasive biomarkers for Alzheimer's disease. Experimental Neurology. 2011;235(2):491–496.
58. Femminella GD, *et al*., The emerging role of microRNAs in Alzheimer's disease. Front Physiol. 2015;6:1-5.
59. Villa C, *et al*., Expression of the transcription factor Sp1 and its regulatory hsa-miR-29b in peripheral blood mononuclear cells from patients with Alzheimer's disease. J Alzheimers Dis. 2016;35(3):487-494.
60. Bekris LM, *et al*.. MicroRNA in Alzheimer's disease: an exploratory study in brain, cerebrospinal fluid and plasma. Biomarkers. 2013;18(5):455-466.
61. Ardekani AM, Naeini MM, The Role of MicroRNAs in Human Diseases. Avicenna journal of medical biotechnology. 2010;2(4):161-179.
62. Butterfield DA, *et al*., Involvements of the lipid peroxidation product, HNE, in the pathogenesis and progression of Alzheimer's disease. Biochim Biophys Acta. 2010;1801(8):924-929.
63. Chen X., Oxidative stress in neurodegenerative diseases. Neural regeneration research. 2012;7(5):376-385.
64. Sultana R., Role of oxidative stress in the progression of Alzheimer's disease. Journal of Alzheimer's Disease. 2010;19(1):341-53.
65. Stadtman ER, *et al*. Free radical-mediated oxidation of free amino acids and amino acid residues in proteins. Amino Acids. 2003;25(3):207-218.
66. Butterfield DA, *et al*., Involvements of the lipid peroxidation product, HNE, in the pathogenesis and progression of Alzheimer's disease. Biochimica et Biophysica Acta. 2010;1801(8):924-929.
67. Ali Yilmaza, *et al*., Diagnostic Biomarkers of Alzheimer's Disease as Identified in Saliva using 1H NMR-Based Metabolomics. Journal of Alzheimer's Disease. 2017;58(2):355-359.
68. Helena Sophia Gleerup, *et al*., Biomarkers for Alzheimer's Disease in Saliva: A Systematic Review, 2019, 1-11.
69. Rani P, *et al*., A Systematic Review on Urinary Biomarkers for Early Diagnosis of Alzheimer's Disease (AD). International Journal of Nutrition, Pharmacology, Neurological Diseases. 2021;10(3):91-98.
70. Watanabe Y, *et al*., Urinary Apolipoprotein C3 Is a Potential Biomarker for Alzheimer's Disease. Dement Geriatr Cogn Dis Extra. 2020;10(3):94-104.
71. Jinny Claire Lee, *et al*., Diagnosis of Alzheimer's disease utilizing amyloid and tau as fluid biomarkers. Experimental & Molecular Medicine. 2019;51(5):1-10.
72. Attems J, *et al*., Olfactory tau pathology in Alzheimer disease and mild cognitive impairment. Clin Neuropathol. 2006;25(6):265-71.
73. Ohm TG, *et al*., Olfactory bulb changes in Alzheimer's disease. Acta Neuropathol. 1987;73(4):365-369.
74. Passali GC, *et al*., Tau protein detection in anosmic Alzheimer's disease patient's nasal secretions. Chemosens. Percept. 2015;8(4):201-206.
75. Prakasam A, *et al*., Differential accumulation of secreted AbetaPP metabolites in ocular fluids. J Alzheimers Dis. 2010;20(4):1243-53.
76. Frederikse PH, *et al*., Oxidative stress increases production of beta-amyloid precursor protein and beta-amyloid (Abeta) in mammalian lenses, and Abeta has toxic effects on lens epithelial cells. J Biol Chem. 1996;271(17):10169-10174.
77. Koronyo Y, *et al*., Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease. JCI Insight. 2017;2(16):1-19.