Alzheimer's Disease

Aso, E. and Ferrer, I. (2014) **Cannabinoids for treatment of Alzheimer's disease: moving towards the clinic,** Frontiers in Pharmacology, 5(37), pg 1-11

> Agonists for CB1 and CB2 show promise as anti-inflammatory agents impacting the progression of AD.

Aso, E. and Ferrer, I. (2016) **CB2 Cannabinoid Receptor as Potential Target against Alzheimer's Disease,** Frontiers in Neuroscience, 10(243), pg 1-10

> CB2 receptors in the brain are increased in AD. Murine models of AD show benefit in treatment with CB2 agonists to reduce amyloid plaque and tau tangles.

Bell, S.J., Gomez-Pinilla, F., and Ling, P.R.(2021) **Beta-caryophyllene, An anti-inflammatory Natural Compound**, **Improves Cognition,** J. Food & Nut. Sci. 3(2), pg 31-43

> A human clinical trial of reduced memory function, dementia, was run using two doses of beta-caryophyllene. Memory tests at 4 and 8 weeks once or twice daily showed a statistically significant improvement with dose response.

Cazarin, C.A., Silveira, N., Goncalves, A.E., de Oliveira, L., Lima, M.G., Biavatti, M. W., and de Souza, M. M.(2022), **Involvement of TRPV1 receptors on protective effect of Acmella ciliata extract and spilanthol in streptozotocin-induced sporadic Alzheimer's disease model.** Academia Journal of Medicinal Plants, DOI:10.15413/ajmp.2022.0112

> A. Ciliata extract and spilanthol activated the TRPV1 receptor to inhibit oxidative stress experienced in AD.

Cummings, J.L., Goldman, D.P., Simmons-Stern, N.R., and Ponton, E.,(2021), **The cost of developing treatments for Alheimer's disease: A retrospective exploration.,** J. Alz. Assoc. DOI: 10.1002/alz.12450

> In over 26 years, only 5 drugs have been approved for AD. Here are estimates for AD R&D since 1995 at $42.5 billion with the greatest costs incurred in phase 3 where 184,000 participants were registered or are currently enrolled in clinical trials.

Fajloun, Z., Wu, Y., Cao, Z., Kovacic, H., and Sabatier, J.M., (2023) **COVID-19 and Alzheimer's Disease: The Link Finally Established. Infectious Disorders-Drug Targets** DOI:10.2174/1871526523666230529162633

> The possible beginning of the Alzheimer's neurodegenerative disease is closely correlated with the defective renin-angiotensin system over activated by the SARS-Co-2 virus and possibly the vaccine spike protein.

Furman, S., Green, K., and Lane, T.E.(2023) **COVID-19 and the impact on Alzheimer's disease pathology**. J. Neurochemistry DOI: 10.1111/jnc.15985

Shared immunomodulators point to expected acceleration of the debilitating effects of AD due to inflammatory agents.

Galan-Ganga, M., Rodriquez-Cueto, C., Merchan-Rubira, M., Hernandez, F., Posada-Ayala, A.M., Lanciego, J.L, Lopez, M.G., Rabano, A., Fernandez-Ruiz, and J., Lastres-Becker, I. (2021) **Cannabinoid receptor CB2 ablation protects against TAU induced neurodegeneration.** https://doi.org/10.1186/s40478-021-01196-5

Modulation of CB2 is proposed to treat tauopathies.

Gotoh, M., Miyamoto, T., and Ikeshima-Kataoka, H. (2023), **Astrocytic Neuroimmunological Role of interacting with Microglial Cells in Neurodengenerative Diseases.** https://10.3390/ijms24021599

Astrocytes and Microglial cells interact to provide protection of the brain. Immune activation causes overstimulation and destruction of brain organization. Treatment with immune modulators is a rational approach to stop or slow loss of brain function.

Gregory, J., Vengalasetti, Y.V., Bredesen, D.E., and Rao, R. V. (2021) **Neuroprotective Herbs for the Management of Alzheimer's Disease.** Biomolecules, https://doi.org/10.3390/biom11040543

The article reviews several herbs with anti-inflammatory, anti-oxidant and cognitive enhancing effects in vitro, in vivo and in preclinical studies. The authors have developed a protocol that includes herbs and positive results even to the point of reversing Alzheimer's symptoms.

Hussain, B., Fang, C., and Chang, J. (2021) **Blood-Brain Barrier Breakdown: An Emerging Biomarker of Cognitive Impairment in Normal Aging and Dementia.** Frontiers in Neuroscience DOI:10.3389/fnins.2021.688090

The normal aging process and dysfunctional brains show mechanisms which allow toxins to enter the brain. TNFa, NO and ROS contribute to inflammation and the breakdown of the blood-brain barrier.

Landreth, G., Jiang, Q., Mandrekar, S., and Heneka, M. (2008) **PPARgamma Agonists as Therapeutics for the Treatment of Alzheimer's Disease.** The Journal of the Society for Experimental NeuroTherapeutics.5(3), pg. 481-489.

PPARgamma is a ligand-activated transcription factor whose biological function is to regulate glucose and lipid metabolism and to suppress inflammatory gene expression. AD contains amyloid plaques deposited at the instigation of inflammatory processes. PPARgamma agonists have now shown in animal models the ability to ameliorate the disease-related pathology with improved learning and memory.

Lawrence, J.M., Schardien, K., Wigdahl, B., and Nonnemacher, M.R. (2023), **Roles of neuropathology-associated reactive astrocytes: a systematic review.** Acta Neuropathologica Communications. https://doi.org/10.1186/s40478-023-01526-9

Neuroinflammation caused by stokes and/or LPS cause activation of the microglia and astrocytes. Signaling by Il-1a, TNFa and C1q induce the neurotoxic phenotype which compromises the neuronal organization. Modulating these signals may be useful for drug targeting.

Linnerbauer, M., Wheeler, M.A., and Quintana, F.J. (2020) **Astrocyte Crosstalk in CNS Inflammation.** Neuron https://doi.org10.1016/jneuron.2020.08.012

Astrocytes are glial cells that are key players in health and disease. Bidirectional communication with microglia regulate inflammatory and anti-inflammatory signaling. Cytokines involved are: TNFa, IL-1b, iNOS, VEGF, NRF2 and TGFb. Modulation of these cytokines and chemokines may allow moving of disease states to normal health states.

Liu, L.R., Liu, J.C., Bao, J.S., Bai, Q.Q., and Wang, G.Q. (2020) **Interaction of Microglia and Astrocytes in the Neurovascular Unit.** Frontiers in Immunology. Doi:10.3389/fimmu.2020.01024

Neuroinflammation induced by stroke or LPS in astrocytes and microglia are activated as M1 and A1. Initially, M1 is more sensitive to assaults and produces IL-1 and TNFa which triggers the A1 to also produce these in a feedback loop, thus amplifying the signal. Thus, the M1 and A1 may be therapeutic targets for future drug development.

Medina-Vera, D., Zhao, H., Bereczki, E., Rossell-Valle, C., Shimozawa, M., Chen, G., de Fonseca, F.R., Nilsson, P., and Tambaro, S. (2023) **The Expression of the Endocannabinoid Receptors CB2 and GPR55 is Highly Increased during the Progression of Alzheimer's Disease in App(NL-G-F) Knock-In Mice.** Biology. https:// doi.org/10.3390/biology12060805

The AD pathology suggests alterations in the endocannabinoid system. This study shows that the AD model when perturbed has increased expression of the CB2 and GPR55 receptors. Thus, monitoring the level of receptors could be useful in diagnosis. These receptors may also provide targets for future treatments.

Medeiros, R., Baglietto-Vargas, D., and LaFerla, F.M. (2010) **The Role of Tau in Alzheimer's Disease and Related Disorders.** CNS Neuroscience & Therapeutics 17(2011) pg 514-524

Tau, the microtubule associated protein, forms insoluble filaments that accumulate as neurofibrillary tangles in AD. Amyloid beta plaques appear to be involved in activating these tangles through upregulation of kinases. Most likely, a therapeutic regimen will include polypharmacy of Amyloid beta control and kinase modulation.

Ramirez-Barrantes, R., Cordova, C., Poblete, H., Munoz, P., Marchant, I., Wianny, F. and Olivero, P. (2016) **Perspectives of TRPV1 Function on the Neurogenesis and Neural Plasticity.** Neural Plasticity https://dx.doi.org/10.1155/2016/1568145

New strategies to repair and renew neuronal networks using plasticity possible through stem cell grafts would be useful. The function of TRPV1 in the brain is under intensive investigation and is now emerging as a molecular tool for survival and control of neural stem cells.

Rietdijk, C.D., van Wezel, R. J.A., Garssen, J., and Kraneveld, A.D. (2015) **Neuronal toll-like receptors and neuro-immunity in Parkinson's disease, Alzheimer's disease and stroke.** N.n. journal DOI: 10.20517/2347-8659.2015.28

TLR receptors have relevance in PD and can point to targets for drug targeting.

Sahiner, M., Yilmas, A.S., Gungor, B. and Sahiner, N. (2023) **A Review on Phyto-therapeutic Approaches in Alzheimer's Disease.** Journal of Functional Biomaterials. Doi.org/l103390/jfb14010050

Phytomedicines have had some success in alleviating some of the symptoms of AD, such as dementia.

Senatorov, V.V., Friedman, A.R., Millikovsky, D.Z., Ofer, J., Saar-Ashenazy, R., Charbash, A.M., Jahan, N., Chin, G., Mihaly, E., Lin, J.E., Ramsay, H.J., Moghbel, A., Preininger, M.K., Eddings, C.R., Harrison, H.V., Patel, R., Shen, Y., Ghanim, H., Sheng, H., Veksler, R., Sudmant, P.H., Becker, A., Hart, B., Rogawski, M.A., Dillin, A., Friedman, A., and Kaufer, D. (2019) **Blood-brain barrier dysfunction in aging induces hyperactivation of TGFb signaling and chronic yet reversible neural dysfunction.** Sci. Transl. Med. 11 eaaw8283

Here is reported that aging in humans and rodents involves the decline in neural function due to a breakdown in the blood-brain barrier. The BBB dysfunction triggers hyperactivation of the TGFb signaling in astrocytes. Blocking TGFb receptors or pharmacological inhibition of the TGFb reversed symptomatic outcomes in aged mice. This study demonstrates that the aging brain may retain a latent capacity which can be revitalized by therapeutic inhibition of TGFb signaling.

Von Bernhardi, R., Cornejo, F., Parada, G.E., and Eugenin, J. (2015) **Role of TGFb signaling in the pathogenesis of Alzheimer's disease.** Front. Cell. Neurosci. Doki: 10.3389/fncel.2015.00426

Aging is the main risk factor in Alzheimer's disease (AD). Conspicuous changes in microglia activation causes increased expression of cytokines leading to oxidative stress and reduced phagocytosis of amyloid beta plaques. This neuroinflammation is self-perpetuating leading to TGFb upregulation. Thus, modulation of the TGFb receptor and/or expression could slow or reverse AD symptoms.

Wang, S., Wang, B., Shang, D., Zhang, K., Yan, X., and Zhang, X. (2022) **Ion Channel Dysfunction in Astrocytes in Neurodegenerative Diseases.** Front. Physiol. DOI: 10.3389/fphys.2022.814285

Astrocytes play an important role in the central nervous system. Ion channels in these cells function not only in ion transport, maintain water/ion metabolism homeostasis, but participate in processes in neurons and glial cells regulating signaling pathways. These are important in AD, PD, Huntington's and ALS. Understanding these mechanisms will play an important role in developing new targets for therapeutics.

Yang, J., Wise, L., and Fukuchi, K.I. (2020) **TLR Cross-Talk with NLRP3 Inflammasome and Complement Signaling Pathways in Alzheimer's Disease.** Front. Immunol. DOI: 10.3389/fimmu.2020.00724

Amyloid plaques and neurofibrillary tangles are two hallmarks of AD. Stress can cause Ab to bind TLR4 and move the inflammasome NLRP3 to cause neuroinflammation, Ab accumulation, synapse loss and neurodegeneration. Interrupting this pathway may lead to a therapeutic approach to treatment.

Youssef, D.A., El-fayoumi, H.M., and Mahmoud, M.F. (2019) **Beta-caryophyllene alleviates diet-induced neurohehavioral changes in rats: The role of CB2 and PPARgamma receptors.** Biomed. Pharmacotherapy https://doi.org/10.1016/j.biopha.2018.11.039

Insulin resistance(IR) and obesity predispose diseases such as diabetes, cardiovascular and neurodegenerative diseases. Beta-caryophyllene, a natural sesquiterpene, exerts neuroprotective, anxiolytic and antidepressant agonist effects via the CB2 receptor. This study suggests that agonists at the CB2 receptor may treat diabetes and other neuro-behavioral problems.