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The Possibility of an Infectious Etiology of Alzheimer Disease

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Abstract

Over the past three decades, there has been constant postulation regarding the infectious etiology of Alzheimer disease (AD), which in turn suggests the vital role of various infectious agents in AD-associated inflammatory pathways. Recent findings indicate anti-microbial properties of Aβ, and suggest that Aβ production and deposition in AD might be induced by infectious agents. Several types of spirochetes have been associated to dementia, cortical atrophy, and pathological and biological hallmarks of AD. A significant association between AD spirochetes and other pathogens like HSV-1 and *Chlamydia pneumonia* has now become well established. In neurons infected by HSV-1 showed Aβ and hyperphosphorylated Tau accumulation. The expression of pro-inflammatory molecules have been found to be enhanced by specific bacterial ligands, and viral and bacterial DNA and RNA, thus activating the immune system. Aβ has now been established as anti-microbial peptide capable of inducing pore formation, thus justifying their infection-mediated accumulation. Thus, a proper combination of anti-inflammatory, anti-viral, and antibiotic therapeutics might potentially prevent the progression of AD. Here, we discussed the potential role of bacterial, fungi, and viral infections in AD causation and progression, and the potential-associated therapies to counter the AD condition.

Keywords Alzheimer disease · Neuroinfection · Neuroinflammation · Microorganism · Neurotropic viruses

Introduction

Alzheimer disease (AD) is a common neurological condition, characterized by a gradual onset of neurocognitive symptom that affects more than 35 million individuals around the world [1–3]. The brain tissue of AD patients show mainly two pathological features: (a) intraneuronal neurofibrillary tangles (NFTs)—formed with Tau protein—and (b) extracellular insoluble senile plaques—formed with amyloid-β (Aβ) peptide—[4, 5]. Additionally, other characteristic features of AD include granulovacuolar degeneration [6], synaptic and neuronal loss, microgliosis, reactive astrocytosis Hirano bodies [7], and the recently neuropil threads (curly fibers) [8].

NFTs and Aβ are not unique to AD, and also are produced in other central nervous system (CNS) conditions [9]. In addition, recent findings have established the potential anti-microbial property of Aβ. In fact, infectious agents may induce the production and deposition of Aβ in patients. Aβ has also been reported to inhibit the replication of pandemic and seasonal strains of influenza virus in vitro, thus further establishing the anti-viral activity of Aβ and its role in modulating the viral interactions with phagocytes [10].

Inflammation is associated to most infectious diseases, though it is not triggered only by infectious pathogens [9, 11]. A number of hypotheses have shown the association of accumulative infections with AD, thus proclaiming the role of neuroinflammation and neuroinfection in AD etiopathogenesis [12–14]. There are three primary contributors in the pathogenesis of AD: neuroinflammatory processes, oxidative stress, and vascular factors [15–17]. Enhanced deposits of pathological Aβ results in the activation of macrophages, microglia, lymphocytes, and astrocytes, which in turn

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stimulate the release of various inflammatory mediators [18]. The well-being of blood brain barrier (BBB) is of prime importance for CNS integrity. This process also leads to the recruitment of peripheral blood leukocytes (PBL) through the BBB and their active participation in local brain tissue inflammation. Leukocytes release more inflammatory factors, escalate the inflammatory state, and exacerbate other AD-related pathologies as well [11, 17, 19]. In the present manuscript, we discuss around the literature the potential risk of several infections for AD initiation and progression.

AD Pathogenesis by Neuroinflammation and Infection

Infectious factors could stimulate the activation of astrocytes in the brain; thus indicating that neuropathology can indeed be a manifestation of an infection (Fig. 1). Neuroinflammation is an injury/infection-induced inflammatory response in CNS. Immune response and inflammation are the two most critical components of AD pathology. The BBB protects CNS by microvascular endothelial cells (pericytes and astrocytes) that selectively control the flux of molecules in and out of the brain. However, a large spectrum of pathogens can gain access to BBB and may result in a number of grave illnesses. Viruses can directly infect endothelial cells to cross the BBB and then into the CNS, but bacteria can cross the BBB through different mechanisms including Trojan-horse, paracellular traversal, and transcellular traversal. Damage to CNS during infection triggers the release of inflammatory mediators and activation of the innate immune response, necessary to eliminate the invasive pathogens. The condition of health hazard switches the inflammatory state from acute to chronic [20, 21].

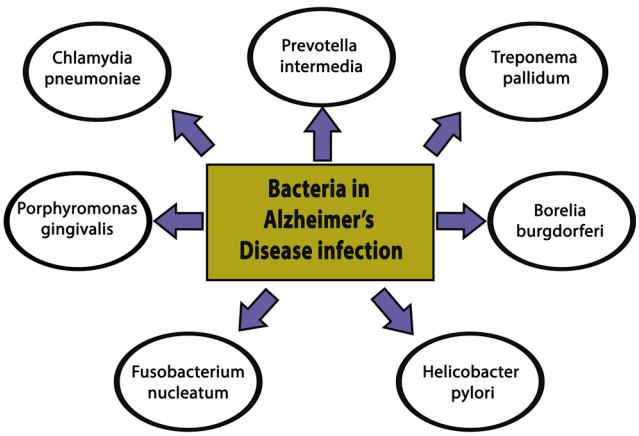

Fig. 1 Bacteria involved in AD pathogenesis. Bacterial infection is likely associated with AD causation and develops. Growing evidence relates the infection of bacteria as *Chlamydia pneumoniae*, *Treponema pallidum*, and *Helicobacter pylori* to AD. Interestingly, the infection of such bacteria is a public health issue in human populations and to date, there is a devoid of studies to determine the relationship of bacterial infection and AD

Inflammatory hypothesis of AD [22] is one of the three most important hypotheses proposed on AD etiopathogenesis [23, 24] which explains that a self-perpetuating progressive inflammation in CNS leads to the activation of molecular pathways and neurodegeneration. Neuroinflammation has been characterized by an accumulation and activation of microglia and astrocytes via cellular and molecular immune factors. A wide range of inflammatory mediators including anaphylatoxins, chemokines, Tau, prostaglandins, cytokines, proteases, free radicals, Aβ, pentraxins, adhesion molecules, activated complement proteins, and pattern-recognition receptors (PRR) has been reported to be present at cortical lesions' site in AD [25–29]. Glial cells have been reported to produce pro-inflammatory cytokines, which in turn may stimulate glial cells to produce additional Aβ [30].

The acute inflammatory response to pathogen-associated molecular patterns (PAMP) may be impaired during aging, thus stimulating the infection sustainability. The pathogens during replication release PAMP (their component molecules) that can be identified by PRR expressed on antigen presenting cells. Examples of PRR include RIG-I-like receptors (RLR), toll-like receptors (TLR), receptors for advanced glycation endproducts (RAGE), c-type lectin receptors (CLR), nucleotide binding oligomerization domain (NOD) like receptors (NLR), and intra-cytosolic DNA sensors [31]. Key cellular mediators of the innate immune and neuroinflammatory response in the CNS are microglia, which express various PRR receptors. Moreover, a strong inflammatory response in the periphery from bacterial or viral infections leads to the peripheral leukocytes (T cells and macrophages) infiltration to the CNS, which share several functional features with microglia. Leukocytes express TLR and are able to be activated by abnormal proteins or PAMPs. Therefore, an acute inflammatory response in the brain is beneficial and leads to repair the affected area of the brain and help to restore brain homeostasis.

The role of inflammation in AD pathogenesis stimulates the research of possible involvement of various infectious agents in inflammatory reactions in the CNS. Recently, the role of infection in AD etiology has increased interest in the literature showing the possible association of various microbial infections with cognitive decline, as well as involvement in onset and AD progression. The evidence for an immune/infectious component in the pathogenesis of AD and for the causation of infection and AD has been shown recently [32]. Infectious factors are responsible for the activation of glial cells that produce several inflammatory molecules [cytokines like IL-1β, IL-6, IL-18, TNF-α, IFN-γ, chemokines, and reactive oxygen species (ROS)], which in turn leads to exacerbate other AD pathologies. Systemic viral, bacterial, fungal, and protozoan infections may enhance the inflammatory state, thereby promoting the susceptibility to develop AD [11, 33, 34]. Likewise, infection burden has been also associated to other NDDs like PD [35] and ALS [36].

Involvement of Microorganisms in AD Pathogenesis

The possibility of the likely involvement of microorganisms in the formation of senile plaques is now being postulated as "infectious etiology for AD" by researchers around the world [37]. A wide range of pathogens including bacteria, fungi, protozoa, and viruses is associated with AD etiology.

Bacteria Involved in AD Pathogenesis

Figure 2 summarizes the major bacteria involved in AD pathogenesis.

Spirochetes Spirochetes are likely to be involved in the pathogenesis of AD [38–40]. Spirochetes are gram-negative, helical bacteria distinguished from other bacteria by the presence of endoflagella, which can invade the brain and generate latent, persistent infection [39, 41, 42]. Spirochetes are the most neurotropic bacteria, which have been detected in the trigeminal ganglia and trigeminal nerve [43]. Indeed, infections with spirochetes can cause serious brain disturbances like cerebral hypoperfusion, cerebrovascular lesions, and a severely disturbed capillary network [44]. Spirochetes can be spread by several mechanism including: (a) hematogenous dissemination, (b) lymphatic path and along nerve fiber tracts, and (c) transmit along the tractus olfactorius and fila olfactoria [45]. Spirochetes and their DNA have been found to be associated with AD, and are strongly concerned as the causative agents leading to dementia [41, 46]. Various types of spirochetes might cause dementia and brain damage similar to AD, as reported by various authors who detected and cultivated spirochetes from AD brains. Miklossy et al. detected spirochetes in the cerebrospinal fluid (CSF), blood, and brain of definite AD cases [39, 41, 47]. In fact, brain tissue of seven demented patients from Brazil and Switzerland (aged 42–82 years) presented spirochetes and they all suffered from slowly progressive neurodegeneration [39]. The transmission of spirochetes along the tractus olfactorius and fila olfactoria confirmed the olfactory hypothesis, and investigations showed that the olfactory bulb and tract are affected in earliest stages of AD degenerative process [44, 48]. In this aspect, innate immune system plays an important role that recognizes spirochetes via PRR, executes pro-inflammatory reactions, and initiates adaptive immune responses.

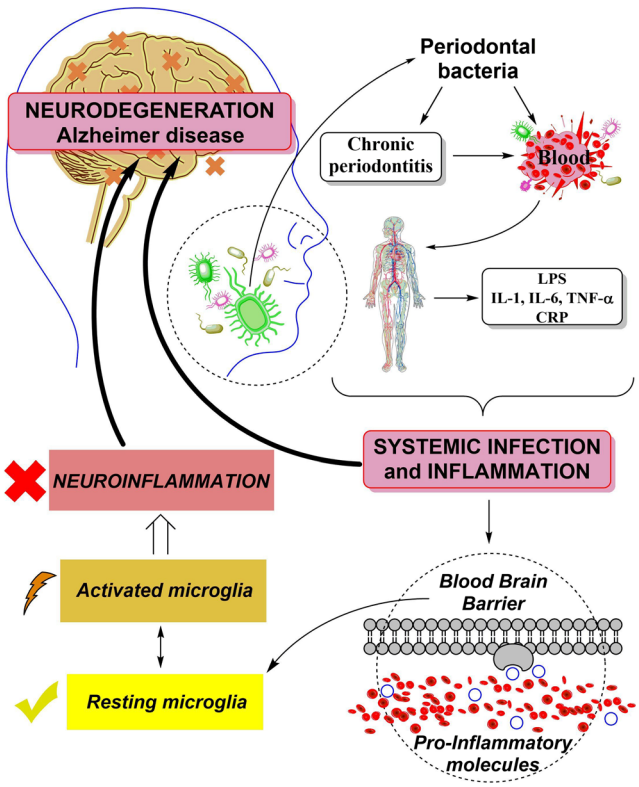

Fig. 2 The relationship between periodontal disease and AD. Periodontal bacteria potentially may be involved with pro-inflammatory states in the human body that promotes the secretion of interleukins as IL-1, IL-6, and TNF-α via the recognition of PAMPs in the bacteria membrane. It is possible that the cytokines secretion involves a systemic infection and inflammation that modifies the protected brain environment, causing the activation of microglia with subsequent neuroinflammation. It is a well-known close relationship between neuroinflammation and AD

Borrelia burgdorferi MacDonald [49], and MacDonald and Miranda [50] for the first time detected *B. burgdorferi* from the cerebral cortex of AD brains by using a specific antibody against *B. burgdorferi*. *B. burgdorferi* is a causative agent of dementia associated with cortical atrophy and microgliosis occurring in late stages of Lyme disease (boreliosis). In recent years, there has been an increased incidence of boreliosis in European countries [51]. *B. burgdorferi* or their synthetic membrane lipoproteins have been reported to be major inflammatory mediators [52, 53]. NFTs have also been reported to be immunoreactive for *B. burgdorferi* [41]. According to recent proposed hypothesis, *B. burgdorferi* causes neurodegenerative changes through an induction of intracellular inflammation in neurons. As a consequence, inflammatory state leads to abnormal Tau phosphorylation, microtubular dysfunction, and NFTs generation. An expanding inflammatory process in the brain leads to the disruption of enzymatic homeostasis [54]. In AD patients who suffered from neuroborreliosis, *B. burgdorferi* antigens were detected in NFTs and Aβ, along with wide neurodegenerative changes in brain tissue [41]. However, exact pathway that involved in this process still remain unknown and requires more detailed study in the near future.

Chlamydia pneumonia The existence of an association between *C. pneumoniae* and AD has been reported by several authors [55–57]. *C. pneumoniae*, an obligate intracellular respiratory pathogen, is currently the most plausible of all infectious bacterial agents proposed to be involved in AD [57]. *C. pneumoniae* may infect various cell types found in the

brain [58], and may reside in an intracellular inclusion that resists immune recognition and lysosomal fusion. This intracellular pathogen interacts with and manipulates the host by gathering nutrients and energy (cholesterol and sphingomyelin) required for its replication [59]. In one study, *C. pneumoniae*-specific DNA was detected in 90% of the sporadic AD brains (it was found in 17 of 19 AD patients compare with other 19 control patients that were negative for *C. pneumoniae*) [60]. Two mRNAs specific to *C. pneumoniae* were also identified in frozen AD brain tissue by RT-PCR [60]. *C. pneumoniae* and related antigens may interact with extracellular proteins and lipids in the brain. The presence of *C. pneumoniae* in AD brain has been confirmed by electron microscopy, immunoelectron microscopy, and immunohistochemical techniques [55, 60–62]. The fascinating relationship between Chlamydia and amyloid (between infection and pathology) in the same cortical regions of the AD brains require further investigations. Manabe et al. successfully demonstrated an intricate relationship between complications of *C. pneumonia* infection and prognosis of dementia [63]. However, due to the complexity of *C. pneumoniae* infections and chronic nature of AD, it has become quite difficult to establish an association with the disease pathogenesis. Validating this association relies on a variety of detection methods for the organism. Currently, the use of immunohistochemistry with a battery of commercially available anti-chlamydia antibodies on cortical and frontal sections of human AD brains provide a valuable insight into the interrelationship between infection and AD pathology [58]. For example, *C. pneumoniae* was cultured from isolated CSF and various brain samples of AD patients originating from different geographic regions of North America [56, 60, 64, 65].

NFTs and amyloid plaques were reported to lead the neurodegeneration in the AD brain, which causes progressive dysfunction of cognitive symptoms like language problems and memory loss. However, the non-cognitive symptoms like psychosis, aggression, and agitation observed in AD patients can be triggered by an infection (e.g., by *C. pneumoniae*) in peripheral organs, and this suggests a contribution of peripheral inflammation in AD pathogenesis [66]. However, more studies require clarifying the exact nature of peripheral inflammation in the pathobiology of AD [67, 68].

Treponema pallidum In fact, Fischer (1907, 1910) has investigated whether the plaques could also be found within brains of patients with dementia paralytica (a common cause of illness associated with tertiary syphilis of the CNS) for almost a century [69–71]. However, although the author (1907, 1910) could not find plaques in the 45 cases with progressively paresis (dementia paralalytica), he has continued his studies. Later, Noguchi and Moore [72] observed the presence of *T. pallidum* in the cerebral cortex of patients with general paresis. Noguchi and Moore [72] also found that some of the patients with syphilis were associated with memory-related health issues. *T. pallidum* has been reported to be responsible for local amyloidosis, cortical atrophy, and slowly progressive dementia in the atrophic form of this chronic bacterial infection [73, 74]. *T. pallidum* can thus cause cortical atrophy, dementia, and the biological and pathological hallmarks of AD. Like *B. burgdorferi*, *T. pallidum* or their synthetic membrane lipoproteins have been reported to be major inflammatory mediators [52, 53]. *T. pallidum* has been reported to frequently co-infect with other bacteria like *B. burgdorferi* and herpes viruses in syphilis [45]. Still, research in this field is in early stage and more studies are needed to determine the association between *T. pallidum* and AD.

Helicobacter pylori *H. pylori* is associated with stomach ulcers and gastric cancer [75]. A number of investigations has reported the role of *H. pylori* with respiratory, neurodegenerative, and other disorders [45]. Increased levels of *H. pylori*-specific IgG antibody were found in the serum and CSF of 27 AD patients in contrast with 27 control patients who did not presented high titter of *H. pylori*-specific IgG [76]. A number of varying pathogenic mechanisms have been hypothesized, including the occurrence of molecular mimicry mechanisms and the induction of a low-grade inflammatory state. The evidences compiled from the literature linking AD to *H. pylori* have been well discussed by Franchesi et al. and Mawanda et al. as well [9, 77]. A significantly higher level of *H. pylori*-specific IgG antibody was reported in the blood and CSF of AD patients [76]. Further research is needed to detect and confirm the presence of *H. pylori* in the brain and to analyze the possibility of a potential relation *H. pylori* and AD.

Actinomycetes The association of *Actinomycetes* with AD has been suggested due to risk four times higher than in other pathological conditions [59, 78]. As revealed by ultrastructural analysis, the fibronectin-immunopositive fibrillary lesions in senile plaques were found to be compatible with filamentous microorganisms, and thus might correspond to *Actinomycetes* [78]. The fact that *Actinobacillus actinomycetemcomitans* is a frequent periodontal pathogen further adds to the possibility of the involvement of *actinomycetes* in various pathological conditions [79].

Propionibacterium acnes *P. acnes*, an atypical anaerobic bacterium, has long been considered to be a commensal bacillus of the skin and is the causative agent of acne vulgaris. However, in a study where an elderly patient with cardiovascular risk factors and glioblastoma served as positive control, *P. acnes* was identified by gas chromatography and microbiological methods in biopsy specimens of the frontal cortex in three of the four AD patients [80]. P. acnes has been shown to be a predominant periodontal pathogen and can reach and infect various organs including the brain by hematogenous

dissemination [81]. The involvement of *P. acnes* in various infections, including osteomyelitis, endophthalmitis, endocarditis, and brain abscesses, is now well established [82]. In two AD cases treated with *P. acnes*-sensitive cephalosporine combined with estrogen and enalapril, a remarkable memory improvement and stabilization of the clinical symptoms were observed [45, 80]. However, more studies are desired to establish definitive association between *P. acnes* with AD.

Other Bacteria Many other pathogens like *P. gingivalis*, *P. intermedia*, *T. forsythia*, and *F. nucleatum* are implicated in the development of several inflammatory diseases at remote organ sites like AD [83]. Periodontitis is common problem in older age because of the poor state of oral hygiene, but it can also start in childhood. Periodontitis can be marked as a "low-grade systemic disease" by the release of pro-inflammatory cytokines into systemic circulation and elevation of C-reactive protein (CRP) [84]. Periodontal disease may in turn stimulate recurrent chronic oral infections, and the periodontal pathogens contribute to the destruction of soft and hard tissues supporting the teeth [85]. Moreover, bacterial LPS also add to the tissue destruction by inducing the immune response and production of pro-inflammatory molecules, like IL-1β, IL-6, and TNF-α. It is well known that inflammation play a pivotal role in periodontitis and AD, and acts as a connecting link between both the diseases [44, 46]. The leptomeningeal cells were shown to transmit systemic inflammatory signals from macrophages to brain-resident microglia by secreting inflammatory mediators during periodontitis. The pathogens can enter to the brain structures from mouth through two possible pathways. Firstly, the periodontal inflammatory process can expand on the brain through circulatory system with pro-inflammatory cytokines, but without the contact of bacteria with brain tissues. Secondly, periodontal bacteria or bacterial molecules can penetrate to the CNS either through blood stream or via peripheral nerves [86]. The relationship between periodontal disease and AD is presented in Fig. 2.

The hypothesis of an association between oral health status and cognitive decline in AD suggests that chronic oral infection promotes inflammation [87], and several pro-inflammatory cytokines enhance the pool of inflammatory mediators in the brain, and lead to confusion and dementia [5, 46]. Therefore, periodontal disease may be a significant source of systemic inflammatory molecules [78]. A link between periodontal disease and AD was tried to be established with a view of identifying the major periodontal disease bacteria and/or bacterial components in brain tissue from 12-h postmortem delay. They confirmed that LPS from periodontal bacteria can access the AD brain during life. The intense neuroinflammation evoked by senescent-type microglia may contribute to the initiation and progression of AD, resulting in the cognitive deficits [88]. Elevated level of TNF-α has been reported in serum of AD patients with periodontal disease [89, 90]. The most neurotropic bacteria are *Spirochetes*, which have been detected in the trigeminal nerve and trigeminal ganglia [43]. Spirochetes and their DNA have been found to be associated with AD, and are strongly concerned as the causative agents leading to dementia [41, 46]. Indeed, infections with spirochetes can cause serious brain disturbances like cerebral hypoperfusion, cerebrovascular lesions, and a severely disturbed capillary network [44] that outcome in most of cases associated with the memory decline and amyloid deposition.

Fungi Involved in AD Pathogenesis

Recently, some authors provided strong evidence for fungal infection in AD patients [91]. Alonso et al. reveal that fungal proteins can be detected in CSF of AD patients with different anti-fungal antibodies [91]. Fungal DNA and proteins were also found in frozen brain tissue from AD patients, but not from control patient tissues. Fungal material was detected both intra-and extracellularly using specific antibodies against several fungi: *C. famata*, *C. albicans*, *C. glabrata*, *P. betae*, *and S. racemosum*. Analysis of different brain sections, including external frontal cortex, cerebellar hemisphere, entorhinal cortex/hippocampus, and choroid plexus of AD patients, revealed the presence of fungal infections [74]. Fungal infection is associated with inflammation, as well as with AD [92]. However, detailed investigations are needed to demonstrate the association between fungal infection-mediated inflammation and AD.

Protozoa Involved in AD Pathogenesis

Chronic infection with the protozoon *T. gondii* results in neuroinflammation, which may explain pathophysiology of AD [73]. This study demonstrated that the protozoon *T. gondii* is involved in pathophysiological process of AD mediated through inducing neuroinflammation [73]. In three studies done in 2010–2011, Prandota suggested that chronic *T. Gondii* infection was the infectious agent responsible for triggering the development of several neurodegenerative diseases associated with an enhanced production of pro- and anti-inflammatory cytokines [93–95]. In a more recent study performed in 2014, Prandota showed that the olfactory dysfunction reported in AD, MS, and schizophrenia was frequently associated with the significantly enhanced levels of serum anti-*T. gondii* immunoglobulin G antibody [96].

Viruses Involved in AD Pathogenesis

Figure 3 summarizes the major viruses involved in AD pathogenesis.

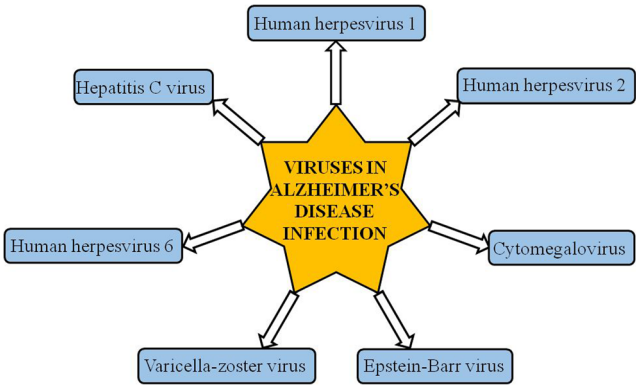

Fig. 3 Viruses involved in AD pathogenesis. A growing body of evidence associates the infection of several virus including HCV, HHV-1, HHV-2, CMV, EBV, and Herpes-Zoster virus with the risk to undergo and develop AD. Currently, it is necessary to perform big-scale studies to confirm that danger

Herpes Simplex Virus-1 Herpes simplex virus (HSV)-1, also known as human herpes virus (HHV)-1, is a common neurotropic virus present in approx. Seventy percent of American population aged above 50 [97]. The reactivation of latent infection of HHV-1 has been suggested as one of the hypothesis behind AD development. Studies with the distribution of HHV-1 DNA in human brains revealed that viral DNA is located primarily within senile plaques. In some elderly dementia patients, HSV-1 DNA was detected in brain samples using in situ hybridization (ISH) [98]. This was probably the first report on the possible association between HSV-1 and dementia. Later on, the role of HHV-1 in AD was proposed by other researchers as well [99, 100]. It was noted that damage of brain tissue in early stages of the disease includes the same areas, which are covered by brain inflammation caused by HHV-1 [33, 99]. Based on the presence of antibodies in the blood, it is estimated that approx. 80% population is infected with HHV-1. A large number of recent findings have detected HSV-1 DNA in AD brains [101–105]. HSV-1 has been reported to be a significant risk factor when present in AD patients who are carriers of apolipoprotein E-e4 (APOE-e4) [30, 103, 106]. The HSV-1 and APOE-e4 combination results in the accumulation of Aβ and AD-like tau, which in turn are the primary components of the characteristic NFTs and amyloid plaques of AD brains [30, 103, 106]; it was observed in brain tissue of 46 AD patients compared with the brain tissue of 44 non-AD elderly people. APOE-e4 has also been reported to modulate the severity of microbial diseases or infection susceptibility, including HHV-1 as well as HHV-2 [102]. It has been demonstrated in studies with neural cells infected with HHV-1 that the reactivation of their infection may induce AD-relevant cellular changes like the formation of Tau protein and Aβ plaques [102, 107]. A high frequency of HHV-1 DNA was reportedly present in elderly brains, which normally was restricted to very small proportion in the brains of children and young people, which in turn can be attributed to the declined immune system of elderly population [108].

Anti-HSV-1 antibodies detected in the CSF by ELISA were found to be significantly higher in AD patients [109]. In long-term studies on elderly population, a significant association was observed between the presence of anti-HSV-1 IgG antibodies and AD [110]. A prospective study with over 3000 participants showed that positivity for anti-HSV-1 IgM, which is a sign of reactivated infection, almost doubled the risk for AD [111]. With the suggested role of HHV-1 in AD, it can be concluded that herpes simplex encephalitis (HSE) causes serious brain damage in a quick time, whereas the neurocognitive changes in AD are gradual and accumulate over the years. This suggests that HSV-1 reactivation probably produce a milder and recurrent disease as described in many cases of recurrent HSE [103, 112, 113], thus proposing that AD might be caused by incidences of mild HSE. The fact that HSE survivors (mild as well as full-blown) experience memory loss, which is the primary symptom of AD, proclaims HHV-1 as the primary reason behind the same. The possible role of HHV-1 contribution in AD pathogenesis is depicted in Fig. 4.

Other HHV HHV-2 (also known as herpes type 2) infection results in strong accumulation of Aβ peptides and hyperphosphorylated tau in human SK-N-MC neuroblastoma cells [114]. Infection is also associated with a marked reduction in the amount of Aβ40 secreted and in the proteolytic fragments of Aβ precursor protein (APP). Nimgaonkar et al. determined whether the temporal trajectories of multiple cognitive domains are associated with the exposure to CMV, HHV-1, HHV-2, or *T. gondii* [115]. They showed that exposure to these viruses is associated with cognitive deterioration in older individuals, independent of general age-related variables. The exposure to *T. gondii*, CMV, or HSV-2 has been reported to be associated with cognitive deterioration in elderly population, which is independent of general age-related variables [115].

HHV-3 (*Varicella zoster virus,* VZV) reactivation are relatively frequent in older people, because of the natural immune system dysfunction and other chronic diseases (diabetes, cancers, immunosuppressive therapy), [116]. Data from Center for Disease Control and Prevention in Atlanta (CDC) indicate that in the USA, one in three people aged over 60 suffers or will suffer from shingles, which indicate toward growing health problem mainly because of recurrent nerve pain. For this reason, shingles is extremely troublesome disease in AD patients as well. It is a growing health problem in Europe and Asia as well.

A relationship between HHV-5 (*Cytomegalovirus*, CMV) infection and AD risk has been reported as well [113]. CMV seropositivity was reported to be associated with a faster rate

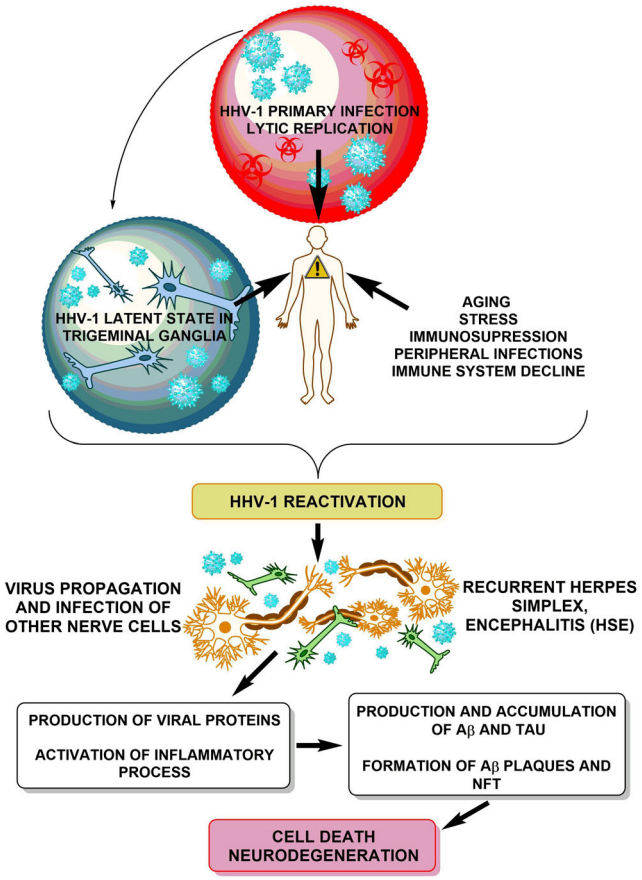

Fig. 4 Possible role of HHV-1 contribution in AD pathogenesis. HHV-1 infections include a lytic and latent state in the individual. Several factors as aging, stress, peripheral infections, and immune system decline predispose the individual to HHV-1 reactivation, for example, in the nerve tissue. The reactivation of HHV-1 in the brain may be related with AD occurrence and Aβ-Tau formation in the neural tissue

of decline in global cognition and an enhanced risk of AD [117]. By demonstrating significant association between CMV-specific serum IgG antibody levels and NFTs, direct and indirect links between CMV and AD pathology were confirmed [118]. DNA obtained from problem-based learning (PBL) brain samples and analyzed for the presence of CMV, EBV, and HHV-6 showed that all samples were negative for CMV but positive for EBV and HHV-6 [119]. During a follow-up period of 5 years within a group of elderly population, EBV- or HHV-6-positive PBL was found to be enhanced in the individuals who developed clinical AD. Moreover, IgG levels for EBV and CMV antigens were also found to be enhanced in the individuals who developed AD during the follow-up period.

Hepatitis C Virus Recent investigations suggest a relationship between hepatitis C virus (HCV) infection and the risk of dementia. HCV infection was reported to be an independent risk factor for dementia, AD, and vascular dementia [120]. However, the mechanisms by which HCV infection enhances the dementia risk are not well understood [120]. Since the first marked role of HCV in the causation of abnormalities in cerebral function about 10 years ago, many researchers have evaluated neuropsychiatric performance in HCV-infected patients with different degrees of hepatic impairment [121]. There are two hypotheses suggesting HCV infection in dementia patients. According to the first hypothesis, the virus causes indirect neurotoxicity via systemic and/or cerebral inflammation. According to the second hypothesis, the virus infects the brain by exerting a direct neurotoxic effect.

HCV RNA has been reported to be associated with CNS tissue, and reports of viral sequence diversity between liver and brain tissues suggest independent viral evolution in the CNS and liver [122]. HCV has the ability to cross BBB and can infect macrophages/monocytes, which secrete large amount of cytokines such as IL-6 and TNF-α, and cause excitotoxicity in the brain tissues. In patients with mild hepatitis C, activation of microglia cells was found to be positively correlated with altered cerebral metabolism and HCV infection [123]. Virus infection caused upregulation of cholesterol 25-hydroxylase (CH25H) gene and production of 25-hydroxycholesterol (25OHC), which induces innate antiviral immunity [124, 125]. Human *CH25H* is susceptible for the AD, as well as deposition of Aβ [126]. These studies are providing a potential mechanistic link between infection and AD [127].

Strategies for AD Therapy

Standard anti-viral drugs inhibit pathological changes observed in AD caused by viral infections. The involvement of HSV-1 in AD suggests that anti-viral agents might prevent further deterioration of patients, and it is possible in the future that vaccination against HSV-1 might prevent the development of AD [128, 129]. The main anti-HHV-1 anti-viral agent is acyclovir (ACV), which targets infected cells and viral DNA replication [130]. Future clinical trials should investigate the usage of anti-herpetics such as ACV and its biodrug VCV (which is converted to ACV) in AD sufferers. ACV does not affect uninfected cells or the normal metabolism of infected cells, so has no harmful side effects like many other treatments. ACV crosses the normal BBB and causes few side effects, apart from patients with renal impairment. Promising results offer studies involving valacyclovir (VCV), which is characterized by high bioavailability and does not cause any obvious adverse effects [69]. ACV has been used for treating MS patients and a clinical trial showed that it crossed the BBB, and no patient demonstrated a damaged barrier [128].

As we have suggested in current study, virus infections are not the unique challenge for the immune system in AD. In fact, persistent and chronic bacterial infections may also play a role in inducing and amplifying chronic neuroinflammation in

AD. Based on the study performed by Fillit et al., it was concluded that unlike other available treatments, anti-viral agents would provide a completely new approach by inhibiting the major cause of the AD rather than just inhibiting the AD-related symptoms [131].

Colostrinin, a proline-rich polypeptide (PRP) complex, showed immunomodulatory properties in various animal models, by inducing maturation and differentiation of thymocytes, and was also found to improve the outcome of AD patients with mild to moderate dementia [132, 133]. This context led us to explore the anti-inflammatory activity of acetylcholinesterase (AChE) inhibitors like donepezil [134]. Increasing evidence now points toward an anti-inflammatory role for AChE inhibitors through their action against free radical generation and by decreasing cytokine release from activated microglia, mostly by enhancement of ACh action on cholinergic receptors on glial cells. Donepezil treatment of AD patients for 1 month caused marked attenuation of the release of cytokines from peripheral blood monocytes and lymphocytes [135]. Donepezil revealed anti-inflammatory activity in experimental animal models [136–138]. Donepezil have been reported to block lipid peroxidation, preclude an increase of malondialdehyde (MDA) in experimental oxidative stress in mice [139], prevent the depletion of reduced glutathione (GSH), and show an efficient neuroprotective effect [140]. Donepezil has also been reported to directly inhibit the canonical inflammatory NF-kβ signaling, decrease the TNF-α level, and suppress the gene expression of inducible nitric oxide synthase (iNOS), interleukin-1, and TNF-β in purified cultures of microglia [141]. These effects were independent of ACh receptors, but well pronounced when the donepezil dose was significantly higher than the therapeutic dose of the drug, demonstrating a potential and novel therapeutic strategy against AD [142, 143]. It is possible that donepezil and other cholinesterase inhibitors exert their anti-inflammatory activity by elevation of the level of acetylcholine (ACh), and ACh-activated cholinergic receptors on glial cells. For example, ACh is perceived as an important modulator of the neuro-immune-endocrine axis [144], and astrocytes and microglia carry cholinergic receptors and adrenergic receptors and activation of adrenergic receptors leads to release of pro-inflammatory cytokines, whereas activation of cholinergic receptors decreases cytokine deliverance from glial cells [145, 146]. Elevation of ACh level in the brain induced by donepezil increases the activation of cholinergic (nicotinic) receptors on microglia, thus leading to decreased release of cytokines [146]. Donepezil may also restore the proper balance between H1R and H2R expression [147].

Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to lower the risk of AD by inhibiting the production of prostaglandin inflammatory mediators [148]. Recent findings show that NSAIDs that attenuate the inflammatory processes in the brain may decrease the production of Aβ peptides and might reduce the risk of developing the disease [148]. NSAIDs have also been suggested to have no effect in patients who have already developed AD, and it was shown that treatment with COX-2 inhibitor increases the amount of Aβ in the brain. Some reports also suggest that NSAIDs might prevent the onset of AD, but it remains controversial [149]. Observational studies in humans provide the evidence that the use of NSAIDs is associated with low AD risk.

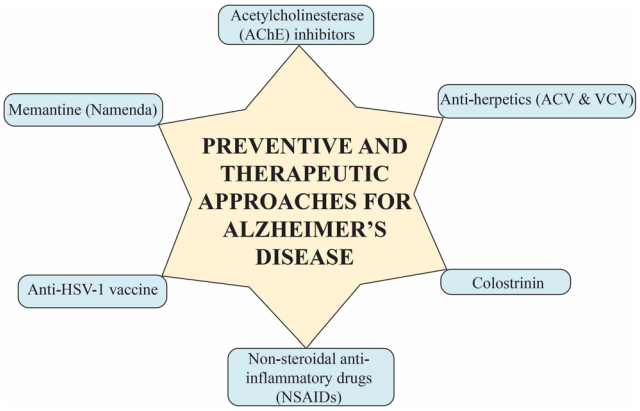

Fig. 5 Currently used therapeutic options for AD treatment. Due that there is no cure for AD, the treatments are intended to diminish the symptoms and reduce the neurodegeneration and cell death. By increasing the levels of acetylcholine in the brain via AChE inhibitors, some treatments reduce the time that brain functions continues to be affected. On the other hand, NSAIDs diminish the constitutive neuroinflammation process triggered by AD. Anti-viral treatments potentially reduce the viral infections that may be associated with the development of AD mainly, by Herpes virus, CMV, EBV, and hepatitis C virus

Several natural products have also been reported to possess anti-inflammatory activity and can be promising agents to treat microbes-mediated inflammation associated AD [149, 150]. More recent reports demonstrated the efficacy of the natural immunosuppressive drugs for AD treatment [149, 150]. For example, Abraham and Johnson (2009) reported that Resveratrol, a polyphenol, supplemented with diet reduced infection-related neuroinflammation and deficits in working memory in aged mice [151]. Probiotics are beneficial microorganisms to human health and reported to possess antimicrobial and anti-inflammatory activities [152–154] It has been demonstrated that probiotics can be therapeutic agents for AD [155]. Hence, more clinical investigations are needed to develop anti-inflammatory and anti-microbial probiotics for therapy and prevention of AD. Figure 5 depicts the most common and effective strategies for AD therapy.

Conclusion and Future Perspectives

The possibility of an infectious etiology for AD, especially late-onset of AD (LOAD), has been postulated repeatedly over the

past three decades [138, 149]. This suggests the crucial role of chronic bacterial, viral, and fungal infections as causative inflammatory pathways for AD. Several studies suggest that certain pathogens are major factors in AD. Anti-microbial therapy has been explored by several investigators to treat AD (Fig. 5). Several natural products have been reported to possess anti-inflammatory and anti-microbial activities, and can be promising agents to treat microbes-mediated inflammation-associated AD [138, 149]. However, it should be noticed that all anti-viral preparations have limited effectiveness against certain viruses. Moreover, the side effects often limited application of these drugs especially in elderly population. This underscores the need for new effective anti-viral therapies and necessity for a vaccine to prevent viral infections, and therefore prevention of AD and/or Ad-like pathology that very often coexist in elderly population [67, 68].

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Abbreviations ACh, acetylcholine; ACV, acyclovir; AD, Alzheimer disease; Aβ, amyloid-β; APOE-e4, apolipoprotein E-e4; BBB, blood brain barrier; CNS, central nervous system; CMV, cytomegalovirus; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; HD, Huntington's disease; HHV, human herpesvirus; IVIG, intravenous immunoglobulin; IAV, influenza A virus; MS, multiple sclerosis; NDDs, neurodegenerative disorders; NFTs, neurofibrillary tangles; PAMP, pathogen-associated molecular patterns; PD, Parkinson's disease; PBL, peripheral blood leukocytes; ROS, reactive oxygen species; VZV, varicella zoster virus

References

1. Alzheimer's A (2015) 2015 Alzheimer's disease facts and figures. Alzheimers Dement 11:332–384
2. Ansari SA, Satar R, Perveen A, Ashraf GM (2017) Current opinion in Alzheimer's disease therapy by nanotechnology-based approaches. Curr Opin Psychiatry 30:128–135
3. Ashraf GM, Greig NH, Khan TA, Hassan I, Tabrez S, Shakil S, Sheikh IA, Zaidi SK et al (2014) Protein misfolding and aggregation in Alzheimer's disease and type 2 diabetes mellitus. CNS Neurol Disord Drug Targets 13:1280–1293
4. Blocq P, Marinescu G. *Sur les lésions et la pathogénie de l'épilepsie dite essentielle* S.L.: s.n.; 1892.
5. Kumar A, Singh A, Ekavali N (2015) A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacological reports: PR 67:195–203
6. Simchowicz T. Histologische Studien über die senile Demenz. Histologische und histopathologische Arbeiten über die Grosshirnrinde mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten [Texte imprimé] / herausgegeben von Franz Nissl,... 1911.
7. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R (1991) Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 30:572–580
8. Gallyas F (1971) Silver staining of Alzheimer's neurofibrillary changes by means of physical development. Acta Morphologica Academiae Scientiarum Hungaricae 19:1–8
9. Mawanda F, Wallace R (2013) Can infections cause Alzheimer's disease? Epidemiol Rev 35:161–180
10. White MR, Kandel R, Tripathi S, Condon D, Qi L, Taubenberger J, Hartshorn KL (2014) Alzheimer's associated β-amyloid protein inhibits influenza A virus and modulates viral interactions with phagocytes. PLoS One 9:e101364
11. Lim SL, Rodriguez-Ortiz CJ, Kitazawa M (2015) Infection, systemic inflammation, and Alzheimer's disease. Microbes and Infection / Institut Pasteur 17:549–556
12. Hardy J (1997) The Alzheimer family of diseases: many etiologies, one pathogenesis? Proc Natl Acad Sci U S A 94:2095–2097
13. Li C, Zhao R, Gao K, Wei Z, Yin MY, Lau LT, Chui D, Yu ACH (2011) Astrocytes: implications for neuroinflammatory pathogenesis of Alzheimer's disease. Curr Alzheimer Res 8:67–80
14. Nagy Z (2005) The last neuronal division: a unifying hypothesis for the pathogenesis of Alzheimer's disease. J Cell Mol Med 9: 531–541
15. Aliev G, Burzynski G, Ashraf GM, Jabir NR, Cacabelos R, Benberin VV, Burzynski SR (2011) Implication of oxidative stress-induced oncogenic signaling pathways as a treatment strategy for neurodegeneration and cancer. In: *Systems Biology of Free Radicals and Antioxidants*. edited by Laher I. Springer Berlin Heidelberg; pp. 2325–2347.
16. Aliev G, Priyadarshini M, Reddy VP, Grieg NH, Kaminsky Y, Cacabelos R, Ashraf GM, Jabir NR et al (2014) Oxidative stress mediated mitochondrial and vascular lesions as markers in the pathogenesis of Alzheimer disease. Curr Med Chem 21:2208–2217
17. Marx F, Blasko I, Pavelka M, Grubeck-Loebenstein B (1998) The possible role of the immune system in Alzheimer's disease. Exp Gerontol 33:871–881
18. Li Y, Tan M-S, Jiang T, Tan L (2014) Microglia in Alzheimer's disease. Biomed Res Int 2014:437483
19. Jacobs AH, Tavitian B (2012) Consortium IN. Noninvasive molecular imaging of neuroinflammation. J Cereb Blood Flow Metab 32:1393–1415
20. Całkosiński I, Dobrzyński M, Całkosińska M, Seweryn E, Bronowicka-Szydełko A, Dzierzba K, Ceremuga I, Gamian A (2009) Characterization of an inflammatory response. Post py Higieny I Medycyny Doświadczalnej (Online) 63:395–408
21. Franceschi C, Campisi J (2014) Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol. Series A, Biol Sci Med Sci 69(Suppl 1): S4–S9
22. Krstic D, Knuesel I (2013) Deciphering the mechanism underlying late-onset Alzheimer disease. Nat Rev Neurol 9:25–34
23. Bartus RT, Dean RL, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. *Science (New York, N.Y.)* 217: 408–414, 1982.
24. Hardy J, Allsop D (1991) Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci 12: 383–388
25. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P et al (2000) Inflammation and Alzheimer's disease. Neurobiol Aging 21:383–421

26. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T et al (2015) Neuroinflammation in Alzheimer's disease. Lancet Neurol 14: 388–405
27. McGeer PL, McGeer EG (2002) Local neuroinflammation and the progression of Alzheimer's disease. J Neurovirol 8:529–538
28. Morales I, Guzmán-Martínez L, Cerda-Troncoso C, Farías GA, Maccioni RB (2014) Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. Front Cell Neurosci 8(112)
29. Schwab C, McGeer PL (2008) Inflammatory aspects of Alzheimer disease and other neurodegenerative disorders. J Alzheimer's Dis: JAD 13:359–369
30. Lin WR, Shang D, Wilcock GK, Itzhaki RF (1995) Alzheimer's disease, herpes simplex virus type 1, cold sores and apolipoprotein E4. Biochem Soc Trans 23:594S
31. Barichello T, Generoso JS, Goularte JA, Collodel A, Pitcher MR, Simões LR, Quevedo J, Dal-Pizzol F (2015) Does infection-induced immune activation contribute to dementia? Aging Dis 6: 342–348
32. Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, Bullido MJ, Carter C et al (2016) Microbes and Alzheimer's disease. J Alzheimer's Dis: JAD 51:979–984
33. Licastro F, Carbone I, Raschi E, Porcellini E (2014) The 21st century epidemic: infections as inductors of neuro-degeneration associated with Alzheimer's disease. Immunity & Ageing: I & A 11(22):22
34. Roubaud Baudron C, Varon C, Mégraud F, Salles N (2015) Alzheimer's disease: the infectious hypothesis. Geriatrie Et Psychologie Neuropsychiatrie Du Vieillissement 13:418–424
35. Ferrari CC, Tarelli R (2011) Parkinson's disease and systemic inflammation. Parkinson's Disease 2011:e436813
36. Nociti V, Frisullo G, Marti A, Luigetti M, Iorio R, Patanella AK, Bianco A, Tonali PA et al (2010) Epstein-Barr virus antibodies in serum and cerebrospinal fluid from multiple sclerosis, chronic inflammatory demyelinating polyradiculoneuropathy and amyotrophic lateral sclerosis. J Neuroimmunol 225:149–152
37. Maheshwari P, Eslick GD (2015) Bacterial infection and Alzheimer's disease: a meta-analysis. J Alzheimer's Dis: JAD 43:957–966
38. Bibi F, Yasir M, Sohrab SS, Azhar EI, Al-Qahtani MH, Abuzenadah AM, Kamal MA, Naseer MI (2014) Link between chronic bacterial inflammation and Alzheimer disease. CNS Neurol Disord Drug Targets (CNS&NDDT) 13:1140–1147
39. Miklossy J (2015) Historic evidence to support a causal relationship between spirochetal infections and Alzheimer's disease. Front Aging Neurosci 7(46)
40. Ramesh G, MacLean AG, Philipp MT (2013) Cytokines and chemokines at the crossroads of neuroinflammation, neurodegeneration, and neuropathic pain. Mediat Inflamm 2013:480739
41. Miklossy J (2011) Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. J Neuroinflammation 8:90
42. Nicolson GL (2008) Chronic bacterial and viral infections in neurodegenerative and neurobehavioral diseases. Lab Med 39:291–299
43. Riviere GR, Riviere KH, Smith KS (2002) Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer's disease. Oral Microbiol Immunol 17:113–118
44. Olsen I, Singhrao SK (2015) Can oral infection be a risk factor for Alzheimer's disease? J Oral Microbiol 7:29143
45. Miklossy J (2011) Emerging roles of pathogens in Alzheimer disease. Expert Rev Mol Med 13:e30
46. Abbayya K, Puthanakar NY, Naduwinmani S, Chidambar YS (2015) Association between periodontitis and Alzheimer's disease. N Am J Med Sci 7:241–246
47. Miklossy J (1993) Alzheimer's disease–a spirochetosis? Neuroreport 4:841–848
48. Christen-Zaech S, Kraftsik R, Pillevuit O, Kiraly M, Martins R, Khalili K, Miklossy J (2003) Early olfactory involvement in Alzheimer's disease. The Canadian Journal of Neurological Sciences Le Journal Canadien Des Sciences Neurologiques 30: 20–25
49. MacDonald AB (1988) Concurrent neocortical borreliosis and Alzheimer's disease. Ann N Y Acad Sci 539:468–470
50. MacDonald AB, Miranda JM (1987) Concurrent neocortical borreliosis and Alzheimer's disease. Hum Pathol 18:759–761
51. Stanek G, Wormser GP, Gray J, Strle F (2012) Lyme borreliosis. Lancet (London, England) 379:461–473
52. Radolf JD, Goldberg MS, Bourell K, Baker SI, Jones JD, Norgard MV (1995) Characterization of outer membranes isolated from Borrelia burgdorferi, the Lyme disease spirochete. Infect Immun 63:2154–2163
53. Ramesh G, Alvarez AL, Roberts ED, Dennis VA, Lasater BL, Alvarez X, Philipp MT (2003) Pathogenesis of Lyme neuroborreliosis: Borrelia burgdorferi lipoproteins induce both proliferation and apoptosis in rhesus monkey astrocytes. Eur J Immunol 33:2539–2550
54. MacDonald AB (2007) Alzheimer's neuroborreliosis with trans-synaptic spread of infection and neurofibrillary tangles derived from intraneuronal spirochetes. Med Hypotheses 68:822–825
55. Appelt DM, Roupas MR, Way DS, Bell MG, Albert EV, Hammond CJ, Balin BJ (2008) Inhibition of apoptosis in neuronal cells infected with Chlamydophila (Chlamydia) pneumoniae. BMC Neurosci 9:13
56. Paradowski B, Jaremko M, Dobosz T, Leszek J, Noga L (2007) Evaluation of CSF-Chlamydia pneumoniae, CSF-tau, and CSF-Abeta42 in Alzheimer's disease and vascular dementia. J Neurol 254:154–159
57. Shima K, Kuhlenbäumer G, Rupp J (2010) Chlamydia pneumoniae infection and Alzheimer's disease: a connection to remember? Med Microbiol Immunol 199:283–289
58. Hammond CJ, Hallock LR, Howanski RJ, Appelt DM, Little CS, Balin BJ (2010) Immunohistological detection of Chlamydia pneumoniae in the Alzheimer's disease brain. BMC Neurosci 11:121
59. Pollack DV, Croteau NL, Stuart ES (2008) Uptake and intra-inclusion accumulation of exogenous immunoglobulin by Chlamydia-infected cells. BMC Microbiol 8:213
60. Balin BJ, Gérard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, Whittum-Hudson JA, Hudson AP (1998) Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. Med Microbiol Immunol 187:23–42
61. Albert NM (2000) Inflammation and infection in acute coronary syndrome. J Cardiovasc Nurs 15:13–26
62. MacIntyre A, Abramov R, Hammond CJ, Hudson AP, Arking EJ, Little CS, Appelt DM, Balin BJ (2003) Chlamydia pneumoniae infection promotes the transmigration of monocytes through human brain endothelial cells. J Neurosci Res 71:740–750
63. Manabe T, Mizukami K, Akatsu H, Teramoto S, Yamaoka K, Nakamura S, Ohkubo T, Kudo K et al (2016) Influence of pneumonia complications on the prognosis of patients with autopsy-confirmed Alzheimer's disease, dementia with Lewy bodies, and vascular dementia. Psychogeriatrics 16:305–314
64. Dreses-Werringloer U, Bhuiyan M, Zhao Y, Gérard HC, Whittum-Hudson JA, Hudson AP (2009) Initial characterization of Chlamydophila (Chlamydia) pneumoniae cultured from the late-onset Alzheimer brain. Int J Med Microbiol: IJMM 299:187–201
65. Gérard HC, Dreses-Werringloer U, Wildt KS, Deka S, Oszust C, Balin BJ, Frey WH, Bordayo EZ et al (2006) Chlamydophila (Chlamydia) pneumoniae in the Alzheimer's brain. FEMS Immunol Med Microbiol 48:355–366

66. Takeda S, Sato N, Morishita R (2014) Systemic inflammation, blood-brain barrier vulnerability and cognitive/non-cognitive symptoms in Alzheimer disease: relevance to pathogenesis and therapy. Front Aging Neurosci 6(171)
67. Alzforum | Networking for a cure. http://www.alzforum.org/papers/uber-eine-eigenartige-erkrankung-der-hirnrinde.
68. Licastro F, Porcellini E (2016) Persistent infections, immune-senescence and Alzheimer's disease. Oncoscience 3:135–142
69. Fischer O (1907) Miliare nekrosen mit drusigen wucherungen der neurofibrillen, eine regelmässige veränderung der hirnrinde bei seniler demenz. Monatsschr Psychiatr Neurol 22:361–372
70. Fischer O (1910) Die presbyophrene demenz, deren anatomische grundlage und klinische abgrenzung. Z Gesamte Neurol Psychiatr 3:371–471
71. Goeman J, Hoksbergen I, Pickut BA, Dom L, Crols R, De Deyn PP (1996) Dementia paralytica in a fifteen-year-old boy. J Neurol Sci 144:214–217
72. Noguchi H, Moore JW (1913) A demonstration of Treponema pallidum in the brain in cases of general paralysis. J Exp Med 17:232–238
73. Möhle L, Israel N, Paarmann K, Krohn M, Pietkiewicz S, Müller A, Lavrik IN, Buguliskis JS et al (2016) Chronic Toxoplasma gondii infection enhances β-amyloid phagocytosis and clearance by recruited monocytes. Acta Neuropathol Commun 4(25):25
74. Pisa D, Alonso R, Rábano A, Rodal I, Carrasco L (2015) Different brain regions are infected with fungi in Alzheimer's disease. Sci Rep 5(15015)
75. Marshall BJ, Warren JR (1984) Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet (London, England) 1:1311–1315
76. Kountouras J, Boziki M, Gavalas E, Zavos C, Deretzi G, Grigoriadis N, Tsolaki M, Chatzopoulos D et al (2009) Increased cerebrospinal fluid Helicobacter pylori antibody in Alzheimer's disease. Int J Neurosci 119:765–777
77. Franceschi F, Gasbarrini A, Polyzos SA, Kountouras J (2015) Extragastric diseases and Helicobacter pylori. Helicobacter 20(Suppl 1):40–46
78. Polepalle T, Moogala S, Boggarapu S, Pesala DS, Palagi FB (2015) Acute phase proteins and their role in periodontitis: a review. J Clin Diagn Res 9:ZE01–ZE05
79. Fenesy KE (1998) Periodontal disease: an overview for physicians. Mount Sinai J Med N Y 65:362–369
80. Kornhuber HH (1996) Propionibacterium acnes in the cortex of patients with Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci 246:108–109
81. Preza D, Olsen I, Aas JA, Willumsen T, Grinde B, Paster BJ (2008) Bacterial profiles of root caries in elderly patients. J Clin Microbiol 46:2015–2021
82. Delahaye F, Fol S, Célard M, Vandenesch F, Beaune J, Bozio A, de Gevigney G (2005) Propionibacterium acnes infective endocarditis. Study of 11 cases and review of literature. Arch Mal Coeur Vaiss 98:1212–1218
83. Kamer AR, Craig RG, Dasanayake AP, Brys M, Glodzik-Sobanska L, Inflammation d LMJ (2008) Alzheimer's disease: possible role of periodontal diseases. Alzheimer's Dement 4: 242–250
84. Gurav AN (2014) Alzheimer's disease and periodontitis–an elusive link. *Revista Da Associação Médica Brasileira (1992)* 60: 173–180
85. Hatipoglu MG, Kabay SC, Güven G (2011) The clinical evaluation of the oral status in Alzheimer-type dementia patients. Gerodontology 28:302–306
86. Kamer AR, Dasanayake AP, Craig RG, Glodzik-Sobanska L, Bry M, de Leon MJ (2008) Alzheimer's disease and peripheral infections: the possible contribution from periodontal infections, model and hypothesis. J Alzheimer's Dis: JAD 13:437–449
87. Ide M, Harris M, Stevens A, Sussams R, Hopkins V, Culliford D, Fuller J, Ibbett P et al (2016) Periodontitis and cognitive decline in Alzheimer's disease. PLoS One 11:e0151081
88. Wu Z, Nakanishi H (2014) Connection between periodontitis and Alzheimer's disease: possible roles of microglia and leptomeningeal cells. J Pharmacol Sci 126:8–13
89. Farhad SZ, Amini S, Khalilian A, Barekatain M, Mafi M, Barekatain M, Rafei E (2014) The effect of chronic periodontitis on serum levels of tumor necrosis factor-alpha in Alzheimer disease. Dental Res J 11:549–552
90. Kamer AR, Craig RG, Pirraglia E, Dasanayake AP, Norman RG, Boylan RJ, Nehorayoff A, Glodzik L et al (2009) TNF-alpha and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. J Neuroimmunol 216:92–97
91. Alonso R, Pisa D, Marina AI, Morato E, Rábano A, Carrasco L (2014) Fungal infection in patients with Alzheimer's disease. J Alzheimer's Dis: JAD 41:301–311
92. Panackal AA, Williamson PR (2015) Fungal infections of the central nervous system. Continuum (Minneapolis, Minn) 21: 1662–1678
93. Prandota J (2010) Autism spectrum disorders may be due to cerebral toxoplasmosis associated with chronic neuroinflammation causing persistent hypercytokinemia that resulted in an increased lipid peroxidation, oxidative stress, and depressed metabolism of endogenous and exogenous substances. Res Autism Spectr Disord 4:119–155
94. Prandota J (2010) Neuropathological changes and clinical features of autism spectrum disorder participants are similar to that reported in congenital and chronic cerebral toxoplasmosis in humans and mice. Res Autism Spectr Disord 4:103–118
95. Prandota J (2011) Metabolic, immune, epigenetic, endocrine and phenotypic abnormalities found in individuals with autism spectrum disorders, Down syndrome and Alzheimer disease may be caused by congenital and/or acquired chronic cerebral toxoplasmosis. Res Autism Spectr Disord 5:14–59
96. Prandota J (2014) Possible link between Toxoplasma gondii and the anosmia associated with neurodegenerative diseases. Am J Alzheimer's Dis Other Dementias 29:205–214
97. Xu F, Sternberg MR, Kottiri BJ, McQuillan GM, Lee FK, Nahmias AJ, Berman SM, Markowitz LE (2006) Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA 296:964–973
98. Sequiera LW, Carrasco LH, Curry A, Jennings LC, Lord MA, Sutton RNP (1979) Detection of herpes-simplex viral genome in brain tissue. Lancet 314:609–612
99. Ball MJ (1982) Limbic predilection in Alzheimer dementia: Is reactivated herpesvirus involved? Can J Neurol Sci 9:303–306
100. Gannicliffe A, Sutton RN, Itzhaki RF (1986) Viruses, brain and immunosuppression. Psychol Med 16:247–249
101. Agostini S, Mancuso R, Baglio F, Clerici M (2017) A protective role for herpes simplex virus type-1-specific humoral immunity in Alzheimer's disease. Expert Rev Anti-Infect Ther 15:89–91
102. Itzhaki RF (2014) Herpes simplex virus type 1 and Alzheimer's disease: increasing evidence for a major role of the virus. Front Aging Neurosci 6(202)
103. Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA (1997) Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet (London, England) 349:241–244
104. Koronyo Y, Salumbides BC, Black KL, Koronyo-Hamaoui M (2012) Alzheimer's disease in the retina: imaging retinal Aß plaques for early diagnosis and therapy assessment. Neurodegener Dis 10:285–293
105. Olsson J, Lövheim H, Honkala E, Karhunen PJ, Elgh F, Kok EH (2016) HSV presence in brains of individuals without dementia: the TASTY brain series. Dis Model Mech 9:1349–1355

106. Itzhaki RF, Wozniak MA (2012) Could antivirals be used to treat Alzheimer's disease? Future Microbiol 7:307–309
107. Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB (2007) Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. Neurosci Lett 429:95–100
108. Wozniak MA, Mee AP, Itzhaki RF (2009) Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. J Pathol 217:131–138
109. Wozniak MA, Shipley SJ, Combrinck M, Wilcock GK, Itzhaki RF (2005) Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. J Med Virol 75:300–306
110. Lövheim H, Gilthorpe J, Johansson A, Eriksson S, Hallmans G, Elgh F (2015) Herpes simplex infection and the risk of Alzheimer's disease: a nested case-control study. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 11:587–592
111. Lövheim H, Gilthorpe J, Adolfsson R, Nilsson L-G, Elgh F (2015) Reactivated herpes simplex infection increases the risk of Alzheimer's disease. Alzheimer's Dementia 11:593–599
112. Fodor PA, Levin MJ, Weinberg A, Sandberg E, Sylman J, Tyler KL (1998) Atypical herpes simplex virus encephalitis diagnosed by PCR amplification of viral DNA from CSF. Neurology 51: 554–559
113. Rodríguez-Violante M, Ordoñez G, Bermudez JR, Sotelo J, Corona T (2009) Association of a history of varicella virus infection with multiple sclerosis. Clin Neurol Neurosurg 111:54–56
114. Kristen H, Santana S, Sastre I, Recuero M, Bullido MJ, Aldudo J (2015) Herpes simplex virus type 2 infection induces AD-like neurodegeneration markers in human neuroblastoma cells. Neurobiol Aging 36:2737–2747
115. Nimgaonkar VL, Yolken RH, Wang T, Chung-Chou HC, McClain L, McDade E, Snitz BE, Ganguli M Temporal cognitive decline associated with exposure to infectious agents in a population-based, aging cohort. Alzheimer Dis Assoc Disord 2015
116. Biesiada G, Czepiel J, Sobczyk-Krupiarz I, Mach T, Garlicki A. [Neurological complications among patients with zoster hospitalized in Department of Infectious Diseases in Cracow in 2001–2006]. *Przegląd Lekarski* 67: 149–150, 2010.
117. Barnes LL, Capuano AW, Aiello AE, Turner AD, Yolken RH, Torrey EF, Bennett DA (2015) Cytomegalovirus infection and risk of Alzheimer disease in older black and white individuals. J Infect Dis 211:230–237
118. Lurain NS, Hanson BA, Martinson J, Leurgans SE, Landay AL, Bennett DA, Schneider JA (2013) Virological and immunological characteristics of human cytomegalovirus infection associated with Alzheimer disease. J Infect Dis 208:564–572
119. Carbone I, Lazzarotto T, Ianni M, Porcellini E, Forti P, Masliah E, Gabrielli L, Licastro F (2014) Herpes virus in Alzheimer's disease: relation to progression of the disease. Neurobiol Aging 35:122–129
120. Chiu WC, Tsan YT, Tsai SL, Chang CJ, Wang JD, Chen PC, Health Data Analysis in Taiwan Research G (2014) Hepatitis C viral infection and the risk of dementia. Eur J Neurol 21:1068–1e59
121. Senzolo M, Schiff S, D'Aloiso CM, Crivellin C, Cholongitas E, Burra P, Montagnese S (2011) Neuropsychological alterations in hepatitis C infection: the role of inflammation. World J Gastroenterol 17:3369–3374
122. Fletcher NF, McKeating JA (2012) Hepatitis C virus and the brain. J Viral Hepat 19:301–306
123. Grover VPB, Pavese N, Koh SB, Wylezinska M, Saxby BK, Gerhard A, Forton DM, Brooks DJ et al (2012) Cerebral microglial activation in patients with hepatitis C: in vivo evidence of neuroinflammation. J Viral Hepat 19:e89–e96
124. Blanc M, Hsieh WY, Robertson KA, Kropp KA, Forster T, Shui G, Lacaze P, Watterson S et al (2013) The transcription factor STAT-1 couples macrophage synthesis of 25-hydroxycholesterol to the interferon antiviral response. Immunity 38:106–118
125. Liu S-Y, Aliyari R, Chikere K, Li G, Marsden MD, Smith JK, Pernet O, Guo H et al (2013) Interferon-inducible cholesterol-25-hydroxylase broadly inhibits viral entry by production of 25-hydroxycholesterol. Immunity 38:92–105
126. Papassotiropoulos A, Lambert J-C, Wavrant-De Vrièze F, Wollmer MA, von der Kammer H, Streffer JR, Maddalena A, Huynh K-D, Wolleb S, Lutjohann D, Schneider B, Thal DR, Grimaldi LME, Tsolaki M, Kapaki E, Ravid R, Konietzko U, Hegi T, Pasch T, Jung H, Braak H, Amouyel P, Rogaev EI, Hardy J, Hock C, Nitsch RM. Cholesterol 25-hydroxylase on chromosome 10q is a susceptibility gene for sporadic Alzheimer's disease. Neurodegener Dis 2: 233–241, 2005.
127. Lathe R, Sapronova A, Kotelevtsev Y (2014) Atherosclerosis and Alzheimer–diseases with a common cause? Inflammation, oxysterols, vasculature. BMC Geriatr 14(36)
128. Friedman JE, Zabriskie JB, Plank C, Ablashi D, Whitman J, Shahan B, Edgell R, Shieh M et al (2005) A randomized clinical trial of valacyclovir in multiple sclerosis. Multiple Sclerosis (Houndmills, Basingstoke, England) 11:286–295
129. Wozniak MA, Itzhaki RF (2010) Antiviral agents in Alzheimer's disease: hope for the future? Ther Adv Neurol Disord 3:141–152
130. Devi G, Schultz S, Khosrowshahi L, Agnew A, Olali E (2008) A retrospective chart review of the tolerability and efficacy of intravenous immunoglobulin in the treatment of Alzheimer's disease. J Am Geriatr Soc 56:772–774
131. Fillit H, Hess G, Hill J, Bonnet P, Toso C (2009) IV immunoglobulin is associated with a reduced risk of Alzheimer disease and related disorders. Neurology 73:180–185
132. Leszek J, Inglot AD, Janusz M, Byczkiewicz F, Kiejna A, Georgiades J, Lisowski J. Colostrinin proline-rich polypeptide complex from ovine colostrum–a long-term study of its efficacy in Alzheimer's disease. Med Sci Monit 8: PI93–96, 2002.
133. Leszek J, Inglot AD, Janusz M, Lisowski J, Krukowska K, Georgiades JA (1999) Colostrinin: a proline-rich polypeptide (PRP) complex isolated from ovine colostrum for treatment of Alzheimer's disease. A double-blind, placebo-controlled study. Arch Immunol Ther Exp 47:377–385
134. Sochocka M, Zaczyńska E, Leszek J, Siemieniec I, Błach-Olszewska Z (2008) Effect of donepezil on innate antiviral immunity of human leukocytes. J Neurol Sci 273:75–80
135. Reale M, Iarlori C, Gambi F, Lucci I, Salvatore M, Gambi D (2005) Acetylcholinesterase inhibitors effects on oncostatin-M, interleukin-1 beta and interleukin-6 release from lymphocytes of Alzheimer's disease patients. Exp Gerontol 40:165–171
136. Jiang L, Miao Z, Kimura RH, Liu H, Cochran JR, Culter CS, Bao A, Li P et al (2011) Preliminary evaluation of (177)Lu-labeled knottin peptides for integrin receptor-targeted radionuclide therapy. Eur J Nucl Med Mol Imaging 38:613–622
137. Jiang Y, Zou Y, Chen S, Zhu C, Wu A, Liu Y, Ma L, Zhu D et al (2013) The anti-inflammatory effect of donepezil on experimental autoimmune encephalomyelitis in C57 BL/6 mice. Neuropharmacology 73:415–424
138. Yoshiyama Y, Kojima A, Ishikawa C, Arai K (2010) Anti-inflammatory action of donepezil ameliorates tau pathology, synaptic loss, and neurodegeneration in a tauopathy mouse model. J Alzheimer's Dis: JAD 22:295–306
139. Saxena G, Singh SP, Agrawal R, Nath C (2008) Effect of donepezil and tacrine on oxidative stress in intracerebral streptozotocin-induced model of dementia in mice. Eur J Pharmacol 581:283–289
140. Meunier J, Ieni J, Maurice T (2006) The anti-amnesic and neuroprotective effects of donepezil against amyloid beta25-35 peptide-induced toxicity in mice involve an interaction with the sigma1 receptor. Br J Pharmacol 149:998–1012
141. Hwang J, Hwang H, Lee H-W, Suk K (2010) Microglia signaling as a target of donepezil. Neuropharmacology 58:1122–1129

142. Butt AM, Fern RF, Matute C (2014) Neurotransmitter signaling in white matter. Glia 62:1762–1779
143. Hösli L, Hösli E, Käser H (1993) Colocalization of cholinergic, adrenergic and peptidergic receptors on astrocytes. Neuroreport 4: 679–682
144. Kim HG, Moon M, Choi JG, Park G, Kim A-J, Hur J, Lee K-T, Oh MS (2014) Donepezil inhibits the amyloid-beta oligomer-induced microglial activation in vitro and in vivo. Neurotoxicology 40:23–32
145. Carnevale D, De Simone R, Minghetti L (2007) Microglia-neuron interaction in inflammatory and degenerative diseases: role of cholinergic and noradrenergic systems. CNS Neurol Dis Drug Targets 6:388–397
146. Haddad JJ, Saadé NE, Safieh-Garabedian B (2002) Cytokines and neuro-immune-endocrine interactions: a role for the hypothalamic-pituitary-adrenal revolving axis. J Neuroimmunol 133:1–19
147. Ashraf GM, Perveen A, Zaidi SK, Tabrez S, Kamal MA, Banu N (2015) Studies on the role of goat heart galectin-1 as an erythrocyte membrane perturbing agent. Saudi J Biol Sci 22:112–116
148. Szekely CA, Zandi PP (2010) Non-steroidal anti-inflammatory drugs and Alzheimer's disease: the epidemiological evidence. CNS Neurol Disord Drug Targets 9:132–139
149. Yip AG, Green RC, Huyck M, Cupples LA, Farrer LA, Group MS (2005) Nonsteroidal anti-inflammatory drug use and Alzheimer's disease risk: the MIRAGE Study. BMC Geriatr 5(2)
150. Newman DJ, Cragg GM (2004) Advanced preclinical and clinical trials of natural products and related compounds from marine sources. Curr Med Chem 11:1693–1713
151. Abraham J, Johnson RW (2009) Consuming a diet supplemented with resveratrol reduced infection-related neuroinflammation and deficits in working memory in aged mice. Rejuvenation Res 12: 445–453
152. Korada SK, Yarla NS, Bishayee A, Aliev G, Aruna Lakshmi K, Arunasree MK, Dananajaya BL, Mishra V (2016) Can probiotics cure inflammatory bowel diseases? Curr Pharm Des 22:904–917
153. Mohammadi AA, Jazayeri S, Khosravi-Darani K, Solati Z, Mohammadpour N, Asemi Z, Adab Z, Djalali M et al (2015) Effects of probiotics on biomarkers of oxidative stress and inflammatory factors in petrochemical workers: a randomized, double-blind, placebo-controlled trial. Int J Prev Med 6:82
154. Tejero-Sariñena S, Barlow J, Costabile A, Gibson GR, Rowland I (2013) Antipathogenic activity of probiotics against Salmonella Typhimurium and Clostridium difficile in anaerobic batch culture systems: is it due to synergies in probiotic mixtures or the specificity of single strains? Anaerobe 24:60–65
155. Mallikarjuna N, Praveen K, Yellamma K (2016) Role of Lactobacillus plantarum MTCC1325 in membrane-bound transport ATPases system in Alzheimer's disease-induced rat brain. BioImpacts: BI 6:203–209