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Review Article

Unraveling therapeutic strategies in Chemicals-induced Sporadic Alzheimer's Disease

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Abstract

Background: Sporadic Alzheimer's disease (SAD) represents one of the major cognitive and memory deficits that is characterized by tau hyperphosphorylation and amyloid beta (Aβ) deposition in the brain. Both are considered AD hallmarks mediated through neuroinflammation, oxidative stress, and cholinergic circuit interruption. There are many genetic and chemical-induced models of SAD. The most used chemical models are Aβ, D-galactose, and streptozotocin (STZ) models due to their reproducibility of pathologic markers of AD, especially the STZ model due to the similarity between this model and the pathogenesis of AD in human. Many studies displayed that targeting several pathways apart from the traditional ones could delay the progression of SAD.
Aim: This review aimed to highlight the most relevant key findings of different studies by targeting mainly wingless-related integration site (Wnt)/β-catenin and c-Jun N-terminal protein kinase (JNK) pathways against chemically induced SAD in experimental animals.
Conclusion: AD pathways are demonstrated with corresponding some of the recent treatments for those pathways as well as commonly used chemical models and their attributed benefits altogether with limitations.

List Of Abbreviations

Aβ: Amyloid beta; Ach: Acetylcholine; AChE: Acetylcholinesterase; AD: Alzheimer's disease; Akt: Protein kinase; APP: Amyloid precursor protein; BACE-1: β-site amyloid precursor protein cleaving enzyme 1; Bcl-2: B-cell lymphoma 2; BDNF: Brain derived neurotrophic factor; CNS: Central nervous system; CREB: cAMP-response element binding protein; CSF: Cerebrospinal fluid; DKK1: Dickkopf Wnt Signaling Pathway Inhibitor 1; D-JNK1: D-JNK-permeable peptide 1; ERK: Extracellular regulated kinase; GSK: Glycogen synthase kinase; ICV: Intracerebroventricular; IL: Interleukin; IR: Insulin resistance, IRS-1: Insulin response elements; JNK: c-Jun N-terminal protein kinase; MAPK: Mitogen-activated protein kinases; MDA :*Malondialdehyde*; MLK: Mixed Linage Kinase; mRNA: *Messenger* ribonucleic acid; NF-κB: Nuclear factor-kappa B; NFT: Neurofibrillary tangles; PFT: Probiotic fermentation technology; PUFA: Polyunsaturated fatty acids; SAD: Sporadic Alzheimer's disease; STZ: Streptozotocin; TLR4:Toll-like receptor 4; TNF-α: Tumor necrosis factor; TrkB: Tropomyosin receptor kinase B; Wnt: Wingless-related integration site.

1. Introduction

SAD, also called late-onset Alzheimer's disease (LOAD), is caused by a complex interplay of vulnerable gene combinations and several protein pathways that are significantly impacted by environmental, lifestyle, and psychological variables forming unique aging patterns [1]. The neuropathological lesions seen in SAD are shared by the various forms of familial AD except that sporadic forms of AD do not have amyloid precursor protein (APP) and presenilin mutations but other pathogenetic events are observed [2].

1.1. Amyloid beta (Aβ) and neurofibrillary tangles (NFT) harmful effects

At a young age, usually, Aβ has a beneficial role in blocking the vascular leaks occurring during cerebral disruptions acute phase response [3]. However, in old-age due to hypoperfusion brought on by age-related cardiovascular failure and cerebrovascular injuries may result in persistent amyloid accumulation forming plaques leading to neuronal apoptosis [4]. Normally, tau protein is present in the cell cytoplasm of neurons in the form of stable tubules but in SAD it becomes hyperphosphorylated forming unstable filaments which lead to loss of neuronal connectivity, neuronal inflammation, and ultimately neuronal death [2,5].

1.2. Chemical/Drug-induced Models of SAD

There are many apparent benefits of using animal models in research, including cognitive and behavioural tests, in vivo toxicity evaluations for novel treatments, and much more. There are numerous available animal models of AD, and every model has advantages and disadvantages of its own. However, it is crucial to remember that no animal model can accurately capture the overall pathophysiology of AD in humans. Herein, we have displayed a brief for the most widely used experimental models that elicited SAD (Figure I), while the summary of benefits and limitations of these models are illustrated in Table I.

1.2.1. Amyloid β model of AD

The brain accumulates amyloid proteins and plaques in a variety of locations, including memory-related areas such as the hippocampus and cortex, which are followed by the striatum and amygdala, when (5 µl) Aβ is injected slowly over 5 sec without pausing intraventricularly [6,7]. The

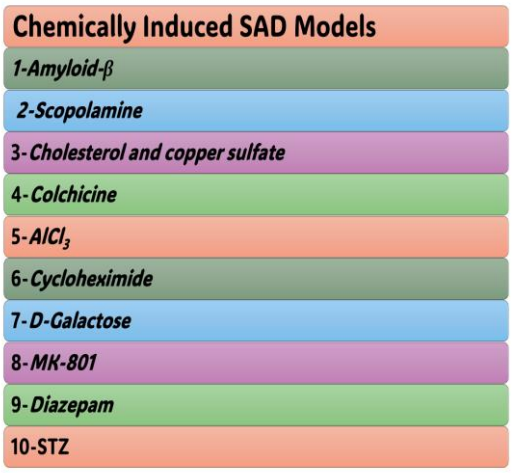

Figure 1: Chemicals-induced SAD-like pathology in animal models

characteristics of the disease, such as neurodegeneration, neurofibrillary tangles, and amyloid plaques, are simulated in an Aβ model. Moreover, behavioral alterations can be evaluated with physiological and neurochemical markers, making this a useful model for AD medication screening. One potential drawback could be infection from an invasive intracerebral injection [8].

1.2.2. Scopolamine model of AD model

The well-known anticholinergic medication scopolamine blocks the cholinergic muscarinic receptor, which raises Acetylcholinesterase (AChE) levels, induces oxidative stress, and inflammation [9], all of which result in damage to the nucleus basalis, cortex, and hippocampus areas. Scopolamine can be administered in two ways: intraperitoneally (1 mg/kg for seven days) in mice [10] or a single dose of (16mg/kg) in rats [11]. This drug interferes with the cholinergic tracts in areas related to cognition and memory. The intraperitoneal route facilitates the easier administration of scopolamine, and the scopolamine model allows for a broad study of cholinergic deficits [12]. Scopolamine, however, alters animal behaviour, resulting in elevated locomotor activity, anxiety, and ancillary effects such as dilated pupils [13].

1.2.3. Cholesterol and copper sulfate model of AD

Copper appears to be necessary for the promotion of cholesterol production in astrocytes and this process is dependent on reactive oxygen species [14]. Furthermore, animal administration of cholesterol with copper sulfate in distilled water indicated the existence of senile plaques because Aβ plaques have two copper-binding sites that

Table I. Summary of benefits and limitations of chemical-induced SAD in experimental models.

Chemical-induced SAD	Dose	Benefits	Limitation	Reference
Amyloid-β	Acute/continuous infusion of Aβ into the third ventricle (5µg/1µl) for adult male rat	➢ Apart from biochemical and neurochemical indicators, other conditions that can be evaluated include neurodegeneration, neurofibrillary tangles, amyloid plaques, and behavioral alterations. ➢ It offers a useful model for AD medication screening.	➢ Infection may occur following invasive ICV injection.	[7,8]
Scopolamine	(1 mg/kg; i.p) for male albino rats	➢ Easy administration due to intraperitoneal route. ➢ It is possible to study cholinergic deficits in detail.	➢ Scopolamine induces alterations in the behavior of animals, including heightened locomotor activity and anxiety, in addition to extra effects including salivation and dilation of the pupils.	[9-14]
Cholesterol and copper sulfate	2% cholesterol + 0.12 ppm of copper ions for adult male mice	➢ It is an easy and reliable model. ➢ It is beneficial for exploring the fibrillar Aβ pathology.	➢ Deleterious effects on the cerebellum structure induced by copper lead to motor performance impairments.	[15-18]
Colchicine	(7.5 µg in 2.5µl artificial cerebrospinal fluid) for adult male Albino mice	➢ It replicates the behavioral, biochemical, and neurochemical alterations in SAD. ➢ Excitotoxicity as well as NMDA activity can be explored. ➢ It is possible to screen nootropic agents and other cholinesterase inhibitors for memory.	➢ The animals may suffer more because of colchicine side effects such as myoclonic twitches, aggressive behavior, and a decreased pain threshold. This model has a high mortality rate, so it requires a considerable number of animals.	[19-23]
Aluminum chloride ($AlCl_3$)	(100 mg/kg; oral) for male Sprague-Dawley rats	➢ It displays all the pathogenic characteristics of the disease. ➢ The oral route makes it easy with lower rates of death.	➢ NFTs in Alzheimer's disease (AD) patients exhibit distinct morphological and biochemical characteristics, including the absence of paired helical filament structures, their dispersion in nerve terminals, and their lack of tau protein immunoreactivity.	[24-28]
Cycloheximide	(120 mg/kg; s.c) for male naïve Sprague-Dawley rats	➢ It studies the role of various neurotransmitters in cognitive deficits. ➢ It can be administered easily through subcutaneous injection.	➢ Genotoxic especially in high doses.	[29-31]
D-Galactose	adult male Swiss albino mice (150 mg/kg s.c or i.p injection;) for 6 weeks.	➢ All pathological hallmarks were observed in this model. ➢ It is a safe and reliable model.	➢ IR has been observed which could lead to diabetes.	[32-37]
MK-801	(0.15 mg/kg; i.p) for adult male Wistar rats	➢ Screening of drugs for cognitive dysfunction can be studied as well as behavioral evaluation.	➢ Animals exhibit schizophrenia-like behavior	[38-41]
Diazepam	Adult male Swiss albino mice (1 m g/kg; i.p)	➢ Memory-enhancing agents can be screened.	➢ Impaired locomotor activity as well as central depression may be observed.	[42-45]
STZ	(3 mg/kg; ICV) for adult male mice	➢ The major pathological hallmarks such as the expression of amyloid plaques, neurofibrillary tangles, elevated oxidative stress, and neuroinflammation can be studied.	➢ No limitation was found in this model.	[46-51]

simple, credible, and useful for investigating fibrillar Aβ pathogenesis [16]. Regrettably, copper causes motor function deficits in rats, which may be related to its detrimental effects on the structure of the cerebellum [17].

1.2.4. Colchicine model of SAD

For many years, the well-known medication colchicine has been used to treat inflammatory diseases like gout [18]. By binding to tubulin, the microtubule's main structural protein, it causes microtubular depolymerization and instability, which ultimately results in the death of neurons [19]. When male Wistar rats are given 15 µg/5 µl of colchicine intracerebroventricularly via the stereotaxic apparatus [20], the cholinergic tract is disrupted. This affects the hippocampus, caudate nucleus, and cerebral cortex in rodents, leading to significant cognitive impairment [21]. Furthermore, mice's spatial memory is impaired by colchicine (7.5 µg in 2.5 µl artificial cerebrospinal fluid; ICV) [20]. Colchicine is neurotoxic because it affects acetylcholine (Ach) receptors and activates N-methyl-D-aspartate (NMDA) receptors, which results in excitotoxicity [22].

1.2.5. Aluminum chloride model of SAD

After extended exposure, aluminum chloride (AlCl3), a neurotoxic and choline toxin, damages the hippocampal CA fields and induces oxidative stress in the body [23]. It induces apoptosis in neurons and upregulates Aβ and tau protein expression [24]. Its capacity to alter the behavioural traits of rodents has also been shown in previous studies [25–27]. All the disease's pathogenic features are present in the AlCl3 model. Furthermore, aluminum is administered orally, which simplifies the process and reduces the death rate below 70% [28]. Additionally, AlCl3 generates distinct neurofibrillary tangles in terms of morphology and biochemistry, including the lack of tau protein immunoreactivity, which is the primary constituent of NFTs in AD patients, absence of coupled spiral filament tau formations, and their uneven distribution in nerve terminals [29].

1.2.6. Cycloheximide model of memory deficits

Cycloheximide, an antibiotic having antifungal properties [30] has been demonstrated to promote serotonergic activity and cause cholinergic and catecholaminergic system disturbances, which impairs memory consolidation [31]. Cycloheximide can be easily injected subcutaneously and is useful for studying the involvement of different neurotransmitters in memory deficits [31], however, excessive dosages of cycloheximide may cause genotoxicity [32].

1.2.7. D-galactose model of cognitive impairment

The primary source of D-galactose, a naturally occurring sugar, is milk. According to studies, too much D-galactose causes aberrant metabolism by reducing sodium ion (Na+), potassium ion (K+), and adenosine triphosphatase (ATPase) activity. It also causes excessive oxidative stress because it increases lipid peroxidation and downregulates superoxide dismutase (SOD) activity [33]. D-galactose enhances advanced glycation [34], neuroinflammation [35], increased senile plaque formation, and tau phosphorylation leading to cognitive decline in rodents [36]. In addition to being a secure and trustworthy model, D-galactose has been the most commonly used animal model to study the pathology of AD and the aging brain [37] for the reason that pathological hallmarks seen in this model. Moreover, following D-galactose therapy, insulin resistance (IR) has been noted, which may result in diabetes [38].

1.2.8. Dizocilpine (MK-801) model of SAD

MK-801 is an NMDA antagonist with anesthetic and anticonvulsant properties [39]. MK-801 triggers neuronal swelling, and inflammation and harms a variety of normal neuronal processes at therapeutic dosages by blocking all NMDA channels for a longer duration than memantine with an increase in free radicals in the brain in contrast to memantine that blocks NMDA channels partially, not totally, so maintains normal physiological function in brain [40]. Memory impairments result from the administration of MK-801 due to its neurodegenerative effects in cognition-related areas [41]. It enhances glutamate release which generates high levels of calcium, resulting in boosting free radicals, proteases, lipases, and nitric oxide synthases production [42]. In MK-801 model, cognitive deficits can be studied in addition to behavioural assessment and medication screening for cognitive impairment but its limitation is that animals could exhibit schizophrenia-like behaviour [41].

1.2.9. Diazepam model of cognitive dysfunction

Diazepam is a member of the hypnotic and sedative drug class causing neurotoxicity by increasing the frequency of opening of chloride channel in neuronal ionotropic gamma-aminobutyric acid (GABAA) receptor causing hyperpolarization and CNS Depression. It also blocks voltage-gated sodium and calcium channels in rats mitigating hippocampal activity and cognition [1]. Additionally, it has been demonstrated that diazepam inhibits the production of acetylcholine in the hippocampal region which affects alertness and memory in mouse brain [43]. Furthermore, preventing long-term potentiation (LTP), a neural process that underpins memory and learning, by benzodiazepines can result in both anterograde and retrograde amnesia [44]. Anterograde amnesia occurs when male Swiss albino mice are administered diazepam (0.5 to 3 mg/kg i.p) 30 minutes before acquisition trials [45]. Since the benzodiazepine paradigm demonstrates cognitive impairments, memory-improving drugs can be screened using this model [46]. Impaired locomotor activity and CNS depression brought on by diazepam are the model's problems [47].

1.2.10.STZ model of SAD

STZ is a natural glucosamine-nitrosourea compound isolated from Streptomyces achromogenes compound, was first discovered as an antibiotic and mainly moves via the glucose transporter 2 (GLUT 2) and is damaging to the beta cells of the pancreas [48]. STZ is administered via intraperitoneal or intracerebroventricular injection in sub-diabetogenic dose (1-3mg/kg) [49], causing a rise in cerebral aggregated Aβ fragments, total tau protein, and Aβ deposits, and finally, cognition is impaired [50]. Because of the similarity with the human SAD pathophysiology, the animal model created by ICV injection of STZ can be considered a promising model to induce SAD [51,52]. STZ model is a reliable model for studies on AD because it replicates the major pathological hallmarks such as the expression of amyloid plaques, neurofibrillary tangles, elevated oxidative stress, and neuroinflammation [53].

2. Aim

We will focus on some recent studies regarding STZ-induced SAD and elaborate on the pathways that could be targeted for SAD amelioration. Besides, a brief for some drugs that target JNK, Wnt/ β-catenin, and PI3k/Akt pathways.

3. Results and Discussion

3.1. STZ and Neuroinflammation

Following administration of ICV-STZ, mice's brain prostaglandin E2 (PGE2) levels rose as a result of increased levels of p38-mitogen-activated protein kinases and cyclooxygenase-2 (COX-2) [56]. Another study showed that extracellular regulated kinase (ERK1/2), one of the MAPK family involved in neuroinflammation in addition to TNF-α, IL-6, and IL-1β, has been induced by the STZ- SAD model [57–59]. Furthermore, STZ stimulated IL-1β and IL-1converting enzyme/caspase-1 in the hippocampal regions of AD animals, resulting in inflammation in the brain [60]. Another AD mouse using lateral ventricle injection of STZ (0.3 mg/kg, 0.5 µl/min, 1 µl/side) dissolved in artificial cerebrospinal fluid (CSF) by the autosampler has shown upon using qPCR and Western blot, the hippocampal mRNA and protein IL-1β, IL-6, and TNF-α were assessed and elevated in STZ injected group, compared to the control group receiving the same volume of artificial CSF [61].

3.2. STZ and Oxidative stress

Malondialdehyde (MDA) concentration, a measure of lipid peroxidation, was elevated by STZ in the hippocampus of rats in research on diabetic encephalopathy in rats [62]. Moreover, STZ reduced Nrf-2 in the hippocampal regions of male Wistar rats in the AD model. Nrf-2 is a transcription factor that suppresses oxidative stress and inflammation by regulating the expression of essential genes, including heme oxygenase-1 (HO-1) [63] and glutamate-cysteine synthetase, which produces glutathione (GSH), that exhibits antioxidant activity and mitigates different types of stress [64].

3.3. STZ and CREB/TrkB/BDNF pathway

An intraperitoneal STZ injections (50 mg/kg) elicit type 1 diabetes [65] which may lower brain-derived neurotrophic factor (BDNF) levels, and cAMP-response element binding protein (CREB) phosphorylation by elevating oxidative stress [63, 64]. A growing body of research indicates that synaptic deficit and memory decline may be caused by anomalies in the CREB/ tropomyosin receptor kinase B (TrkB)/BDNF pathway because this pathway

protects against Aβ-induced neuronal toxicity and tau hyperphosphorylation [68]. BDNF, an important neurotrophic factor produced by neurons in rodents' frontal cortex and hippocampus, is engaged in learning, memory, synaptogenesis, and neural development [68]. BDNF activates TrkB as well as enhances CREB phosphorylation in neurons [69].

3.4. JNK signalling pathway

3.4.1.STZ and JNK signalling pathway

Activation of JNK pathway in AD occurs in response to oxidative stress [70]. STZ increases the phosphorylation levels of JNK signalling, hence its activation [71]. The JNK signalling pathway has been reported to cause oxidative stress, activation of BACE-1, tau hyperphosphorylation [72]. Furthermore, the JNK signalling pathway can also induce neuronal death in AD by increasing caspase-3 through oxidative stress that is implicated in APP cleavage, contributing to tau hyperphosphorylation [73–75]. Sub-diabetogenic doses of ICV-STZ resulted in high levels of p-JNK, oxidative stress, IR, and deficits in brain cholinergic function and cognition [76,77]. It has been suggested that neurodegeneration in early-age AD patients could be a result of an increased vulnerability of neurons through the activation of different apoptotic pathways as a consequence of elevated levels of ROS, intracellular calcium due to mitochondrial dysfunction, down-regulation of the anti-apoptotic B-cell lymphoma 2 (Bcl-2) together with caspase-3 activation mediated by JNK activation [78–81]. So, STZ could induce neuronal oxidative stress and apoptosis through the JNK pathway.

3.4.2. Targeting JNK signalling in AD

Figure II represents examples of drugs targeting JNK signalling to combat AD.

A. Omega-3 fatty acids

Omega-3 fatty acids are considered as JNK inhibitors that can be used to treat AD [82]. Nowadays, omega-3 fatty acids, the polyunsaturated fatty acids (PUFAs), have a role in neurodegenerative illnesses [83]. It has been proposed that administration of PUFAs increases mental and motor skill development, enhances brain glucose uptake for use as a neuronal fuel, protects CNS oligodendrocytes from damage, hence preserving axonal myelination of neurons,

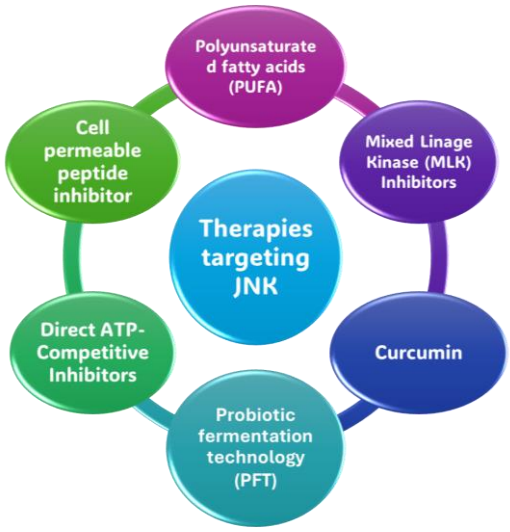

Figure II: Drugs used to target JNK signaling in AD

and down-regulates brain inflammation [84]. Another study shows that alpha-linolenic acid attenuated Aβ-induced oxidative stress via regulation of MAPK signalling, one of the JNK family, as indicated by down-regulation of ERK1/2 and JNK phosphorylation as well as preventing neuronal apoptosis through the up-regulation of Bcl-2 in amyloid beta-induced SH-SY5Y neuronal cells [85]. Treatment with docosahexaenoic acid was able to decrease p-JNK levels and prevent p-tau pathology in the hippocampus of SAMP8 mice by inhibiting JNK signalling [86].

B. Curcumin

Curcumin belongs to the plant family Zingiberaceae. In addition to its potential applications as an antioxidant through inhibition of the ROS/JNK pathway [87] by reducing MDA content and increasing SOD activity in the hippocampus [88]. Curcumin has been suggested to play a fundamental role in the inhibition of JNK, exhibiting its ability to improve neuronal loss models induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and 1-methyl-4-phenylpyridinium [89]. Additionally, curcumin reduced Aβ40-42 levels within the hippocampal structures in APPswe/PS1 mice after a 6-month administration of curcumin [90]. Furthermore, following a three-month dose regimen, it also showed a marked improvement in spatial learning and memory skills, as well as decreased presenilin 2 expression and enhanced activity of Aβ-degrading enzymes such as neprilysin [88]. In 3xTg AD mice, a combination of curcumin and docosahexaenoic acid decreased the phosphorylation of tau and JNK as well as decreased degradation of insulin response elements

(IRS-1), leading to enhanced Y-maze performance. This reported the possible role of curcumin in an insulin-sensitization process which directly supports and preserves the insulin tropism within the brain [91]. In this way, curcumin could be considered an encouraging proposition as a therapeutic potential drug in AD.

C. Probiotic fermentation technology (PFT)

Kefir (fermented milk) is the source of PFT, which is made by fermenting milk with kefir grains consisting mostly of Lactobacillus kefir [92]. In STZ-induced SAD, PFT administration (100, 300, and 600 mg/kg; orally) in adult male albino mice for 21 days, improved cognitive performance in a dose-dependent manner, which was revealed by an increase in hippocampal Ach and suppression of Aβ1-42, oxidative stress through the decrease in MDA levels, enhancing Nrf-2, and HO-1 levels GSH activity [93–95]. This could be attributed to lactobacillus which produces an exopolysaccharide that displays high scavenging activity against oxidative stress, increasing the activity of antioxidant enzymes, and enhancing the overall antioxidant capacity [96]. PFT also suppressed inflammatory markers including nuclear factor kappa B (NF-κB), IL-1β, and TNF-α in the hippocampus of SAD mice [97]. PFT administration ameliorated the expression of phosphorylated tau by decreasing ERK1/2, p38-MAPK, glycogen synthase kinase -3 beta (GSK-3β), and mammalian target of rapamycin (mTOR) in the hippocampus [97]. Furthermore, PFT has been demonstrated to be a non-toxic, safe substance with no negative side effects which makes it a well-tolerated treatment in AD patients [98].

D. Mixed Lineage Kinase (MLK) Inhibitors

Indolocarbazole, an MLK inhibitor, has shown neuroprotection to Aβ-exposed hippocampal cell culture from C57BL/6 mice, through down-regulation of the JNK signalling pathway resulting in antiapoptotic and neuroprotective outcomes within neuropathological models [99].

E. Direct ATP-Competitive Inhibitors

SP600125, also called anthra [1,9-cd] pyrazol-6-(2H)-one, is a direct ATP competitive inhibitor, improved spatial learning impairment in the Morris Water Maze, and reduced p-tau and Aβ oligomeric burden in TgCRND8, transgenic mice AD model [5]. However, it is to be noted that SP600125 has shown a lack of specificity as they indiscriminately inhibit phosphorylation of all JNK substrates, not only those included in AD [100].

F. Cell permeable peptide inhibitor

Peptide sequences that specifically bind to the JNK binding domain and inhibit it are known as peptide inhibitors of JNK [101]. One of the most important disadvantages shown by other synthetic JNK inhibitors, such as SP600125 or MLK inhibitors, is their lack of specificity toward their target [100]. D-JNK-permeable peptide 1 (D-JNK1) is the most frequently used inhibitor in experimental neurodegenerative models as it reverses ischemia-induced neuronal damage [102]. D-JNK1 has shown the ability to decrease levels of APP in human neuroglioma H4 cell lines with the consequent reduction of the APP levels and Aβ burdens [103]. D-JNK1 chronic treatment in the TgCRND8 AD mice model demonstrated prevention of JNK action leading to rescue memory impairments as well as the LTP deficits of TgCRND8 mice [103]. For those effects, peptide inhibitors might serve as a beneficial treatment option for AD, adding to the available treatments.

3.5. Wnt/β-catenin pathway

3.5.1. STZ and Wnt/β-catenin

Amyloid beta formation through BACE-1 activation as well as GSK-3β activation has been proved in the STZ-induced AD model [104,105]. Transcription of the BACE-1 protein responsible for the amyloidogenic processing of APP is inhibited by Wnt/β-catenin signalling, besides increasing neuronal survival, neurogenesis, and LTP by the same signalling pathway [106,107]. Wnt/β-catenin signalling activation decreases Aβ42 generation and aggregation [108], besides inhibition of GSK-3β, a key enzyme linked to hyperphosphorylation of tau protein and one of the major kinases responsible for β-catenin phosphorylation and degradation [109]. Dickkopf Wnt signalling pathway inhibitor 1 (DKK1) is a protein-coding gene induced by Aβ peptides and inhibits Wnt/β-catenin signalling which may contribute to reduced neurogenesis and cognitive impairment [110,111]. Additionally, DKK1 expression in the hippocampus can induce synaptic degeneration [112], this has been confirmed by using DKK1-neutralizing antibodies in mouse brain slices

which attenuated Aβ-induced synaptic loss [113]. Additionally, DKK1 is upregulated in case of increased activity of GSK-3β of postmortem AD brain as well as transgenic AD-like mouse models and colocalizes with p-tau [114,115].

3.5.2. Targeting Wnt/β-catenin signalling in AD

Targeting Wnt/β-catenin signalling pathways in AD is illustrated in Table II

A. Physical exercise as a non-pharmacological treatment to activate Wnt/β-catenin signalling

Adults and the elderly can minimize age-related cognitive deterioration and enhance brain health by adopting physically active lifestyles [116]. According to reports, Wnt gene expression upregulation in the hippocampus of adult rats is linked to prolonged moderate exercise [113,114].

B. Estrogen-induced neuroprotection is associated with inhibition of DKK1 expression

Numerous protective effects of estrogens on the adult brain have been documented, and lower levels of estrogen in adulthood are linked to a higher risk of AD in women [119]. Long-term estrogen deprivation in female rats causes Wnt/β-catenin signalling in the CA1 hippocampus area to be suppressed and basal DKK1 expression to increase [120]. Furthermore, DKK1 inhibition and the consequent stimulation of Wnt/β-catenin signalling are linked to estrogen-induced neuroprotection and the reduction of tau phosphorylation [114]. Taken together, these results point to a possible mechanism for estrogen-induced neuroprotection via DKK1 inhibition.

C. Statins

Statins are a class of medications that are commonly used to lower blood levels of cholesterol by reducing the production of cholesterol by the liver [121]. Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibiting mevalonate, a precursor necessary for the synthesis of cholesterol, that counteracts the effect of statins on Wnt/ β-catenin pathway [122]. Interestingly, it has been shown that simvastatin stimulates Wnt/β-catenin signalling after spinal cord injury and improves locomotor recovery [123]. Besides, it promotes Wnt/β-catenin signalling in the adult mouse hippocampus and enhances neurogenesis in both cultured adult neural stem cells and the mouse hippocampus [124]. Taken together, these findings imply that activation of Wnt/β-catenin signalling is one of the mechanisms by which statins are beneficial in AD and other neurological disorders.

D. Indirubins

Edible mollusks, invertebrate animals collected from freshwater, ocean, and the land including members of the classes example of which are gastropods or snails were shown to have indirubins [125]. 6-Bromo-indirubin-3′-oxime (6BIO), the first identified as gastropod metabolites, is considered a potent and selective GSK-3β inhibitor, thus having neuroprotective properties during aging [126] via inhibiting tau hyperphosphorylation and activation of Wnt/β-catenin signalling in the brain [122,123].

3.6. PI3K/Akt pathway

3.6.1.STZ and PI3K/Akt

Activation of phosphatidylinositol 3-kinase (PI3K) through growth factors including insulin promotes cell survival and synaptic plasticity [129]. PI3K inhibits the downstream kinase, GSK-3β with subsequent reduction in p-tau and Aβ levels [130]. GSK-3β is also thought to mediate neuroinflammation through the positive regulation of TNF-α and NF-κB [50]. ICV-STZ can induce SAD in mice by amelioration of PI3K/Akt signalling with subsequent increase of GSK-3β leading to upregulation of p-tau and Aβ levels [131].

3.6.2. Targeting PI3K/Akt signalling in AD

A. Intranasal Metformin

IRS-1 triggers the signalling pathway phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), which is responsible for the metabolic effects of insulin, synaptic plasticity, and the expression of genes required for LTP [132–134]. The ICV-STZ AD model interferes with the insulin signalling system by reducing the amounts of p-Akt, IRS-1, and IR mRNA and protein as well [135]. The intranasal route of metformin is more targeted than the oral route because mice showed higher amounts of the drug in their hippocampus, and less in the plasma than those treated orally, suggesting that intranasal administration restricts

Table II: Examples of recent therapies targeting Wnt/β-catenin signaling in AD

		Dose / Regimen	Reference
The active lifestyle	➢ Excessive accumulation of white adipose tissue is the key feature of obesity clinically defined by a body mass index over 30 kg/$m^{2.}$ ➢ Physically exercise can minimize age-related cognitive deterioration and enhance brain health by Wnt gene expression upregulation in the hippocampus of adult mice through endurance exercise as well as high-intensity interval training fed a high-fat diet (45% kcal fat). ➢ Both exercise programs significantly prevented the increase in total body fat mass, and inflammatory markers, and improved insulin sensitivity which in turn enhances memory.	Mice were trained and performed either endurance exercise or high-intensity interval training for 10 weeks (3 x 40 min sessions/week).	[112-114]
Estrogen-induced neuroprotection is associated with inhibition of DKK1 expression	➢ 17β -estradiol induces neuroprotection by upregulation of anti-oxidative proteins, Akt activation, GSK3 inhibition, DKK1, and tau phosphorylation inhibition, and 10 weeks of estrogen deprivation in female rats causes Wnt/β-catenin signaling in the hippocampus area to be suppressed and the consequent.	Oral administration in rats 10 µg/kg	[115,116]
Statins	➢ Simvastatin enhances neurogenesis in both cultured adult neural stem cells and the mouse hippocampus by stimulating Wnt/β-catenin signaling after spinal cord injury and improves locomotor recovery.	In mice, Simvastatin was administered for 90 days as follows: 20 mg/ kg/day for 3 days, increased to 30 mg/kg/day for 4 days, and then to 40 mg/kg/day for the remainder of the treatment.	[117-119]
Indirubins	➢ Indirubins are naturally potent and selective GSK-3β inhibitors. ➢ They prevent tau hyperphosphorylation and activate Wnt/β-catenin signaling in the brain, causing neuroprotection during aging.	Mice take 0.4 mg/kg/day in 2.5% DMSO in saline, i.p for 7 days.	[120-123]

the entry of metformin into the peripheral circulation which means less side effects [136]. Using intranasal metformin (200 mg/kg) for 4 weeks, after one week of ICV-STZ injection has raised p-Akt levels in hippocampi and cerebral cortices of model mice, hence, activation of insulin signalling and memory [137].

B. Intranasal Insulin

Hyperinsulinemia due to IR has been shown to inhibit the breakdown of Aβ in the brain due to consumption of insulin-degrading enzyme, an important enzyme that breaks down Aβ protein [138]. Using peripheral insulin supplementation to increase the activation of the insulin signalling pathway in the brain does not produce ideal results, therefore, the intranasal route is preferred in treating STZ-induced SAD as insulin passes from the nasal cavity to the brain through the olfactory receptor cells in the nasal cavity [139–141]. It has been shown that intranasal insulin treatment (20 µl per side containing 1 IU insulin glargine for 14 days) in the ICV-STZ group decreased Aβ deposition and increased IRS-1 phosphorylation in the hippocampus via recovering the expression levels of p-PI3K, p-Akt, and serine 9-phosphorylated GSK-3β that decreased by STZ [142].

4. Conclusion

This review demonstrated AD pathways and some of the recent treatments for those pathways and commonly used chemical models and their attributed benefits altogether with limitations.

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