2.0. Review of literature

Alzheimer's disease (AD), the most common neurodegenerative disorder associated with dementia. AD pathology, is typified by the pathological accumulation of amyloid-β (Aβ) peptides into senile plaques and hyper phosphorylated tau into neurofibrillary tangles (NFT) within the brain (Gamba et al., 2015; Spires-Jones and Hyman, 2014). Literature studies specifies that many events contribute to AD progression, including oxidative stress, inflammation, altered cholesterol metabolism and neuronal apoptosis. Oxidative stress is intimately associated with neuro inflammation, and a vicious circle has been found to connect oxidative stress and inflammation in AD (Louboutin et al., 2014; Elmarakby and Sullivan, 2012). Altered cholesterol metabolism and hypercholesterolemia also considerably contributes to neuronal damage and to advancement of AD (Testa et al., 2016; Fukui et al., 2015; Orth and Bellosta, 2012). Deregulation of apoptosis is associated with a list of pathologies, including neurodegenerative disorders like Alzheimer's diseases, Parkinson's disease, Huntington's disease and Amyotrophic lateral sclerosis. (Ghavami et al., 2014).

AD modifying therapies that are currently being pursued are based on the amyloid cascade theory (Evin and Hince, 2013). As quoted by Brier et al., 2016, Underwood, 2016 and Bloom, 2014 the amyloid hypothesis postulates that amyloid-beta (Aβ), in a variety of forms, triggers a cascade harming synapses and ultimately neurons, producing the pathological presentations of Aβ plaques, tau tangles, synapse loss and neurodegeneration, leading to dementia. Target centered therapy techniques were increasingly being used to improve the speed and efficiency of the drug discovery and development process mainly to develop new chemical entities or lead molecules (Amineni et al., 2010). The regulator proteins involved in Aβ plaque aggregation, NFT
formation, oxidative stress and apoptotic regulation from amyloid pathway in the pathology of AD were considered in the present study.

2.1. Amyloid-β plaque formation and aggregation

Wang et al., 2017, postulated that the amyloid β peptide (Aβ) is a key player in the etiology of Alzheimer disease. AD is associated with the aggregation of monomeric amyloid-β (Aβ) peptides into oligomers well-organized supramolecular complexes called amyloid fibrils, which causes synaptic dysfunction and neurodegeneration, is influenced by the relative ratio of the longer (Aβ42/43) to shorter Aβ (Aβ40) peptides (Lindberg et al., 2017; Hoshino, 2017; Zoltowska and Berezovska, 2017). Lindberg et al., 2017 and Wang et al., 2017 stated that strategies targeting Aβ production would suggest new insight to reduce amyloid fibril deposition in the brain may have therapeutic findings of AD.

2.1.1. BACE1

β-site amyloid precursor protein cleaving enzyme 1 (BACE1) is the β-secretase enzyme required for the production of the neurotoxic β-amyloid (Aβ) peptide that is widely considered to have a crucial role in the etiology of AD (Sadigh-Eteghad et al., 2015; Vassar, 2014; Murphy and LeVine, 2010). BACE1 initiates processing of the amyloid precursor protein (APP) into Aβ peptides, which have been implicated as central players in the pathology of Alzheimer disease and subjects with mild cognitive impairment (MCI) (Shen et al., 2017; Liebsch et al., 2017).

Cleavage of APP by BACE1 is the rate limiting step in Aβ production and elevated levels in the AD patients brain has emerged as a prime target for reducing the levels of Aβ (Vassar et al., 2014; Evin and Hince et al., 2013). Marumoto et al., 2017, Shen et al., 2017, Vassar et al., 2014 and Evin and Hince et al., 2013, postulated that development of BACE1 inhibitors as therapeutic agents is currently regarded to provide a
safe therapy treatment strategy for AD. 74B, HEM, P6M and P6U as aminomethyl-derived BACE1 inhibitors were proposed by Butler et al., 2017; 954, 60Y, 60X, 60W, 60V, 60U and 60S by Mandal et al., 2016; 3-imino-1,2,4-thiadiazinane 1,1-dioxide derivatives like 66F, 66H and 66J by Scott et al., 2016; 1W0, 1W2, 1WP, 2X4, 2X5 a series of spirocyclic pyranochromene by Volgraf et al., 2014; 0GO, 0GS, 0GT, 0GU, BXD and BXQ as cyclic sulfone hydroxy ethylamines by Rueger et al., 2012.

2.1.2. γ-secretase

γ-secretase is another important secretase involved in Aβ formation and accumulation into senile plaques. Aβ generation requires two sequential cleavages by β-secretase and γ-secretase of APP, to produce the C-termini of the Aβ peptide (Hunter and Brayne, 2017; Cai et al., 2011; Xu, 2009; Tabaton et al., 2007). γ-secretase is an intramembranous multi-subunit protein complex that mediates intramembranous proteolytic cleavage (Zoltowska and Berezovska, 2017; Yun et al., 2016). The catalytic core of this enzyme apparently resides on Presenilin 1 (PS1), but amyloidogenic activity requires three other sub-unit proteins: Nicastrin, anterior pharynx-defective phenotypes (APH-1) and Presenilin-2 (Pen-2) (Bustos et al., 2017; Yun et al., 2016).

γ-secretase cleaves APP more efficiently, resulting in greater accumulation of Aβ deposits in the brain (Yun et al., 2016). Inhibitors that target γ-secretases are promising candidates for treatment of Alzheimer's disease (Epis et al., 2012, Wolfe, 2012). Thus, γ-secretase emerged as an attractive target for reducing the Aβ42 production (Matz et al., 2015). CHEMBL3397728, CHEMBL3397726, CHEMBL3397722, CHEMBL3397708, CHEMBL1171834, CHEMBL461883 and CHEMBL1819479 were proposed as potent γ-secretase inhibitors by Flesch et al., 2015; BDBM50036340, BDBM50036330 by Velter et al., 2014; MK-0752, RO4929097 by Andersson and Lendahl, 2014; Cook et al., 2010.
and Tolcher et al., 2012; DAPT, L-685,458 and LY 411575 by Mouedden et al., 2006, Williams et al., 2008 and Tomita et al., 2006.

2.1.3. PKCγ

Among PKC isoforms, PKCγ is specifically expressed in the central nervous system (Ding et al., 2005; Ito et al., 1990). Overexpressed PKCγ, increase Aβ level by altering the PKC-MAPK signaling in the AD brain (Shi et al., 2013; Kim et al., 2011). Overexpression of PKCγ is sufficient to form amyloid-like fibrils and promotes cytotoxic amyloid fibril aggregates in pathophysiological conditions (Takahashi et al., 2015; Asai et al., 2009; Seki et al., 2009). Elevated levels of PKCγ induces ROS, which generates an imbalance between ROS levels and antioxidant systems and might underlie hippocampal histological damage of the brain (Caceres et al., 2010; Lee et al., 2010).

Postsynaptic functional plasticity, responsible for memory and learning is reduced with the over expression of PKCγ (Zhao et al., 2011). Thus PKCγ inhibition might be a constructive target for treating AD (Shi et al., 2013; Mochly-Rosen et al., 2012). BDBM50391388, BDBM50345577 proposed by George et al., 2015; Bisindolylmaleimide-VIII by Cataldi et al., 2016; CHEMBL2333365, CHEMBL3356472 by Takeuchi et al., 2013; CHEMBL2148106 by Kikumori et al., 2012; BDBM50348877, CHEMBL1929238, CHEMBL3356474 and CHEMBL3356470 by Moffett et al., 2011 and Piao et al., 2011; CHEMBL1090360, CHEMBL590109, Bisindolylmaleimide-I and CHEMBL236002 by Fidanze et al., 2010, and Mutulis et al., 2007; Enzastaurin and Gö 6983 were in clinical trials as PKC-γ antagonists proposed by Stummer, 2006 and Zhao et al., 2004.

2.1.4. BDNF

Brain-derived neurotrophic factor (BDNF), the most widely distributed neurotrophin in the central nervous system, has a pivotal role in synaptic plasticity and
neuronal survival (Tanila, 2017; Diniz and Teixeira, 2011). Reduced expression of BDNF has a crucial role in the formation of neuritic plaques and neurofibrillary tangles associated with synaptic and neuronal loss with cognitive impairment (Tanila, 2017, Jiao et al., 2016). Diluted levels of BDNF exhibited cognitive dysfunction in AD patients (Peng et al., 2015; Platenik et al., 2014; Ventriglia et al., 2013; Gezen-Ak et al., 2013; Yasutake et al., 2006).

Restoration of the BDNF level attenuated the behavioral deficits, prevented neuron loss, alleviated synaptic degeneration, reduced neuronal abnormality, improved their spatial learning along with the memory and also reduced brain amyloid plaque load (Jiao et al., 2016; Prakash and Kumar, 2014; Fukumoto et al., 2014; Shin et al., 2014). Budni et al., 2015, stated that elevating BDNF levels can be a possible therapeutic strategy for improving cognitive dysfunction in AD. AP-263 and 5HT proposed as BDNF agonists by Sawamura et al., 2016 and Voter et al., 2016; Amphetamine, Aripiprazole, Dextroamphetamine, Dopamine and Raclopride by Heal et al., 2013, Miller, 2011, Lile et al., 2006, Canive et al., 1998 and Farde et al., 1997.

2.1.5. ApoE4

Among the three apolipoprotein E (apoE) isoforms, ApoE4 constitutes the most important genetic risk factor for Alzheimer’s disease (AD) given with the potency rank order of neuronal Aβ production as ApoE4 > ApoE3 > ApoE2 (Huang et al., 2017; Holtzman et al., 2012). ApoE4 activates non-canonical MAP kinases that induces transcription factors and enhances transcription of APP and thereby increasing Aβ production (Huang et al., 2017). Apolipoprotein E co-localizes with Aβ in basement membrane drainage pathways in the walls of arteries and the attachment of ApoE4/Aβ complexes to basement membrane laminin is significantly weaker than ApoE3/Aβ.
complexes resulting in reduced elimination of apoE4/Aβ levels and increased accumulation of Aβ (Zekonyte et al., 2016; Tai et al., 2014).

The Aβ-induced inflammatory response in neural cells promotes ApoE4 by suppressing ApoE2 in AD (Dorey et al., 2014). ApoE4 mediates negative regulation of BDNF levels to decrease by 3 to 4 fold which also could lead to AD pathophysiology (Nelson et al., 2017). By modulating Arg or Thr with small molecules, abolishes apoE4 intra molecular domain interactions and Aβ production (Chen et al., 2012; Ye et al., 2005). Statin drugs such as Atorvastatin and Fluvastatin were specific inhibitors for ApoE4 by Saeedi et al., 2017; EZ-482,Donepezil and Angiotensin by Mondal et al., 2016, Waring et al., 2015 and Qiu et al., 2014; Donepezil and Galantamine by Lee et al., 2015, Birks, 2006 and Rouleau et al., 2005.

2.2. Neurofibrillary tangles (NFT) formation

Aβ and Tau-targeting treatments may individually prove effective, however the convergent progression of dual Aβ and tau targeting approach through combination therapy may eventually be more likely to produce an effective breakthrough in treating AD (Lansdall, 2014). The degree of cognitive impairment in AD is significantly correlated with the presence of neurofibrillary tangles (Umeda et al., 2014; Braskie et al., 2010).

The neurofibrillary tangle comprises a dense whorl of fibres occupying the cytoplasm of cortical neurons termed as paired helical filaments (PHFs) (Wischik et al., 2014). Intra-neuronal aggregates of hyper phosphorylated and misfolded tau that become extra neuronal and those neurons bearing tangles will die. NFTs have a stereotypical spatiotemporal progression that correlates with the severity of the cognitive decline (Serrano-Pozo et al., 2011).

2.2.1. GSK-3β
Glycogen synthase kinase-3β (GSK-3β) is a serine/threonine kinase which has attracted significant attention during recent years in drug designing studies (Kirouac et al., 2017; Hernández et al., 2008). Overexpression of GSK-3β results in increased loss of hippocampal neurons by mediating production of neurofibrillary tangles triggering cytoskeleton destabilization, Tau aggregation and neuronal dysfunction/death which alleviates memory deficits in AD (Tahir-Ali et al., 2015; Beurel et al., 2015; Credele et al., 2015; Llorens-Maríñ-tin et al., 2014; Ly et al., 2013; Thotala et al., 2012; Tang et al., 2010; Arboleda et al., 2010; Avila et al., 2010). Activated GSK-3β phosphorylate α-Synuclein and Tau in PD (Credele et al., 2015; Fernández-Nogales et al., 2015) as well as in Huntington’s disease (Pandey and DeGrado, 2016).

Stimulation of GSK-3β both in vitro and in vivo induces tau hyper phosphorylation with impairments of the cognitive functions, whereas inhibition of GSK-3β improves tau pathologies, memory deficits, reduces Aβ pathology (Ly et al., 2013; Peng et al., 2013; Liu et al., 2004). ADP, ANP by Aoki et al., 2014; 6LQ, 7YG, GR9 and KDI by Berg et al., 2012; ZRK, ZRL and ZRM by Gentile et al., 2011; AG1 by Atilla-Gokcumen et al., 2008; 679, ANP, ATU, IXM and STU by Bertrand et al., 2003; axin-APC scaffold ADZ by Yost et al., 1998.

2.2.2. Akt1

Activated RAC-alpha serine/threonine-protein kinase (Akt1) phosphorylates GSK-3β which increases the activity and leads to Tau hyper phosphorylation leading to form neurofibrillary tangles (NFT) (Jazvinscak et al., 2015; Kitagishi et al., 2014; Bhat et al., 2004; Lee et al., 2003). Akt1 may regulate tau phosphorylation in the adult brain by affecting activities for PKA, GSK-3α/β and also enhances the binding affinity of tau resulting in 12-14 fold increased tau phosphorylation (Wang et al., 2015; Sadik et al., 2009).
The increased ratio of phosphorylated Akt1 were found in AD temporal cortex than normal Akt1 when compared with controls (Griffin et al., 2005). Kitagishi et al., 2014 and Cheng et al., 2013 stated that Akt1 inhibition may play a therapeutic role in neurodegenerative diseases. Cheng et al., 2014 quoted that inactivation of Akt1 in neuronal cells exhibited reduced GSK-3β activity. Thus, Akt1 was selected as critical target for AD intervention. BDBM8727, BDBM9048, BDBM15131, BDBM16532, BDBM16534, BDBM25013, BDBM102310 and BDBM182473 were proposed as potent Akt1 inhibitors by Davis et al., 2011, Pevet et al., 2011 and Bencsik et al., 2010; BDBM182480, BDBM182489, BDBM182551, BDBM182602, BDBM182624, BDBM182671, BDBM182680 and BDBM182688 were postulated as Akt1 specific inhibitors by Freeman-Cook et al., 2010, Tong et al., 2007, Donald et al., 2007 and Borzilleri et al., 2006; BDBM182699, BDBM50237622, BDBM50298443, BDBM50298444, BDBM50322373 and BDBM50316192 were proposed as Akt1 inhibitors by Liu et al., 2005, Berger et al., 2003 and Hennequin et al., 2002.

2.2.3. PKA-Cα

Cyclic AMP (cAMP)-dependent protein kinase-C alpha, (PKA-Cα), key kinase that interacts with many of the proteins involved in the etiology of AD as well as other tauopathies (Di et al., 2016; Shi et al., 2011). Decreased PKA-Cα levels alters equimolar ratio of 3R to 4R Tau in several disease and may be sufficient to drive 4R tau assembly followed by aggregation is sufficient to trigger neurodegeneration(Saijo et al., 2017; Malmanche et al., 2017; Wobst et al., 2017; Shi et al., 2011; Adams et al., 2010; Yoshida, 2006; Bronner et al., 2005).

Down regulation of PKA-Cα-CREB signaling, consequently causes learning and memory deficits in AD subjects (Xie et al., 2016). Increasing 4R-tau expression, induced more severe seizures and nesting behavior abnormality, increased tau phosphorylation,
elucidating the 4R-specific role in causing disease (Schoch et al., 2016). Thus, PKA-Cα was considered as a critical target in AD intervention. 1SB, 2SB, 3SB, 4SB, LGY, S69, YTP potent PKA-Cα agonist by Behnen et al., 2012.

2.2.4. Tau

Tau protein belongs to the family of natively unfolded microtubule-associated proteins that binds to microtubules, is involved in their assembly and stabilization and in regulation of the motor-driven axonal transport (Guo et al., 2017; Kadavath et al., 2015). Tau phosphorylation induces changes in tau conformation which, results in hyper phosphorylation and in decreased binding to microtubules which is important in tau-mediated neurodegeneration collectively called tauopathies (Rodriguez et al., 2013; Hanger et al., 2009; Dixit et al., 2008; Liu and Gong, 2008). Oligomeric Tau contributes to the NFT toxicity in which tau aggregation leads to activation of caspase cascades and ends in neuronal cell death (Mietelska et al., 2014; Kopeikina et al., 2012; Kimura et al., 2010; Gendron and Petrucelli., 2009; Spires-Jones et al., 2009).

Dysfunction of tau protein may contribute to collapse of cytoskeleton through microtubule breakdown, synaptic withdrawal, neuritic dystrophy followed by neural cell death in a range of neurodegenerative disorders (Florenzano et al., 2017; Guo et al., 2017; Mietelska et al., 2014; Nelson et al., 2012; Bunker et al., 2006). Tau phosphorylation at GSK3-target sites, has prominent effects on tau toxicity (Ando et al., 2016). Several findings suggest that correcting signal for hyper phosphorylation of Tau in AD may offer a potential therapeutic approach (Kitagishi et al., 2014). Thus, Tau was considered as a critical target for AD intervention. 2KC, ADP, ANP, DTQ and F8E were proposed as specific and potent Tau inhibitors by Kiefer et al., 2014 and Xue et al., 2013.
2.2.5. CDK5

Cdk5 is indispensable for brain development and in the adult brain, it is essential for numerous neuronal processes, including higher cognitive functions such as learning, memory formation and delayed neuronal migration (Tran et al., 2017; Shah et al., 2014; Zechel et al., 2005). Tran et al., 2017 and Shah et al., 2014 established higher levels of CDK5 which leads to neuro toxicity was observed in AD. CDK5 is aberrantly activated by Aβ and cell stress, results in the formation of CDK5/p25 complex, known to cause hyper phosphorylation of Tau, leading to atypical cell cycling, synapto-toxicity and neuronal apoptosis (Shupp et al., 2017; Grant et al., 2015; Lopes et al., 2010).

Oxidative stress induced CK5/p35 or CDK5/p25 complexes alters the CDK5 activity in different neurodegenerative diseases with varied degrees was encountered (Shupp et al., 2017; Büchner et al., 2015). Thus, targeting CDK5 for the development of potent CDK5 inhibitor might provide an effective therapeutic intervention for AD, HD and PD etc, (Shah et al., 2014). Z3R, 3O0, ALH and RRC were proposed as potent CDK5 inhibitors by Malmström et al., 2012, Ahn et al., 2005 and Mapelli et al., 2005.

2.2.6. ERK2

Extracellular signal-regulated kinase (ERK) is a versatile protein kinase that regulates many cellular functions (Qi et al., 2017; Qi et al., 2016). Growing evidence suggests that ERK2 plays a crucial role in neuronal plasticity, memory formation and promoting neuronal cell death in a varied neurodegenerative diseases (Danis et al., 2016; Morrison et al., 2013; Subramaniam and Unsicker, 2010; Sweatt, 2001). ERK2 was detected in CSF of patients with neuropsychiatric disorders was reported with pathological prion proteins directly associated with the rapid pathophysiological neurodegeneration processes (Steinacker et al., 2010).
Up-regulated ERK2 activates MAPK signaling cascade which induces both release of cytochrome C and mitochondrial oxidative stress appears to contribute α-synuclein mediated neuronal apoptosis and abnormally phosphorylate Tau at multiple sites to increase NFT formation (Qi et al., 2017; Qi et al., 2016; Danis et al., 2016; Kim and Choi, 2010; Devi et al., 2008; Parihar et al., 2008). 2SH as 5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine inhibitors of ERK2 were proposed by Blake et al., 2014; 38Z, 390, ANP were proposed as ERK2 inhibitors by Chaikuad et al., 2014; 19A, 33A, 82A as pyrazolylpyrrole ERK2 inhibitors were proposed by Alex et al., 2007; H2B, H4B, HAR, HEM as ERK2 inhibitors were proposed by Fischmann et al., 1999; CME, SB2 as pyridinyl imidazole inhibitors for ERK2 were proposed by Fox et al., 1998.

2.2.7. P35

P35 is predominantly expressed in post-mitotic neurons (Kanungo et al., 2012) essential for normal neuron function (Peterson et al., 2010). CDK5 is activated in post-mitotic neurons via the neuron-specific activator p35. CDK5/p35 plays a critical role in brain development and physiological synaptic activity (Kimura et al., 2014). Aβ can evoke an increase in CDK5 activity by calcium-dependent calpain-mediated proteolysis of p35 (Wilkaniec et al., 2016; Yildiz-Unal et al., 2015).

The overexpressed Cdk5 evokes increased phosphorylation of parkin that results in its aggregation and is also a direct cause of mitochondrial dysfunction, oxidative stress and elevated autophagy that altogether lead to dopaminergic neurodegeneration (Wilkaniec et al., 2016). P35/CDK5 may also activates PI3K/Akt pathway resulting increased Tau accumulation (Wilkaniec et al., 2016). Thus, p35 was considered as a critical target for AD intervention. Isopropyl-olomoucine was proposed as potent p35 antagonists by Reznickova et al., 2015; Aloisine and 9-Cyanopaullone as potent p35 inhibitors by Gao et al., 2013 and Becker et al., 2010; Indirubin-3'-monoxime,
Hymenialdisine and Roscovitine were proposed as p35 antagonists by Polychronopoulos et al., 2004, Wan et al., 2004 and De Azevedo et al., 1997; CHEMBL440411, CHEMBL190760 and CHEMBL126077 were proposed as potent p35 antagonists by Fedorov et al., 2007, Ferandin et al., 2006 and Tandon et al., 2005.

2.2.8. P25

Proteolytic cleavage of p35 generates p25, leading to aberrant CDK5 activation. CDK5-p25 acquires a longer half-life, resulting in the net activation of CDK5 (Minegishi et al., 2010; Tsai et al., 1999). The resulting CDK5/p25 complex regulates the process of amyloidogenesis by STAT3-dependent increase in BACE1 activity or increased phosphorylation of amyloid precursor protein (APP) (Wilkaniec et al., 2016). The accumulation of p25 is implicated in abnormal Tau phosphorylation that causes neurotoxicity (Kimura et al., 2014; Kanungo et al., 2012; Peterson et al., 2010).

In diseased brains, CDK5 is thought to be hyper activated by p25 there by preferentially increasing the Tau hyper phosphorylation, which highlights the importance of CDK5/p25 in abnormal tau phosphorylation (Kimura et al., 2014; Kanungo et al., 2012; Cruz et al., 2003; Tsai et al., 1999). Thus, p25 was considered as a critical target for AD intervention. Isopropyl-olomoucine was proposed as potent p25 antagonists by Reznickova et al., 2015; Aloisine and 9-Cyanopaullone as potent p25 inhibitors by Gao et al., 2013 and Becker et al., 2010; CHEMBL440411, CHEMBL190760 and CHEMBL126077 were proposed as potent p25 antagonists by Fedorov et al., 2007, Ferandin et al., 2006 and Tandon et al., 2005; Indirubin-3’-monoxime, Hymenialdisine and Roscovitine were proposed as p25 antagonists by Polychronopoulos et al., 2004, Wan et al., 2004 and De Azevedo et al., 1997.
2.2.9. BIN1

Bridging integrator-1 (BIN1) is a member of the amphiphysin family of proteins. BIN1 is the second most important protein for late onset AD, after APOE (Tan et al., 2013). BIN1 were significantly associated with the tau pathology, APP endocytosis/intracellular trafficking, immune/inflammation of the brain by altering neural degeneration and glucose metabolism contributes to the risk of AD (Wang et al., 2016; Tan et al., 2013).

BIN1 increases cellular BACE1 levels through impaired endocytic trafficking of APP and reduces BACE1 lysosomal degradation, resulting in increased Aβ production (Miyagawa et al., 2016; Muller et al., 2003). Decreased expression of BIN1 suppressed Tau-mediated neurotoxicity (Chapuis et al., 2013). Thus, BIN1 is considered as a critical target for AD intervention. Adenocard, Levomenthol and Dimethylaniline were proposed as potent BIN1 antagonists by Carman et al., 2011, Watt et al., 2008 and Brimecombe et al., 2006; Bupivacaine, ZINC504665976 and CHEMBL170902 were proposed as potent BIN1 antagonists by Hansen et al., 2007.

2.3. Oxidative stress liaised proteins

The generation of reactive oxygen species (ROS) and/or free radicals-induced oxidative stress which is the major age-related changes, can lead to hippocampus damage and increase vulnerability to impaired learning and memory (Zhao et al., 2011). Oxidative stress is induced by an imbalanced redox states, involving either excessive generation of reactive oxygen species (ROS) or dysfunction of the antioxidant system (Kim et al., 2015). Antioxidants have long been considered as an approach to slow down AD progression (Pocernich and Butterfield, 2012).

Accumulation of Aβ has also been observed in the mitochondria, which may affect mitochondrial respiratory function, increase ROS production and change
mitochondrial membrane potentials in various brain regions initiates reduced GPX in AD (Picone et al., 2014; Zhao and Zhao, 2013; Castellani et al., 2002). Therapeutic efforts to achieve attenuation of oxidative stress could be beneficial in AD treatment, attenuating Aβ-induced neurotoxicity and improve neurological outcomes in AD (Rojas et al., 2017).

2.3.1. Glutathione peroxidase (GPx1 and GPx2)

The most abundant endogenous antioxidant, glutathione peroxidase (GPx1 and GPx2), plays a significant role in combating oxidative stress. The ratio of oxidized GPX to reduced GPX is utilized as a measure of intensity of oxidative stress (Murakoshi and Osamura, 2017). GPX contains a family of multiple isoenzymes which catalyse the reduction of H₂O₂ and lipid peroxides utilizing GSH as an electron donor (Jablonska et al., 2015; Gandhi and Abramov, 2012; Dasuri et al., 2013). Increasing significant evidences suggest that reduced antioxidant activity of GPX (GPx1 and GPx2) promotes the activity of β, γ-secretase and correlates with overproduction of free radicals and peroxides that damages the mitochondrial respiratory chain thus inducing or amplifying neuronal dysfunction thereby triggering neurodegeneration (Hwang et al., 2016; Dai et al., 2014; Zorov et al., 2014; Zhao and Zhao, 2013; Rahman et al., 2012; Cui et al., 2012; Chen et al., 2008; Gemma et al., 2007).

The upregulation of GPX (GPx1 and GPx2) could be one of the protective responses against neuronal injury (Power and Blumbergs, 2009). Increased free radicals and absurdity in potentiality to detoxify reactive intermediates associated with diluted activity of GPX has made it as attractive therapeutic target for AD intervention. Glutathione, Proanthocyanidin, Melatonin and NADPH were proposed as potent GPX agonists by Couto et al., 2013, Pesca et al., 2013, Birben et al., 2012 and Attia et al., 2008.
2.3.2. SOD1

Superoxide dismutase-1 (SOD1), is a homo-dimeric protein that functions as an antioxidant by scavenging for superoxides (Healy and Cervantes, 2016). Regardless of the presence or absence of metal binding and/or disulphide formation, excess of ROS or increased oxidative stress decreases the structural stability of SOD1 (Furukawa and O’Halloran, 2005; Rodriguez et al., 2005). The SOD1 monomer structural stability decreases upon oxidative stress, which may lead to partial local misfolding into a toxic conformers and consequently increases the propensity of aggregation, and co-localizes with Aβ plaques that contributes to neuropathy in AD development (Petrov et al., 2016; Helferich et al., 2015; Grad et al., 2014; Morales et al., 2013; Kerman et al., 2010).

Small drugs that can bind at the dimer interface or bind at the alternative site significantly slowed the aggregation (Wright et al., 2013; Antonyuk et al., 2010; Nowak et al., 2010; Ray et al., 2005). Thus, inhibition of SOD1 would be a possible alternative strategy for AD therapeutics (Ren et al., 2011). ALE, 5FW and 5UD were proposed as SOD1 inhibitors by Wright et al., 2013; 5UP, ZO0 and ZZT were proposed as potent inhibitors by Antonyuk et al., 2010.

2.4. Apoptotic regulators

Alzheimer's disease (AD), which is characterized by excessive early apoptosis of neurons (Liu et al., 2017). In neuronal apoptosis, there can be cross-talk between the intrinsic and extrinsic pathways (Ghavami et al., 2014). The intrinsic pathway is usually activated by the recruitment of BAX and BAD to outer mitochondrial membrane, causing cytochrome c release formation of apoptosome and subsequent activation of caspase-9. (Ghavami et al., 2014; Wang and Youle, 2009). The extrinsic pathway is initiated through the stimulation of pro-caspases-8, -10 to cleave themselves to form active and mediates apoptosis cascade through effector caspases (Ghavami et al., 2014; Elmore, 2007; Wang
and El-Deiry, 2003). Oxidative stress and apoptosis are the major mechanisms that induce dopaminergic cell death in neurodegenerative diseases (More and Choi, 2017).

2.4.1. BAX

BAX, one of the important apoptosis-inducer proteins, which have been reported to change expression levels in the hippocampus of AD patients, are thought to be involved in tau hyper phosphorylation and neuronal death in AD brains (Peng et al., 2012; Zhang et al., 2006; Chen et al., 2005). Oligomeric Aβ increases Bcl-2 levels, leading to the activation of BAX and neuronal cell death in hippocampal region (Kudo et al., 2012). BAX enhances the loading of the ER Ca\(^{2+}\) store and thus boosts the Ca\(^{2+}\) load to which the apoptotic effector systems, including mitochondria are exposed upon physiological and/or pathological challenges (D'Orsi et al., 2015; Pinton and Rizzuto, 2006).

Inhibition of BAX activity either by BAX-inhibiting peptide or BAX gene knockout significantly prevented oligomeric Aβ-induced neuronal cell death (Kudo et al., 2012). Thus, BAX mediated neuronal apoptosis has made it as attractive therapeutic target for AD intervention. CHEMBL3417402, CHEMBL3417397, CHEMBL3417396, CHEMBL3417399, CHEMBL3417396, CHEMBL3417403 and CHEMBL3417409 were proposed as potent BAX antagonists by Stornaiuolo et al., 2015.

2.4.2. BAD

Bcl-2-associated death protein (BAD), is a member of the Bcl-2 family of proteins that promotes apoptosis (Stankiewicz et al., 2015). BAD mediated apoptosis is likely to be influenced by the levels of phosphorylated BAD (Stickles et al., 2015). As downstream events after BAD dimerization with Bcl-XL, BAX translocation to mitochondria and cytochrome c translocation could affect the β-amyloid (Aβ)-fibrinogen
interaction in AD pathology and vascular dementia (Chung et al., 2016; Chakrabarti et al., 2015; Ray et al., 2013; Wang et al., 2012; Baydas et al., 2005).

Overexpression of BAD in cerebellar granule neurons causes cell death (Stickles et al., 2015; Akhtar et al., 2004). Thus, targeting BAD might open an alternative possibility in withdrawing the degenerative process involved in neuroprotection and AD therapeutics. ABT-737 were proposed as potent BAD antagonist by Modi and Sankararamakrishnan, 2017; Deguelin by Hafeez et al., 2016; CHEMBL503454, BDBM50293171 and CHEMBL462308 by Yan et al., 2010, Janssen et al., 2009 and Bernardo et al., 2008; BDBM50254587 and CHEMBL1215012 by Porter et al., 2008; CHEMBL121501 by Scozzafava and Supuran, 2000.

2.4.3. Caspase-8

In the mature nervous system, caspases are not only involved in mediating cell death but also regulatory events that are important for neural functions, such as axon pruning and synapse elimination, which are necessary to refine mature neuronal circuits (Hyman and Yuan, 2012). Aβ induced caspase-8 initiates apoptosis either directly activating executioner caspase (-3, -6, -7), or activates the intrinsic apoptotic pathway to induce efficient neuronal cell death in AD pathology (Qian et al., 2015; McIlwain et al., 2013).

Elevated levels of BAX and caspase-8 increases the hippocampal neuronal apoptosis synaptic loss and ischemic neuronal degeneration in cerebral cortex of AD brain (Zhao et al., 2017; Nam et al., 2016; Shabanzadeh et al., 2015; Gao and Chen, 2011). Thus, caspase-8 was considered as a critical target for AD intervention. BDBM50340547 and PKR Inhibitor were proposed as potent caspase-8 inhibitor by Chu et al., 2011; CHEMBL1762360, CHEMBL597796, CHEMBL490851 and CHEMBL521972 by Loser et al., 2009; Glycylphenylalanine 2-naphthylamide and
BDBM10357 by Qiu et al., 2009 and Chu et al., 2009; Granzyme B, Caspase Inhibitor-VI and Q-VD-OPh by Stanic et al., 2008 and Liu et al., 2007, Patil et al., 2004.

2.5. Tertiary structure prediction

One of the established challenges in computational biology is the native and functional fold prediction for amino acid sequences (Marks et al., 2012). Molecular modelling methods are used in the fields of computational chemistry, drug design, computational biology and materials science to study molecular systems ranging from small chemical systems to large biological molecules and material assemblies (Parsons et al., 2005).

Comparative modeling relies on the principle that sequences which are related phylogenetically exhibit similar three dimensional folded structures that is sequence similarity suggests structural similarity (Lundin et al., 2012 and Vyas et al., 2012). Munikumar et al., 2013 predicted tertiary structure for DnaE of Neisseria meningitides using comparative modeling protocol. Meier and Soding et al., 2015 and Larsson et al., 2008 stated that, using multiple templates the quality of homology models was improved. Li et al., 2016 stated that multi-template protein model generation, effectively removes atomic clashes commonly encountered in template based or comparative modeling.

2.5.1. Validation of homology models

Priyadarshini et al., 2013, performed fold prediction assessments with GA341 score and stability of the model with DOPE score. Priyadarshini et al., 2013, Amineni et al., 2010, Umamaheswari et al., 2010 referred the stereo chemical quality of a protein structure using Ramachandran’s plot. Pradhan et al., 2015, Munikumar et al., 2013, Pradhan et al., 2013, Wiederstein and Sippl, 2007 predicted the stable conformation of the model with Z-Score using ProSA and quality of the predicted models using ProQ.

2.6. Lead identification
2.6.1. Virtual screening

Virtual screening, is to computational screening of large chemical libraries with complement targets of known structure (Shoichet, 2004). Similar structures have similar function, similarly from one or several parent ligands and the goal is to find different compounds with similar inhibitory properties (Lionta et al., 2014). Arimont et al., 2017, Kooistra et al., 2016 and Roy et al., 2015 incorporated an index based ligand searching tool into ligand based virtual screening.

2.6.2. Pharmacophore based screening

Natarajan et al., 2016, Pradhan et al., 2016, Katari et al., 2016 and Sun et al., 2008, stated that pharmacophore-based virtual screening increases the speed and accuracy efficiency in preparing ligand dataset for drug discovery process. Dubey et al., 2016, Pradeep et al., 2015 and Sun et al., 2008 stated that e-pharmacophore based virtual screening increases efficiency by profiling the selective available structural information in predicting the active compounds against chemical libraries.

2.6.3. QSAR based screening

Neves et al., 2016, Awasthi et al., 2015, Swargam et al., 2016 and Sakkiah et al., 2010 stated that QSAR model was built for the ligand data set with known activity and QSAR based virtual screening followed by docking would be efficient in the process of lead identification. Oluic et al., 2017, Neves et al., 2016 and Ko et al., 2016 quoted that QSAR models can be used as a predictive tool for virtual screening of chemical libraries with consensus range of known chemical properties to identify novel drug candidates.

2.7. Molecular docking

Molecular docking has become an increasingly important tool for drug discovery (Meng et al., 2011). Docking is used for optimizing known drugs and for identifying novel binders by predicting their binding mode and affinity (El-Hachem et al., 2017;
Natarajan et al., 2016; Katari et al., 2016; Pradeep et al., 2015). Fast ranking of ligands of potential pharmaceutical interest based their binding-free energies (or affinity) toward a given protein is successfully implemented in many drug design and discovery process (Katari et al., 2016; Hema et al., 2016; Pradhan et al., 2013; Umamaheswari et al., 2010a; b).

Pradeep et al., 2016, Katari et al., 2016, Hema et al., 2016, Sandeep et al., 2016 stated that Glide molecular docking method was successfully implemented to find potent inhibitors against several drug targets and also been thoroughly reviewed in the literature over the decades. Cho et al., 2005 implemented mixed quantum mechanical/molecular mechanics (QM/MM) methods to compute the ligand charge distribution in the protein environment, thus incorporating polarization effects in an accurate fashion, revealed quantum polarized ligand docking protocol.

Wang et al., 2017 and Hu et al., 2016 demonstrated the core hopping strategy is to screen multiple scaffolds against a receptor structure, searching for alignments of fragments for the potential attachment points on the scaffold ligand compound with the attachment points on the receptor. Pradeep et al., 2016, Sandeep et al., 2016, Hema et al., 2016, Katari et al., 2016, Pradhan et al., 2016 clearly demonstrated that the performance of the IFD method is superior to that of the Glide RRD.

Du et al., 2011 and Das et al., 2009 stated that performance of RRD, IFD and QPLD along with rescoring by Prime/ MM–GBSA and reported QPLD in combination with Prime/MM-GBSA showed best correlation to experimental binding affinity. Du et al., 2011 evaluated and postulated that ranking the leads with binding free energy is better than ranking the leads with Glide score. The result revealed combination of molecular docking and Prime/MM–GBSA simulation can be used to rapidly and accurately predict the binding free energy and rank the ligands for lead discovery and optimization.
2.8. Molecular dynamics simulations

Molecular dynamics (MD) simulation stands as the fundamental computational tool for capturing dynamic aspects of protein structure, function and ligand interactions and dynamics with utmost detail (Lindahl, 2008). MD simulations is useful for analysing the dynamic properties of structural bioinformatics from studying single structures to analyse conformational ensembles (Hospital et al., 2015). Molecular docking coupled with MD have made important strides in advancing drug discovery (Natarajan et al., 2016). Desmond has been effectively used to check the stability of protein ligand complexes for proposing potent lead molecules for drug targets (Natarajan et al., 2016; Sandeep et al., 2016; Hema et al., 2016; Katari et al., 2016).

2.9. ADME predictions

ADME properties elucidates the drug disposition within the organism, ADME properties were calculated to avoid the failure of drug molecules in the clinical trials with poor drug like properties. Wang et al., 2017, Shin et al., 2016 and Kovacevic et al., 2014 stated that in silico prediction of ADME models introduces the physiochemical properties of lead molecules that influences the pharmacokinetics and pharmacological properties.

2.10. Database development and deployment

Biological databases are libraries of life sciences information, collected from scientific experiments, published literature, high-throughput experiment technology, and computational analysis (Altman et al., 2004). With the explosive growth of biological data, there is an increasing number of biological databases that have been developed in aid of human-related research (Zou et al., 2015). Priyadarshini et al., 2013, has developed database on the causative pathogens involved in infective endocarditis as, Database Infective endocarditis drug targets and inhibitors (http://svimsbic.org/IEDB/index.html). Pradhan et al., 2015, has developed database on the drugs and vaccine candidates for
Leptospira as, Database on Leptospira Drug targets (http://svimsbic.org/LPDB/index.html). Munikumar et al., 2012, has deployed database on the pathogens involved in Bacterial meningitis as, Database on Drug targets and vaccine candidates of bacterial meningitis (http://svimsbic.org/CBMTTD/index.html).