10.1 General

Alzheimer’s disease (AD) is caused by accumulation of abnormally folded A-beta (amyloid beta peptide) and tau proteins in the brain. This peptide can build up in the brain to form clumps called amyloid plaques, which are characteristic of AD. The present drugs available for AD are not suitable for controlling the disease fully nor are enough for preventing the disease. Hence there is a sudden requirement for introducing some techniques to speed up the drug designing process as well as for introducing some new pharmacophoric species. Computational drug designing technique definitely helps to reduce the time required for the process. A proper screening method helps to minimize the possibility of failure of the drug molecule in the clinical trial. Phytochemicals derived from medicinal plants can be tried with proper modification for controlling AD.

10.2 Gene analysis

Microsatellite instability occurs in the sequences of APP, PSEN1 and APOE genes. In the case of PSEN2 gene, none of the reported mutations were present in the microsatellite region and there was not much difference in its functional domains. Moreover, the percentage of similarity between the normal and mutated PSEN2 gene is 99% and those observed mutations do not make much variation in the functional domains of the protein. APOE gene is the major risk factor for the late onset of AD, and only one of the reported mutations is seen in the microsatellite region. This mutation is not making much difference in the functioning and structure of protein. Therefore, besides mutation in this gene, some other mutations may also contribute to late onset AD. APOE gene is a major risk factor for late onset of Alzheimer’s disease, and many other disorders like diabetes, stroke hyperlipidaemia, hypertension, lipoprotein glomerulopathy, hyperlipoproteinaemia III and others. This may be the reason for higher chances of AD for patients with other disorders.
10.3 Protein analysis

Most of the AD protein molecules are structurally and thermodynamically stable keeping a common motifs of ‘ILVDTGSSNFAV’. AD proteins are mainly present in the membrane region of the cell. The proteins 1SO8 and 1U7T are present in the mitochondria and are reported to be functioning in mitochondrial tRNA maturation. Most of the protein molecules are found to be hydrophilic. Protein molecules with a higher half life period like 1AAP may be responsible for the accumulated tangles and plaques. Molecular modeling and simulation studies support for strong intramolecular interaction. No conformational change is expected with pH changes. In simulation studies, the polar surface area decreases only slightly along with increase in number of simulation steps. This shows that all protein molecules have well binding capacities.

10.4 RNA based drug designing

Antisense siRNA strands strongly interacts with argonaute protein leading into the formation of RNA-protein complex. This complex can recognize target mRNA sequence by considering base pair complementarity and can bind through hydrogen bonds. Antisense siRNA strands designed with comparatively low GC content, and their interaction with protein argonaute indicates feasibility of designed siRNA strands to be used in RNA interference pathway to silence AD specific mutations.

10.5 DNA-protein based complexes.

There are only three reported protein-DNA complexes found in the repository. They are 3DXC, 3DXD and 3DXE. The complexes 3 DXE and 3DXD are found to unaffected by variation in potential and ionic concentration. 3DXC was found to be dissociated at a potential head of 240 mV or at a concentration head of 0.6 M K+. All these molecules are found to thermodynamically and structurally stable. Moreover, no drastic change in structure, geometry or configuration is expected on changing the pH.
10.6 Ligand identification

Based on pharmacophore studies, ADMET analysis and docking studies curcumin has been identified as a potential candidate for treating AD. By the quantum mechanical modeling studies of curcumin in the DFT level it has been found that the syn-enol form and the anti-diketo form are with stable structures. Among the isomers considered here, the syn-enolic form was found to be most stable in both gas phase and aqueous solution. The syn-enolic form exhibits very large dipole moments of 10.77 D. Keeping this isomer in the drug molecule probably provide the sufficient solubility for the molecule. It is further identified that curcumin has a higher tendency to be deprotonated to form the anion, which is further stabilized by extension of conjugation.

10.7 Fine tuning of the ligand molecule

Curcumin is found to be targeting the DNA and AD protein molecules. Hence Curcumin or its derivatives can be used for the pre transcriptional gene silencing technique to prevent the disease. Similarly the same drug molecule can be given to control the disease as these molecules can effectively interact with the AD proteins. To improve the bioavailability and solubility of the drug dissolution and modification techniques have been tried.

Two forms of modified curcumin have been proposed here to be used as potential drugs for AD, the OH and NH2 substituted curcumnis. Bioavailability of these compounds has been computed based on the ADME studies. Substitution of curcumin in the 4th position of the aryl group by NH2 group (1-[4-(aminooxy)-3-methoxyphenyl]-5-hydroxy-7-(4-hydroxy-3-methoxy phenyl) hepta-1,4,6-trien-3-one) enhances bioavailability without affecting the drug likeness or any other vrequired properties of the molecule.

Moreover, addition of glycerol linolenate to the ligand as solvent improves the primary solubility of the compound. Toxicity studies predict the molecule to be safe.
10.8 Scope for further studies

The computational method can be extended to other disease also. Similar to the targets mentioned here (protein, DNA and RNA) other targets may also be tried. The analysis made here has to be evaluated by wet analysis. In a similar manner, pharmacophoric properties of all the phytochemicals, which are reported as having some medicinal effects can be characterized.

10.9 Summary

The amino curcumin has been suggested and recommended to be used in pre-transcriptional gene silencing of AD, as an antimitagenic agent to silence APP, PSEN1 and PSEN2 and to treat the disease in the protein level.