In-Silico Studies of *Momordicacharantia L.* Extract as a Potential Treatment Against Alzheimer's Disease Targeting Amyloid Beta Protein (3NYL)

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Abstract:- One of Medicinal plant, *Momordicacharantia*belonging to Cucurbitaceae family contains various essential phytocompounds which shows antifungal, antibacterial, antiviral, anti-neuronal properties. Alzheimer's disease is a brain disorder that slowly destroys memory and thinking skills. And also reducing the ability to carry out the simplest tasks.In an insightful In-silico analysis and potential therapeutic efficacy of *Momordicacharantia* phytochemicals against amyloid beta (Aβ) protein, a key player in neurodegenerative disorders like Alzheimer's disease. In the present study, in silico molecular docking analysis of report phytocomponents present in *M. charantia* fruit was studied against Amyloid beta protein of Alzheimer's disease.. The result revealed 38 phytochemicals constituents of *Momordicacharantia* derived from several literature of Review. Out of these 38 phytocompounds, Laurifolin , gamma Isomorphine, Armepavine, 3-Epi-Schelhammericine and Flabelline were ranked the highest with binding scores ranging from –10.0 kcal/mol to –9.4 kcal/mol compared with the standard, Cholamide, with a binding score of –7.7 kcal/mol. From the results obtained, it can be concluded that Laurifolin , gamma Isomorphine, Armepavine, 3-Epi-Schelhammericine and Flabelline act against Alzheimer's disease inhibiting the Amyloid Beta Protein and therefore can be further developed into potent drugs for Alzheimer's disease treatment.

Key Words:-*Momordicacharantia*, docking, Phytocomponents, Amyloid Beta Protein

Introduction:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the central nervous system that results in the gradual loss of memory and other cognitive capacities. The hallmarks of AD are the accumulation of extracellular protein plaques containing amyloid and intracellular neurofbrillary tangles (NFTs) containing hyper-phosphorylated tau protein. However, it is still uncertain if these plaques and NTs actually cause the associated neuronal and functional impairments. Moreover, epidemiological, neuroimaging, and neuropathological studies suggest that AD results from a combination of genetic, lifestyle, and environmental triggers and that multiple pathomechanisms contribute to neuro-degeneration. Alzheimer's disease is the most prominent cause of dementia1 and the sixth most prevalent cause of premature death worldwide. Over 55 million people globally currently suffer from dementia, and this number is expected to rise above 150 million by 2050 due to population aging. Further, more than 75% of these patients are undiagnosed and lack access to treatment and care (1). Only four drugs have been approved for AD therapy, and these only treat symptoms to improve patient quality of life, but do not stop the progression of the underlying neurodegenerative processes (2). Moreover, drug development for AD has a high failure rate, presumably due to the many unknown aspects of disease pathogenesis. Therefore, there is an urgent need to identify novel pathogenic mechanisms and therapeutic targets (3). Mounting evidence suggests that normal age-related functional decline and diseases of aging arise at least in part from the accumulation of molecular damage due to oxidative stress and inflammation (4) The oxidative stress (OS) theory of aging proposes that the slow and steady accumulation of macromolecular damage from reactive oxygen species (ROS) eventually leads to the functional impairment or irreversible loss of terminally diferentiatedcells(5). Related theories include the mitochondrial theory of aging (6) , the cellular senescence theory of aging , and the molecular inflammation theory of aging(7). In all these theories, the accumulation of ROS-induced damage is posited as a potential mechanism leading to age related functional decline, failure of endogenous repair mechanisms, and neurodegenerative diseases, of which AD is the most common(8). Acetylcholinesterase (AChE) is an essential enzyme in the cholinergic nerve system, as this special issue reviews in great detail. Although there is a significant loss of forebrain cholinergic neurons and a steady decrease in acetylcholine, numerous distinct types of neurons degenerate as AD progresses (9). *Momordicacharintia* is a tropical and subtropical vine of the family Cucurbitaceae and is commonly called bitter melon or bitter apple (10). *Momordicacharantia* was chosen as the subject of the investigation due to its widespread use in traditional medicine systems as a remedy for a number of illnesses, including diabetes, eczema, kidney stones, gout, jaundice, piles, pneumonia, psoriasis, rheumatism, fever, and scabies. It is also popular as an abortifacient, anthelmintic, contraceptive, and dysmenorrhea, its use in diabetes and

its complications (nephropathy, cataracts, insulin resistance), as an antibacterial agent as well as an antiviral agent (including HIV infection), has been verified by over 100 investigations utilizing contemporary methods (11). The characterization of anti-Neuronal compounds from *Momordicacharantia* with more potent Amyloid Beta Protein(APP) inhibitory activity could thus help provide an excellent therapeutic option against Neurodegenerative disease like Alzheimer's

2.Materials and Methodlogy:

2.1 Selection of Phytocomponents:

Important phytocomponents have been determined for the current study's analysis after an extensive review of the literature. Our research aims to understand the mechanisms of action of these particular phytocomponents and investigate their potential use in medication development and controlling illnesses.

2.2 Ligand Preparation and Filtration:

Momordicacharantia contained 38 phytocompounds, which were utilized as ligands in the docking analysis. The PubChem database provided the 3-D structures of these compounds. Following that, the ligands were cleaned, their 3D coordinates were calculated, and the "prepare ligand protocol" tool in Discovery Studio 4.0 was used to create the ligand conformations. Following synthesis, the compounds were filtered based on their molecular properties in order to predict their solubility and permeability in medication development. The most well-known physical property filter is Lipinski's "rule of five," which places an emphasis on bioavailability. The rule states that the compounds have molecular mass less than 500 daltons, not more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors and an octanol-water partition coefficient log P not greater than 5 **(12)**. The filtered compounds were then used for docking analysis.

2.3 Genes selection

The reported molecular targets responsible for Amyloid Beta protein ,which are associated with Alzheimer's Disease , in Human **(13)** were retrived from Roberta software.

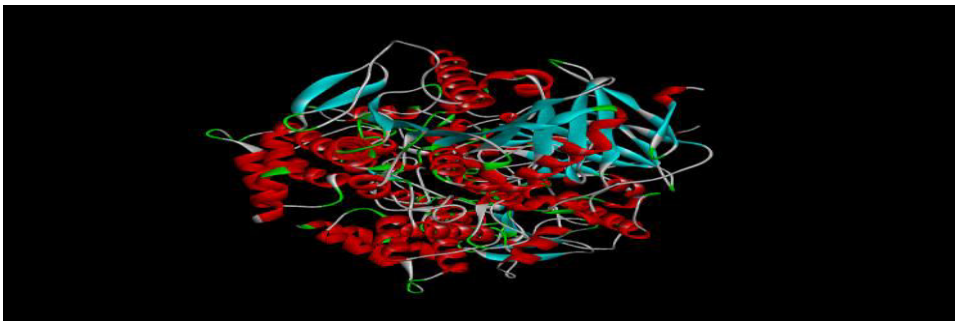

Figure 1: It shows the validation of Amyloid Beta Protein(3NYL) by using Biovia Discovery Studio4.0(13)

2.3 Molecular Docking:

By docking each of the 9 phytochemicals identified in *Momordicacharantia* against the corresponding active site of the target protein, the anti-inflammatory efficacy of each component was evaluated. In this work, *Momordicacharantia's* interaction molecules with the chosen targets of amyloid beta protein (APP) were identified using Discovery Studio 4.0. One of Discovery Studio 4.0's strategies is to score or dock every potential location for a ligand in a protein's binding site. Using natural compounds produced from *Momordicacharantia*, a docking analysis of the target proteins was conducted to determine the most effective position and binding affinity of the compounds with each target protein using scoring functions. After predicting the binding sites of the selected proteins taken for the study molecular docking was performed using the auto dock vina tool **(14)** and the molecular interaction viewed using the Biovia Discovery tool **(15)**. Ligands were docked to the proteins followed by scoring them for their relative strength of interaction to identify candidates for drug development. The final poses were then scored based on the total docking energy, which is composed of intra molecular energy of ligand and the ligand-protein interaction.

2.4 Drug Likeness

A subjective thought called "drug-similarity" is applied in drug plan to survey how a compound acts like a medication as far as things like bioavailability. A particle's drawn out helpful viability is recognized as one of the essential elements of its true capacity for effective medication improvement, alongside sub-atomic qualities influence retention, circulation, digestion, discharge, and harmfulness (15). Predicting ADMET qualities is crucial for the process of discovering novel treatments because, as stated in , these factors account for nearly 60% of all medication failures during the clinical phases. As a result, it has become crucial to create lead compounds that do not readily transform into harmful metabolic products and are quickly absorbed by the stomach and delivered to their intended site of action. It is currently fundamental to make lead intensifies that are effectively consumed by the stomach, immediately conveyed to their planned site of activity, hard to change into unsafe metabolic items, and immediately discharged from the body prior to arriving at huge enough focuses. The ADMET properties of the compounds were examined for drug-like candidates.

3 Results &Discussion

Various pharmacophores of *Momordicacharantia* fruits have been listed through distinctive literature surveys and their pharmacokinetic and toxicological profile (ADMET properties) was analyzed/ viz. Swiss-ADME software and Pro-TOX II. The canonical smiles of all the pharmacophores of bael leaves listed are copied from PubChem and pasted into the Swiss ADME software and Pro-TOX II software one by

one to confirm their therapeutic efficacy and toxicity profile. The outcomes obtained from the studies were observed.

3.1 Protein Preparation and Active Site Identification

Different literatures study were reffered to select out the compounds which can have better effect on Oxidative Stressed Genes, that are associated with Alzheimer's disease (AD), and progressive neurodegenerative disorder. Around nine-teen compounds were selected for the study . With reference to literature review 38 phytocomponents from *Momordicacharantia* were taken as ligand for docking analysis. The ligand molecules with least binding energy are considered as compounds with highest binding affinity. The result shows that out of 38 phytocomponents , 5 phytocomponents shows high binding accuracy against Amyloid beta Protein(3NYL).

3.2 ADMET Analysis

Taking into account the equivalent Auto Dock Vina energy, collaboration energy and restricting energy, three mixtures were sent for ADMET investigation. These examinations depend on the ADMET (Assimilation, Appropriation, Digestion, Discharge and Poisonousness) properties of the mixtures. These properties give experiences in to the pharmacokinetic properties of the mixtures and were checked utilizing SWISS-ADME worked in ADMET convention. The different boundaries tried in this study were watery solvency, Blood Cerebrum Boundary (BBB) level, Hepatotoxicity, Assimilation level. Pharmacokinetic properties of the best fit phytochemicals showed that 19 of the mixtures had passed all the pharmacokinetic boundaries. These mixtures were consequently chosen as the best mixtures in this concentrate as they had great cooperation scores alongside ADMET properties.

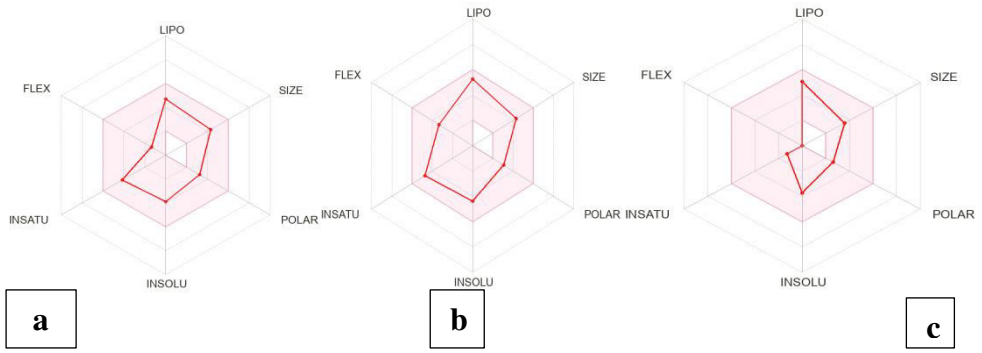

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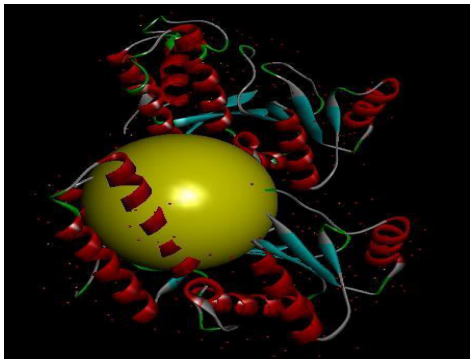
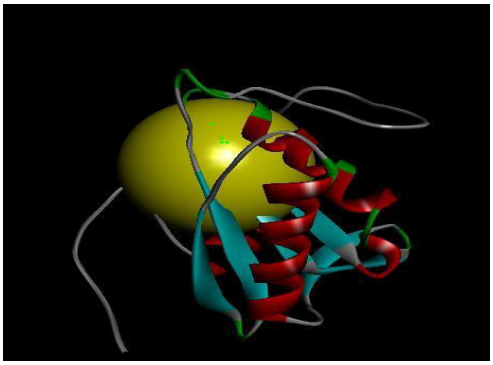
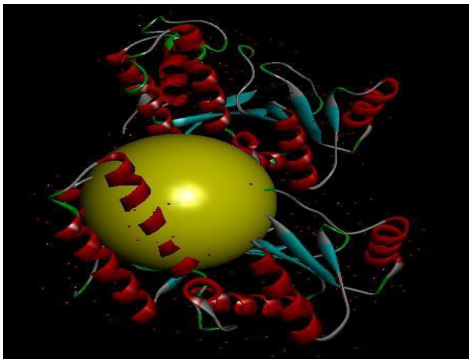
Figure 2: ADMET Analysis report of Best Bioavalibility lipophilic Phytocomponents : (a) Laurifolin – ADMET (b)gamma Isomorphine - ADMET (c) Armepavine - ADMET (d) 3-Epi-Schelhammericine –ADMET (e) Flabelline - ADMET

3.3 Prediction of binding sites and molecular docking analysis.

The active sites of Amyloid Beta Protein(3NYL) are Asn233, Glu313, Ile316, Pro410, Gln413, Try503, Gln508, Cys529, Asn533, and the grid box dimension value for this are ; X-36, Y-40 and Z-62.Out of these 38 phytocompounds, Laurifolin , gamma Isomorphine, Armepavine, 3-Epi-Schelhammericine and Flabelline were ranked the highest with binding scores ranging from –10.0 kcal/mol to –9.4 kcal/mol compared with the standard, Cholamide, with a binding score of –7.7 kcal/mol. From the results obtained, it can be concluded that Laurifolin , gamma Isomorphine, Armepavine, 3-Epi-Schelhammericine and Flabelline act against Alzheimer's disease inhibiting the Amyloid Beta Protein and therefore can be further developed into potent drugs for Alzheimer's disease treatment.







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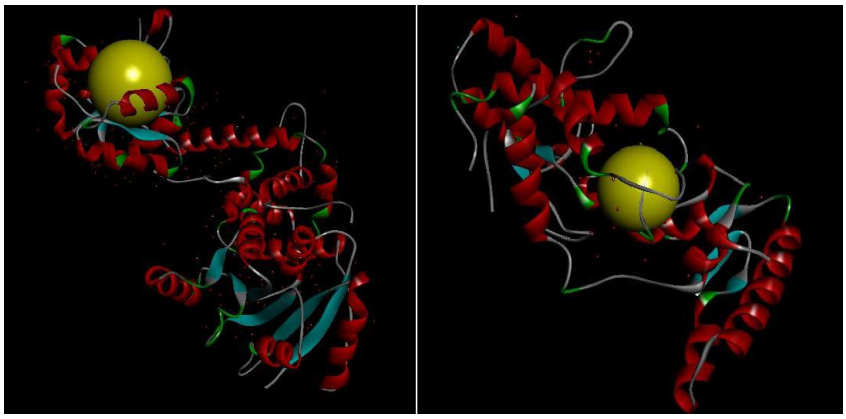

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Figure 3. Molecular 3d-Interaction of (a) Laurifolin – Amyloid Beta Protein (b)gamma Isomorphine - Amyloid Beta Protein (c) Armepavine - Amyloid Beta Protein (d) 3-Epi-Schelhammericine -Amyloid Beta Protein (e) Flabelline - Amyloid Beta Protein

4. Discussion:

Alzheimer`s disease (AD) is a progressive neurodegenerative disorder of the central nervous system that results in the gradual loss of memory and other cognitive capacities. Alzheimer`s disease is the most prominent cause of dementia1 and the sixth most prevalent cause of premature death worldwide. Only four drugs have been approved for AD therapy, and these only treat symptoms to improve patient quality of life, but do not stop the progression of the underlying neurodegenerative processes (2). Related theories include the mitochondrial theory of aging (6) , the cellular senescence theory of aging , and the molecular inflammation theory of aging(7). In all these theories, the accumulation of ROS-induced damage is posited as a potential mechanism leading to age related functional decline, failure of endogenous repair mechanisms, and neurodegenerative diseases, of which AD is the most common(8).Although there is a significant loss of forebrain cholinergic neurons and a steady decrease in acetylcholine, numerous distinct types of neurons degenerate as AD progresses (9). *Momordicacharantia* was chosen as the subject of the investigation due to its widespread use in traditional medicine systems as a remedy for a number of illnesses, including diabetes, eczema, kidney stones, gout, jaundice, piles, pneumonia, psoriasis, rheumatism, fever, and scabies.The characterization of anti-Neuronal compounds from *Momordicacharantia* with more potent Amyloid Beta Protein(APP) inhibitory activity could thus help provide an excellent therapeutic option against Neurodegenerative disease like Alzheimer`s .In-silico molecular docking analysis of phytoconstituents present in *Momordicacharantia* was studied against Amyloid beta

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