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In Silico Screening and Identification of Phytoconstituents for Alzheimer's Disease

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Abstract: Cognitive decline and neuronal degradation are hallmarks of Alzheimer's disease (AD), a progressive neurodegenerative illness. There are currently few therapy options for the buildup of tau tangles and amyloid-beta plaques, which are important pathological hallmarks. Through antioxidant, anti-inflammatory, and neuroprotective processes, phytoconstituent; bioactive substances derived from plants—have demonstrated promising role in slowing the course of AD.

The current research work is about Identification of natural components useful in Alzheimer's disease. Using *in silico* techniques. Swiss Dock was used for molecular docking investigations. The various steps included analysis of the binding affinities of specific phytoconstituent with important AD targets, such as tau protein, beta-secretase (BACE1), amyloid-beta, and acetylcholinesterase (Ache), using Auto Dock and Glide software. According to the findings, natural substances like Quercetin, Resveratrol, and Curcumin showed potent binding interactions with AD-related targets, indicating natural inhibitory properties. Docking scores were used to evaluate binding affinities, and interaction analysis showed strong hydrophobic and hydrogen bonding interactions.

Further, *in vitro and in vivo* validation is needed. The study emphasizes how computational screening can speed up the process of finding new drugs for neurodegenerative illnesses.

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I. INTRODUCTION

Alzheimer's disease is a degenerative neurological disorder that affects memory, conduct, and thought processes. It is the most common cause of dementia, a general term for cognitive deterioration that affects daily functioning. Alzheimer's disease is characterised by the build-up of abnormal protein deposits in the brain, such as beta-amyloid plaques and tau tangles, which result in the death of brain cells. As the symptoms gradually worsen from mild confusion and memory loss, they also impact language, problem-solving, and even basic bodily functions. Although there is currently no known cure, medications may be able to manage symptoms and slow the progression of the illness in certain cases.

There are many approaches for the treatment of disease. The cornerstone of contemporary pharmaceutical treatments includes cholinesterase inhibitors like donepezil and rivastigmine which are designed to reduce symptoms but do not halt the disease's progression and often have adverse consequences. Consequently, there is growing interest in exploring phytoconstituents as potential AD therapeutic agents. Phytoconstituent derived from plants have demonstrated a variety of neuroprotective properties, including anti-inflammatory, antioxidant, and cholinergic actions.

- *Phytoconstituent in Alzheimer's Disease*

Phyto constituents are bioactive compounds derived from plants. The main ingredient in turmeric, curcumin, has potent anti-inflammatory and antioxidant qualities. Its potential advantages in treating diseases like cancer, heart disease, arthritis has been reported along with its activity in neurological illnesses like Alzheimer's disease.

In addition to curcumin, Resveratrol, Berberine, Naringenin, Quercetin, Caffeine, Kaempferol, Piperine, and Luteolin are some of agents that reduce oxidative stress, and stop the formation of amyloid plaque. (Anand et al., 2014) (Gupta et al., 2013) (Mani & Venkatesan, 2019). The various molecules with their molecular structures are given in table 1.

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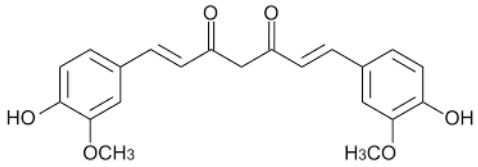
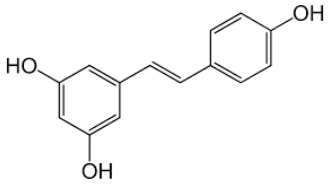
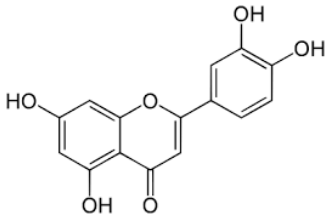
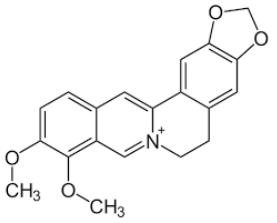
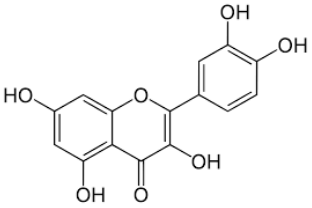
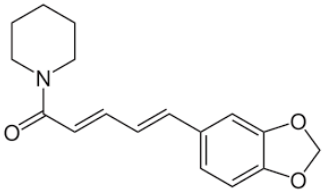
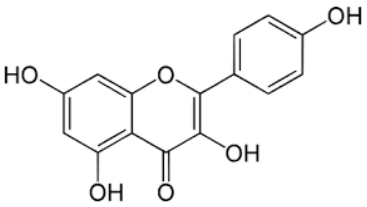
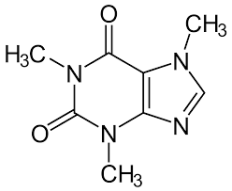
Table 1 Phytoconstituent and their Molecular Structure

 CURCUMIN	 RESVERATROL
 LUTEOLIN	 NARINGENIN
 QUERCETIN	 BERBERINE
 KAEMPFEROL	 CAFFEINE

The discussion of the properties, sources and biological action of the components used for docking in the current research work.

➢ *Curcumin*

Curcumin's though a bioactive molecule has limited bioavailability. It is frequently taken with black pepper or fat piperine to improve absorption. Supplements containing curcumin are easily accessible, however dosages should be closely watched because excessive amounts may cause stomach problems or interfere with prescription medications. It prevents the development and buildup of β-amyloid plaque. reduces neuroinflammation and oxidative stress. improves amyloid-beta autophagic clearance. (Gupta et al., 2013) This mechanism of action has proved it as a potential agent for treatment of AD.

➢ *Resveratrol*

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a stilbenoid, a type of natural phenol or polyphenol obtained from various plant sources. Red grapes, berries, and peanuts are natural sources of resveratrol. Red wine, blueberries, cranberries, mulberries, peanuts, pistachios, and Japanese knotweed are all good sources of resveratrol. It has anti-aging, anti-inflammatory and antioxidant properties. It aids in combating inflammation and oxidative stress, which lead to chronic illnesses and ageing.

➢ *Berberine*

Berberine is a naturally occurring alkaloid found in a variety of plants, including Oregon grape, berberis, and goldenseal. Because of its antibacterial, anti-inflammatory, and metabolic properties, it has been utilised for a long time in Ayurvedic and traditional Chinese medicine. Berberine's health benefits include Blood Sugar Regulation It acts by increasing insulin sensitivity and decreasing the liver's synthesis of glucose. It is frequently compared to metformin in terms of its efficacy.

➢ *Naringenin*

Citrus fruits, such as tomatoes, oranges, and grapefruits, contain the flavonoid naringenin. It also has strong anti-inflammatory, antioxidant, and metabolic advantages Research is being done on how it affects liver function, heart health, and metabolic problems.

It lowers bad cholesterol (LDL), raises good cholesterol (HDL), and reduces blood pressure. It is also beneficial in preventing non-alcoholic fatty liver disease (NAFLD). By activating AMPK, a crucial regulator of energy balance, it increases metabolism and decreases fat storage and hence useful in Weight management. It prevents inflammation and oxidative stress in cells, potentially reducing the incidence of chronic illnesses. By lowering oxidative stress in the brain, it may help prevent Parkinson's and Alzheimer's diseases. (Anand et al., 2014) as well.

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➢ *Quercetin*

Green tea, onions, and apples all contain quercetin, a kind of flavonoid. Its immune-stimulating, anti-inflammatory, and antioxidant qualities are widely established. It helps in lowering the risk of diseases including cancer and heart disease by combating oxidative damage and chronic inflammation. Immune support helps prevent viral infections and boosts the immune system. It is commonly utilised in in addition to zinc to boost antiviral activity. It reduces the symptoms of asthma, hay fever, and other allergic reactions by acting as a natural antihistamine. It is reported to control blood sugar levels and increases insulin sensitivity.

➢ *Caffeine*

Caffeine is a xanthine derivative found in tea and coffee. It is a naturally occurring stimulant, which acts on the central nervous system by inhibiting the brain's adenosine receptors. Increased energy and alertness are among the impacts of caffeine. It elevates adrenaline levels, which improves physical performance and focus and cognitive function. Overuse may cause anxiety, insomnia, or other symptoms.

➢ *Kaempferol*

Berries, spinach, and broccoli all contain kaempferol; a naturally occurring flavonoid. It possesses potent anti-inflammatory, anti-cancer, and antioxidant qualities. Antioxidant qualities: lessen cell damage and oxidative stress. Anti-inflammatory properties: These could reduce the risk of developing chronic illnesses. Possible effects against cancer: Research indicates that it could help avoid preventing the growth of cancer cells. Heart health: Associated with better circulation and reduced blood pressure. potential protection against neurodegenerative illnesses.

➢ *Piperine*

Black pepper, or piperine, increases the bioavailability of other phytoconstituents. Black pepper (Piper nigrum) contains a bioactive component called piperine, which gives it its strong taste. It may offer health benefits and is well known for improving nutrient absorption.

It aids in lowering oxidative stress and inflammation. It may enhance gut health by triggering digestive enzymes. Research indicates that it could increase metabolism of the body and the rate at which fat is broken down.

Natural flavonoids like luteolin can be found in a wide variety of fruits, vegetables, and medicinal plants. It possesses potent neuroprotective, anti-inflammatory, and antioxidant qualities. One of the benefits of antioxidants is that they shield cells from oxidative damage. Its anti-inflammatory properties may be beneficial for autoimmune disorders and chronic inflammation. It is also known to have advantages in Parkinson's and Alzheimer's diseases. Studies have also indicated that it might stop the growth of cancer cells.

Antioxidant activity reduces oxidative stress, which is a major contributor to Alzheimer's disease. The compounds known as antioxidants aid in protecting cells from the harm that these free radicals can do. They work by eliminating free radicals before they have an opportunity to cause harm. Antioxidants are found in strawberries, bell peppers, and citrus fruits. Vitamin E is found in spinach, nuts, and seeds. Beta-carotene is obtained from dark leafy greens, sweet potatoes, and carrots. Good sources of selenium include whole grains, salmon, and Brazil nuts. Polyphenols can be found in tea, coffee, dark chocolate, and berries. Their ability to reduce oxidative stress, slow down ageing, strengthen the immune system, and lessen the risk of chronic diseases like cancer and heart disease. This also reduces the chance of neurodegeneration and improve brain function. (Anand et al., 2014)

Anti-inflammatory effects: Chronic inflammation can be harmful, thus anti-inflammatory foods and behaviours can improve overall health.

By preventing neuroinflammation, brain cells are preserved. Anti-inflammatory agents can reduce inflammation, which is linked to heart disease, arthritis, and autoimmune illnesses Natural anti-inflammatory foods include fruits such as grapes, oranges, cherries, and berries (high in polyphenols and antioxidants). Vegetables include bell peppers, broccoli, and leafy greens like spinach and kale. Nuts (walnuts, almonds), avocados, and olive oil are good sources of healthy fats. Omega-3 fatty acids are abundant in fatty fish, such as salmon, mackerel, and sardines. Spices and Herbs: cinnamon, ginger, garlic, and turmeric (curcumin). Polyphenols found in green tea have anti-inflammatory properties. (Gupta et al., 2013)

One of the most important methods for controlling and preventing Alzheimer's disease (AD) and other neurodegenerative diseases is to limit the buildup of amyloid beta (Aβ). A protein called amyloid beta can misfold and create plaques in the brain, which can harm neurons and impair cognitive function.

Aβ synthesis may be decreased or its clearance may be improved by some antioxidants and anti-inflammatory substances: Turmeric's curcumin possesses anti-inflammatory and Aβ aggregation-reducing qualities. EGCG (found in green tea) helps stop Aβ from misfolding and encourages its breakdown, whereas resveratrol (found in red grapes, red wine, and peanuts) improves Aβ clearance by autophagy. Omega-3 fatty acids (found in flaxseeds and fatty fishlike salmon) may lessen inflammation and Aβ accumulation. Besides, Beta-secretase (BACE) inhibitors is a group of drugs which prevent the production of Aβ by blocking the enzyme. (Anand et al., 2014) (Gupta et al., 2013)

➢ *Target Identification*

Acetylcholine (Ach), a neurotransmitter necessary for memory, learning, muscle contraction, and autonomic nervous system function, is broken down by the enzyme Acetylcholinesterase (Ache). Raising Ach levels, inhibiting Ache improves muscular control and cognitive performance. The various approaches for significant antialzeihmer effect are discussed here.

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Ache inhibitors increase the amount of Ache accessible in synapses by preventing its breakdown. They are used to improve cognitive function, treat myasthenia gravis, and treat Alzheimer's disease. pharmaceutical inhibitors of ache. Alzheimer's disease is frequently treated with donepezil (Aricept). Both Parkinson's and Alzheimer's dementia are treated with rivastigmine (Exelon). Galantamine (Raza dyne) also modulates nicotinic receptors for additional cognitive benefits. Pyridostigmine (Martinon) used for myasthenia gravis, a condition affecting muscle strength.

Natural & Dietary Beta-Secretase: Some natural compounds may help reduce amyloid beta formation indirectly. These include Curcumin (Turmeric) which possess Anti-amyloid and anti-inflammatory properties. Resveratrol (Red Grapes, Wine, Peanuts) that promotes amyloid clearance. Green Tea (EGCG) which reduces Aβ aggregation and may modulate secretase activity. Omega-3 fatty acids (Fish Oil, Flaxseed) which supports brain health and reduces neuroinflammation. (Anand et al., 2014) (Gupta et al., 2013). Amyloid-beta (Aβ) Aggregates cause neurotoxicity. Compounds preventing aggregation are beneficial in neurodegeneration. Amyloid beta (Aβ) is a protein fragment derived from the amyloid precursor protein (APP). It is normally cleared from the brain, but in Alzheimer's disease (AD) and other neurodegenerative conditions, it accumulates to form plaques that contribute to neuronal damage, inflammation, and cognitive decline. Strategies to Reduce Amyloid Beta Accumulation include BACE Inhibitors, Gamma-Secretase Modulators and other approaches as discussed below:

BACE Inhibitors – Block beta-secretase to reduce Aβ production. (E.g. Lanabecestat—trials discontinued due to side effects).

Gamma-Secretase Modulators – Reduce toxic Aβ42 formation while preserving other essential functions of APP. Monoclonal antibodies help clear amyloid plaques from the brain: Aducanumab (Adu helm) is one such monoclonal antibody which is FDA approved but controversial.

Tau is a microtubule-associated protein that aids in maintaining the stability of neuron cytoskeletons. Tau normally maintains neuronal structure and intracellular trafficking. However, tau experiences hyperphosphorylation in neurodegenerative illnesses including Alzheimer's disease (AD) and other tauopathies, resulting in neurofibrillary tangles (NFTs) that impair neuronal function.

Despite being the most widely accepted explanation, the cholinergic hypotheses failed to offer any AD asymptomatic therapy. The "Glutamatergic and Excitotoxic hypothesis," which asserts that glutamate-mediated neurotoxicity plays a role in the pathophysiology of AD, was another theory put forth.

The primary focus of earlier research on tau protein, beta-secretase (BACE1), amyloid-beta (Aβ) aggregates, acetylcholinesterase (Ache), and receptors was NR. However, receptor Amyloid-beta (Aβ) aggregates, tau, beta-secretase (BACE1), and acetylcholinesterase (Ache) protein receptors are heterotetrametric complexes composed of two necessary NR1 subunits and two NR2 subunits that can form a dimer alone or in combination with one NR2 or NR3 subunit. The NR1 subunit contains a glycine binding site, and receptors for tau protein, beta-secretase (BACE1), acetylcholinesterase (Ache), and amyloid-beta (Aβ) aggregates have several modulatory sites. The tau Protein also has a glutamate binding site, and the receptors have allosteric sites on the amino-terminal domain and a binding site at channel blockers. Each of these distinct receptor binding sites permits a variety of allosteric interactions with distinct ligands. Recently, focus has been done on creating antagonists targeting the subunits, which are also an essential component of tau protein, receptor complex, beta-secretase (BACE1), amyloid-beta (Aβ) aggregates, and tetra acetylcholinesterase (Ache) due to the negative effects they are associated with.

By blocking receptor-mediated acetylcholinesterase (Ache), beta-secretase (BACE1), amyloid-beta (Aβ), and the NR1 subunit from becoming phosphorylated aggregates, tau protein, and beta-secretase (BACE1), curcumin was found to reduce the toxicity of these enzymes.

Another study found that in genetically epilepsy-prone DBA/2 mice, the aqueous extract of P. nigrum L. reduced the amplitude of Acetylcholinesterase (Ache), Beta-secretase (BACE1), Amyloid-beta (Aβ) Aggregates, tau Protein, and receptors depolarization, indicating an antagonist activity at race. Beta-secretase (BACE1), tau protein, receptors, amyloid-beta (Aβ) aggregates, and acetylcholinesterase (Ache).

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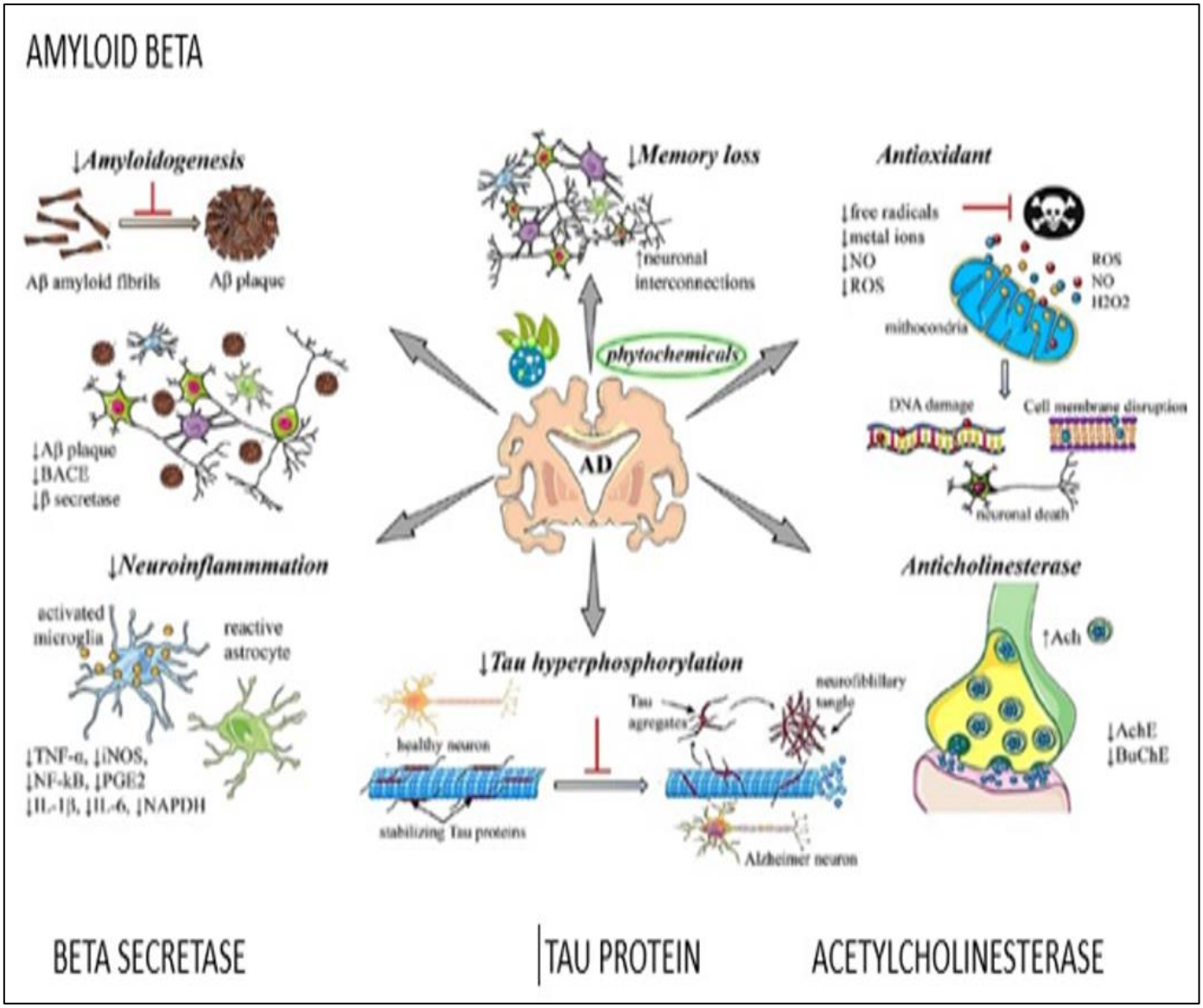

Fig 1 Target Identification for Anti-Alzheimer Activity

The following table summarizes the target identification for the mentioned proteins.

Table 2 Target Protein and Therapeutic Strategy in AD

Target Protein	Role in Disease	Function	Therapeutic Strategy	Examples of Inhibitors/Modulators
Acetylcholinesterase (Ache)	caused by a cholinergic deficiency in Alzheimer's disease	Breaks down acetylcholine	Inhibition to increase acetylcholine levels	Donepezil, Rivastigmine, Galantamine
Beta-Secretase (BACE1)	Causes Alzheimer's disease by starting the development of amyloid-beta plaques.	Cleaves amyloid precursor protein (APP)	Inhibition to reduce amyloid-beta production	Lanabecestat
Amyloid Beta (Aβ)	Builds up in the brain, causing Alzheimer's disease neurodegeneration.	A peptide that aggregates into plaques	Immunotherapy, clearance enhancement	Aducanumab,
Tau Protein	In Alzheimer's disease and other tauopathies, hyperphosphorylation results in neurofibrillary tangles.	Microtubule-associated protein	Inhibition of aggregation, stabilization of microtubules	Anti-tau antibodies, Seminoma

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➢ *Molecular Docking Approach:*

Molecular docking, a computer technique that forecasts the binding interactions between small molecules (ligands) and target proteins, is a crucial tool in drug discovery and development. It provides crucial details regarding molecular recognition, receptor-ligand interactions, and the potential therapeutic efficacy of drug candidates. One advantage of molecular docking is its ability to screen large chemical libraries quickly, which significantly reduces the time and cost associated with more traditional drug development methods. The technique of docking is used to perform Lead Optimization where phytochemicals with the greatest promise for additional development or modification are determined. (Anand et al., 2014) (Bukhari et al., 2015) (Fadaka et al., 2020)

Before moving on to experimental validation, researchers can rank the most promising drug candidates according to its accurate predictions of binding affinities and interaction processes. By evaluating the ability of current medications to bind to new targets, the method also speeds up the discovery of new therapeutic uses and aids in drug repurposing. Additionally, by allowing ligand structure alterations to enhance binding affinity and specificity, molecular docking supports structure-based drug design and optimizes medication efficacy. Molecular docking has some drawbacks despite its many benefits. Its dependence on static structures is one of its main drawbacks since it assumes that the receptor and ligand are rigid or semi-flexible, which may not adequately capture the dynamic character of biomolecular interactions under physiological conditions. Furthermore, docking techniques frequently oversimplify entropic contributions and solvation effects, which could result in inaccurate binding energy estimations. The reliance on the quality of the protein and ligand structures, where mistakes in homology-modeled or crystallographic structures might affect docking accuracy, is another drawback. Furthermore, molecular docking is not always able to differentiate between genuine biological binding and nonspecific interactions, requiring additional verification via experimental tests or molecular dynamics simulations. Molecular docking is widely used in many areas of structural biology and pharmacological research. By finding lead compounds for therapeutic targets like enzymes, receptors, and ion channels, it serves a critical role in drug discovery. Drug repurposing shortens development timeframes by assessing the potential of licensed medications for different uses. By clarifying ligand-receptor interactions in sick situations, molecular docking is also used to understand disease causes and assist in the development of targeted therapeutics. (Bukhari et al., 2015) (Goyal et al., 2017)

➢ *Software Used for Molecular Docking:*

Flexible docking with effective scoring features is provided by Auto Dock & Auto Dock Vina. Two popular molecular docking algorithms, Auto Dock and Auto Dock Vina, are made to anticipate how ligands, or tiny molecules, would attach to receptors, which are typically proteins. They are mostly employed to screen possible drug candidates in computational chemistry and drug discovery. More customizable than Vina, Auto Dock was created by Scripps Research and uses the Lamarckian Genetic Algorithm (LGA) for docking. It requires pre-calculated grid maps for docking computations. The iterated local search global optimizer of Auto Dock Vina, a more recent version of Auto Dock, is frequently 10–100 times faster than Auto Dock. Automatic scoring and search space configuration make it easier to use; it's a little less customizable, but it often yields better accuracy.

Molecular Operating Environment (MOE) (easy-to-use molecular modeling and docking) Chemical Computing Group (CCG) created MOE, a comprehensive drug discovery and molecular modeling program. For applications like molecular docking, virtual screening, and structure-based drug design, it is extensively utilized in computational chemistry, bioinformatics, and structural biology. The various tools and methods used are:

- Molecular Docking & Virtual Screening: This tool facilitates ligand-protein docking, offers adaptable docking methods, and integrates scoring features for predicting binding affinity.
- Energy minimization and conformational analysis, molecular dynamics simulations for stability evaluation, and molecular dynamics simulations 3. Pharmacophore modeling, which identifies important chemical characteristics for a medication creates three-dimensional pharmacophore models.
- Quantitative Structure-Activity Relationship (QSAR) models are built using QSAR and ADMET predictions. Forecasts qualities related to absorption, distribution, metabolism, excretion, and toxicity (ADMET)
- Homology Modelling: Refines and models loops, constructs protein structures from sequences.
- Molecular databases and cheminformatics, overseas chemical libraries, supports ligand-based design, and 2D/3D visualization. Advanced scoring and high-precision docking are features of Glide (Schrödinger Suite).

Schrödinger Inc. created Glide, a molecular docking tool that is frequently used in structure-based drug development to accurately anticipate ligand-receptor interactions. It is renowned for its speed, accuracy, and sophisticated scoring features and is a component of Schrödinger's Maestro package.

Swiss Dock is a web-based, free molecular docking application that facilitates rapid docking. Swiss Dock is a free online molecular docking application developed by the Swiss Institute of Bioinformatics (SIB). Auto Dock, its cornerstone, allows ligand-receptor docking without requiring software installation. It is widely used in drug discovery, virtual screening, and molecular interaction studies.

Steps in Molecular Docking: The various steps in docking involves the following steps:

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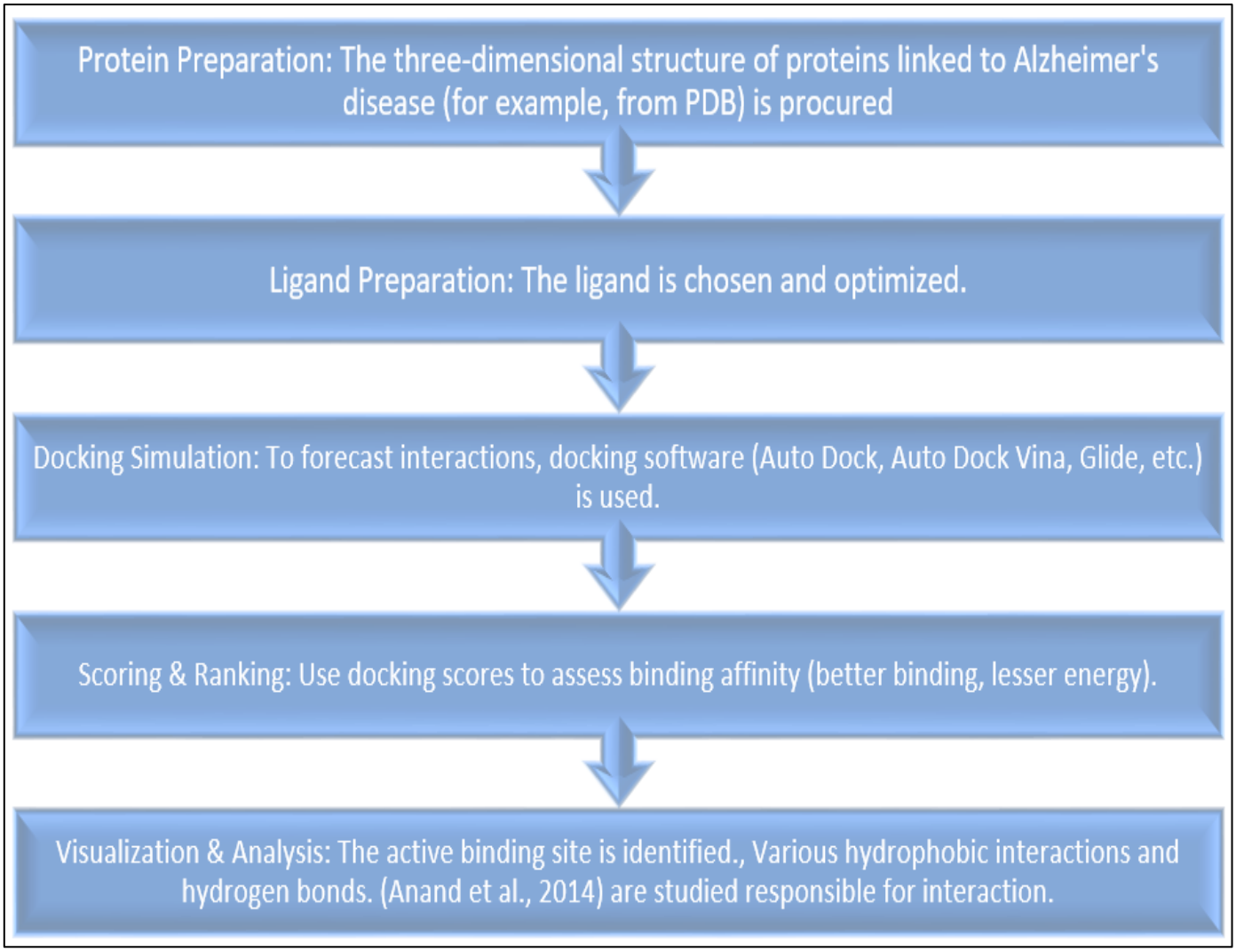

Fig 2 Steps in Docking

II. MATERIALS & METHODS

The current study discovers phytoconstituent that have the ability to bind to key Alzheimer's disease locations and helps in identification of produce natural inhibitors of the enzymes responsible for the development of disease. An Intel® Court i7 3770 CPU running Windows 8 Pro was used for a molecular docking experiment using the Glide (Grid-based Ligand Docking with Energetics) application. Numerous ligand conformations were created by preserving the flexibility of the ligand structure. More precise docking was then done using the receptor protein that had been produced. Force fields from Optimised Potential for Liquid Simulations were used in these calculations. Every result was examined using XP Visualise. Molecular docking was used thoroughly to examine the phytoconstituent molecular interactions and binding affinities with the NMDA receptor Acetylcholinesterase (Ache), Beta-secretase (BACE1), Amyloid-beta (Aβ), and Tau Protein, which inhibits tau protein and forms neurofibrillary tangles.

➢ *Screening, Retrieval, and Preparation of Ligands*

About nine phytoconstituent were selected based on the literature review. These included curcumin, resveratrol, berberine, naringenin, quercetin, caffeine, kaempferol, piperine, and luteolin. The phytoconstituents' two- or three-dimensional structures were obtained in.sdf format from the National Centre for Biotechnology Information's PubChem chemicals database. Swiss dock tool software was used to prepare the ligands by standardizing their geometry, neutralizing any charged groups, adding missing hydrogen atoms, and creating tautomer and ionized states at pH 7.0 ± 2.0. (Gupta et al., 2013)

➢ *Pharmacokinetic Parameters:*

In order to determine whether the top lead phytoconstituents could be administered orally to the human body, their pharmacokinetic characteristics were also examined using Lipinski's rule of five. According to the rule, the chemical must have an octanol-water partition coefficient log P of less than 5, a hydrogen donor of less than 5, a hydrogen acceptor of less than 10, and a molecular weight of less than 500 Daltons. According to the study, only two phytoconstituents—p-coumaric acid and caffeic acid—broke the rule. Even though they were still adhering to Lipinski's rule of five, which states that a drug intended for oral formulation should have no more than one transgression, their octanol-water partition coefficient was higher than five.

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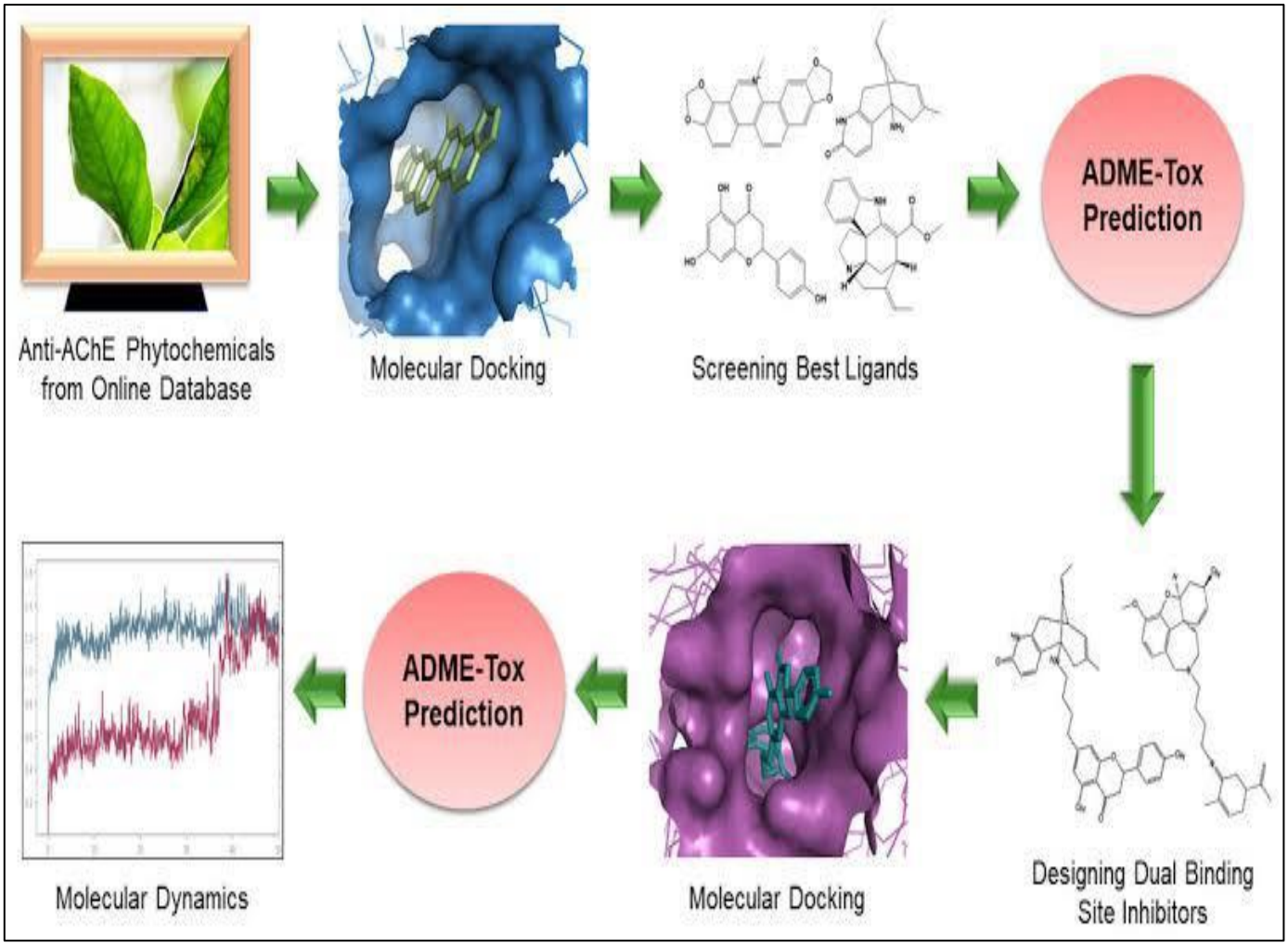

Fig 3 Parameters in Silico Screening and Identification of Phytoconstituents for Alzheimer's Disease. (Anand et al., 2014)

III. METHODOLOGY

Swiss Dock, an online molecular docking program that forecasts how small chemicals (ligands) will attach to target proteins, is based on the EADock DSS algorithm. The detailed process for using Swiss Dock to screen phytoconstituents for Alzheimer's disease in silico is shown below. 1**. Database Search for Phytoconstituent Selection**: Databases such as PubChem, ChEBI, IMPPAT, or literature reviews were used to find bioactive phytoconstituents from therapeutic plants that have neuroprotective properties.

- **Preparation of Compounds to get the 3D structure from PubChem** or Chermside in either SDF or MOL format. Use of Avogadro, Pymol, and Open Babel is done to convert to required PDB format. For optimization, Avogadro or Chem3D is used to reduce energy and optimize the ligand structure. (Anand et al., 2014) (Bukhari et al., 2015**)**

- **Swiss Docking for Molecular Docking:** The target protein and ligand is uploaded on Swiss Dock. The docking mode is set to accurate. The docking process is launched. Depending on its complexity, it could take several minutes to several hours. For analysis, retrieve the docking results in PDB format. (Bukhari et al., 2015)

- **Examination of Docking Outcomes Ranking and Scoring**: The binding free energy (ΔG in kcal/mol) is identified. Higher binding is indicated by lower values. To check binding postures and interactions, Discovery Studio, PyMOL, or Chimaera is used. The ligand-protein π-π stacking, hydrophobic interactions, and hydrogen bonds is determined.

- **Choosing Possible Lead Compounds**: The phytoconstituent that rank highest based on their strong docking score and high binding affinity, favourable ADMET characteristics (excellent BBB permeability, low toxicity) and strong contact and hydrogen bonding with the target protein for AD is chosen.

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IV. RESULT

Table 3 Docking Score

S.NO	Ligand	Protein	Docking Score
1A	Curcumin	Beta sectetare1	12.263
B		Acetylcholinesterase	-5.889
C		Amyloid beta	-6.747
D		Tau protein	-6.137
2A	Resveratrol	Beta secretase 1	-5.846
B		Acetylcholinesterase	-6.609
C		Amyloid beta	**-7.884**
D		Tau protein	-5.549
3A	Luteolin	Beta secretase 1	-6.549
B		Acetylcholinesterase	34.616
C		Amyloid beta	**-8.805**
D		Tau protein	-3.627
4A	Berberine	Beta secretase 1	-6.07
B		Acetylcholinesterase	64.487
C		Amyloid beta	**-6.862**
D		Tau protein	-4.216
5A	Naringenin	Beta secretase 1	-6.541
B		Acetylcholinesterase	-5.73
C		Amyloid beta	-6.31
D		Tau protein	**-7.182**
6A	Quercetin	Beta secretare1	-6.122
B		Acetylcholinesterase	-6.227
C		Amyloid beta	-6.602
D		Tau protein	**-7.42**
7A	Piperine	Beta secretase 1	-6.32
B		Acetylcholinesterase	-6.048
C		Amyloid beta	-6.321
D		Tau protein	**-6.915**
8A	Kaempferol	Beta secretase 1	-6.018
B		Acetylcholinesterase	-6.162
C		Amyloid beta	**-9.083**
D		Tau protein	-7.176
9A	Caffeine	Beta secretase 1	-4.94
B		Acetylcholinesterase	-4.671
C		Amyloid beta	-4.638
D		Tau protein	**-4.737**

After selecting the top five leads, their ADMET attributes were examined in further detail. Kaempferol exhibited highest glide score followed by luteolin.

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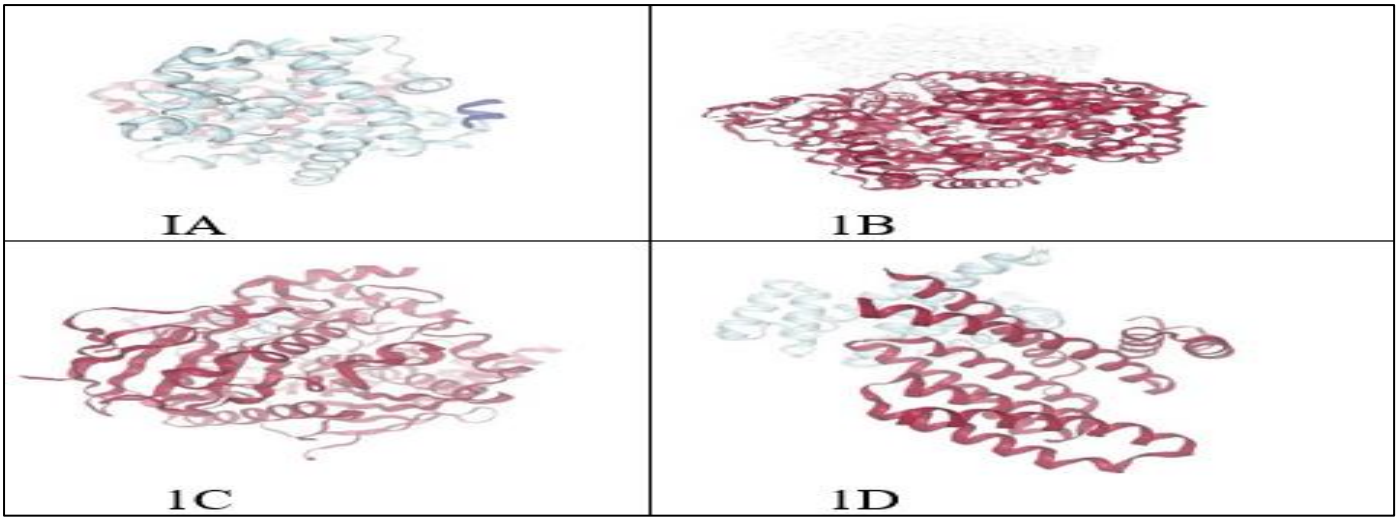

Fig 4 Ligand Protein Binding of Curcumin (Gupta et al., 2013)

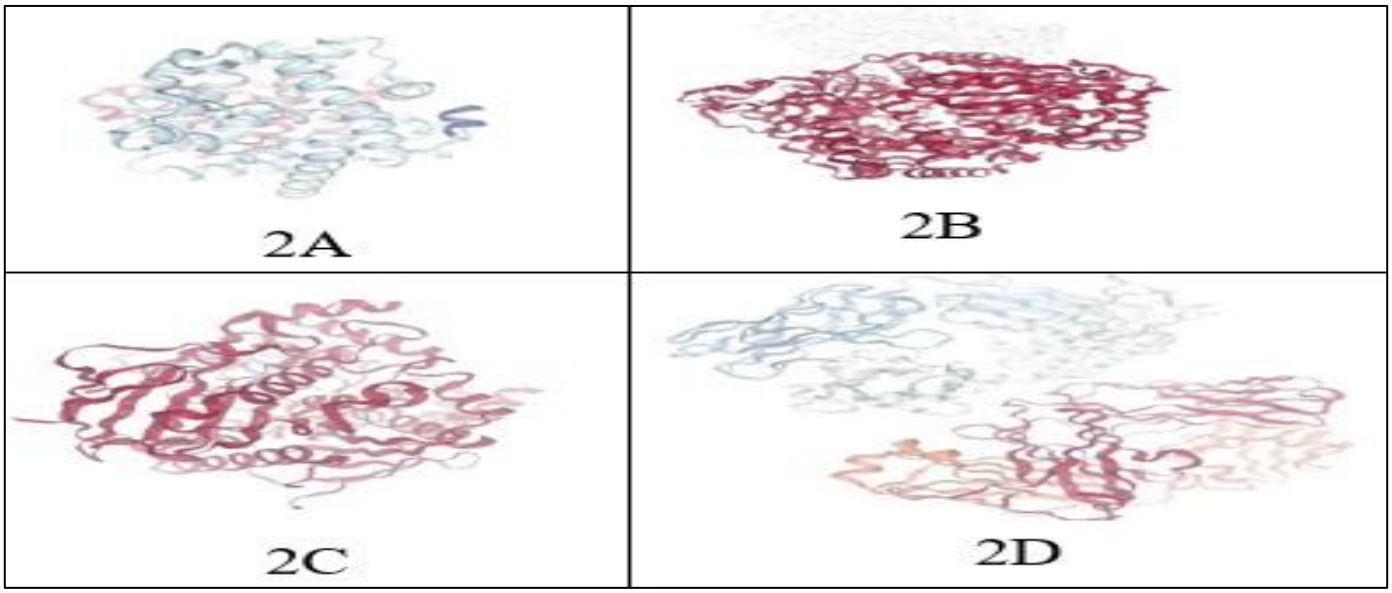

Fig 5 Ligand Protein Binding of Resveratrol

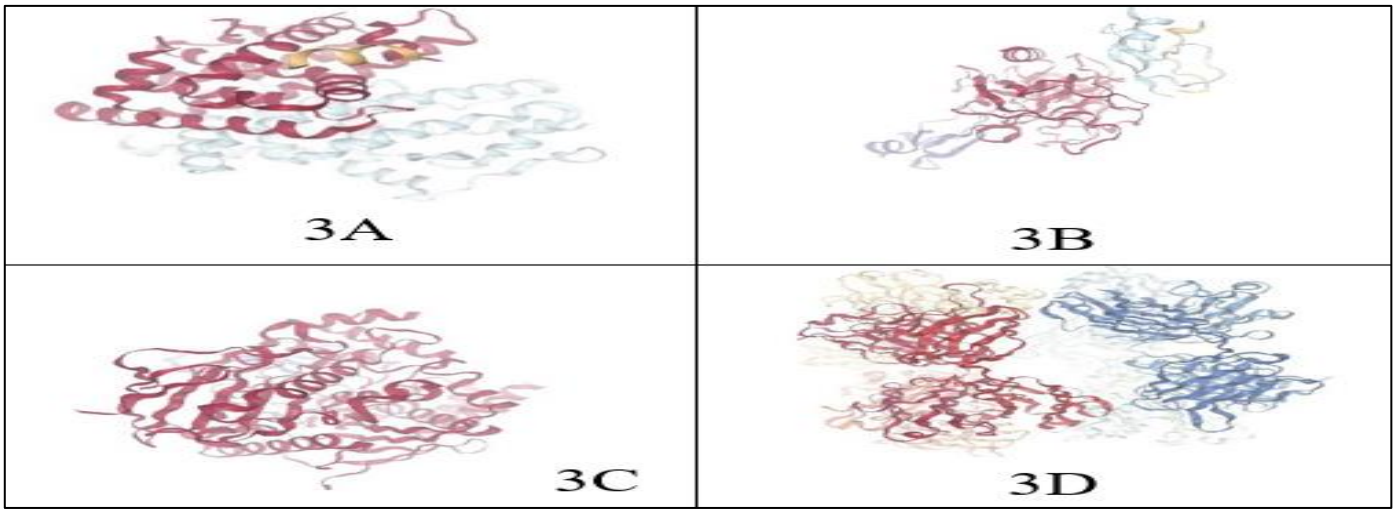

Fig 6 Ligand Protein Binding of Luteolin

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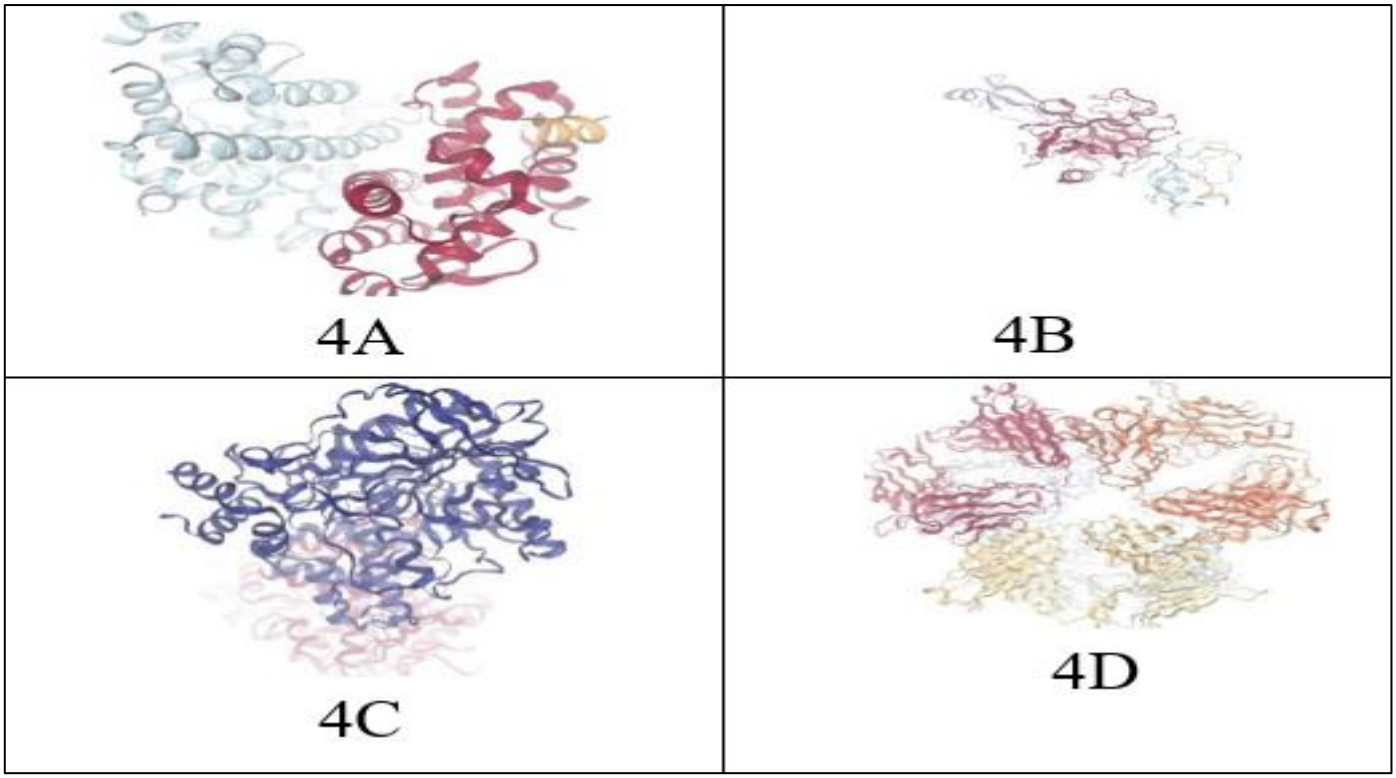

Fig 7 Protein Ligand Binding of Berberine

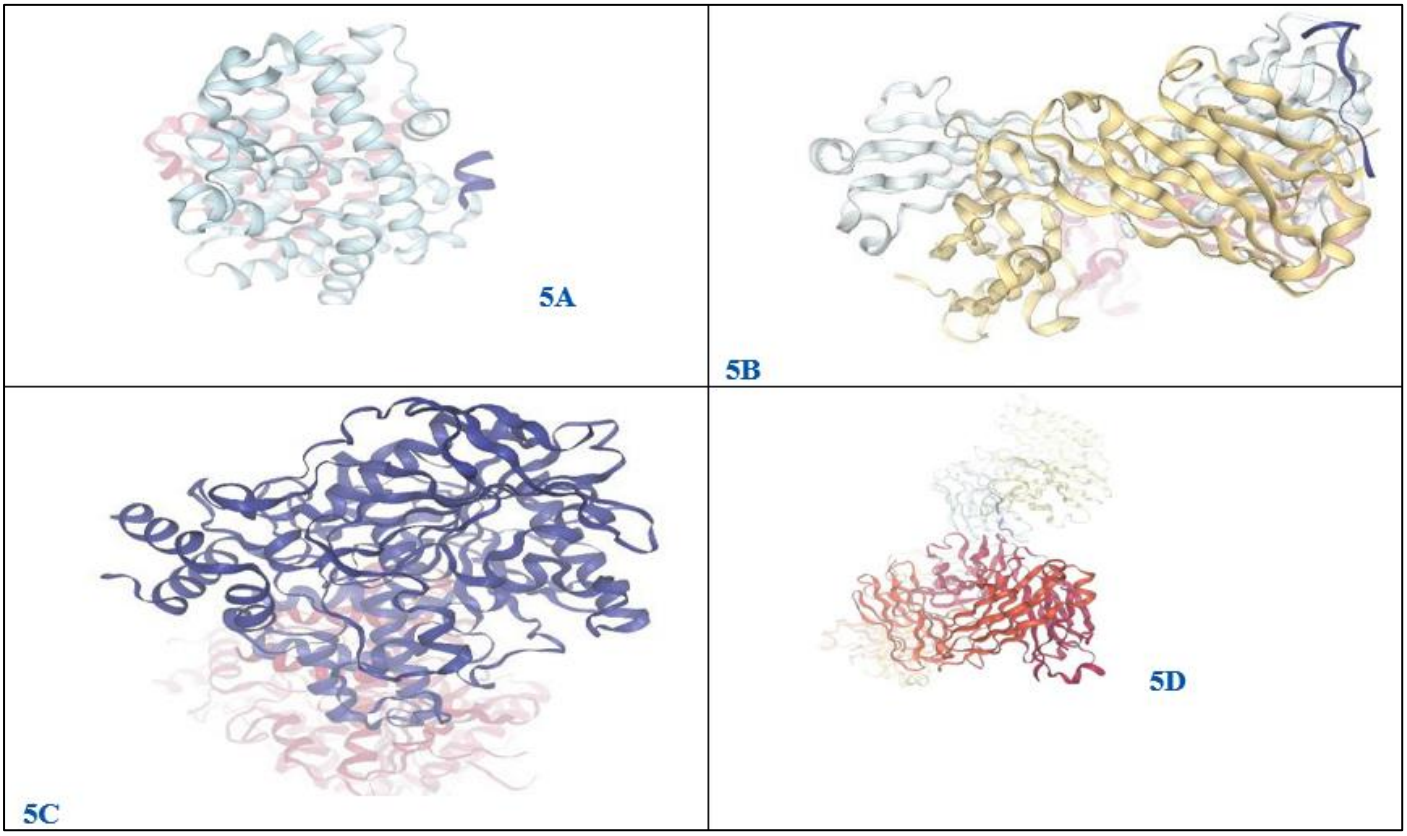

Fig 8 Ligand Protein Binding of Naringenin

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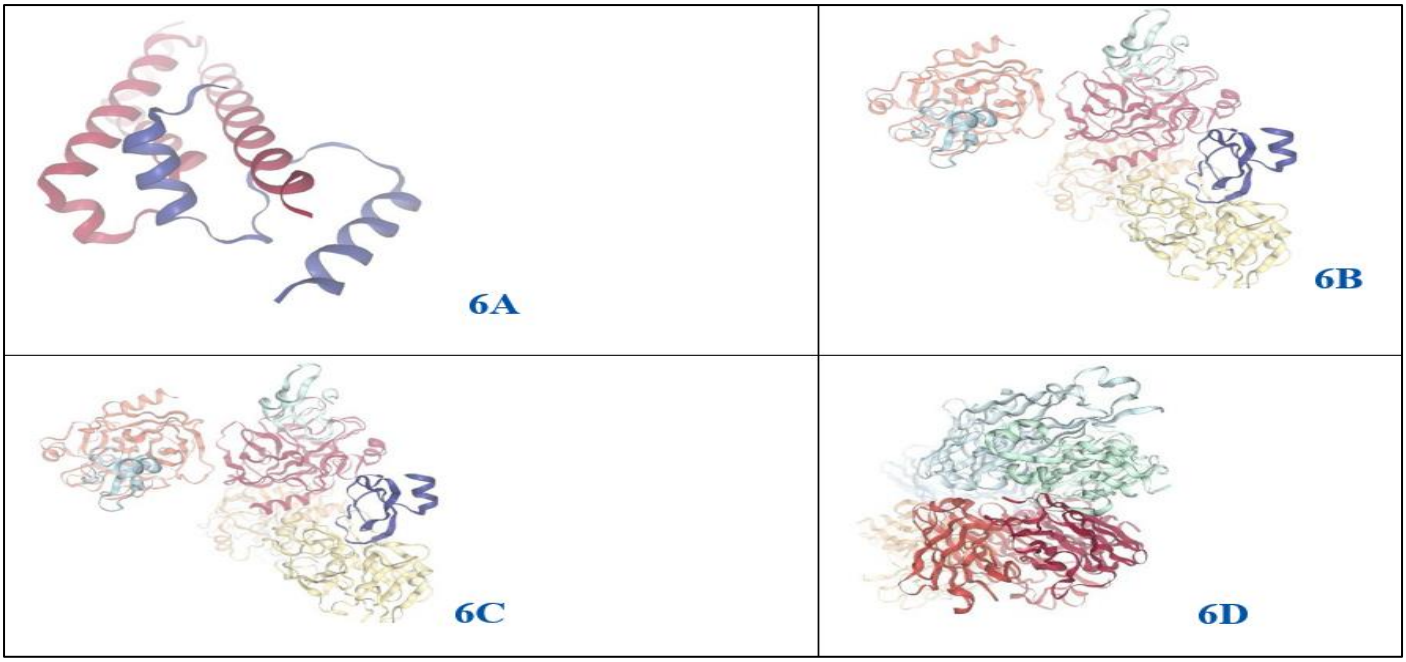

Fig 9 Ligand protein Binding of Quercetin

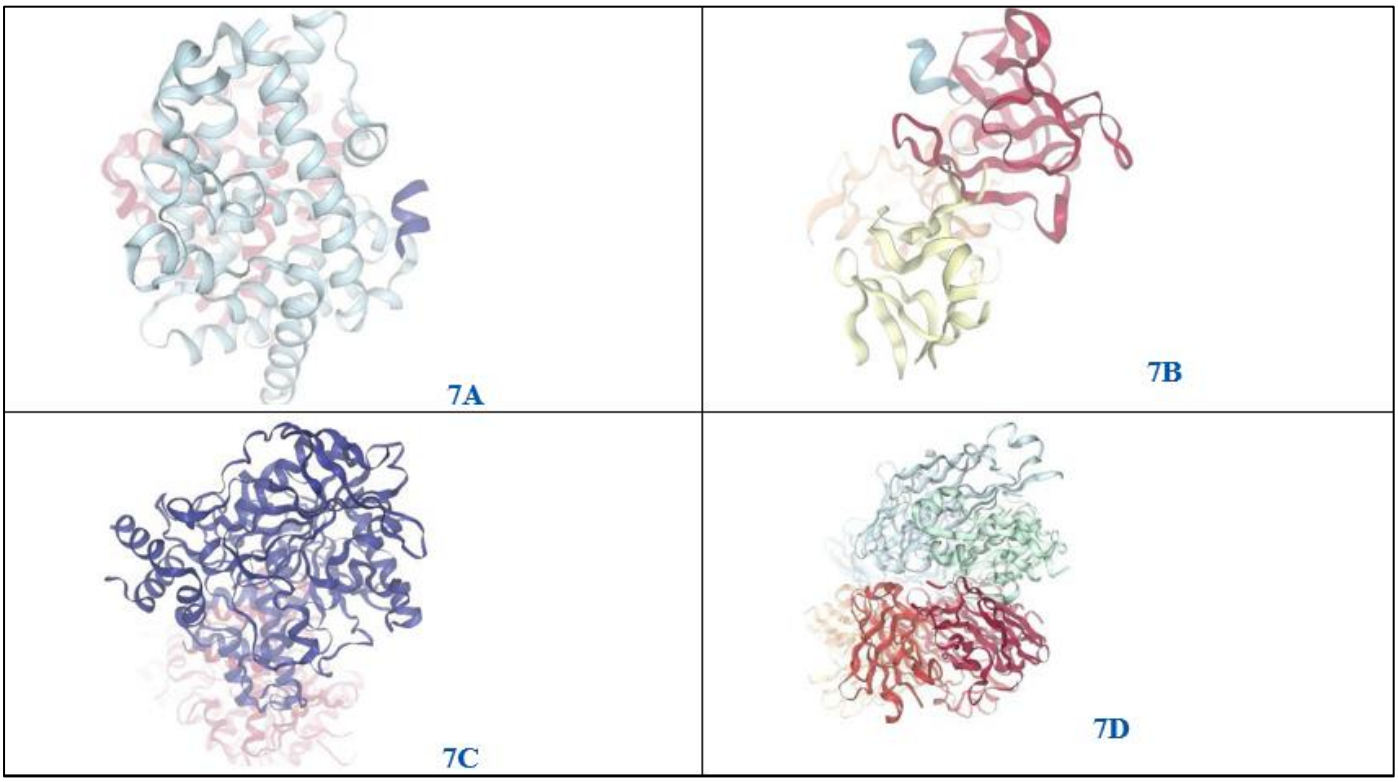

Fig 10 Ligand Protein Binding of Piperine

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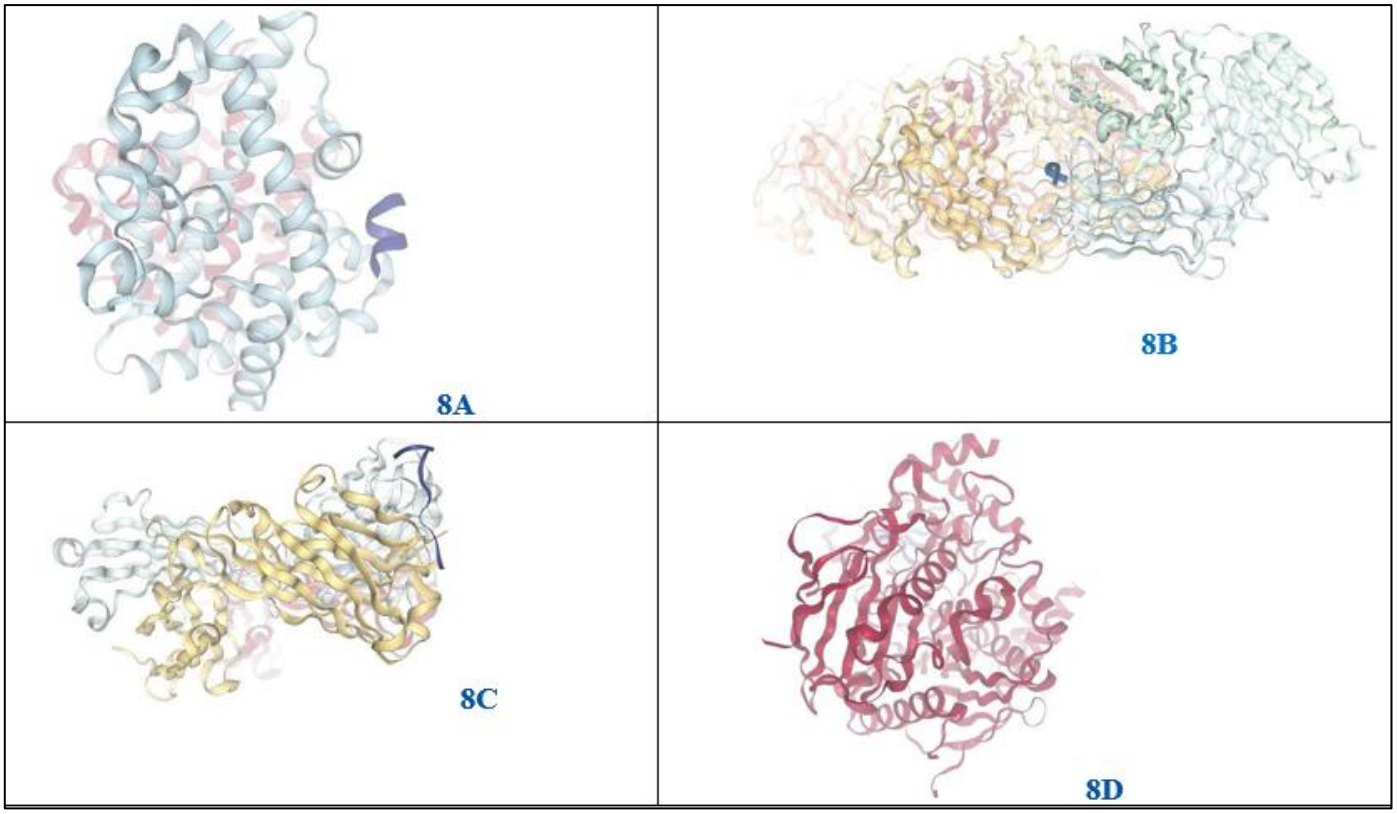

Fig 11 Ligand Protein Binding of Kaempferol

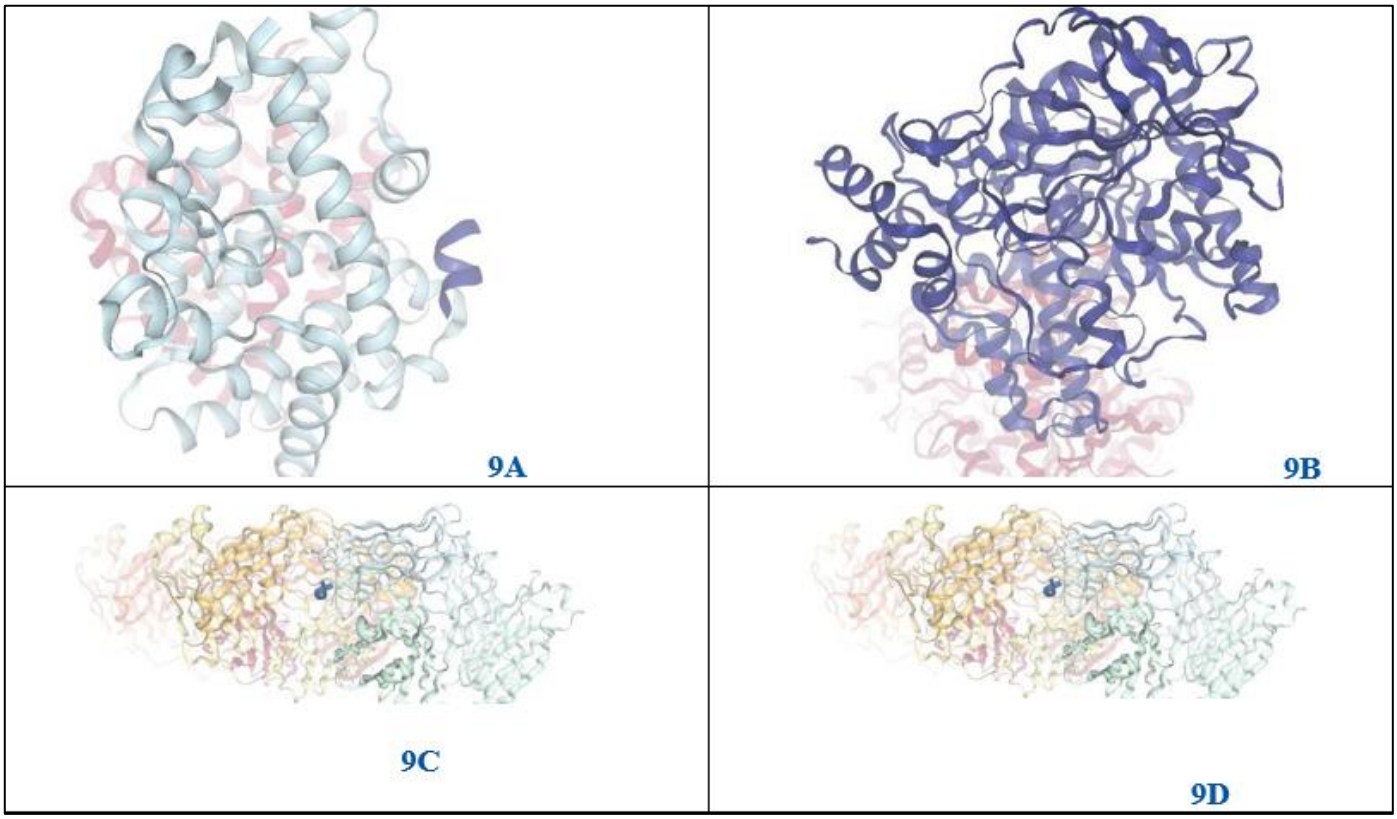

Fig 12 Ligand Protein Binding of Caffeine

The pharmacokinetic properties of the phytoconstituents were also shown to be highly advantageous in accordance with Lipinski's rule as shown in table below.

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Table 4 MADME Data (Swiss ADME Tool)

S. NO	PHYTOCONSTITUTENT	MOLECULAR WEIGHT	Log *S* (ESOL)	GI absorption	Lipinski Rule Compliance
1	Curcumin	368.38 g/mol	-3.94	High	Yes, 0 violation
2	Resveratrol	228.24 g/mol	-3.62	High	Yes; 0 violation
3	Luteolin	286.24 g/mol	-3.71	High	Yes; 0 violation
4	Berberine	336.36 g/mol	-4.55	High	Yes; 0 violation
5	Naringenn	272.25 g/mol	-3.49	High	Yes; 0 violation
6	Quercetin	302.24 g/mol	-3.16	High	Yes; 0 violation
7	Piperine	285.34 g/mol	-3.74	High	Yes; 0 violation
8	Kaempferol	286.24 g/mol	-3.31	High	Yes; 0 violation
9	Caffeine	194.19 g/mol	-1.48	High	Yes; 0 violation

The primary phytoconstituent, caffeic acid, a phenolic acid, has previously been shown to have anticholinesterase action. Furthermore, caffeine can decrease Aβ-induced neurotoxicity on PC12 (pheochromocytoma) cells of the rat adrenal medulla, as well as lipid peroxidation and nitric oxide generation. , was investigated. Because of their multipotent impact, these chemicals may be beneficial in the future to develop new treatment strategies that target receptors, tau protein, beta-secretase (BACE1), amyloid-beta (Aβ) aggregate, and acetylcholinesterase (Ache). (Bukhari et al., 2015) (Gupta et al., 2013) (Kumar & Singh, 2015). Among all the phytoconstituent tested for antialzheimer activity, luteolin may be considered most potent with significant pharmacokinetic properties.

V. CONCLUSION

Curcumin, Resveratrol, Kaempferol and Quercetin exhibit strong inhibitory potential against key AD targets and possess favorable pharmacokinetic properties. These findings support further experimental validation to confirm their therapeutic efficacy in Alzheimer's disease. Computational drug discovery accelerates the identification of natural neuroprotective compounds, contributing to novel plant-based AD therapeutics. High docking scores and binding energies with the receptor were demonstrated by the molecular docking technique. Thus, the use of phytoconstituents in the treatment of AD may help generate new acetylcholinesterase (Ache), beta-secretase (BACE1), tau protein, amyloid-beta (Aβ) aggregates, and receptor antagonists. More in vitro and in vivo studies are required to validate the in-silico results reported in this work.

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