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Review Article

Review On: Molecular Docking of Coumarin

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ABSTRACT

The study examines coumarins, which are naturally occurring phytochemicals, as potential therapeutic candidates for intricate neurodegenerative and cardiovascular disorders using molecular docking and computational methods. By functioning as strong dual-binding AChE inhibitors (e.g., Compound C8 approached donepezil efficacy, IC_{50} = 2.42 µM) and blocking BACE1 and MAO-B, coumarins exhibit strong anti-Alzheimer's potential. Coumarins are useful ACE inhibitors for the treatment of hypertension; docking revealed that Compound 2 had a higher binding energy (-8.46 Kcal/mol) against the N-ACE target than Captopril (-7.41 Kcal/mol) in that particular situation.By preventing calcium entry through voltage-dependent and receptor-operated calcium channels, they also have dose-dependent, endothelium-independent vasorelaxant effects. The study comes to the conclusion that the coumarin scaffold is a great building block that can be structurally modified to effectively increase inhibitory action, which holds promise for the creation of new, multipurpose medicinal medicines.

INTRODUCTION

Alzheimer's disease (AD)is the most common form of neurodegenerative disorder and the most prevalent cause of dementia, particularly affecting the elderly. This condition is defined as a progressive disorder of the brain, characterized by symptoms that worsen over time, leading to an irreversible decline in cognitive, social, and physical function, along with associated issues like depression, abnormal behaviour, and anxiety. The underlying pathology involves the accumulation of beta-amyloid protein (beta) outside neurons, forming senile plaques, and the hyperphosphorylation of tau protein.This results in neurofibrillary tangles (NFTs); both processes induce neuronal cell death by disrupting neuronal transmission and obstructing the transfer of necessary chemicals. Since there is currently no known cure for AD, scientists are looking for ways to slow the disease's progression. One major strategy is to inhibit important enzymes likebeta-

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secretase (BACE1), acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), and monoamine oxidase (MAO). Because of their wide range of pharmacological characteristics and capacity to function as inhibitors against certain targets, natural phytochemicals called coumarins, which are members of the benzopyrone family, are being extensively studied as possible lead compounds for anti-Alzheimer medications.

Pathological Causes:-

Ultimately, the abnormal processing of Aβ by -and -secretases is the cause of the pathogenic mechanism. The production and clearance of the A peptide are critically out of balance as a result of this aberrant cleavage. Senile plaques are the resultant fibrils of Aβ that are extremely insoluble and resistant to proteolysis. These plaques become extremely harmful once they are deposited because they prevent synaptic transmission between neurons. Information transfer fails as a result of this synaptic disruption, which eventually results in the death of neuronal cells. One pathogenic event that greatly contributes to the symptoms' gradual worsening and eventual development of dementia and cognitive impairment is the ensuing Aβ deposition.Given this core pathology, a major therapeutic approach involves inhibiting the -secretase (BACE1) enzyme to lower -amyloid accumulation, while current treatments like Acetylcholinesterase inhibitors (AchEIs) are known to not only facilitate cholinergic transmission but also interfere with the synthesis, deposition, and aggregation of toxic.[40].

Neurofibrillary tangles:-

One of the two primary pathogenic causes of Alzheimer's disease (AD), a degenerative brain condition, is neurofibrillary tangles (NFTs). The tau amyloid protein fibrils are the basic building block of these tangles. Tau is an important part of microtubules, which provide the internal support structure for the movement of nutrients and other vital components in a healthy neuron. On the other hand, tau forms insoluble fibrils that define the NFTs when it becomes hyperphosphorylated. Because these insoluble fibrils successfully obstruct the movement of nutrients and other vital molecules within the cell, this structural alteration has detrimental effects on the neuron and eventually results in neuronal cell death.

Acetylcholinesterase and Butyrylcholinesterase:-

Acetylcholinesterase (AchE) and Butyrylcholinesterase (BuChE) are crucial enzyme targets in the therapeutic strategies designed to slow the progression of Alzheimer's disease (AD). Since AchE inhibitors (AchEIs) promote cholinergic transmission and prevent the production, accumulation, and deposition of hazardous (beta-amyloid) substances, they are the first line of treatment for AD patients. However, since BuChE and AchE both play a part in hydrolyzing acetylcholine in the synaptic cleft, it must also be taken into account for effective treatment. In regions like the hippocampus and temporal cortex, the activity of BuChE significantly increases as AD advances, but the activity of AchE diminishes. Therefore, the /activity ratios observed in the healthy brain are restored when BuChE is inhibited.Recent investigations are now increasingly focusing on developing dual / inhibitors, as these compounds possess very good therapeutic importance by simultaneously enhancing cholinergic transmission and effectively preventing aggregation. The structural differences between the enzymes, specifically the presence of aromatic amino acids in versus aliphatic amino acids in , are key factors influencing the selectivity of

inhibitors, guiding the synthesis of compounds like coumarin derivatives for potent / inhibition.

Monoamine oxidase:-

Due to its crucial role in oxidative stress and the development of Aβ plaques, monoamine oxidase (MAO) is an important therapeutic target in Alzheimer's disease (AD). In different cells, this enzyme, which contains flavin adenine dinucleotide (FAD), is firmly attached to the outer membrane of the mitochondria and functions as a catalyst in the oxidative deamination of monoamines. There are two isoforms of MAO: MAO-A, which is generally utilized to treat mental illnesses like depression, and MAO-B, which is mostly present in glial cells and serotoninergic neurons in the human brain. Patients with AD may have a threefold increase in MAO-B activity in their cortex, which raises oxidative free radical generation and is directly linked to plaque formation. Therefore, MAO-B inhibitors, like rasagiline and selegiline, have the potential to become excellent anti-Alzheimer's medications since they can delay the evolution of the disease and greatly improve learning and memory deficiencies. In order to attain multifunctional benefits such simultaneous MAO-B inhibition, Aβ anti-aggregation, and metal chelation properties, researchers are actively exploring selective and reversible MAO-B inhibitors. Because coumarin analogues have strong inhibitory activity, they are frequently used in these studies.

Beta-Secretase (BACE1):-

Since secretase is a transmembrane aspartyl protease that causes the abnormal N-terminal cleavage of the Amyloid Precursor Protein (1), which directly results in the peptide's synthesis, it is an essential therapeutic target in Alzheimer's disease (AD). Inhibiting BACE1 is the main method to reduce the level because the imbalance caused by the abnormal processing by β- and γ-secretases leads to senile plaques. Because they are thought to aid in reducing amyloid buildup, BACE1 inhibitors are thought to offer a great deal of promise for development into anti-dementia medications. Dihalophenyl acid derivatives of coumarins are among the synthetic substances that researchers have studied; compound C87H exhibits great promise as a BACE1 inhibitor.According to docking experiments, the inhibitor's coumarin core was incorporated into the enzyme's pocket and formed important interactions with the side chain of Arg235, including a hydrogen bond. Additionally, esculetin, daphnetin, and umbelliferone 6-carboxylic acid are examples of natural coumarins that show encouraging BACE1 inhibitory action.

Coumarin:-

Coumarins are a broad class of compounds with over 1300 members that are widely distributed as secondary metabolites in the kingdom of plants. They are also known as 2H-1-benzopyran-2-ones or, less frequently, as o-hydroxycinnamic acid-8-lactones. Additionally, their presence has been found in bacteria, fungi, and animals. Both free and glycoside forms of coumarins are found in plants, and numerous more coumarins have been produced [1–4]. The plant Coumarouna odorata Aube (Dipterix odorata), from which the archetypal chemical coumarin was discovered in 1820, is the source of the name [2]. The average dietary coumarin consumption for a 60-kg consumer has been calculated to be 0.02 mg/kg/day based on an epidemiological survey research. According to estimates, coumarin exposure from the use of fragrance in cosmetic items is 0.04 mg/kg/day [4].Ethyl 7-Hydroxy-4,8-dimethylcoumarin-3-propanoate (1) can be synthesized according to the synthesis method in the lit erature(Abuknesha& Darwish, 2005).

Amide structure is obtained by nucleophilic reaction of ethyl carboxylate moiety of 7-hydroxy-4,8-dimethylcoumarin-3-propanoate.

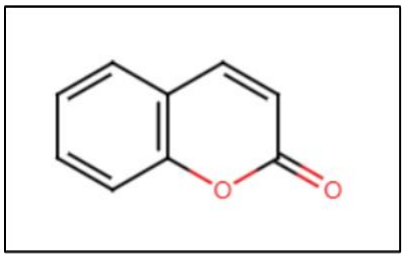


Fig.1 Structure of Coumarin.

Molecular Docking:-

As algorithms become more accurate, computational techniques have grown in importance in the drug development process. To ascertain the structural interactions between possible therapeutic compounds and their targets, numerous docking techniques based on various algorithms are continuously being developed [35]. Furthermore, research in this field clarifies the pharmacodynamic characteristics, affinity, and selectivity of the potential medications [36]. Drug repositioning (repurposing), structure- and ligand-based drug design techniques employing virtual and reverse screening are the primary molecular docking applications in drug development [36–39].

Drug repositioning looks for novel targets for existing medications, natural chemicals, or candidate ligands in order to uncover their untapped therapeutic potential [32]. The literature contains a large number of successful repositioning studies [32-34]. Techniques for reverse screening (RS) and virtual screening (VS) are widely employed in repositioning and drug discovery. When compared to conventional procedures, VS provides a more logical and efficient approach [31]. Virtual screening investigations provide us with atomic-level analyzable results that help us comprehend the target's function and uncover new drugs [28, 29, 30].

One ligand molecule is the focus of the RS method, and a biological target for this molecule is being sought [27]. The search library is made up of possible target receptors, in contrast to virtual screening (VS). approach has the potential to lead studies such as testing toxicity or side effects of the existing drugs [25]. The drug discovery process requires assessing a medicine's possible negative effects. In this context, molecular docking studies can provide a valuable viewpoint, and inverse (reverse) docking studies can yield bioactivity information by identifying off-target binds [26]. Finally, the pharmaceutical business has benefited greatly from the applications of machine learning (ML) and deep learning (DL), two subclasses of artificial intelligence (AI) [23].

AI can be used for a variety of processes, including computational planning of drug manufacturing, de novo drug molecule formation, and drug design with VS [24]. Recent advancements suggest that machine learning techniques could eventually be more advantageous for molecular docking technologies [23].

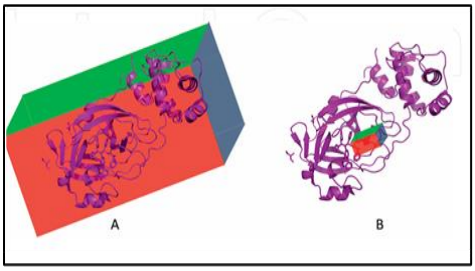


Fig.2 Molecular docking of protein-Ligand binding

Coumarin Analogues as AchEinhibitors:-

The ability of coumarin derivatives as strong acetylcholinesterase inhibitors (AChEIs) has been demonstrated by numerous researchers' investigations, underscoring their therapeutic potential in the management of Alzheimer's

disease (AD). After screening a library of 29 synthetic and natural coumarins, Fallarero et al. found that compound C1 (coumarin 106) was the most potent inhibitor. C1 efficiently binds to both the peripheral anionic site (PAS) and the active-site gorge of AChE, according to molecular docking, indicating a dual-binding method that may lessen β-amyloid accumulation, a crucial component of AD pathogenesis.

In a different investigation, Razavi et al. created a number of 4-hydroxycoumarin derivatives and assessed how well they inhibited butyrylcholinesterase (BuChE) and AChE. Compound C3, a derivative of N-(1-benzylpiperidin-4-yl)acetamide, showed the highest inhibitory efficacy among them (IC_{50} = 1.2 μM). According to docking studies, the coumarin core's π-cation and π–π stacking interactions with aromatic residues like Phe330 and Trp279 within the enzyme's active region are responsible for this potency. These interactions stabilize the ligand and increase its inhibitory efficacy.

Using mouse brain homogenates, Nam et al. created a number of aminoalkyl-coumarin hybrids that were modeled after scopoletin and evaluated their anti-AChE activity. The strongest inhibition was demonstrated by the pyrrolidine-substituted derivatives C6 and C7, which had IC_{50} values of 6.85 and 2.87 μM, respectively. Interestingly, C7 showed similar efficacy to galantamine, a therapeutically used AChEI, and 160-fold higher inhibition than scopoletin. Additionally, both substances improved mice's memory impairments brought on by scopolamine, demonstrating their pharmacological significance.

In order to investigate dual-site binding interactions, Singla and Piplani also synthesized fifteen new coumarin–amine hybrids. With a phenylpiperazine moiety, compound C8 showed the strongest AChE inhibition (IC_{50} = 2.42 μM), coming very near to donepezil (IC_{50} = 1.82 μM). A characteristic of strong dual-binding AChE inhibitors is their ability to attach to both catalytic (CAS) and peripheral (PAS) sites simultaneously. Docking findings showed that C8 generates extensive π–π and hydrophobic interactions with critical residues Trp86, Trp286, His447, and Tyr72.

AChEIs like donepezil, rivastigmine, and ensaculin, using information from the AChE active site structure as a guide. The findings demonstrated that series A (position 6) exhibited less inhibition than series B and C, which included replacements at positions 3 and 4 of the coumarin ring. With respective IC_{50} values of 4.5 μM and 5.3 μM, two compounds from series C, C9 and C10, shown substantial inhibitory action.

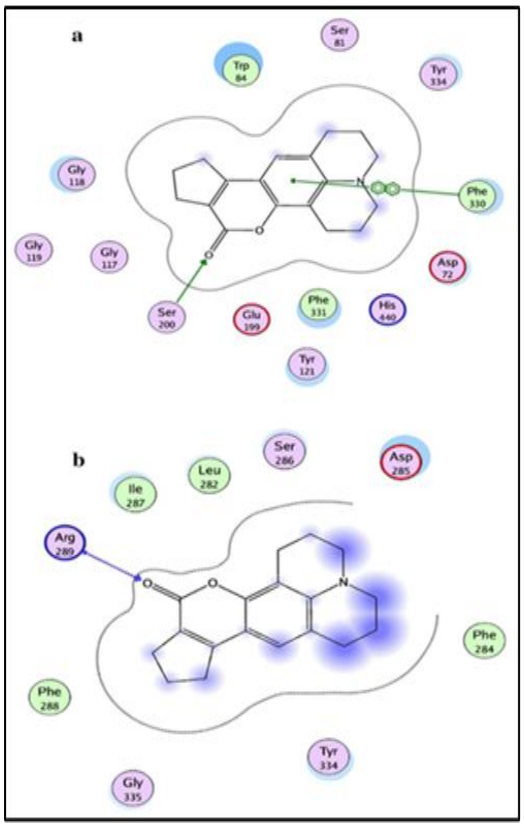


Fig. 3. a Propose binding of C1 at the active gorge site. b Propose binding of C1 at the peripheral anionic site.

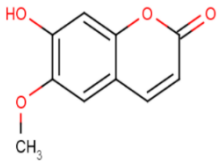
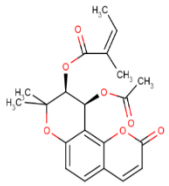
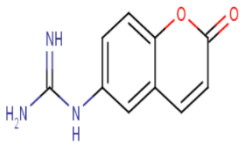
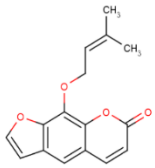
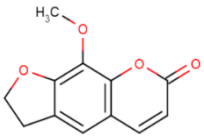
Vasorelaxant Properties: -

Many coumarins have been shown to relax the contractions of vascular smooth muscle induced by various mediators, in particular by the sympathomimetics norepinephrineand phenylephrine or by high doses of potassium chloride(KCl), as well as by endothelin-1 and an analogue of theendoperoxide prostaglandin H2 named U-46619[1].Many coumarins primarily work through a mechanism that is independent of the endothelium. These compounds were able to ease contractions brought on by the aforementioned inducers, but they had no effect on the steady-state of vascular rings [1–3].

Many coumarins primarily work through an endothelium-independent mechanism. These drugs were able to ease contractions caused by the aforementioned inducers, but they had no effect on the steady-state of vascular rings [18–20]. Coumarins function in a dose-dependent manner and most likely prevent calcium entry via the membrane of vascular smooth muscle cells' voltage-dependent calcium channels (VDCC) and receptor-operated calcium channels (ROCC), as well as by preventing calcium release from the sarcoplasmic reticulum.

It appears that imperatorin's effects on blood vessels were unaffected by muscarinic receptors [27]. By adding a nitrogen atom to the molecule, imperatorin's solubility can be increased, improving its vasorelaxant effect. Imperatorin is less efficacious than 8-(2-(azepan-1yl)ethoxy)psoralen (Table 1-C6). Other modifications include adding a morpholine ring, lengthening the side chain, or adding a hydrophobic benzene.

Table 1.- Overview of coumarins in in-vitro studies and vasorelaxant effect on vascular smooth muscle.

Ref.	Coumarin	Chemical Fornula	KCL	Sympath-omimetics	Serotonin	Others
[3]	Scopoletin(7-hydroxy-6-Methoxycoumarin,C1)		1	1^{A}	1	C
[9,10]	(+)-praeruptorin A/(+)-cis-4-acetly-3-angeloylkhellactone,C4/		3-4	3^{B}		
[11]	6-guanidinocoumarin			1		
[1,3,6 12,13]	Imperatorin/8-(3-methyl But-2-enoxy)psoralen,C7/			3		
[8]	8-methoxypsoralen(C8)		0			

Angiotensin-1-Converting Enzyme Inhibitor Activity of Coumarin From Angelica Decursiva:-

One of the most prevalent conditions in the world, hypertension has numerous risk factors, including aneurysms, heart disease, stroke, and chronic renal failure [41,22]. Approximately 25% of adults worldwide suffer from hypertension, and by 2025, that number is expected to increase to 29%. 1.56 billion individuals will be impacted in total. One well-established contemporary treatment strategy for hypertension is inhibition of the angiotensin-converting enzyme (ACE) [1]. The rennin–

angiotensin system (RAS) contains the multifunctional enzyme membrane-bound zinc (Zn) metallopeptidases ACE (EC 3.4.15.1), which increases blood pressure by producing the vasoconstrictor angiotensin II and breaking down the vasodilator bradykinin [43].The heart, brain, adrenal cortex, kidneys, leukocytes, alveolar macrophages, peripheral uterus, placenta, vascular tissue, liver, monocytes, and neuronal and epididymal cells—especially in the vascular endothelium lining—are among the several tissues that contain ACE of the lungs [44]. As a result, one of the main goals in the prevention and management of hypertension is ACE inhibition. ACE inhibitors like captopril have been synthesized by numerous researchers.

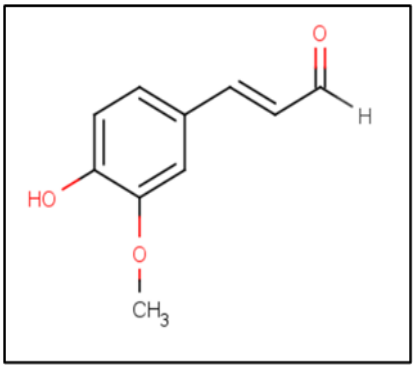


Fig.4:-4′-Hydroxy Pd-C-III; R1 = H; R2 = Angeloyl

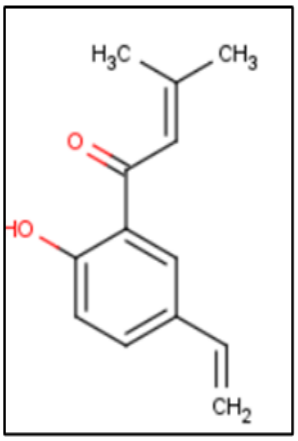


Fig.5:-Pd-C-I; R1 = H; R2 = Senecioyl

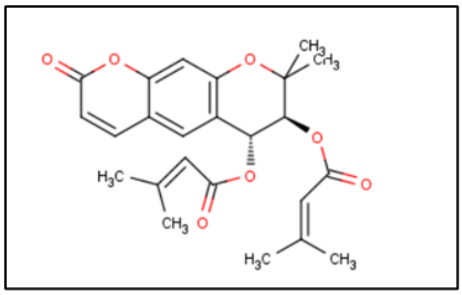


Fig.6:-Decursidin

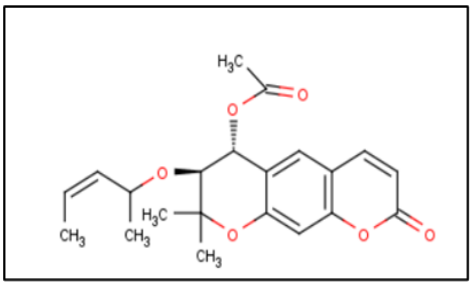


Fig.7:-(+)-trans-decursidinol

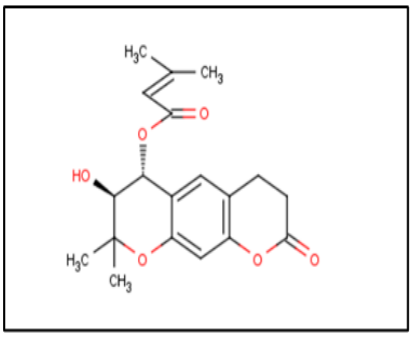


Fig.8: -Pd-C-II; R1 = Senecioyl; R2 = H

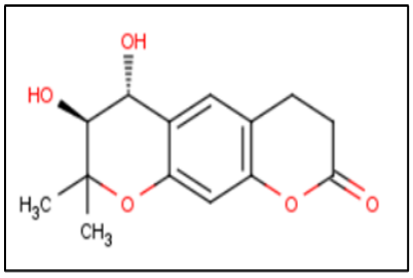


Fig.9:-Pd-C-III; R1 = Acetyl; R2 = Angeloyl

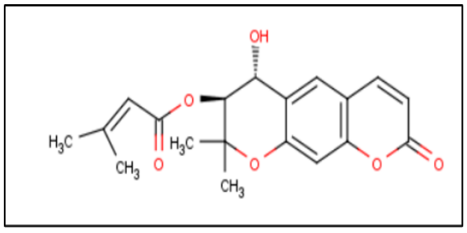


Fig.10:-4′-Methoxy Pd-C-I; R1 = Methyl; R2 = Senecioyl

Table 2:- Molecular interaction between ACE inhibitor and ACE.

Compound	Docked Energy (Kcal/mol)	Hydrogen Bond Interaction	Van der Waals Interaction	Hydrophobic Interaction	Others
Target Enzyme: C- ACE (PDB:2xy9)					
1	-7.86	His353(1),Ala356(2), Asp358(1),His513(1) Tyr523(1)	ZN	His387,Trp357,Phe391, His410.	-
2	-8.03	His353(1),Ala356(1), His513(1),Glu384(1), His387(1)	ZN	His410,His387,Phe391,	-
3	-8.03	His513(1),Ala356(3), Tyr523(1),hia353(1)	ZN	Phe391, His410,His387	Glu384 (Pi-Anion)
Captopril[a]	-8.95	Gln281(1),His353(1), Lys511(1),Glu384(1), His513(1)	ZN	Ala345,His353,His383, Phe457,Tyr523	His385,His387 (Pi-S)
FII[b]	-7.92	Lys118(1),Asn66(1), Arg522(1),Trp59(1)	-	Met223,Trp59,Tyr62, Trp220,Trp357,Val518, Pro519,Ala63	Arg124,Arg52 (Pi-Cation), Met223(Pi-S)
Target Enzyme:N-ACE (PDB:2xyd)					
1	-8.15	His331(1),His491(1), Asp393(1),Lys432(1)	ZN	His369,Phe505,Phe435	Tyr501 (Pi-Lone pair)
2	-8.46	His331(1),Ala334(2), His491(1),Glu362(1) Ser333(1)	ZN	His388,His365	Glu389 (Pi-Anion)
3	-7.98	Glu259(1),Lys489(1), His491(1),Asp393(2), His331(1)	-	Phe435,Tyr501,Phe505	-
Captopril[a]	-7.41	Gln259(1),His331(2), Lys489(1),His491(1), Glu362(1),Tyr498(1)	ZN	Ala332,His331,Tyr501	His361(Pi-S)

Current clinical hypertension medications include fosinopril, lisinopril, and enalapril [45]. Nevertheless, those medications frequently have unfavorable side effects, including angioedema, postural hypotension, chronic cough, and renal failure [46]. Numerous studies have been conducted to Natural products that contain ACE inhibitors may have superior pharmacological profiles and fewer adverse effects. It has been reported that a number of plant extracts and pure substances, including phenolics, anthraquinone, flavonoids, alkaloids, terpenoids, peptides, hydrolyzable tannins, and proanthocyanidins, block ACE. [47–52].

Reported ctalytic ACE inhibitor. [b]Reported peptic mixed type C-ACE inhibitor and Co-ligand of 2xy9.

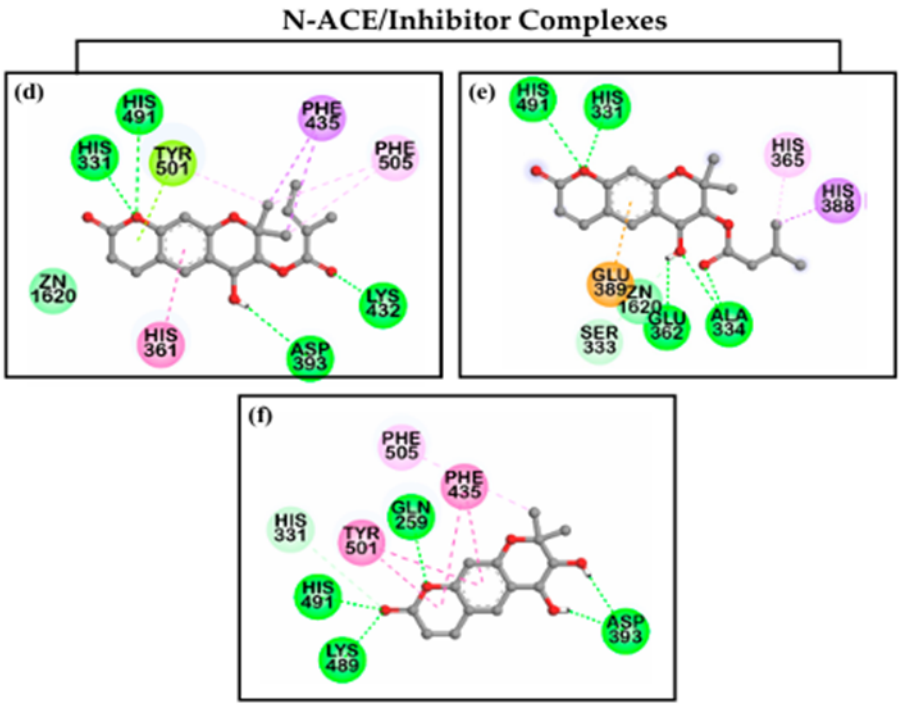


Fig.11: - Molecular Docling Model of (a) C-ACE and (b) N-ACE

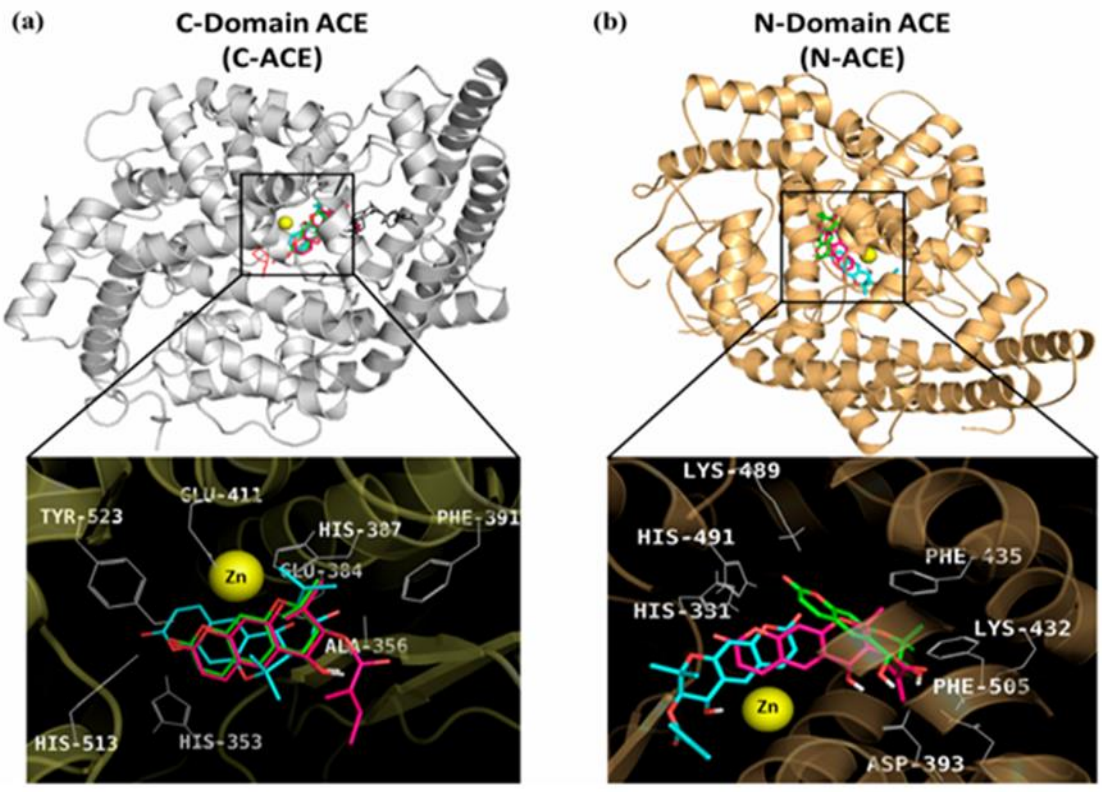


Fig.12: - Cont.

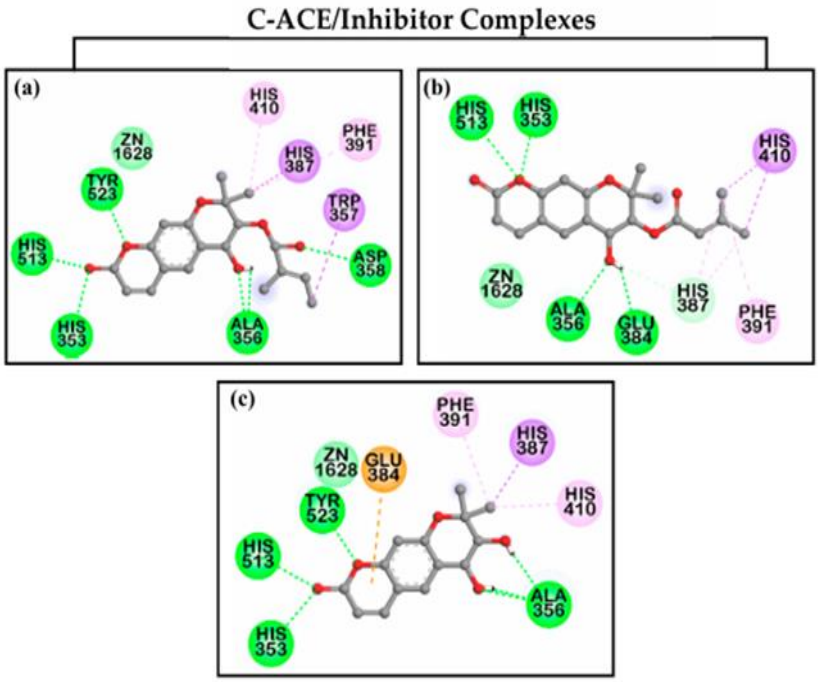


Fig.13. 2-D Diagram of C-ACE and N-ACE inhibition

RESULT: -

The thorough findings support the therapeutic potential of coumarins, which are naturally occurring phytochemicals that have been thoroughly assessed utilizing computational molecular docking. This process elucidates atomic-level structural interactions that are essential for virtual screening and drug development. Coumarin derivatives have strong inhibitory activity for Alzheimer's disease (AD), where it is important to inhibit enzymes such as AChE, BuChE, BACE1, and MAO. Many of these compounds work as strong Acetylcholinesterase inhibitors (AChEIs) through a dual-binding mechanism. Compound C3 has the highest inhibitory efficacy (IC_{50} = 1.2 μM) because of important π-cation and π–π stacking interactions, and Compound C8 achieves an inhibition (IC_{50} = 2.42 μM) that is very close to donepezil's efficacy (IC_{50} = 1.82 μM). Additionally, coumarins are promising BACE1 inhibitors; the synthetic molecule C87H integrates into the pocket of the enzyme and interacts with Arg235 via a hydrogen bond.

Coumarins proved effective as Angiotensin-1-Converting Enzyme (ACE) inhibitors in cardiovascular applications for the management of hypertension. According to docking results, Compound 2 had a better docked energy of -8.46 Kcal/mol against the N-ACE enzyme (PDB:2xyd) than Captopril, which had a docked energy of -7.41 Kcal/mol in that particular situation. Last but not least, a number of coumarins, such as Scopoletin and Imperatorin, have strong vasorelaxant effects that are dose-dependent and generally endothelium-independent. Their main mechanism of action is to block voltage-dependent and receptor-operated calcium channels (VDCC and ROCC), which prevents calcium entry.

CONCLUSION: -

The main conclusion drawn from the sources is that coumarins, which are naturally occurring phytochemicals that are widely dispersed, are

extremely promising lead compounds for creating multifunctional medications. This potential is fully validated by computational studies and molecular docking. Coumarin derivatives are powerful inhibitors of important enzymes for neurodegenerative diseases such as Alzheimer's disease (AD). They exhibit promising activity as BACE1 and MAO-B inhibitors and strongly inhibit Acetylcholinesterase (AChE), frequently through an efficient dual-binding mechanism (e.g., Compound C8 approached the efficacy of donepezil, IC_{50} = 2.42 µM vs 1.82 µM).

At the same time, coumarins show promise as Angiotensin-1-Converting Enzyme (ACE) inhibitors in the treatment of hypertension. Molecular docking shows that certain compounds, such as Compound 2, have a binding energy against the N-ACE target (PDB:2xyd) that is higher (-8.46 Kcal/mol) than the clinical medication Captopril (-7.41 Kcal/mol) in that situation. Additionally, coumarins' general vasorelaxant qualities—which are mainly attained by preventing calcium from entering vascular smooth muscle cells—confirm their value as building blocks for the creation of new, safer treatment agents for complicated diseases.

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