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IN SILICO MOLECULAR DOCKING STUDY FOR BINDING AFFINITY OF *GUDUCHI* (TINOSPORA CORDIFOLIA WELLD) ON TGF-β1 & TNF-α WITH SPECIAL REFERENCE TO DIABETIC NEPHROPATHY

Dr. Rajshree Dinesh Gavand[1], Dr. Nivedita Valvi[2]
[1]*Professor, Department of Dravyaguna, APM's Ayurved Mahavidyalaya, Sion, Mumbai-22*
[2]*MD Scholar, Department of Dravyaguna APM's Ayurved Mahavidyalaya, Sion, Mumbai-22*

ABSTRACT

Diabetic nephropathy (DN) is a major complication of diabetes mellitus, characterized by progressive renal damage mediated by inflammatory and fibrotic cytokines such as Transforming Growth Factor Beta-1 (TGF-β1) and Tumor Necrosis Factor Alpha (TNF-a). Current therapeutic strategies are often limited by side effects and incomplete efficacy, highlighting the need for safer, natural alternatives. Tinospora cordifolia *(Guduchi), a traditional medicinal plant, possesses potent anti-inflammatory, antioxidant, and antidiabetic properties, making it a promising candidate for targeting molecular pathways involved in Diabetic Nephropathy.*

The present in silico *study aims to evaluate the molecular docking interactions and binding affinity of bioactive compounds from* Tinospora cordifolia *with key target proteins TGF-β1 and TNF-a, which play a central role in the pathogenesis of diabetic nephropathy.*

KEYWORDS: *Diabetic Nephropathy,Guduchi,TGF-B1, TNF-A, Molecular Docking.*

INTRODUCTION

Molecular docking is essential for evidence-based research because it provides a computational and cost-effective method for predicting and visualizing the binding interactions between a drug and its target. It provides a strong scientific basis for selecting the most promising candidates to validate with time-consuming and expensive in vitro studies.

It estimates the strength of the interaction between the compound and the protein, with lower binding energies indicating a more favorable and stable interaction.

Molecular docking of *Guduchi* (Tinospora cordifolia welld) was done against TGF-β1 & TNF-α with special reference to Diabetic nephropathy.

Aim: To do in silico Molecular docking on binding affinity of Guduchi (Tinospora cordifolia willd) on TGF-β1 & TNF-α with special reference to Diabetic nephropathy.

OBJECTIVES

1. To do in silico study -molecular docking study for binding affinity of Guduchi (Tinospora cordifolia willd) on TGF-β1 & TNF-α
2. To compile and review both Ayurvedic and contemporary scientific literature of Diabetes Nephropathy.
3. Conduct a literature review of molecular docking.

MATERIALS & METHODOLOGY

The study will be carried out at Computational Simulation laboratory of reputed institute.

Tools used for in silico study

1. IMPPAT Database
2. Protein Data Bank
3. ADMETLAB 2.O
4. PubChem
5. BIOVIA Discovery Studio
6. Chimera 1.15
7. PyRx

METHOD OF DATA COLLECTION

Data will be collected from:

1. Ayurveda Samhitas
2. Other modern textbooks
3. Websites- Pubmed, Ayush Research Portal, DHARA, Google Scholar, MRDB, Research Gate, Science Direct, Indian Journal of Pharmacology, etc.
4. Research Articles- Recently Published

REVIEW OF DIABETIC NEPHROPATHY

Pathophysiology of Diabetic Nephropathy (DN): Diabetic nephropathy is a chronic, progressive kidney disease that occurs as a complication of long-standing diabetes mellitus (both Type 1 and Type 2). It is characterized by albuminuria, declining glomerular filtration rate (GFR), and glomerulosclerosis (scarring of the kidney's filtering units).Chronic hyperglycemia, Hypertension, Genetic predisposition, Dyslipidemia, Smoking, Advanced age are contributing factors for Diabetic Nephropathy.

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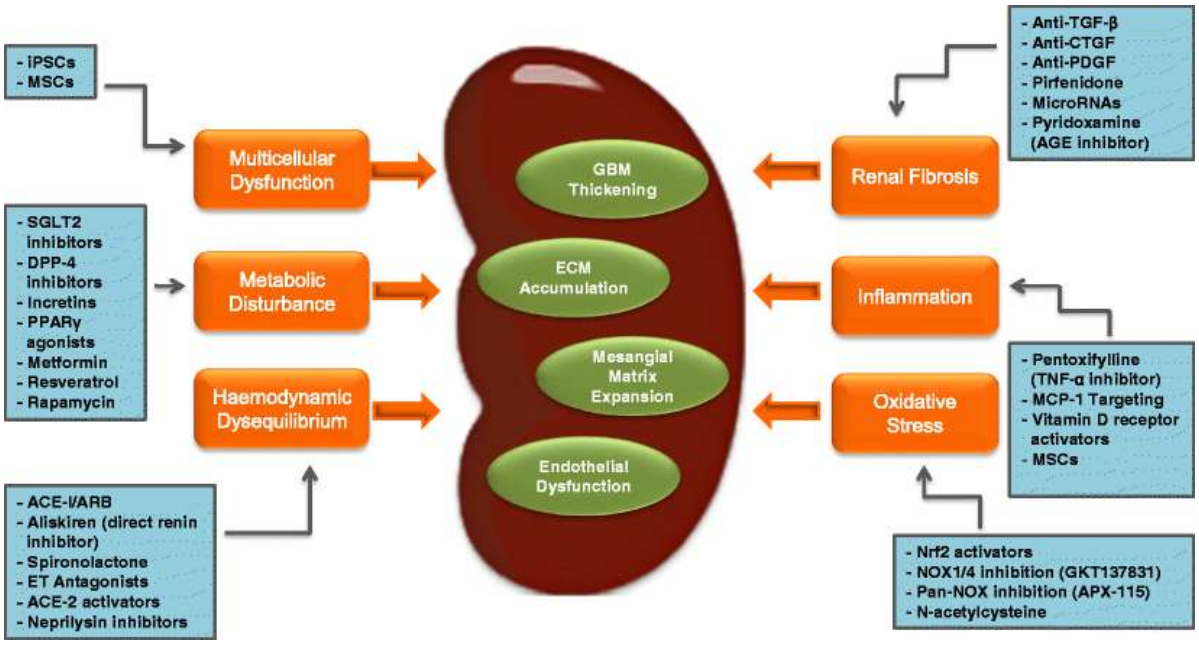
Pathahogenesis of Diabetic Nephropathy



Ayurvedic pathogenesis (Samprapti) of Diabetic Nephropathy:
Dosha–Dhatu–Srotas involvement

- **Doshas**
  - Predominantly **Kapha** and **Vata**, with Pitta also involved secondarily.
  - Initially, Kapha and Meda vitiation leads to srotorodha (blockage) of Mutravaha channels.
  - Later, Vata becomes aggravated due to dhatu-kshaya (tissue depletion), causing degenerative and functional changes in renal tissue.
- **Dhatus Affected**
  - **Meda**, **Mamsa**, **Rakta**, and **Shukra** dhatus (deep metabolic tissues).
  - Progressive **Ojas kshaya** (depletion of vital essence) and **Rasadhatu dushti** (impaired plasma nutrition) occur.
- **Srotas Involved**
  - **Mutravaha Srotas** (renal/urinary tract)
  - **Medovaha Srotas** (fat metabolism channels)

Potential Protein Targets for Molecular Docking in Diabetic Nephropathy.

Sr No	Mechanistic Pathway	Key Protein Target	Rationale for Targeting	PDB ID Examples
1	**RAAS activation**	**Angiotensin II type 1 receptor (AT1R)**	Mediates vasoconstriction & profibrotic effects of Ang II	4YAY
2	**Fibrosis & ECM accumulation**	**Transforming Growth Factor-β1 (TGF-β1)**	Master regulator of renal fibrosis; promotes ECM synthesis	3KFD
3	**Inflammation**	**TNF-α**	Inflammatory cytokine implicated in podocyte damage	2AZ5
4	**Lipid metabolism**	**PPAR-γ (Peroxisome Proliferator-Activated Receptor gamma)**	Improves insulin sensitivity; regulates renal inflammation and fibrosis	3DZY

Role of Guduchi (Tinospora cordifolia willd) in the prevention and treatment of Diabetic Nephropathy: Anti-Diabetic/Hypoglycemic Action: By regulating blood sugar levels (the primary cause of diabetic nephropathy) with Tikta, Katu, kashay rasa and laghu guna, it helps prevent or slow the progression of kidney damage. Guduchi with Tikta rasa does agnideepana (Promotes Digestive Fire). It helps improve metabolism and the functionality of Agni (digestive and metabolic fire), which is considered impaired in Prameha. Guduchi is a potent antioxidant, helping to reduce free radical damage to the kidney tissues and blood vessels which is a key mechanism in the pathogenesis of diabetic nephropathy. Guduchi's anti-inflammatory and immunomodulatory effects can help mitigate chronic low-grade inflammation which plays a role in the progression of kidney damage. Guduchi is traditionally used for urinary disorders (Mutrakṛcchra), suggesting an effect on the Mutravaha Srotas (urinary system/channels), which is directly affected in nephropathy.

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MOLECULAR DOCKING TECHNIQUE

Ligand

- Phytochemical constituents of *stem* of the *Guduchi* was found on IMPPAT Database. The phytoconstituent to be docked was selected.
- The chemical ID of the selected phytoconstituent was copied and pasted in PubChem.
- The SMILES of that phytoconstituent was copied from PubChem and pasted in ADMETLAB 2.0.
- The ADMET properties of that phytoconstituent were verified through ADMETLAB 2.0.
- Then the 3D structure of the selected phytoconstituent was downloaded through PubChem.

Protein

- The 3D structure of target protein (TGF-β1 PDB ID: 3KFD & TNF- α: PDB ID: 2AZ5) available in Research Collaboratory for Structural Bioinformatics Protein Data Bank are downloaded and imported to Biovia Discovery Studio 2021 Tool.
- Chimera 1.15 was chosen to prepare the protein by eliminating ligands, making corrections in protein structure and eliminating water.
- Visualisation of the results was done using PyRx Tool.
- Following are the results:

RESULT OF MOLECULAR DOCKING

Table 1: Binding affinity Guduchi (Tinospora cordifolia willd) on TGF-β1 PDB ID: 3KFD

Sr. no.	Phytoconstituent	Binding Affinity
1.	Beta-sitosterol	-8.2
2.	Magniflorine	-8.0
3.	Berberine	-7.1
4.	Kaempferol	-8.0

Table 1: Binding affinity Guduchi (Tinospora cordifolia willd) on TNF- α: PDB ID: 2AZ5

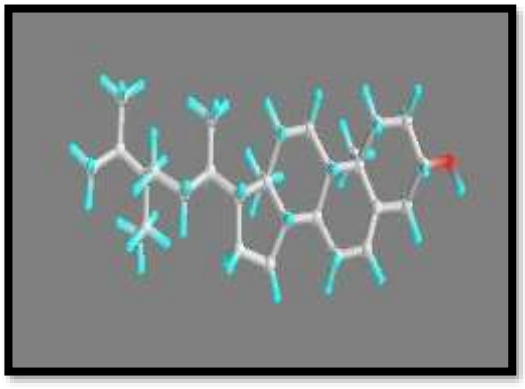
Sr. no.	Phytoconstituent	Binding Affinity
1.	Beta-sitosterol	-9.5
2.	Magniflorine	-8.0
3.	Berberine	-8.6
4.	Kaempferol	-8.1

1.1 Binding affinity of Phytoconstituent Beta-sitosterol & Magniflorine present in Guduchi (Tinospora cordifolia willd) on TGF-β1 PDB ID: 3KFD

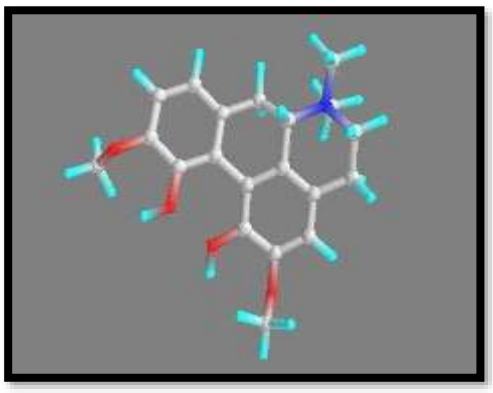
SUGGESTION

1) Preclinical, clinical studies can be done with Guduchi (Tinospora cordifolia willd) in Diabetic Nephropathy.
2) Molecular docking of other herbal drugs can be done in Molecular docking.

Ligand- Beta-sitosterol



Ligand- Magniflorine



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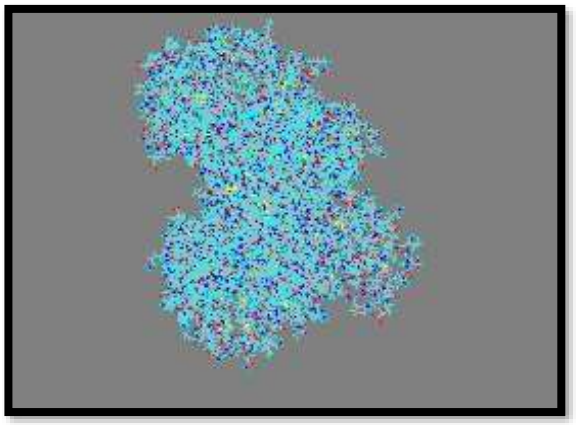
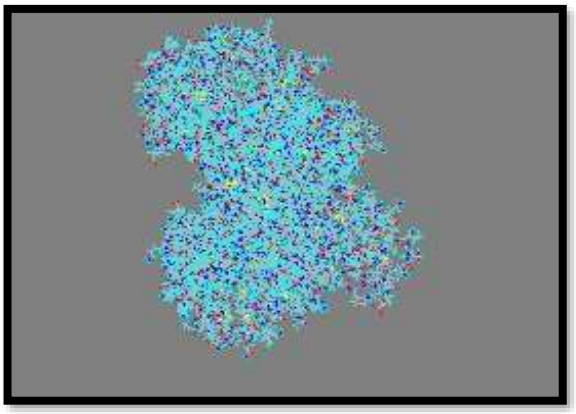
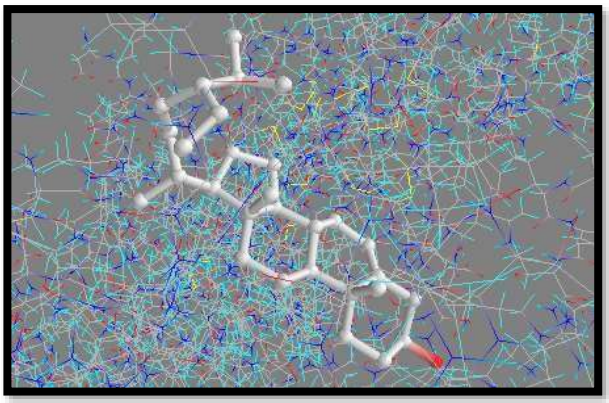
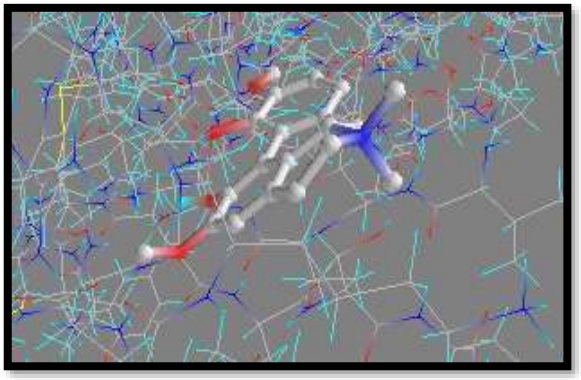
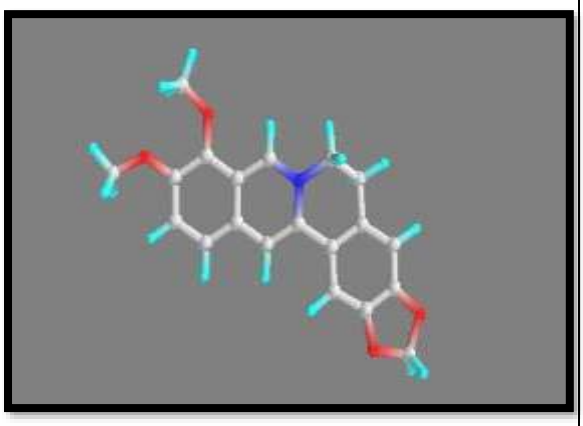
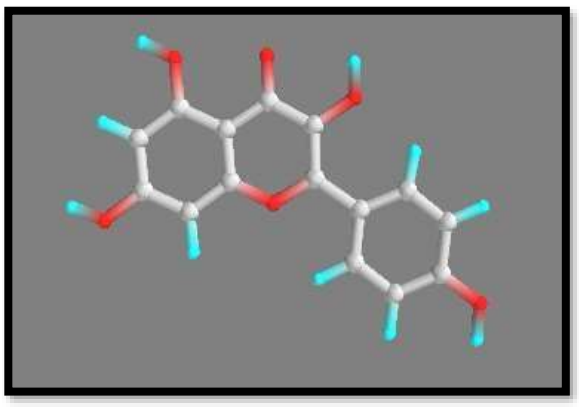
Macromolecule- 3KFD	Macromolecule- 3KFD
	
Binding Affinity	**Binding Affinity**
	

1.2 Binding affinity of Phytoconstituent Berberine & Kaempferol present in Guduchi (Tinospora cordifolia willd) on TGF-β1 PDB ID: 3KFD

Ligand- Berberine	Ligand- Kaempferol
	

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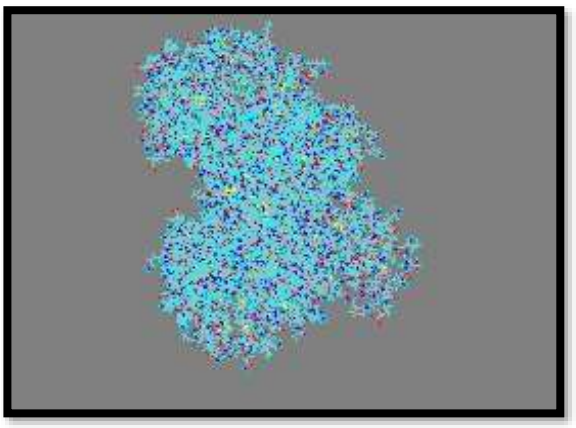
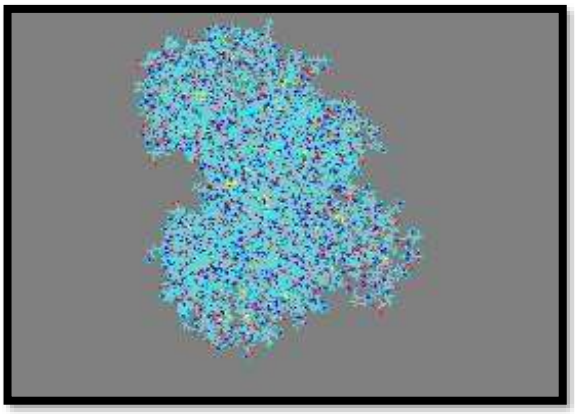
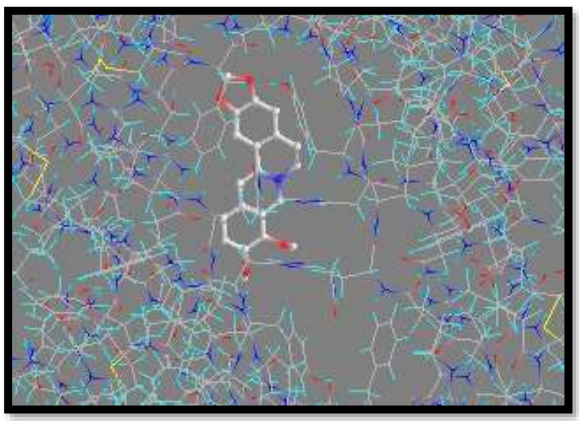
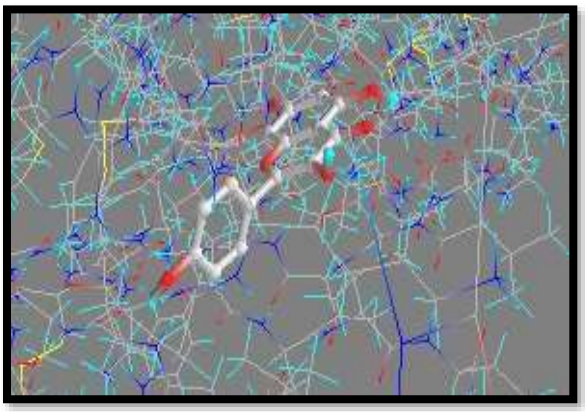
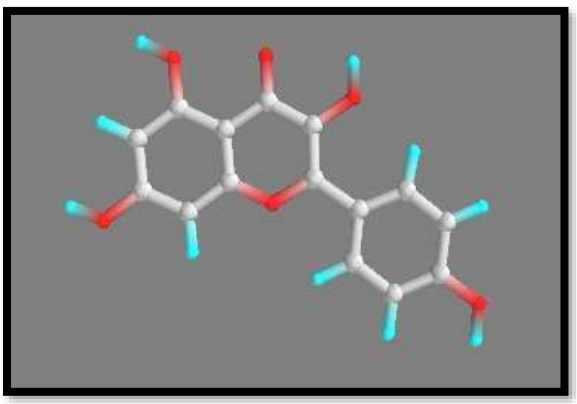
Macromolecule- 3KFD	Macromolecule- 3KFD
	
Binding Affinity	**Binding Affinity**
	

Table 1.3 : Binding affinity Guduchi (Tinospora cordifolia willd) on TNF- α: PDB ID: 2AZ5

Ligand- Beta Sitosterol	Ligand- Magniflorine
	

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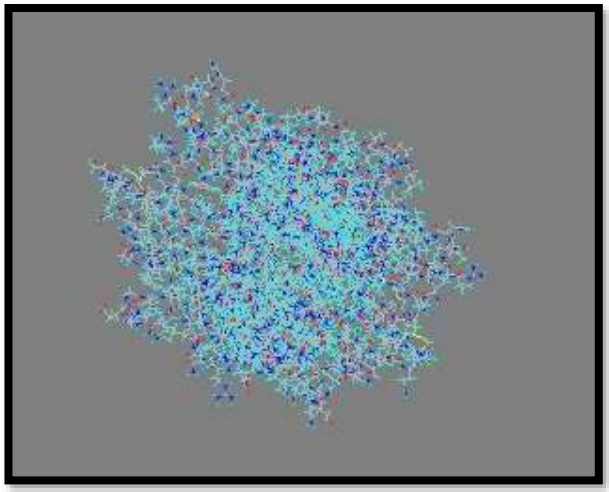
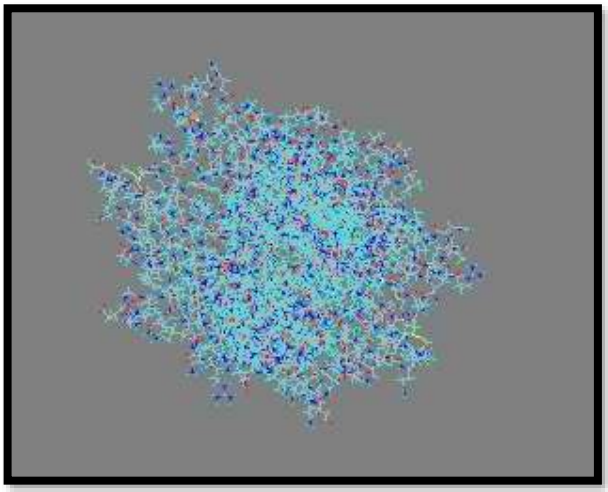
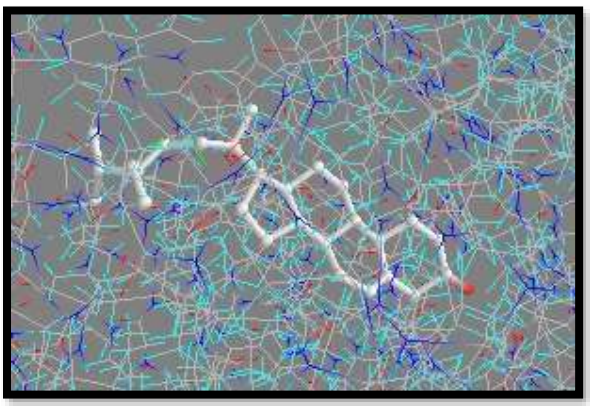
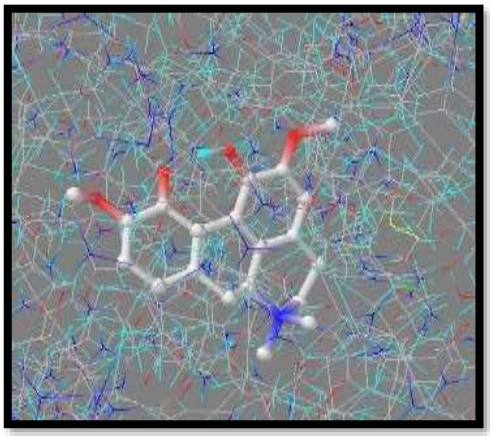
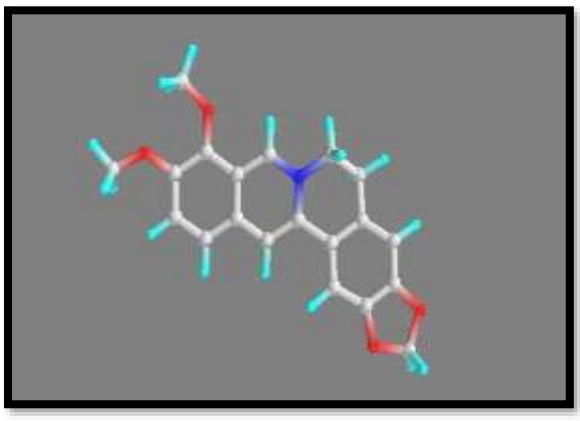
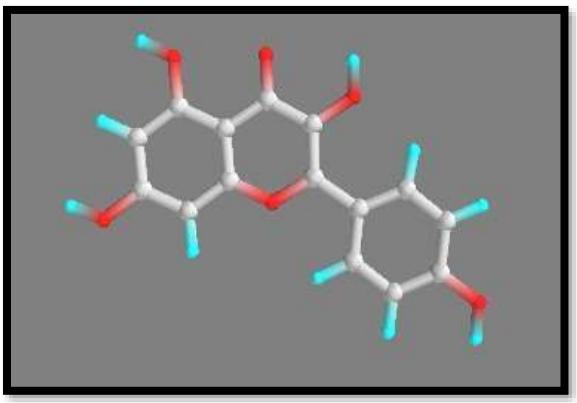
Macromolecule- 2AZ5	Macromolecule- 2AZ5
	
Binding Affinity	**Binding Affinity**
	

Table 1.4 : Binding affinity Guduchi (Tinospora cordifolia willd) on TNF- α: PDB ID: 2AZ5

Ligand- Berberine	Ligand- Kaempferol
	

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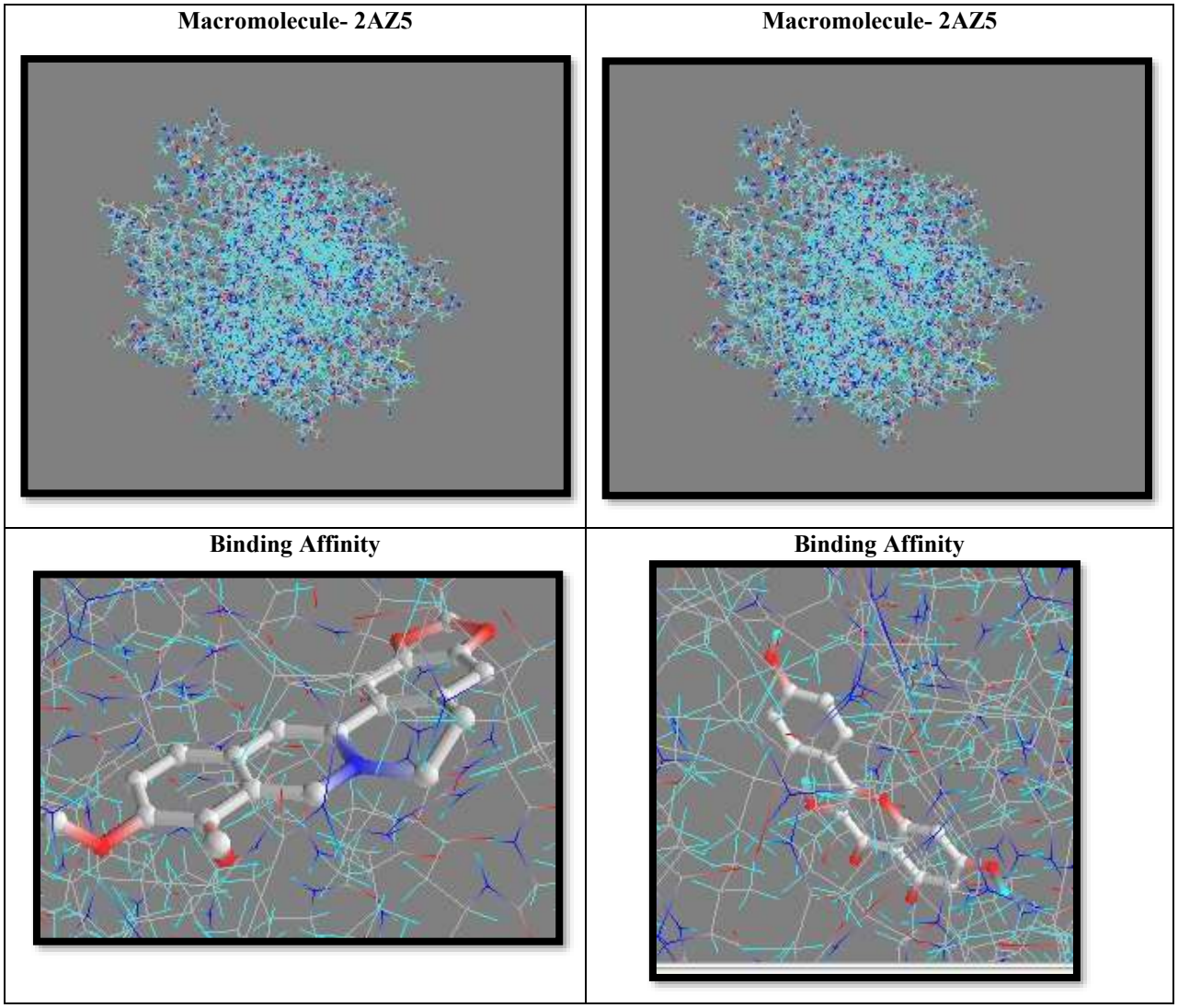

CONCLUSION

Results of molecular docking of Guduchi (Tinospora cordifolia willd) against TGF-β1 & TNF- α with special reference to Diabetic Nephropathy are obtained. Binding affinities estimates the strength of the interaction between the phytoconstituent and the protein, with lower binding energies indicating a more favorable and stable interaction. So, Beta sitosterol present in Guduchi (Tinospora cordifolia willd) shows promising binding affinity on TGF-β1 PDB ID: 3KFD and TNF- α: PDB ID: 2AZ5 which are the proteins involved in the pathogenesis of Diabetic Nephropathy among the other phytoconstituents.

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