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Original Research Article

Targeting growth factors for chronic heart failure: Molecular docking insights of telmisartan compared with sorafenib

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Abstract

Background: Chronic heart failure is a progressive disorder characterized by cardiac fibrosis and pathological hypertrophy, primarily mediated by dysregulated growth factors such as VEGF, PDGF, TGF-β, and FGF. While Sorafenib is a known multi-kinase inhibitor, the potential role of Telmisartan in modulating growth factor pathways remains underexplored.

Objective: This study aimed to investigate the inhibitory potential of Telmisartan, an angiotensin II receptor blocker, in comparison with Sorafenib, a multi-kinase inhibitor, against key growth factor signaling pathways implicated in chronic heart failure (CHF).

Materials and Methods: An in-silico molecular docking study was performed using AutoDock Vina, targeting FGFR1 (4QAL), PDGFRα (6JOL), TGFβ1R (5QTZ), TGFβ2R (5QIN), and VEGFR2 (6XVK). The binding affinities of Telmisartan and Sorafenib were calculated, and molecular interactions were visualized using Biovia Discovery Studio 2024.

Results: Telmisartan demonstrated stronger binding to FGFR1 (–7.7 kcal/mol), TGFβ1R (–11.1 kcal/mol), and VEGFR2 (-9.9 kcal/mol) compared to Sorafenib, suggesting a higher affinity for receptors involved in fibrosis and vascular remodeling. Conversely, Sorafenib showed superior binding to PDGFRα (–10.2 kcal/mol) and TGFβ2R (-9.5 kcal/mol). Structural analysis revealed hydrogen bonds and van der Waals forces as the primary stabilizing interactions.

Conclusion: The results indicate that Telmisartan may possess growth factor-inhibitory properties beyond its established antihypertensive role, particularly in pathways linked to cardiac fibrosis and hypertrophy. These findings highlight the therapeutic potential of Telmisartan in chronic heart failure, warranting further in vitro and preclinical validation.

Keywords: Chronic heart failure, Growth factor, Telmisartan, Sorafenib, In-silico study

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1. Introduction

Chronic heart failure is a complex disorder characterized by impaired left ventricular filling and/or emptying, leading to a range of symptoms. The most common manifestations include shortness of breath, fatigue, and ankle swelling.[1,2] A strong association exists between chronic heart failure and cardiac fibrosis, a key histological feature of pathological hypertrophy. The excessive accumulation of extracellular matrix proteins within cardiac tissue contributes to ventricular dilation and reduced contractile efficiency.[3] Cardiac hypertrophy, marked by a sustained increase in myocardial mass, arises due to persistent systolic or diastolic wall stress.[4] As cardiac enlargement and fibrosis progress, they ultimately lead to heart failure. Growth factors such as Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-Beta (TGF-β), and Fibroblast Growth Factor (FGF) play critical roles in the progression of cardiovascular diseases. Fibroblasts are key contributors to extracellular matrix (ECM) production and the development of fibrosis. PDGF isoforms and receptors become upregulated in response to cardiac stress, accelerating fibrotic processes. Excessive PDGF-A expression in myocytes can cause severe

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cardiac fibrosis and lead to an extreme increase in heart size, sometimes up to eight times its normal volume, often resulting in fatal outcomes. Overexpression of PDGF-B, on the other hand, induces moderate cardiac hypertrophy with localized and less severe fibrosis.[5,6] FGF-2 contributes to cardiac hypertrophy and fibrosis by activating the MAPK pathway through FGFR1c, whereas FGF-23 directly induces left ventricular hypertrophy (LVH) in rodent models.[7] VEGF, whose expression is influenced by mechanical stress, is secreted by stretched cardiomyocytes. By binding to VEGFR2, a receptor present in cardiac tissue, VEGF triggers signaling pathways that promote cardiac hypertrophy.[6]

TGF-β plays a central role in cardiac fibrosis, acting as a key regulator that drives the differentiation of fibroblasts into myofibroblasts.[8] This transition leads to excessive ECM deposition and scar tissue formation, particularly after cardiac injuries such as myocardial infarction. TGF-β is often considered the "master switch" that governs the progression from inflammation to fibrosis in damaged heart tissue. Additionally, during hypertrophic growth caused by pressure overload, TGF-β1 levels increase significantly within the myocardium, further contributing to pathological remodeling.[2,9]

Telmisartan, an angiotensin II receptor antagonist, is widely prescribed for the management of hypertension, while Sorafenib, a multi-kinase inhibitor, is primarily used as an antineoplastic agent. Sorafenib targets Raf serine/threonine kinase, VEGFR, PDGFR tyrosine kinases, and c-kit tyrosine kinase.[10,11]

Dr. Owens and his research team have highlighted the role of Angiotensin II (Ang II) as a growth factor involved in cellular hypertrophy, particularly in the cardiovascular system. Ang II promotes cell growth and proliferation by regulating key growth factors, including TGF-β, PDGF, and VEGF. This establishes a complex interaction between the renin-angiotensin system (RAS) and growth factor signaling. This interplay is crucial in vascular remodeling and tissue fibrosis. The angiotensin II receptor type 1 (AT-1) has been identified as a key mediator in hypertension and cardiac fibrosis.[12]

In this study, we conducted a molecular docking analysis comparing Telmisartan and Sorafenib to assess their potential in inhibiting growth factor signaling. The goal was to determine whether Telmisartan exhibits inhibitory effects on growth factor pathways similar to Sorafenib, thereby exploring its therapeutic role beyond its conventional antihypertensive action.

2. Methodology

2.1. Molecular docking study

The three-dimensional structures of the target proteins FGFR1 (PDB ID: 4QAL),[13] PDGFRα (PDB ID: 6JOL),[14] TGF β1R (PDB ID: 5QTZ),[15] TGF β2R (PDB ID: 5QIN),[16] and VEGFR2 (PDB ID: 6XVK)[17] were selected from the Protein Data Bank (PDB), an online repository for protein structures. Molecular docking studies were performed using AutoDock Vina to assess the interactions between the target proteins and the Telmisartan and Sorafenib ligands. Before docking, the protein and ligand files were prepared in PDBQT format. Preprocessing included removing water molecules and adding polar hydrogen atoms and Kollman charges to ensure proper charge distribution and polarity of the proteins. A receptor grid box was generated around each macromolecule, with dimensions and center coordinates tailored for each target as shown in **(Table 1)**.

Table 1: Grid box dimensions and center coordinates for molecular docking

Protein (PDB ID)	Grid box size (Å) [x × y × z]	Grid box center coordinates (Å)
4QAL (FGFR1)	18 × 18 × 18	13.988 × 24.494 × 99.449
6JOL (PDGFRα)	36 × 54 × 44	–37.294 × 156.770 × -0.242
5QTZ (TGFβ1R)	30 × 28 × 30	5.490 × 8.524 × 4.345
5QIN (TGFβ2R)	32 × 30 × 36	13.389 × –0.603 × 9.214
6XVK (VEGFR2)	54 × 34 × 38	–3.158 × –1.359 × 18.847

The prepared protein structures in PDBQT format were then utilized for molecular docking to investigate potential binding affinities and interaction patterns between the ligands and target proteins. Molecular docking studies were conducted using the prepared protein structures in AutoDock Vina to explore the binding affinity and interactions of the ligands with key target proteins: FGFR1 (PDB ID: 4QAL), PDGFRα (PDB ID: 6JOL), TGFβ1R (PDB ID: 5QTZ), TGFβ2R (PDB ID: 5QIN), and VEGFR2 (PDB ID: 6XVK). Docking was performed within an optimized grid box, generating ten poses for each ligand. The binding energy of Telmisartan was evaluated and compared with Sorafenib. The docking interactions were visualized and analyzed using Biovia Discovery Studio 2024 for a detailed understanding of ligand-protein interactions.

3. Results

Table 2: Comparative interaction profile of Telmisartan and Sorafenib with Fibrosis-Related targets

Target protein (PDB ID)	Drug	Binding energy (kcal/mol)	Key interaction types	Representative residues involved
FGFR1 (4QAL)	Sorafenib	–6.4	Conventional H-bonds	ASP (B:70), ASN (A:114), LYS (A:113)
	Telmisartan	–7.7	Van der Waals + H-bond	LEU (B:72), GLN (A:127), ASN (A:114), LYS (A:112)
PDGFRα (6JOL)	Sorafenib	–10.2	H-bonds + Van der Waals	ASP (A:681), ARG (A:597), LYS (A:627), ILE (A:672), TYR (A:679)
	Telmisartan	–9.8	Predominantly Van der Waals	CYS (A:677), PHE (A:678), TYR (A:676), VAL (A:598), TYR (A:685)
TGFβ1R (5QTZ)	Sorafenib	–10.0	H-bonds + Van der Waals	GLU (A:284), LYS (A:232), ASP (A:290), PHE (A:262)
	Telmisartan	–11.1	Van der Waals + H-bonds	TYR (A:249), GLY (A:286), SER (A:280), LYS (A:232)
TGFβ2R (5QIN)	Sorafenib	–9.5	Multiple H-bonds + Van der Waals	CYS (A:396), ASN (A:332), HIS (A:340), VAL (A:250)
	Telmisartan	–9.2	Mostly Van der Waals	LEU (A:305), ASN (A:332), GLY (A:331), ARG (A:339)
VEGFR2 (6XVK)	Sorafenib	–9.6	H-bonds + Van der Waals	LYS (A:920), SER (A:930), ASP (A:1046), PHE (A:921)
	Telmisartan	–9.9	Predominantly Van der Waals	PHE (A:1047), VAL (A:848), ASN (A:923), THR (A:926), TYR (A:927)

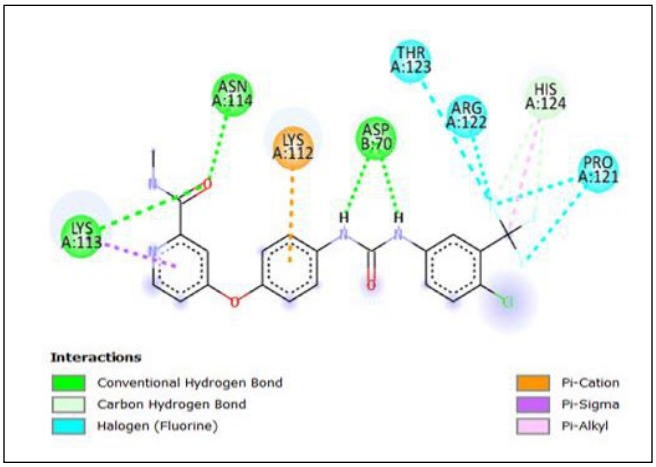

Figure 1a: Interaction of sorafenib with FGFR1

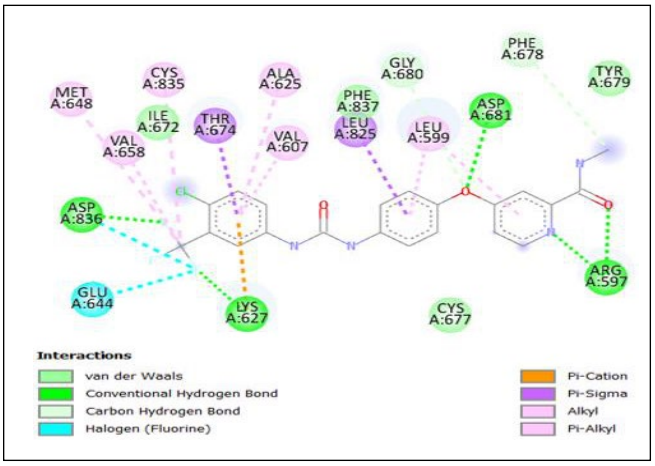

Figure 2a: Interaction of sorafenib with PDGFR α

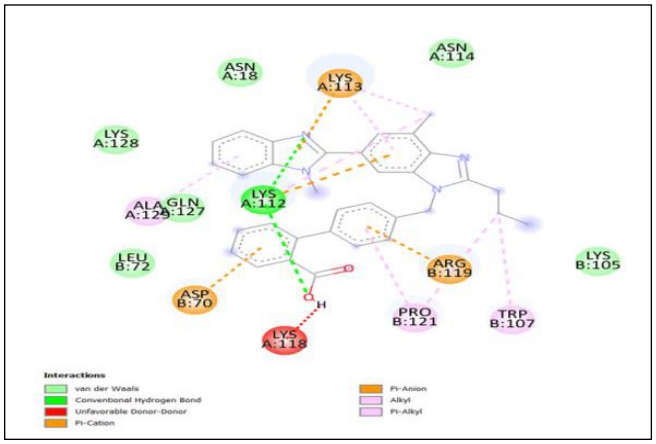

Figure 1b: Interaction of telmisartan with FGFR1

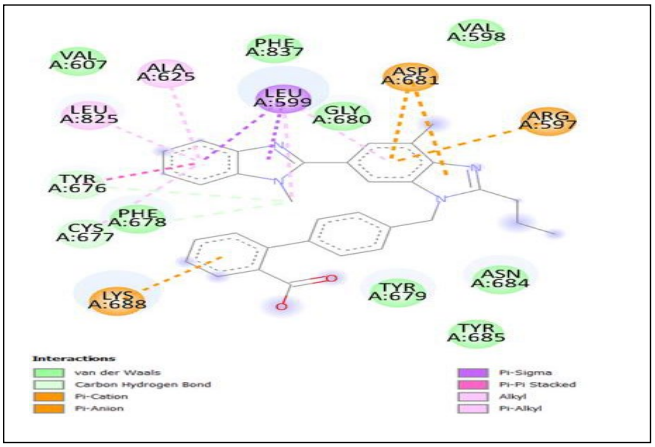

Figure 2b: Interaction of telmisartan with PDGFR α

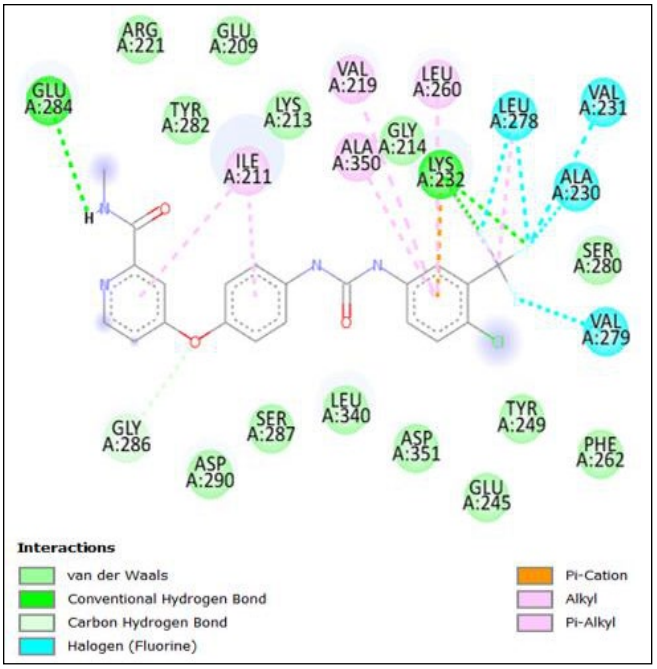

Figure 3a: Interaction of sorafenib with TGFβ1R

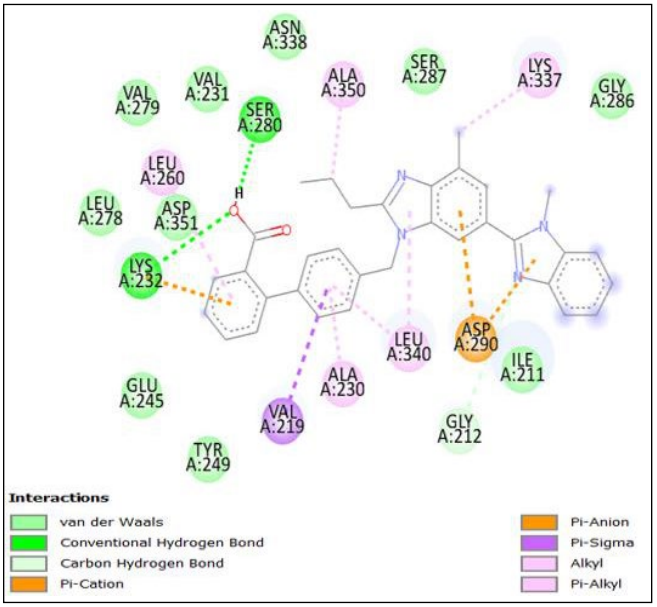

Figure 3b: Interaction of telmisartan with TGFβ1R

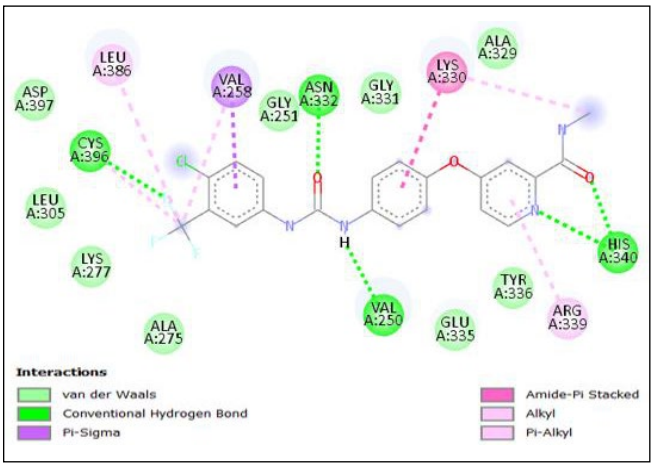

Figure 4a: Interaction of sorafenib with TGFβ2

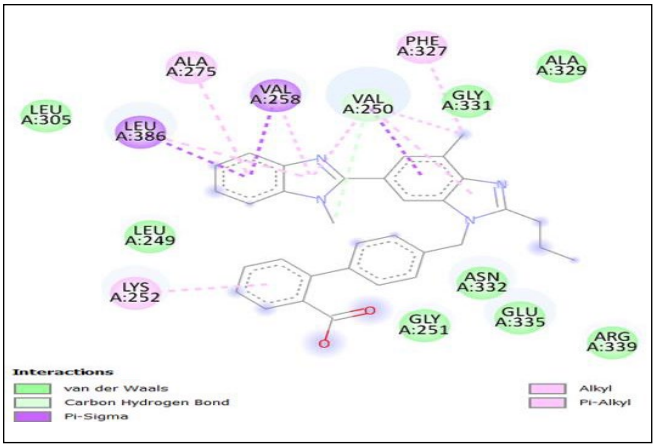

Figure 4b: Interaction of telmisartan with TGFβ2

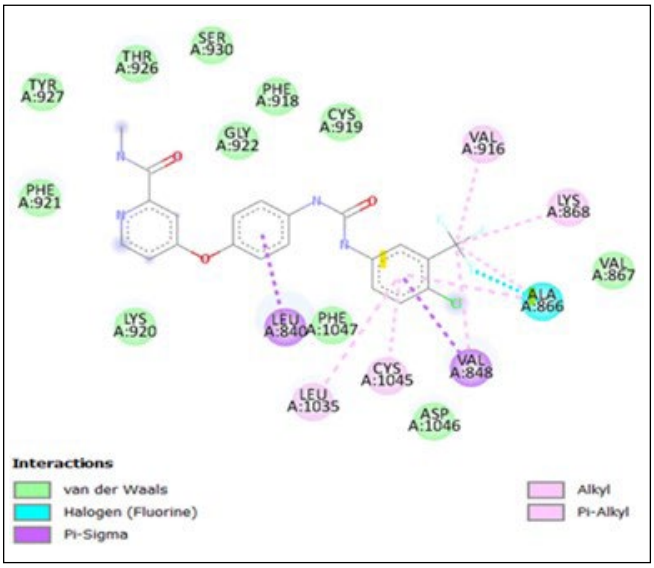

Figure 5a: Interaction of sorafenib with VEGFR2

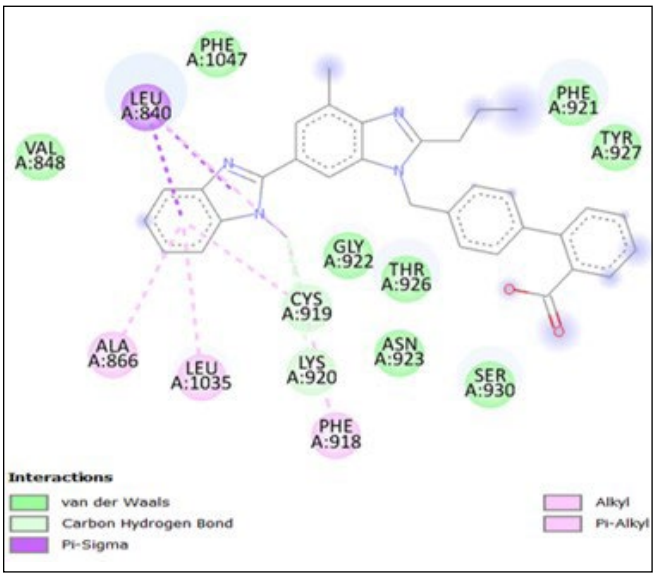

Figure 5b: Interaction of telmisartan with VEGFR2

4. Discussions

The molecular docking analysis revealed distinct binding preferences of Telmisartan and Sorafenib toward the

selected fibrosis-related targets. As shown in **(Table 2)**, Telmisartan demonstrated stronger binding affinities with FGFR1, TGFβ1R, and VEGFR2 compared to Sorafenib, while Sorafenib exhibited greater affinity for PDGFRα and TGFβ2R. These findings suggest that Telmisartan may preferentially modulate receptors associated with fibroblast activation and vascular remodeling, whereas Sorafenib shows a stronger influence on platelet-derived and TGFβ2-mediated signaling.

The interaction profiles further highlighted mechanistic differences between the two drugs. Sorafenib predominantly formed multiple conventional hydrogen bonds, such as with ASP, ASN, and LYS residues in FGFR1 **(Figure 1a)**, while Telmisartan interacted largely through van der Waals forces with several hydrophobic residues, complemented by a hydrogen bond with LYS **(Figure 1b)**. This suggests that Sorafenib's binding stability is strongly hydrogen bond–driven, whereas Telmisartan relies on hydrophobic interactions with selective hydrogen bonding for stabilization.

In PDGFRα binding **(Figure 2a)** and **(Figure 2b)**, Sorafenib displayed a combination of hydrogen bonds (ASP, ARG, and LYS) and van der Waals contacts, which may explain its superior binding affinity. Conversely, Telmisartan engaged extensively with hydrophobic residues, particularly TYR, VAL, and PHE, but lacked multiple stabilizing hydrogen bonds, consistent with its slightly lower binding score. Similar trends were observed in the TGFβ1R complex, where Sorafenib established hydrogen bonds with GLU and LYS residues, alongside van der Waals contacts **(Figure 3a)**, while Telmisartan relied on widespread hydrophobic interactions supplemented with two hydrogen bonds (SER and LYS) **(Figure 3b)**. Interestingly, Telmisartan still demonstrated stronger binding affinity at this receptor, implying that van der Waals interactions played a more dominant stabilizing role.

For TGFβ2R **(Figure 4a)** and **(Figure 4b)**, Sorafenib again formed a greater number of hydrogen bonds with residues such as CYS, ASN, HIS, and VAL, alongside van der Waals contacts, which contributed to its higher binding energy compared to Telmisartan. In contrast, Telmisartan engaged mostly through hydrophobic contacts, with fewer hydrogen bonds, accounting for its slightly weaker affinity. Finally, in the VEGFR2 complex **(Figure 5a)** and **(Figure 5b)**, Sorafenib displayed interactions with multiple aromatic and polar residues, including hydrogen bonding with key residues such as SER and ASP. However, Telmisartan formed an extensive hydrophobic network with residues like PHE, VAL, and TYR, which stabilized the binding despite fewer hydrogen bonds, resulting in its stronger affinity score.

Taken together, these observations suggest that Telmisartan, while not traditionally classified as a multi-kinase inhibitor, exhibits strong and selective binding to critical fibrosis-related growth factor receptors, particularly FGFR1, TGFβ1R, and VEGFR2. Its interaction profile, dominated by van der Waals forces with selective hydrogen bonding, highlights a distinct binding mechanism compared to Sorafenib, which relies more heavily on hydrogen bond stabilization. These results indicate that Telmisartan may offer therapeutic benefits beyond its antihypertensive role by interfering with signaling pathways central to cardiac fibrosis and pathological hypertrophy.

5. Conclusion

Molecular docking analysis indicates that Telmisartan exhibits notable binding affinity to key growth factors involved in cardiac fibrosis and remodeling, comparable to the established growth factor inhibitor, Sorafenib. While Sorafenib demonstrated stronger interactions with PDGFRα and TGFβ2R, Telmisartan exhibited superior affinity for FGFR1, TGFβ1R, and VEGFR2, suggesting its potential role in modulating fibrosis and hypertrophic signaling. These findings provide insights into Telmisartan's potential repurposing as a growth factor inhibitor in CHF management, warranting further experimental validation.

6. Declarations

6.1. Ethics approval and consent to participate

Not Applicable

6.2. Consent for publication

Not Applicable

6.3. Availability of data and material

Not Applicable

6.4. Competing interests

Both authors declare no conflict of interest.

6.5. Funding

Not Applicable

7. Authors Contribution

1. **Anil Kumar Prajapati:** Designed, conceived, collected data, and wrote the manuscript.
2. **Gaurang B. Shah:** Supervised the work and reviewed the manuscript

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