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Research Article

Prediction of MMP-9 Polymorphism Impacts on MDR-TB by Molecular Simulation and Network Interaction

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ABSTRACT

MMP-9 overexpression is associated with a poor outcome in MDR-TB patients, indicating that MMP-9 is a suitable target for MDR-TB therapy. MMP-9 also includes SNPs that occur at inhibitor binding areas as well as zinc ions. As a result of polymorphisms, the usage of MMP-9 inhibitors for MDR-TB might vary. Through molecular simulation, it has been found that the mutant MMP-9 has a larger cavity and a more lipophilic surface. The docking tests revealed that EGTA had the least amount of binding energy to both wild-type and mutant MMP-9. The wildtype MMP-9 can bind zinc when EGTA is in the active site. This shows that using EGTA to chelate Zn is only partially successful. However, the binding energy of EGTA at the active site suggests that it may be a competitor to MMP-9 substrates. On the other hand, Zn is not involved in the interaction of the mutant MMP-9-EGTA complex.

Key words: Matrix metalloproteinase 9, Multidrug resistantTB, Gene polymorphism, Molecular simulation.

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BACKGROUND

Tuberculosis (TB) is a contagious infectious disease that is one of the leading causes of death in the world. Tuberculosis is caused by Mycobacterium tuberculosis which is transmitted when a person with tuberculosis releases bacteria into the air (such as coughing). About 90% occur in adults and men are infected more often than women. The global number of deaths will be around 1.3 million by 2020, and almost double the number caused by HIV/AIDS (0.68 million). This death rate is also affected by the COVID-19 pandemic in 2020.[1]

In addition to the problem of the COVID-19 pandemic, the emergence of a mutated strain of Mycobacterium tuberculosis that is resistant to the main anti-tuberculosis drugs is a threat to control efforts. Multidrug-resistant tuberculosis (MDR-TB) has been reported in all regions of the world. Multidrug-resistant TB (MDR TB) is caused by organisms that are resistant to at least isoniazid and rifampin, the two most potent TB drugs. This drug is used to treat all people with TB disease.[2]

Matrix metalloproteinases (MMPs) and tissue inhibitors (TIMPs) of metalloproteinases are potential regulators of tuberculosis (TB) pathology.[3] The main function of MMPs is the degradation and regulation of extracellular matrix (ECM) proteins. They also liberate bio-active proteins, including cytokines, chemokines, and growth factors.[4] Additionally, MMP-9 can degrade type IV collagen and destroy the basement lung membrane. Several studies have exhibited the crucial role of MMP-9 in manifestations of tuberculosis, including active cavitary tuberculosis,[5] meningitis,[6] and pleurisy.[5] The ECM plays an important role in the structure and composition of granulomas in terms of leukocyte trafficking to and from this dynamic environment and may contribute to the relative location of leukocyte subpopulations.[7] Upregulation and overexpression of matrix metalloproteinases in tuberculosis infection are associated with granulomas and suggest a specific role of matrix metalloproteinase-9 in the inflammatory response in tuberculosis.[8,9]

MMP-9 overexpression in patients with MDR-TB is associated with a poor prognosis, suggesting the use of MMP-9 as an ideal target for MDR-TB treatment.[10,11] Additionally, MMP-9 has SNPs that occur around binding sites of inhibitors as well as zinc ions. Therefore, the use of MMP9 inhibitors can be varying for MDR-TB due to polymorphisms. This study aims to analyze the impact of MMP-9 polymorphism on MDR-TB.

MATERIALS AND METHODS

This study utilized a computer with system specification Intel® Inside CORE i5 CPU 2.00 GHz, 6,00 GB of RAM and OS Windows 8.1.

SNP selection

The MMP-9 SNP investigated in this study was chosen based on the domain where the mutation occurs and causes protein change. We narrowed it down to rs55789927 which occur in the catalytic domain of MMP-9 to study its effect on MMP-9 inhibitors binding affinity to MMP-9. This SNP causes amino acid change L187F with GMAF 0.002.

Gene-Gene interaction

The interaction of the MMP-9 gene to other genes was explored using Gene Cards. The network of interaction was illustrated using STRING.

Preparation of receptor

MMP-9 wild-type structure was downloaded from www.rcsb.org in .pdb format (PBD ID: 1GKC). The MMP-9 SNP rs55789927 sequence was investigated using BLAST and PsiPred to predict any differences

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between SNP and the wildtype. The 3D structure was modelled using the Swiss Model webtool. Then, the chain receptor was separated from the co-crystalized ligand. The preparation of protein includes protonating in 3D, minimizing energy, and removing water.

Preparation of ligand

Every MMP-9 inhibitor found in https://www.medchemexpress.com under the "MMP-9 inhibitor" keyword was retrieved. Seventeen ligands were selected and each structure in .sdf format was obtained from the Pubchem database. As positive control, we use marimastat, a known MMP-9 inhibitor to enhance treatment for MDR-TB. The .mol format of each ligand was converted from .sdf format using OPENBABEL.

Validation of docking method, docking analysis

The MMP-9 protein obtained from the Protein Data Bank (PDB) and each target compound were docked using MOE 2020. The possible active sites of the protein were predicted in MOE 2020 as well and visualize the interacting residues of the ligand-receptor complex.

RESULTS

Main effect of MMP-9 polymorphism

Matrix metalloproteinases (MMPs) family proteins are known to have a variety of crucial physiological tasks, including modifying the extracellular matrix, promoting cell migration, cleaving cytokines, and activating defensins. The pathogenesis of pulmonary disorders such as lung cancer, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, sarcoidosis, and tuberculosis is linked to dysregulated MMP activity (TB).[12] From this effect mechanism of MMP-9 of above, we conducted network interaction by gene interaction with cytoscape and strings as figure 1.

Gene-Gene interaction

From figure 1 showed that MMP-9 promotes contraction and helps TGFB1 become activated. One potential method might be the direct stimulation of TGF- MMP-9, which can induce contraction.

String analysis showed that KEGG pathway MMP-9 connected to tuberculosis hsa05152 with tuberculosis pathway. Hsa05152 pathway have 168 connected gene with strength 1.22 (strength 1-3 is high) and false positive 0.0446. https://string-db.org/cgi/network?taskId. The genesis and progression of lung damage is impacted by the imbalance of MMPs and TIMPs, which also impacts the metabolism of the extracellular matrix (ECM). A new approach to treating MDR-TB may involve inhibiting MMP2 and MMP9 activity, which may lessen ECM deterioration and lessen lung harm.[13] According to its mechanism, the development of MMP inhibitors with high selectivity and high bioavailability may offer a significant research path and serve as a new entry point for MDR-TB prevention and treatment options.

Through the downregulation of MMP9, FAK, and Rho/ROCK activity, the knockdown of CTSB compromised the development of leader cells, disturbed cytoskeletal structure, changed cell shape, and prevented ECM remodeling. These findings show that CTSB may play a role in the control of protease- and force-mediated ECM remodeling.

Inhibitor MMP9 from Pubchem database

The inhibitor used in this study is based on a Pubchem database, which will then be analysed using molecular docking predictions. Marimastat (BB-2516), a broad-spectrum matrix metalloproteinase (MMP) inhibitor with IC50 values of 3, 5, 6, and 13 nM for MMP-9, MMP-1, MMP-2, MMP-14, and MMP-7, respectively,[14] was used as a positive control. MMPs, a homologous family of enzymes, are

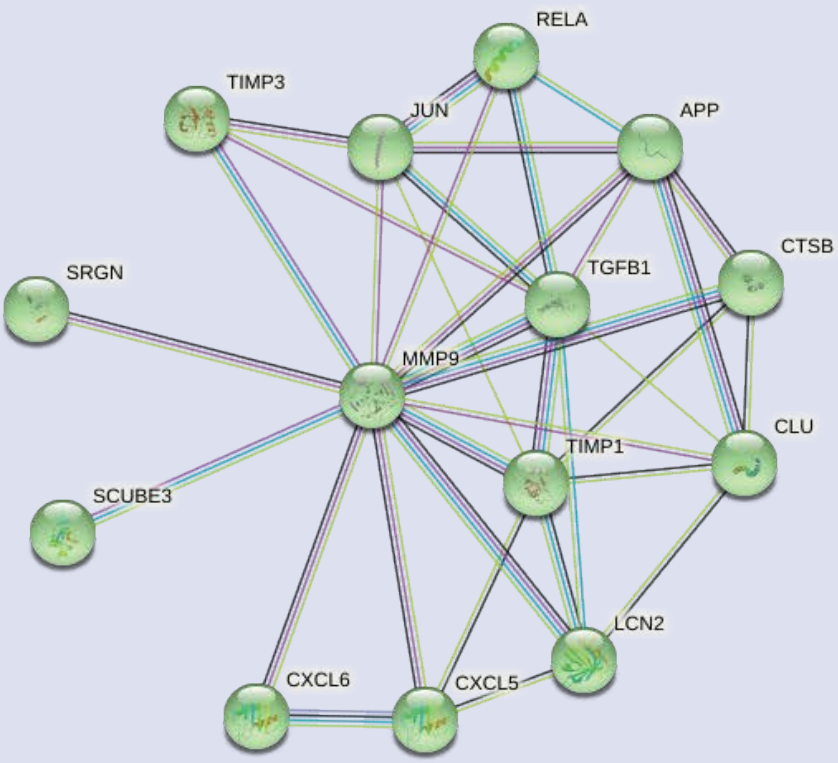

Figure 1: Gene-gene interaction of MMP-9 related to MDR-TB.

involved in tissue remodelling and morphogenesis. Individually, these enzymes can degrade every component of the extracellular matrix, making them essential for wound healing and other tissue remodelling processes. Marimastat, with an IC50 of 1 uM, suppresses soluble TNF-alpha production caused by lipopolysaccharide (LPS) as well as CD30 shedding in Karpas 299 cells in a dose-dependent manner. Marimastat, with an IC50 of 3.8 nM, specifically inhibits the enzyme Tumor necrosis factor alpha convertase (TACE), which is thought to be linked to matrix metalloproteinases and is involved in the conversion of pro-TNFalpha to TNFalpha.[15]

Marimastat treatment decreases the degradation of the mannose-binding protein and extracellular matrix turnover in Mtb-infected animals.[16] Both histological examination and vascular-permeability tests show that Marimastat therapy stabilized the blood vessels in the TB granulomas. Instead of leaky arteries, healthy blood vessels might increase the quantity of medication that is taken orally that is delivered to the lung. As a result, tiny molecules and anti-TB medications are better retained in tissue.[16] Furthermore, the accessibility of drugs to the bacteria at the core of a limited structure may be improved by healthy blood vessels.

3D comparison of MMP-9 polymorphism to wildtype

Sequence alignment of MMP-9 polymorphism rs55789927 to wildtype shows protein change in amino acid residue number 187, from leucine to phenylalanine. We purposefully only investigated MMP-9 protein from residue number 107-215, i.e. around the active site of MMP-9. The protein change also causes differences in secondary structure. (Figure 2)

The 3D structure of MMP-9 mutant was obtained with 94.39% of the residues in favour of Ramachandran plot. There is no outlier found in the Ramachandran plot, indicating the model has good structure stereochemically. Furthermore, the colour of the structure model shows confidence in the result, the bluer it is, the higher the confidence. The structure model only has low confidence in the terminals of the structure. (Figure 3)

To visualise the difference in 3D structures of MMP-9 mutant to wildtype, the homology model and protein crystal of MMP-9 wildtype (PDB ID: 1GKC) were aligned. The RMSD of the alignment is lower than 2 A (0.425 A). There are two beta-sheets with different length. (Figure 4)

The results from the MOE 2020 site finder show that MMP-9 has two cavities with the active site around Gln2, Phe4, Asp71, Gln72, Tyr73, His84, Ala85, Phe86, Pro87, Ile92, Leu 187 and the second cavity is around Arg56, Val61, Gln63, His69, Gly70, Asp71, Gly91, Ile92, Asp95 and His97

Molecular docking of MMP-9 and inhibitor

The molecular docking results revealed that the MMP-9 inhibitor compound with a positive control of marimastat had the lowest energy value when compared to the marimastat control. ARP100, EGTA, Tapi-1, Salvianolic acid, BR351, Tapi-2, Prinomastat, and Cipemastat are the inhibitor compounds with the lowest energy compared to controls on wildtype MMP-9 targets. ARP100, EGTA, Tapi-1, BR351, Tapi-2, Prinomastat, Apigenin, and Luteolin were the inhibitor compounds with the lowest energy compared to controls on the target MMP-9 mutant, as shown in table 2. The docking results revealed MMP-9 wildtype or mutant complex. The MMP-9 complex with the inhibitor EGTA had the lowest energy.

Figure 6 shows a wildtype MMP-9 backbone complex with EGTA, from the backbone it can be seen that EGTA is at the active site of the wildtype MMP-9, Figure 6 A.2 shows a 2D complex docking results, the EGTA ligand is able to bond with Zn in MMP-9 with metal bonds at the Glu111 and His41 sites, while hydrogen bonds with amino acids MMP-9 at the Ala191 site, and Ala Figure 6.A. 3 depicts the surface topology of MMP-9's active site; the EGTA inhibitor is able to enter the cavity of MMP-9's active site. Figure 6.B depicts the complex between MMP-9 mutant and EGTA inhibitor. Figure 6.B.1 depicts a mutant MMP-9 backbone complex with EGTA, with the mutant MMP-9 backbone exhibiting a change in the alpha helix approaching EGTA, whereas Figure 6.B.2 depicts a 2D complex resulting from the docking of EGTA ligands entering the cavity of MMP-9 mutant by binding to the amino acid site Arg162 and in the mutant demonstrating that the EGTA inhibitor does not bind to Zn as the mutant complex alters the cavity topology of the MMP-9 cavity, as shown in Figure 6.B.3. The cavity of MMP-9 is larger, and the surface is lipophilic.

Figure 7a shows that wildtype MMP9 in the presence of EGTA can bind ZN with Glu111 and His41, indicating that wildtype functions as a transcription factor, inducing genes that confer resistance to methylating agents. whereas in 7b, the MMP-9 mutant inhibitor complex was shown to be unable to bind to Zn.

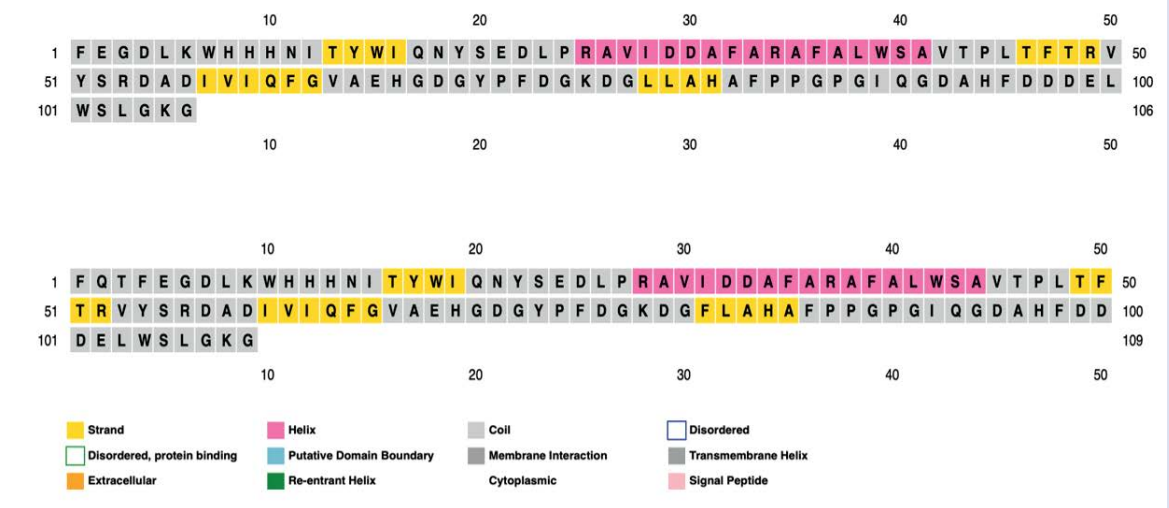

Figure 2: Secondary structure comparison of MMP9 wildtype and mutant.

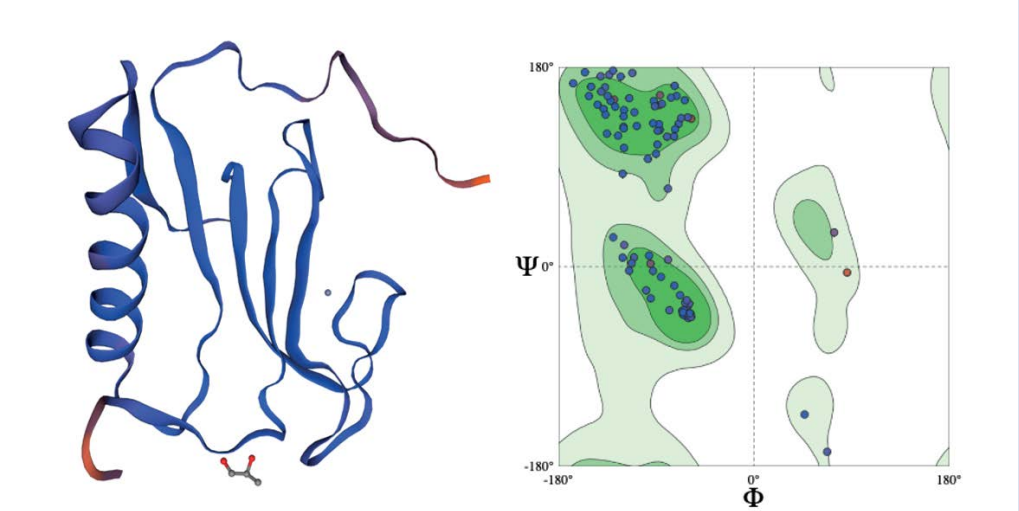

Figure 3: Swiss Model result of MMP9 mutant structure and corresponding Ramachandran plot as validation.

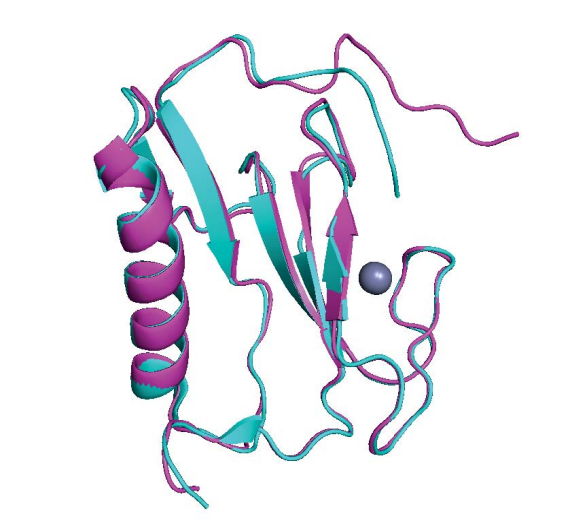

Figure 4: Wildtype (cyan) and mutant (pink) structure alignment.

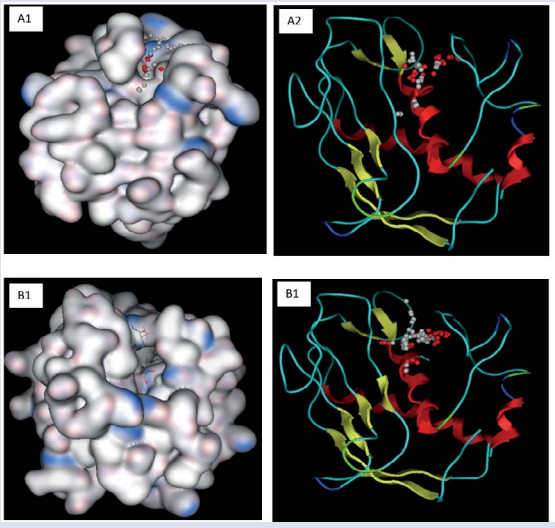

Figure 5: Cavity and native ligand conformation of MMP-9, A) 1. Cavity MMP-9 mutant and 2. 3D conformation of MMP-9 mutant, B) 1. Cavity MMP-9 wildtype and 2. 3D conformation of MMP-9 wildtype.

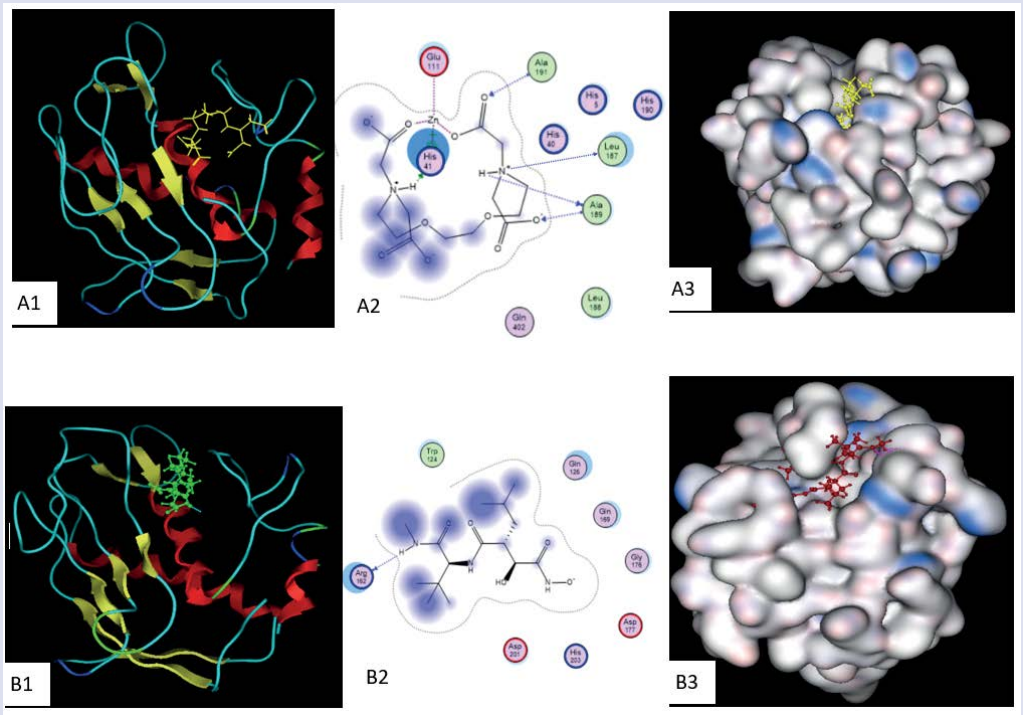

Figure 6: Complex docking MMP-ligand. A1. The backbone of complex mmp9 wildtype-EGTA, A2. Complex 2D mmp9 wildtype-EGTA, A3. complex 3D mmp9 wildtype-EGTA. B1. The backbone of complex mmp9 mutant-EGTA, B2. Complex 2D mmp9 mutant-EGTA, B3. The Complex 3D mmp9 mutant-EGTA.

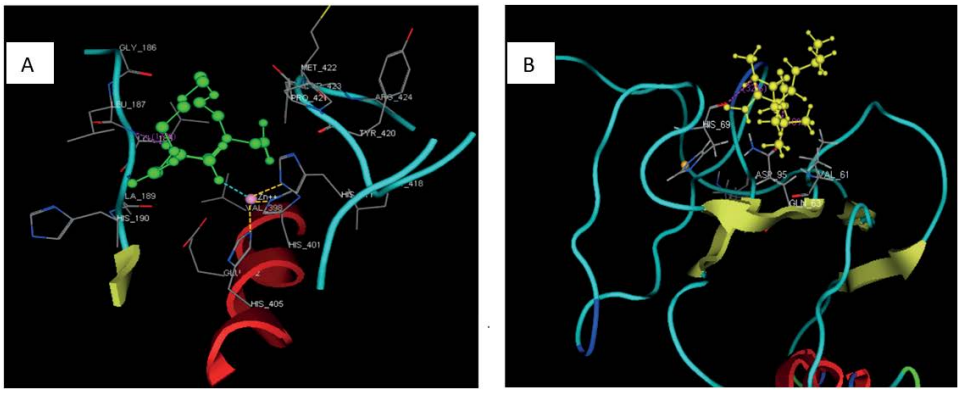

Figure 7: Zinc interaction MMP9-inhibitor a) complex Zinc-MMP-9 wildtype-EGTA, b) complex Zinc-MMP-9 mutant-EGTA.

DISCUSSION

SNPs in the MMP-9 gene may be potential candidates for genetic factors affecting the onset and signs of tuberculosis (TB).[10,11] High levels of MMP-9 have been seen in the cerebral fluid of patients with tuberculous meningitis and in the pleural fluid of patients with tuberculous pleuritis.[8] MMP-9 is generated by *M. tuberculosis infection*. Additionally, individuals with more advanced pulmonary TB have greater MMP-9 levels than do patients with less advanced TB.[5]

There is not much information on the rs55789927 SNP effect *in vitro* or *in vivo*. Leucine (Leu) and phenylalanine (Phe) are both non-polar amino acid residues. Basic amino acids' R groups either contain aliphatic or aromatic groups. Because of this, they are hydrophobic (fearful of water). To encapsulate these hydrophobic side chains in the center of the protein, globular proteins will fold into a three-dimensional form in aqueous solutions. Phe has a far lower solubility than Leu because it has an aromatic ring that is extremely hydrophobic.[17]

Zinc in proteins can either participate directly in chemical catalysis or be important for maintaining protein structure and stability. In all catalytic sites, the zinc ion functions as a Lewis acid.[18] Finally, in structural zinc sites, the zinc ion mainly stabilizes the tertiary structure of the enzyme in a manner analogous to disulfide bonds. In all cases, removal of the bound zinc can lead to a loss of enzymatic activity. A systematic analysis of the structure and function of a number of zinc proteins has established distinct features of catalytic and structural zinc sites. the biochemical role of zinc in these biological macromolecules increases, the connection between the detailed biochemical functions and physiological phenotypes can be established.[19]

From PPI figure 1 showed that Alternatively, MMP-9 could induce contraction by a different method, and the resulting contraction might

Table 1: MMP-9 inhibitors.

No.	MMP-9 inhibitors
1.	Marimastat
2.	EGTA
3.	Ilomastat
4.	Prinomastat hydrochloride
5.	Salvianolic acid A
6.	Apigenin 7-glucuronide
7.	Isoliquiritin apioside
8.	Cipemastat
9.	Tapi-1
10.	ARP100
11.	Tapi-2
12.	Luteolin
13.	Morroniside
14.	MMP-9 Inhibitor
15.	BR351
16.	CMC2.24
17.	MMP-9-IN-1

Table 2: Molecular docking of MMP-9 to inhibitors.

No.	Inhibitor	MMP-9 Wildtype		MMP-9 Mutant	
		S Value	pKi	S Value	pKi
1.	ARP100	-19.7617	36,72962	-15.4877	26,140298
2.	EGTA	-19.8330	35,16215	-16.5703	33,030952
3.	Tapi-1	-19.4018	32,74656	-16.2638	30,319485
4.	Salvianolic Acid A	-18.0176	30,41029	-13.3168	22,476231
5.	BR351	-17.3141	29,22291	-15.1745	25,611676
6.	Tapi-2	-16.6137	28,04077	-16.0830	27,145051
7.	Prinomastat hydrochloride	-17.8870	26,81424	-14.2232	24,006062
8.	Isoliquiritin apioside	-15.6418	26,40039	-13.0965	22,104406
9.	Apigenin 7-glucuronide	-13.3454	25,90013	-16.3339	28,412428
10.	Ilomastat	-14.9386	25,21352	-12.9571	21,869126
11.	Cipemastat	-16.6414	24,71190	-13.5213	22,821388
12.	Luteolin	-14.5775	24,60405	-14.5169	24,501772
13.	**Marimastat**	**-16.0922**	**23,78496**	**-14.0322**	**24,460083**
14.	MMP-9 Inhibitor	-15.9033	23,46613	-16.3056	27,520758
15.	CMC2.24	-12.8131	21,62608	-10.4938	17,711543
16.	MMP-9-IN-1	-12.5792	21,2313	-7.3163	12,348526
17.	Morroniside	-9.7226	16,40990	-9.9001	16,709490

activate TGF-. This suggests that MMP-9 and TGF- may be involved in a positive feedback loop that controls fibroblast activity and is dependent on contraction. Since TGF- may control MMP-9 release, the possibility of positive feedback between TGF and MMP-9 is further established.[20]

p38 MAPK activates the transcription factor c-Jun, and the activated c-Jun subsequently recruits p38 as a cofactor into the promoter of matrix metalloproteinase 9 (MMP-9) to cause its trans-activation and cell invasion. By interacting with c-Jun, overexpressed p38 caused a rise in c-Jun synthesis, MMP9 transcription, and MMP9-dependent invasion, which started this signaling sequence.[21,22]

The zinc ion's primary function in zinc proteins can be catalytic, cocatalytic, or structural. The zinc ion directly takes part in the bond-forming or -breaking process at a catalytic zinc site. Several metal ions are bonded together and close to one another at a co-catalytic zinc site, where one of the metal ions catalyzes the reaction while the other metal ions increase the site's catalytic activity.[23] In structural zinc sites, the zinc ion primarily stabilizes the enzyme's tertiary structure in a way similar to how disulfide bonds do. Any time the bonded zinc is taken out, the enzymatic activity may be lost. Different characteristics of catalytic and structural zinc sites have been identified by a thorough examination of the structure and function of many zinc proteins.[24] The relationship between specific biochemical operations and physiological phenotypes can be established as knowledge of zinc's biochemical activity in various biological macromolecules grows.

An enzyme's active site is where a catalytic zinc ion is found, directly participating in the catalytic mechanism by interacting with the substrate molecules being processed. Histidine is the most often seen ligand at catalytic zinc sites, followed distantly by glutamic acid, aspartic acid, and cysteine. Although coordination with Nε atoms has also been noted, the bulk of histidine zinc ligands discovered in zinc protein structures coordinate zinc through the Nδ atom.[25,16] The metal ion likes to approach the nitrogen atom's sp2 lone pair in-plane and head-on for these interactions.[26]

Three domains typically make up human MMP-9 proteins: An N-terminal propeptide domain, a catalytic domain, and a hemopexin-like domain at the C-terminus. Human MMP-9's catalytic domain, which lacks the repetitions of fibronectin, has the same molecular make-up as other MMPs: a five-stranded beta-sheet and three alpha helices. It is made up of the crucial glutamic acid residue, the active-site zinc ion, and three histidine residues. Proteolytic action requires the catalytic zinc ion.[27]

Over the last three decades, multiple synthetic MMP inhibitors have been created and developed[28-30] by using the presence of a metal ion and diverse substrate-binding pockets. A hydroxamic acid zinc-binding group (ZBG) was added to the native peptide substrates of MMPs in the first generation of MMPi to chelate the catalytic Zn2+ ion and inactivate the protein.[29] These were strong, all-purpose MMP inhibitors that could block MMPs at low doses without favoring one MMP over another. Meanwhile second- and third-generation MMPi were no longer constrained to substrate-like compounds as additional MMPs had their structures established by crystallographic techniques, and novel inhibitors were developed with a range of peptidomimetic and non-peptidomimetic structures. With an IC50 value against the target MMP up to three orders of magnitude better (i.e., lower) than the IC50 values against all other non-target MMPs, these next-generation compounds were created to achieve improved selectivity.[31]

Genetic polymorphism is the main factor for interindividual variations in medication metabolism. Many of them have a significant influence on drug metabolism and need to be taken into account when administering medications and to prevent drug toxicities.[32] L187F mutation happens in the catalytic domain of MMP-9. Though not much has been revealed about this SNP, leucine and phenylalanine have different shape, size, and aromaticity. Leucine results in a floppy but native-like structure whose Zn affinity is maintained by substantial entropy-enthalpy compensation, meanwhile phenylalanine is a part of three architectural elements of classical Zn finger: β-hairpin, an α-helix, and a Zn^{2+}-binding site. So, theoretically, L187F mutation might change the MMP-9-Zn ion interaction.[33]

Conformation of Zn, functions as a transcription factor, inducing genes that confer resistance to methylating agents. The proposed role of the zinc ion in targeted, coordinating the cysteine thiolate enhances the reactivity of this group,[34] is similar to the role being proposed for zinc in several enzymes that catalyze S-alkylation reactions, such as cobalamine. Zinc metalloproteins may indicate a new catalytic function of the zinc ion: to enhance the nucleophilicity of a thiol group at neutral pH.[35]

CONCLUSION

Potential options for genetic variables influencing the onset and symptoms of tuberculosis include SNPs in the MMP-9 gene (TB). The rs55789927 SNP which occurs in the catalytic domain of MMP-9 causes L871F change. It has been noted that the mutant MMP-9 has a bigger cavity and a more lipophilic surface. According to the docking studies, EGTA had the lowest binding energy to both wild-type and mutant MMP-9. When EGTA is present in the active site, the wildtype MMP-9 is able to bind zinc. This suggests that chelating Zn with EGTA is only partially effective. The binding energy of EGTA at the active site, however, indicates that it has the potential to be a rival to MMP-9 substrates. The mutant MMP-9-EGTA complex, on the other hand, does not interact with Zn.

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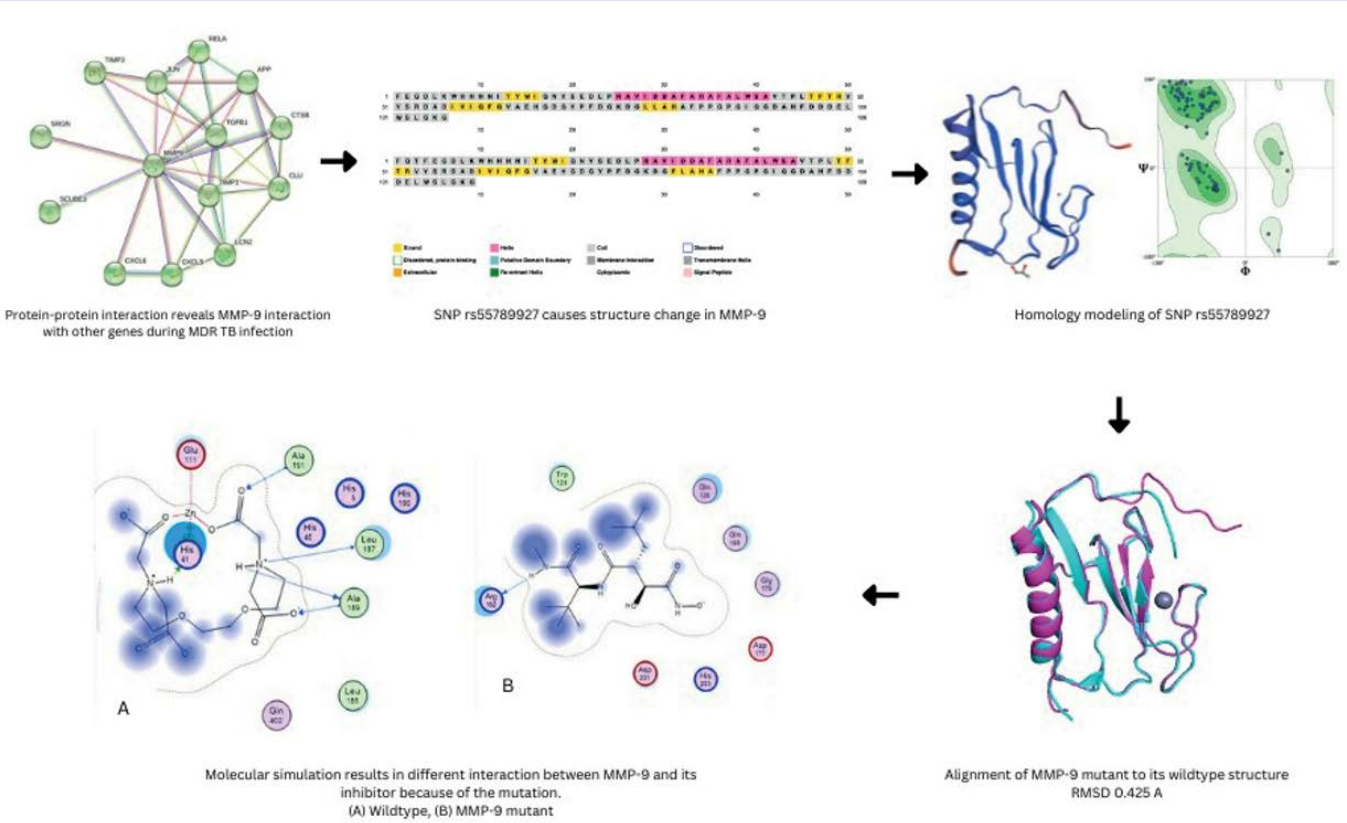
GRAPHICAL ABSTRACT



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