

# Matrix Metalloproteinase – 7 (MMP-7) and its Biodiversity in Health and Disease: A Comprehensive Literature Review.

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## Abstract

Matrix metalloproteinases, because of their ability to degrade the extracellular matrix, play a vital role in various cellular processes like apoptosis, invasion, cell proliferation, and distant metastasis. A comprehensive review was done to evaluate the role of MMP-7 in health and disease. Among all MMPs, MMP-7 is the smallest one, also known as Matrilysin and possesses structural differences from the rest of MMPs with diverse roles in diseases like cancer, inflammation, cardiovascular diseases, and fibrotic diseases. Its overexpression through various signal-mediated pathways and association with diseases has highlighted its implication as a diagnostic as well as a prognostic marker. Out of the two most studied SNPs of MMP-7, the A to G transition at the -181 base pair position (-181 A/G) shows variable expression of MMP-7 in different patients. MMP-7 activity, being more evident on the surface of immune cells and tumour cells, points towards targeting MMP-7 in mucosal and epithelial tumours as well as to reduce inflammatory processes and pave the way to future therapeutic strategies by inhibiting MMP-7 expression in modulating diseases.

**Keywords:** MMP-7, cancers, fibrosis, inflammatory disease, cardiovascular disease, serum levels of MMP-7, single nucleotide polymorphisms of MMP-7

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## Introduction

Extracellular matrix (ECM) is a dynamic non-cellular environment around cells imparting structural support [1]. This ECM is made up of substances like collagen, fibronectin, laminin, and glycosaminoglycans that undergo continuous remodelling [2] and take part in many vital events by signalling through cell surface receptors [3]. Matrix metalloproteinases (MMPs) are calcium-dependent zinc-containing endopeptidases that participate in degrading all kinds of protein in ECM [4]. Because of the ability of MMPs to process and cleave a number of active biomolecules like cell surface receptors and Fas ligands, these MMPs play a vital role in biological processes of cells, like proliferation, migration, apoptosis, distant metastasis, being a part of normal health and diseases [5].

Based on domain arrangement, these MMPs are subdivided into the following four groups: Gelatinase, furin-activatable MMP, archetypal and Matrilysin type [6]. According to substrate specificity, they are grouped into six groups: Collagenase, Gelatinase, Stromelysin, Matrilysin, Membrane type

and others [7].

MMPs were discovered for the first time in 1962 by Woessner, who mentioned them as a protein enzyme that can degrade collagen in the uterus of mammals. Jerome Gross discovered the first MMP-1 and Charles Lapiere during tadpole tail metamorphosis identified the collagenolytic enzyme activity in tadpole tail. To date, a total of 28 MMPs have been discovered [8]. Among all MMPs, MMP-7 is the smallest MMP, known as Matrilysin, Matrilysin-1, or PUMP-1[9]. MMP-7 was discovered in a rat uterus in 1988, for which it is also called uterine metalloproteinase [10]. A thorough review of all published articles on matrix metalloproteinase-7 was done to understand its impact on health and disease and to postulate its role as a surrogate biomarker in diagnosis.

The literature search was done by using PubMed and Google Scholar search engines. All the recently published articles on MMP-7 in various health and disease conditions were included, i.e., from 2006 to 2023. Keywords used in the search engines were MMP-7, MMP-7 as a biomarker, [MMP-7] and [different diseases]. After data collection, the authors thoroughly reviewed and compiled it

based on its diagnostic and therapeutic importance.

### Structure of MMP-7

MMP-7 reveals itself structurally little different from typical Zn-containing MMPs, having a Pro-peptide domain, a Catalytic domain, and a linker or hinge between them where one hemopexin domain remains attached to the catalytic domain. In the catalytic domain, three Histidine sequence holds the Zn ion in the active site, and the glutamate residue activates a Zn-bound H<sub>2</sub>O molecule, providing nucleophile activity for cleaving the peptide bond [7]. This Matrilysin (MMP-7), i.e., Matrixins, does not contain the hemopexin domain nor the linker and consists of 267 amino acids. MMP-7, secreted as a precursor molecule, the pro-peptide domain is degraded proteolytically stepwise, resulting in a 19 kDa peptide with endopeptidase activity. Two calcium ions are also bound with MMP-7, which helps stabilize the protein's secondary structure. The gene coding for MMP-7 is located on chromosome 11q21-22 [11].

### Functions of MMP-7

MMP-7 is expressed physiologically in tissues like the uterus, pancreas, salivary glands, and the glandular epithelium of the intestine [11]. Some tissues express very low levels of MMP-7, like the kidney, bladder, gallbladder, and adult lungs [11,12]. Besides ECM remodelling, MMP-7 promotes angiogenesis and cell proliferation (by disrupting the E-cadherin/β-catenin complex) and decreases apoptosis [13]. These observations suggest its oncogenic role in different types of cancer progression in our body. It is involved in the regulation of inflammation, podocyte function, and MMP-7 also regulates cell adhesion molecules, growth factors, and growth factor receptors like epidermal growth factor receptor (EGFR), transforming growth factor-β (TGF-β) [11,14–16]. MMP-7 also promotes myelination, showing decreased expression in multiple sclerosis [17].

### Role of MMP-7 in cancers

Role of MMP-7 as a biomarker in tumour progression and tumour invasion have been studied by many. Increased levels of MMP-7 were seen in prostate cancer, non-small cell lung cancer, and tongue squamous cell carcinoma (TSCC) [18–20]. Genetic studies have shown MMP-7 181 A-G promoter site single nucleotide polymorphism (SNP) in stomach, breast, oesophageal, squamous cell, lung, and ovarian carcinoma [19, 21–23].

Several mechanisms, like remodelling of ECM, angiogenesis that leads to invasion and metastasis, can explain the role of MMP-7 in carcinogenesis and tumour progression (12). It also mediates the proliferation and differentiation of cancer cells. Its contribution to tumours is also explained by findings from previous studies like strong proteolytic action against different ECM substrates, lack of C-terminal domain in MMP-7 allows TIMP to inhibit MMP-7 only with lower K<sub>i</sub>, and MMP-7 itself is also produced by tumour cells [24–26]. In triple-negative breast cancer (TNBC), MMP-7 is upregulated through wnt/β-catenin pathway activation that can lead to the loss of tumour suppressor gene PTEN and promote metastasis [27–29]. Similarly, it has prognostic role in pancreatic duct carcinoma, showing that the higher the levels of MMP-7, the poorer the prognosis [30]. Expression of MMP-7 in these tumours has stated that MMP-7 can be used both as a diagnostic and prognostic marker of cancer progression and might be used as a therapeutic target [12].

Overexpression of MMP-7 in different cancers is well documented

in many studies. In 2015, Soleyman-Jahi et.al. also concluded with the poor prognostic association of MMP-7 in the survival of gastric carcinoma [31]. Combined expression of MMP-7 and MMP-9 can be used as a marker to detect nodal metastasis and degree of invasion in oesophageal cancers, which is known for its poor prognosis [32].

Using tissue immunohistochemistry, microarray, and western blot technique together revealed an association of active expression of MMP-7 with more aggressive buccal squamous cell carcinoma. The same study has also shown that active MMP-7 can help invade buccal cancer by activating the RANK-RANKL pathway [33]. A study by Yuan Shuo on tongue squamous cell carcinoma (TSCC) also got similar results, i.e., elevated expression of MMP-7 in TSCC specimens. They concluded that MMP-7 has an oncogenic role and can be a potential therapeutic target [20]. A study on MMP-7 in the cases of salivary gland cancer was followed up for a minimum of 10.6 years, in which worse survival was noted in patients with low staining intensity of MMP-7 in immunohistochemistry, the most significant association being seen in actinic cell cancer and mucoepidermoid cancer [34]. A cohort analysis by Kubik et al., with systematic review and meta-analysis, assessed the prognostic role of circulating MMP-7 in urothelial carcinoma. They found that higher serum values of MMP-7 are linked with cases of urothelial cancer patients as compared to controls, and higher values were associated with lymph node-positive patients. Higher levels of Matrilysin were also seen with the poor survival in the cases [35].

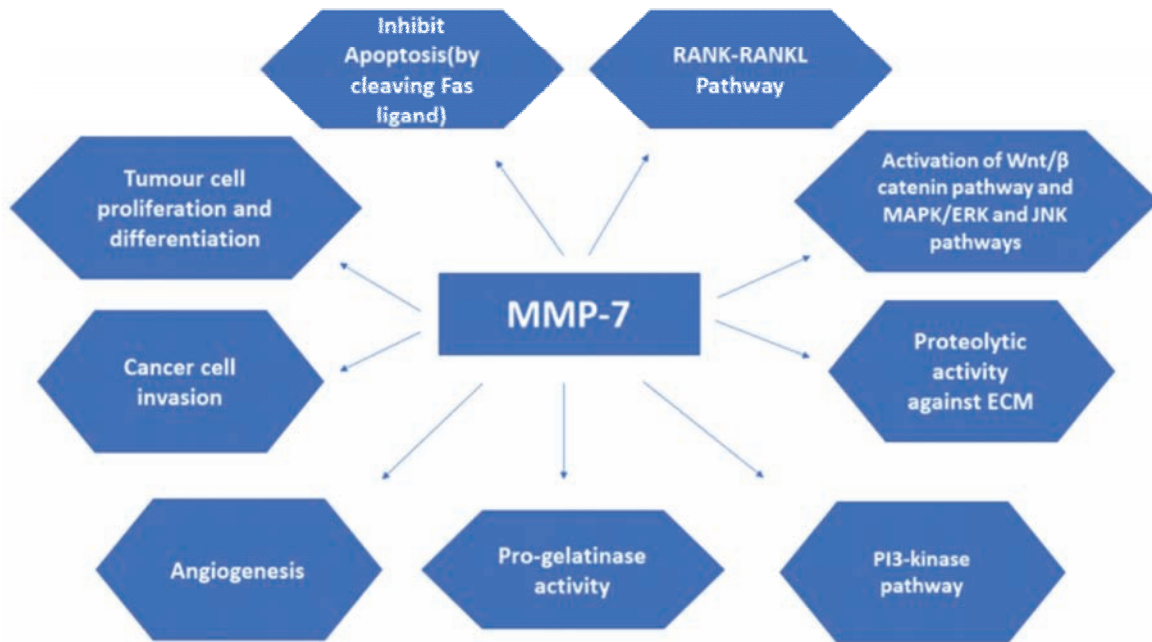
Mysona David et al., in an immunohistochemistry study of cervical cancer, revealed the expression of six proteins (CA153, OPG, CEA, IGFBP7, IGFBP4, and MMP-7) with MMP-7 having the highest sensitivity (92%) and specificity (95%) [36]. Studies have also suggested MMP-7's oncogenic role in ovarian cancer by its proteolytic activity; MMP-7 can lead to invasion in ovarian cancer [37]. MMP-7 can also act through mesothelin (MSLN) activated MAPK/ERK and JNK pathways, leading to tissue invasion in ovarian cancer [38]. In 2018, Garalla H M et al. studied MMP-7 levels in oesophageal adenocarcinoma cell lines (EAC), showing high levels of pro-MMP-7 secretions in EAC cell lines (OE33). Both invasion and migration of myofibroblasts in conditioned media from EAC cell lines decreased after the knockdown of MMP-7, highlighting the activation mechanism of PI3-kinase (phosphatidylinositol-3 kinase) [39].

Yamada et al. explored the role of MMP-7 in spread through air spaces, i.e., a modality of local tumour invasion in lung adenocarcinoma by immunohistochemical analysis using microarray technique in the resected lung adenocarcinoma tissues. Their findings suggested that MMP-7 expression is associated with these patients' tumour severity and poor prognosis [40].

Possible mechanisms by which MMP-7 acts in tumour progression and invasion are given in Fig. 1.

### Role of MMP-7 in inflammation

MMP7-activated α-defensins, a pro-inflammatory mediator which points towards its role in acute inflammation [41]. Abbas et al. in 2020 have shown that MMP-7 may participate actively in the disruption of extracellular matrix and inflammatory response in Psoriasis patients, making it a predictor of psoriasis dermatosis [14]. Jakubowska et al. in 2015 showed that the overexpression of metalloproteinases (MMP-2, MMP-7, MMP-9) associated with development of inflammatory bowel diseases [42]. In the work of Rath et al., it was noted that MMP-7, like MMP-13, is expressed



**Fig. 1.: Possible mechanisms by which MMP-7 acts in tumour progression and invasion**

on the tumour cell surface primarily and is found elevated in inflammatory bowel disease that possesses more chance to transform into malignancy compared to normal tissue [43].

### Role of MMP-7 in cardiovascular diseases

Elevated MMP-7 levels have been observed in many CVDs like carotid atherosclerosis, carotid stenosis, pulmonary artery hypertension (PAH), and myocardial infarction (MI) [44–46]. It is also noticed from different studies that with its proteolytic activity and potential to cleave N-cadherin, MMP-7 can also contribute to plaque rupture and thrombotic complications [47].

MMP-7 role was also studied in post-MI related changes in the heart, and it also mentioned that Connexin-43 is the substrate of MMP-7. It was seen that the conduction pattern in post-MI hearts improved after the deletion of MMP-7 [48]. After that, many studies were conducted to establish the role of MMP-7 in association with coronary artery disease (CAD). In 2014, Abbas et al. concluded that MMP-7 has some role in plaque instability in carotid atherosclerosis. They evaluated plasma mRNA of MMP-7 among 182 patients of carotid artery stenosis ( $\geq 70\%$ ), found significantly higher levels of plasma MMP-7 and mRNA levels of MMP-7, especially in cases with recent symptoms. Immunohistochemistry studies in these patients gave hints that it involves macrophage-related mechanisms [44].

Arvidsson et al. in 2019 suggested that MMP-7 can be used as an additional tool to distinguish PAH patients from other pulmonary hypertension (PH) patients like HFpEF (heart failure with preserved ejection fraction), TEPH (thromboembolic pulmonary hypertension). It was noted that plasma values of MMP-7 were increased among PAH cases, but it was not significantly increased in cases of TEPH, and HFpEF patients. The possible mechanism they suggested was MMP-7's activity in the E-cadherin/ beta-catenin pathway and HB-EGF signalling pathway [46].

Moreno-ajona et al. in 2020 has studied prospectively the circulating MMP-7 among carotid stenosis cases ( $>70\%$ ) to assess the prognostic role of MMP-7 along with other MMPs and TIMP-1

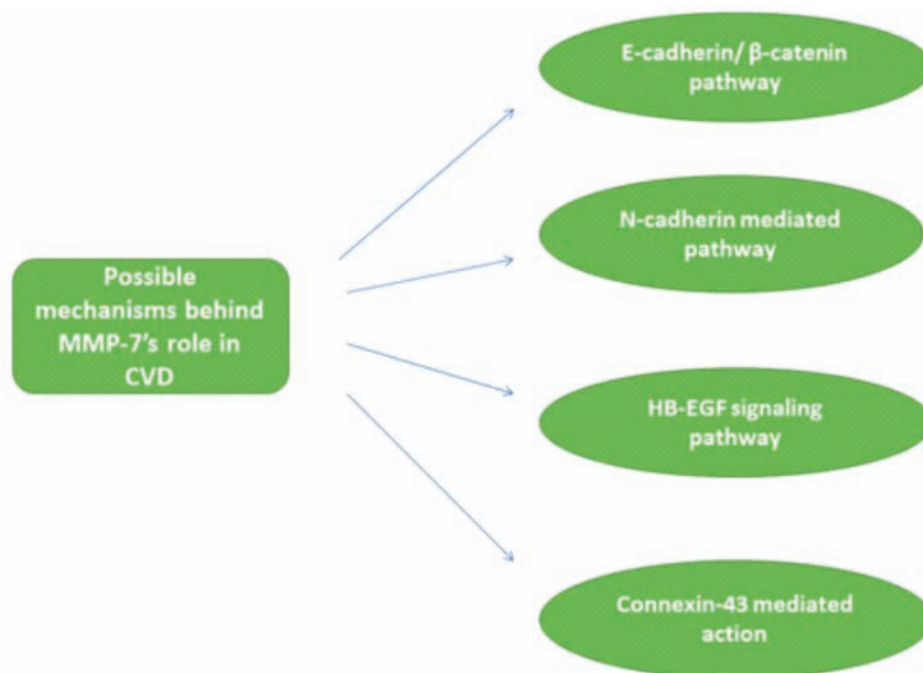
in relation to the risk of development of CVD after undergoing carotid endarterectomy. Blood samples were collected within two days before their carotid endarterectomy surgery, and found that plasma levels of MMP-1,7,10 were significantly higher compared to that of the control group with no significant difference in circulating levels of other MMPs and TIMP-1. Follow-up of these patients also proved that MMP-7 was capable of predicting cardiovascular events in those patients [49]. MMP-7's role in cardiovascular disease is shown in Fig. 2.

### Role of MMP-7 in fibrotic disorders

It has been seen that MMP-7 levels also vary in different fibrotic disorders as a diagnostic or prognostic biomarker of fibrosis like idiopathic pulmonary fibrosis (IPF), non-alcoholic fatty liver disease (NAFLD) interstitial lung disease (ILD), Chronic kidney disease (CKD), biliary atresia [11,50-53].

Many studies about MMP-7's role in fibrosis suggested overexpression of MMP-7 in the IPF cases lungs. Bauer et al. showed that MMP-7 circulatory levels could predict patients who were prone to getting severe, emphasizing that MMP-7 can be used as a biomarker to predict disease progression in IPF. Another fibrotic disorder of the lungs is ILD, is a cause of death in many patients with systematic sclerosis [54]. Gabal et al. in 2020 showed that the extent and severity of ILD can be predicted by MMP-7 levels. They studied MMP-7 levels in 30 scleroderma patients and found that the sensitivity and specificity of MMP-7 as a diagnostic marker of ILD were 85% and 80%, respectively, with a cut-off value of MMP-7 being 367.4 ng/ml [52]. Diseases like IPF, which has limited treatment options, have also shown increased MMP-7 expression. In a genetic study by Cui et al., they studied the increased expression of some differentially expressed genes in 11 IPF patients out of a total of 87 patients. MMP-7 was one of those differentially expressed genes [55].

Chronic kidney disease (CKD) is an irreversible disorder of the kidney without any effective curative treatment. Progressive fibrosis in CKD patients leads to a decline in kidney function, which is



**Fig. 2. : MMP-7's role in cardiovascular disease**

detected by biopsy, an invasive technique. In 2017, Zhou et al. suggested that MMP-7 can be used as a non-invasive biomarker of kidney fibrosis, hypothesizing the underlying Wnt/beta-catenin pathway being responsible [56]. Similarly, in 2022, Sarangi et al. also concluded that MMP-7 can be used as an early predictor of kidney fibrosis in hypertensive patients [57].

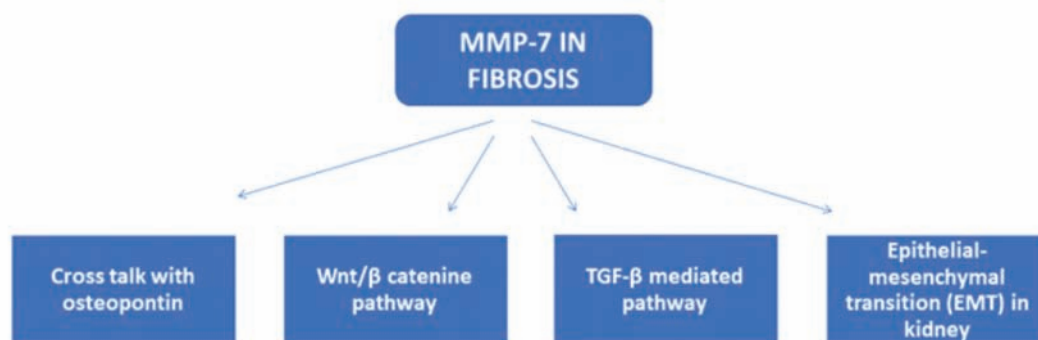
Not only in lung and kidney fibrosis, MMP-7 is also associated with liver fibrosis and biliary atresia. Irvine et al., in 2021, did a study, expecting MMP-7 can be used as a biomarker of fibrosis in cases with NAFLD. There are non-invasive tests like elastography to assess liver fibrosis, but it has some limitations like, such as being costly and less widely available. In their study, they combined serum MMP-7 levels with enhanced liver fibrosis (ELF) scores, which are serum-based tests, and identified increased sensitivity of diagnosing liver fibrosis by 8.5% in the total cohort. Similarly, for the diagnosis of liver fibrosis and biliary atresia, MMP-7 showed a promising role with good accuracy, according to some researchers [51,58]. Corroborating to the above findings, Aldeiri et al. found that MMP-7 had 93% specificity in diagnosing biliary atresia in infants and hence could have a contributory value to the gold standard method of diagnosing biliary atresia [59].

In contrast to the above observation, it was documented in 2020 by Yang et al. that in uremic mice with cardiac fibrosis, MMP-7 revealed maximum down-regulation. In the study, it was also mentioned that MMP-7 can be used in intervention for cardiac remodelling as a novel therapeutic target (60). Different mechanisms that explain MMP-7's role in fibrotic disorders are shown in Fig. 3.

**Single nucleotide polymorphism of MMP-7 in different diseases**

MMP-7 single nucleotide polymorphism (SNP) at the promoter site has been associated with many cancerous and non-cancerous conditions. Two SNPs of MMP-7 which are largely studied in the last decade are A to G SNP at the -181 (-181 A/G) and C to T SNP at -153 (-153C/T) with variable expression of MMP-7 in different patients [61].

MMP-7's association with the gastrointestinal system is not unknown. In 2011, a study conducted on 135 esophageal cancer patients and 185 healthy controls in the Kashmir valley by Malik et al. found that patients with the MMP-7 (-181 A>G) GG genotype had a higher risk of developing esophageal squamous cell carcinoma



**Fig. 3: Different mechanisms that explain MMP-7's role in fibrotic disorders**

[62]. However, a meta-analysis published in 2019 by Zare et al. concluded that colorectal cancer is not associated with MMP-7 -181 A>G polymorphism (63). Fu et al. conducted MMP-7 SNP by “Polymerase chain reaction-restriction fragment length polymorphism” (PCR-RFLP) method, noted that the GG genotype at MMP-7 A -181G base pair position was associated with an increased risk of developing gastric cancer. They concluded that MMP-7A -181 G may act as an early predictor of gastric cancer [21].

One of the earliest studies on genetic polymorphism of MMP-7 was done by Beeghly-Fadiel et al. They recruited 1079 breast cancer patients from 1996 to 1998. Eleven types of polymorphisms of MMPs have been studied in these patients and followed up few years. They found that mainly two SNPs are associated with poor prognosis of breast cancer. Cases with homozygous rs11568818 rare allele G had a poorer prognosis than A homozygous allele, which is the common allele type. In contrast, patients with Rs.11225297 T allele had improved survival [64]. In 2015, another study of MMP-7 polymorphism in breast cancer patients was done in the Western Iran population, in which Yari et al. studied the MMP-7-A-181G variants. However, they couldn't find any difference between the control and cases [65].

It has also been seen that many gynaecological cancers, like ovarian cancer, endometrial cancer and cervical cancer, are associated with MMP-7 polymorphism (23,66,67). Yi et al., in their study, recruited 118 patients with endometrial carcinoma and 229 healthy controls. Genotyping was done for polymorphisms of gene MMP-2,3,7 by PCR-RFLP. Among these MMPs, only MMP-7 (Rs. 11568818) showed significant association. They suggested that MMP-7181 G/G and A/G genotypes may possess more risk for developing endometrial cancer [66]. Recently, in 2018, Białkowska et al. suggested that increased serum zinc may have some association with polymorphism rs11568818 in the MMP-7 gene with an increased risk of prostate cancer [68].

MMP-7 polymorphism has been shown with inflammatory conditions. SNP Rs. 11568818 and raised MMP-7 expression were limited to rheumatoid nodules, stating that the outcome of the MMP-7 polymorphism is mostly monocyte/macrophage-mediated immune/inflammatory activities [69].

It was found that patients with genetic polymorphisms of MMP-7 are susceptible to developing cardiovascular diseases like myocardial infarction (MI), coronary artery disease (CAD) and hypertension [70]. Alp et al. studied the association of MMP-7 promoter polymorphism in CAD and MI patients. Using the PCR-RFLP method, they found no significant difference between MMP-7 A-181G, C-115T polymorphism. However, there was a significant difference between allele frequency of C-153T polymorphism in between cases and control groups [70]. Similarly, Subramanian et al. showed the relation of MMP-7 polymorphism in hypertension patients and noted that MMP-7-181AG heterozygous patients showed elevated MMP-7 levels with elevated blood pressure [71]. Many studies also give evidence about the relation of MMP-7 polymorphism in different lung-related disorders like chronic obstructive pulmonary disease (COPD) and coal workers pneumoconiosis (CWP) [72,73]. A study on COPD patients by Tacheva et al. showed that MMP-7A>G promoter variants may lead to the early development of COPD. They found that carriers of the G allele (AG, GG) have a higher risk of developing COPD in the significantly early stage of life [72].

In contrast to the above findings, Liao et al. evaluated the role of MMP-7 promoter A-181G (Rs. 11568818) and C-153T (Rs.

11568819) in relation to prostate cancer risk in the Taiwan population but found no correlation with the development of prostate cancer [73].

## Conclusion

MMP-7 activities for proteolytic removal of the protein ectodomains are most prevalent on the surfaces of innate immune, epithelial, and tumour cells, which influences biological processes associated with tumours like apoptosis, proliferation, migration and invasion. These warrants targeting of MMP-7 selectively in tumours of mucosal epithelia. MMP-7 upregulation provides hopes for the implication of uMMP-7(urinary MMP-7) as a non-invasive biomarker. Along with MMP-9, MMP-7 may be a potential therapeutic target to reduce inflammatory processes like UC progression as a pathogenic mediator. Future clinical studies may plan for suitable strategies to inhibit MMP-7 expression for modifying the course of diseases as a therapeutic target.

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**Ethics:** There is no ethical violation as it is based on voluntary anonymous interviews

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