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Indian Journal of Pharmacy and Pharmacology

Journal homepage: https://www.ijpp.org.in/

Review Article

Matrix metalloproteinase-9: A master regulator of cancer invasion, angiogenesis, and therapeutic resistance

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Abstract

Cancer still ranks among the highest causes of death in the world, and the invasion and metastasis of tumor cells are mostly contributed to by the remodelling of the extracellular matrix (ECM). A key process associated with ECM remodelling, angiogenesis, epithelial to mesenchymal transition, and the modulation of the tumor microenvironment involves matrix metalloproteinase-9 (MMP-9), a zinc-requiring endopeptidase. The present review aims to systematically present the current evidence available for the expression, regulation, and clinicopathological significance of MMP-9 in the most prominent human malignancies, including breast, colon, brain, lung, liver, pancreatic, cervical, prostatic, and gastric cancers. High expression of MMP-9 is consistently correlated with the advancement in the stage, metastasis, and an unfavourable prognosis in the above-listed cancers, thus validating its significance as a potential biomarker for diagnosis and prognosis. Additionally, the rapid progress in the use of natural compounds, regulators of gene expression, and inhibitors of signaling pathways illustrates promising MMP-9-targeted therapeutic approaches, aiming to alleviate the toxicity associated with the existing broad-spectrum MMP inhibitors in cancer therapeutics.

Keywords: Matrix Metalloproteinase-9, Cancer Progress, Extracellular Matrix, Metastasis, Biomarker, Target therapy

Received: 28-01-2026; **Accepted:** 25-02-2026; **Available Online**: 13-04-2026

1. Introduction

One of the main causes of death worldwide is cancer, which is an aberrant cell proliferation. It is regarded as the second leading cause of death, following heart disease.[1] It's interesting to note that overexpressed molecules with vital functions in cell survival and proliferation are the focus of anticancer medication development research. For example, the extracellular matrix (ECM) has a significant role in cancer-related processes such as apoptosis, survival, and cell cycle regulation. Proteoglycans, glycosaminoglycan's, structural proteins (collagen and elastin), adhesion proteins (fibronectin and laminin), and proteases known as matrix metalloproteases (MMPs) make up the extracellular matrix (ECM). Extracellular proteinases (MMPs) have been shown to play a crucial role as possible modulators of cell–cell and cell–ECM communication, which regulates vital tissue homeostasis.[2]

Zinc-dependent proteolytic metalloenzymes are called matrix metalloproteinases (MMPs). One of the most complicated types of matrix metalloproteinases is MMP-9. MMP-9 plays a significant part in pathophysiological processes and has the capacity to break down extracellular matrix (ECM) components. Numerous illnesses are linked to MMP-9 overexpression and dysregulation. Therefore, controlling and inhibiting MMP-9 is a crucial therapeutic strategy for treating a variety of illnesses, including cancer. MMP-9 inhibitors may be employed as anticancer drugs. No selective MMP-9 inhibitors have yet completed clinical trials.[3] They comprise the MA clan of metallopeptidases, the M10A subfamily, and the M10 family. Collagenases, gelatinases, stromelysins, matrilysins, and membrane type MMPs are among the more than 27 distinct MMPs found in humans.[4] All MMPs, with the exception of MMP7, MMP26, and MMP23, have a hemopexin domain that is joined to the catalytic domain by a hinge or linker region. The catalytic domain is where proteolytic cleavage takes place, whereas the hemopexin domain mostly influences TIMP and substrate

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https://doi.org/10.18231/j.ijpp.15500.1772871172

binding. Two such MMPs that are distinguished by their capacity to break down denatured collagens (gelatin) are MMP2 (gelatinaseA) and MMP9 (gelatinaseB). These MMPs have been linked to a number of abnormal physiological processes in humans, including autoimmune, neurological, cardiovascular, and inflammatory disorders.[5,6]

2. Materials and Methods

A comprehensive and scientific literature research approach was employed to examine MMP-9 involvement and its targeting in cancers. A vast search was done on electronic databases like PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect to fetch relevant scientific articles published in English. The keywords and MeSH terms employed can be seen: 'MMP-9,' 'matrix metalloproteinase-9,' 'cancer,' 'metastasis,' 'extracellular matrix,' 'biomarker,' 'prognosis,' 'natural inhibitors,' and 'MMP-9 signaling pathway.' All these were employed either separately or jointly to cover the entire gamut.

Original research papers, clinical studies, experimental papers (in vitro and in vivo), review papers, and meta-analysis papers assessing the expression, regulation, role, and therapeutic significance of MMP-9 in various cancers such as breast, colon, brain, lung, liver, pancreatic, cervical, prostatic, and gastric cancers were considered. The search was biased towards research papers dealing with molecular aspects, signaling pathways, diagnostic and predictive values, gene polymorphisms, and/or natural or synthetic inhibitors of MMP-9. Publications without the text, foreign language publications, and publications not directly related to MMP-9 research were excluded.

2.1. Connection between cancer and MMP9 inhibitors

One of the common matrix metalloproteinases, MMP9 (gelatinase B), is linked to tissue degradation in several disease states, including cancer invasion and metastasis, fibrotic lung disease, dilated cardiomyopathy, and rheumatoid arthritis. According to a recent study, myopathy is worse with more inflammation and fibernecrosis when MMP9 expression is elevated.[7] MMP9 has been proposed as a potential marker candidate for cancers such breast, colorectal, ovarian, and non-small cell lung cancer because it was discovered that elevated MMP9 levels are positively connected with cancer patients.[8-11] Tumor invasion, metastasis, angiogenesis, and the tumor microenvironment have all been linked to MMP-9. In the majority of situations, MMP-9 stimulates the growth and spread of cancer; yet, in certain instances, such as colon cancer linked to colitis, it may also have a suppressive effect. Research on MMP-9 as a biomarker for many cancer types has advanced significantly in recent years. Accordingly, in recent years the spotlight has moved towards the utility of MMP-9 as a biomarker. High levels of MMP-9 expression in its latent as well as active forms have been identified in various bodily fluids, including extracellular fluids. There is robust evidence for its clinicopathological use as a diagnostic as well as prognostic factor in the case of giant cell tumor of the bone, Non-Small Cell Lung Carcinoma, Cervical Carcinoma, Epithelial Ovarian Carcinoma, Pancreatic Adenocarcinoma, Osteosarcoma, as well as Breast Cancer. Moreover, in the context of some cancers, its expression has been found to predict the progression of cancer as well as mortality.[12]

2.2. Breast cancer

Its level of expression is highly elevated in breast cancer compared to normal tissue and also in advanced grade tumors, hormone receptor-negative tumors, and poor prognosis. Overexpression of MMP-9 is more evident in the aggressive variants, such as triple-negative and HER-2-positive breast cancers. High expression of MMP-9 is associated with cytoskeletal and adhesion molecules, such as EGFR, CD44, CDC42, Ki-67, and CK-17, suggesting an aggressive tumor behavior. Cytoplasmic MMP-9 independently predicts the occurrence of metastasis, recurrence, and poor survival, making it a reliable prognostic marker in breast cancer.[13,14] Tumoral MMP2 and MMP9 show promise as prognostic indicators for BC patients.[10] Elevated expression of these enzymes is strongly associated with lymph node metastasis and advanced tumor stage. Transcriptomic studies reveal marked upregulation of MMP-9 in higher histological grades of invasive ductal carcinoma.

MMP-9 expression is particularly prominent in aggressive tumor phenotypes and poorly differentiated cancers. High MMP-2 and MMP-9 levels correlate with increased tumor invasiveness and metastatic potential. Survival analyses indicate that overexpression of MMP-2 and MMP-9 is linked to poorer patient outcomes.MMP-9, in particular, shows a strong association with overall survival and disease progression. Collectively, these findings support MMP-2 and MMP-9 as important biomarkers of breast cancer aggressiveness and potential therapeutic targets.[15,16]

2.3. Colon cancer

The clinical studies clearly demonstrated that MMP-9 expression was significantly higher in colon cancer tissues than in normal colonic mucosa and was significantly associated with lymph node metastasis and Dukes' stage. Moreover, high MMP-9 expression was significantly associated with lower overall survival and was an independent prognostic factor. On the other hand, higher MMP-2 gene expression was significantly associated with invasive tumor, higher mortality rate, and lower overall survival. Furthermore, multi-omics and experimental studies have clearly suggested that there is a coordinated regulation of MMP in the pathogenesis of colorectal cancer, with MMP-2 and MMP-9 playing a crucial role in the pathogenesis of EMT and immune regulation. Additionally, the nitric oxide-regulated pathways modulate gelatinase, and natural inhibitors such as Emotion demonstrated efficacy in the inhibition of MMP. Furthermore, VEGF-α gene expression

was significantly associated with MMP-2, MMP-9, and TNM stage, and was also significantly associated with overall survival.[17-21]

2.4. Brain cancer

MMP-9 was originally characterized by a substrate overlap with other metzincin proteases but has rapidly emerged as a uniquely regulated and functionally critical enzyme within the brain because of its highly localized and temporally restricted activation. Under physiological conditions, the expression of MMP-9 is low, while transcriptional, protein, and enzymatic induction of this enzyme is strongly upregulated in response to either neuronal activity or pathological insults. In neurons, it serves to modulate synaptic plasticity through remodeling of the extracellular matrix surrounding excitatory synapses, thereby shaping dendritic spine morphology and influencing learning and memory and cortical reorganization. Dysregulated activity of MMP-9 contributes to a wide spectrum of neurological disorders, including epilepsy, autism spectrum disorder, schizophrenia, stroke, neurodegeneration, pain, and brain tumors-mostly by mediating neuroinflammation, cytokine and chemokine activation, and disruption of the blood-brain barrier. Its ability to facilitate leukocyte extravasation further propagates inflammatory cascades within the brain parenchyma. Clinically, MMP-9 bears strong translational relevance, as evidenced by its upregulation in Fragile X syndrome and subsequent therapeutic trials targeting its inhibition.[22,23] In brain tumors, enhanced MMP-9 promotes invasion and metastasis and correlates with poor prognosis. Notably, MMP-9 captured in small extracellular vesicles is capable of crossing the blood-brain barrier, making it a promising liquid biopsy biomarker. Lower vesicular MMP-9 burden is associated with improved survival in patients with glioblastoma, whereas higher burden reflects tumor aggressiveness and recurrence. Experimental evidence further implicates MMP-9 as a determinant of metastatic cell arrest, BBB penetration, and micro metastatic growth in the brain through nonclassical mechanisms of basement membrane degradation, underscoring the value of MMP-9 as both a prognostic marker and as a therapeutic target.[24,25]

2.5. Lung cancer

LOX expression in NSCLC was significantly overexpressed and was closely related to the remodelling of the ECM and the prognosis, and was regarded as an independent prognostic factor. There is a strong positive correlation between LOX and MMP-2/MMP-9. The expression of LOX and MMP-2/MMP-9 could play a crucial role in facilitating the upregulated expression and activity of MMP-9, further supporting its pivotal role in more advanced disease. This emphasizes the LOX-MMP signalling pathway as a target for therapeutic intervention in lung cancer.[26,27] MKL1 drives lung cancer cell migration and invasion via the epigenetic activation of MMP9 transcription via ASH2-dependent H3K4 methylation, underpinning the important role of MKL1 in tumor aggressiveness.[28] Adipocyte exosomal MMP3 secretion promotes lung cancer cell invasion and metastasis via the activation of MMP9, thus providing a novel insight into the mechanism of obesity-related tumor progression.[29] High expression levels of MMP-7 and MMP-9 in NSCLC relative to normal and benign lungs reflect the central role that both play in the development and proliferation of malignancies, whereas the increased expression levels of TIMP-1 suggest a process-specific role within carcinogenesis. Advanced malignancy is characterized by an imbalance between the amount of circulating MMP-9 and TIMP-1 levels, which is increased within SCLC and NSCLC, that may contribute towards invasiveness and malignancy dissemination.[30,31] Overall, the evidence highlights matrix metalloproteinases as pivotal modulators of the tumor microenvironment and major contributors to invasiveness, migration, and angiogenesis within non-small cell lung cancer and targets for therapy.[32]

2.6. Liver cancer

Liver cancer is one of the most frequent malignant tumors globally, with high morbidity and mortality, and there are no proven clinical treatments for it.MMP-9-responsive liposomes facilitate the targeted release of drugs, specifically in the case of liver cancer, thereby enhancing the infiltration and activity of CD8+ T cells.[33] In fact, an MMP9-responsive fluorescence/MR probe has been shown to provide sensitive imaging and distinction of the metastatic potential of hepatocellular carcinoma, and this may represent a valuable analytical technique for the prognosis of HCC. Moreover, the identification of SERPING1 as an important biomarker that significantly affects sorafenib responsiveness and HCC progression through the p-ERK/MMP2/MMP9 signalling pathway may provide an important clue for understanding the resistance to sorafenib and the rationale for molecular-targeted therapies.[34,35] and further study illustrates that alcohol exposure can trigger the MMP9-dependent cleavage of the CCN1 protein exclusively in oesophageal adenocarcinoma cells to release a pro-tumorigenic fragment that can promote cell survival. Thus, the action of alcohol changes the role of the CCN1 protein from an antitumor modulator to an oncogenic factor in the context of oesophageal adenocarcinoma.[36]

2.7. Pancreatic cancer

The studies point out that the overexpression of MMP-9 in pancreatic cancer is regarded as a central mediator of progression, and AHNAK2 enhances tumor proliferation, migration, and invasion by activating the NF-κB/MMP-9 pathway. Drug repurposing analysis further identifies MMP-9 as a promising therapeutic target, with agents such as dasatinib and pioglitazone showing strong predicted interactions with MMP-9. Moreover, network pharmacology has identified MMP-9 as one of the central nodes in the multitarget actions of Huachansu injection, supporting its role in the suppression of cell growth and migration in

pancreatic cancer.[37-39] The MMP-9 expression is highly increased in the advanced stages of pancreatic cancer, thereby supporting the use of this protein as a marker of disease advancement. MMP-9 expression, however, was not clearly identified to be associated with early pancreatic cancer.[40] MMP-9 levels are substantially increased in acute pancreatitis, which correlates well with its severity, establishing its importance as a relevant biomarker. Use of MMP-9 in combination with ultrasound techniques significantly increases the sensitivity for diagnosing AP over ultrasonography alone.[41]

2.8. Cervical cancer

MMP-9 is an important prognostic indicator of cervical cancer, and high levels of tumoral and stromal MMP-9 expression are known to be useful predictors of survival benefit, contrasting MMP-2 and TIMP-2, which are predictors of poor prognosis. Furthermore, polymorphisms within the gene MMP-9 (MMP-9 rs3918242) can affect the genetic susceptibility to cervical cancer by combining with the gene MMP-2, thus making MMP-9 both a genetic marker and a prognostic indicator of cervical cancer.[42,43] The MMP-9 expression is lower in HPV-positive cervical cancer tissues than in premalignant cervical intraepithelial neoplasias, and this suggests the loss of oncogene-induced senescence-related signaling. The reduced expression of MMP-9, among other senescent markers, indicates its role in the development from premalignant lesions to cervical cancer.[44] The Carica papaya seed essential oil significantly suppresses cervical cancer cell migration and invasiveness through the repression of matrix metalloproteinase-related pathways closely associated with MMP-9-driven tumor progression. While MMP-2 was directly measured, the strong antimigratory effect suggests a broader regulatory impact on MMP activity, supporting the potential relevance of MMP-9 inhibition in cervical cancer therapy.[45]

2.7. Prostate cancer

Matrix metalloproteinase-9 (MMP-9) is a key player in the pathogenesis of prostate cancer as it accelerates the degradation of the extracellular matrix, invasion, and metastasis of cancer to various sites within the body. There are also clinical trials showing higher levels of expression of MMP-9 in the blood and cancer tissues of patients with prostate cancer compared to normal controls, and its expression has also been associated with reduced overall and disease-free survival.[46-48] The experimental results showed that aqueous and ethanolic extracts of Rosmarinus officinalis induced significant cytotoxic effects on DU-145 prostate cancer cells and thus could inhibit tumor cell survival effectively. More importantly, in silico molecular dynamics and binding energy analyses revealed strong and stable interactions between rosemary-derived bioactive compounds, especially rosmarinic acid and carnosol, and MMP-9, indicating that rosemary metabolites may be capable of inhibiting MMP-9 activity, thus limiting extracellular matrix degradation and tumor cell invasion. Therefore, due to the very low toxicity profile of rosmarinic acid, the targeting of MMP-9 by rosemary-based compounds is a promising natural and multi-target strategy for the development of novel anti-prostate cancer therapeutic drugs that is naturally progressive with further in vitro and in vivo validation.[49]

2.8. Gastric cancer

MMP-9 plays a pivotal role in gastric cancer progression by mediating H. pylori-induced inflammatory responses and promoting tumor cell proliferation, migration, and survival. Additionally, lncRNA LINC01016 enhances MMP-9 expression by inhibiting EIF4A3-mediated mRNA decay, highlighting MMP-9 as a potential therapeutic target for controlling gastric cancer development and metastasis.[50-52] miR-146a-5p suppresses gastric cancer cell migration and invasion by downregulating MMP-9, highlighting its potential role in inhibiting EMT-mediated metastasis.[53] From the former studies, it is demonstrated that MMP-9 is important in causing gastric tissue injury and cancer development, where the expression of Vitamin D3 inhibits MMP-9 expression in protecting the gastric tissues from aspirin-related injury. Furthermore, the overexpression of MAP17 in gastric cancer cells further increases the expression of MMP-9, indicating that it is a promising target molecule.[54,55] Quercetin as a highly effective natural compound for the inhibition of gastric cancer via the suppression of tumor growth, inflammation, angiogenesis, and metastasis through the regulation of various oncogenic pathways, which include the extracellular matrix degradation processes mediated by MMP-9. Quercetin has the potential to be a low-toxicity therapeutic strategy for targeting gastric cancers mediated by MMP-9.[56]

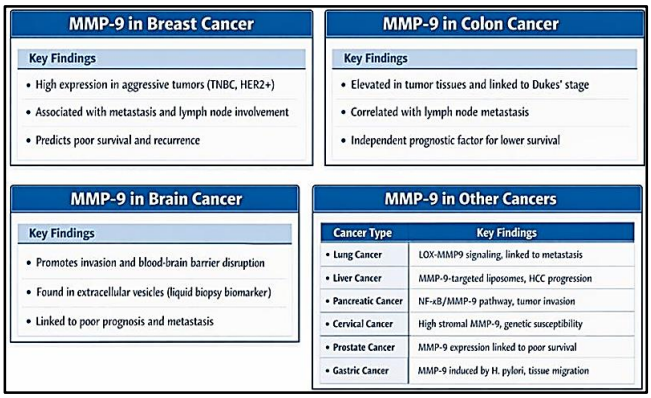

Figure 1: Key findings of MMP-9 in different cancer types

3. Discussion

Among these, MMP-9 has emerged as a central mediator in cancer biology because of its pivotal role in the degradation of the ECM, tumor invasion, metastasis, angiogenesis, and modulation of the tumor microenvironment. The present review consolidates extensive evidence that dysregulated MMP-9 expression is a common molecular event across multiple malignancies, including cancers of the breast, colon,

brain, lung, liver, pancreas, cervix, prostate, and stomach. Clinically, high levels of MMP-9 have been consistently associated with advanced tumor stage, lymph node involvement, distant metastasis, poor prognosis, and reduced overall survival, underlining its strong clinicopathological relevance.

Overexpression of MMP-9 in breast and colon cancers correlates with aggressive tumor phenotypes, EMT activation, and unfavourable survival outcomes, positioning it as both a prognostic biomarker and a potential therapeutic target. The use of MMP-9 in invasion, disruption of the blood–brain barrier, neuroinflammation, and remodelling of the ECM in brain tumors and lung cancers and the emerging evidence for its detectability in circulating extracellular vesicles extend its diagnostic utility. In liver and pancreatic cancer, MMP-9 engages in tumorigenesis through the oncogenic ERK, NF-κB, and PI3K/AKT signalling pathways and contributes to therapeutic resistance, immune cell infiltration, and disease severity.

Gastric cancer research, in particular, shows the complex involvement of MMP-9 in inflammatory signaling, H. pylori-induced carcinogenesis, EMT, and metastasis. Regulatory factors like microRNAs, lncRNAs, MAP17, and inflammatory cytokines have demonstrated modulation of MMP-9 expression, indicating its complex regulation. More importantly, natural compounds like Vitamin D3, quercetin, and rosemary extract-derived phytochemicals indicate promising MMP-9 suppressive action, which may be explored as low-toxic, multi-target agents. The lack of specificity for selective MMP-9 inhibitors in overcoming the challenges in clinical application is evident for the past several years, mainly due to complex physiological functions and involvement of MMP-9.

Taken together, the importance of the discussed results highlighted through this review is to convey the view that MMP-9 is a degradative enzyme with further roles as a central signaling molecule in cancer-stroma interactions and immune modulation. The use of targeted therapies in inhibiting MMP-9 may prove effective with less toxicity.

4. Conclusion

The involvement of MMP-9 is complex and crucial in cancer development, growth, invasion, metastasis, and prognosis. The consistent overexpression of MMP-9 has been a reliable indicator of advanced cancer and a predictor of poor patient outcomes, making MMP-9 a promising biomarker for evaluation, prognostic purposes, and monitoring of cancer development. Although none of the broad-spectrum MMP inhibitors have been a success in clinical trials, promising studies indicate that targeted inhibition of MMP-9 might become a reality through the use of natural agents, gene regulators, and targeted pathway inhibitors. Future research should aim at creating highly specific inhibitory agents of MMP-9, evaluating them through large-scale human trials, and incorporating MMP-9 targets into personalized cancer medicine.

5. Acknowledgement

Department of Pharmacology, SNS College of Pharmacy and Health Sciences.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Jose S. Matrix metalloproteinase-9: A master regulator of cancer invasion, angiogenesis, and therapeutic resistance. *Indian J Pharma Pharmacol.* 2026;13(1):4-10.