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Review Article

MATRIX METALLOPROTEINASES 2 AND 9 IN AVOCATION OF MULTITUDINAL COMPLICATIONS IN EXPLICITLY TO CARCINOMA: REVIEW

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ABSTRACT

Matrix metalloproteinases (MMPs) are a large group of calcium-dependent zinc containing endopeptidases which are mainly concerned with the remodeling of tissue along with degradation of the extracellular matrix. At the present scenario, there is knowledge of about 26 MMPs which are found to be highly regulated by the growth hormones, cytokines, etc., present within the body. At times of normal homeostasis, their levels within the body are low, and their number usually increases at times of pathological conditions. Its generation is known to occur from the pro-inflammatory cells and connective tissues. They may even lead to the process of apoptosis by its interactions with surface receptors. In the clinical trials sectors, various MMPs along with their inhibitors are examined to import the properties of being a high biomarker in the cancer diagnosis, antiangiogenic agents, various other disorders such as chronic allograft nephropathy, diabetic nephropathy, cardiovascular diseases, neuropathic pain, wound healing, angiogenesis processes, immune response, corneal ulceration, embryonic development, and nervous system disorders. As a result, enormous number of studies on this particular enzyme in the marking of cancer and their elevation in the above-mentioned diseases has to be carried out so that it would remain as a useful tool in their diagnosis. The present work is designed to emphasize the concise review of MMPs, in particularly MMP-2 and MMP-9 along with their variant roles, keeping in mind, that it would be advantageous for the researchers to bring out more promising results and to intensify diagnosis of various infirmities, especially in cancer.

Keywords: Matrix metalloproteinase-2, Matrix metalloproteinase-9, Biomarker, Matrix metalloproteinases, Carcinoma, Extracellular matrix, Malignancy, Gelatinases, Tumor.

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INTRODUCTION

In cases of physiological conditions such as angiogenesis, embryonic development, and wound healing, changes in the extracellular matrix (ECM) like that of in breakdown, remodeling and synthesis are found to be classically important. This remodulation of the ECM is found out to be carried out by a variety of proteases systems which are broadly divided into four subgroups, depending on the amino acid residue required for its catalytic activity [1]. They are [2]:

1. Metalloproteinases
2. Cysteine proteases
3. Serine proteases
4. Aspartic proteases.

Metzincin is found to be an important superfamily under the subgroup metalloproteinases. Matrix metalloproteinase (MMP) is found to fall under this superfamily, and thus, it could be classified based on the substrate specificity (Fig. 1).

Their regulation occurs by hormones, growth factors, cytokines, etc., with its involvement even in ovarian functions. They are generally expressed as zymogens and then processed by some of the proteolytic enzymes such as furin, serine proteases, and plasmin into their active forms. Studies on the inhibition of MMP tumor models gave positive results indicating its inhibition would be a strong tool in fighting against cancer. The quantitative structure-activity relationships resulted on the inhibiting action of various compounds against most of the classes of MMPs. Some of their important actions were molar refractivity and hydrophobicity remaining the important determinants of their activity [3].

The designing and testing of MMP inhibitors in the role of MMPs with cancers progression based on their degradative activity has been carried out, but most of the results have found to be discouraging, then too studies were carried out on this biomarkers and that too especially focusing on acute leukemia [4]. The research works on the synthesis of MMP inhibitor with the anticancer property had been continuously failing due to the shortcomings in chemistry of compounds. Due to the complexity in the biology of MMP cell, the inhibitor must possess MMP selectivity against the subtype of MMP. Some of the MMP inhibitors, according to the studies and research, carried out are as follows [5]:

1. Pioneering hydroxamate structure - collagen-based peptidomimetic hydroxamate.
2. New generation hydroxamate-based MMP inhibitors - peptidomimetic hydroxamates and carboxylates, new diaryl ether hydroxamates, peptidomimetic hydroxamates
3. New generation thiol-based MMP inhibitors
4. Pyrimidine-based inhibitors
5. Hydroxypyrone-based MMP inhibitors
6. Phosphorous-based MMP inhibitors
7. Tetracycline-based MMP inhibitors
8. Endogenous MMP inhibitors.

These MMP inhibitors are administered at that time when the role of MMP is very critical, like that during the time of early events in metastasis the dosage of these inhibitors is based on the biomarkers and not on the toxicity produced due to the limiting of dose. These MMPs professedly conciliate some of the conspicuous steps in the commencement of inflammatory demyelination like that of blood-brain/nerve barrier breakdown, demyelination and cytokine activation,

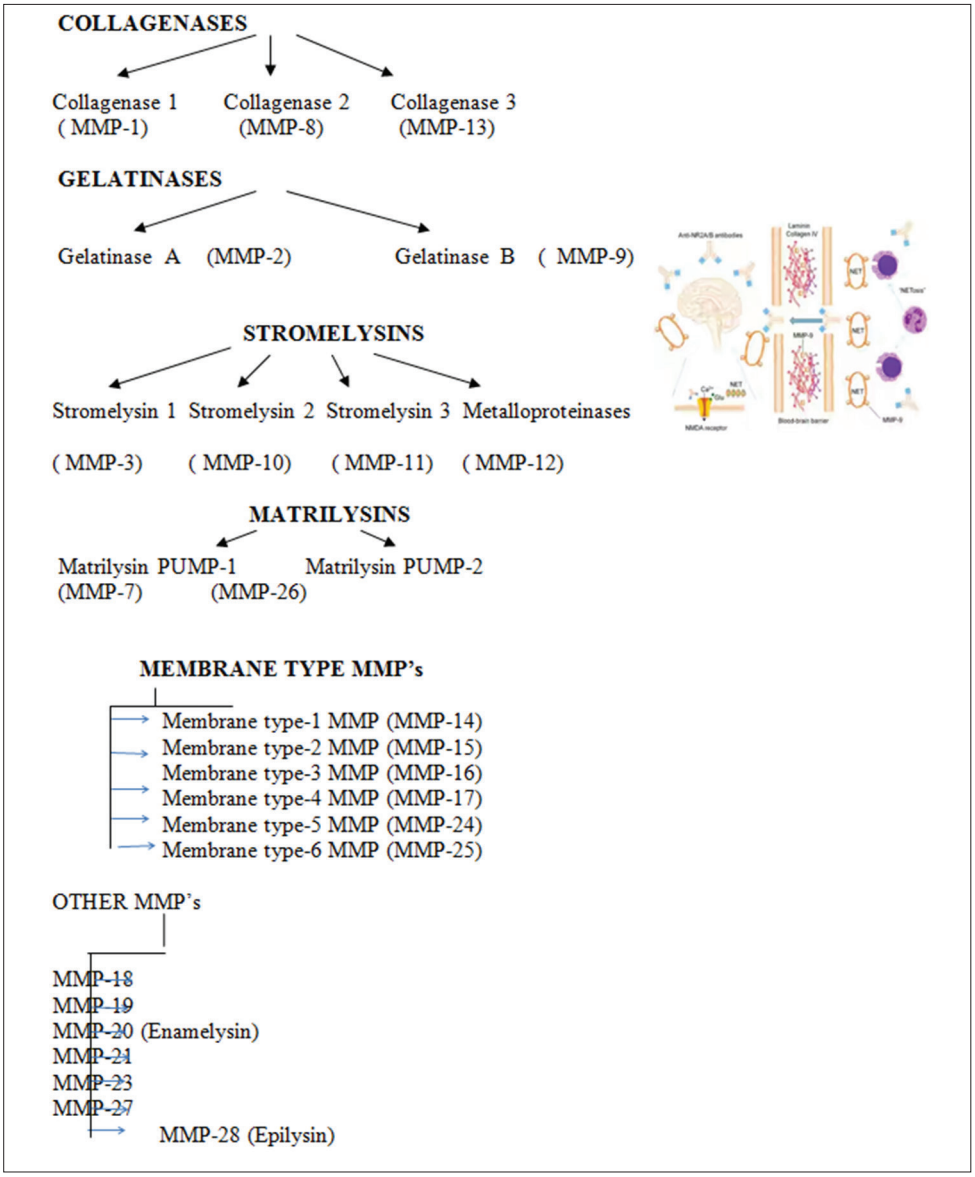

Fig. 1: Classification of matrix metalloproteinase

cell migration, etc. Hence, it is known to play important roles in the pathogenesis of demyelinating inflammation disorders of both the peripheral and central nervous system [6].

There has been the declaration of direct or indirect effects of MMPs on the ion channels on vascular and endothelium smooth muscle including some of its roles in relaxation and contraction of the muscles. The equivalence between MMPs and tissue inhibitors of matrix metalloproteinases (TIMPs) performs in angiogenesis and, vascular remodeling, uterine, and systemic vasodilatation at the time of normal pregnancy whose imbalance may result in various vascular disease such as varicose veins, hypertension, AAA, and pre-eclampsia, the isolationism of MMPs by synthetic pharmacological inhibitors such as BB-94 or genetic manipulations of TIMPs could be effective in decreasing the vascular dysfunction due to MMP and the vessel wall damages due to vascular diseases [7].

Some of the actions of MMPs used as biomarkers in the detection of cancers

MMP-2 and MMP-9 generally denoted as gelatinases are known to have actions at the time of metastasizing and at the stage of invasion of malignant cells. They are known to have roles in hematological malignancies. In most cases, treatment of hematological malignancy generally includes production of treatment-related toxicity depending on the severity of the treatment. Hence, there has been the requirement of such prediction choices which could minimize the toxicity generation and produce more accurate results. Metalloproteinase inhibitors, tyrosine inhibitors, angiogenesis inhibitors, and imatinib mesylate are all safe markers for the treatment of chronic myeloid leukemia. Clinical trials already have the usage of MMP inhibitor drugs. Thus, the improved role of gelatinases in solid malignancies is to be more increased [8].

There was the upregulation of MMP-9 expression, and no changes were found to occur in the MMP-2, TIMP-1, or TIMP-2's expression along with no changes in the proliferation were found by inhibition of MMP-9, but there was colocalization in the retinoblastoma cells with their differentiation. At all the times of inhibition of MMP-2, not much change in the cellular viability was observed, but there was the attenuation of neurite outgrowth and the neurofilament expression of the retinoblastoma cells was differentiated. Hence, in particularly, MMP-2 could be used in the process of malignancy studies [9]. Studies were carried on the expressions of MMP-2 and MMP-9 in the tumor cells of prostate cancers and its biochemical recurrences as being markers. Multivariate analysis proved that MMP-9 was an incredible

signaling agent of biochemical recurrence. MMP-2 levels were found to be high in that of positive margins than those in main tumors. Hence, these two biomarkers could be made use of in detecting the condition of prostate cancers along with +ve and −ve surgical margins after prostatectomy [10,11].

As earlier as the detection of polyps, otherwise known as colorectal carcinoma, has been done deaths associated with it could be more effectively reduced. MMP-9 could be used as an effective marker for the identification of colorectal carcinoma. The most significant prediction of neoplasia was found to be MMP-9. The other related factors associated with them were smoking, sex, age, abdominal pain, weight loss, and history of the patient. Sampling of the serum could be done to avoid the anxiety of patient, iatrogenic, morbidity, mortality, colonoscopy, cost, etc. [12-15]. Due to their interactions with the receptors of growth factors, cell adhesion molecules, apoptotic ligands, cytokines, chemokines, angiogenic factors, etc., they are known to have a holding function in the modification of colorectal cancer. One of the subtypes of CRC is colitis-associated carcinoma. There may be the development of it to adenocarcinoma through the process of inflammation-dysplasia-carcinoma. Hence, studies have been carried out even in colitis-associated cancer by means of which MMPs play a protective role regarding the localization and the mechanism associated with its production [16]. There were studies carried on whether MMP-2s level has an influence on the endometrial adenocarcinoma whose evaluation has been done from patients as immune reactive. These MMP-2 patients were found in about 80% of the primary tumors inclusion of the histological grades. As a result, the favorable prognosis of endometrial adenocarcinoma was MMP-2 immunostaining negativity [17,18].

In the cases of hepatocellular carcinomas (HCCs), the levels of membrane Type 1 MMP, MMP-2, and MMP-9 mRNAs were particularly expressed, MMP-9 was mainly observed by the cells of the neoplastic epithelium. In gelatin zymography, amount of latent and active MMP-2 were found in the tumor samples of HCC. In addition to all this, the latent form of MMP-9 was found in equal amounts within the normal and tumor liver samples, and its active form was present only in HCC. As a result, the studies indicated that an elevated MTI-MMP mRNA expression by tumor cells in cases of HCCs and pancreatic adenocarcinomas may show prognostic significance [19]. There was the exertion of action of gelatinases on the activities of stromal cells and in tumor parenchymal cells proved by *in situ* zymographic studies. Immunohistochemistry and some studies regarding the activation ratio of the papillary thyroid carcinoma were found to be a useful tool in the prediction of tumor behavior in clinical pathology. On application of MMP-2 inhibitor, the rest of the gelatinase activity concerned with MMP-9 was found to be high in the case of cancer along with tumor infiltration [20,21].

A novel difluorinated benzylidene analog of curcumin was found to show anticancer activity *in vivo* with increased bioavailability. Docking studies were carried out of MMP-2 along with difluorinated curcumin (CDF) and curcumin along with many other studies like ELISA, a number of biological assays like miRNA analysis, etc. The property of MMP-2 being an appropriate anticancer agent was still more conformed by its inhibition with CDF more than curcumin by an n-number of mechanisms [22].

MMP-2 from U87 glioblastoma cells obtained from secretions of brain tumor was found to be inhibited by chalcones (especially 1,4,5,6) extracted from dorstenia barteri twigs. The factors which attributed toward the inhibitory action of MMP-2 was its hydroxyl 1,2,3-double bond, the prenyl group thus leading to the ECM degradation and progression of brain tumor [23,24].

These protein expressions were known to play very important roles in the prognosis, progression, tumorigenesis of laryngeal cancer. The protein expression of MMP-2 was found to higher in the poorly and moderately differentiated laryngeal cancers when compared to that of the highly differentiated one. The elevation of MMP-2 expressions was also found to be increased in the condition of laryngeal cancers with lymph node metastasis than those without it [25-28].

There was the elevation of MMP-9 in the macrophages bearing tumors in the cases of patients with ovarian cancer along with underlying symptoms of chronic stress, depressive symptoms, low seizures, low social support, etc. There was the *in vitro* development of stromal MMP-9 directly by the stress hormones. These stromal cells are known to play an effective role in angiogenesis and tumor growth. Norepinephrine and cortisol were the stress hormones involved [29].

There has been the indication of an increase in the expressions of MMP-2 and MMP-9 in the tumor tissues of the bladder cells. Their levels were found to be high in the urine or serum of the patients with advanced cases of bladder cancer, where their exact roles have not yet been validated [30]. By causing the remodulation of the ECM, there is the control of MMP in the growth patterns of dermato fibrosarcoma protuberans and common fibroces histiocytoma. It has been found that the synthesis of MMP-9, 2, 14, and 1 occurs by dermal fibroblasts, which comes to be the major constituent of these two tumors. From the immune-histochemical studies, there has been no upregulation of MMP-1 and 9 in the case of dermatofibrosarcoma protuberans. The expression of MMP-14 in the case of CFH has shown that there is the role of MMP regarding its control over the growth pattern of the lesion by causing the cultivation of MMP-2, in the tumor cells and this MMP-2 plays the role of tumor angiogenesis in the case of DGSP [31,32].

American cranberry, known as *Vaccinium macrocarpon,* is known to consist of several phytochemicals, which is known to play roles in the prevention of cardiovascular diseases, urinary tract infections, and cancers, etc., including their roles in oral health care. An investigation carried out in this study further elaborated that the activity of MMP and urokinase plasminogen activator were found to be decreased by flavonol-enriched fractions of cranberry by causing a change in either the phosphorylation status or the expressions of various other kinases associated with it. Thus, it has been found that the species poses the property of protecting against certain cancers [33].

A known way of the inhibition in the activation of MMPs by inositol hexaphosphate, being a plant component, is by its ability in chelating minerals depending on the concentration levels and the time of interaction of the phytic acid. The modulation to MMP-2, TIMP-1, and 2's gene expression was found out at their transcriptional level concerned with colon cancer. There was neither the induction nor the expression of MMP-9 by the phytic acid related with the Caco-2 cells [34].

Action in other disease conditions

The earlier markers for the detection of diabetic nephropathy have been identified to be gelatinases A and B which are found to get accumulated in the kidneys. Studies were carried out to find the value of MMP-2 and MMP-9 as diagnostic markers in the case of Type 2 diabetic patients in the presence and absence of microalbuminuria. It has been clearly found out that there was the drastic increase in the levels of these markers in the presence of microalbuminuria and normoalbuminuria of diabetic patients when compared with those of normal ones [35-37].

One of the major complications of diabetes is found to be the poor wound healing process. There leads to the condition of amputation and deep-seated infection due to the failure in healing of wounds. Thus, there case of improvement is found to be important for preventing the large-scale morbidity to occur. There is the abnormal expression of MMPs in the cases of diabetic wounds besides their role in repair process of normal wounds. By their ability in regulation of inflammatory cytokines, growth factors, and chemokines, their roles in the remodulation of ECM, especially in the situations of diabetic wound healing could be underveined [38,39].

The treatment of diabetes by pharmacological and nonpharmacological interventions led to a disturbance in the system of MMP along with

their inhibitors. These inhibitors of MMP are known to degrade the ECM components and play major role in the improvement and progression of vascular lesions. There is the belief that the inhibitors of MMP would act in the decrement of pathological vascular remodeling's progression in the case of diabetes [40].

For the proper healing of wounds, there has to be a balance between their remodeling and accumulation of collagenous, noncollagenous ECM components by MMPs. In the case of chronic diabetic foot ulcers, the concentration of MMPs is found to be terribly increased with decreased concentrations of TIMP-2 which indicate that an increment in the proteolytic environment causes failure to the healing of diabetic wounds. Hence, improvements in the treatment of diabetic wounds could be concentrated in reducing the levels of MMPs in addition to increasing the TIMPs levels [41].

Proteinases are the enzymes which act on the protein molecules and thus produce actions in the process of wound healing. The substrates may include gelatin, collagen, and proteoglycans. The metal ion present at the active center, in this case, is zinc. Their production generally occurs either at the inflammatory cells or the wound cells. In general, they are required in the process of migration of cells, remodeling of scar, contraction, removal of the extracellular material which has got damaged in the case of normal wound healing [42].

Studies were carried out to detect the activity of an inhibitor of MMP-2 and MMP-9, namely, AQU-118 on the spinal nerve ligation models of neuropathic pain and on the models of chronic constriction injury of the infraorbital nerve. It was found out that AQU-118 attenuates this mechanical allodynia in the cases of this neuropathic pain. Hence, it remained a possible supportive role in the etiology of neuropathic pains. The inhibition also remained a suitable choice for treatment options [43-45].

The different phases of therapeutic approach for the treatment of neuropathic pain may be achieved by the inhibition of MMP-9 or MMP-2. There is the involvement of MMP-9 and MMP-2 in the early and the later phases of the neuropathic pain induced due to nerve injury. Usually, the treatment involves the blockage in the neurotransmission which is not much effective [46].

An inhibitor of MMP-9, minocycline was known to suppress experimental autoimmune carditis more effectively when compared to the MMP-2 inhibitor, TISAM. Moreover, minocycline treatment was involved in the causing of infiltration of macrophages and suppressing of T-cells which are not possible by TISAM. Hence, it has been found out that minocycline and the other inhibitors of MMP-9 produce vast amounts of benefits in the therapies for experimental autoimmune carditis and dilated cardiomyopathy [47,48].

There were activities reported to be carried on the brown algae "*Ecklonia cava* (EC)" with the inhibitory actions of phlorotannins regarding the MMP activities in cultured human cell lines. On assay by sensitive fluorometry, it revealed that there was the inhibition of MMP-2 and MMP-9 by the extracts of EC. There was the inhibition of MMP-2 and MMP-9 activities which were artificially produced in human dermal fibroblasts and HT/080 cells by EC extracts. The expression levels of MMPs vary from one of the cell type to other. The extracts of EC could inhibit both the activity and expressions of MMP which were clearly revealed by gelatin zymographic studies. No production of cytotoxic activity was even observed with this extracts at high doses too thus remaining an efficient MMP inhibitor [49].

Involvement of MMPs in the pathogenesis of equine laminitis and other conditions of inflammation due to their role in the remodulation of ECM has been observed. There is the involvement and increased synthesis of MMPs in the laminitis of horses. In relation with systemic inflammation, MMP-9 was found to be upregulated in the cases of horses with insulin-induced diabetes laminitis. The concentration of pro-MMP-2 was found to be the same, and MMP-9 found to be increased at the time of the auto phase of laminitis. As a result, MTL-MMP, MMP-2, TIMP-3, and ADAMTS-4 did not play any roles in the pathogenesis of laminitis along with insulin. MMP-9's action was believed to be the direct effect of hyperinsulinemia [50].

There was the observation of significant levels of MMP-2, MMP-9, TIMP-2, and TIMP-9 in the lymphocytes and keratinocytes of the oral lichen planus where there was the strong expression of both TIMP-1,2 and only about 1/5-1/10 of MMP-2,9 activity was found in the positive control groups. A clear cut disproportion was found in the MMP and TIMP on the comparison of normal mucosa and OLP samples. The autogenous protection of the membrane across the humiliating effects of MMP enzymes was found due to an increased intensity of TIMP [51].

Studies were carried on the antioxidant activities of the metabolites, namely, δ(3-methoxy-4 hydroxy phenyl)-γ-valerolactone (M2) and δ(3,4 dihydroxyphenyl)-γ-valerolactone (M1) on MMPs to find out the effect of their antioxidant and anti-inflammatory activity. The metabolites were found to be active than pycnogenol even in the case of MMP inhibition they were active than (+) catechin which is its precursor. Somehow, the scavenging activity was displayed by M1 more than M2 even on comparisons with (+) catechin, trolox, ascorbic acid, etc., there antioxidant activity was based on a redox-linked calorimetric assay. These data were found to be useful in the case of prophylaxis and treatment of disorders related to imbalance or excessive activity of MMPs [52].

ST104P, a poly-sulfated-cyclo-tetrachromo-tropylene soluble compound is known to extend the actions of being antithrombic and antiviral agent. It is known to cause inhibition to the secretion and expression of MMP-2. There is an indication that it is a strong inhibitor of angiogenesis and holds a good treatment option for diseases like cancer which propagate highly due to angiogenesis [53].

The pathogenesis of cardiovascular diseases involves major roles played by the MMPs, and their levels were found to be elevated in the serum of those who had undergone surgery due to the aortic valve diseases. These MMPs are known to cause the degradation of the ECM components which is known to contribute toward maintaining the functional and structural integrity of the heart and in the repair process of post-myocardial infraction centrally. These two enzyme levels in the serum could be used as markers for the diagnostic purpose of myocardial remodeling process [54-57].

There may be a rise in the C-related protein (CRP) by the linking of conjugated equine estrogen (CEE) along with a progestin or alone resulting in increased cardiovascular events. This causes no changes in the mechanism carried out by interleukin-6 (IL-6) in inflammation, dysfunctioning of endothelium or increment of MMP activity. About 121-150% increment was found in the levels of CRP with or without the making use of progestin, respectively, about 6-8% of decrement in intercellular adhesion molecule was observed in women with CEE and about 26-33% in MMP-9 [58].

MMP-9 along with its involvement in inflammation and degradation of matrix, even contribute to rupturing of coronary plaque. Failure in the regulation of MMP-9 in the systemic circulation of coronary artery disease patients has been hypothesized by a dysfunctional cortisol response. The regulation of MMP-9 in the patients is by hypothalamic-pituitary-adrenal axis dysfunction, and this MMP-9 has a possibility in staying as a link between cardiovascular disease and stress [59,60].

The visceral fat accumulation is found to be decreased by L-arginine and vitamin-C's supplement; as a result, the metabolism of carbohydrate is also found to be increased. These two actions are known to be even influenced by MMPs levels. So, the remodeling and adipocyte development is found to be caused due to MMPs levels [61].

Thickening of blood vessels at the time of atherosclerosis and tissue injury is known to occur intimately. A steady balance between the

migration and proliferation of the cells of vascular smooth muscles by means of apoptosis is known to have influence on the final size of the blood vessel or have effects on the stability of the atherosclerotic plaque. These factors are known to be regulated by the MMPs. The behavior of the vascular smooth muscle cell (VSMC) is further being controlled by factors such as cell matrix, cell-cell interactions, and growth factors, thus both the nonmatrix and the matrix substrates are known to have influence on the actions of VSMC [62].

Amelioration of the plasma leakage in the cases of infection due to dengue virus and a decrement of severe complications of dengue, dengue shock syndrome, dengue hemorrhagic fever, etc., due to *Zingeber officinale* Roscoe was found out. It was progressed by the inhibition of MMP-2 and 9 and upregulation of TIMP-1 and 2 expressions. The production of gelatinases MMP-2 was found to rise and MMP-9's synthesis was decreased due to the infection of vero cells by the dengue virus [63].

There were findings such as mesenchymal cell MMP-2 and macrophage-derived MMP-9 were found to have influence and their requirement was essential for the production of abdominal aortic aneurysm [64].

The changes caused at the time of intake of antidepressants which include neurogenesis, axonal sprouting, dendritic arbors, and endothelial cell proliferation are found to be effectively regulated by MMP and their regulators like TIMPs. There were the alterations of the expression of TIMPs due to the chronic and acute pharmacological antidepressants without any changes in the MMP2/9 activity or its expression. Hence, these proteins may serve as markers for the structural plasticity contributed due to the antidepressant treatment [65].

One of the major causes of long-term kidney allograft failure is chronic allograft nephropathy which is mainly concerned with fibrosis, and MMPs are found to have actions on this case, as a result of ECM degradation control. An inhibitor of MMP-2, 3, and 9, BAY12-9566 was made use of in the early and later stages of CAN and studies were carried out in knowing its actions. It was then conformed by the studies that early inhibition of MMPs lead to the reduction in the spreading and development of CAN, but there was its induction in its later stages. Thus, their involvement was found in the progression of CAN [66].

Due to their activity against Type IV collagen both MMP-2 and 9 are believed to be important. Through the studies of immune-electron microscopy, it has become evident that the immune-reactivity of MMP-2 is found to be located within the glomerular basement membranes of the glomerulus normally and the mesangial matrix. The mRNA for MMP-9 was not able to be localized by IEM. MMP-2 was already found to exist in the inactive form in the kidneys whose activation could lead to its degradation. There was the involvement of MT-MMPs in the penetration of leukocyte inflammation of the basement membranes [67].

Infection caused due to *Pseudomonas aeruginosa* was linked with the synthesis of MMP from the airway epithelium whose activation may lead to the injury of tissues and airway remodeling. It led to the induction of IL-8 and MMP-9 in the bronchial epithelial cells of humans whose pathway was mediated by nuclear factor-kappa B. There is a high inflammatory response by the releasing of IL-8 leading to the destruction of pulmonary tissues by the activation of MMP-9. One of the effective therapeutic activities is by the inhibition of ERK or JNK in the earlier stages of pulmonary infection by *P. aeruginosa* [68].

Community-acquired pneumonia patients were known to show an increased serum level of MMP-2 and MMP-9. Usually, after the treatment of antibiotics, there was generally the decreased serum level of these two enzymes in patients. TIMP-1 was also known to be increased [69].

When a study on the levels of native pathway proteins related with the vitreous proteome was conducted IL-12, heme-oxygenase 1, platelet-derived growth factor receptor beta Tyr 751, BCL-2 associated death promoter Ser 12, MMP-9 in the vitreous of a group of wet age-related macular degeneration patients with subretinal fluid was found to be increased in comparison with those without SRF. Variation in the levels of MMPs with the level of SRF in the vitreous proteome was found but not edema of the retina. Thus, MMP-9 was known to act as a biomarker even for the subretinal fluid accumulation [70].

The activation of pro-MMP-2 is found to be done efficiently in the fibrovascular tissues of PDR, along with the interaction of MTI-MMP and TIMP-2 indicating its activity in the formation of fibrovascular tissues. This PDR is found to be an important cause of visual impairment which is due to proliferation of fibrovascular tissue. Vascular endothelial growth factor is found to be one of the major angiogenic factors in the neovascularization retinopathy. Some species of the MMPs which have the capacity of degrading of various macromolecules of ECM have been detected in the sectors of vitreous and fibrovascular tissues in eyes with that of PDR. The MTI-MMP which is expressed by the endothelial cells is known to be directly involved in the formation of blood vessels of the fibrovascular tissues. More number of studies is yet to be done to make the hypothesis strong [71].

At times of pathological conditions, the levels of MMPs were found to increase tremendously leading to conditions such as inflammation, metastasis, and growth of tumors. One of the examples of the unwanted activity of the MMPs in periodontitis is by MMP-8. Plasmin-dependent or extracellular MMP-dependent cleavage reactions are involved in the dissolving of matrix components. The degradation of mineralized matrices occurs through pathway carried out by osteoclast whose degradation occurs through lysosomal proteinases. MMPs could cleave and degrade the connective tissue and collagen at physiological pH and temperature. In future, there is the requirement of finding appropriable diagnostic tools to decrease the levels of MMPs [72-74].

One of the common reasons of osteoarthritis in dogs is a fragmented medial coronoid process, which possesses a serious problem in its diagnosis. There were some studies carried out which indicated a possible association between the levels of some of the biomarkers in the synovial fluid and alterations of the articular cartilage in its structure due to FMCP related OA. CTX-11, MMP-2 levels were higher in the case of younger animals than when compared to older ones. FMCP affected joints showed higher concentrations of MMP-2, MPO, and MMP-9 activities where MMP-9 was found to show the disease severity activity [75].

MMP-9 is known to play a key role in the degradation of Type IV collagen, thus contributing toward the maintaining of muscle structure and its plasticity. Its inactivation by homologous recombination resulted in enrichment of fast twitch fiber types in adult hindlimb muscles. The plasma concentration of MMP-9 was found to increase immediately after exercise whose inactivation resulted in a decrease in muscle sarcolemmal damage. Its main source was from white blood cells and not the muscles which showed its activity in immune cells infiltration of those damaged muscles. When aging remains a factor along with the basal lamina's composition, the role of MMP-9 in this case is not found to be critical. Thus, aging remains the main exception in most of its role expressed in remodeling [76].

There is a tight regulation of matrix degrading activity at the time of regeneration of muscles in remodeling of ECM. The levels of MMP-2 remained constitutive in normal muscles and induction of MMP-9 occurred within 24 hrs. Northern blot results support the finding that in the mdx muscles levels of both pro and active forms of MMP-2 and MMP-9 are expressed. Myogenic cells produce only MMP-2 which was confirmed by zymography studies in case of C2612-conditioned medium. Thus, the study helped in understanding the correlation between various expressions of pro and active forms of MMP-2 and MMP-9 in different stages of regeneration degeneration process. MMP-2 expression is found to be concomitant with regeneration of myofibrils, whereas MMP-9 is associated with inflammatory response and activation of satellite cells [77].

Pathogenesis of preterm labor involves an imbalance between MMPs and TIMPs or if not the aberrant degradation of ECM. The levels of serum MMP-9, TIMP-1 and MMP-9, TIMP-2 are found to be tilting in the favor of gelatinolysis. All these levels in the serum provide an invasive method to determine the essential enzymes in the remodeling of ECM at times of pregnancy and parturition [78].

Many studies have reported on the localization and activity of MMP-2 and MMP-9 in the amniotic fluid, tissue cultures, etc., but studies on tissue localization and expression pattern of MMP-2 and MMP-9 in pre-eclampsia in human is found to be limited. In general, there was a high incidence of intrauterine growth restriction and mean birth weight was low in these patients. MMP-9 was absent or found in weak levels in pre-eclamptic placentas, and MMP-2 proteins were found in the majority of pregnant women placenta with pre-eclampsia [79].

The TIMPs are known to enhance the action of MMP in the time of placentation and embryo implantation by causing an invasion toward the maternal endometrium by trophoblast cells. As a result, it is found to play an increased role in causing the termination of pregnancy spontaneously [80].

CONCLUSION

The present review focuses on the therapeutic efficacy of the enzyme MMPs which is known to have a wide range of actions in the process of remodeling of the extracellular matrix. The selected drugs in the regimen of cancer and other diseases that have been discussed act as an inhibitor of gelatinases (MMP-2 and MMP-9), making its use as a biomarker in the detection and identification of many diseases. New trends in the development of MMP inhibitors have been carried out which included three methods, nonhydroxamate inhibitors, design of subtype selective MMP inhibitors in the treatment of cancer, and making use of the MMP nucleus as the basis for the development of other inhibitors. Hence, it enables its use as a source of markers in the identification of various cancers and in the diagnosis of many other diseases. More studies could be carried out for the further progression of its usage.

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