



E-ISSN: 2278-4136
P-ISSN: 2349-8234
JPP 2018; SP6: 56-60

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(Special Issue- 6)

Innovation development and standardization of Novel Herbal Formulation

(September 24-25, 2018)

Matrix metalloproteinase's in atheroma formation in arteriosclerotic vascular disease

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DOI: <https://doi.org/10.22271/phyto.2018.v7.isp6.1.13>

Abstract

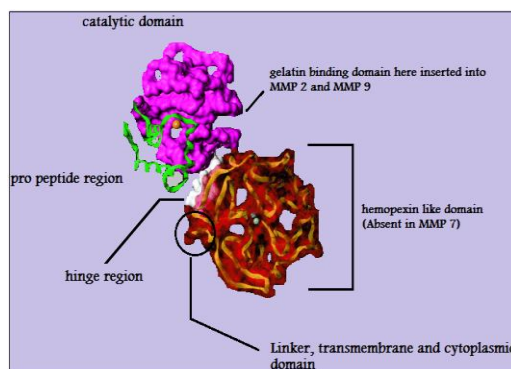
Matrix metalloproteinase's (MMPs) which are also called as matrixins belongs to a group of zinc-dependent proteins (endopeptidases), which play a vital part in the depletion of extracellular matrix. This group of enzymes consists of expanded spectrum of proteases type of enzyme (like collagenases, stromelysins, and gelatinases) which plays an influential and conspicuous role in tissue reformation and remodeling mechanism which is associated with different cascades of processes like morphogenesis, angiogenesis, arthritis, cancer etc. Atherosclerosis is a pathological condition where the innermost layers of the arteries becomes thick due to the accumulation of WBC's (like macrophages, foam cells) and also due to the rapid multiplication of cells present in the intimate layers of artery that creates a plaque. Studying the role and importance of MMP'S in plaque formation has now become an important field of interest. Excessive tissue alteration process and increased activities of matrix metalloproteinase enzyme have been authenticated in plaque interruption. These enzymes represent a fundamental target for the therapeutic innovations in vascular pathology.

Keywords: Matrix metalloproteinase enzyme, Atheroma formation, Atherosclerosis, MMP as targets for therapy, herbal and marine drugs

Introduction

Matrix metalloproteinase's (MMPs) are calcium-dependent zinc-containing endopeptidases belonging to a broader family of enzyme proteases. These enzymes are having the capability to destroy all sort of extracellular matrix (ECM) proteins. They are known to be participating in the splitting of receptors, ligands present in the cellular surfaces and also participate in various cascade systems of our body. These enzymes are also having crucial role in various cellular mechanisms such as proliferation, migration like adhesion or dispersion like phenomenon, differentiation of cells, angiogenesis, apoptosis, defense mechanisms.

Structure and classification of matrix metalloproteinase's



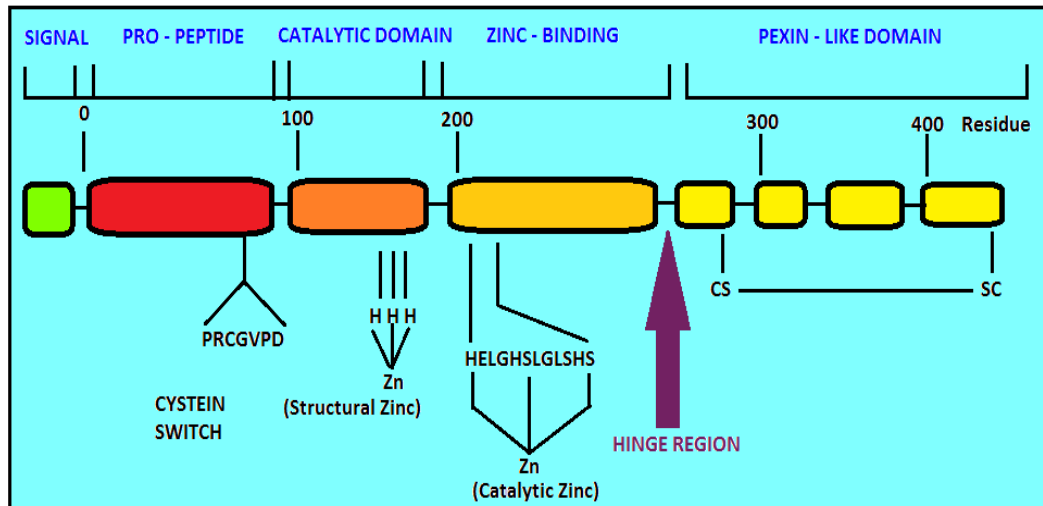


Fig 1: Common structure of MMP

These enzymes are having a common distinct structure. The common domains are the pro-peptide, the catalytic domain, and the haemopexin-like C-terminal domain, which is linked to the catalytic domain by a flexible hinge region.

- **The pro-peptide**

The MMPs are initially synthesized as inactive zymogens with a pro-peptide domain that must be removed before the enzyme is active. The pro-peptide domain is part of the "cysteine switch." This contains a conserved cysteine residue that interacts with the zinc in the active site and prevents binding and cleavage of the substrate, keeping the enzyme in an inactive form.

- **The catalytic domain**

Various X-ray crystallographic data's revealed that the structures of several MMP's catalytic domains are having a

shape of oblate sphere. The active site runs across the catalytic domain. In the part of the catalytic domain forming the active site there is a catalytically important Zn^{2+} , which is bound by three histidine residues Hence, this sequence is a zinc-binding motif.

- **The hinge region**

The catalytic domain is connected to the C-terminal domain by a flexible hinge or linker region. This is up to 75 amino acids long.

- **The C-terminal domain**

The C-terminal domain has structural similarities to the serum protein hemopexin. It has a four-bladed β -propeller structure. β -Propeller structures provide a large flat surface that is thought to be involved in protein-protein interactions. The hemopexin-like domain is absent in several MMPs.

Table 1: Types and subtypes of Matrix metalloproteinase along with its enzymes and substrates

Classes of Mmp's	Enzymes	Substrates Which Are Principally Known For Its Action
Collagenases MMP-1 MMP-8 MMP-13 MMP-18	interstitial collagenases neutrophil collagenases collagenases - 3 Xenopus collagenase	Collagens I, II, III, VII, VIII, X, gelatin, aggrecan, MMP 9 and MMP 2 Collagens I, II, III, V, VII, VIII, X, gelatin, aggrecan Collagens I, II, III, and IV, gelatin, aggrecan, PAI-2
Gelatinases MMP-2 MMP-9	Gelatinase A (72 kDa) Gelatinase B (92 kDa)	Gelatin, collagen types I, IV, V, VII, X, XI, XIV, elastin, fibronectin, aggrecan Gelatin, collagen types IV, V, VII and X, elastin
Stromelysins MMP-3 MMP-10 MMP-11	Stromelysin 1 Stromelysin 2 Stromelysin 3	Collagens III, IV, IX and X, gelatin, aggrecan, MMP 1, MMP 7, MMP 8, MMP 9 and MMP 13
Membrane type MMP-14 MMP-15 MMP-16 MMP-17	MT1-MMP MT2-MMP MT3-MMP MT4-MMP	Collagens I, II, III, gelatin, MMP 2, MMP 13 MM 2, gelatin MMP 2
Others MMP-7 MMP-12	Matrilysin macrophage metalloelastase	Collagens IV and X, gelatin, fibronectin Collagens IV, gelatin, elastin, fibronectin

Role of Matrix Metalloproteinase's In Atheroma Formation

Alterations in Extra cellular matrix equilibrium occur due to modification in the synthesis, degradation or both of the arterial extra cellular matrixes that is affiliated with vascular disorders. There is building proof that the metalloproteinase's

are involved in all levels of the Atheroma progression, from the initial development of lesion to destruction of plaque. Plaque development occurs as a aftereffect of cellular migration and multiplication that leads to accumulation of extra cellular matrix in the deepest layer of artery. MMP-2 enzyme was found to be initiating the degradation of extra

cellular matrix and stimulates smooth muscle cells (SMC's) to migrate towards the arterial wall and causes plaque formation. As the nascent development of plaque occurs there is an outward growth which produces remunerative extension that involves matrix alteration. Thrombotic complications are observed due to the disruption of the atheromatous plaque and breaching of outer erosion of the endothelial layer which ultimately depend on excessive degradation of extra cellular matrix. Recent activities suggest that all these processes are mediated by the enzymes MMP-2 and MMP-9. This boosts the activities of metalloproteinase's enzymes in developing atheromatous lesions that further enhances the constitutional changes and permits their growth. The action of these enzymes has been studied in alliance to the formation of abrasions on the intimal layer of artery and remodeling, as these both require sustained changes in the structure and dimensions of the arterial wall.

Instability of plaque and disruption of Atheroma

Atheroma or in general plaque formation occurs through structural depletion of walls of artery that stimulates the process of thrombosis and causes various types of cascade systems or events to occur in the body. It is observed that plaque disruption occurs in either of the two ways that is by sudden rupturing process or due to erosion of arterial wall this rupture involves distortion of fibrous cap side the plaque. A study on MMP's reveals that active synthesis of mmp-9 type of enzyme by macrophages and SMC's were observed in Atheroma formation both in case of stable and unstable angina. In case of acute vascular syndromes MMP-2 production was also observed. Apart from the above mentioned MMP's other subtypes of these classes of enzymes were also produced in different stage of Atheroma.

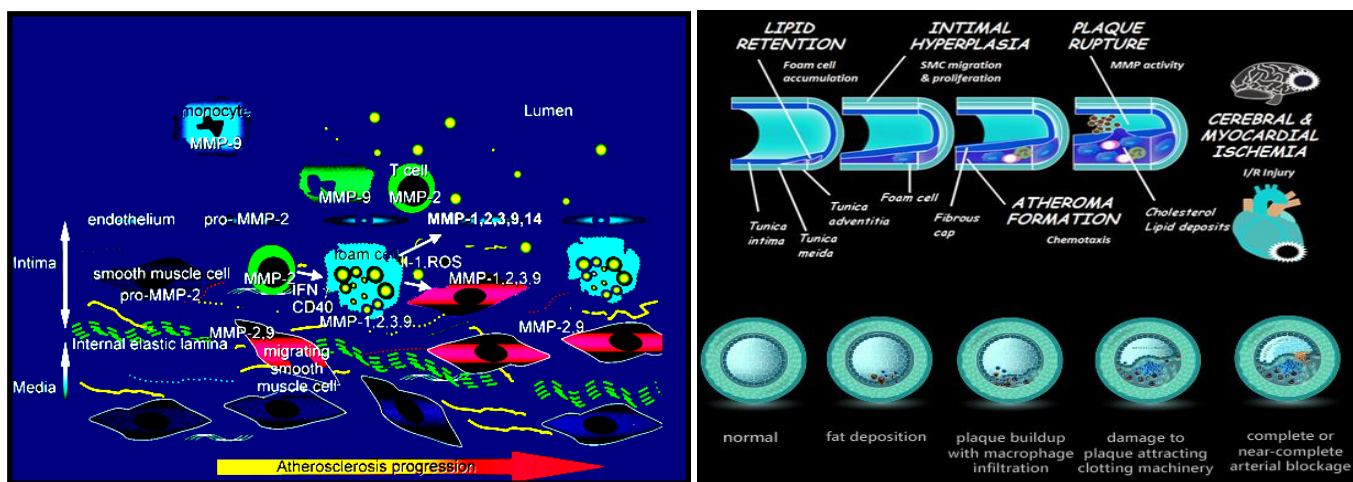


Fig 2: Stages of atherosclerotic progression that secretes various types metalloproteinase's enzymes and arterial remodeling process

MMP's as therapeutic targets for treating Atheroma formation

As we know that the MMP's play an important role in atherosclerotic plaque formation it is also very important to inhibit such enzymes and this inhibition represents a potential therapeutic strategy that stabilizes the plaque formation by the degradation of ECM and restoring the equilibrium of MMP's. There are different methods opted for the inhibition of these enzymes but mostly two broad classes of MMP inhibitors are found to be effective namely the Exogenous and Endogenous type if MMP inhibitors.

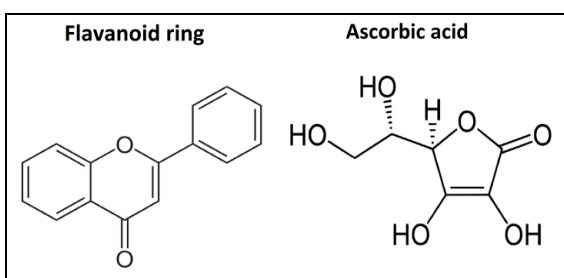
In most of the cases increase in the MMP level is controlled by the endogenous type if inhibitors found in the body called as TIMP'S (Tissue Inhibitors of Metalloproteinase's). MMP's can be by increasing the concentration of TIMP in the body and this is achieved by externally administering recombinant TIMP into the human body. This method is restricted to animal bodies and some type of *in vitro* human vascular cell culture. Recent observations on these studies suggest that increase level of TIMP amount markedly decreased the size of Atheroma and also decreased the MMP activity over these plaques. But this type of method are not giving satisfactory data's on human studies as these externally introduced TIMP gets rapidly denatured and metabolized in the human tissues. Studies revealed that TIMP'S consist of four families of four protease inhibitors: TIMP 1, TIMP 2, TIMP 3 and TIMP 4 type of MMP's found in the body that controls and depletes the increased level of MMP.

Herbal drugs used for the inhibition of MMP in Atheroma formation

Emblica officinalis

Emblica officinalis which is also called as Indian Gooseberry or *Amla* is a type of deciduous tree that belongs to family Phyllanthaceae and is an edible fruit. The dried and flesh fruits are used for various traditional Indian preparations like Ayurvedic, Unani and Herbal preparations.

Studies revealed that the chemical constituents in amla like flavanoids, ascorbic acid, phenolic compounds etc. was found to show inhibitory action on MMP in the plaque formation.



Cucurma longa

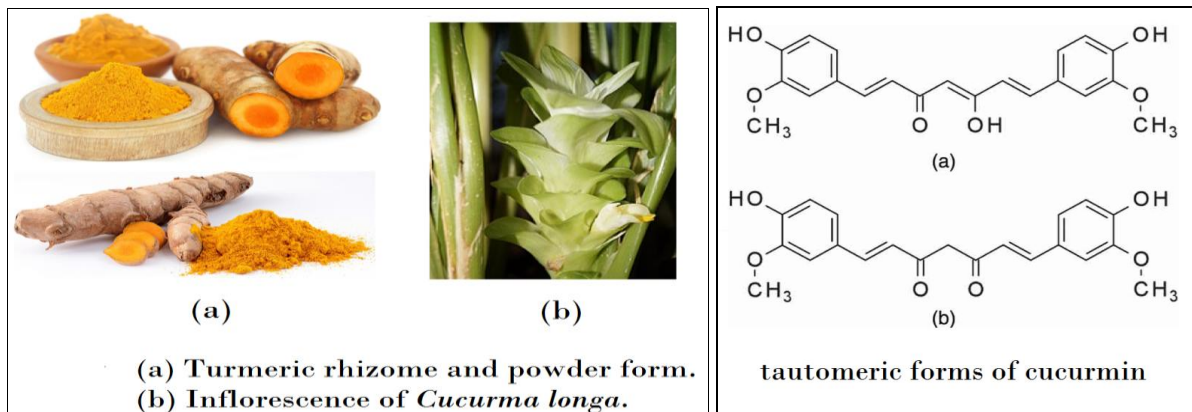
These are the rhizomes obtained from the herbaceous perennial plant of ginger family, Zingiberaceae. It's commonly called as turmeric or *haldi*. The rhizomes are boiled in water for about 30–45 minutes and then dried in hot ovens, after which they are ground to obtain a deep-orange-yellow powder which is commonly used as a coloring and flavoring agent in many Asian cuisines, especially for curries, as well as for dyeing purposes.

It is used as one of the important ingredient in the Ayurvedic and Siddha preparations and also among various Indian

traditional medicinal formulations. Also used as flavoring agent in various dishes. Turmeric is also used for manufacturing dye and also used as food additive in various processed food items to protect them from light.

In traditional medicinal preparations used for treatment of internal diseases like throat infections, indigestion, common colds. It is applied topically for treating skin sores and also to cleanse the wounds by giving anti septic action.

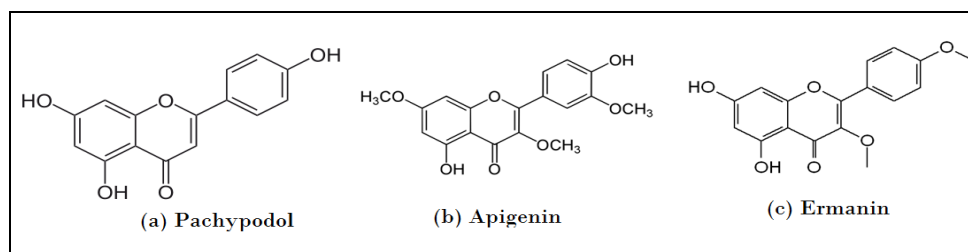
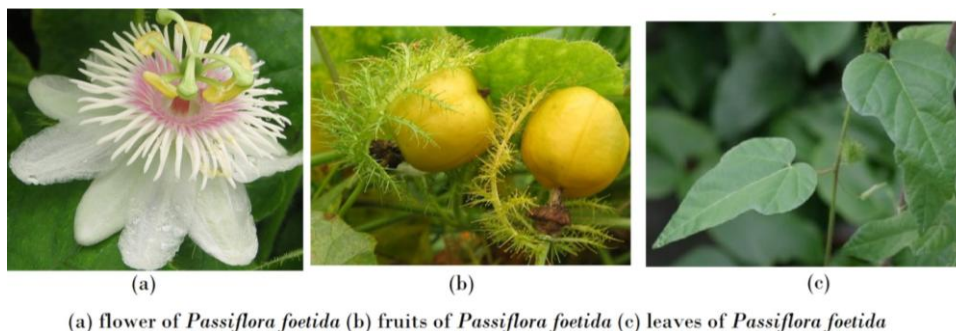
Cucurmin from *Cucurma longa* was found to be effective in inhibition of MMP 2 and MMP 14 in the various stages of atherosclerotic formation.

***Passiflora foetida***

Passiflora foetida commonly called as wild water lemon or wild maracuja is a species of passion flower that belongs to the family Passifloraceae. It's a slender climber with palmate leaves and the leaves contain 3 lobes

It contains flavanoids, indole alkaloids, cyanogenetic

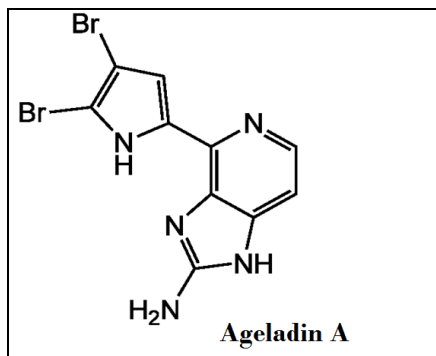
glycosides, hydrogen cyanide. Flavanoids like pachypodol, 4, 7-dimethylnaringenin, 4, 7-O-dimethyl naringenin and 3, 5-dihydroxy-4, 7-dimethoxy flavanone which are isolated from the leaves. Apart from the flavanoids present in the leaves several flavanoids are also isolated from the stem portion of the plant namely, ermani and apigenin.

***Agelas nakamurai***

Agelas is a type of marine sponge of genus Domisponge that belongs to the family Agelasidae. The members of this genus are filter feeders and occur in the West Indies, the Mediterranean Sea, the Red Sea and the Indian Ocean in shallow tropical and subtropical waters.

Agelas nakamurai is a marine fungus that belongs to the

family Agelasidae. Studies reveal that inhibition of several metallo proteinases enzymes namely MMP-1, MMP-2, MMP-8, MMP-9, MMP-12 and MMP-13 by Ageladin A. Ageladin A is a chemical compound that occurs in the marine fungus like *Agelas nakamurai* and other species of sponges that belongs to the Agelasidae family.



Orange elephant ear sponge, *Agelas clathroides*

Conclusion

During the last few decades studies revealed that there are several factors which are directly or indirectly responsible for atherosclerotic progression but the role of MMP in Atheroma progression provided a unique vision for the scientific studies. Different type metalloproteinases enzymes have been studied in a detailed manner to unfold the role of MMP's in atherosclerotic plaque formation and studies and inquisitions reveals that MMP's are having crucial role in the remodeling and development of atherosclerotic plaque formation and finally that will lead to the rupturing of plaque which will create further complications and disorders.

Nowadays Matrix metalloproteinase's enzymes are study of interest in targeted therapy. We can believe that future studies will develop the drugs for the inhibition of MMP's along with other promising outputs combined with biomarker or multimarker approach.

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