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New Microbial Collagenase Inhibitors Discovered

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Abstract

Antimicrobial resistance is spreading globally, making healthcare specialists fear "a return to the dark age of medicine". Great efforts are being made to develop new antimicrobials or to repurpose discontinued or shelved drugs to be used against resistant "superbugs". Antibiotic resistance develops in part because the antibiotics we use kill the bacteria. However, this creates a strong selection pressure: a resistant bacterium multiplies while its non-resistant competitors die. As a result, resistance will emerge quickly in the presence of that antibiotic. Another option is to simply disable bacteria, reducing their ability to infect the host. In other words, rather than inhibiting bacterial viability, Bacterial pathogenesis and infectivity are mediated by virulence factors. Collagenases are virulence factors produced by a variety of bacteria, including Clostridium, Bacillus, Vibrio, and Pseudomonas. These enzymes are among the most efficient collagen degraders, and they play an important role in host colonisation. Because of their critical roles in the infection process, they are an important target for the development of new anti-infective agents. The inhibitory activity of 77 compounds on collagenase A was experimentally evaluated using a fluorescence resonance energy-transfer assay in a primary screening.

Keywords: Capsaicin • Clostridium histolyticum • Antivirulence • Palmatine chloride

Introduction

Bacteria quickly learn to avoid antibiotic attacks due to their high adaptability to environmental changes. As a result, the efficacy of antibiotics is reduced. Antibiotics at high concentrations or for long periods of time cause an increase in resistant mutants while suppressing susceptible strains. Antibiotic overuse or misuse resulted in a high number of bacterial populations resistant to multiple antimicrobials over time, having a tragic impact on the morbidity and mortality associated with numerous infectious diseases. One important underlying cause is the mechanism of most antibiotics: they either kill bacteria (bactericidal) or inhibit their growth, promoting the selection of resistant variants. One approach to avoiding this problem is to disarm the bacterial pathogens rather than kill them.

Literature Review

Inhibiting pore-forming toxins, pili biogenesis by targeting the chaperone-usher pathway, attachment of surface proteins to the peptidoglycan wall of Gram-positive bacteria by targeting sortases, quorum-sensing regulatory proteins, interference with quorum-sensing signal detection, disruption of the biosynthesis of functional membrane microdomains, and reduction of biofilm formation or distortion of its structure are all promising antivirulence strategies. Furthermore, many bacteria's pathogenicity is associated with the production and spread of tissue-destructive enzymes that aid the bacteria's invasion of the host organism.

Bacterial collagenases are proteolytic enzymes that cleave both water-insoluble and water-soluble collagens, promoting the destruction of some extracellular structures and the penetration into anaerobic sites, thus spreading the infection. Their inhibition is a conceptually appealing antimicrobial strategy because it should prevent bacteria from colonising and infiltrating the host, reducing Darwinian selection pressure. Targeting extracellular collagenases has another advantage: inhibitors do not need to cross the bacterial cell wall, which is difficult in many cases. The majority of mature collagenases are made up of an N-terminal collagenolytic unit of about 78 kD and two or three accessory domains that perform various functions such as binding to fibrillar collagen. The peptidase domain contains a catalytic zinc atom that is coordinated by two histidine residues and one glutamate.

Discussion

Several groups worked on clostridial collagenase inhibitors, focusing on C. histolyticum collagenases G (ColG) and H (ColH). This included amino-acid hydroxamate sulfonylated derivatives, 5-amino-2-mercapto-1,3,4-thiadiazoles, aryl sulfonyl-urea derivatives, and N-aryl mercaptoacetamides. However, synthetic collagenase inhibitors have a poor safety profile, making them unsuitable for antibacterial therapy in humans. This can be explained, at least in part, by their mechanism of action: the zinc-binding group in their structure chelates the catalytic zinc ion irreversibly. According to some studies, plant-derived oligosaccharides, polyphenols, and fatty acids bind reversibly to the catalytic zinc, making natural compounds an appealing alternative to synthetic collagenase inhibitors. However, information on the subject is limited.

The goal of this study was to find plant-derived collagenase A inhibitors as well as synthetic compounds with a well-known safety profile that could be used as novel adjuvant antibacterial therapy. We conducted a thorough preliminary screening, testing the inhibitory activity of 77 compounds on collagenase A. We determined the corresponding half maximal inhibitory concentration (IC50) for the most promising derivatives and performed molecular modelling to understand the potential interactions between the isolated compounds and the enzyme.

Dihydrorobinetin's development as an antivirulence agent is hampered by its poor water solubility, whereas biochanin A's estrogen-like effect may be an impediment. The most promising flavone derivative inhibitor of ColA is 4′,5-dihydroxyflavone. Juglone is a natural naphthoquinone derivative found in several walnut species. Juglone's inhibitory effect on ColA, combined

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with its low impact on the bacterial growth of various bacteria, including Staphylococcus aureus, Enterococcus faecalis, and Staphylococcus epidermidis, suggests a potentially selective antivirulence profile. The toxicity of juglone on normal fibroblast cells was not found to be significant at 1 M concentration. This dose is close to the calculated IC50 for ColA, indicating that there is a low risk of toxicity at low concentrations.

Capsaicin and curcumin both had IC50 values less than 5 M. Capsaicin is a naturally occurring vanilloid that has previously been shown to have antimicrobial and antivirulence activities on Group A streptococci, as well as antifungal and antiparasitic properties. Curcumin was also found to have antibiofilm, antieflux, and anticapsule activities against hypervirulent Klebsiella pneumoniae in another study. The vanillyl functional group and the ketone moieties are structural features shared by capsaicin and curcumin that may explain their inhibitory activity on ColA. A large number of clinical trials have shown that administering capsaicin and curcumin at therapeutic doses is safe [1-5].

Conclusion

Palmatine chloride is a natural compound that has been shown to have a wide range of pharmacological effects, including anticancer, anti-inflammatory, neuroprotective, and antibacterial properties. Palmatine was discovered to have a strong inhibitory effect on the neuraminidase protein of Clostridium perfringens in a screening study. Palmatine chloride may be a future antivirulence agent with a dual mechanism, based on the newly discovered ColA inhibition. Palmatine was found to be moderately toxic in an acute toxicity study on mice, with a lethal dose 50 of 1533.68 mg/kg.As collagenase inhibitors, capsaicin, 4′,5-dihydroxyflavone, curcumin, dihydrorobinetin, palmatine chloride, biochanin A, 2′-hydroxychalcone, and juglone were identified. Piperine, 4′,5-dihydroxyflavone, and capsaicin all had nanomolar IC50 values. According to our findings, these molecules could be used to treat infections caused by multidrug-resistant bacterial pathogens that express collagenase A.

Acknowledgement

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Conflict of Interest

There are no conflicts of interest by author.

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