RESEARCH PAPER

Therapeutic Potential of Enzymes in Biofilm Degradation and Antibiotic Potentiation: A Systematic Review

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ABSTRACT

Biofilms are microbial communities encased in a protective matrix that adhere to living or non-living surfaces. This matrix enhances resistance to antimicrobial agents, presenting a major challenge in the treatment of device-related and chronic infections. There is growing interest in exploring the potential of enzymes that degrade the matrix to increase the penetration of antibiotics. Using PRISMA guidelines, a systematic search of 68 peer-reviewed articles published between August 2007 and August 2025 in PubMed, Scopus, and Web of Science was conducted. The review identified enzymes like DNase, cellulases, proteases, and lipases which are capable of degrading key biofilm components like extracellular DNA, polysaccharides, and proteins, thereby reducing the bacterial density and increasing the susceptibility to antibiotics. DNase demonstrated enhanced activity against Pseudomonas aeruginosa and Staphylococcus aureus, whereas cellulases and proteases showed variable but promising results contingent upon biofilm structure. Combination therapy with β-lactams, aminoglycosides, or antifungals yielded satisfactory results, indicating its potential as an adjunctive treatments. However, clinical translations have been limited by challenges related to enzyme interaction, degradation, administration, and possible immunological responses. In summary, enzymatic therapy is a promising alternative for treating biofilm-associated infections, but further optimisation and controlled clinical studies are needed to evaluate its therapeutic effectiveness.

Keywords: Drug resistance, Antimicrobial resistance, Biofilms, Enzymes, Synergy

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INTRODUCTION

Biofilms are complex microbial societies that adhere to surfaces and are guarded by a self-produced extracellular polymeric substance (EPS) matrix. Unlike singular planktonic microbes, these biofilm-forming societies have increased tolerance to environmental stress and resistance to antimicrobial agents [1]. More than 80% of persistent bacterial infections, such as lung infections in people with cystic fibrosis, wound infections, urinary tract infections, and infections associated with medical devices like catheters, prostheses, and implants, are caused by biofilms [2, 3, 4].

Since standalone antibiotic therapy fails to treat biofilm-related infections, researchers are looking into alternative or complementary treatment options, such as enzyme therapy as a technique for breaking down biofilm components and possibly improving antibiotic penetration [5, 6]. Studies have demonstrated that using enzymes to break down biofilms makes bacteria more susceptible to antibiotics [7,8]. Structural components of biofilms can be degraded by proteases such as serratiopeptidase, which degrade protein components, glycoside hydrolases such as Dispersin B degrade exopolysaccharides, and DNase I targets extracellular DNA [9, 10]. Furthermore, bacteriophage enzymes, including depolymerases and endolysins, have been shown to break biofilms and kill bacteria [11]. In addition to destroying the biofilm matrix, these enzymatic therapies, in combination with conventional antibiotics, minimise the amount of antibiotic required [12]. Studies have reported synergism between enzymes and antibiotics against microbes. For example, Dispersin B has been shown to improve the susceptibility of *Staphylococcus epidermidis* biofilms to ciprofloxacin and rifampicin [13]. DNase I, in conjunction with aminoglycosides like tobramycin, significantly reduced *Pseudomonas aeruginosa* biofilm [14]. Lysostaphin, a protease, works well with β-lactam antibiotics to treat MRSA biofilms [15].

While traditional antimicrobials focus on cellular pathways, enzymes act directly on the extracellular matrix [16]. Additionally, it is reported that enzyme

therapy could be rendered less hazardous and more biocompatible than dangerous chemical dispersants [17]. Nevertheless, enzyme treatments do have certain drawbacks. Clinical applicability is hampered by factors such as enzyme stability, the cost of large-scale manufacture, and potential immunological adverse reactions [18]. Furthermore, because different species and infection sites have different types of biofilms, precision engineering or the selection of enzymes for specific clinical settings is necessary [19]. However, the stability and effectiveness of enzymes are always being improved by advancements in protein engineering, recombinant technologies, and delivery systems [20]. Evaluation of enzyme activity as anti-biofilm agents, particularly in combination with antibiotics, is necessary in light of the urgent demand for novel strategies to overcome biofilm-based illnesses. This review summarises available knowledge about methods for using enzymes to eliminate biofilms, discusses their mechanism of action with antibiotics, evaluates preclinical and clinical evidence, and proposes future research options for translational research.

METHODS

Search Strategy

We conducted a systematic literature search employing PubMed, Scopus, and Web of Science for studies that investigated the use of enzymes in biofilm treatment and their synergistic action with antibiotics. Search was done across studies from 2007 to August 2025. Controlled vocabulary as well as free-text terms were employed for maximal relevant hits. Enzymes, biofilm, antibiotics, synergy, and combination therapy were among the search terms, in addition to MeSH terms for finding articles about the enzymatic therapy of biofilms. Boolean operators assisted in narrowing the search, including "Enzymes AND Biofilm AND Antibiotics AND Synergy" in PubMed. We applied similar terms in titles, abstracts, and keywords in Web of Science and Scopus. We looked for specific enzymes such as DNase, cellulase, protease, and lipase to identify studies that evaluated their effects separately or in combination. We also screened the reference lists of key studies and related reviews to add other relevant articles.

Eligibility Criteria

We included studies with primary data on the application of enzymes as antibiofilm agents, with and without antibiotic combinations. Inclusion criteria were of in-vitro, in vivo, and clinical trials studies in peer-reviewed indexed journals showing biofilm-related results such as decreased biofilm biomass, dispersal, or recovered antibiotic sensitivity. Only English-language articles were taken into consideration.

All review papers, editorials, conference abstracts without original data, non-microbial biofilm studies that were not medically relevant, and research without quantitative results of biofilm disruption or synergism were excluded from this study.

Study selection: The original search yielded 1,243 results; 346 duplicates were removed, leaving 897 unique articles to screen. Thereafter, two reviewers independently selected titles and abstracts for relevance, finalizing 142 full-text publications to be evaluated for eligibility. The final reviewincluded 68 papers that met the inclusion and exclusion criteria. We recorded the selection process using a PRISMA flow diagram (Figure 1).

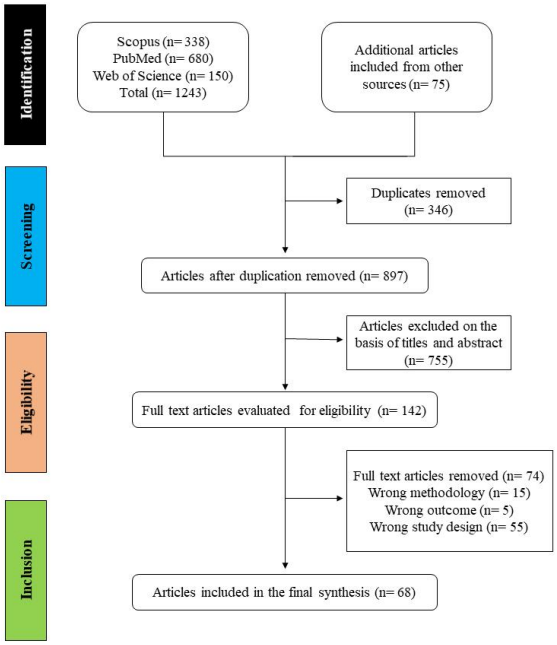

Figure 1: PRISMA flowchart for systematic review

Data Extraction and Quality Assessment

Two independent reviewers checked the data from studies included to reduce the errors and ensure its accuracy. Any kind of discrepancies were resolved through discussion or with a third reviewer.

The collected data included information about enzyme type and source, the target organisms, and biofilm models used. The experimental parameters, such as enzyme concentration, incubation time, and temperature, are included, along with details regarding the antibiotic combinations. The results across the research evaluated variations in biofilm growth type and dispersal, bacterial survival and metabolic activity, and the antibiotic susceptibility.

Furthermore, the statistical analysis performed in each study were recorded.

The screening procedure was divided into two parts. First was the screening of titles and abstracts, and secondly, the full-text screening of the relevant articles. We checked the methodology quality using biofilm model repeatability, outcome definitions, and the reliability of experimental design. In vivo studies and clinical trials were evaluated for randomization, sample size, and the use of adequate controls.

Data Synthesis

We were unable to conduct a meta-analysis due multiple variations in study designs, enzymes, biofilm models, and the outcomes. We did a narrative synthesis instead. The study was divided into enzyme classes, target species, and biofilm models, with the aim of combining enzyme mechanisms, antibiotic synergy, and in vivo or clinical data to assess their therapeutic potential against biofilm-related infections.

Ethical Considerations

Ethical approval was not required because the study relies on secondary data and publically accessible literature. No identifiable personal information or patient-level data was used.

RESULTS

The initial search produced 1,243 results from PubMed, Scopus, and Web of Science. Following the removal of 346 duplicates, 897 titles and abstracts were reviewed. Among these, 142 full-text articles were assessed for eligibility, and 68 fulfilling the inclusion criteria and being included in the final synthesis. The majority of studies showed that enzymatic treatment strongly disorganized biofilm structure, decreased biomass, and often synergistically stimulated the effectiveness of traditional antimicrobials.

Mechanisms of enzymatic biofilm disruption

Disruption of the biofilms is facilitated by enzymatic degradation of components of extracellular polymeric substance (EPS), such as extracellular DNA, polysaccharides, proteins, and lipids. For example, DNase I, hydrolyses extracellular DNA (eDNA), which is an important structural component of the biofilm matrix in Staphylococcus and Pseudomonas species, allowing antibiotics to penetrate and reduce biomass. [21].

Likewise, alginate lyases specifically degrade the alginate polysaccharide in mucoid *Pseudomonas aeruginosa* strains, causing biomass depletion and enhanced antibiotic susceptibility [22,23]. Dispersin B is directed against the poly-N-acetylglucosamine (PNAG) polysaccharide that is pivotal in staphylococci biofilm formation, with resulting biofilm dispersal and potentiated antibiotic activity [24]. Proteases like proteinase K and aureolysinhydrolyze structural proteins and adhesins, and lipases break lipid interactions that stabilize the EPS [25,26]. Enzyme cocktails, which are blends of hydrolases and proteases, tend to give synergistic biofilm destruction over single enzymes [27,28]. Mechanistic summary of these enzymes is presented in Table 1.

Table 1. Mechanisms of Enzymatic Biofilm Disruption

Enzyme	Target EPS component and mechanism	Representative reference
DNase I	Hydrolyzes extracellular DNA (eDNA) within the EPS, causing structural destabilization and increased antibiotic penetration.	[21]
Alginate lyases	Degrades alginate polysaccharide in mucoid *P. aeruginosa* biofilms, reducing biomass and increasing antibiotic susceptibility.	[22,23]
Dispersin B	Hydrolyzes poly-N-acetylglucosamine (PNAG/PIA) polysaccharide, dispersing PNAG-dependent staphylococcal biofilms.	[24]
Cellulase	Cleaves cellulose/β-1,4glycosidic bonds in cellulose-like EPS components, promoting dispersal in certain bacterial and mycobacterial	[29,30]

	biofilms.	
Proteinase K / Aureolysin / Staphopains	Proteolytically degrades proteinaceous matrix components and adhesins, weakening structural integrity.	[31,32]
Lipase / Phospholipase	Hydrolyzes lipid components and alters matrix hydrophobic interactions, modifying matrix architecture.	[33,34]
Mutanase / Dextranase	Hydrolyzes glucan linkages in cariogenic biofilms (e.g., *S. mutans*), inhibiting formation and reducing biomass.	[35]
β-1,3/1,6-glucanases	Degrade glucans in fungal (e.g., *Candida*) biofilm matrices, enhancing antifungal penetration.	[25]
Amylase / α-glucosidases	Hydrolyze starch-like polysaccharides, used in mixed-species and food-surface biofilms to reduce adherence.	[26]
Multienzyme cocktails	Combine glycoside hydrolases, proteases and lipases to attack multiple EPS components concurrently, producing greater eradication than single enzymes.	[28,36]

Enzyme organism interactions

Studies covered under this review compared a series of clinically significant microorganisms. DNase I and alginate lyases decreased biovolume and rendered biofilms more susceptible to aminoglycosides and colistin in *Pseudomonas aeruginosa* biofilms [21-23]. Staphylococcal biofilms detached significantly and exhibited increased antibiotic penetration in response to Dispersin B and protease treatments [24,37]. In *P. aeruginosa*-*S. aureus*, enzymatic mixtures of DNase I and proteases compromised matrix integrity and lowered the minimum biofilm eradication concentration (MBEC) of meropenem and amikacin [31].

Aside from bacterial biofilms, fungal biofilms like those of *Candida albicans* were also found to be sensitive to β-1,3-glucanases that broke down biomass and enhanced fluconazole efficacy [25]. Various studies also demonstrated impacts on mixed foodborne microbial communities where blends of proteases and amylases had efficacies in lowering biofilm burdens on industrial surfaces [26]. The specifics of enzyme-organism interactions and their results are given in Table 2.

Table 2. Enzyme - organism interactions and anti-biofilm efficacy

Organism / biofilm model	Enzyme(s) applied	Observed effect (summary)	Reference
Pseudomonas aeruginosa (in vitro, flow cell)	DNase I	Reduced biovolume; enhanced tobramycin penetration and killing compared with antibiotic alone.	[21]
Mucoid *P. aeruginosa* (CF isolates)	Alginate lyase (AlyP1400)	Reduced biofilm biomass and potentiated multiple antibiotics in vitro.	[22,23]
Staphylococcus aureus and *S. epidermidis*	Dispersin B	Detachment of PNAG-dependent biofilms; sensitization to antibiotics/antiseptics.	[24,37]
Dual-species *P. aeruginosa-S. aureus*	DNase I + proteases (cocktail)	Disruption of matrix and decrease in MBECs of meropenem and amikacin.	[31]
Vibrio parahaemolyticus	Lipase + Cellulase + Proteinase K (cocktail)	~90% inhibition of biofilm formation; significant eradication of mature biofilms.	[36]
Mixed foodborne communities on polypropylene/stainless steel	Protease + Amylase	2-5 log10 reductions on polypropylene and near-complete removal on stainless steel.	[26]
Candida albicans biofilms (in vitro + in vivo models)	β-1,3-glucanase	Reduced biofilm biomass and increased susceptibility to fluconazole and amphotericin B.	[25]
Mycobacterial biofilms (environmental model)	Cellulase	Promoted dispersal responses associated with altered metabolite signaling.	[30]
Klebsiella pneumoniae clinical isolates	DNase I + antibiotic	Decreased biofilm formation and increased antibiotic killing in ex vivo assays.	[38]
Surface colonization	Proteases and other hydrolases	Reduced settlement and biofilm formation by marine organisms.	[39]

Synergistic effects of enzymes with antibiotics

A large percentage of studies included in this analysis evaluated whether enzymatic treatments had the ability to synergize with conventional antibiotics. As an example, supplementation of DNase I significantly increased tobramycin's bactericidal activity against *P. aeruginosa* biofilms, leading to up to 42% more reduction in biofilm biovolume than with the antibiotic alone [21]. Alginate lyases additionally enhanced antibiotic efficacy, and AlyP1400 synergized with aminoglycosides and colistin against mucoid *P. aeruginosa* [22,23]. In staphylococcal biofilms, Dispersin B in conjunction with β-lactam antibiotics resulted in enhanced penetration and killing of bacteria [37,40]. In a similar fashion, protease pretreatment stimulated ciprofloxacin activity against mixed biofilms on abiotic surfaces [27]. In the case of fungal biofilms, sensitization of *Candida albicans* to fluconazole and amphotericin B was achieved by β-1,3-glucanases [25]. These synergistic effects highlight the potential of enzymes as adjunct therapy components in combination therapy, as shown in Table 3.

Table 3. Synergistic enzyme-antibiotic studies

Enzyme(s)	Antibiotic(s)	Target(s)	Outcome (summary)	Reference
DNase I	Tobramycin	*P. aeruginosa* biofilms	Addition of DNase I to tobramycin reduced biovolume and increased antibiotic efficacy compared to tobramycin alone.	[21]
Alginate lyase	Tobramycin, colistin	Mucoid *P. aeruginosa*	Alginate Lyase when combined with antibiotics, resulted in greater biofilm reduction than antibiotics alone.	[22, 23]
Dispersin B	Cefamandolenafate (antibiotic)	Staphylococcal biofilms	Dispersin B enhanced antibiotic penetration and activity in vitro.	[37,40]
Protease (Proteinase K)	Ciprofloxacin (surface biofilm models)	Mixed bacterial biofilms	Enzyme pretreatment reduced viable counts and potentiated antibiotic effect on surfaces.	[26,27]
DNase I + protease cocktail	Meropenem, amikacin	Dual-species *P. aeruginosa*-*S. aureus* biofilms	MBECs of tested antibiotics decreased ≥2.5-fold after enzymatic pretreatment.	[31]
β-1,3-glucanase	Fluconazole, Amphotericin B	*Candida albicans* biofilms	Enzyme enhanced antifungal susceptibility in vitro and in vivo biofilm models.	[25]
Cellulase	Ceftazidime	*P. aeruginosa* biofilms	Combination showed additive/synergistic reduction of viable biofilm cells vs either agent alone.	[41]
Enzyme cocktail (protease/lipase/amylase)	Various antibiotics (experimental)	Multispecies surface biofilms	Combined regimen achieved greater log reductions than antibiotics alone in industrial models.	[36,42]

Supplementing these findings, the use of enzymes that target important EPS components, primarily eDNA, polysaccharides, and proteins, can have a considerable impact on biofilm. Enzyme therapy works synergistically with antibiotics, reducing biofilm mass while enhancing bacterial death.Although the effectiveness varies according on the enzyme, microbial species, and biofilm structure, there are general tendencies towards complementing treatments that use enzymes that destroy the EPS.

DISCUSSION

This systematic review demonstrates that enzymatic treatments have the ability to break down biofilms and increases the efficacy of antibiotics. Enzymes such as DNase I against extracellular DNA, alginate lyases against polysaccharides, and Dispersin B against PNAG allow for selective targeting of a variety of microbial biofilms. Multiple studies shows an increased efficiency when the enzymes and antibiotics were used together [21-24]. While Dispersin B increases β-lactam activity against *S. aureus* [37], DNase I increases aminoglycoside penetration into *P. aeruginosa* biofilms [21]. The enzyme-antibiotic combinations decreased the minimum biofilm eradication concentrations (MBECs) and enhanced the bacterial killing rates [25,31,37,40]. Keeping in view the enzyme stability under physiological conditions, potential immunological reactions, and production costs are still obstacles in clinical application [28,32].

Additionally, most supporting data is derived from in vitro settings, which differ greatly from those found in the real world. The need for more translational research is highlighted by the continued lack of human clinical trials and animal studies. Enzyme stability and bioavailability are being improved by advances in immobilization, enzyme engineering, and nanoparticle-based delivery techniques [27]. The potential for managing enzymatic biofilms is expanded by industrial application. Biofilm burdens on food processing surfaces have been successfully decreased by enzyme-based cleaning techniques, which may also be used for non-clinical biofilm treatment [26]. However, widespread adoption will require inexpensive formulations and standardized testing methods. In conclusion, enzyme-based anti-biofilm therapy is a cutting-edge strategy for biofilm management and infection prevention. There is a lot of evidence to support their potential for effectiveness and antibiotic improvement, even though there are still some issues that need to be resolved, such as thorough clinical testing of their effectiveness. For treating human infections, optimizing enzyme-antibiotic combinations, creating efficient delivery strategies, and conducting randomized controlled trials to evaluate their effectiveness should constitute top priorities going forward.

CONCLUSIONS

This systematic review focuses on evidence supporting enzymatic techniques as efficient anti-biofilm agents. Enzymes can break down biofilm matrix, reduce biomass, and increase antibiotic efficacy against many bacterial and fungal diseases. Emerging advancements in recombinant protein engineering, enzyme immobilization, and nanoparticle-based delivery technologies are making it possible to create more stable and effective medicinal formulations. To determine efficacy and safety in humans, follow-up research should prioritize experimental approaches, in vivo studies, and randomized clinical trials. The application of enzyme combinations capable of targeting various biofilm components at once is an emerging area of research. Enzyme-based anti-biofilm therapy has the potential to complement infection management and standard antimicrobials strategies in both clinical and industrial settings.

DECLARATIONS:

Conflicts of interest: There is no any conflict of interest associated with this study

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors contributions: Author equally contributed the work.

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