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Review

An Overview of the Antimicrobial Activity of Some Microbial Enzymes

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Abstract: Enzymes are substances produced by living organisms that are used to catalyze some biological and biochemical reactions as they either catalyze some types of polysaccharides and proteins or lyse complex materials such as polymers and lipids. Microbial enzymes are defined as the enzymes that can be extracted and purified from bacterial strains such as *Bacillus* spp., *Pseudomonas* spp., *Streptomyces*, or fungal strains such as *Aspergillus* spp., these enzymes have a substantial impact on various uses in medical and pharmaceutical fields. The antimicrobial and antibiofilm properties of these enzymes are extensively researched and recognized as their primary applications in fighting microbial infections and resistance across different fields. Numerous enzymes, including Chitinase, Lipase, and L-Asparaginase, demonstrate broad antimicrobial activity with low MIC values and large inhibition zones, while only chitinase exhibits antiparasitic activity, and Chitosanase exhibits antifungal activity. Also, the antibiofilm activity of microbial enzymes is widely reported among various types of enzymes such as Keratinase, Pectinase, and Cellulase. It was observed that the antiviral activity is still under investigation and limited to L-asparaginase and Lipase only. More studies need to be carried out to discover more biological activities of several microbial enzymes contributing to the upgrading, improvement, and advancement of the pharmaceutical industry. Therefore, this review aims to determine and summarize the commonly reported microbial enzymes and their activity as antimicrobials to be used in pharmaceutical and medical applications. To the best of our knowledge, it is the first review that summarizes the most important microbial enzymes that report different antimicrobial activities.

Keywords: Antimicrobial Activity, Microbial Enzymes, Anti-Fungal, Anti Biofilm, Anti-Bacterial, Lipases, Glucanase, L-Asparaginase, Cellulases, Chitinase, Chitosanase

Introduction

Pathogenic microbes such as bacteria (Thallinger *et al*., 2013), fungi (Kriegl *et al*., 2024), viruses, and parasites (Melese *et al*., 2023) pose a significant threat to human health (Sharifi *et al*., 2020), causing various infectious disorders that contribute to high mortality and morbidity rates globally (Sharifi *et al*., 2020; Liu and Kokare, 2023). Also, these pathogenic bacteria can form biofilms on industrial production lines and hospitals, which are highly resistant to several antibiotics and disinfectants (Mishra *et al*., 2020). As reported by the World Health Organization and Centers for Disease Control and Prevention at year of 2022, microbial infections are the main cause of death in the Western and Eastern world, resulting in around 150,000 annual deaths in Europe, 210,000 in the United States and 163,000 in eastern regions (WHO, 2021). This health issue shed light on the need for inventing antimicrobial agents and disinfectants to eradicate these pathogens and decrease mortalities worldwide.

Antimicrobial agents are a class of agents that are mainly used to treat various fungal, viral, bacterial, and parasitic infections (Joerger *et al*., 2024), they become less effective and restricted to use due to microorganisms' ability to develop drug resistance (Salah *et al*., 2024), to antibiotics misuse and their toxicity to human tissues (Anbu *et al*., 2017; Singh *et al*., 2019), so, there is a rising interest in producing antimicrobial agents for various

medical and health needs (Sanchez and Demain, 2017; Vittaladevaram, 2017), in addition to reporting that the rising incidence of infectious diseases is a significant driver of market expansion in addition to the influence of the COVID-19 pandemic (Sanchez and Demain, 2017; Khouja *et al*., 2022; Saravanan *et al*., 2021) which leads to an increase in the total consumption of antimicrobials globally (Fellows and Hill, 2024). However, it has been observed that developing novel antibiotics is a costly process that may further take a long period due to limited research and the need for innovating novel broad-spectrum antimicrobials that may cause several adverse events to humans (Reshma, 2019; Barreiro and Barredo, 2021).

The University of Oxford reports that global antimicrobials' use rates had a 46% increase from 2000-2018, as it has been estimated that the value of the antimicrobials market was USD 50.91 billion in 2023, globally and is suggested to increase at a compound annual growth rate (CAGR) of around 4.2% from the year 2024-2030 (WHO, 2021; Barreiro and Barredo, 2021).

It is important to discover new antimicrobial agents that have unique mechanisms of action and targets, either singly or in successful combinations, to achieve better efficacy (Saravanan *et al*., 2021), selective toxicity (Nisar *et al*., 2019), cheaper costs in large-scale production (Ogueji *et al*., 2017) and a broader range of activity (Ren *et al*., 2024).

Microbial enzymes which are defined as catalysts that are produced in large quantities from either bacteria or fungi, are utilized in a variety of industries and applications (Kashef and Hamblin, 2017). They are commonly used as potent antimicrobial agents in nature (Nisar *et al*., 2019), as most of them are characterized by antimicrobial and antibiofilm activity which is essential for protecting them as a defense mechanism against invading other pathogens (Mohd Yusof *et al*., 2019; Dimkić *et al*., 2022; Ramakrishnan *et al*., 2019).

Several bacterial strains produce antimicrobial enzymes like chitinase, chitosanase, protease, and alpha-amylase (Cavalier *et al*., 2021). These enzymes exhibit antimicrobial effects through mechanisms such as degrading pathogen cell walls (Jadhav *et al*., 2017), disrupting membranes (Sallenave, 2002), incorporating lipids into bacterial membranes, and cleaving peptide bonds in bacterial proteins (Chen *et al*., 2018) and their efficacy to combat biofilm by destructing the bacterial cell wall individually or by combination to other substances (Li, 2021). Bacterial Enzymes exhibiting several antimicrobial activities are summarized (Fig. 1).

There are no studies that reported the antimicrobial activity of microbial enzymes with collecting the main findings and comparing the differences and alignments between those studies, as all previous studies reported a certain enzyme with its antimicrobial and/or antibiofilm activity. Therefore, this review aims to determine and summarize the commonly reported microbial enzymes and their activity as antimicrobials to be used in pharmaceutical and medical applications.

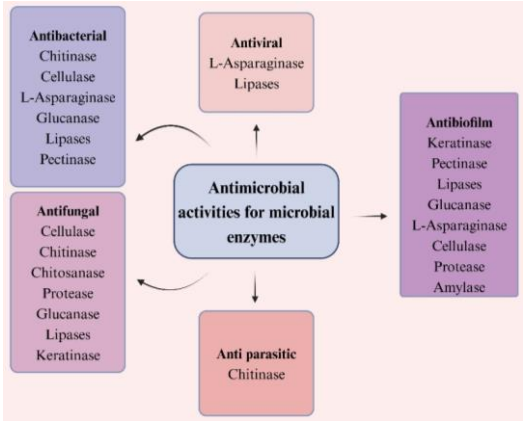

Fig. 1: A summary of the antimicrobial activities among different microbial enzymes (Abd El-Baky and El-Baroty, 2020; Al-Kadmy *et al*., 2023; Barreiro and Barredo, 2021; Chen *et al*., 2018; Costa *et al*., 2014)

Materials and Methods

This review assists in covering and summarizing several studies on the antimicrobial and antibiofilm activity of some microbial enzymes reporting the main findings relating to the review aim. The data search was done using the Web of Science, Science Direct, EBSCO, MEDLINE, BIOMED CENTRAL, CINAHL, PubMed, Google Scholar, and Scopus and only the English language was used for studies done through the last 40 years to make a wider search databases and reports. These databases were the most commonly trusted search engines used to investigate the reports regarding this topic with more relevant data, all databases except for Web of Science were used by selecting a few keywords such as microbial enzymes, anti-bacterial, antifungal, antiviral, anti-parasitic, antibiofilm to get all topics related to the review aims, while Web of science was a research engine used by adding a small phrase to get all reports related to the review aim.

Using search engines that were identified through a series of brainstorming and searching a thesaurus, the database, and preexisting knowledge on the topic. The thesaurus helped in finding and using the control terms to ensure accurate and high-level coherency among the terms. Following the studies' selection, some references in the studies were also selected. Subsequently, the results were screened based on the study aim and these criteria allowed a broad search to be conducted while keeping the scope as precise as possible.

Results and Discussion for Microbial Enzymes Exhibiting Various Antimicrobial Activities

Chitinases

Chitinases are enzymes that fall under the category of glycoside hydrolases. Their primary function is to

facilitate the process of chitin breakdown (Veliz *et al*., 2017). These enzymes are generated by various fungi such as *Trichoderma* spp. and *Aspergillus* spp. and bacteria such as *Bacillus* spp., *Actinomyces* spp., *Enterobacter* spp., *and Pseudomonas* spp., higher plants, insects and animals (Singh *et al*., 2021; Poria *et al*., 2021). Chitinase enzymes are composed of at least three functional domains (Oyeleye and Normi, 2018), which enable them to break down chitin and other polymers like chitosan and cellulose in some instances.

Firstly, the Chitinase enzyme shows moderate antifungal properties against various phytopathogenic fungi, including *Bipolaris* spp., *Aphanomyces raphani*, *Alternaria brassicicola*, *A. fumigatus* and *Rhizopus oryzae* and showed the highest antifungal activity with large inhibition zones (>18 mm) against *A. niger, Penicillium oxysporium and A. oryzae* and low inhibition activity (<12 mm) against *Rhizoctonia solani, Fusarium solani and Candida albicans*, while they did not exhibit any activity against *F. graminearum, S. sclerotiorum and T. reesei* when were subjected to be tested on plates containing potato dextrose agar by agar well diffusion assay (Zarei *et al*., 2011), as well as, only the purified chitinase with an activity of 50 U derived from *Bacillus* spp. and *P. aeruginosa* are effective when tested for their antibacterial activity against various Gram-positive as well as Gram-negative bacterial species demonstrating the highest inhibition (inhibition zone diameter of 14 mm) against *S. aureus*, followed by *S. typhi* and *P. aeruginosa*, while enzymes showed moderate activity against *S. typhimurium, K. pneumoniae*, Methicillin-resistant *Staphylococcus aureus* (MRSA), *Aeromonas hydrophila and Photobacterium damselam E. coli and S. pneumoniae* and there was no observed efficacy against *P. damsela* (Yasir *et al*., 2021; Carneiro de Medeiros *et al*., 2018; Farag *et al*., 2016).

Secondly, Chitinase was found to inhibit biofilm formation based on the crystal violet assay to reveal that *Francisella* biofilms were responsive to chitinase which disrupts the biofilms' proteins, exopolysaccharides, and extracellular DNA, additionally, introducing the external chitinase increased the biofilms' susceptibility to gentamicin which reduces the amount of biofilm because chitinase influenced the attachment and penetration of bacteria, as well as the multiplication of bacteria within the cells (Chung *et al*., 2014).

Thirdly, there have been limited reports regarding the role of chitinase in combating nematodes and parasites and all studies regarding the activity of chitinase against parasites reported that this activity is significantly high (Steinfeld *et al*., 2019) and parasites have been susceptible to chitinase to believe that chitinase plays a role in the host's defense against parasites and in promoting $T(H)^2$ inflammation (Elias *et al*., 2005).

Amylase

Amylase is a type of saccharolytic enzyme that falls into various subtypes, including alpha, beta, gamma, iso-amylase, and glucoamylase (Paul *et al*., 2021). Alpha and beta-amylase enzymes can catalyze the hydrolysis of chitosan, causing a reduction in its molecular weight too. The activity of the amylase enzyme involves breaking down cell-membrane components and weakening their attachment to the solid surface (Elyasi Far *et al*., 2020), leading to cell lysis and breaking down the biofilm (Singh *et al*., 2022).

Amylase enzymes inhibit the synthesis of adhesives and the development of extracellular polymeric substances, hence reducing the formation of biofilm in the oral cavity (Minami *et al*., 2023). Because saliva contains a significant amount of amylase, it has been seen that plaque cannot form when this enzyme is present (Aljerf and Mashlah, 2017). Furthermore, laboratory investigations demonstrated that alpha-amylase can act as an antibiofilm agent against biofilm-forming bacteria such as *P. aeruginosa*. *C. glabrata, C. albicans, E. faecalis, V. dispar, S. mutans F. nucleatum.* and *S. aureus* when applied for 5 min, resulting in a significant 79% decrease in the biofilm and when the enzyme concentration increases from 72-90%, the inhibition of Extra Polymeric Substances (EPS) in biofilm decreases by 82%, while this enzyme had a limited impact on the biofilm created by *S. epidermidis* (Lahiri *et al*., 2021).

Protease

Proteases are a unique class of proteolytic enzymes that are involved in several physiological and economic uses that catalyze the complete breakdown of proteins (Razzaq *et al*., 2019; Sharma *et al*., 2017).

Protease with antifungal properties was isolated from a strain of *P. aeruginosa* to investigate the effects of this microbial enzyme on the growth of the fungus *F. solani*, showing that the protease was found to inhibit both spore formation and the germination of hyphae in *F. solani* (Yen *et al*., 2006).

Testing the biofilm formation assay using 96-well polystyrene plates demonstrated that the greatest effectiveness of protease in inhibiting biofilm on *P. aeruginosa*, followed by *Rhodococcus ruber and S. aureus* as the extracellular protease activity hindered the *S. aureus* from producing biofilms and caused the detachment of existing biofilms (Park *et al*., 2012). A modified form of proteases, called serine protease produced from *S. epidermidis* also hindered the production of *S. aureus* biofilm while they had no antibiofilm activity against *S. epidermidis* biofilms (Martí *et al*., 2010). Thus, it is plausible that the extracellular protease plays a significant role as an antibiofilm (Gilan and Sivan, 2013).

Cellulases

Cellulases are enzymes that degrade the cellulose present in the cell walls of plants, converting it into simple sugars that can be used as raw materials for biofuels, as well as various biobased chemicals (Jayasekara and Ratnayake, 2019) and other materials (Barbosa *et al*., 2020). The antibacterial activity of cellulase was observed against different strains of bacteria, as it breaks down the bacterial cell walls peptidoglycan by catalyzing the hydrolysis of β-(1,4) linkages between the NAM and NAG saccharides (Zhang *et al*., 2022).

The activity of cellulase enzyme against Gram-positive and Gram-negative when bacteria, as well as fungi, revealed that the cellulase enzyme exhibited greatest activity with the escalating concentration of enzyme against *vibrio damsela*, with a large inhibition zone (42 mm), followed by *Enterococcus faecalis* (28 mm), while the lowest level of activity against *E. coli, Klebsiella pneumonia, Staphylococcus aureus and Pseudomonas fluorescence* (15 mm) and against *A. niger* (19 mm), followed by *A. cristatus* and *A. terreus* (18 mm), while least activity was observed against *A. fumigatus* (11 mm) when compared to the standard ciprofloxacin (5 µg/disc) and amphotericin B (100 U/well) (Gad *et al*., 2021).

It has been found that antibiofilm activity was observed from cellulase-producing strains by breaking down the exopolysaccharide matrix, which primarily consists of polysaccharides and some proteins matrix which is partially responsible for bacterial adhesion and the accumulation of biofilm on surfaces, cellulase shows an antibiofilm activity against *B.cepacia* and *P. aeruginosa* biofilms, which also exhibited quorum quenching (QQ) activity against the biofilm-forming strain at high concentrations of this enzyme (9.4 units/mL) at pH 5 (Rajasekharan and Ramesh, 2013; Loiselle and Anderson, 2003).

L-Asparaginase

L-asparaginase facilitates the breakdown of L-asparagine into L-aspartic acid and ammonia, which is necessary for the growth of certain types of tumor and bacterial cells (Muneer *et al*., 2020) and it has been reported that this enzyme has an affinity for penicillin-binding proteins, which are the target of its action with low MIC values (20-84 mg/mL) against various bacterial strains such as *Pseudomonas aeruginosa, Salmonella typhimurium, Klebsiella pneumoniae, Staphylococcus aureus, Proteus vulgaris and Listeria monocytogenes* (Wang *et al*., 2021; Vimal and Kumar, 2021).

The antibiofilm activity was also assessed for this enzyme to find that L-asparaginase exhibited a higher inhibition rate against *Pseudomonas aeruginosa*, with a biofilm formation rate of 41%, followed by *Klebsiella pneumoniae* with a rate of 32%. However, L-asparaginase has lower inhibition rates of 79 and 86% against *Staphylococcus aureus and Acinetobacter baumannii*, respectively. Most antibiofilm agents alter the physical properties of bacterial cells and non-living surfaces (Darvishi *et al*., 2022), while L-asparaginase acts as signaling molecules that alter the gene expression of bacteria that form biofilms to prevent their growth and biofilm formation with highest effectiveness (Nsayef Muslim *et al*., 2016).

Furthermore, it was observed that L-asparaginase derived from *S. maxima* exhibited antiviral properties against Coxsackie B3 Virus by its ability to hinder attachment, as well as impede the penetration and adsorption stages of the viral replication cycle, resulting in inhibition rates of more than 89.24% (Abd El-Baky and El-Baroty, 2020).

Glucanase

Glucanase is of great importance in breaking down glucan-like substances (Edison *et al*., 2018). Its potential applications in the food and pharmaceutical industries have generated significant interest among scientists (Ueki *et al*., 2020).

The bacterial beta-1,3-1,4-glucanase produced by *Halomonas meridiana* exhibited a wide range of antibacterial activity with high inhibitory effects (>30 mm) against different bacterial and fungal strains, including *S. aureus, Shigella dysenteriae, E. faecalis, S. typhi, K. pneumoniae, E. coli, and S. paratyphi*. However, it exhibited moderate inhibitory effects (16-27 mm) on *S. agalactiae, B. subtilis and V. damsela.* (Jin *et al*., 2011; Chai *et al*., 2018; Gadallah *et al*., 2023).

It has been demonstrated that β-Glucanase produced from *A. niger* has significantly strong antifungal activity against *Penicillium digitatum* and *Fusarium* oxysporum, *Cryptococcus neoformans, and Candida albicans*, while it exhibited a weaker antifungal effect against *A. niger* and *A. oryzae* (Gadallah *et al*., 2023; El-Shora *et al*., 2021).

Identifying the elevated levels of β-1,3 glucan which are present in the surrounding biofilm environment and are part of the biofilm models in the cell wall structure of *C. albicans* affirms the potential role of β-Glucanase in disrupting *C. albicans* biofilms (Nett *et al*., 2007; Tan *et al*., 2022). Through the adhesion assay, microscopic images revealed alterations in the morphologies of *Candida* biofilm treated with beta-1,3-glucanase to report that beta-1,3-glucanase disrupts biofilms in a concentration-dependent manner as the concentration of 10 µg/mL decreased the biofilm mass by 55.96%. However, when biofilms were treated with both antifungal agents and beta-1,3-glucanase, the number of viable cells decreased by 62.40%, with the extent of reduction varying depending on the specific antifungal agent used (Tan *et al*., 2018).

Lipase

Serine hydrolases or lipases are classified as members of the triacylglycerol ester hydrolase family (Chandra *et al*., 2020). They can accelerate the hydrolysis of long-chain triglycerides into fatty acids, monoacylglycerol, and glycerol (Thorn *et al*., 2020).

The lipase enzyme exhibits activity against Gram-positive bacteria such as *S. epidermidis* and *S. aureus* and Gram-negative such as *E. coli* with low MIC values (0.1 and 0.05 mm) due to the cell wall of bacteria being composed of a substantial peptidoglycan layer that has reduced negative charge and increased affinity for lipase, allowing for easy attachment and subsequent degradation (Park *et al*., 2023) and there is no variation in its effectiveness when paired with other various antibiotics (Doss *et al*., 2017; Prabhawathi *et al*., 2014).

The antibiofilm activity of lipase from *A. niger* was assessed using spectrophotometric methods and the results demonstrated a substantial reduction in biofilm development in E. *coli*, MRSA, *Proteus mirabilis*, and *P. aeruginosa* with notable levels of inhibition were 95.3, 93.6 77.1 and 74.9%, respectively (Yassein *et al*., 2021).

The Lipase enzyme can break down the integrity of cell membranes and disrupt the cell walls of various fungal strains such as *Candida albicans*. However, researchers are currently combining the Lipase enzyme with other antifungal agents to enhance its effectiveness in treating severe fungal infections (Yang *et al*., 2019; Uroro *et al*., 2022).

The antiviral activity of lipase enzymes is currently being studied, with limited research available on this approach (Park *et al*., 2023). Previous studies have shown that administered lipase enzyme exhibited its highest antiviral activity at its slowest concentration against Herpes simplex virus-I (Isaacs *et al*., 1992; Yu *et al*., 2022).

Pectinase

Pectinases are a group of enzymes that break down pectic compounds, which are mostly found in microbes and higher plants (Amin *et al*., 2019). To assess the antibacterial activity of pectinase, the good diffusion method on nutrient agar medium against various bacterial isolates was carried out. Pectinase derived from *Actinomycetes* exhibited limited antibacterial effects against *B. cereus, B. subtilis, K. pneumonia, S. aureus, and P. auroginosa* (Suman and Yugandhar, 2021). Pectinase derived from the *Bacillus* strain exhibited the largest area of inhibition against *E. coli* and *A. Oryzae and* there is no inhibition was detected for *A. flavus* and *A. nodulans* (Sarsar and Pathak, 2019).

Multi-enzyme formulations containing microbial enzymes capable of breaking down microbial DNA, proteins, polysaccharides, and quorum-sensing molecules, EPS matrix, which are the key components of bacterial biofilms (Amin *et al*., 2019). The efficacy of the purified pectinase in inhibiting biofilm formation and adhesion by all biofilm-producing bacteria was assessed using Congo red agar methods to demonstrate that the extracellular pectinase produced by *Pseudomonas stutzeri* exhibited superior antibiofilm and antiadhesive activity against *P. aeruginosa,* with rate of 72% while it showed lower rates of inhibition against E. *faecalis* and *S. aureus* with rate lower than 30% (Nsayef Muslim *et al*., 2016) while Pectinase derived from *A. niger* demonstrated a decrease in biofilm formation by 2 and 3.5 log 10 units when exposed to a concentration of 0.022 U/cm^2 (Villa *et al*., 2015).

Keratinase

Microbial keratinases are a type of protease enzyme that crucially facilitates the conversion of keratin-containing waste materials into valuable products by aiding in the breakdown of keratin (Li, 2021). These enzymes are widely distributed in nature and may be found in various organisms such as Bacteria, Eukarya, and Archaea (Moghnieh *et al*., 2018).

Keratinase purified from different isolates of *A. baumannii* showed that their antibiofilm activity by damaging the bacterial cell wall was found to be relatively low compared to the keratinase/rGO system which exhibited increased anti-biofilm activity by inhibiting biofilm formation on Congo red agar plates, surpassing the activity of keratinase alone (Sharma *et al*., 2012; Nasipuri *et al*., 2020; Al-Kadmy *et al*., 2023).

Keratinases demonstrate potent antifungal properties when tested against various fungal strains showing that the Minimum Inhibitory Concentration (MIC) values of microbial keratinase were lower than those of other enzymes like Lipase and DNase against fungal strains and dermatophytes such as *T. mentagrophytes, M. canis and M. gypseum*. This suggests that certain microbial keratinases are as effective as itraconazole, a commonly used antifungal agent (Costa *et al*., 2014; Sharifzadeh *et al*., 2016).

Chitosanase

Chitosanases facilitate the breakdown of the β-1,4-linked glycosidic bonds in chitosan by hydrolysis (Cahyaningtyas *et al*., 2021). Previous reports indicate that chitosanases have been discovered in a range of microbes, including bacteria and fungi to only exhibit notable antifungal properties (Jiang *et al*., 2021) against *F. solani, A. niger and A. oryzae* with MIC 68 µg/mL and less (Jiang *et al*., 2021; Pang *et al*., 2021) and there are no previous reports prove any other antimicrobial activity of chitosanase enzyme.

Conclusion

Microbial enzymes play a significant role in many pharmaceutical and medical applications and antimicrobial and antibiofilm activities by these enzymes must be studied and reported as main applications for these enzymes in combating microbial infections and resistance in diverse fields, most microbial enzymes such as Chitinase, Lipase, Cellulase, and L-Asparaginase exhibit broad antimicrobial activity against several bacterial strains such as *E. coli*, *Pseudomonas aeruginosa*, *Enterococci faecalis* and *Staphylococcus aureus* and fungal strains such as *A. niger*, *F. solani*, *A. oryzae*, *Candida albicans*, and *Rhizopus oryzae*. Also, the antibiofilm activity of microbial enzymes is widely reported among various types of enzymes such as Keratinase, Pectinase, Lipases, and Cellulase. A few enzymes showed limited antimicrobial activity such as the Chitosanase enzyme which exhibits only antifungal activity and the antiparasitic activity was reported only in chitinase enzymes. The antiviral activity is still being investigated and is limited to L-asparaginase and Lipase enzymes only against Coxsackie B3 and Herpes simplex virus-I. Further research must be carried out to investigate other microbial enzymes' antimicrobial activities such as antiviral and anti-parasitic activity, in addition to the urge need to study the synergistic effects of some microbial enzymes with the lowest concentrations of antibiotics, also, testing these enzymes' efficacy when synthesized in a nanoparticle form and more studies about production of these microbial enzymes in industrial scale must be performed.

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Author's Contributions

Akram N. Salah: Wrote the main item and first draft form of review, methodology, introduction and revised all reviewed manuscript items.

Hayam Atallah Alwabsi: Wrote the main item of the first 4 enzymes, abstract, and the conclusion.

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