REVIEW

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Various types of *extended spectrum β-lactamases*: a literature review

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ABSTRACT

The inappropriate use of antibacterials causes the spread of resistance in bacteria and increases the health burden of infection due to the nature of resistance to many classes of antibiotics which are referred to as multi-resistant (multidrug resistant). Extended spectrum β-lactamase (ESBL) is one of the enzymes that cause multi-resistance, where bacteria with this enzyme become resistant to third-generation cephalosporin antibiotics which are often used to treat gram-positive and gram-negative bacterial infections in humans with minimal side effects. β -lactamase is an enzyme capable of hydrolyzing the β-lactam ring in β -lactam class antibiotics so that antibiotics become inactive. Mutations in the gene that encodes this enzyme produce a β-lactamase enzyme which can break down the β-lactam ring in all penicillin and cephalosporin antibiotics. The classification of β-lactamases is complex due to genetic, biochemical properties, and substrate affinity for β-lactamase inhibitors. There are also various types of ESBL enzyme-coding genes including TEM, SHV, CTX-M, VEB, PER, OXA, SFO-1, BEL-1, BES-1, TLA-1, and GES. This study aims to review various types of extended-spectrum β-lactamases.

Keywords: antibiotic resistance, extended spectrum β-lactamases.
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INTRODUCTION

In the last few decades, the use of antibacterial has been widespread but there are still many who use it inappropriately so that it is susceptible to causing the spread of resistance in bacteria.[1] Antibiotic resistance is a problem of deep scientific concern both in hospitals and the community. The increasing use/misuse of antibiotics in human medicine, agriculture, and veterinary medicine has mainly contributed to this phenomenon. This causes a high health burden in an infection due to the nature of resistance to many classes of antibiotics, referred to as multi-resistant (multidrug resistant).[2]

One of the multi-resistance that often occurs is due to the Extended Spectrum β -Lactamase (ESBL) enzyme produced by bacteria, where this enzyme can hydrolyze β-lactam-type antibiotics thereby reducing their ability to work.[2] β-lactam antibiotics are the most common treatment used for bacterial infections, but they are also a major cause of resistance to β -lactam antibiotics among gram-negative bacteria worldwide. Continuous exposure of bacterial strains to various β -lactam antibiotics have induced dynamic and sustained β -lactamase production and mutation in these bacteria. The enzymes produced by these bacteria are known as *extended-spectrum β*-lactamases.[3]

ESBL is an enzyme that causes bacteria to become resistant to third-generation cephalosporin antibiotics where these antibiotics are often used to treat gram-positive and gram-negative bacterial infections in humans with minimal side effects.[4] Any delay in the identification and treatment failure of severe infections by ESBL will result in increased morbidity and mortality. Because ESBL-producing strains often exhibit multidrug resistance, such as resistance to aminoglycosides and fluoroquinolones, the therapeutic options associated with these strains are limited. It is thus clear that there is an increasing prevalence of ESBL producers and ESBL-producing strains leading to higher rates of morbidity, mortality, and healthcare-related cost.[5] ESBL isolates have been found in humans, animals, the environment, meat and vegetables.[6] The purpose of this literature review is to describe *extended-spectrum β-lactamases* and their various types.

β-lactam antibiotics class

β-lactam antibiotics class are antibiotics that have a β -lactam ring component. There are 4 types of antibiotics in this group including penicillin, cephalosporin, monobactam, and carbapenem. This antibiotic works by inhibiting the synthesis of the bacterial cell wall through the binding of the β -lactam ring component to the penicillin-binding protein which will stop the process of cell wall synthesis. The cessation of the cell wall synthesis process causes the cell to die due to osmotic imbalance.[7]

β-lactam antibiotics work by forming bonds with penicillin-binding protein (PBP)-trans-carboxypeptidase which has an important role in the formation of the peptidoglycan chain of the bacterial inner membrane. The presence of PBP and β-lactam antibiotics causes inhibition of peptidoglycan synthesis, stops cell division, and causes cell death. The bond between PBP and β-lactam antibiotics occurs based on the affinity of the β-lactam structure on the active site of PBP. However, during the evolution of PBP a point mutation appeared which caused the bacteria to produce β-lactamase enzymes

that were able to hydrolyze the lactam ring in β-lactam antibiotics.[8]

ESBL definition

β-lactamase is an enzyme that is capable of hydrolyzing the β-lactam ring in β-lactam class antibiotics so that antibiotics become inactive. Enzymes specific for penicillins, cephalosporins and carbapenems include penicillinase, cephalosporinase, and carbapenemase. A mutation in the gene that encodes this enzyme produces a β-lactamase enzyme which can break down the β-lactam ring in all penicillin and cephalosporin antibiotics, making them no longer effective at killing bacteria.[3]

β-lactamases are called *extended-spectrum β-lactamases* which cause problems because most of the coding genes are located on plasmids so that they are easily transferred between organisms.[9] ESBL can be inhibited by clavulanic acid, tazobactam or sulbactam, and the encoded genes are exchangeable between bacteria. The most common ESBL genetic variant today is CTX-M.[3] ESBL production is a significant resistance mechanism that inhibits antimicrobial treatment of infections caused by Enterobacteriaceae and poses a serious threat to the currently available arsenal of antibiotics.[3] ESBL has a β-lactamase gene (bla) which can be found on both chromosomes and plasmid.[10]

Classification of β-lactamases

The classification of β -lactamases is complex due to genetic, biochemical properties and substrate affinity for β-lactamase inhibitors (clavulanic acid).[11] The β –lactamase enzyme gene (bla) is usually located on a large self-transporting plasmid, this plasmid also frequently encodes other resistance determinants such as the aminoglycoside-converting enzyme.[12] β-lactamases are generally classified according to two general schemes, namely the Ambler molecular classification and the Bush-Jacoby-

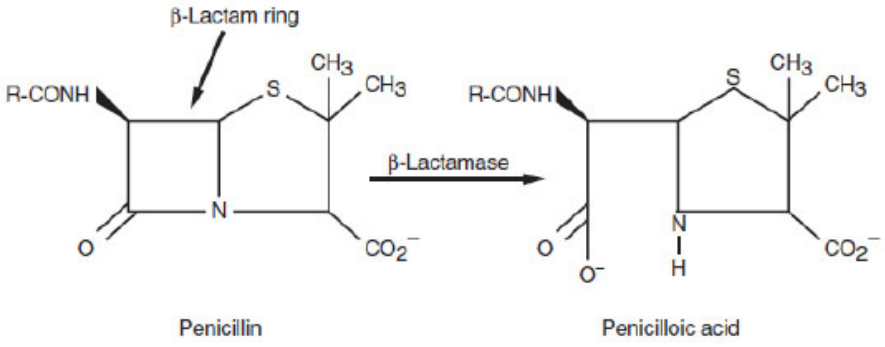

Figure 1. β-lactam antibiotic structure.

Figure 2. Location of the *bla*$_{TEM-1}$ gene.[11]

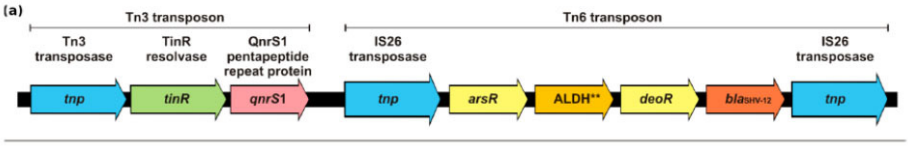

Figure 3. Location of the *bla*$_{SHV-12}$*gene.* [4]

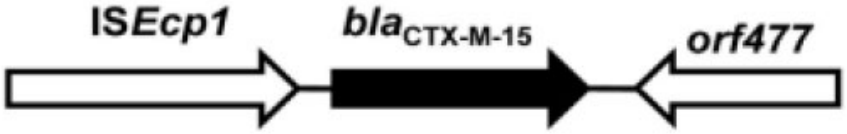

Figure 4. Location of the *bla*$_{CTX-M\ 15}$*gene*[5]

Table 1. Distribution of ESBL SHV-type[12]

Enzyme	Species other than *K. pneumoniae* and *E. coli*	Country
SHV-2	*P. mirabilis, K. Oxytoca, Salmonella* (various serotypes), *E. gergoviae, S. marcescens*	Germany, Tunisia, Senegal China, Argentina, France, UK, Greece, Egypt, Croatia, Hungary, Switzerland, USA, Denmark, South Africa, Spain
SHV-2a	*P. aeruginosa*	Germany, Switzerland, Korea
SHV-3	*E. aerogenes*	France, USA
SHV-4	*P. mirabilis, E. aerogenes, Citrobacter diversus*	France, USA, UK, Belgium, Portugal
SHV-5	*P. mirabilis, K. oxytoca, Salmonella* (various serotypes), *E. cloacae, E. aerogenes, S. marcescens*	Chile, Greece, UK, Australia, Argentina, France, USA, Italy, Austria, Poland, Croatia, Hungary, Denmark, Spain, South Africa, Taiwan, India
SHV-6	-	France
SHV-7	-	USA, UK
SHV-8	-	USA
SHV-9	*E. cloacae, S. marcescens*	Greece
SHV-12	-	Switzerland, Korea

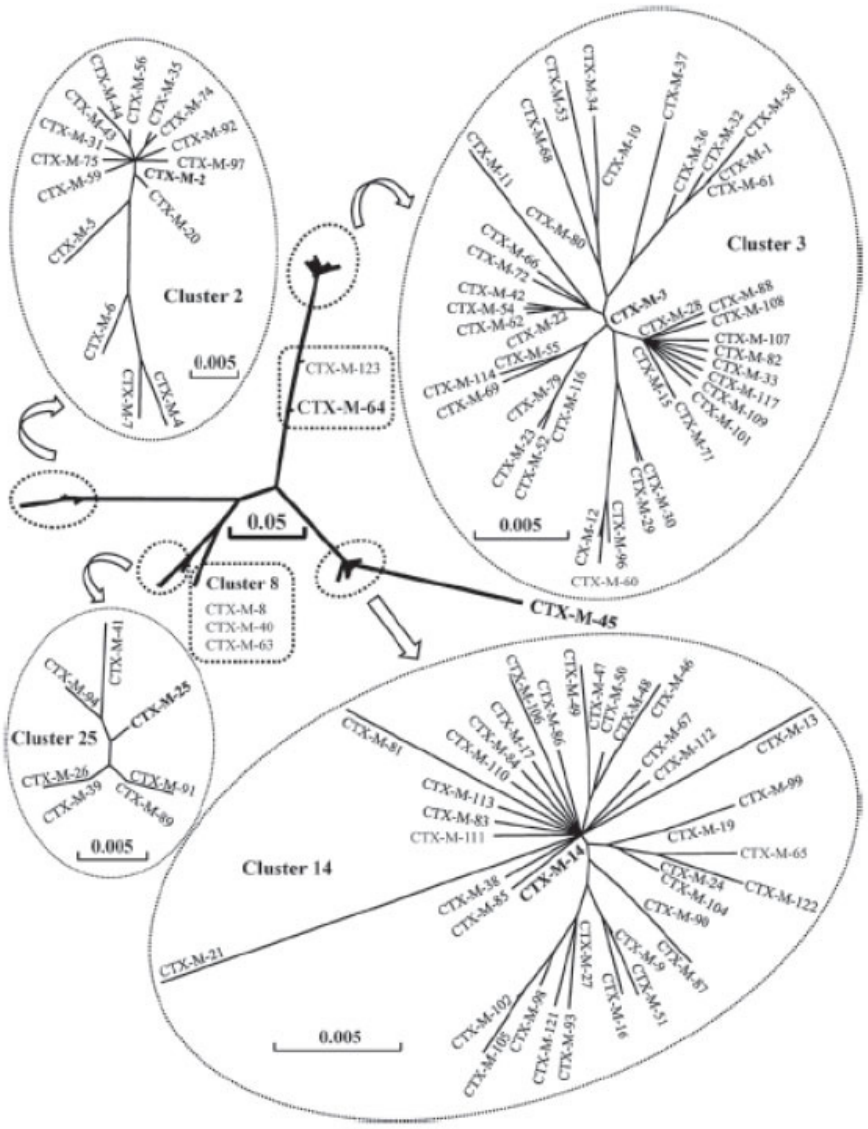

Figure 5. Phylogenetic tree of CTX-M family based on amino-acid sequences.[12]

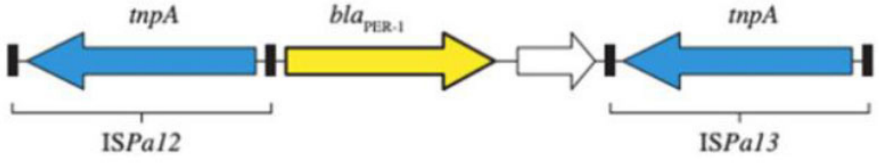

Figure 6. Location of the bla_{PER-1} gene.[11]

Medeiros functional classification. The Bush-Jacoby-Medeiros functional scheme is the most well-known in which the classification in this scheme is based on the functional properties of the enzyme, namely the profile of the substrate and inhibitor. While the Ambler scheme classifies β-lactamases into four classes based on their amino acid and nucleotide sequences.[3] This classification is divided into A, B, C, and D. Where β-lactamase classes A, C, and D are enzymes based on serine mechanisms. While class B is a metallo β-lactamase that requires zinc ion.[13]

ESBL types

Among different types of ESBL encoding genes, TEM, SHV, and CTX-M are the main ESBL coding genes.[14] SHV, TEM, and CTX-M types are also the most common ESBL coding genes found in clinical isolates.[15]

TEM-type

TEM-type ESBL consists of TEM-1, TEM-2, and TEM-3. TEM-1 was first discovered in *E. coli* in 1966 by a patient named Temoneira, so this enzyme was named TEM. The TEM type is the largest group of ESBL enzymes and has been widely distributed.[11]

TEM-1 can hydrolyze penicillins and first-generation cephalosporins but cannot hydrolyze oxyimino cephalosporins. TEM-2 is the first derivative of TEM-1 that has a single amino acid substitution from the native β-lactamase.[3] In 1984, TEM-3 was first discovered in *Klebsiella pneumoniae* in France.[5] TEM type of ESBL is the most common in *E.coli* and *Klebsiella pneumoniae.* The TEM type can also occur in other Gram-negative bacteria and other Enterobacteriaceae genera such as *Enterobacter aerogenes, Enterobacter cloacae, Morganella morganii, Proteus mirabilis,* and *Salmonella spp.*. TEM-type ESBL can also be found in *non-Enterobactereriaceae*, namely in *Pseudomonas aeruginosa*.[5]

SHV-type

SHV comes from the word variable sulfhydryl. SHV-1 was first discovered in *Klebsiella pneumoniae*.[3] SHV is an enzyme whose coding gene is located on plasmid. SHV in the plasmid causes the replacement of serine to glycine at position 238, there is also a change in lysine to glutamate at position 240. The serine residue at position 238 is important for hydrolyzing ceftazidime and lysine residues are very important for hydrolyzing cefotaxime. SHV type ESBLs are found in *Pseudomonas aeruginosa, Citrobacter diversus* and *E.coli*.[13]

Currently, there are 182 different SHV variants listed in the NCBI Reference Gene Catalogue. Their spectrum ranges from β-lactamases (eg, blaSHV-4) to broad-spectrum β -lactamases (e.g., blaSHV-1) to ESBLs (blaSHV-2) to broad-spectrum ESBLs (blaSHV-10). The most common SHV variant in *E. coli* ESBL from the food chain is SHV-12.[4] SHV variants have spread worldwide, following their distribution:[12]

CTX-M-type

CTX-M was first described by Tzouvelekis in 2000. The term CTX-M β-lactamase indicates its ability to hydrolyze the antibiotic cefotaxime. Kinetic studies have shown that CTX-M type hydrolyze cephalothin or cephaloridine better than benzylpenicillin and they hydrolyze cefotaxime more preferably than ceftazidime. The CTX-M enzyme was inhibited better by the β-lactamase inhibitor tazobactam than by sulbactam and clavulanate.[11]

Unlike TEM and SHV enzymes, there are no point mutations in CTX-M. The origin of the CTX-M enzymes is different from TEM and SHV ESBL. Meanwhile, SHV-ESBL and TEM-ESBL are produced by the substitution of amino acids from their parent enzymes. CTX-M ESBLs are obtained by horizontal gene transfer from other bacteria using genetic tools such as conjugative plasmids or transposons. It is believed that CTX-M was first identified from the chromosomes *of Kluyvera spp.* after turning into a plasmid, because the sequence of the gene encoding the CTX-M enzyme shows a high similarity to the *Kluyvera* spp. gene. In addition, the gene sequences adjacent to the *Enterobacteriaceae* CTX-M gene are also similar to those surrounding the β-lactamase gene on the *Kluyvera spp.* chromosome. So far, 128 CTX-M strains have been reported, they are found in different *Enterobacteriaceae,* including *Salmonella* spp.[5]

CTX-M type ESBLs are mainly classified into five groups (CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25) and minor variants based on the similarity of the acid amino residues. Bla_{CTX} -m is mostly found in transferable plasmids which are known to be dispersed among bacteria of the Enterobacteriaceae family via plasmid conjugation. Among some of insertion sequence elements that are involved in mobilizing the bla_{CTX-M}, the ISEcp1 is recognized as one of the most important elements and is present in the upstream region of $bla_{CTX-M.}$[11-15]

Besides TEM, SHV and CTX-M types, there are several other types of ESBL enzyme coding genes including:

PER-type

PER-1 (*Pseudomonas extended resistance*) type was first discovered in France in 1991 in *P.aeruginosa isolates* from a patient from Turkey. The PER-type enzymes are resistant to penicillin, cefotaxime, ceftazidime and aztreonam. PER activity can be inhibited by clavulanate, sulbactam and tazobactam.[9-11] Similar to the TEM type, the PER enzyme is not effective at hydrolyzing cephamycins and carbapenems. Until now there have been 7 types of PER found. PER-1 was again found in Turkey but in different bacteria namely *Salmonella spp.* and *Acinetobacter* spp., as well as *P. vulgaris* and *P. stuartii* from Algeria.[11-15]

A survey in Turkish intensive care units found the presence of *Acinetobacter spp.* and *P. aeruginosa* with PER-1 enzyme in ceftazidime-resistant nosocomial isolates. PER-1 has also been found in *Proteus mirabilis* and *Alcaligenes faecalis* in Italy. Turkey and Korea are countries where PER-1 is often found, while PER-2 is often found in South America.[5-9] PER-2 was first discovered in Argentina in 1996 and has 87% homology with PER-1. In France, PER-3 was also found in *Aeromonas punctata* isolate. Then PER-4 was found in *P. vulgaris*, while PER-5 and PER-7 were found in *Acinetobacter baumannii*, and PER-6 in *Aeromonas* environmental species.[7-11]

VEB-type

Vietnam extended spectrum β-lactamase (VEB-1) was first discovered in *E. coli* isolated from a 4-month-old Vietnamese boy while being treated in a French hospital in 1996. However, it was later found in *P. aeruginosa* isolates from a patient from Thailand.[5-11]

After that VEB-1 was reported in many gram-negative bacteria such as *P. aeruginosa*, *K. pneumonia*, *A. baumannii*, *P. mirabilis*, *E. cloacae*, *C. freundii*, and *P. stuartii*. ESBLs VEB-1 type which are widespread in Southeast Asia have reportedly been found in several countries including France, Belgium, England, Bulgaria, Iran, Kuwait, Algeria, China, Korea and India.[15]

The gene coding for VEB-1 is located on the plasmid and integron, and their amino acid has 38% similarity with PER-1 and PER-2. VEB-1 exhibits a high degree of resistance to cefotaxime. Clavulanate, sulbactam, tazobactam, moxalactam, imipenem and cefoxitin are able to inhibit VEB-1 well.[13-15]

OXA-type

This enzyme is named OXA because of its ability to hydrolyze oxacillin and cloxacillin more quickly than benzylpenicillin. OXA enzymes have been widely distributed and are often found in Enterobacteriaceae and *P. aeruginosa*.[12] OXA types are grouped as class D in the Ambler classification and group 2d enzymes in the Bush-Jacoby-Medeiros functional classification.[3-10] The presence of OXA will make bacteria resistant to ceftazidime, but can be well inhibited by clavulanic acid. Not all OXA enzymes are ESBLs, some of them are plain oxacillinases but some have ESBL phenotypes and some are carbapenemases. Of the 244 OXA-type β-lactamases, 16 had phenotype ESBL.[15]

SFO-1-type (*Serratia fonticola*)

In Japan in 1988 SFO-1 was discovered for the first time from a clinical isolate of *Enterobacter cloacae*. This enzyme is named SFO-1 because of its similarity to the β -lactamase of *S. Fonticola*.[11-15] SFO-1 can hydrolyze cefotaxime very well but not ceftazidime, this enzyme is also able to separate cephamycins and carbapenems. The encoding gene SFO-1 is located on the plasmid so that it can be transferred and its activity can be inhibited by clavulanic acid and imipenem.[12] Unlike other ESBLs, SFO-1 has the AmpR gene and is strongly induced by imipenem.[15]

TLA-1-type (Tlahuicas (Indian tribe))

TLA-1 was first discovered in 1993 in an *E. coli* isolate from a patient in Mexico. The coding gene is located on the plasmid so it is self-transferred. Tazobactam can inhibit TLA-1 well, but at a lower level this enzyme can be inhibited by clavulanate and sulbactam.[13-15] This enzyme is capable of hydrolyzing broad-spectrum cephalosporins, including cefotaxime, ceftazidime, aztreonam and cefepime, but not imipenem and cefoxitin. TLA-1 has an amino acid sequence that is 40% similar to the VEB and PER-types.[14]

BES-1-type (Brazilian extended spectrum β-lactamase)

In 1996 BES-1 was first isolated from *Serratia marcescens* from a hospital in Rio de Janeiro, Brazil. The coding gene for this enzyme is located on the plasmid and can be inhibited well by clavulanate.[15]

BES-1 has a higher degree of resistance to aztreonam and cefotaxime than ceftazidime. BES-1 is similar to the CTX-M type against cefotaxime, but its activity is more active against ceftazidime and its affinity is 1000 times higher for aztreonam.[15]

BEL-1-type (Belgium extended spectrum β-lactamases)

BEL-1 was identified in Belgium in 2004 in *P. aeruginosa*. This enzyme significantly hydrolyzes most of the broad-spectrum cephalosporins and aztreonam, but not cephamycins or carbapenems. The bla_{BEL-1} gene is located on the chromosome and embedded in the integron class 1.[15] Its activity was well inhibited by clavulanate, cefoxitin, moxalactam and imipenem, while tazobactam was unable to inhibit BEL-1 as well as BES-1.[14]

GES (Guyana extended-spectrum β-lactamase)

GES is the most common type of minor ESBL. Initially, GES was reported in Enterobacterales species but is now more common in *P. aeruginosa* and *A. baumannii* isolates. GES is known to obtain single or multiple amino acids and broaden its spectrum to become carbapenems. The original GES enzyme was originally an ESBL capable of hydrolyzing penicillins and cephalosporins well, but not aztreonam. GES activity was also well inhibited by clavulanate and tazobactam.[13-15]

GES-1 was first discovered in *K. pneumoniae* isolates from France in 1998. The encoding gene GES-1 is located on the plasmid and integron. There is also GES-2 originating from South Africa. GES-5, GES-6, GES-7 and GES-8 originate from Greece, then GES-3 and GES-4 originate from Japan. Recently it was reported that GES-5 was found in Korea, China, and Brazil.[11]

GES β-lactamases can be divided into 2 categories namely enzymes that are ESBLs and enzymes which have simple carbapenemase activity such as GES-2. GES-2 has a single amino acid substitution (Gly170Asp) when compared to GES-1. GES-2 also showed hydrolytic activity against carbapenem.[9]

CONCLUSION

Extended-spectrum β -lactamase (ESBL) is one of the enzymes that cause multi-resistant, with its ability to hydrolyze the β -lactam ring in third-generation cephalosporin antibiotics so that antibiotics become inactive. Several types of ESBL show changes in characteristics such as the GES-type, so information regarding these ESBL types must always be updated.

CONFLICT OF INTEREST

No competing interests regarding the manuscript.

ETHICAL CONSIDERATION

This review article has the following Committee on Publication Ethics (COPE) and International Committee of Medical Journal Editors (ICMJE) guidelines regarding publication ethics.

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AUTHOR CONTRIBUTION

Rastuti MR conducted literature searches and wrote manuscript. Budayanti NNS reviewed the conceptual framework and final draft of the manuscript.

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