

## NATURAL ANTIMICROBIALS IN THE PIPELINE AND POSSIBLE SYNERGISM WITH ANTIBIOTICS TO OVERCOME MICROBIAL RESISTANCE

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### ABSTRACT

The unresponsive use of antibiotics led to the appearance of multiple drug-resistant bacteria strains. Studying the mechanism by which bacteria can resist antibiotics, the so called quorum sensing and biofilm formation, enabled the researchers to find bioactive compounds, derived from eukaryotes and prokaryotes. The disrupt of this mechanism is called quorum sensing inhibitors or quorum quenchers. This article provides an overview on the current research done on such bioactive compounds, the possible use of them as antibiotic alternatives, what are the advantage and disadvantages, the source from which it has been extracted, and how it may succeed to overcome bacterial resistance. The recommendation of researchers is to use some of these natural antimicrobial compounds combined to lower doses of antibiotics for treatment, the fastest way to limit the adverse effects of the exploitation of antibiotics and to avoid bacterial resistance.

**Keywords:** Bacterial resistance, Antibiotic adjuvants, Antimicrobial enzymes, Antimicrobial peptides, Essential oils, Phytobiotic.

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### INTRODUCTION

The innovation of antibiotics solved many health problems to human beings and animals from plenty of life-terrifying diseases [1]. The excessive irresponsible use of antibiotics, for human and veterinary therapy, resulted in the appearance of several bacterial strains resistant to antibiotics [2]. Plenty of research work was done to find alternative approaches to control these resistant organisms and the high mortality caused by them [3]. It is worthy to mention that bacterial infections cause approximately 65% of the total sum of infectious diseases. Bacterial communities produce pheromones or autoinducers act as cell-to-cell signaling to monitor population density and to coordinate the activities of the population such as biofilm formation, virulence, multiplication, spore formation, and horizontal gene transfer. This process is called bacterial quorum sensing [4]. Inside the biofilm, bacteria are more resistant to antibiotics around 1000 times more than their planktonic ones [5,6]. Research work done to interfere biofilm formation has enabled us to identify some compounds derived from eukaryotes and prokaryotes with the ability to quench or inhibit the quorum sensing system, called as quorum quenchers (QQ) or quorum sensing inhibitors (QSIs) [7-9]. These compounds gave a chance to develop new drugs to kill pathogens [10,11]. The objective of this work is screening of some QSIs and their possible applications as antimicrobial agents aiming to overcome antibiotic resistance and prolong the effective life span of antibiotic.

### DEVELOPMENT OF ANTIBIOTIC RESISTANCE AND HEALTH THREATS

The development of several drug-resistant pathogens was listed by the World Health Organization as one of the top threats to public health in the world [12]. It was anticipated to evolve the bacterial resistance to antibiotic within 50 years approximately after its first use [13]. Unexpectedly, resistance to some antibiotics such as tetracyclines started to develop within a year of its approval by drug FDA [14].

Methicillin was discovered in 1959 and introduced to treat penicillin-resistant *Staphylococcus aureus*, and then, methicillin-resistant

phenotype strains were isolated 2 years later [15]. Similarly, the aminoglycoside streptomycin, which inhibits bacterial protein synthesis was introduced for the treatment of tuberculosis in 1945, but the emergence of rRNA mutations conferring streptomycin resistance to *Mycobacterium tuberculosis* strains was soon reported in 1956 (Table 1).

### MECHANISMS BY WHICH BACTERIA RESIST ANTIBIOTICS

Antibiotic resistance takes place in bacteria by either innate resistance [17] or acquired resistance through gene transfer from adjacent organism [18-20] or increased mutation rates [21-23] or adaptive environmentally induced resistance [24].

Bacterial enzymatic modification leads to inactivation of the antibiotic (this happens to streptomycin which is chemically modified and become no longer able to bind to the ribosome to block protein synthesis) [25-27]. Furthermore, bacteria carry out alteration of the antibiotic target by degrading enzyme (like beta-lactamase proteins, formed by bacteria, might cut beta-lactam ring of the penicillin atom) [28].

In the same time, bacteria can change its cell wall permeability to push the antibiotic outside the cell [29-31].

The infectious disease society of America highlighted *S. aureus*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacter* (ESKAPE) as species capable of "escaping" the antibacterial action of antibiotics by the above-mentioned mechanisms. These species constitute a new paradigm in virulence, transmission, and antimicrobial resistance [32].

### QUORUM SENSING

It is the language by which bacterial cell-to-cell communication takes place. It connects different bacterial cells of the same or different species as well as bacteria and the eukaryotic host cell. With the increased bacterial cell number, the production of signals, called autoinducers, grows and reaches a threshold level, whereas a wide alteration in gene expression takes place including genes encoding for adhesins,

Table 1: History of The Development of Antibiotic Resistance [16]

Years	Developed	Showed bacterial resistance
Before 1935	Sulfonamides	
1941-1945	B-lactam (penicillin)-streptomycin	Sulfonamides
1946-1950	Chloramphenicol-tetracycline colistin	B-lactam (penicillin)
1951-1955	Erythromycin	Tetracycline
1956-1960	Vancomycin	Streptomycin-chloramphenicol colistin
1961-1965	Cephalosporins-quinolones	
1966-1970		Cephalosporins and quinolones
1986-1990		Erythromycin-vancomycin
1996-2000	Oxazolidinones (linezolid)	
2001-2005		Oxazolidinones (linezolid)

exopolysaccharides (a major component of the biofilms), and virulent factors production. This gives the bacteria a chance to achieve specific actions that occur only when living in a community not when has been sporadic so that quorum sensing controls production and development of biofilms, virulence factors, sporulation, bioluminescence, and conjugation [33].

Biofilm and virulence disruption agents are called QQ or QSIs. They are considered a feasible alternative to antibiotics [34].

Three approaches were investigated to inhibit microbial QS:

First, disruption of autoinducer synthesis; second, the inhibition of ligand/receptor interactions; and third, degradation of the autoinducer through enzymatic destruction [35].

#### ADDRESSING ANTIBIOTIC RESISTANCE

A combination of antimicrobials may give synergistic effect due to the diversity of mechanisms which is necessary to overcome recurrent bacterial communication and kill persisting cells [36]. These multidrug cocktails were not confined to antibiotics but extended to combinations of antibiotics with natural compounds that have the ability of QQ and act as non-antibiotic adjuvants.

This combination usage promotes the antimicrobial effect and prevents the bacterial resistance because the disruption of biofilm makes bacteria more disposed to even low doses of antibiotics [37]. The synergism between antibiotics and QSIs showed good results in regulating the resistant strains of *Staphylococcus* pathogenesis, where the bacterial sensitivity to the commercial antibiotics was elevated by RNAIII-inhibiting peptide [38,39]. QSIs such as furanone c30, patulin, penicillic acid, and garlic extract have been reported to improve the sensitivity of *P. aeruginosa* to tobramycin and leukocyte phagocytosis [40,41]. Intensive research work was done to study such natural antimicrobial compounds that may be used as adjuvants to antibiotics.

#### SCREENING OF SOME NATURAL ANTIMICROBIAL AGENTS:

##### Enzymes

More than 2000 different enzymes are currently known. They are produced by pancreatic ribonuclease and regulated by hormone-sensitive lipase.

Enzymes were grouped into six classes known as oxidoreductase, transferases, hydrolases, lyases (synthases), isomerases, and ligases.

At present, there are several commercial hydrolase preparations, effective against microbial biofilm, such as Spezyme GA300, Pandion, Resinase A2X, and Paradigm. The substrates for the hydrolases are peptidoglycan, the cell wall component which is responsible for the bacterial cell wall rigidity. Degradation of the cell wall leads to cell lyses due to disturbed osmotic pressure inside the cell. Gram-negative bacteria are less sensitive to bacteriolytic enzymes than Gram-positive bacteria due to differences in the cell wall structure.

Proteases are protein hydrolyzing enzymes, out of which subtilisins that are used widely for the control of biofilm in industry [42]. Lysostaphin is a metalloendopeptidase hydrolyzing enzyme. It cleaves *Staphylococci* cell walls including methicillin-resistant *S. aureus* (MRSA) [43]. Administration of lysostaphin in combination with oxacillin or vancomycin enhanced the antimicrobial effect against MRSA [44].

Among the polysaccharide hydrolyzing enzymes; lysozymes, alginate lysases, Dispersin B and amylases were reported. Lysozyme immobilized in chitosan was effective in inhibiting food spoilage microorganisms [45].

Alpha-amylase hydrolyzes existing biofilms of *S. aureus* [46]. Combination of proteases and amylases was effective in removing a *Pseudomonas fluorescens* biofilm [47].

The peroxidases, such as lactoperoxidases and myeloperoxidases, use the H<sub>2</sub>O<sub>2</sub> to oxidize halides (bromide, chlorine, and iodine) and isocyanate producing more potent antimicrobial compounds active against invading pathogens [48].

##### Antimicrobial Enzymes Derived from Bacteria

Quorum quenching enzymes that have an ability to degrade QS signal acylated homoserine lactone (AHL) autoinducers are AHL-lactonases, AHL-acylase, decarboxylases, and deaminase [9]. These enzymes were derived from different kinds of bacteria such as *Actinobacteria*, *Rhodococcus*, *Arthrobacter*, *Streptomyces*, *Firmicutes*, *Bacillus*, *Oceanobacillus*, *Anabaena*, *Cyanobacteria*, *Proteobacteria*, *Alteromonas*, *Comamonas*, *Halomonas*, *Hyphomonas*, *P. aeruginosa*, *K. pneumoniae*, *Ralstonia*, and *Stappia* [49-52]. The mentioned organisms have either AHL-acylase or -lactonase enzymes while *Rhodococcus erythropolis* might be the only organism which has both enzymes [53,54]. Interestingly, *Bacillus thuringiensis* does not produce the QS signal AHL but produce AHL-lactonase [55]. Microorganisms that produce bacteriolytic enzymes (e.g., streptomycetes) usually express a complex of several cell wall degrading enzymes with different specificities.

Lipase enzymes are considered an innovative and environmentally friendly approach for biofilm control due to their lytic and dispersal activities. Most of lipase enzymes used in industries are of microbial origin. It catalyzes the hydrolysis of esters for long chain aliphatic acids; several microorganisms produce lipases such as eukarya, fungi, actinomycetes, yeast, bacteria, and archaea. Bacterial lipases include *Bacillus*, *Penicillium*, *Staphylococcus*, *Pseudomonas*, and *Aspergillus* [56].  $\alpha$ -amylase,  $\beta$ -glucanase, lipase, and protease were examined to disrupt flow-generated biofilms of *P. fluorescens*. The four enzymes showed modest reduction of biofilm colony-forming units [57].

##### Antimicrobial Enzymes Derived from Bacteriophage

Bacteriophages are viruses that replicate inside infected bacteria and then secrete endolysins, called lytic system, to weaken the bacterial cell wall resulting in bacterial lysis to come out and spread to infect other bacterial cells. Endolysins, such as glucosidase, endopeptidase, amidase,

and transglycosylase, showed bacteriolytic activity against *Listeria monocytogenes*, *Bacillus anthracis*, *Staphylococcus*, and *Clostridium butyricum* [4]. Furthermore, they can clear some Gram-positive bacterial infections such as *Enterococcus faecalis* and *Clostridium perfringens*, [58]. The pairing of an antibiotic with a bacteriophage adjuvant is currently used and available in Georgia. Combination of ciprofloxacin and a lytic phage cocktail is currently produced, by PhagoBioDerm, in a biodegradable polymer matrix. Amidase PAL and endopeptidase Cpl1 from phage Cpl1 are synergistically capable to control the systemic pneumococcal disease [59,60]. Endolysins separated from phage phi3626 can treat *Clostridium* contaminations [61]. The type PAL of endolysin can kill the *Streptococcus* Group A. The type LYSK endolysins kill *Staphylococcus*, especially methicillin safe *S. aureus* [62]. Endolysins PlyV12 demonstrates a decent lytic movement against vancomycin, safe *E. faecium*, *Enterococci*, and *E. faecalis* [63].

#### Antimicrobial Enzymes Derived from Animal

Quorum quenching enzymes have been isolated from animals such as rats, mice, and zebrafish.

Porcine kidney acylase I inactivated QS signals and prevented the formation of biofilm in *Pseudomonas putida* and *Aeromonas hydrophila* [64]. Mammalian paraoxonases have hydrolytic effect on esters and lactones [65]. Mammalian type of lactonases differs from that derived from bacteria as the first type needs calcium ion to be active [65]. Epithelial cells of human have the ability to inactivate the autoinducer, AHLs, synthesized by *P. aeruginosa* [66].

Foods such as chicken breast, turkey patties, beef steak, beef patties, and homemade cheeses revealed inhibition for the Gram-positive bacteria autoinducer (AI-2) activity by 84.4–99.8% [67]. These QSIs vary in their effect on the expression of virulence-related genes [68].

Pancreatic lipase enzymes catalyze fatty acid synthesis in bacteria; therefore, it can serve as a potential antibacterial agent that is effective against many bacterial strains [69]. Lactonase, AHL acylase, and oxidoreductases are from mammalian paraoxonase. They are QSIs and can modulate *P. aeruginosa* infection [70].

#### Antimicrobial Enzymes Derived from Plants

Laccases, are QSIs enzymes, have been found in plant extracts derived from fruit, flowers, leaves, and bark of *Laurus nobilis*, *Combretum albiflorum*, and *Sonchus oleraceus* [71,72]. Alliinase and thiol enzyme group separated from garlic and other medicinal plants act as QSIs [73,74], lactonase presents in clover, lotus, legumes, peas, yam beans, and alfalfa showed AHL degrading abilities [75,76]. Papaya (*Carica papaya* L.) is rich in cysteine protease enzyme which has a crucial role in many vital antimicrobial processes in living organisms [77].

#### Quorum Quenching Enzymes Derived from Marine Organisms

Algae like *Laminaria digitata* has bromoperoxidase enzyme that has QQ ability by oxidation process to AHL signal group (3OC<sub>6</sub>HSL) [78]. *Delisea pulchra* contain halogenated furanones which similar in shape to bacterial AHLs and can block the receptors (LuxR) and hinder QS process [79,80].

Alginate lyases are enzymes, found in algae, invertebrates, and marine microorganisms, used in combination with gentamicin to control *P. aeruginosa* in the respiratory tracts of patients with cystic fibrosis [81-83].

#### Antimicrobial Digestive Enzymes

Digestive enzymes supplemented to improve the feed efficiency ratio and stimulate the absorption of nutrients, also affect on the bacterial population in the alimentary tract [84]. Some of these enzymes such as carbohydrates and phytases were synthesized and are commercially sold as feed additives to monogastric animal [85]. These enzymes will affect on the nourishment of intestinal flora which will compete the other pathogenic or harmful types of bacteria [84]. Furthermore,

when xylanase and lysozyme enzymes were added to broiler chicken diet, it minimized the gastrointestinal lesions of *C. perfringens* in the ileum [86,87].

In conclusion, combination of certain types of enzymes, polysaccharide-degrading enzymes, DNases, proteases, and anti-quorum sensing enzymes, is required for successful control of microbial infection. Unfortunately, industrial enzyme production is somewhat expensive, especially for biomedical applications where pure enzymes are required [88].

#### ANTIMICROBIAL PEPTIDES (AMPs)

AMPs are found among all living organisms as a component of the innate immune response [90,89]. Most of the reported AMPs were of animal origin such as glycine/arginine-rich peptides, tachyplesin, brevinin peptides, and alpha- and beta-defensins [91]. In plants, few AMPs have been isolated from seeds, roots, stems, flowers, and leaves from various species and have demonstrated activities against different pathogens such as viruses, fungi, bacteria, protozoa, and parasites. Thionins, defensins, lipid transfer proteins, puuroindolines, and snakins were different groups of AMPs reported in plants [92]. >880 different AMPs with the same biological activity to the naturally occurring AMPs have been designed and engineered from natural nucleic acid sequences [93] or selected from online combinatorial libraries [94].

Bacterial resistance against AMPs is apparently more difficult to be emerged in comparison with existing antibiotics as they have several targets and several modes of actions [95]. However, some bacteria developed resistance against human AMPs during evolution [96,97]. Hence, plant AMPs could be better than human ones because they rarely contact human pathogens to induce such resistance.

AMPs range from 4 to about 40 amino acids in length, engineered AMPs are identical to natural ones and all of them are hydrophobic and cationic in nature. It plays its role inducing changes in membrane permeabilization, destabilization, inhibition of macromolecules synthesis, intracellular translocation of the peptide, and inhibition of DNA/RNA/protein synthesis [98]. As polycationic peptides, AMPs interact electrostatically with negatively charged bacterial surface structures including lipoteichoic acids, and then, they interact with the lipid bilayers of the cytoplasmic membrane forming transmembrane pores and resulting in weakening of the membrane [99]. AMPs exert its effect on microbial plasma membranes, within few seconds of addition. Then after, within 1 h, bacterial membrane vesiculation, fragmentation release of DNA, cell aggregation, and destruction of cell morphology were noted. Thus, AMPs should rapidly pass through outer membrane thick proteoglycan layer of Gram-positive bacteria and the lipopolysaccharide layer of Gram-negative bacteria [100].

It is apparent not always biomembrane permeabilization is required for AMPs activity as it can translocate inside microbial membranes as well. This translocation results in membrane leakage and may occur at low concentrations of AMP before inducing permeabilization. For example, both the defensin cryptdin-4 of human and the AMP magainin 2 of frog translocate across bacterial cell wall bilayers within average 10 min [101,102].

#### AMPs Derived from Bacteria

The bacterial enzymes peptide synthetases produce the AMPs such as polymyxin, gramicidin, bacteriocin, and sugar peptide. The polypeptide polymyxin is obtained from *Bacillus polymyxa*. It is effective against different pathogenic bacterial species such as *P. aeruginosa*, *Salmonella*, *Escherichia coli*, and *K. pneumoniae*. The polypeptide bacteriocin is effective against Gram-negative cocci and spirochetes. Bacteriocin has been used commercially as feed additive for animals combined with bacitracin methylene salicylic acid and zinc [103]. There are several products of bacteriocins such as nisin, fermenticin, subticin, plantacin, helveticin, lactacin, and sakacin that have antimicrobial effect against resistant pathogenic strains [104], bacteriocin can kill bacterial cell by interfering its protein metabolism on molecular bases.

Many bacteriocins are applied as bacteriostatic in food products [105] as it can inhibit foodborne pathogens such as *Clostridium botulinum*, *S. aureus*, *Bacillus* spp., *L. monocytogenes*, and *E. faecalis* [106,107].

#### AMPs derived from plants

Major AMPs reported in plants were 5–13 kDa. Such small AMPs were shown to demonstrate good antibacterial activity against some bacteria such as *S. aureus*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. Plant AMPs like other AMPs have higher activity against Gram-positive than Gram-negative bacteria [108-110]. Different kinds of antimicrobial substances were reported such as saponins [111], canavanine, and some important antifungal defensins [112]. Antimicrobial activity of AMPs obtained from wheat endosperm was reported against *S. aureus* and *Micrococcus luteus* [113]; other studies showed that extracts of AMPs from different germinating and ungerminated seeds of *Pisum sativum*, *Punica granatum*, *Cocos nucifera* L., and *Phaseolus vulgaris* showed broad spectrum of antibacterial activity against *Micrococcus luteus*, *S. aureus*, *Staphylococcus epidermidis*, *Salmonella typhi*, *K. pneumoniae*, *E. coli*, *Proteus vulgaris*, *Pasteurella multocida*, and *P. aeruginosa* [114].

#### AMPs derived from marine organism

Marine green growth is rich in peptides and high assorted proteins [115]. Crypteins, the recently produced peptides, have novel therapeutic effect [116,117]. Brown seaweed *Saccharina longicruris* is rich in AMPs (>10 kDa MW) resulting from trypsin enzymatic hydrolysis and extracted using HPLC. Other subfractions of peptide precursors were identified such as ubiquitin, leucine, and histone that play a part of the innate immune defense of the seaweed [118].

#### PLANT EXTRACT & ESSENTIAL OILS (EOS)

Plant materials, known as phytobiotics, have been introduced in animal nutrition as antioxidative, antimicrobial, anti-inflammatory, and antiparasitic factors [119,120]. The phytobiotic compounds were classified into phenolics/polyphenols, alkaloids, terpenoids/EOs, and lectins/polypeptides [121]. Plant extracts exert the antimicrobial effect at MIC 100~1000 µg/ml *in vitro* [122]. These phytobiotics have different modes of action against pathogens. First, tannins act by iron deprivation and enzymes interactions [123]. Second, cryptolepine may act as DNA intercalator and an inhibitor of topoisomerase enzyme [124]. Third, saponins act on the bacterial membrane by binding with sterols causing membrane damages and deformity of cells [125]. In the same time, some plant compounds act as QSI as their chemical structure is like those of AHL so it can bind its receptors (LuxR/LasR) [126]. Furthermore, degradation of AHL signal takes place under the effect of  $\gamma$ -aminobutyric acid which promotes the bacteriolytic enzyme, lactonase [127]. Flavonoids such as kaempferol, naringenin, quercetin, and apigenin work as QSIs by inhibition of the QS autoinducers, HAI-1 or AI-2, mediated bioluminescence in *Vibrio harveyi* [128]. Catechins produced by herbal plants like tea can stimulate AHL-lactonase and clear the plasmid of *E. coli* [129]. Furocoumarins and rosmarinic acid present in grapefruit juice and the roots of sweet basil corrupt the biofilm formation by *E. coli* and *P. aeruginosa*, respectively [130,131]. Thymol is currently used in combination with vancomycin and EDTA as antimicrobial [132]. Furthermore, the combined effect of the antibiotic, tobramycin, and some plant extracts (cinnamaldehyde and baicalin hydrate as QSI) was effective to clear the infected lungs with *Burkholderia cenocepacia* and *P. aeruginosa* [133-135]. The usage of EO to combat epidemic infection by multiresistant bacteria is promising. The EO of lemon, thyme white, cinnamon, and lemongrass showed high antibacterial effect against some problematic strains such as *Streptococcus*, MRSA, and *Candida* strains [136,137]. The synergistic effect between the EO and antibiotics was reported where *Mentha piperita*, *Thymus vulgaris*, and *Rosmarinus officinalis* oils when combined with ciprofloxacin showed more efficient antimicrobial effect [138]. Hydrophobicity of EOs is the main reason of increased bacterial cell permeability and consequent leakage of cell constituents [139], followed by disturbance of vital functions such as nutrient processing, synthesis of structural macromolecules, secretion

of many growth key enzymes and protein synthesis. EO disrupts and lowers the intracellular PH of bacteria and consequently impairs many crucial cellular processes such as DNA transcription, protein synthesis, and enzymatic activity [140]. Furthermore, the production of ATP in prokaryotes occurs both in the cell wall and in the cytosol by glycolysis. Hence, the alterations on intracellular and external ATP balance will be affected due to the action of the EO on the cell membrane [141].

The anti-QS activity of EOs or its components was reported as they affect on the autoinducer expression [142].

#### CONCLUSION & RECOMMENDATION

We have to put in mind that alternatives to antibiotics should be non-toxic, easily excreted from the body and have low residues, not stimulate bacterial resistance, be stable and do not decompose inside GIT, do not cause environmental pollution, have good taste, and kill the pathogen without destroying the normal flora.

Actually, till present, there is no antibiotic alternative that meets all the above-mentioned criteria. All proteinaceous compounds, such as feed enzymes and AMPs that have been put into market as well as bacteriophage lysins, enzymatic biofilm inhibitors, and quorum quenching enzymes under development, are naturally unstable and easily degraded in the digestive tract. On the other hand, antibiotics can directly kill bacteria or inhibit with better antibacterial effect than all antibiotic replacements. Antibiotics are made by single and relatively pure active ingredient with consistency, high stability, and quality ensured by good manufacturing practice. However, researchers appreciate the combination of more than antimicrobial compound to avoid the development of bacterial resistance. Combination of biofilm inhibitors with antibiotics showed good results than when used sporadic. Hence, we have to put in mind that we have to use the natural antimicrobials to prevent than to cure disease or in combination to antibiotics as adjuvant to improve its function and waiting for updates from scientific research.

#### AUTHORS' CONTRIBUTIONS

Ementan Mohamed is specialized in veterinary medicine and her area of interest is to find natural product that may improve animal health and decrease the risk of disease. Enas is specialized in enzymology. Hence, both authors shared in throwing light on most antimicrobial products and the last updates in this respect. Editing and scientific revision were done by Ementan.

#### CONFLICTS OF INTEREST STATEMENT

Authors declared that there is no competing interest between them.

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