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Development of Antimicrobials against *Escherichia coli* - Environmental Microbiology meets Chemical Biotechnology

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Escherichia coli (*E. coli*) is the commonest infecting uropathogen with its incidence climbing from 50% to 60% of Urinary Tract Infections (UTIs). A recent report has demonstrated a diverse antimicrobial-resistant *E. coli* population distributed over various areas (nasal, oral, rectal, abdomen and hindquarter) of a companion animal's body, thereby suggesting potential transfer of resistant micro flora to human hosts during contact. Epidemiological patterns in UTIs show large inter-regional variability, and rates of bacterial resistance are continually changing due to different regional antibiotic treatment regime [1]. *E. coli* is also one of the most important causes of nosocomial infections. In hospitals, trimethoprim or nitrofurantoin is usually recommended for empirical treatment of uncomplicated cystitis whilst parenteral cephalosporins, aminoglycosides, quinolones and co-amoxyclav are reserved for complicated UTIs. Bloodstream Infections (BSIs) are often treated with fluoroquinolones and β-lactams (mainly gentamicin, ciprofloxacin and third-generation cephalosporins). The antimicrobial susceptibility pattern of uropathogenic *E. coli* strains (isolated from urine specimens) was determined using 13 common antibiotics [2]. The rates of antibiotic resistance of bio film producing *E. coli* were found to be 100% for chloramphenicol and amoxyclav (amoxicillin and clavulanic acid), 86% for gentamicin and cefotaxime, 84% for ceftazidime, 83% for cotrimoxazole and piperacillin/tazobactam, 75% for tetracycline, and 70% for amikacin. An ecological study investigating the correlation between the level of antimicrobial consumption and resistance, however, resistance to these compounds was reported with increasing frequency [3]. The dramatic rate increase in gentamicin resistance is of paramount concern. Neither ampicillin nor trimethoprim represent suitable empirical antimicrobials for UTI, and ciprofloxacin resistance renders it unsuitable empirical therapy for nosocomial UTIs. BSIs caused by 3GC-resistant *E. coli* are associated with excess mortality and prolonged hospital stay, adding to the suffering of patients and posing a considerable burden on healthcare costs [4]. Global efforts to reduce the consumption of broad-spectrum antimicrobial agents are hence warranted. Fortunately, *E. coli* - induced UTIs have remained extremely sensitive to nitrofurantoin and the resistance rate has not changed significantly over the last decade.

Antimicrobial agent usage is common in animal agriculture for therapeutic and prophylactic purposes. Selective pressure exerted by these antimicrobials on soil bacteria could result in the selection of strains that are resistant due to chromosomal- or plasmid-derived genetic components [5]. Analysis of antibiotic resistance showed that 67% (n = 29/43) of the enterotoxigenic *E. coli* strains were resistant to one or several of the antimicrobial agents tested. The presence of colonization factors was associated with antibiotic resistance [6]. Cephalosporinase producing *E. coli* has recently been detected in meat and animals [7]. Antimicrobial resistance was common among 95 strains of *E. coli* from pre-weaned dairy calves, occurring particularly in calves from herds experiencing calf diarrhea problems [8]. *E. coli* isolates from both dogs and cats exhibited resistance to all antimicrobials tested with the exception of amikacin, cephalothin and kanamycin. Resistance to ampicillin was the most prevalent resistance phenotype detected (dogs, 33/199; 17%; and cats, 27/118; 23%) [9]. A high prevalence of antimicrobial-resistant *E. coli* (producing extended-spectrum β-lactamase) can have significant health implications for the horse population [10], and methods to minimise their potential spread should be considered [11]. Antimicrobial Peptides (AMPs) have potential for use as alternatives to antibiotics in diets fed to weaned piglets; cecropin AD appeared to reduce diarrhoea incidence after *E. coli* challenge [12].

Development of antimicrobials against *E. coli* in water is another peaking research field. Previous literatures stated that optical density at 640 nm would be a good parameter to measure anti-bacterial activity against *E. coli* in water. Organic compounds could be a feasible approach towards killing *E. coli* in water. They concluded that % NH_2 was the most important factor for antibacterial activity of claimed chemicals. This specific OD would tell us whether the applied antimicrobials have any demonstrable bacteriostatic property towards *E. coli*. Addition of amino acid to Phosphatidyglycerol (PG) of the membrane is one of the mechanisms used by bacteria to lower the net charge of their cellular envelope, thereby decreasing its affinity for several antibacterial agents [13]. An appropriate antibacterial needs to be as strong as to be able to supersede this auto-induced power in bacteria against antibacterial compounds. AMPs with broad-spectrum activity, which can physically destroy the bacterial membrane through several targets to kill the microbes, may be considered a promising approach to overcome the problem. A rapid method, which coupled cell membrane affinity extraction with offline liquid chromatography time-of-flight mass spectrometry, was developed for screening and identifying antimicrobial peptides obtained by proteolytic enzyme hydrolysis [14]. A cationic antimicrobial peptide was successfully isolated, and antimicrobial assay indicated that it was active against *E. coli* ATCC 25922. Antimicrobial susceptibility was tested by determination of minimum inhibitory concentration, which was found to be 29 ± 1 μg/mL for the peptide, showing no increase in optical density at 600 nm. This antimicrobial induced significant morphological alteration of the microbe surface by transmission electron microscopy, indicating strong membrane disruption. The antimicrobial activities of caseicin A and B AMPs were assessed against a selection of verocytotoxigenic

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Escherichia coli strains. The mean number of *E. coli* surviving after exposure to 2 mg/mL caseicin A and B was reduced by 4.96 and 4.19 $\log_{10}$ cfu/mL compared to the respective controls [15].

Polydopamine (PDA) is well-known for its adhesive property in water [16]. One could use chitosan/chitin (which is an easily available hydrophilic polymer) in combination with PDA as a coating material on Magnetic Nanoparticles (MNPs) perhaps to simultaneous seize and kill *E. coli* in water. Chitosan, in its own right, can be used to enhance the antibacterial effect of PDA. This N-acetyl glucosamine polymer can also be used to stabilize the MNPs@PDA particles [17]. Antibacterial activity of chitosan against *E. coli* was demonstrated previously [18]. Development of Molecularly Imprinted Polymer (MIP) to seize the bacteria from waters by the aid of external magnetic field would be a promising green strategy. Although imprinting of small organic and biomolecules is well achieved nowadays, large proteins, bacteria and viruses still present challenges due to their molecular size, complexity, conformational flexibility and solubility factors. Bacteria are not always compatible with mainstream MIP preparation in organic solvents. Highly cross-linked rigid networks of MIPs often result in low binding capacity and poor site accessibility due to slow diffusion of bacteria in the interior of three-dimensional polymeric matrices. The flexible structure and conformation of protein can be easily affected by the surrounding microenvironment of the imprinted cavity [19]. New functional monomers with good biocompatibility and multifunctional groups are a necessary requirement in order to eliminate these problems. PDA is a very good candidate in this regard as because the monomer DA is a small molecule mimic of proteins and it has plenty of non-covalent functionalities such as amino, imino, hydroxyl, catechol-containing groups as well as π-π interactions. PDA forms a 2-dimensional fishnet over a solid surface (or around a solid particle). DA can create a 2-dimensional fishnet around any bacterium. Thus the DA could encapsulate bacteria or any other types of microorganisms in water. In addition, PDA (produced from oxidative polymerization of DA in water) may have bacteriostatic property due to its amino and imino functional groups. Therefore, the use of ammonia, an organic amine, or acryl amide (as a secondary functional monomer for the preparation of MIP) together with PDA would increase MIP's bacteriostatic property extensively. Thus, an appropriate method for simultaneous seizing and killing of bacteria in water could be developed. This research would emerge as one step forward in the field of environmental biotechnology.

Increasing resistance of all microbes is a growing worldwide problem. The increased use of antimicrobial agents in human medicine and food animal production is a significant factor in the emergence of antibiotic-resistant bacteria. Multiple antimicrobial resistances in *E. coli* and the direct relationship between antimicrobial agent uses over time have been extensively studied. The emergence and development of antimicrobial-resistant *E. coli*, as in other bacteria, may be a major public health problem. Particularly, extended-spectrum beta-lactamase producing *E. coli* pose real challenge to clinical microbiologists, clinicians, antibacterial researchers, veterinarians and food scientists [20]. More knowledge is required for prudent use of antimicrobials, and new development of alternative therapies against *E. coli* needs to be explored.

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