

# Elimination of antibiotic resistance genes and control of horizontal transfer risk by UV-based treatment of drinking water: A mini review

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## HIGHLIGHTS

- Antibiotic-resistant bacteria and antibiotic resistance genes are in water bodies.
- UV/chlorination method is better to remove ARGs than UV or chlorination alone.
- Research on UV/hydrogen peroxide to eliminate ARGs is forthcoming.
- UV-based photocatalytic processes are effective to degrade ARGs.

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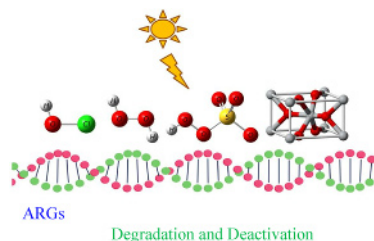
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## GRAPHIC ABSTRACT



## ABSTRACT

Antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) have been recognized as one of the biggest public health issues of the 21st century. Both ARB and ARGs have been determined in water after treatment with conventional disinfectants. Ultraviolet (UV) technology has been seen growth in application to disinfect the water. However, UV method alone is not adequate to degrade ARGs in water. Researchers are investigating the combination of UV with other oxidants (chlorine, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), peroxymonosulfate (PMS)<sub>2</sub> and photocatalysts) to harness the high reactivity of produced reactive species (Cl·, ClO·, Cl<sub>2</sub>·<sup>-</sup>, ·OH, and SO<sub>4</sub>·<sup>-</sup>) in such processes with constituents of cell (e.g., deoxyribonucleic acid (DNA) and its components) in order to increase the degradation efficiency of ARGs. This paper briefly reviews the current status of different UV-based treatments (UV/chlorination, UV/H<sub>2</sub>O<sub>2</sub>, UV/PMS, and UV-photocatalysis) to degrade ARGs and to control horizontal gene transfer (HGT) in water. The review also provides discussion on the mechanism of degradation of ARGs and application of q-PCR and gel electrophoresis to obtain insights of the fate of ARGs during UV-based treatment processes.

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## 1 Introduction

One of the most significant discoveries in the field of medicine is the development of antibiotics to treat human and animal diseases (Travis et al., 2018). The consumption of antibiotics is rising because of increase in human population and its demands (e.g., use of antibiotics

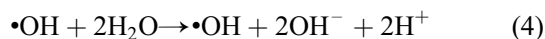
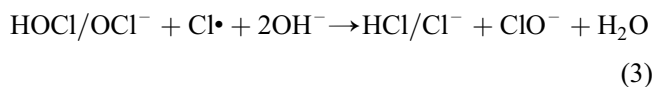
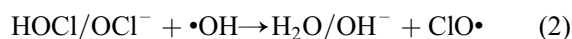
increased up to 35% between 2000 and 2010) (Van Boeckel et al., 2014, 2015). Consumption of antibiotics in livestock and aquaculture is also on the rise (Kim et al., 2013; Sharma et al., 2016; Blaskovich, 2018; Hu et al., 2019a). Antibiotics undergo incomplete metabolic transformation that results in significant excretion of antibiotics and their residues into the environment (Khetan and Collins, 2007; Lee et al., 2017). In addition, the excessive consumption of antibiotics has led to significant increase of antibiotic residues in different compartments of the environment such as sources of drinking water supply, wastewater effluent, sludge, and soil (Rodríguez-Chueca et al., 2019; Zhang et al., 2019b). In the past few years, studies have shown that applications of antibiotics in human and animal health care could accelerate the occurrence of antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) in different water bodies, which include hospital waste effluents, water treatment plant effluents, and tap water (Michael et al., 2013; Shao et al., 2018; Yang et al., 2018). Excessive antibiotics have caused the proliferation of ARB and subsequently horizontal gene transfer (HGT) results in widespread ARGs in the environment (Sharma et al., 2016; Garner et al., 2018). In different water bodies of the world, diverse ARGs correspond to macrolides, tetracyclines, quinolones, and sulfonamides (*erm*, *tet*, *qnr*, and *sul*, respectively) (Lee et al., 2017). The appearance of ARB and ARGs in water resources has caused a great concern due to the possibility of millions of deaths by 2050 (Vindenes et al., 2016). According to the Center for Disease Control (CDC) and the World Health Organization (WHO), ARGs in the environment are one of the most critical public health issues of this century (World Health Organization, 2018). Consequently, control of the release of ARB and ARGs to the aquatic environment is of utmost importance.

Most of the wastewater treatment plants (WWTPs) are not adequate to be fully designed to remove antibiotics (Cizmas et al., 2015; Sousa et al., 2017, 2018). Unfortunately, when high levels of activated sludge are applied in biological treatments, the microbes caused proliferation of ARB and ARGs (Li et al., 2017; Ezzariai et al., 2018; Krzeminski et al., 2019). In treatment of drinking water, chlorination, chloramination, and ultraviolet (UV) radiation are employed to inactivate pathogenic microorganisms (Wang et al., 2017a; Yoon et al., 2017; Ren et al., 2018; Chang et al., 2019; Rodríguez-Chueca et al., 2019; Zhang et al., 2019c). The use of chlorine to inactivate ARB and ARGs has given conflicting effectiveness (Zhang et al., 2009; Munir et al., 2011; Li et al., 2016a). Sodium hypochlorite was able to inactivate tetracycline-resistant bacteria containing *tetA* and *terC* (Zhang et al., 2009). In another study, chlorination was found to have no effectiveness in treating ARB and ARGs (Munir et al., 2011). However, one of the studies showed that the residual chlorine after treatment behaved like

antibiotics that prompted development of ARGs (Li et al., 2016b). Additionally, low dosages of free chlorine and chloramine caused facilitation of the HGT of ARGs through altering the cell permeability of bacteria (Sinha and Häder, 2002). Direct UV photolysis may be suitable to control ARGs because it can transform nitrogen bases of DNA (Cutler and Zimmerman, 2011). However, the damage to DNA varies with cell structure and environmental conditions (Zhang et al., 2019c). To completely inactivate ARGs, high dose of UV may be needed (Chen and Zhang, 2013; Lee et al., 2017; Mauter et al., 2018). The effectiveness of UV technology to control ARGs remains a challenge. In recent years, researchers have been investigating a combination of UV technology with other oxidation processes to achieve efficient control of ARGs and HGT (Lin et al., 2016; Pang et al., 2016; Sharma et al., 2016; Wang et al., 2017c; Michael-Kordatou et al., 2018; He et al., 2019; Hu et al., 2019b; Yang et al., 2019). This review focuses on the recent investigations on the combination of UV with oxidants, which include chlorine, hydrogen peroxide, and photocatalysts (i.e., to create advanced oxidation processes (AOPs)). Examples of each combined process are briefly summarized.

## 2 UV/chlorination

Studies have shown that the combination of UV and chlorination (UV/chlorine) is more effective in degrading micropollutants than UV or chlorination alone (Cheng et al., 2018; Zhang et al., 2018). Studies on micropollutants included hormones, pharmaceuticals, taste and odor compounds (Ting and Praveena, 2017; Fang et al., 2018; Chang et al., 2019). In the UV/chlorine process, hydroxyl radical ( $\bullet\text{OH}/\text{O}\bullet$ ) and reactive chlorine species ( $\text{Cl}\bullet$ ,  $\text{ClO}\bullet$ , and  $\text{Cl}_2\bullet^-$ ) are generated (reactions 1–5) (Wu et al., 2016, 2017; Kong et al., 2018; Hua et al., 2019; Zhao et al., 2019).



The advantages of UV/chlorine process through involvement of reactive oxidizing species have been investigated in removing *sul1*, *tetX*, *tetG*, *int11*, and 16S rRNA genes in municipal wastewater treatment plant (MWTP) effluent by chlorination, UV, and sequential UV/chlorine

process (Zhang et al., 2015b, 2019c). Higher N-content in samples decreased the removal efficiency by chlorination process. This study showed that the removal efficiency of ARGs was higher by the UV irradiation followed by chlorination than UV or chlorination alone (Zhang et al., 2015b).

In a recent study, the removal of ARGs was studied by isolating ARB (HLS-6) with *sul1* and *sul2* from a drinking water sample (Zhang et al., 2019c). UV, chlorination, and UV/chlorine treatments of drinking water were sought to remove ARGs and to control HGT. The order of degradation of both *sul1*-qPCR and *int11*-qPCR in the less than 20 min using different processes was UV/chlorine>chlorination>UV. The UV/chlorine was able to obtain log reductions of 3.50 and 4.00 for *sul1*-qPCR and *int11*-qPCR, respectively. Increase in pH of the water from 5.0 to 9.0 decreased the removal efficiency of ARGs. In presence of sulfamethoxazole antibiotic, removal efficiency of ARGs by UV/chlorine was more than either UV or chlorination alone (Zhang et al., 2019c). Significantly, damage of DNA was possible in the UV/chlorine process, confirmed by electrophoresis technique.

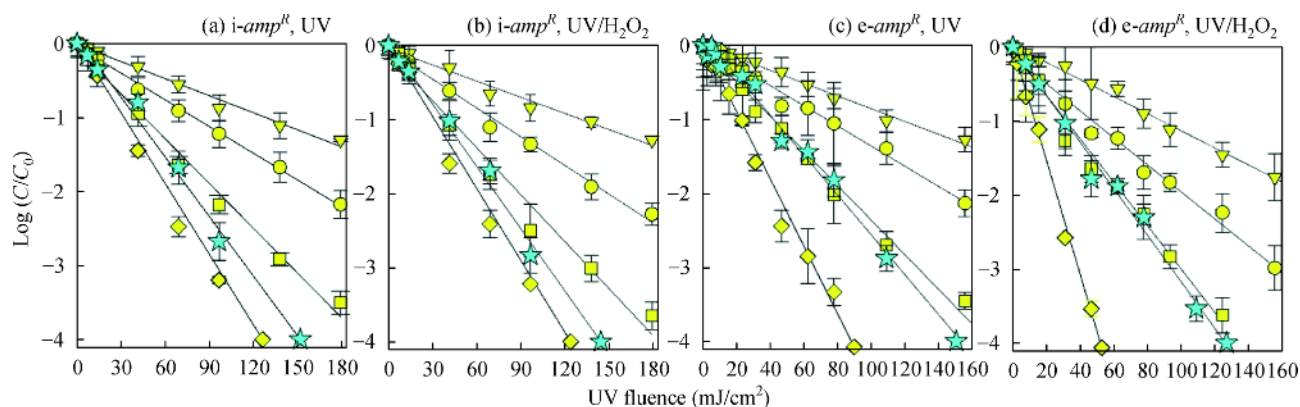
### 3 UV/hydrogen peroxide

UV/hydrogen peroxide (UV/H<sub>2</sub>O<sub>2</sub>) process has been studied extensively to degrade contaminants in water (Wols and Hofman-Caris, 2012; Wols et al., 2013; Miklos et al., 2018; Nihemaiti et al., 2018). This method is based on the production of •OH, which has a high redox potential (1.8–2.7 V) (Buxton et al., 1988). The nature of •OH is electrophilic and can attack electron-rich organic contaminants at high rate constant (~10<sup>8</sup>–10<sup>9</sup> L/mol/s (Buxton et al., 1988; Sharma, 2008; von Gunten, 2018) that ultimately leads to their transformation to CO<sub>2</sub> and H<sub>2</sub>O. The interest in the role of •OH in treatment of ARGs is because of damage of DNA, induced by •OH attack to

sugar backbone oxidized products (Naumov and von Sonntag, 2008). Investigation has been performed on UV/H<sub>2</sub>O<sub>2</sub> treatment of plasmid-encoded ARGs (Chang et al., 2017; Guo et al., 2017; Yoon et al., 2017; Hu et al., 2018; Yoon et al., 2018; Chen et al., 2019; Rodríguez-Chueca et al., 2019). Both ARGs of *Escherichia coli* (*E. coli*), i.e., extracellular (e-ARG) and intracellular (i-ARG), were determined (Yoon et al., 2017, 2018). Concentrations of ARGs were evaluated by qPCR and structure changes were determined by gel electrophoreses (Buxton, 2008; Yoon et al., 2017).

A recent study investigated UV<sub>254 nm</sub> and UV<sub>254 nm</sub>/H<sub>2</sub>O<sub>2</sub> treatments of *E. coli* and ARGs (Yoon et al., 2017). The damages to *amp<sup>R</sup>* (850 bp) and *kan<sup>R</sup>* (806 bp) amplicons, situated in the pUC4K of ARGs in host *E. coli*, were observed. The inactivation of *E. coli* was faster than the damages to ARGs. The dose of UV<sub>254 nm</sub> to obtain 4 log reduction of ARGs was 50–130 mJ/cm<sup>2</sup>. The increase in pH did not have any influence on damage to ARGs by UV<sub>254 nm</sub>/H<sub>2</sub>O<sub>2</sub>. In contrast, in the case of chlorination, performance decreased with increasing pH (Yoon et al., 2017). In the UV<sub>254 nm</sub>/H<sub>2</sub>O<sub>2</sub> treatment, the damage of e-ARGs was at a much faster rate than the damage to i-ARGs. This was expected because the reactive •OH species in the case of i-ARGs could not penetrate the cell and the oxidizing species were easily consumed by the cellular components.

In a recent study, deactivation of transforming activity of an ARG was investigated to elucidate the mechanism of elimination of ARGs in *E. coli* (host) (Yoon et al., 2018). The log<sub>10</sub> reduction was ~1 for the plasmid-encoded ARGs under UV<sub>254 nm</sub> of 40 mJ/cm<sup>2</sup>, which is usually applied in UV disinfection processes (Yoon et al., 2018). However, UV<sub>254 nm</sub> of 150 mJ/cm<sup>2</sup> achieved more than 4 log reduction. When UV<sub>254 nm</sub>/H<sub>2</sub>O<sub>2</sub> method was applied, no enhanced degradation efficiency was seen (i.e., compared with UV<sub>254 nm</sub> irradiation). Figure 1 presents the logarithmic relative concentrations of *amp<sup>R</sup>*



**Fig. 1** Logarithmic relative concentration of the transforming activity (green color star) and *amp<sup>R</sup>* qPCR amplicons (192 bps (trigonal), 400 bps (circle), 603 bps (square) and 851 bps (diamond)) as a function of UV fluence during treatment of (a) and (b) intracellular and ((c) and (d)) extracellular pUC19 with (a) and (c) UV and ((b) and (d)) UV/H<sub>2</sub>O<sub>2</sub> ([H<sub>2</sub>O<sub>2</sub>]<sub>0</sub> = 10 mg/L) at pH 7.0. The symbols represent the measured data and the error bars represent one standard deviation from triplicate experiments. The lines are linear regressions of the data. (Adapted from Yoon et al. (2018) with the permission of the Royal Society of Chemistry).

amplicons that had variable length after UV<sub>254 nm</sub> and UV<sub>254 nm</sub>/H<sub>2</sub>O<sub>2</sub> treatments of i-ARGs (Yoon et al., 2018). The degradation followed first-order kinetics (Fig. 1). Significantly, the rate of destruction of *amp<sup>R</sup>* increased with increase in size of *amp<sup>R</sup>* in both treatment processes. The obtained first-order rate constants for *amp<sup>R</sup>* (pUC19) were  $3.4 \times 10^{-2}$ ,  $7.0 \times 10^{-2}$ ,  $1.1 \times 10^{-1}$ , and  $1.5 \times 10^{-1}$  cm<sup>2</sup>/mJ for 192 bps, 400 bps, 603 bps, and 851 bps qPCR amplicons for both UV<sub>254 nm</sub> and UV<sub>254 nm</sub>/H<sub>2</sub>O<sub>2</sub> treatments, respectively. The suggested mechanisms of the elimination of transforming activity of plasmids (both extra- and intracellular) in both treatments include damage to DNA. The rate of the transformation of pUC19 was lower than the rate of the formation of cyclobutene-pyrimidine dimer (CPD); suggesting the repair of CPD in the cell (host).

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#### 4 UV/peroxymonosulfate

The UV/peroxymonosulfate (PMS) process has shown increasing attention in the last few years due to high redox potential of PMS (+1.82 V) and generation of sulfate radical (SO<sub>4</sub><sup>•-</sup>) (Rodríguez-Chueca et al., 2019; Umar et al., 2019). The generated SO<sub>4</sub><sup>•-</sup> has comparable redox potential to •OH (2.5–3.1 V versus 1.8–2.7 V) (Neta and Huie, 1985; Sharma, 2013). Many investigations showed the effective degradation of organic contaminants by SO<sub>4</sub><sup>•-</sup> (Zhang et al., 2015a; Ghanbari and Moradi, 2017; Liu et al., 2018; Wojnárovits and Takács, 2019). An attempt has been made on studying the role of UV/PMS in deactivation of ARGs (Rodríguez-Chueca et al., 2019). This study tested the UV-C, UV-C/H<sub>2</sub>O<sub>2</sub> (0.05–0.5 mmol/L), and UV-C/PMS (0.05–0.5 mmol/L) processes at 4–18 s contact time of UV-C. The combined methods of UV-C/PMS and UV-C/H<sub>2</sub>O<sub>2</sub> using 0.5 mmol/L PMS were more effective to remove antibiotics than UV-C alone at a contact time of 0.7 s. Interestingly, the removal of ARGs had the quite opposite trend, i.e., UV-C was more effective in removing ARGs than combined UV-C/oxidant methods. It suggests that the oxidants in the combined methods (H<sub>2</sub>O<sub>2</sub> and PMS) could also absorb UV-C irradiation that decreased the direct photolysis of DNA compared with UV-C alone. Furthermore, in the removal of ARGs by UV/H<sub>2</sub>O<sub>2</sub> and UV/PMS methods, both photolysis of DNA and oxidation by generated •OH and SO<sub>4</sub><sup>•-</sup> were operational, but cumulative effects were lower than the direct removal of ARGs by UV-C alone. In removing antibiotics, generated radicals were efficient because of high reactivity with target contaminants in water, while UV-C alone had no or low effect.

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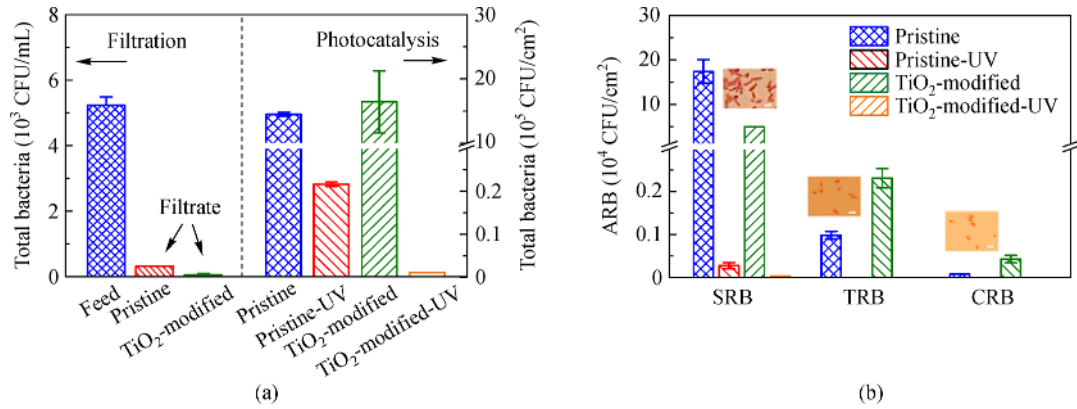
#### 5 UV-photocatalyst

Heterogeneous titanium dioxide (TiO<sub>2</sub>) photocatalytic

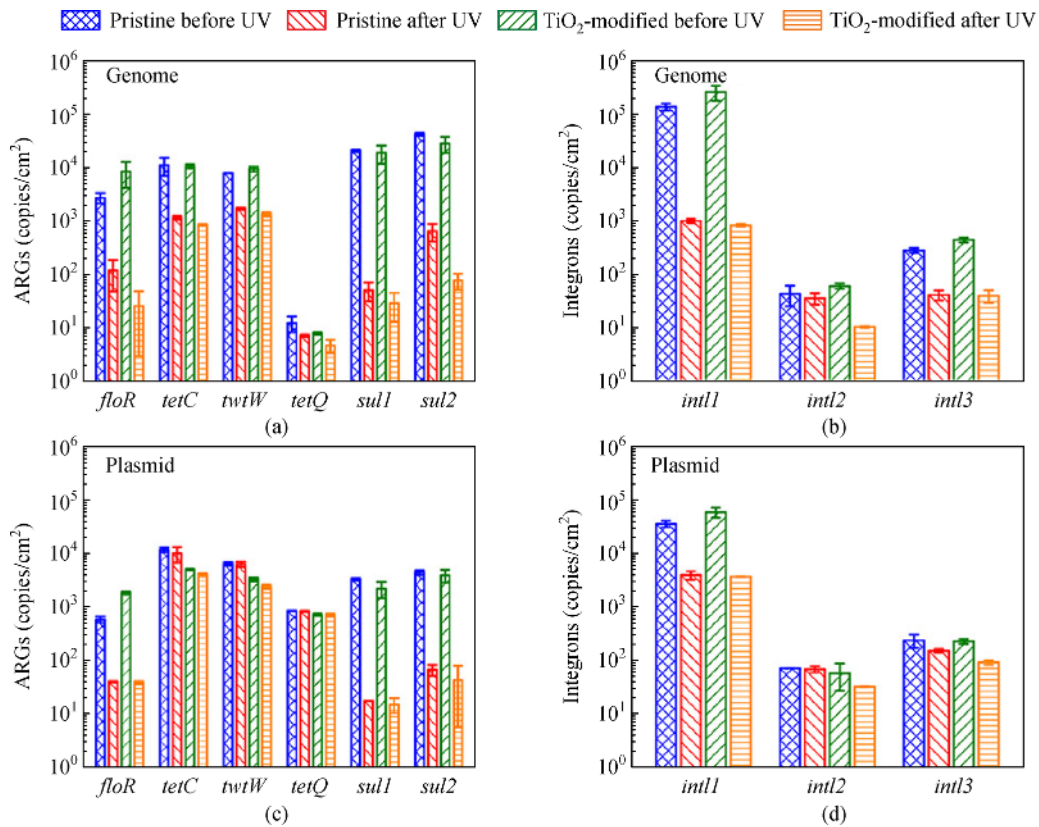
process has numerous applications, including the inactivation of microorganisms (Wang et al., 2017b; Uyguner Demirel et al., 2018). TiO<sub>2</sub> under UV irradiation generates reactive oxygen species (ROS), which could inactivate ARB and ARGs (Rizzo et al., 2014; Dunlop et al., 2015; Krzeminski et al., 2019; Özkal et al., 2019; Zhang et al., 2019a). In an earlier work, photocatalytic disinfection of three strains of *E. coli* (J-53R and HT-99, rifampicin and chloramphenicol resistant strains, respectively, and K12, antibiotic sensitive strain) resulted in decrease of viable cell numbers of ARB from 3 log<sub>10</sub> to 0.5 log<sub>10</sub> after 180 min of treatment (Dunlop et al., 2015). Interestingly, after post-treatment incubation for 180 min for both ARB (37°C and 24 h), a bacterial recovery of 3 log<sub>10</sub> was observed. Comparatively, at 150 min post-treatment, no *E. coli* K12 was recovered. This study recommended that the photocatalytic disinfection must be carried out for a long period of time to avoid post-treatment recovery, which will minimize the highly unwanted transfer of ARGs among bacteria (Dunlop et al., 2015).

An attempt has been made to remove ARB and ARGs from wastewater effluent using photocatalytic reactive ultrafiltration membrane (Ren et al., 2018). In this study, TiO<sub>2</sub> modified polyvinylidene fluoride (PVDF) membrane was used in the wastewater effluent, which could retain ARB. The removal efficiency was tested for ARGs (plasmid-mediated *floR*, *sull*, and *sul2*). Almost complete removal and inactivation of total ARB were observed by both filtration and UV treatment (Fig. 2(a)). Significantly, retention of ARB by using pristine PVDF membrane was 98.9%, which was lower than the retention by TiO<sub>2</sub>-modified PVDF (>99.9%) (Fig. 2(a), left). As shown in Fig. 2(a) (right), removal of total bacteria by TiO<sub>2</sub>-modified PVDF membrane was much higher than that by pristine PVDF membrane. This finding was again confirmed by determining abundance of eRNA in the permeate (Ren et al., 2018).

Figure 3 shows the results of photocatalytic experiments performed to study the degradation of ARGs and integrons, retained by pristine PVDF and TiO<sub>2</sub>-modified PVDF membranes. The membrane was exposed to UV irradiation for 1 h. Higher degradation efficiency of ARGs and integrons present in genome was seen than those located in plasmid (Figs. 3(a) and 3(b) versus Figs. 3(c) and 3(d)). Results clearly demonstrated the role of location of ARGs and integrons in the bacterial cell. It appears that the large size genome could allow the attack by ROS easily compared with the feasibility of the reactions of ROS with ARGs and integrons of relatively small size plasmid. Generally, the UV-treatment using the TiO<sub>2</sub>-modified PVDF membrane had higher efficiency of degradation of ARG and integrons than that of applying PVDF membrane alone (Fig. 3). Results of Fig. 3 agree with the results seen on inactivation of ARB (see Fig. 2). The efficiencies of degradation of *floR*, *tetC*, *sull*, and *intI1* in the plasmid in the UV-TiO<sub>2</sub>-modified PVDF membrane were somewhat



**Fig. 2** ((a), left) Total bacteria abundance in the feed and filtrate obtained from UF experiments. The secondary wastewater effluent was filtered by the pristine PVDF and TiO<sub>2</sub>-modified PVDF membranes until the permeate volume reached 250 mL, at a pressure of 1.4 bar (20 psi) and temperature of 25.0°C±0.5°C. ((a), right) Photocatalytic degradation of total bacteria on the surface of the pristine PVDF and TiO<sub>2</sub>-modified PVDF membranes before and after exposure to UV for 1 h. (b) CFU of antibiotic resistant bacteria (ARB) on the surfaces of the pristine PVDF membrane and TiO<sub>2</sub>-modified PVDF membrane, respectively, before and after exposure to UV irradiation, measured via spread plate method. Microscopic images of ARB are shown in the inset with a 2- $\mu$ m scale bar. (Adapted from Ren et al. (2018) with the permission of the American Chemical Society).



**Fig. 3** Photocatalytic degradation of ARGs and integrons on the surface of pristine PVDF and TiO<sub>2</sub>-modified PVDF membranes after UV treatment. ARGs and integrons in genome ((a), (b)) and plasmid ((c), (d)) were extracted using bacteria DNA kit and plasmid kit, respectively, and analyzed via quantitative PCR method (Adapted from Ren et al. (2018) with the permission of the American Chemical Society).

higher than those by UV-pristine PVDF membrane. The located sulfonamides resistance genes (*sul1* and *sul2*) in genome and plasmid had higher degradation efficiency

than that of tetracycline resistance genes (*tetC*, *tetW*, and *tetQ*). The sulfonamides resistance genes tend to be degraded more easily than tetracycline resistance genes



(Auerbach et al., 2007). Overall, results of Fig. 3 indicated the enhanced activity of UV-TiO<sub>2</sub> to degrade ARG and integrons.

Research is also in progress on using TiO<sub>2</sub>-reduced graphene oxide (TiO<sub>2</sub>-rGO) composite photocatalysts under solar radiation to remove selected ARGs (namely *sull*, *ampC*, *ermB*, *mecA*) and species-specific sequences (*ecfX* for *Pseudomonas aeruginosa* and enterococci-specific 23S rRNA) in real urban wastewaters (Karaolia et al., 2018). Results showed complete inactivation in 180 min of photocatalytic treatment using the composite. Significantly, post-treatment of 24 h had no regrowth of *E. coli* bacteria (less than limit of detection). The composite photocatalysts removed *ampC*. Also, abundance of *ecfX* decreased. However, *sull*, *ermB* and 23S rRNA remained persistent throughout photocatalytic treatment. Importantly, the total concentration of DNA did not change significantly in the photocatalytic process, which suggested high stability of genomic DNA in treated wastewater (Karaolia et al., 2018).

## 6 Conclusions

Presence of ARB and ARGs in water has become a major issue of public health and studies are forthcoming to determine their removal efficiency during disinfection. In the past decade, the use of UV disinfection has increased and recent efforts are exploring increase in UV effectiveness for degrading ARB and ARGs in water by combining UV radiation with other oxidants/catalysts (chlorine, H<sub>2</sub>O<sub>2</sub>, PMS, and photocatalysts) to generate reactive species that can more effectively destroy ARB and ARGs. A few studies using UV/chlorine and UV/H<sub>2</sub>O<sub>2</sub> to destroy ARB and ARGs have been performed. The UV/chlorine had shown better efficiency to remove ARGs than the individual UV or chlorination process. The trend of UV/H<sub>2</sub>O<sub>2</sub> is not clear compared with UV alone to degrade ARGs. A few studies on UV/PMS method have been conducted and SO<sub>4</sub><sup>•-</sup> generated in the UV/PMS has advantages under certain conditions over •OH, generated in UV/H<sub>2</sub>O<sub>2</sub> to degrade ARGs. The qPCR and gel electrophoresis techniques are being applied to understand mechanism of damages to ARGs. Mechanistic studies showed that e-ARGs are easier to be degraded than i-ARGs. The photocatalytic treatment has effectiveness to decrease ARGs, but constituents in the matrix of the treated water greatly influence the efficiency of removal of ARGs. The inorganic and organic constituents of the water scavenge ROS to reduce the efficiency of photocatalytic treatment method. The photocatalytic degradation of ARGs using TiO<sub>2</sub>-modified PVDF membrane was about 98%; more efficient in the genome than in plasmid. The UV-TiO<sub>2</sub>-modified PVDF membrane treatment process was effective in controlling HTG. Future studies should emphasize to elucidate mechanism of degradation of

ARGs and controlling HGT. Future work may include removal of ARGs in real water samples by UV-based disinfection/treatment methods.

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