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Evaluation of degradation performance toward antiviral drug ribavirin using advanced oxidation process and its relations to ecotoxicity evolution

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**HIGHLIGHTS**

- Efficient degradation of ribavirin was achieved using UV/TiO$_2$/H$_2$O$_2$ process.
- A toxicity increase of treated water due to by-products was inspected.
- The degradation pathway of ribavirin during UV/TiO$_2$/H$_2$O$_2$ process was proposed.
- Most transformation products exhibited higher predicted toxicity than ribavirin.

**ABSTRACT**

The rapid spread of coronavirus disease 2019 has increased the consumption of some antiviral drugs, wherein these are discharged into wastewater, posing risks to the ecosystem and human health. Therefore, efforts are being made for the development of advanced oxidation processes (AOPs) to remediate water containing these pharmaceuticals. Here, the toxicity evolution of the antiviral drug ribavirin (RBV) was systematically investigated during its degradation via the UV/TiO$_2$/H$_2$O$_2$ advanced oxidation process. Under optimal conditions, RBV was almost completely eliminated within 20 min, although the mineralization rate was inadequate. Zebrafish embryo testing revealed that the ecotoxicity of the treated RBV solutions increased at some stages and decreased as the reaction time increased, which may be attributed to the formation and decomposition of various transformation products (TPs). Liquid chromatography-mass spectrometry analysis along with density functional theory calculations helped identify possible toxicity increase-causing TPs, and quantitative structure activity relationship prediction revealed that most TPs exhibit higher toxicity than the parent compound. The findings of this study suggest that, in addition to the removal rate of organics, the potential ecotoxicity of treated effluents should also be considered when AOPs are applied in wastewater treatment.

1. Introduction

Ribavirin (RBV; 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide) has been widely recommended for the treatment of viral diseases, such as herpes, hepatitis C, and Lassa fever (Ye et al., 2020). The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 has raised international concern owing to its rapid spread and poor controllability. Consequently, for controlling the spread of COVID-19, the consumption of antiviral drugs, including RBV, has increased remarkably worldwide (Liu et al., 2021). With their increased consumption, more antiviral drugs are now entering aquatic environments (Kumar et al., 2021; Peng et al., 2014), thereby posing a threat to natural ecosystems and human health (Kumar et al., 2021; Kuroda et al., 2021).

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Increasing evidence suggests that the accumulation of RBV and its metabolites in animal bodies can cause several adverse effects, including genetic and reproductive toxicity, hemolysis, and congenital malformations (Ma et al., 2019; Ye et al., 2020). Therefore, antiviral drugs, including RBV, have become emerging pollutants of global concern.

However, pharmaceuticals such as RBV cannot be efficiently removed or transformed using conventional water treatment processes owing to their low biodegradability and high stability (Kuroda et al., 2021; Nannou et al., 2020). Therefore, effluents from conventional wastewater treatment plants (WWTPs) may contain high concentrations of such pharmaceuticals, which could pose high risks to aquatic life (Fig. 1). To address these issues, recent research has focused on developing advanced oxidation processes (AOPs), including ozonation, Fenton, electrocatalysis and photocatalysis (Chen et al., 2021; Fedorov et al., 2022; Gadinelly et al., 2014; Midassi et al., 2020; Yi et al., 2021), which can non-selectively oxidize pollutants by producing hydroxyl radicals (⋅OH) and other reactive species. In addition, AOPs based on sulfate radical (SO4−) have also aroused great attention recently as promising technologies for pharmaceuticals degradation (Yuan et al., 2020a; Yuan et al., 2020b). Compared with other AOPs, the UV/TiO2/H2O2 process has some distinctive advantages, such as low cost, simple operation, no secondary pollution, and a wide range of applications. The catalyst TiO2 is widely used and studied due to its low cost, high reactivity, non-toxicity, availability and chemical stability (Al-Mamun et al., 2019; Elmolla and Chaudhuri, 2010). Many researchers have investigated the modification of TiO2, such as sensitization, doping, and heterostructures synthesizing (Fernandes et al., 2020; Khan et al., 2020). Moreover, it has also been reported that TiO2 photocatalysis coupled with H2O2 could significantly improve the degradation of target pollutants by generating more radicals (Bai et al., 2016; Fernandes et al., 2019; Rott et al., 2017). Therefore, the UV/TiO2/H2O2 process is recognized as one of the most promising, eco-friendly, and cost-efficient technologies for practical engineering applications.

Nevertheless, inadequate mineralization of pollutants is commonly observed during these advanced treatments, leading to the generation of diverse transformation products (TPs), which may exert more severe ecotoxicity than their parent compounds (Liu et al., 2020; Rueda-Marquez et al., 2020). In fact, the formation of toxic TPs such as nitro-products during AOPs is very common (Gagol et al., 2020; Rayaroth et al., 2022), but this ecological risk was not well addressed in many related studies. The feasibility of a technology cannot be simply evaluated based on its degradation efficiency of target pollutants. Its mineralization and detoxification performance (Maniakova et al., 2021) should also be considered, especially for the discharge and reclamation of secondary effluents (Hong et al., 2020). Therefore, TP identification, degradation pathway, and ecotoxicity assessment of treated effluents are vital to consider when developing advanced water treatment processes. Nevertheless, these issues have seldom been reported in previous studies and are currently neglected in WWTPs.

Given the above mentioned shortcomings, the present study aimed to assess the following: 1) evaluate the performance of the UV/TiO2/H2O2 oxidation process on RBV degradation and mineralization; 2) monitor the ecotoxicity evolution of RBV solutions during the UV/TiO2/H2O2 process using zebrafish embryo testing; 3) identify the possible toxicity increase-causing TPs, using liquid chromatography-mass spectrometry (LC-MS) analysis combined with density functional theory (DFT) calculations; and 4) estimate the multi-endpoint toxicities of each TP using quantitative structure activity relationship (QSAR) predictions and investigate the mechanism of toxicity evolution. This study attempts to overcome the limitations of current research and proposes some implications for WWTPs regarding the toxicity assessment of treated effluents.

2. Materials and methods

2.1. Chemicals

RBV was purchased from Meryer Chemical Technology Co., Ltd. (Shanghai, China). TiO2 powder (P25) was purchased from Degussa (Germany), hydrogen peroxide (30 wt%) from Modern Oriental Corporation (Beijing, China), and potassium dihydrogen phosphate from Titan Scientific Co. Ltd. (Shanghai, China). All solutions were prepared using ultrapure water obtained from a Milli-Q water purification system (Milli-Q Integral 3; Millipore, USA).

2.2. Degradation experiments and toxicity testing

The degradation experiments were performed in a glass reactor (250 mL) with a quartz cover and a double-walled cooling water jacket to maintain a constant solution temperature (25 ± 1 °C) throughout the experiment (Fig. S1). RBV solution (150 mL of 50 mg/L) with the required amounts of TiO2 and H2O2 was added to the reactor according to the experimental design values. The suspension was sonicated for 3 min and magnetically stirred...
in the dark for 30 min to reach absorption equilibrium before subjecting to UV irradiation. Above the reactor, a high-pressure mercury lamp (CEL-M500; Aulight Corporation, Beijing, China) with a nominal power of 500 W was used as the light source. The highest output energy of the mercury lamp was determined to be 365/366.3 nm (Fig. S2) and the UV intensity was adjusted to 0.4 W cm⁻². During the UV irradiation process, samples were collected at given time intervals using a syringe and filtered through a 0.22-μm PTFE syringe filter for further analysis.

For evaluating the toxicity, zebrafish was chosen as an experimental animal model in this study (Fig. S3). A wild-type adult zebrafish (Danio rerio) were maintained at 28 ± 0.5 °C on a 14/10-h light/dark cycle in a fish breeding circulatory system (Yixi, Shanghai, China) and were fed twice daily with live brine shrimp (Artemia salina). Four pairs of male and female zebrafish were placed in a single mating box separated by a divider 1 day prior to spawning, and 10 mating boxes were prepared each time. Spawning was triggered by removing the divider the next morning, and the embryos were collected 3 h later. Using a stereomicroscope (Mshot MZ62, Guangzhou, China), healthy and fertilized embryos at 4 hpf (hour post fertilization) were selected and placed in wells; 40 embryos were placed per well. Each well was then filled with 12 mL of test sample filtrate or water as a negative control. Three replicates were carried out for each treatment. The developmental status of zebrafish embryos and larvae was observed at 48 and 72 hpf and on day 7. Toxicological endpoints included hatching interference, phenotypic abnormalities, and mortality (embryo necrosis).

2.3. Analytical procedures

The concentration of residual RBV in the filtrate was determined using a high-performance liquid chromatography system (Alliance e2695, Waters, USA), equipped with a UV–vis detector and a C18 column (4.6 mm × 250 mm, 5 μm) at 30 °C. The mobile phase consisted of 10 mM potassium dihydrogen phosphate (pH = 5.1) at a flow rate of 1 mL/min. The injection volume was 10 μL, and the detection wavelength was 207 nm.

The TPs were detected using a UHPLC-Q-Orbitrap HRMS system (Dionex Ultimate 3000 Series; MS, Thermo Q Exactive Plus). Chromatographic separation was conducted using an ACQUITY UPLC HSS T3 C18 column (2.1 mm × 100 mm, 1.8 μm; Waters, USA) maintained at 30 °C. Gradient elution was performed with 0.1 % (v/v) formic acid in water (solvent B) and acetonitrile (solvent A) at a flow rate of 0.2 mL min⁻¹. Further details regarding the analytical methods are provided in the Supplementary material (Text S1).

2.4. Theoretical calculations

To investigate the reactive active sites of RBV, theoretical calculations based on DFT were performed using the Gaussian 16 C.01 software. The structural and electronic performances were calculated using the DMOl3 code. The generalized gradient approximation (GGA) with the Perdew–Burke–Ernzerhof (PBE) functional and all-electron double numerical basis set with polarized function (DNP) were used. The details of the DFT calculations are presented in the Supplementary material (Text S2).

To evaluate the ecotoxicity of RBV and its TPs, fathead minnow LC₅₀,96 h, developmental toxicity, bioconcentration factor, and mutagenicity were simulated and calculated using the Toxicity Estimation Software Tool (T.E.S.T., version 5.1, EPA) based on QSAR methodologies. Based on the relationship between the numerical description of the molecular structure and the reported toxicity of compounds, QSARs can predict the potential toxicity of compounds with similar structures. This makes it a good alternative when standards of target compounds are not available, which has been reported in some recent studies (Pan et al., 2021; Sun et al., 2021).

3. Results and discussion

3.1. Degradation of RBV

To observe the effect of TiO₂ concentration, its initial concentration was varied in the range of 0–1.0 g/L (suspension turbidity 0–1590 NTU). As shown in Fig. 2a, the removal efficiency of RBV gradually increased with increasing TiO₂ concentration, but concentrations above 0.5 g/L did not induce significant improvements. This may be attributed to the decrease in light penetration and increase in light scattering, agglomeration, and sedimentation of TiO₂ under high concentrations (Chen and Liu, 2016; Tsai et al., 2009). Based on these results, the optimum TiO₂ concentration for the degradation of RBV was 0.5 g/L. To further investigate the effect of H₂O₂ addition, experiments were conducted by varying the initial H₂O₂ concentration in the range 0–2 % with a constant TiO₂ dosage (0.5 g/L). The optimum H₂O₂ concentration was 1 % (Fig. 2b), and the corresponding molar ratio of oxidant to pollutant was 43:1. An appropriate amount of H₂O₂ could significantly improve the degradation efficiency of RBV, while excess H₂O₂ may cause self-quenching and therefore limits the increase in degradation efficiency (Wols et al., 2015).

UV/TiO₂, UV/H₂O₂ and UV/TiO₂/H₂O₂ are well-known for their effectiveness in advanced water treatment. To select the most effective process for RBV degradation, experiments were conducted using three different systems. As shown in Fig. 2c and d, the combination of TiO₂ and H₂O₂ performed best at removing organic compounds from the system. After 20 min of irradiation, with almost complete elimination (97.8 % removal rate) of RBV, the mineralization rate of the UV/TiO₂/H₂O₂ process reached 53.3 %, which was higher than that of UV/TiO₂ (14.6 %) and UV/H₂O₂ (41.9 %). These results demonstrate that the UV/TiO₂/H₂O₂ process is potentially effective for RBV degradation but inadequate for mineralization, which may be attributed to the formation of more recalcitrant TPs. The comparison results of these three different systems are also in good agreement with those reported previously (Harir et al., 2008; Li et al., 2016), which emphasizes the synergetic effect between TiO₂ and H₂O₂. Specifically, the coexistence of TiO₂ and H₂O₂ could promote the generation of radicals (e.g., ·OH and ·O₂⁻), thus accelerating the degradation of organics (Eqs. 1–(4)) (Harir et al., 2008; Li et al., 2001). To clarify the contribution of ·OH and ·O₂⁻ on RBV degradation, the isopropyl alcohol (IPA) and benzoquinone (BQ) were added as scavenger of ·OH and ·O₂⁻, respectively. The degradation efficiencies were obviously inhibited in the presence of IPA, while the influence of BQ was negligible (Fig. S4), implying that ·OH played a major role during the UV/TiO₂/H₂O₂ degradation of RBV.

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\begin{align*}
H_2O_2 + e^- & \rightarrow \cdot OH + OH^- \\
H_2O_2 & \rightarrow H_2O + O_2 \\
O_2 + e^- & \rightarrow O_2^- \\
H_2O/OH^- + h^+ & \rightarrow \cdot OH
\end{align*}
\] 

(1) (2) (3) (4)

Besides, UV/TiO₂/H₂O₂ process was also efficient for RBV removal in the real water matrix (secondary effluent of pharmaceutical wastewater and domestic sewage) (Table S1), as the removal rate of RBV reached higher than 80 % after 20-min irradiation (Fig. S5). However, the degradation rates in real water matrix were slower than that in ultrapure water, which could be attributed to the quenching and competition effect induced by inorganic anions and organic pollutants in the real water. Compared with other processes (Fig. S6), UV/TiO₂/H₂O₂ process exhibited higher degradation effectiveness than powder activated carbon (PAC) adsorption under the same condition. Although Fenton process was more efficient on RBV removal, the issues of pH adjustment, iron sludge and effluent color still require resolution. In contrast, the UV/TiO₂/H₂O₂ process has some distinctive advantages, including low cost, high efficiency, simple operation and no secondary pollution. Furthermore, the catalyst TiO₂ proved to be photochemically stable and continuously presented high catalytic activity during degradation cycles (Fig. S7). In practical engineering applications, a membrane separation unit could be equipped after the UV/TiO₂/H₂O₂ process, so that catalysts will be separated from the suspension after usage rather than being directly discharged into the environment.
3.2 Toxicity evolution during UV/TiO2/H2O2 treatment

The performance of an oxidation process should be evaluated by both the decomposition of the target pollutants and the potential toxicity of the degradation products. Over the past few decades, laboratory zebrafish has been widely used as an experimental animal model for assessing the toxicity of pharmaceutical compounds or environmental pollutants. This small tropical fish has many advantages, such as simplicity of cultivation, prolific reproductive capacity, a large number of synchronously developing offspring, and genetic similarities with humans. Their high fecundity and rapid development outside of their mother’s body support high-offspring, and genetic similarities with humans. Their high fecundity proli
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To better understand the toxicity evolution of RBV, we first attempted to propose the transformation pathway of RBV in the UV/TiO2/H2O2
reaction system. To achieve this, DFT calculations were made to elucidate the ROS (reactive oxygen species) attack on RBV molecules more precisely. As shown in Fig. 4b and c, the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) represent the electron-rich and electron-poor regions, respectively. The HOMO and LUMO can describe the sites where organic pollutant molecules easily lose or gain electrons (Yi et al., 2021). The HOMO of RBV molecule mainly locates on the amide group, which prefer to be attacked by the electrophilic species like OH. To further describe the reactivity of different sites, Fukui indices for electrophilic attack ($f^-$) and radical attack ($f^0$) were calculated according to the natural population analysis (NPA) charge distribution of the RBV molecule. A site with a higher Fukui index usually has a greater tendency for radical attack. As shown in Fig. 4c, C6 ($f^0 = 0.18$), C15 ($f^0 = 0.141$), and C8 ($f^0 = 0.061$) had higher electrophilic attack Fukui values and were the most active sites in the RBV molecule.

To identify the TPs of RBV generated during the UV/TiO2/H2O2 process, LC-MS was used, and the molecular weight (MW) and formula of twelve TPs were deduced accordingly (Fig. S9, Table S1). Based on both DFT calculations and LC-MS analysis, a possible transformation pathway of RBV in the UV/TiO2/H2O2 photocatalysis system was proposed and is displayed in Fig. 4d. Two pathways were involved in the initial attack on the RBV molecule. For the carbon attack (red line) process, OH favored the attack of electron-rich C8 and C15 sites; then, TP-B (MW = 276.07) was produced after hydroxyl addition and was further transformed into TP-C (MW = 258.06) via H2O deduction. For the nitrogen attack (green line) process, N1 was directly attacked and then cleaved into TP-F (MW = 112.04). The N14 site with a high $f^-$ value likely underwent OH attack and transformation into TP-G (MW = 113.02) via hydroxylation. The subsequent degradation mainly included the conversion mechanisms of the triazole ring opening, C—N cleavage, hydroxylation, and other oxidation procedures. For deep oxidation, the intermediates could further decompose into low-molecular-weight compounds such as TP-J (MW = 90.03), TP-K (MW = 72.02), TP-L (MW = 76.02), and TP-M (MW = 60.02), which were finally mineralized to CO2, H2O, and N2. In general, the proposed transformation pathway was in good agreement with the DFT calculation results for the Fukui index.

3.4. Toxicity estimation of TPs

Following TP identification, further investigation was conducted on their toxicity. First, based on the LC-MS results, the TPs were divided into three groups according to their normalized peak area (Fig. 5a), reflecting the possible increase in toxicity caused. The maximum peak areas of these three groups were observed at irradiation times of 0–20, 40–60, and 80–100 min, respectively. Specifically, TP-B, TP-C, TP-F, and TP-I were generated rapidly in the initial stage of the oxidation process and soon reached their highest concentrations within 20 min, which is highly consistent with the trend of embryonic hatching rate (Fig. 3b). After the toxicity-increase region (0–20 min), the concentrations of these TPs declined significantly. In contrast, the maximum peak areas of TP-D, TP-E, and TP-H arrived much later than the former group, which might be associated with the increase in mortality rates at approximately 60 min (Fig. 3a). Similarly, TP-G, TP-L, and TP-M reached their highest concentrations at 90 min, which coincided with the time at which abnormalities increased (Fig. 3c). These results further confirm that the increase in embryonic toxicity of the treated RBV solutions could be attributed to the formation and accumulation of toxic TPs.

Based on QSAR methodology, the T.E.S.T. software was used for toxicity estimation of each TP in this study, as most TPs are difficult to acquire commercially. The acute toxicity (fathead minnow LC50), developmental toxicity, mutagenicity, and bioconcentration factor of RBV and its TPs were calculated, and the results are shown in Fig. 5b–e and Table S2. The LC50 of fathead minnow was 10,698 mg/L for RBV, which is categorized as “Not Harmful” (Fig. 5b). However, most of the degradation products showed lower LC50 values than that of the parent compound, indicating higher acute toxicity. Similarly, Fig. 5c demonstrates that most TPs, except...
for TP-D, TP-E, and TP-H, had higher developmental toxicity than RBV. In addition, Fig. 5d and e suggest that UV/TiO2/H2O2 photocatalysis reduces mutagenicity while increasing the bioconcentration factor of most TPs. Furthermore, the ECOSAR software was also used to additionally evaluate the toxicity of intermediates, and the evaluation results (Table S4) further confirmed that most of the degradation products had high toxicity than the parent compound RBV. In summary, the toxicity estimation above was in good agreement with the experimental results shown in Fig. 3.

Although RBV is rapidly removed in the UV/TiO2/H2O2 process, the trend of effluent toxicity is not consistent with the residual RBV, as shown in Fig. 6. During the advanced oxidation process, the effluent toxicity first increases due to the formation and accumulation of TPs with higher toxicity than the parent compound. Subsequently, toxicity gradually decreases as the toxic TPs are decomposed into smaller compounds until complete mineralization. However, some small-molecule compounds exert higher toxicity, resulting in a toxicity rebound in the later stages of the reaction.

In conclusion, the evolution trend of effluent toxicity is complicated and completely different from the monotonically decreasing concentration of RBV. Therefore, future studies should not only focus on the removal rate of organic matter but also pay more attention to the toxicity assessment of TPs and effluents during water treatment.

### 4. Conclusions

In summary, this study investigated the removal performance, transformation pathways, and ecotoxicity evolution of RBV using the advanced oxidation process UV/TiO2/H2O2. The results of this study suggest that the UV/TiO2/H2O2 process could effectively eliminate the pollutant RBV (almost complete removal after treatment for 20 min). However, the mineralization rates were relatively low ($\leq 53.3\%$), indicating the formation of more recalcitrant TPs. The experimental bioassays (i.e., zebrafish embryo toxicity test) demonstrated that the acute toxicity of the treated RBV solutions increased at some stages and decreased later as the reaction time was prolonged, which may be attributed to the adverse effect induced by the complicated TPs during the treatment. The possible toxicity increase-causing TPs were identified based on the combined results of LC-MS and DFT calculations, and the degradation pathway of RBV was also proposed. Additionally, the QSAR predictions suggested that most TPs exhibited higher toxicity than the parent compound, further emphasizing that the toxicity increase of treated RBV was caused by the formation and accumulation of more toxic TPs.

These findings provide deep insights into the degradation mechanisms of RBV under the UV/TiO2/H2O2 process through experimental and theoretical approaches.
investigations. Although the results demonstrate that the UV/TiO₂/H₂O₂ process is a promising remediation technology for the effective removal of RBV, the potential ecotoxicity of the oxidation intermediates requires further attention. Moreover, considering the coexistence of other contaminants in real wastewater, the combined toxic effects could be much more complicated in practical treatment processes. Our results underpin the necessity of considering the potential toxicity of degradation products after wastewater treatment, especially if the treated effluent is discharged directly into the aquatic environment. To obtain clean and safe effluents, WWTPs should be prudent in the selection of a specific water treatment process, considering both the removal and detoxification performance of the contaminants. Integrated high-throughput screening techniques should also be introduced.

Fig. 5. (a) Normalized peak area of the transformation products at different irradiation times. (b)–(e) Toxicity prediction for RBV and its identified transformation products: (b) fathead minnow LC₅₀ (96 h), (c) developmental toxicity, (d) mutagenicity, and (e) bioconcentration factor.

Fig. 6. Contrast between RBV degradation and toxicity evolution during the UV/TiO₂/H₂O₂ treatment process.
Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

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Appendix A. Supplementary data

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