An efficient simultaneous degradation of sulfamethoxazole and trimethoprim by photoelectro-Fenton process under non-modified pH using a natural citric acid source: study of biodegradability, ecotoxicity, and antibacterial activity

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Abstract
In this work, the use of natural organic wastes (orange and lemon peels) as sources of citric acid was evaluated along with the application of the photoelectro-Fenton (PEF) system under non-modified pH as a novel alternative to degrade a complex mixture of pharmaceuticals: sulfamethoxazole (SMX—7.90 × 10−5 mol/L) and trimethoprim (TMP—6.89 × 10−5 mol/L). The system was equipped with a carbon felt air diffusion cathode (GDE) and a Ti/IrO2 anode doped with SnO2 (DSA). A 3.6 × 10−5 mol/L solution of commercial citric acid was used as a reference. The pharmaceuticals’ evolution in the mixture was followed by high-performance liquid chromatography (HPLC). The addition of natural products showed an efficient simultaneous degradation of the antibiotics (100% of SMX and TMP at 45 min and 90 min, respectively) similar to the performance produced by adding the commercial citric acid to the PEF system. Moreover, the addition of natural products allowed for an increment of biodegradability (100% removal of TOC by a modified Zahn Wellens test) and a decrease in ecotoxicity (0% in the bioassay with D. Magna) of the treated solutions. The antibacterial activity was eliminated after only 45 min of treatment, suggesting that the degradation by-products do not represent a significant risk to human health or the environment in general. Results suggest that, because of the efficient formation of Fe-citrate complexes, the PEF could be enhanced by the addition of natural organic wastes as a sustainable alternative ecological system for water contaminated pharmaceuticals. Additionally, the potential of reusing natural organic wastes has been exposed, contributing to an improved low-cost PEF by decreasing the environmental contamination produced by this type of waste.

Keywords Photoelectro-Fenton system · Natural iron-citrate complex · Citrus peels · Circumneutral pH · Organic waste reuse · Pharmaceuticals mixture

Highlights
• SMX and TMP were simultaneously degraded with the PEF system by the addition of citric acid.
• Efficiency in the degradation was maintained with extracts from lemon and orange peels.
• Complete degradation of SMX and TMP increased the biodegradability of the treated solutions.
• The treated SMX-TMP solutions showed lower ecotoxicity.
• Degradations of 100% of SMX and 71% of TMP lead to the complete elimination of antibacterial activity.

Introduction
Antibiotics, considered contaminants of emerging concern (CECs), are powerful medications used to treat or prevent bacterial infections. When used correctly, antibiotics can be life-saving for humans and animals. However, using antibiotics poorly (in incorrect doses, with premature interruption of treatment or with low-quality drugs, and in situations where antibiotics are unnecessary) prevents them from functioning correctly. This common practice is harmful to healthy individuals as well as to the environment. According to the World Health Organization (WHO), the misuse of antibiotics...
Two specific antibiotics, sulfamethoxazole and trimethoprim (SMX-TMP), are frequently prescribed to patients with bronchitis and symptoms of infection caused by *Staphylococcus* and *Streptococcus* bacteria since these antibiotics inhibit the synthesis of tetrahydrofolate and subsequently the DNA acting as bactericidal and bacteriostatic compounds (Suárez Olivares 2011; Daza et al. 2017). These drugs are commercially found in combination with a 1: 5 ratio (TMP: SMX) to carry out their mechanism of action (Arredondo-García 2007) synergistically blocking successive steps of folate metabolism in bacteria, which is necessary for the production of cell wall proteins, puric and pyrimidine bases of DNA, thereby acquiring maximum antibacterial activity (Sass 2017; Montiel 2018).

The high consumption of these antibiotics promotes their appearance in wastewaters, where the bacterial diversity is high, which leads to an increase in antibiotic-resistant bacteria. Local data in Bogotá shown that approximately 74% of resistance to SMX and TMP was found in 1769 strains of *E. coli* (Pallares & Martínez 2013; López & Garay 2016; Daza et al. 2017; Bello-Fernández et al., 2018). SMX and TMP were detected in the influent of the Bogotá D.C wastewater treatment plant (WWTP-Salitre) at concentrations of 0.63 μg/L and 0.32 μg/L, respectively. In the effluent, similar concentrations (0.64 μg/L for SMX and 0.34 μg/L for TMP) were observed, showing a none elimination by the WWTP (Botero-Coy et al. 2018). Therefore, complementary processes are necessary to remove this kind of compound. Advanced oxidation processes (AOPs) are effective systems in the elimination of mixtures of CECs from water (Qiu et al. 2015), and among AOPs, the Fenton reaction can be highlighted, which is mainly based on the Fenton reaction, where ferrous ion (Fe²⁺) reacts with hydrogen peroxide (H₂O₂) producing hydroxyl radical (•OH, Reaction 1) (Barbosa et al. 2016; Boczkał & Fernandes 2017).

\[
\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \cdot \text{OH} \tag{1}
\]

Although the Fenton reaction has been recognized as an efficient way to produce hydroxyl radicals, it is significantly limited by different variables such as the permanent requirement of the reaction precursors to promote a continuous process, consequently, the generation of the hydroxyl radicals is also limited. An interesting alternative to overcome this limitation is the Electro-Fenton (EF) process, in which the hydrogen peroxide could be electro-generated on the surface of a cathode (generally graphite cathode) such as gas diffusion electrode—GDE—in the presence of oxygen (Reaction 2) (Luo et al. 2015; Martínez-Pachón et al. 2019).

\[
\text{O}_2 + 2\text{H}^+ + 2\text{e}^- \rightarrow \text{H}_2\text{O}_2 \tag{2}
\]

To increase the degradation of contaminants, anodes such as a DSA (dimensionally stable anodes) can also be used, where direct or indirect oxidation could take place. In the direct oxidation (anodic oxidation, AO), the formation of the •OH is attributed to the oxidation of water molecules on the surface of the anode, (Reaction 3) (Jojoa-Sierra et al. 2017; Espinosa-Barrera et al. 2021; Hussain et al. 2017, 2015; Eleotério et al. 2013), while during the indirect oxidation, secondary species are electro-generated regarding the electrolyte. Such is the case of chloride, which rapidly induces a high production of active chlorine species (ACS) such as Cl₂, HClO, and ClO⁻ (Reactions 4 - 6) which can also yield oxidation of pollutants (Perea et al. 2019; Ferreira de Melo et al. 2020).

\[
\text{H}_2\text{O} \rightarrow \cdot \text{OH} + \text{H}^+ + \text{e}^- \tag{3}
\]

\[
2\text{Cl}^- \rightarrow \text{Cl}_2 + 2\text{e}^- \tag{4}
\]

\[
\text{Cl}_2 + \text{H}_2\text{O} \rightarrow \text{HClO} + \text{H}^+\text{Cl}^- \tag{5}
\]

\[
\text{HOCI} \rightarrow \text{H}^+ + \text{ClO}^- \tag{6}
\]

When the electro-Fenton (EF) system is irradiated with a light source, the degradation efficiency tends to be improved. In this case (photo-electro-Fenton process (PEF)), different light irradiation sources can be used, such as light-emitting diode (LED). Under these conditions, extra •OH are obtained through the direct photolysis of the aqua-complexes [Fe(OH)]⁺² (Reaction 7) (Eskandarian et al. 2016; Davididou et al. 2017; Matafonova & Batoev 2018), and simultaneously the ferrous ion is regenerated from the ferric ion. The ferrous ion has much higher water solubility than ferric ion and, it could promote easier the Fenton reaction (Reaction 1). Therefore, the formation of soluble ferrous ions from low or insoluble ferric ions by the single light interaction becomes an enhancement of the Fenton-based process.

On the other hand, different organic acids are known as excellent ligands of photo-active ferric complexes that could undergo photolysis leading to the reduction of Fe³⁺ to Fe²⁺ (Reaction 8) facilitating the production of the hydroxyl radicals by the Fenton reaction during the PEF system (Casado 2019; Brillas 2020). According to the ligand nature, during the organo-ferric complexes photolysis, organic radicals are produced, and could also
contribute to the degradation of the organic matter in the water. Furthermore, organo-ferric complexes present an extra advantage to the Fenton-based process, since the formation of these complexes leads to the solubilization of ferric ion (highly insoluble) at near-neutral pH, avoiding the use of acid pH (2.8) conditions, the main limitation of the classic Fenton reaction (in the absence of organic ligands, ferric ion precipitates under pH above 3 and the reaction is restricted) (Dias et al. 2014; Ruales-Lonfat et al. 2016).

\[
\text{[Fe(OH)]}^2+ + \text{hv} \rightarrow \text{Fe}^{2+} \cdot \text{OH} \quad (7)
\]

\[
\text{[Fe(OOCR)]}^2+ + \text{hv} \rightarrow \text{Fe}^{2+} + \text{CO}_2 + \text{R}. \quad (8)
\]

Among the organic acids, citric acid stands out given its proven high photoactive capacity to produce reactive species and to increase soluble iron in the system (Clarizia et al. 2017; Villegas-Guzman et al. 2017; Casado 2019). In addition, citric acid could be easily extracted from diverse organic wastes, especially from the citrus food industries, which contains significant amounts of this acid (Villegas-Guzman et al. 2017; Amanollahi et al. 2019). Hence, it becomes an interesting organic acid source to be tested during Fenton-based water treatment.

The evaluation of natural products as possible sources of organic acids becomes an interesting alternative, especially for Colombia, where orange or lemon juices are part of the agro-industrial economic sector, and consequently, a large amount of orange and lemon peel waste have been reported (Domingos et al. 2019). In the specific case of the orange, it occupies second place in the Colombian national production with 456,301 tons (DANE 2019). Additionally, during the production of industrial orange juice, only half of the fresh weight of orange is transformed into juice and the 50% remaining (228,150 tons) consists of pulp, peel, and seeds (Rezzadori et al. 2012). Approximately 95% of these agro-industrial wastes are made from peels (orange and lemon peel residues) generating a serious disposal problem which implies the use of extensive economic and energy resources, in addition to a rise in air, water, and soil pollution (Ortiz et al. 2020).

Therefore, in this work, the simultaneous degradation of antibiotics SMX and TMP in an aqueous medium (doped Milli-Q water) by the PEF system, with the addition of citric acid extracted from organic citrus residues (lemon and orange peels), under circumneutral pH, was studied. The efficiency of the PEF system was evaluated in terms of the initial degradation rates of the pollutants (Ct/Co×100) and variations on parameters such as biodegradability, toxicity and, antibacterial activity (AA) of the treated solutions.

### Materials and methods

#### Reagents

Sulfamethoxazole and trimethoprim (98% purity) standard HPLC-grade was purchased from Sigma Aldrich. Iron (II) sulfate heptahydrate (FeSO₄·7H₂O ≥ 99.5%), dibasic potassium phosphate (K₂HPO₄ ≥ 98.0%), orthophosphoric acid (H₃PO₄ ≥ 85.0%), monopotassium dihydrogen phosphate (KH₂PO₄ ≥ 99.0%), potassium bicarbonate (KHCO₃ ≥ 99.9%), potassium carbonate (K₂CO₃ ≥ 99.0%), sodium chloride (NaCl ≥ 99.5%) and citric acid (C₆H₈O₇·7H₂O ≥ 99.5%) were analytical quality obtained from Merck. The HPLC grade acetonitrile (CH₃CN ≥ 99.9%) was obtained from Panreac. All solutions were prepared with ultrapure water from a Millipore Milli-Q system with resistivity > 18 MΩ cm at 25 °C.

D (+)-Glucose (C₆H₁₂O₆ ≥ 99.0%), calcium chloride dihydrate (CaCl₂·2H₂O ≥ 99.0%), iron(III) chloride hexahydrate (FeCl₃·6H₂O ≥ 97.0%), copper (II) sulfate pentahydrate (CuSO₄·5H₂O ≥ 98.0%), manganese (II) sulfate heptahydrate (MnSO₄·7H₂O ≥ 98.0%), zinc sulfate heptahydrate (ZnSO₄·7H₂O ≥ 98.0%), magnesium chloride hexahydrate (MgCl₂·6H₂O ≥ 99.5%), ammonium chloride (NH₄Cl ≥ 99.5%) and sodium sulfate (Na₂SO₄ ≥ 99.0%) were analytical-quality obtained from Panreac.

#### Electrochemical system

The degradations assays were carried out in a 250-mL undivided glass cell. Two hundred milliliters of a solution with 7.90×10⁻⁵ mol/L of SMX and 6.89×10⁻⁵ mol/L of TMP, 0.050 mol/L sodium chloride was used as the supporting electrolyte and 3.6×10⁻⁵ mol/L of Fe²⁺ was treated. For the electrochemical cell, a 2-cm² carbon felt air diffusion cathode (GDE) and a 2.89 cm² Ti/IrO₂ anode doped with SnO₂ (DSA) were used and was operated at a constant current density mode of 5.19 ma/cm² and a voltage of 3 V (current density with lower energy consumption for both compounds, Figure SM1). The solution was irradiated with a white light LED radiation source wrapped around the cell (UK; 3.8 W) with 60 LEDs (1.0 m). The PEF system was previously described (Martínez-Pachón et al. 2018, 2019). The experiments were carried out at neutral pH and using 3.6×10⁻⁵ mol/L of citric acid (analytical grade reagent or extracted from organic citrus residues).

#### Extraction of citric acid from natural products

The extraction procedure was based on an already registered protocol with modifications (Villegas-Guzman et al. 2017).
Commercial fruits such as orange (*Navel orange*) and lemon (*Subtle lemon*) were used. Infusions of the husks as natural sources of citric acid for the PEF system were tested. The peels were dried at 60 °C for 24 h and ground. Two grams of the dry material were weighed and mixed with 40 mL of boiling water for 5 min to help the extraction of soluble organic acids (Dias et al. 2015; Ozkan 2019). The mixture was then centrifuged for 5 min at 5000 rpm. Extractions were prepared just before the experiments and immediately used.

### HPLC degradation analysis

A Shimadzu LC-20AT HPLC equipped with an SPD-M20A photodiode array detector and a C18 column (Waters Spherisil ODS2, 250 mm×4.6 mm ID with particle sizes of 5 μm) was used. The mobile phase was composed of a phosphate buffer (pH 3.5, 0.01 mol/L)/acetonitrile (50/50 v/v) at 25 °C, under isocratic conditions. The mixture was pumped with a flow rate of 1.0 mL/min, resulting in a maximum system pressure of 98 bar, detection was set at 270 nm for SMX and 204 nm for TMP. Twenty microliters of sample was injected by full loop injection. Under these conditions, SMX and TMP were eluted at 3.61 min and 5.57 min, respectively.

### Biodegradability analysis with activated sludge

The biodegradability analysis was carried out separately from the photoelectro-Fenton system. The biodegradability was evaluated over a period of 12 days, using aerobic microorganisms from the purge of a plastic processing plant in Bogotá D.C-Colombia. 100 mg/L of biomass was added to the SMX and TMP solutions to obtain a biomass ratio of 5:1 in 230 mL of total volume. The tested solutions were: 1. [SMX]₀: 7.90×10⁻⁵ mol/L, [TMP]₀: 6.89×10⁻⁵ mol/L, 2. After 45 min of treatment, 3. After 90 min of treatment, 4. [Glucose]₀: 1.11×10⁻⁴ mol/L as a positive control. Each solution contained micronutrients (calcium chloride, iron chloride, copper sulfate, manganese sulfate, and zinc sulfate), and macronutrients (magnesium chloride, ammonium chloride, sodium sulfate, dipotassium phosphate, and monopotassium phosphate).

The process was slowly aerated with an aquarium pump (AP-005 XILONG), constantly stirred, and the temperature was maintained at 37 °C in a shaker (Wise Shake SHO-1D Digital Orbital Shaker). Before undergoing the activated sludge treatment, residual oxidizing species were inactivated by mixing with sodium disulfite (0.1 mol/L). Samples were monitored on days 2, 4, 6, 8, and 12 by analyzing the total organic carbon (TOC) in the Shimadzu TOC-LCSH equipment. Dissolved oxygen concentration to evaluate respirometry was measured using a HI 9829 multiparameter meter (HANNA Instruments), equipped with the HI 76×9829 series probes.

### Toxicity analysis with Daphnia magna bioassay

The standard methodology described in the ISO 6341 and other studies was used (Khan et al. 2017; Espinosa-Barrera et al. 2021). The *D. magna* media with reconstituted water was applied and fed with *Scenedesmus subsppicatus* algae (Vidal et al. 2016). The reconstituted water was prepared with deionized distilled water (Álvarez-Manzaneda et al. 2017; Barrera Herrera et al. 2019). Before placing the *D. magna* in the solutions, the pH of the samples was adjusted to 7.0 using sodium hydroxide (1.0 mol/L). The solution was slowly aerated with an aquarium pump (AP-005 XILONG) and the temperature was maintained at 20 °C on a stirrer (Wise Shake SHO-1D digital orbital shaker). The bioassay was carried out for 48 h following the mobility of 10 *D. magna* in different solutions (described in point 3.9. Biodegradability analysis with activated sludge). Potassium dichromate was used as the positive control and reconstituted water as the negative control.

### Analysis of antibacterial activity

The antibacterial activity was determined by analyzing the inhibition zone during the agar diffusion test, using *Escherichia coli* ATCC 25,922 as an indicator microorganism. Following the Kirby-Bauer method described by (Serna-Galvis et al. 2016), 30 μL of the solutions were added (samples along with the degradation treatment) on white filters. Subsequently, they were placed in Petri dishes containing 25 mL of Müller-Hinton agar inoculated with an *E. coli* solution (with an optical density of 0.500 to 580 nm). After 24 h of incubation at 37 °C, bacterial growth was observed and the diameter of the inhibitory halo was measured with a Vernier. The analyses were performed in duplicate to ascertain the reproducibility of the methodology.

### Results and discussion

#### Effect of the citric acid on the degradation of SMX and TMP by PEF system

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#### Effect of citric acid source (comparison of natural and commercial sources)

Several studies have shown the positive effect of using organic acids in the degradation of CECs by Fenton-based processes (Dias et al. 2014; Moreira et al. 2015; Villegas-Guzman et al. 2017; Giannakis 2018; Zhang et al. 2019) to avoid the acidification stage since pH 3.0
is the recommended condition to performed the Fenton-based process (Gozzi et al. 2017; Nogueira et al. 2017; Brillas 2020). Several natural products have organic acids as main constituents in their juices, peels, and pulps (Pliego et al. 2016; Ruales-Lonfat et al. 2016; Kowalski et al. 2019). In this work, the citric acid extracted from lemon and orange peel (Villegas-Guzman et al. 2017), were compared with the citric acid reactive-grade like iron-complexing agents to the degradation of the SMX and TMP by PEF process. The addition of natural products was set taking into account the amount of citric acid that was obtained in the extraction, maintaining in the system the molar ratio 1:1 (Citric acid: Iron) (Moreira et al. 2017; Serna-Galvis et al. 2020).

Significant differences in the degradation rates and the efficiency of the treatment after 30 min were observed in presence of the citric acid from different sources (Table 1). With the commercial reagent, higher degradation rates were obtained, approximately twice the value obtained with extracted acid, and degradation percentages around 10–20% higher than citric acid extracted from natural orange and lemon peels for both compounds.

When the time of degradation was increased, similar efficiencies were obtained in presence of the citric acid extracted from the natural products and in the presence of the analytical grade reagent. SMX was completely degraded at 45 min (Fig. 1A) and TMP at 90 min (Fig. 1B) in the three evaluated cases. In all cases, the PEF system was carried out without modifying the pH (the pH value obtained by adding citric acid was approx. 4.8). These results show that the presence of organic matter in the extractions probably does not represent significant competition for the produced oxidant species responsible for promoting the target molecules degradation (antibiotics) (Ouiriemmi et al. 2017; Villegas-Guzman et al. 2017; Villegas-Guzman et al. 2017), and on the contrary, helps to the process due to the formation of iron-citrate complexes (Reaction 9), which present a photocatalytic activity even under visible light (SM3) (Daviddou et al. 2017; Oturan et al. 2018), by photons absorption (Reaction 10), maintaining the ferrous ion in solution.

Table 1 Degradation efficiency of the antibiotics SMX and TMP in terms of initial degradation rate and elimination percentage after 30 min of treatment

| Name                | Sulfamethoxazole | Trimethoprim |
|---------------------|------------------|--------------|
| Chemical formula    | S_10H_11N_3O_3S | C_14H_18N_4O_3 |
| **a Rate constant (mol/min)** |                  |              |
| Reagent             | 0.0476           | 0.0208       |
| Lemon peel extract  | 0.0232           | 0.0106       |
| Orange peel extract | 0.0242           | 0.0128       |
| **b Efficiency in 30 min (%)** |                  |              |
| Reagent             | 96.04            | 65.44        |
| Lemon peel extract  | 77.73            | 54.25        |
| Orange peel extract | 82.77            | 56.31        |

*a Average of three repetitions, Standard Deviation (SD) < 1.0%  
*b Average of three repetitions, Standard Deviation (SD) < 5.0%

Fig. 1 Simultaneous degradation of SMX and TMP using PEF system in the presence of citric acid from commercial reagent, lemon peel extract and orange peel extract. A. SMX degradation, [SMX]: 7.90×10^{-5} mol/L, B. TMP degradation [TMP]: 6.89×10^{-5} mol/L. Conditions: pH_{init}: 4.8 by adding citric acid (without modifying the pH), [citric acid]: 3.6×10^{-5} mol/L, [Fe^{2+}]: 3.6×10^{-5} mol/L, current density: 5.19 mA/cm^2, radiation source: LED
Furthermore, the photoactivity of the formed organo-ferric complexes can promote the formation of extra-oxidative species (O$_2^\bullet$/$\text{HO}_2^\bullet$, •OH and R•) by the ligand-to-metal charge transfer (LMCT) (Feng et al. 2012; Jho et al. 2012), allowing the degradation of both SMX and TMP without the pH adjustment.

Fe$^3+$ + C$_6$H$_8$O$_7$ $\rightarrow$ Fe$^{3+}[\text{C}_6\text{H}_5\text{O}_7]^{3-}$ + 3H$^+$ \hspace{1cm} (9)

Fe$[^{[\text{C}_6\text{H}_5\text{O}_7]^{3-}}$ + hv $\rightarrow$ Fe$^{2+}$ + C$_6$H$_8$O$_7$\(^2\) \hspace{1cm} (10)

The radiation emits by the LEDs used in the PEF system (emission wavelength 450—620 nm) enhances the efficiency of the process, acting on the breakdown of the iron-citrate complex. Direct photolysis or indirect generation of oxidizing agents by the radiation was negligible (Figure SM4) since SMX or TMP have absorption bands in the UV range (204 and 270 nm, respectively) (Abellán et al. 2009; Ryan et al. 2011; Kwon et al. 2018). The generation of oxidizing species usually occurs synergically by the different components of the system; H$_2$O$_2$ by GDE, ACS by DSA, O$_2^\bullet$/$\text{HO}_2^\bullet$, •OH and R• by Fenton reaction (Feng et al. 2012; Dias et al. 2014; Martínez-Pachón et al. 2019).

To provide deeper information about the citric acid source, additional experiments were performed in which pH was tested (Figure SM2). Similar degradation times were observed for SMX in the case of degradations at pH 3.0 and adding of citric acid, reaching 100% of SMX elimination after 45 min showing the positive effect of the citric acid as an additive (Figure SM2A). In the case of TMP, at pH 3.0 it was completely degraded after 45 min. However, with a citric acid extract from the orange peel, total degradation of TMP was obtained after 90 min (Figure SM2B). These results indicate a positive effect on degradation by the addition of citric acid (green line). It was confirmed when these results were compared with the degradation controls at pH 7.0 (yellow line) and 4.8 acidified with HCl (pH like that obtained by adding citric acid; red line), where lower degradation efficiency was observed. At high pH values, the iron complexing agent is not present, and iron (III) aqua-complex are preferentially formed (Reaction. 11), decreasing the possible generation of hydroxyl radicals by the Fenton reaction and affecting the efficiency of SMX and TMP degradation (Boczkaj & Fernandes 2017; Clarizia et al. 2017).

Fe$^{2+}$ + OH$^2+$ $\rightarrow$ [Fe$^{3+}$(OH)]$^{2+}$ \hspace{1cm} (11)

Considering that experiments were carried out to promote the simultaneous degradation of SMX and TMP, the addition of citric acid seems to be a promising alternative instead of acidifying the solution, since after 45 min of treatment when SMX is eliminated, the biodegradability of the treated solutions should be increased with less toxic character and lower antibacterial activity (properties discussed in the subsequent points) (Cai & Hu 2017; Martínez-Costa et al. 2018; Alharbi et al. 2019; Ruales-Lonfat et al. 2016; Sági et al. 2018a, 2018b).

### Comparative analysis of the degradation of SMX and TMP by PEF system proposed

Degradation rate constants ($k$, mol/min) and elimination efficiencies percentages (Efc, %) for SMX and TMP by the different PEF systems (in the presence of citric acid from commercial reagent, lemon peel extract, and orange peel extract) as given in Table 2.

| Name | Sulfamethoxazole | Trimethoprim |
|------|------------------|--------------|
| **Chemical formula** | C$_{10}$H$_{11}$N$_3$O$_3$S | C$_{14}$H$_{18}$N$_4$O$_3$ |
| **Structure (Potential cleavage sites)** | | |
| **pKa** | pKa$_1$ | 1.71 | 3.24 |
| | pKa$_2$ | 5.65 | 7.87 |

Table 2 Chemical information of SMX and TMP
extract) are presented in Table 1. Results show that both $k$ and $E_{fc}$ of SMX were higher than those of TMP. The $k$ values for TMP degradations are four times lower than the $k$ values for SMX, and $E_{fc}$ after 30 min of treatment was significantly lower compared to SMX (54–65% for TMP and 77–95% for SMX). These differences between the antibiotic’s degradation can be endorsed to the chemical properties of the molecules represented by the $pK_a$, which is closely related to the reactivity of the molecules (Table 2). The medium pH affects the reactive sites by modifying the hydration of the target molecule. Consequently, an important impact on the apparent mass transfer coefficient of the SMX can be promoted by the oxidizing species action, favoring SMX degradation in a wide range of pH (Lin et al. 2013; Zhang et al. 2016).

By the addition of the citric acid from the different sources, the pH solution reached was 4.8. At this pH value, the SMX molecule is protonated maintaining an aniline group in the structure (a benzene ring with an amine) (Dias et al. 2014; Martínez-Costa et al. 2018), which is susceptible to nucleophilic attacks by hydroxyl radicals, cleaving amine groups to release nitrogen in volatile forms such as $N_2$ and $N_xO_y$ (Thiam et al. 2015). In the same way, a similar break in the benzene ring takes place for the TMP molecule leading to the generation of typical by-products in the degradation of organic molecules such as short-chain organic acids (oxalic, oxamic, maleic, and fumaric acids), which could act similarly to the citric acid during in the PEF system, favoring the formation of organo-ferric complexes, and improving the degradation efficiency (Gimeno et al. 2016; Peng et al. 2017; Liu et al. 2018). In a parallel way, the use of DSA anode in the PEF system produces active chloride species (ACS) that lead to the breakdown of the benzene ring of the SMX causing the total oxidation of the amine group, directly producing gaseous nitrogen ($N_2$), nitrates ($NO_3^-$) and chlorides ($Cl^-$) (García-Espinosa et al. 2018; Liu et al. 2020).

On the contrary, based on the $pK_a$ the TMP (Table 2), the pH of the solution reached by the addition of citric acid, did not affect the molecular hydration of the SMX (Dias et al. 2014; Moreira et al. 2015, 2017). Hence TMP degradation could be attributed to the ACS, mainly by hypochlorous acid ($E^0 = 1.49\, \text{V}$), which is the ACS predominant at pH values close to neutral ($3.0 < \text{pH} < 7.0$). At other pH values, different ACS prevalent, the Cl$_2$ species at pH $\leq 3.0$ (Reaction 4) ($E^0 = 1.36\, \text{V}$), and hypochlorite ions at pH $> 7.0$ ($E^0 = 0.89\, \text{V}$) (Reactions 5 - 6) (Brillas & Martínez-Huitle 2015; Martínez-Pachón et al. 2019; Zhao et al. 2019). It should be noted that during the simultaneous degradation of SMX and TMP by PEF system with the addition of natural citric acid, the pH did not change significantly ($\text{pH}_{\text{initial}}: 4.8–\text{pH}_{\text{final}}: 5.2$), so then the predominant ACS during the time degradation was the hypochlorous acid, which promotes the efficient breakdown of antibiotics molecules.

Additionally, SMX and TMP have potential cleavage sites according to their structures and are consistent with the identified degradation products (DPs) promoted by oxidative species ($\cdot OH$ and ACS) (Andrade et al. 2009; de Amorim et al. 2013). Four potential cleavage points for SMX have been highlighting, located around the functional groups with nitrogen (primary amine of aniline and secondary amine) and aromatic rings (benzene ring of aniline and 3-methylisoxazole). In the case of TMP, only one site in the middle of the two aromatic rings is potentially cleavage (Table 2) (Murillo-Sierra et al. 2018). Therefore, there is a higher probability and degradation rate for the SMX than TMP to undergoing a breakdown.

### Degradation extent of SMX and TMP by PEF system with orange peel extract added

The biodegradability, ecotoxicity, and antibacterial activity tests were carried out only with citric acid present in the orange extract. The orange extract was chosen, due to the rates constants ($k$) in the degradations of SMX and TMP were higher with this extract compared to the extract from the lemon peel, showing low competition for oxidants despite the organic matter extra present in the orange peel extract (Villegas-Guzman et al. 2017; Villegas-Guzman et al. 2017; Ortiz et al. 2020). Moreover, in Colombia, the production of organic waste from the orange fruit is high, mainly due to its high consumption and production (Rezadori et al. 2012; Hurtado & Villa 2016; Rodríguez Leyton 2019).

### Biodegradability of SMX and TMP solutions treated with PEF system

Previous degradation results show the ability of the PEF system to eliminate both antibiotics SMX and TMP in a simultaneous process. However, a degradation extent analysis showed that total mineralization of the treated samples did not occur, indicating the formation of stable DPs during the treatment (Figure SM5) and more time required to induce their degradation. Consequently, additional experiments should be performed to establish the possible environmental and human risk of these DPs. The biodegradability tests of the treated solutions are a good indicator of the possible bioaccumulation DPs that could be even more toxic than the initial molecule (Jojoa-Sierra et al. 2017; Rossetti 2017; Maurício et al. 2018). Therefore, a modified Zahn Wells test was carried out to evaluate biodegradability to the treated solutions at different times along the PEF process (0, 45, and 90 min of treatment).

Figure 2 shows that for the untreated SMX and TMP solutions, no significant change of the TOC was observed even after 12 days of biological treatment. This data is
in correspondence to the null biodegradability of both SMX and TMP, bioaccumulating and toxic affecting the activated sludge biomass leading to a decrease in the microbiological population and an increase of dissolved oxygen (observed in respirometry test) (Figure SM6). Consequently, antibiotics inhibit the action of the microorganisms, and the TOC remains constant (Alvarino et al. 2015; Sági et al. 2018a, 2018b; Mendes Barros et al. 2020).

However, the solutions treated for 45 min by PEF process and submitted to the biological test, showed ~55% TOC removal after the 12 days. This increase in the elimination of organic matter (TOC%) by the activated sludge indicates a higher biodegradability character of the residual organic matter present in the treated solution. Interesting results of biodegradability of treated solutions during 90 min by PEF process were observed. Total mineralization by the biological system was obtained after 12 days, a result confirmed by the respirometry assay reaching values of the dissolved oxygen of 3.4 mg/L, the closest value to the positive control (~2.1 mg/L O₂) (Figure SM6). The final TOC removal for this solution indicating that the microorganisms within the active sludge live and consume oxygen even after the TOC removal suggesting that microorganisms within the active sludge were not affected by the compounds of the residual organic matter (varied DPs from SMX and TMP) and continue to consume the dissolved oxygen, confirming the biodegradable character of the treated solutions (Vasiliadou et al. 2018; Karlkanovaitė-Balikci and Yagci 2019). Therefore, the addition of orange peel extract to the PEF system under non-modified pH can transform recalcitrant compounds such as SMX and TMP into biodegradable compounds that could be released into the environment without apparent consequences (Serna-Galvis et al. 2015, 2019).

**Ecotoxicity analysis of treated solutions by the D. magna bioassay**

A high biodegradability character is commonly related to low toxicity; however, these are different parameters and so a biodegradable compound does not imply null toxicity. Therefore, the toxicity of the treated solutions was evaluated with a D. magna bioassay, which is widely used as an environmental bioindicator (Libralato et al. 2018; Galhano et al. 2020). The sensitivity of D. magna to potassium dichromate was evaluated following the ISO 6341 standard (Espinosa-Barrera et al. 2021), obtaining 100% of inhibition with potassium dichromate 6.8×10⁻⁹ mol/L after 48 h (Fig. 3). An acute ecotoxicological test was performed using D. magna against the treated (45 and 90 min) and untreated SMX-TMP solutions.

Figure 3 shows the inhibition level of D. magna by direct contact with the untreated solution and those treated with the PEF system in which 40% of inhibition after 48 h was observed for the untreated SMX-TMP solution indicating the high toxicity of the tested solution, representing the risk of waters contaminated with these antibiotics. On the other hand, a remarkable effect was observed for both treated solutions based on the survival of the organisms (0% of inhibition after 48 h) attributed to the fact that for both cases, 45 min sample and 90 min sample, SMX and TMP were completely degraded, respectively, by the process. This fact indicates the low ecotoxicological character of the treated solutions by the PEF system when orange peel extract is added into the system.

Additionally, the use of orange peel extract in the PEF system does not imply an ecological risk since the average lethal dose (LD₅₀) of citric acid is registered between 5–11.7 g/kg (for animals), which is equivalent to...
0.026–0.061 mol/L of citric acid, values a thousand times higher than those used in the experiments (3.6 \times 10^{-5} \text{ mol/L}) (Usui et al. 2016; Oyebadejo & Solomon 2019). Furthermore, citric acid participates as a crucial component in various metabolic pathways, such as energy production and amino acid synthesis. This facilitates its degradation in the environment by vegetation, algae, and bacterial biomass (Kaur et al. 2017; Nasser et al. 2020).

Respirometry assay can be used as a standard measure of a possible inhibition respiratory process of the activated sludge, providing valuable information of the activated sludge activity and the toxicity of the subjected solutions (Copp & Spanjers 2002; Tobajas et al. 2016; Vasiliasdou et al. 2018). The respiration rate of activated sludge can be reduced in the presence of CECs as a consequence of its toxicity against the sludge microorganisms (such as heterotrophic and nitrifying bacteria). According to the results, the SMX-TMP solution causes inhibition of 75.13\%, presuming a toxic character (Figure SM6) under previous reports (Chen et al. 2019; Mendes Barros et al. 2020). On the contrary, treated solutions showed 70.37\% of inhibition for the 45 min sample and 31.67\% for 90 min sample after 25 h of the modified Zahn Wellens test. Results suggest that the produced DPs presented in the treated solutions are less toxic than their precursor molecules (SMX-TMP). Therefore, the application of the PEF system in the presence of orange peel extract eliminates these types of CECs, allowing to DPs more biodegradable and non-ecotoxic, which favors the possible releasing of the treated solutions into the environment without serious consequence to aquifer ecosystem organisms, consistent data with previous studies based on other CECs (Oropesa et al. 2017; Kovacevic et al. 2018; Libralato et al. 2018).

Antibacterial activity (AA) evolution during SMX and TMP degradation by the PEF system adding orange peel extract

In the case of antibiotics treatment, in addition to the biodegradability and ecotoxicity evaluation as degradation extent, it is important to determine the residual antibacterial activity (AA) since the previous report indicates that even if the initial molecule is degraded degradation products keep an AA evaluated, temperature: 20 °C, pH: 7.0. Conditions in the PEF system: [SMX]o: 7.90 \times 10^{-5} \text{ mol/L}, [TMP]o: 6.89 \times 10^{-5} \text{ mol/L}, pH_{\text{initial}}: 4.8 by adding citric acid present in orange peel extract (non-modified pH), [citric acid]: 3.6 \times 10^{-5} \text{ mol/L}, [Fe^{2+}]: 3.6 \times 10^{-5} \text{ mol/L}, current density: 5.19 mA/cm\text{^2}, radiation source: LED.

Fig. 3 Toxicity test of the untreated and treated solutions by the PEF system adding orange peel extract: Potassium dichromate (positive control), SMX-TMP (untreated solution) and treated solutions after 45 min and 90 min. Conditions: 10 organisms (D. magna) per test, 10 mL of reconstituted hard water, 20 mL of the solution to be treated, temperature: 20 °C, pH: 7.0. Conditions in the PEF system: [SMX]o: 7.90 \times 10^{-5} \text{ mol/L}, [TMP]o: 6.89 \times 10^{-5} \text{ mol/L}, pH_{\text{initial}}: 4.8 by adding citric acid present in orange peel extract (non-modified pH), [citric acid]: 3.6 \times 10^{-5} \text{ mol/L}, [Fe^{2+}]: 3.6 \times 10^{-5} \text{ mol/L}, current density: 5.19 mA/cm\text{^2}, radiation source: LED.

Fig. 4 Evolution of antibacterial activity (AA) along 45 min of treatment with the PEF system in the presence of citric acid reagent commercial reagent (CAreagent—dashed line) and orange peel extract (Orange ext.—solid line). Conditions: [SMX]o: 7.90 \times 10^{-5} \text{ mol/L}, [TMP]o: 6.89 \times 10^{-5} \text{ mol/L}, pH_{\text{initial}}: 4.8 by adding citric acid (non-modified pH), [citric acid]: 3.6 \times 10^{-5} \text{ mol/L}, [Fe^{2+}]: 3.6 \times 10^{-5} \text{ mol/L}, current density: 5.19 mA/cm\text{^2}, radiation source: LED.
iron complexing agent) in the simultaneous degradation of the mixture of the two antibiotics (SMX-TMP) was determined (Fig. 4).

Figure 4 shows the AA evolution, which was eliminated after 45 min of treatment, at the same time in which 100% of SMX and 77% of TMP were degraded when adding citric acid reagent grade, and 100% of SMX and 71% of TMP when adding the orange peel extract, with similar degradation percentages for SMX and TMP in both experiments, which demonstrates that citric acid performs its iron complexing function efficiently regardless of the extraction source, enhancing the simultaneous degradation of antibiotics. On the other hand, the possible additional organic matter obtained in the extract does not affect the degradation or loss of AA, highlighting the great efficiency of the application of orange peel extract as a source of natural citric acid in the PEF system for the treatment of water contaminated with CECs (Villegas-Guzman et al. 2017; Martínez-Pachón et al. 2019). The AA observed by the Kirby Bauer test was attributed to the synergistic combination of antibiotics (SMX—TMP) because the orange peel extract used during the degradation (with a citric acid concentration of 3.6×10⁻⁵ mol/L) did not show an antibacterial character (No obvious halo was detected) as other authors have shown (Fernandez-Lopez et al., 2005; El-Shawaf et al. 2012; Guo et al. 2020).

Considering that the evolution of AA could be related to the antibiotic’s transformations, the rapid elimination of antibacterial activity suggests that the synergistic effect of the combination of the antibiotics has been disrupted. The minimum inhibitory concentration (MIC) of the SMX and TMP mixture has been reported at 2.38 µg/mL of TMP:SMX against the ATCC 25,922 strain (Smanthong et al. 2015; Suhartono et al. 2016; Sági et al. 2018a, 2018b) where the two successive steps of folic acid metabolism become completely blocked due to the loss of the synergistic effect (due to the total degradation of SMX and thus loss of its 1:5 (TMP:SMX) ratio) (Smanthong et al. 2015; Suhartono et al. 2016; Castillo et al. 2018; Sági et al. 2018a, 2018b; Thiebault 2020). Therefore, results suggest that after only 45 min of treatment neigthed the powerful mixture of the antibiotic or possible antibiotic by-products are not concentrated enough to show AA. Hence, submitting the synergistic mixture of SMX and TMP to the PEF system in the presence of citric acid (independently of extraction source) turns the proposed system into a promising alternative to mitigate the increase in bacterial resistance, due to the formation of DPs without residual AA.

Conclusions

This research demonstrated the efficiency of the PEF system with citric acid present in orange peel extract (as an iron complexing agent) in the simultaneous degradation of the antibiotics SMX and TMP. Additionally, using organic waste such as orange and lemon peels as citric acid sources can mitigate air, water, and soil contamination due to the bad disposal of these agro-industrial wastes. Degradation efficiency was significantly improved by the formation of the photoactive iron-citrate complex since a photoassisted LMCT is produced causing the rapid exchange of iron from its ferric to ferrous state, which immediately undergoes into the Fenton reaction favoring the hydroxyl radical’s production. Moreover, the use of citric acid allows an efficient degradation process compared to the classic Fenton reaction which required acidic media instead of in the presence of citric acid no modification pH is required before and after the processes.

During the simultaneous degradation of SMX and TMP, a higher rate constant (k) and degradation efficiencies (Efc, at 30 min of treatment) were observed for SMX, attributed to the protonation form of the SMX at the working pH (pH 4.8 by adding citric acid, non-modified pH) favoring its breakdown at the four potential cleavage points. Additionally, treated solutions showed an increase in biodegradability character (elimination of 100% of TOC of the 90 min treated solution), a significant decrease of ecotoxicity (0% inhibition in the bioassay with D. manga after 45 min of treatment), and the loss of antibacterial activity (total loss of AA after 45 min of treatment). Results indicate the capacity of the PEF system under non-modified pH due to the addition of citric acid to promote a simultaneous degradation of SMX and TMP leading to the generation of less dangerous products than the initial antibiotics regarding the environment and possibly for human health. This way, this investigation proposes an ecological and efficient alternative for the elimination of CECs present in water, demonstrated with the tests of biodegradability, ecotoxicity, and antibacterial activity on the treated SMX and TMP solutions, evaluations that in many investigations omit, despite being an important key for the future scaling up of AOP treatments without generating a greater risk.

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- PE performed the methodology; analyzed and interpreted data; wrote the original draft and wrote, revised & edited the final manuscript.

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**Data availability** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

**Declarations**

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