

Article

Degradation of Losartan in Fresh Urine by Sonochemical and Photochemical Advanced Oxidation Processes

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Received: 30 October 2020; Accepted: 29 November 2020; Published: 3 December 2020



Abstract: In this work, the degradation of the pharmaceutical losartan, in simulated fresh urine (which was considered because urine is the main excretion route for this compound) by sonochemistry and UVC/H₂O₂ individually, was studied. Initially, special attention was paid to the degrading action of the processes. Then, theoretical analyses on Fukui function indices, to determine electron-rich regions on the pharmaceutical susceptible to attacks by the hydroxyl radical, were performed. Afterward, the ability of the processes to mineralize losartan and remove the phyto-toxicity was tested. It was found that in the sonochemical treatment, hydroxyl radicals played the main degrading role. In turn, in UVC/H₂O₂, both the light and hydroxyl radical eliminated the target contaminant. The sonochemical system showed the lowest interference for the elimination of losartan in the fresh urine. It was established that atoms in the imidazole of the contaminant were the moieties most prone to primary transformations by radicals. This was coincident with the initial degradation products coming from the processes action. Although both processes exhibited low mineralizing ability toward losartan, the sonochemical treatment converted losartan into nonphytotoxic products. This research presents relevant results on the elimination of a representative pharmaceutical in fresh urine by two advanced oxidation processes.

Keywords: advanced oxidation process; elimination routes; fresh urine; pharmaceutical degradation; processes selectivity; theoretical analysis

1. Introduction

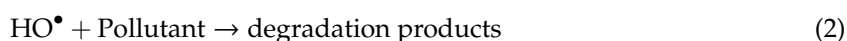
Losartan was the first commercialized angiotensin II antagonist pharmaceutical. This is an antihypertensive consumed widely around the world [1]. Urine is the main route of excretion of losartan from the human body, ~35% of the oral dose is expelled without alterations [2], reaching the wastewater systems. In fact, losartan has been determined in ranges of 0.0197–2.76 µg L⁻¹ in wastewater treatment plants influent (WWTP) [3,4]. This indicates that losartan is not effectively removed by the conventional systems in WWTP.

In the aquatic environment, losartan can promote noxious effects on organisms, and it can be transformed into more toxic and persistent substances [5–7]. The recalcitrance to conventional treatment systems, negative environmental impact, and high excretion of losartan in urine lead

to consider alternative options to eliminate this pharmaceutical from aqueous media. Particularly, the application of degradation processes should be focused on primary contamination sources, such as human fresh urine.

Advanced oxidation processes (AOPs, which are based on the production and utilization of radical species to attack pollutants) are interesting options for losartan elimination from urine, to avoid entering into the wastewater systems. Indeed, AOPs such as UVC/H₂O₂ and sonochemistry have been successfully applied for the elimination of different pharmaceuticals in diverse aqueous matrices [8].

In the UVC/H₂O₂ process, UVC light (e.g., photons of 254 nm) promotes the homolysis of hydrogen peroxide, generating hydroxyl radicals (Equation (1)) available to degrade organic contaminants (Equation (2)) [9].



Meanwhile, the sonochemical process, which uses high-frequency ultrasound waves “)))”, produces hydroxyl radicals from the breaking of water molecules and dissolved oxygen (Equations (3)–(5)) [10].



It should be mentioned that some previous works have evidenced the high potentiality of AOPs to eliminate pollutants in urine [11–20]. However, until now, the treatment of losartan in fresh urine, considering the intrinsic degradation abilities of UVC/H₂O₂ and sonochemistry has not been reported. Moreover, computational analyses about the reactivity of this pharmaceutical toward hydroxyl radical species or phytotoxicity tests of the treated water have not been considered. Thereby, the present research was focused on the losartan treatment in fresh urine by UVC/H₂O₂ and ultrasound individually. The selectivity of the processes toward the pollutant degradation in the urine matrix was established. Firstly, special attention was paid to the action routes of the processes involved in the elimination of losartan. Besides, computational analyses using DFT/Fukui functionals were performed to determine the most regions on losartan reactive to hydroxyl radicals, and these theoretical results were related to primary degradation products coming from the processes action. Additionally, considering the possible reuse of treated urine for water irrigation extra analyses such as mineralization and phytotoxicity were carried out.

2. Materials and Methods

2.1. Reagents

Losartan tablets (50 mg each) were purchased from La Santé S.A. Acetonitrile (HPLC grade), ammonium heptamolybdate (>99.3%), methanol (HPLC grade), potassium iodide (>99.5%), potassium perchlorate (>99.5%), sodium acetate (>99%), sodium chloride (99.9%), sodium dihydrogen phosphate (>99.0%), sodium hydroxide (>99.0%), sodium sulfate (>99.0%), sulfuric acid (95–97%), and urea (>99.0%) were provided by Merck. Ammonium chloride (>99.8%), calcium chloride dihydrate (>99.0%), ferrous sulfate heptahydrate (>99.0%), formic acid (99.0%), hydrogen peroxide (30% w/v), and magnesium chloride hexahydrate (>99.0%) were provided by PanReac. All the reagents were used as received.

The solutions were prepared using distilled water. In all cases, the initial losartan concentration was 43.38 µM (i.e., 20 mg L^{−1}, which is a plausible amount of the antihypertensive excreted in human urine [21]). The fresh urine used for the tests was prepared according to Table 1. The fresh urine was used immediately after its preparation and the pH was adjusted to 6.1.

Table 1. Composition of fresh urine ¹.

Compound	Concentration (M)
Urea	0.2664
NaCH ₃ COO	0.1250
Na ₂ SO ₄	0.01619
NH ₄ Cl	0.03365
NaH ₂ PO ₄	0.02417
KCl	0.05634
MgCl ₂	0.003886
CaCl ₂	0.004595
NaOH	0.00300
pH: 6.1	

¹ Composition taken from Amstutz et al. [22].

2.2. Reaction Systems

For the UVC/H₂O₂ process, a homemade aluminum reflective reactor box equipped with UVC lamps (OSRAM HNS[®], with the main emission peak at 254 nm, 60 W) was used (Figure 1a). Losartan solutions (50 mL) were placed in beakers under constant stirring. Meanwhile, the sonochemical treatments were performed in a Meinhardt cylindrical glass reactor containing 250 mL of losartan solution. Ultrasonic waves of 375 kHz and 106.3 W L⁻¹ (actual ultrasound power density determined by the calorimetric method) were emitted from a transducer at the bottom of the reactor (Figure 1b). For both processes, the experimental conditions (i.e., reagents concentrations, ultrasonic frequency, light power) were selected based on previous works [23,24].

2.3. Analyses

2.3.1. Chromatographic Analyses

Losartan evolution was followed by using a UHPLC Thermo Scientific Dionex UltiMate 3000 instrument equipped with an Acclaim[™] 120 RP C18 column (5 µm, 4.6 × 150 mm) and a diode array detector (operated at 230 and 254 nm). The mobile phase was methanol (10% v/v), acetonitrile (44% v/v), and formic acid (46% v/v, 10 mM, and pH 3.0) at a flow of 0.6 mL min⁻¹. Primary transformation products were elucidated by HPLC–MS analyses in our previous work [24]. For the chromatographic analyses, samples of 0.5 mL were periodically taken from the reaction systems (the total taken volume was always lower than 10% of the initial volume in each system). All experiments were performed at least in duplicate.

2.3.2. Oxidizing Species Accumulation

Accumulation of sonogenerated hydrogen peroxide was estimated by iodometry [25]. An aliquot of 600 µL from the reactors was added to a quartz cell containing 1350 µL of potassium iodide (0.1 M) and 50 µL of ammonium heptamolybdate (0.01 M). After 5 min, the absorbance at 350 nm was measured using a Mettler Toledo UV5 spectrophotometer.

2.3.3. Mineralization Determinations

Mineralization degree was established as removal of total organic carbon (TOC). TOC content of the samples was measured using a Shimadzu LCSH TOC analyzer (previously calibrated), according to Standard Methods 5310B (high-temperature combustion method), in which the water sample is homogenized and injected into a heated reaction chamber packed with an oxidative catalyst (platinum spheres). The water is vaporized, and the organic carbon is oxidized to CO₂. The CO₂ from oxidation is transported by a carrier gas stream and is then measured using an IR detector. The TOC analyzer performed the catalytic combustion at 680 °C using high-purity oxygen gas at a flow rate of 190 mL min⁻¹. The apparatus had a nondispersive infrared detector. For the TOC analyses, samples of

7.0 mL were taken from the reaction systems, and for the TOC analyses, the experiments were carried out independently from the initial tests of degradation (to avoid retire amounts higher than 10% of the initial volume in each system).

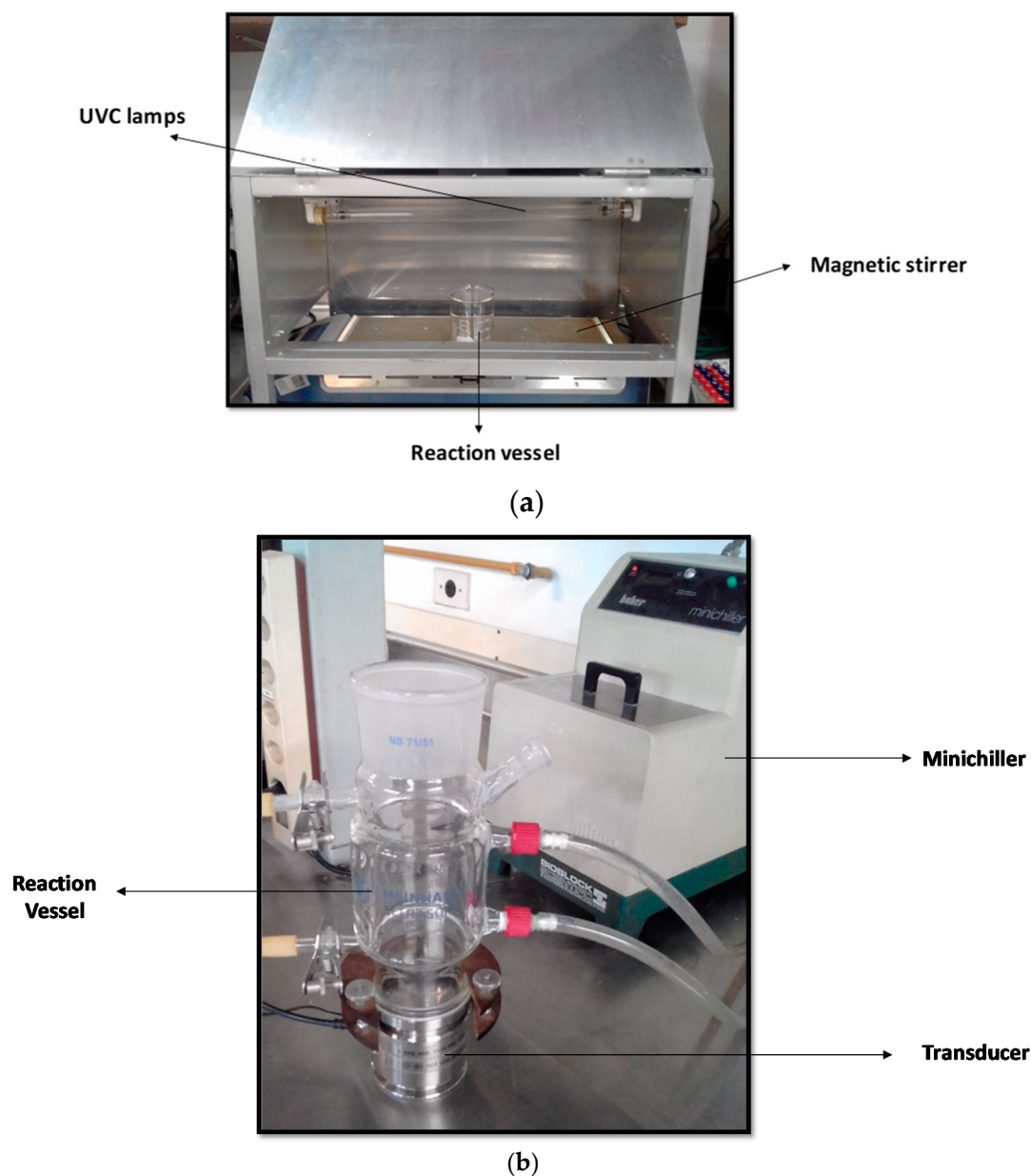


Figure 1. Reactors used in the degradation of losartan. (a) UVC/H₂O₂ process; (b) sonochemical treatment.

2.3.4. Phytotoxicity Tests

Toxicity against radish seeds (*Raphanus sativus*) was considered. For such purpose, the ratio of seeds germinated (RSG, Equation (6)) and the ratio of root length (RRG, Equation (7)) were determined. As a phytotoxicity parameter, the germination index (GI, Equation (8)) was assessed according to N.J. Hoekstra et al. [26]. For the phytotoxicity tests, samples of 5.0 mL were taken.

$$\text{RSG (\%)} = \frac{\text{Number of seeds germinated in sample}}{\text{Number of seeds germinated in control}} \times 100 \quad (6)$$

$$\text{RRG (\%)} = \frac{\text{mean root length in sample}}{\text{mean root length in control}} \times 100 \quad (7)$$

$$GI(\%) = \frac{RSG \times RRG}{100} \quad (8)$$

2.3.5. Computational Analyses

For the determination of regions on losartan most susceptible to the attack of radical species and electrophilic oxidants, computational analyses were performed by applying the framework of functional density theory (DFT). The antihypertensive structure was optimized with the B3LYP hybrid functional density [27], 6-311++G(2d,2p) method [28] using the dielectric constant for water to simulate the aqueous environment. Thus, f^+ and f^- (i.e., nucleophilic and electrophilic Fukui function indices) values and the average between such values (f_{ave}) were calculated.

3. Results

3.1. Treatment of Fresh Urine Loaded with Losartan

The two processes were individually applied to degrade losartan in the simulated fresh urine (FU, whose composition is presented in Table 1). In addition to degradation in urine, losartan was also treated in distilled water (DW). The degradations followed pseudo-first-order kinetics, and their respective rate constants (k) in both matrices were established (see Figure S1 in Supplementary material). Then, the ratio between the degradation rate constants ($Rk: k_{FU}/k_{DW}$) was calculated. This Rk parameter is an indicator of both the selectivity of processes toward the antihypertensive degradation in the complex matrix and the inhibitory effect of losartan elimination caused by the fresh urine components. Table 2 contains the k and Rk values for each process.

Table 2. Kinetic constants (in min^{-1}) determined in the degradation of losartan in fresh urine (k_{FU}) and distilled water (k_{DW}) for each advanced oxidation processes¹.

AOP	k_{DW} (R^2)	k_{FU} (R^2)	$Rk = k_{FU}/k_{DW}$
Sonochemistry	0.0549 (0.9972)	0.0437 (0.9975)	0.796
UVC/ H_2O_2	0.0532 (0.9987)	0.0245 (0.9981)	0.461

¹ Experimental conditions: [Pollutant] = 43.38 μM , pH: 6.1. Sonochemistry: 106.3 W L^{-1} (375 kHz). UVC/ H_2O_2 : [H_2O_2] = 500 μM , 60 W.

3.2. Degradation Routes of Losartan (LOS) in Different AOPs

To elucidate the routes of the processes action, some specific experiments and measures in distilled water were carried out and results were compared to those obtained in the urine to understand the effect of the matrix components. Results for each treatment in distilled water are detailed in the following subsections.

3.2.1. Action Routes of the UVC/ H_2O_2 Process

The UVC/ H_2O_2 process may include the action of light of 254 nm, hydrogen peroxide, and radicals. To identify the routes involved in the process, control tests for the individual effects of UVC and H_2O_2 were carried out. Figure 2 compares the degrading effect of individual components of the process in distilled water, plus the losartan elimination in both distilled water and fresh urine (FU) by UVC/ H_2O_2 .

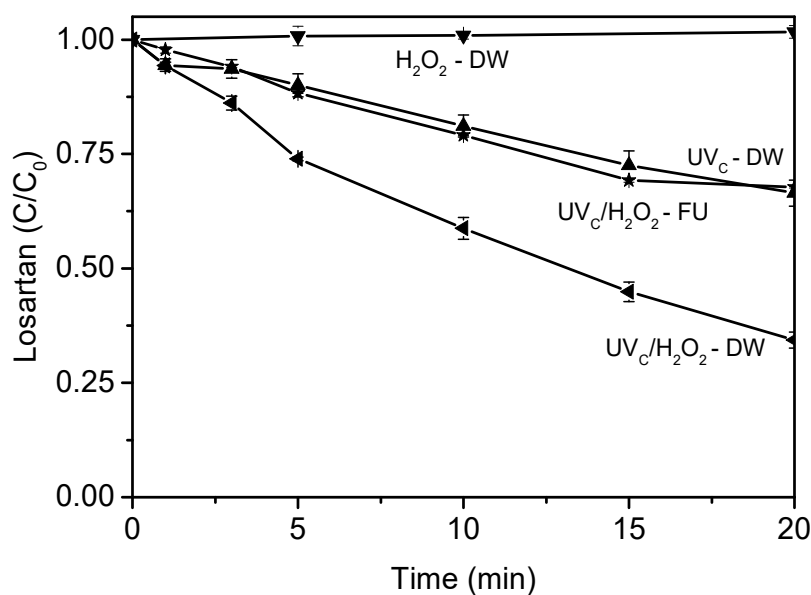


Figure 2. Determination of action routes of the UVC/H₂O₂ process on losartan degradation in distilled water (DW) and fresh urine (FU). Conditions: [LOS] = 43.38 μ M, [H₂O₂] = 500 μ M, UVC light: 60 W, pH: 6.1.

3.2.2. Degradation Routes Involved in the Sonochemical Treatment

Figure 3 depicts the degradation of LOS in both distilled water and fresh urine (FU) by ultrasound. To determine the degradation route in the sonochemical process, the accumulation of sonogenerated hydrogen peroxide in the presence and absence of the pollutant was also measured (results also presented in Figure 3).

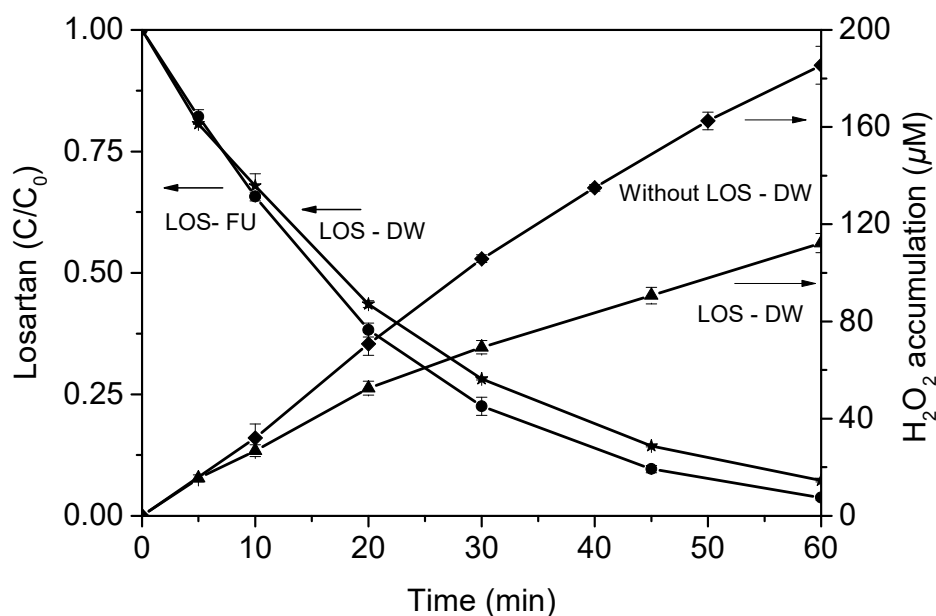


Figure 3. Determination of action routes of the sonochemical treatment on losartan in distilled water (DW) and fresh urine (FU). Conditions: [LOS] = 43.38 μ M, 106.3 W L⁻¹ (375 kHz), pH = 6.1.

3.3. Analysis of Losartan Susceptibility to Attacks by Radical Species

To establish electron-rich regions on losartan susceptible to attacks of radicals, computational analyses were performed [29–31], and the results from the theoretical calculations were used to better understand the formation of the degradation intermediaries. Table 3 depicts the moieties on

losartan having more electron density according to Fukui function indices. In addition to these indices, other related quantities such as local softness and global hardness were determined, the values of which were 17.513 and 0.0571 eV, respectively. Moreover, a donor–acceptor diagram (DAM), to show the donor capability of the pharmaceutical concerning hydroxyl radical ($\text{HO}\cdot$), hydroperoxyl radical ($\text{HOO}\cdot$), and superoxide anion radical ($\cdot\text{O}_2^-$), was elaborated (Figure S2).

Table 3. Results of computational analysis for losartan ¹.

Structure and Numeration	Atoms	Fukui Function Indices		
		f^-	f^+	f_{ave}
	1 C	0.045	0.054	0.049
	2 C	−0.027	0.005	−0.011
	3 C	0.066	−0.022	0.022
	4 C	0.006	0.004	0.005
	5 C	0.055	−0.015	0.020
	6 C	0.004	−0.007	−0.002
	7 C	−0.103	−0.012	−0.058
	8 C	−0.100	−0.031	−0.066
	10 C	−0.112	0.160	0.024
	11 C	−0.094	−0.088	−0.091
	12 C	0.160	−0.104	0.028
	13 C	−0.050	−0.045	−0.048
	14 C	−0.660	0.117	−0.272
	15 C	0.402	0.126	0.264
	16 C	0.007	0.009	0.008
	17 C	0.000	−0.044	−0.022
	18 C	1.841	1.119	1.480
	19 C	−0.661	−0.739	−0.700
	21 C	0.216	−0.116	0.050
	22 C	0.008	−0.141	−0.067
	1 N	0.053	−0.005	0.024
	2 N	−0.043	0.003	−0.020
	3 N	0.016	0.005	0.011
	4 N	0.022	0.000	0.011
	5 N	−0.258	0.044	−0.107
	6 N	−0.066	0.179	0.057
	Cl	0.061	0.058	0.060
	O	0.061	0.000	0.031

¹ Boxes in gray color contains atoms having high values for the Fukui function indices. It should be mentioned that the computational calculations were done for LOS in water.

3.4. Mineralization and Toxicity Evolution in Distilled Water

The ability of the two processes to mineralize losartan was analyzed. The experiments were carried out in distilled water to avoid interfering effects of matrix and understand the fundamental aspects of the mineralizing action of the processes. We can mention that if mineralization is carried out in the fresh urine matrix, the urea that has a higher concentration masks the contribution of losartan, making it difficult to evaluate the mineralization of the contaminant under the oxidation processes. The TOC removal, at different treatment times normalized concerning the time necessary to completely degrade losartan in distilled water, was evaluated. Two different treatment times were considered: T (when losartan is 100% degraded) and 2T (the double of time required to 100% remove the antihypertensive). Results for mineralization are presented in Figure 4A.

On the other hand, toxicity modifications exerted by treatment with ultrasound and UVC/ H_2O_2 to the distilled water loaded with losartan were tested. Radish seeds (*Raphanus sativus*) were used as probe organisms. The growth index (GI) was used as the toxicity measure (phytotoxicity). Phytotoxicity was established at 2T of treatment for both processes (Figure 4B).

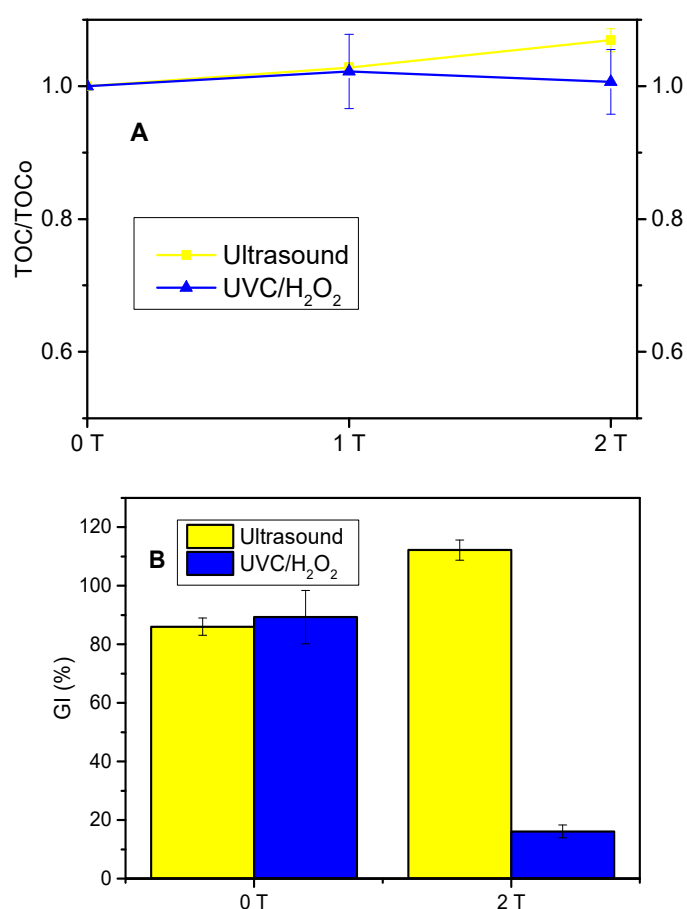


Figure 4. Extent of advanced oxidation treatments in distilled water. (A) Mineralization of losartan during the application of different processes; (B) evolution of the toxicity of losartan treated solutions against radish seeds. Note: the time was normalized concerning the time necessary to completely degrade losartan. Then, T is the time when losartan is 100% degraded, and 2T means the double of time required to 100% remove the antihypertensive. Experimental conditions as described in Figures 2 and 3.

4. Discussion

4.1. Treatment of Fresh Urine Loaded with Losartan

The R_k values for the ultrasound and UVC/H₂O₂ were 0.79 and 0.46, respectively (Table 2). It can be noted that ultrasound had the highest value for R_k ; indicating that the losartan degradation through such process is affected at a low extent (21%) by urine matrix components. Meanwhile, for UVC/H₂O₂, the urine matrix presented a moderate inhibition (54%) of the antihypertensive elimination. These results suggest that the matrix components decreased the efficiency of the processes, which can be related to modifications of degradation routes. The explanations are presented in detail in the next subsections.

4.2. Degradation Routes of Losartan (LOS) in the Different AOPs

4.2.1. UVC/H₂O₂ Process

After the application of the individual components of the UVC/H₂O₂ system to LOS, it was found that hydrogen peroxide (even at 500 μ M) did not induce significant removal of losartan (less than 5% elimination after 20 min of treatment). On the contrary, the treatment with the UVC light degraded $\approx 33.5\%$ of the antihypertensive at 20 min of irradiation. The ultraviolet spectrum of losartan shows light absorption at 254 nm (Figure S3), which suggests that this molecule can be transformed by the UVC light. This is corroborated with the relative high photodegradation coefficient for losartan at UVC

light (Cp, 123–190 L Einstein⁻¹ cm⁻¹ [32]). In fact, organic compounds having Cp values higher than 40 L Einstein⁻¹ cm⁻¹ can experience direct photolysis [33], which is currently related to the presence of aromatics rings, π -conjugated systems, and heteroatoms [34], as contained in the losartan structure (e.g., biphenyl, imidazole, and tetrazole). These aspects explain the losartan degradation by the UVC light. When losartan was treated by the complete UVC/H₂O₂ system, 65.7% of removal after 20 min was observed (Figure 2). The significant improvement of losartan elimination with the combination of hydrogen peroxide and UVC suggests the participation of radical species in the pollutant degradation. Indeed, as indicated earlier, the UVC/H₂O₂ process generates hydroxyl radical by homolytic rupture of peroxide by UVC light (Equation (1)). Hence, it can be indicated that in this process, the main action routes are the UVC photolysis and the attacks of hydroxyl radicals.

4.2.2. Ultrasound Process

The sonochemical system has three reaction zones: the inner part of cavitation bubbles, where volatile molecules are pyrolyzed by high temperatures and pressures [35–37]; the interfacial region, where hydrophobic substances can react with the sonogenerated hydroxyl radical [38]; the solution bulk, where a small number of hydroxyl radical can react with hydrophilic compounds [39].

When losartan in distilled water was treated by high-frequency ultrasound (375 kHz and 106.3 W L⁻¹), this process led to 97% of pollutant concentration reduction after 60 min of treatment (Figure 3). Since losartan is a nonvolatile compound, degradation by pyrolysis is negligible. Thus, the antihypertensive elimination would be associated with the attack of hydroxyl radicals. On the other hand, it is well-known that during the sonochemical process, hydrogen peroxide is formed by the combination of hydroxyl radicals (Equation (9)). Indeed, H₂O₂ production is an indicator of pollutant interaction with sonochemically formed HO• [40]. Thereby, to prove the participation of sonogenerated HO• in the pollutant degradation, the accumulation of H₂O₂ was determined. Figure 3 shows that the accumulations of H₂O₂ after 60 min of sonication in the absence and the presence of losartan were $\approx$ 180 and $\approx$ 110 μ M, respectively.



The oxidation of losartan by the accumulated hydrogen peroxide was discarded because pollutant removal by H₂O₂ even at 500 μ M was not observed (Figure 2). Then, the lower accumulation of hydrogen peroxide in the presence of losartan is an indicator of the reaction between the HO• and losartan. Moreover, due to the hydrophobic character of losartan (denoted by its high Log K_{OW} value, which is >4.0) [24]), its degradation is expected to occur in the interfacial zone of the system [41] by the sonogenerated hydroxyl radicals.

4.2.3. Understanding the Interference of Urine Matrix

Based on the degradation routes previously established, the interference of the urine matrix on the pharmaceutical degradation by the considered processes can be rationalized. During the application of UVC/H₂O₂ (which has both radical and photolytic routes), the antihypertensive removal was inhibited (by $\approx$ 55%) by the urine matrix components (see R_k value in Table 2). This was related to two aspects: the shielding of UVC light and scavenging of hydroxyl radicals. The shielding effect of the urine matrix was demonstrated through the evaluation of the only action of UVC light on losartan in both matrices (i.e., urine and distilled water), which showed a R_k value of 0.8 (Figure S4).

In turn, it is recognized that the inorganic anions such as chloride or bicarbonate, and organic substances like urea and acetate, present in the fresh urine, have relatively high rate constants with hydroxyl radicals (see Table 4), and as a result, they also affect the losartan degradation. It can be remarked the significant contribution of UVC photolysis to the degradation of losartan, as well as to the relative low interference of urine components for the light absorption (see R_k value for photolysis in Figure S4). Considering these findings, a scheme of losartan degradation by UVC/H₂O₂ was proposed

in Figure 5a. It can be mentioned that the action of the photogenerated hydroxyl radicals induces transformations to losartan (such topic discussed below in Section 4.3), which is also schematized in this figure.

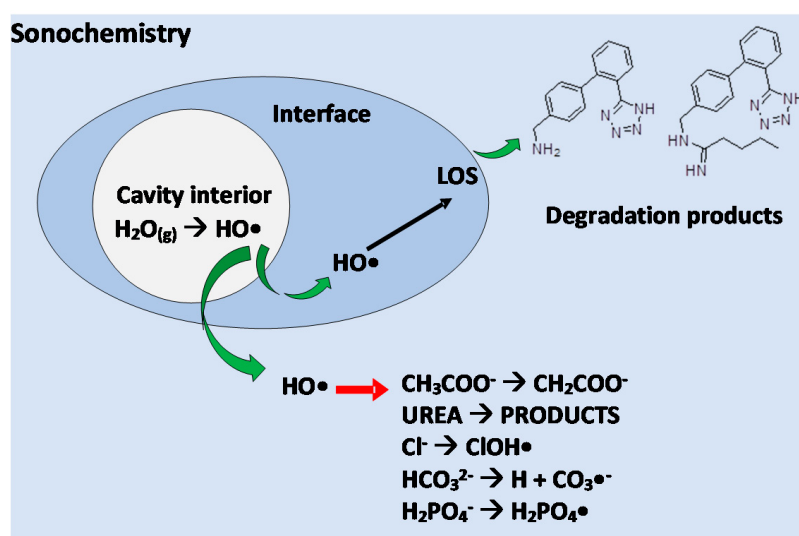
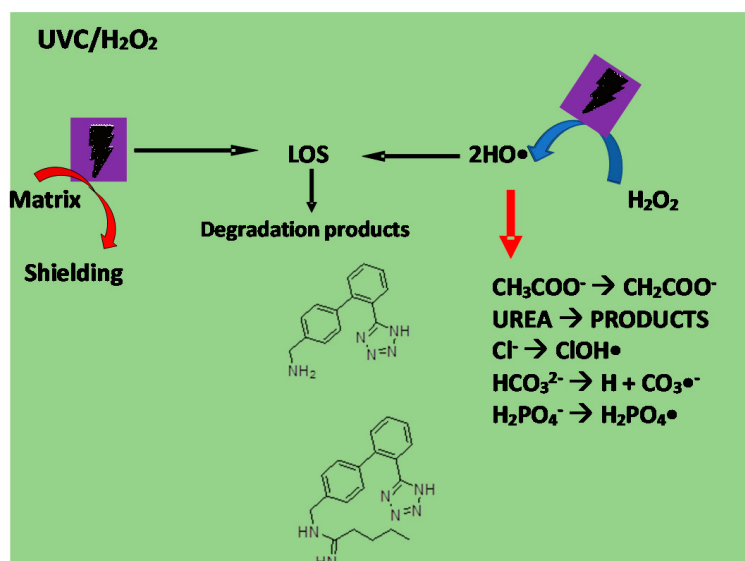


Figure 5. Scheme of degradation routes and interfering action of the urine components on the tested processes and generation of primary degradation products. (a) UVC/H₂O₂; (b) sonochemical treatment. Note: black arrows mean degradation routes and red arrows represent interfering action of the urine components.

Table 4. Rate constants of the reactions between hydroxyl radical and the diverse components of fresh urine.

Reaction	Second-Order Rate Constant (k^{2nd} , $M^{-1} s^{-1}$)	References
$HO^{\bullet} + Cl^{-} \rightarrow ClOH^{\bullet-}$	4.3×10^9	[42]
$HO^{\bullet} + H_2PO_4^{-} \rightarrow HO^{-} + H_2PO_4^{\bullet}$	$\approx 2 \times 10^4$	[43]
$HO^{\bullet} + CH_3COO^{-} \rightarrow H_2O + CH_2COO^{\bullet-}$	7.0×10^7	[44]
$HO^{\bullet} + H_2NCONH_2 \rightarrow \text{products}$	7.9×10^5	[43]
$HO^{\bullet} + HCO_3^{-} \rightarrow CO_3^{\bullet-} + H_2O$	8.5×10^6	[45]

In the case of the sonochemical process, for the rationalization of the low inhibitory effect of the urine matrix for the degradation of losartan (Figure 3), we must consider both the degradation route of losartan and the hydrophobic/hydrophilic nature of the substances in the matrix. The urine components are very hydrophilic, as evidenced by their Log Kow values (which are close to zero or negative, see Table S1). Thus, such components are mainly placed in the bulk of the solution and losartan is in the interfacial zone (where there is a high concentration of the sonogenerated $\text{HO}^\bullet$). Consequently, this pharmaceutical is slightly affected by the ions and/or organic compounds of the urine matrix (as schematized in Figure 5b). It should be indicated that the action of the sonogenerated hydroxyl radicals modifies the structure of losartan (such topic discussed below in Section 4.3), which is also schematized in this figure.

4.3. Analysis of Losartan Susceptibility to Attacks by Radical Species

The values of the hardness and softness for losartan indicate its high donor capacity. This is advantageous for attacks of the radicals to the pharmaceutical. Such behavior was also observed in the DAM (Figure S2), which shows that the losartan molecule has a better donor capacity concerning hydroxyl radical, hydroperoxyl radical, and superoxide anion radical. Besides, the computational analyses revealed that atoms on the imidazole moiety (15C, 18C, and 6N), aromatic rings (3C, 5C, 10C, and 12C), tetrazole (1C, 1N, 3N, and 4N), alcohol (O), and alkyl chain (21C) on losartan have the highest values for f_{ave} (this suggests that such regions on losartan are the most susceptible to transformations by radicals such as $\text{HO}^\bullet$). Indeed, we can mention that the atom with the highest Fukui function indices is more reactive to hydroxyl radical (the main degrading radical species in the tested AOPs). In the case of losartan, its C18 atom presents a f_{ave} of 1.480, the highest value concerning all the atoms in the entire molecule. This behavior can be associated with the stabilization by resonance among the imidazole ring for the radical generated (Figure S5). In contrast, the attack of hydroxyl radical on the C1 atom in the tetrazole ring for the hydroxyl radical does not lead to such stabilization (Figure S6). In fact, the Fukui function indices for the tetrazole system are smaller than for the imidazole ring. Additionally, in a previous work from our research team, it was reported that for losartan molecule, the HOMO is located in the imidazole ring, whereas LUMO is on the tetrazole ring [46].

The primary products of losartan degradation in distilled water present a good agreement to the computational analysis on reactive regions of losartan (see Table S2 and Table 3). In the sonochemical treatment, three transformation products coming from imidazole ring rupture (TP1, TP2, and TP3), several isomers of biphenyl hydroxylation (TP4a-f), and one product of alcohol moiety oxidation (TP5) have been observed. Additionally, products of hydroxylation/oxidation of the alkyl chain on the antihypertensive have been found (TP6 and TP7, Table S3). Furthermore, analogous primary transformations of losartan induced by UVC/ H_2O_2 and photo-Fenton were recently reported. Kaur and Dulova also found the formation of TP2 TP3, TP4, TP5, TP6, and TP7, in addition to TP8 (product of hydroxylation at the imidazole ring) and TP9 (transformation coming from a chlorine removal of the imidazole structure, see Table S3) [4]. In this sense, the region attackable by the hydroxyl radical, indicated by theoretical results correlates with the reported primary transformation products. This highlights the usefulness of computational analysis as a tool to establish the regions on losartan susceptible to degradation by the radicals from the AOPs.

4.4. Mineralization and Toxicity Evolution

The ability of the two processes to mineralize losartan in distilled water was tested, showing that none of these processes transformed losartan into carbon dioxide, water, and inorganic ions even at longer treatment times (2T) (Figure 4A). These results can be understood based on the degradation routes involved in each process. In the case of ultrasound, the attack of sonogenerated radicals in the interfacial zone (main route above described) led to hydroxylations/oxidations and rupture of pollutant molecules (see Table S3), which typically generates products more hydrophilic than the parent compound [47]. Hence, due to the hydrophilic nature of losartan degradation products, they are

placed far away from the cavitation bubble, and consequently far away from the sonogenerated $\text{HO}^\bullet$. Thereby, the mineralization of losartan by ultrasound is not observed.

In the case of losartan elimination by the UVC/ H_2O_2 process, it was noted the high participation of light (Section 4.2.1). Although UVC has a strong degrading ability through isomerizations or carbon-heteroatoms bond cleavages, its mineralizing power is very low [48]. On the other hand, although the mineralizing ability of $\text{HO}^\bullet$ is widely recognized, under the tested conditions (moderate H_2O_2 concentration; i.e., 500 μM), the formed amount of such species seems to be not enough to reach some mineralization of losartan. Due to the nonmineralizing ability of ultrasound and UVC/ H_2O_2 toward LOS, it was necessary to test the toxicity. To establish the potential reuse of the treated urine for irrigating crops; toxicity tests against radish seeds (*Raphanus sativus*) were performed (Figure 4B). It should be noted that the UVC/ H_2O_2 process inhibits the germination of the seeds, this is associated with noxious substances generated in this system. In fact, recent research on losartan degradation by UVC/ H_2O_2 process also evidenced that toxicity of solutions against *Daphnia magna* and *Desmodesmus subspicatus* augmented after the treatment [49].

Unlike UVC/ H_2O_2 , in the sonochemical process, the growth of the radish seeds increased with treatment (see 2T in Figure 4B). This suggests that the losartan by-products generated at large treatment periods of the sono-treatment are beneficial/less toxic for the indicator organism than the parent compound. Such results are coincident with several studies, which reported that the treatment of polluting substances using ultrasonic irradiation reduces the toxicity of solutions [50]. It must be indicated that although both UVC/ H_2O_2 and sonochemistry can generate similar primary transformation products by hydroxyl radical attacks to losartan in distilled water (Section 4.3) at long treatment periods they may differ. Additionally, it must be considered that in the sonochemical process mainly acts hydroxyl radicals, whereas in the UVC/ H_2O_2 both the radicals and UVC light are responsible for pollutant degradation (Section 4.2.2). Then, the observed differences in toxicity between both processes would be associated with their degradation mode. In the UVC/ H_2O_2 , the noxious substances could come from the action of UVC light on losartan or its primary degradation products (indeed, a previous work about the treatment of other emerging concern pollutants by UVC also reported the generation of toxic products for some organisms produced by this irradiation [32]).

5. Conclusions

It can be concluded that this research provides relevant information to understand the elimination of a representative pharmaceutical in fresh urine by two advanced oxidation processes having different nature (a photochemical treatment and other sonochemical system). The application of ultrasound and UVC/ H_2O_2 individually, for the removal of the model pharmaceutical (antihypertensive losartan) in simulated fresh urine, showed that the sonochemical process was little affected by the urine matrix, exhibiting a high selectivity ($R_k = 0.79$) for the removal of losartan, which was related to degradation of the pharmaceutical at the interface of the cavitation bubble by the action of $\text{HO}^\bullet$. Meanwhile, the UVC/ H_2O_2 process experienced moderate impacts of the matrix ($R_k = 0.46$) on the removal of losartan, because their degradation routes involved both photolysis and radical attacks. In turn, both ultrasound and UVC/ H_2O_2 processes showed no mineralization of the pollutant in distilled water. Nevertheless, differently to UVC/ H_2O_2 , the sonochemical system transformed losartan into nonphytotoxic products (evidencing the potential reuse of sono-treated urine to irrigate crops). This illustrates the positive potentiality of ultrasound for the treatment of pharmaceuticals with hydrophobic characteristics in the simulated fresh urine. On the other hand, the computational analyses indicated that atoms on imidazole moiety on losartan were the most susceptible to transformations by the radical species. Such analysis was in good agreement with primary degradation products coming from UVC/ H_2O_2 and sonochemical treatments, evidencing that theoretical methods are a useful tool to predict and rationalize the attacks of degrading species in the considered AOPs. Finally, it must be mentioned that losartan degradation was carried out at a pH value of 6.1; however, urine ranges from 4.5 to 8, and the modification of such parameter may change the results about the degradation of

pharmaceuticals by the AOPs. Thus, the effect of the urine pH should be evaluated in more detail in future studies.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4441/12/12/3398/s1>, Text S1: Determination of pseudo-first-order kinetic constants (k), Figure S1: Determination of the kinetic constants, Figure S2: Donor–acceptor diagram (DAM), Figure S3: Absorption spectra of losartan, Figure S4: Comparison of R_k for UVC/H₂O₂ and UVC alone, Figure S5: Resonance hybrid, Figure S6: Hydroxyl radical attack to the tetrazole ring, Table S1: Log K_{OW} of losartan and the components of urine, Table S2: Primary transformation products of losartan during sonochemical treatment, Table S3: Additional products of losartan transformation by UVC/H₂O₂ and photo-Fenton.

Author Contributions: Conceptualization: R.A.T.-P. and E.A.S.-G.; methodology: J.F.G.-L. and E.A.S.-G.; software: Y.Á.-T.; formal analysis: J.F.G.-L. and E.A.S.-G.; investigation: J.F.G.-L.; resources: R.A.T.-P. and Y.Á.-T.; writing—original draft preparation: J.F.G.-L.; writing—review and editing: E.A.S.-G., R.A.T.-P. and Y.Á.-T.; supervision: Y.Á.-T. and R.A.T.-P.; project administration: Y.Á.-T. and R.A.T.-P.; funding acquisition: Y.Á.-T. and R.A.T.-P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by UNIVERSIDAD SANTIAGO DE CALI, project DGI No. 934 621120-G04; Universidad de Antioquia UdeA; MINCIENCIAS COLOMBIA (before named COLCIENCIAS), grant “Jóvenes investigadores por la Paz 2018- J19-18-1, 5381” and project No. 111577757323.

Acknowledgments: Researchers from Grupo de Investigación en Remediación Ambiental y Biocatálisis (GIRAB) thanks Universidad de Antioquia UdeA for the support provided through “PROGRAMA DE SOSTENIBILIDAD”; E. A. Serna-Galvis thanks MINCIENCIAS COLOMBIA for his PhD fellowship during July 2015–June 2019 (Convocation 647 de 2014).

Conflicts of Interest: The authors declare no conflict of interest.

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