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Abstract

In the past few years, pharmaceutical compounds have appeared as emerging category of environmental pollutants. These microcontaminants can exhibit adverse acute and chronic effects on natural flora and fauna. The detection of pharmaceutical residues in surface waters (rivers, streams, and lakes), seawater, groundwater, soils, sludges, and wastewater treatment plants has been widely documented. Advanced oxidation processes (AOPs) have garnered extensive attention for abetment of emerging pharmaceutical contaminants and minimize their associated environmental risks. Given a clean and efficient oxidizing agent, hydrogen peroxide (H_2O_2) has been extensively utilized in AOPs. Integration of H_2O_2 with different substrates/catalysts boosts up its oxidizing features. H_2O_2 may be combined with ozone, UV, Fe^{2+}/Fe^{3+} ions (Fenton and photo-Fenton-like processes) and with heterogeneous systems (TiO_2). The generation of strong oxidative hydroxyl radical ($HO_{\bullet}$) in H_2O_2-assisted AOP by various types of activating methods is likely to play a critical role in micropollutants treatment, reusing, and risk reduction. Advanced oxidation process catalyzed by H_2O_2 may consists of combination of following catalysts: UV/H_2O_2, O_3/UV/H_2O_2, H_2O_2/TiO_2/UV, Fe^{2+}/H_2O_2, Fe^{2+}/H_2O_2 /UV, Electro –Fenton, O_3/H_2O_2). In this review, we have discussed current

reports on various hydrogen peroxide-based advanced oxidation processes for degradation of pharmaceutical pollutants of emerging concern. The ongoing challenges, conclusive remarks and imperative future directions are also outlined.

Keywords: Hydrogen-based catalyst; Pharmaceutical pollutants; Fenton reaction; Water treatment; Photocatalytic degradation

Introduction

Pharmaceutical products contained several pollutants after disposal in water bodies that include drugs, medicines, empty drugs vials and others (Aguilar-Pérez et al., 2021). These pharmaceutical wastes originate from two different sources one from the production unit and second from consumption unit like hospitals and medicals centers (Voudriaz et al., 2012; Vallini et al., 2010). The dumping of these waste needs special treatment at high temperature to avoid maximum contaminations chances. This method is used in some developing countries but not in others. During their disposal in outer environment generate great risk for water bodies. These contaminants can be mixed with water and produce some diverse effects on human health and biological balance (Torres et al., 2020; Américo-Pinheiro et al., 2021; Storto et al., 2021). This includes in toxicity of aquatic medium, development of resistance in pathogenic bacteria, endocrine disruption, acute and chronic damage, and hormonal disruption (Emmanuel et al., 2005; Wu et al., 2012; Allagui et al., 2015; K'oreje et al., 2016; Bilal et al., 2019; Aguilar-Pérez et al., 2020; Aguilar-Pérez et al., 2021). Due to their persistent nature in aquatic region conditions change from bad to worse for their removal as conventional techniques are not enough for this purpose (Achilleos et al., 2010; Mozia and Morawski 2012; Al-Odaini et al., 2013; Bilal et al., 2020). They also have the ability of bioaccumulation and cause negative impact on aquatic and terrestrial ecosystems, inhibition of reproduction, mortality, inhibition of growth and immobilization (Quadra et al., 2016).

The pharmaceutical wastes in water are divided into eight main classes based on their therapeutic action and specific mode. These include antibiotic, central nervous system stimulant, antipyretic, beta blocker, steroids and lipid regulator, analgesic, and antidepressant. The pharmaceutical waste present in natural water resources is an emerging pollutant and a global issue now (Nasuhoglu et al., 2011; Mozia and Morawski

2012; Wu et al., 2012; Parra-Saldivar et al., 2020). The extensive application of pharmaceutical materials for multipurpose on all over the world need a significant attention to control their pollution in water bodies (Mozia and Morawski 2012; Nasuhoglu et al., 2011; Wu et al., 2012; Aguilar-Pérez et al., 2021). Until now, world health organization (WHO) does not mention pharmaceutical pollutants as high risk in drinking water due to a low detection level. Whereas high demand of these materials increases their level significantly and need high attentions as their data baseline study in water bodies is still under process (Al-Odaini et al., 2013). In addition of this, their effects on human health are not completely open until now or limited and going worse as days pass. Pharmaceutical pollutants in water bodies mostly shows some hidden effects, which accumulate with the passage of time unexpectedly and irreversibly. More importantly, present techniques for wastewater treatment are not sufficient to remove these pollutants completely and efficiently due to their high persistent in water bodies (Achilleos et al., 2010; Mozia and Morawski 2012; Bagheri et al., 2016; Cai and Hu 2017; Bilal et al., 2020). Pharmaceutical waste pollutants are polar, water soluble, non-volatile, and non-biodegradable, which limited the application of wastewater treatment process such as sedimentation and biological treatment (Aguilar et al., 2011; Al-Odaini et al., 2013; Bagheri et al., 2016; Luo et al., 2015; Maroga Mboula et al., 2012; Palominos et al., 2009). Similarly, other water treatment methods such as reverse osmosis, carbon adsorption and air stripping only convert these pharmaceutical pollutants from one phase to another without removal (Elmolla and Chaudhuri 2010; Rasheed et al., 2021). Considering the above deliberated criticus, this review conferred current reports on various hydrogen peroxide-based advanced oxidation processes for degradation of pharmaceutical pollutants of emerging concern. The ongoing challenges, conclusive remarks and imperative future directions are also outlined.

Sources and effects of pharmaceuticals waste

A bulk number of drugs are produced every year to save veterinary and human health from the attack of different types of bacteria and viruses (Quadra et al., 2016). These medicines are used in the form of antibiotics, painkillers, antidepressants, and vascular drugs and some of their waste remains in water bodies from ng/l to µg/l depending on their usage and disposal path (Sangion and Gramatica 2016). The sources and path of

pharmaceutical waste to enter in aquatic system is very important for save disposal and control (Figure 1) (Bagheri et al., 2016; Helwig et al., 2016). The main source of these waste is veterinary use for breeding and therapeutic purpose, human use, industrial production waste and agriculture use for farming. The major path of these waste is from hospitals, healthcare centers, clinics, medicine waste from household like dormitories, hotels, and private residences (Abella´n et al., 2007; Chang et al., 2010; LA Ioannou et al., 2011; Rasheed et al., 2020). Among them, hospitals waste is the major contributor toward contamination of aquatic media through patients' excretions (feces and urines) in original form or by metabolite entered in sewage water (Bagheri et al., 2016; Straub 2016; Helwig et al., 2016). In addition, microbial treatment in wastewater treatment plant also produces pharmaceuticals residues and discharge in aquatic environment and become major producer of pharmaceuticals waste. Similarly, manure of livestock applied as a fertilizer in agriculture contains several pharmaceuticals residual contaminants and can be entered in water bodied through precipitation or infiltered toward ground water. Pharmaceuticals compound also used in aquaculture and agricultural field to prevent from the attack of microbial and bacterial attack and their remains also can entered water bodies through leaching process (Kümmerer 2009; Fukahori et al., 2012; Mozia and Morawski 2012). The production of pharmaceuticals compounds itself can entered in aquatic life due to waste management problem like disposal issues, direct discharge in water bodies and spillage by accident (Yang et al., 2008; Al-Odaini et al., 2013; Rasheed et al., 2020). The lifetime of these pharmaceuticals waste can be controlled by multiple factors involved solubility, persistence, climate factor, chemical structure, adsorption and sorption, temperature, pH, precipitation, composition of sediments, redox potential value, organic carbon content and environmental degradation (Quadra et al., 2016).

The biological activity of pharmaceuticals waste can cause acute or chronic abundant effects toward wildlife and ecosystem (Sangion and Gramatica 2016; Wilkinson et al., 2016). The major problems caused by these pollutants include hormonal disruption, reproduction issues and endocrine disruption (Khataee et al., 2013; Yang et al., 2008). In this direction, Kidd and his coworkers and Sangion et al. study the effect of steroid estrogen on fishes at lakes in Canada and found the feminization effect and collapse of fish population with gonadal intersex, reduce testicular histopathology disrupted ovarian

and reduced gonad size (Kidd et al., 2007; Sangion and Gramatica 2016). Furthermore, the presence of pharmaceutical waste in water bodies cause ecotoxic effects, such as enrofloxacin and ciprofloxacin antibiotics are frequently found in water bodies and toxic toward algae, tetracycline an antibiotic toxic toward plants, early-stage aquatic organism and bacteria present in sewage sludge by decreasing protein production rate (Ebert et al. 2011; Yahiat et al., 2011). Pharmaceutical waste also shows negative impact on microorganism, flora, and fauna in aquatic bodies. Furthermore, the mixture of different pharmaceutical compound can cause negative impact like ibuprofen and diclofenac cause more immobilization in microcrustacean to inhibit the algae growth rate. Until now, the harm of pharmaceutical waste in water bodies on human health does not disclose yet, somehow long-term exposure can cause problem as they are designed to be highly interactive toward human and animals (Abella´n et al., 2007; Jelic´ et al., 2012). It is a high concern to mention the increasing amount of pharmaceutical waste in water bodies and can cause adverse effects on human and aquatic organism.

Advanced oxidation processes based on hydrogen peroxide (H_2O_2) for pharmaceuticals degradation

Free radicals and reactive oxidative species are oxidants, which are responsible to initiate advance oxidation processes (AOPs) to degrade organic pollutants (Allagui et al., 2013; Almomani et al., 2020; Almomani and Saad, 2021a). Free radicals possess unpaired electrons as $OH^{\cdot}$ (hydroxyl radical), $HO_2^{\cdot}$ (hydroperoxyl radical), $RO^{\cdot}$ (alkoxy radical) radicals etc. (Almomani et al., 2021b; Bhosale et al., 2017a; Bhosale et al., 2016a). Hydroxyl radical is very important in this field because of its non-selective behavior, excellent reactivity and great oxidizing power and they can attack a wide range of organic pollutants (Bhosale et al., 2016b; Bhosale et al., 2017b). Hydroxyl radicals may directly react with organic pollutants either through removal of hydrogen from organic compounds (Equation 1), or radical radical interactions, i.e., formation of peroxyl radical by oxygen addition (Equation 2), or via electron transfer (Equation 3) lead to the formation of oxidized intermediates and in case of complete mineralization it forms carbon dioxide, water, and other acids. Hydrogen peroxide (H_2O_2) is reagent present in large amount and easy to use, so it is used for treatment of contaminants. H_2O_2 does not alone show good oxidizing features so it is combined with different substrates/catalysts to become highly effective.

H_2O_2 may be combined with ozone, UV, Fe^{2+}/Fe^{3+} ions (Fenton and photo-Fenton-like processes) and with heterogeneous systems (TiO_2). These reagents may be useful in existence of UV radiations, ultrasound to develop the oxidation processes. Advanced oxidation process catalyzed by H_2O_2 may consists of combination of following catalysts: UV/H_2O_2, $O_3/UV/H_2O_2$, $H_2O_2/TiO_2/UV$, Fe^{2+}/H_2O_2, Fe^{2+}/H_2O_2 /UV, Electro –Fenton, O_3/H_2O_2). In this review, we have discussed various hydrogen peroxide-based advanced oxidation processes for degradation of pharmaceuticals (Figure 2).

$$RH + OH^{\cdot} \longrightarrow R^{\cdot} + H_2O \quad \text{Eq. 1}$$

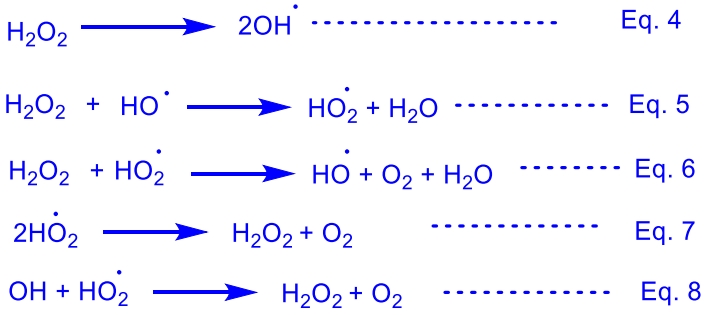
$$R^{\cdot} + O_2 \longrightarrow RO_2^{\cdot} \quad \text{Eq. 2}$$

$$RX + OH^{\cdot} \longrightarrow RX^{+\cdot} + OH^{-} \quad \text{Eq. 3}$$

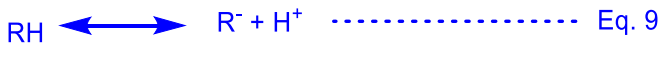
UV/peroxide processes

For treatment of wastewater, ultraviolet radiations have been used widely. Various studies showed that this process is useful to remove pharmaceutical based contaminants from different water sources (Gou et al., 2021; Yuan et al., 2011). This process works effectively for those kind of wastewater which possess photosensitive molecules and presence of large amount of organic molecules in sewage water can inhibit process (Jiao, Zheng, Yin, Wang, & Chen, 2008). The UV process effectiveness for pharmaceutical removal depends on UV absorption potential of pharmaceuticals. Combination of UV with hydrogen peroxide (UV/H_2O_2) is attractive tool to enhance the removal potential for pharmaceutical compounds having low UV absorption and less reactivity towards hydroxyl radicals and ozone but are photoactive. Combination of UV/H_2O_2 give benefit of two chemical processes as (i) Photocatalytic potential of UV, (ii) homolytic cleavage of oxygen bond in hydrogen peroxide produces hydroxyl radical which reacts with organic pollutants. The concentration of $H2O_2$, intensity of UV light, structure of pharmaceutical, rate of hydroxyl radical generation, water contents and pH are main factors in UV/H_2O_2 processes (Baeza & Knappe, 2011). The first step of photocatalytic degradation involves hydrogen peroxide decomposition which leads to formation of hydroxyl radicals. The two hydroxyl radicals are formed with absorption of applied wavelength (Goldstein, Aschengrau, Diamant, & Rabani, 2007) and then series of radical reactions occurs. From reactions (Equation 5-8), it is evident that photocatalytic cleavage of H_2O_2 generates

hydroxyl radicals (OH·) (Eq. 4). Initial concentration of H_2O_2 should be adjusted with care to enhance the removal efficacy. Generated hydroxyl radicals react with organic molecules through various processes wither hydrogen abstraction, addition to carbon-carbon doubles, electron transfer and nature of mechanism depends on functional group of compounds. Mostly reaction route is hydrogen atom abstraction and formation of organic radical (R·). These organic radicals decompose through bi-molecular reactions leading to various degradation products of starting material along with various by-products (hydrogen peroxide, hydroperoxide radicals, formaldehyde, etc.)



At last the dimerization of hydroxyl radicals itself (the reverse of eq 4) (Ross & Ross, 1977) and hydroperoxide radicals (Eq. 7) (Bielski, Cabelli, Arudi, & Ross, 1985), leads to reformation of H_2O_2 which in turn sequester hydroxyl radicals and regenerate hydroperoxide radicals (Eq. 5) (Christensen, Sehested, & Corfitzen, 1982). At same time the dissociation equilibrium of organic molecules itself and of various intermediates (hydrogen peroxide, hydroperoxide radicals) generated must be noted.



Various factors as UV intensity, pH, temperature, and nature of organic molecules play key role in overall cycle. However, UV/H_2O_2 is considered as most advanced oxidation process.

Sulfasalazine is anti-rheumatic drug, and it was found photostable at UV photolysis. It was able to degrade its two human metabolites (sulfapyridine and 5-aminosalicylic acid). The quantum yields of sulfapyridine and 5-aminosalicylic acid were (8.6 ± 0.8) $x10^{-3}$ and (2.4 ± 0.1) $x10^{-2}$ mol $Einstein^{-1}$, respectively. While addition of However, addition of peroxides, H_2O_2 and peroxy-disulfate to the UV system obtained 93.1% and 96.2% removal of sulfasalazine as a result of the highly reactive free radicals HO· and $SO^{\cdot-}_4$ (Ji

et al., 2018). Upon UV exposure, the degradation rates of ketoprofen, diclofenac and carprofen were compared. The carprofen showed high degradation rate (1.54×10^{-4} s^{-1}) followed by ketoprofen (5.91×10^{-5} s^{-1}) and diclofenac (7.78×10^{-6} s^{-1}) (J. Li, Ma, Li, & Xu, 2017). Perisic and his colleagues compared the efficacy of UVC/H_2O_2 with UVA/TiO_2 for the degradation of diclofenac. Under UVC/H_2O_2, the diclofenac degraded completely in 2 minutes while under UVA/TiO_2, 156 minutes were required to completely degrade diclofenac (Perisic et al., 2016). Four different pharmaceuticals venlafaxine (VEN), sulfamethoxazole (SFX), fluoxetine (FLU) and carbamazepine (CBZ) were degraded under two different conditions *i.e*. UV/H_2O_2 and UV/peracetic acid (Hollman, Dominic, & Achari, 2020). UVC/Peracetic acid degraded all pharmaceuticals and obeyed pseudo-first order. Complete degradation of all pharmaceuticals took place under UVC/H_2O_2 and SFX degraded fastly ($k = 0.037$ s^{-1}) followed by FLU, CBZ and VEN ($k = 0.011$ s^{-1}, 0.0105 s^{-1} and 0.009 s^{-1} respectively) @100 mg/L of H_2O_2. Degradation mechanism is simple and involves formation of hydroxyl radicals. In a latest study UV-C/H_2O_2 was used to degrade three different pharmaceuticals i.e. hydrochlorothiazide, naproxen and gemfibrozil in different matrix (Surface water, deionized water, and sewage treatment plant effluent). Hydrochlorothiazide was photodegraded most quickly followed by naproxen and gemfibrozil. Matrix composition is also main factor in increasing or decreasing the rate of pharmaceutical degradation. The degradation rate mostly decreased in sewage treatment plant effluents followed by surface water and deionized water. Better degradation was obtained by addition of H_2O_2, when results were compared with isolated usage of UVC. Conclusively, UVC/H_2O_2 was found useful for degradation of pharmaceuticals in different kind of matrix (Paniagua, Amildon Ricardo, Marson, Gonçalves, & Trovó, 2019). In municipal wastewater, the four different pharmaceuticals (carbamazepine (CBZ), erythromycin (ERY), atenolol (ATL) and clofibric acid (CA)) were detected and degraded in presence of UV/H_2O_2. Degradation followed the pseudo first order kinetics. CBZ showed high rate of degradation (1.32×10^{-3}-4.55×10^{-3} s^{-1}). Rate of degradation were found to be 0.96×10^{-3} -3.64×10^{-3} s^{-1} for ATL and 0.97×10^{-3} -2.98×10^{-3} s^{-1} for CA while ERY showed lowest degradation rate (0.65×10^{-3} -2.23×10^{-3} s^{-1}) UV/H2O2 enhanced the degradation rates of pharmaceuticals showing indirect photolysis played key role in degradation (Shi et al., 2021). Luo and his colleagues reported the effects of quantum

yield, extinction coefficient and degradation of ibuprofen and sulfamethoxazole at variable pH (3 & 7.55). The values of quantum yield for ibuprofen at pH 3 and 7.55 were found 0.0161 and 0.1030 mol/Einstein respectively and for sulfamethoxazole the values were found to be 0.0885 and 0.0236 mol/Einstein respectively. The difference in values in comparison of previous studies is attributed to experimental conditions. The developed model was described to be used in photolysis of pharmaceutical pollutants at various pH in different samples (Luo et al., 2018) (Table 1).

Fenton (Fe^{+2}/H_2O_2) and Fenton like (Fe^{+3}/H_2O_2) approaches

Fenton process is attractive approach for degradation of various organic contaminants. But it has some disadvantages which arise from usage of iron salts which play role for decomposition of hydrogen peroxides to hydroxyl radicals. This process is expensive because large quantity of iron salts is required. These drawbacks are associated with conventional Fenton process while developments have been made to develop system to lessen the existence of iron species in environment without affecting process efficacy. Different options have been put forward to enhance the generation of Fe (II) species which are used to decompose the hydrogen peroxide for formation of hydroxyl radicals. This may lead to decrease the quantity of Fe (II) in reaction medium (Navalon, Alvaro, & Garcia, 2010). For this purpose, the Fenton process may be combined with UV- radiations and overall process known as Photo-Fenton process. Development of solid catalyst for the Fenton process is also attractive approach which may assist to reduce the existence of Fe(II) salts present in the media and this approach provides wide group of processes called heterogenous Fenton processes (Ribeiro & Nunes, 2021). The Fenton reaction involves the use of iron salts (Fe^{+2}) and hydrogen peroxides (H_2O_2) generating hydroxyl radicals in acidic medium (pH = 3-5) (Eq. 10). The Fe^{+2} can be regenerated via reaction of Fe^{+3} with other various intermediates (Eq. 11).

$$Fe^{+2} + H_2O_2 \longrightarrow Fe^{+3} + OH^- + HO^{\bullet} \quad \text{Eq. 10}$$

$$Fe^{+3} + H_2O_2 \longrightarrow Fe^{+2} + H^+ + HO_2^{\bullet} \quad \text{Eq. 11}$$

It is important for Fenton process that the pH of treated water must be in between 3-5 because at higher Ph, the iron gets precipitated which may deactivate the system. Hydrogen peroxide should be added slowly to avoid decomposition. Role of Fenton process for degradation of different pharmaceuticals has been presented in Table 1.

Fenton process has drawback of expensive reagents which are used in this process. To replace the Fe (II) with Fe (III) salts, different methods have been developed. Fe(III) salts are less expensive in comparison of Fe(II) salts. Generally, this process is called “Fenton like” in which mixture of Fe^{+3} and H_2O_2 is used and hydrogen peroxide decomposed to hydroxyl radicals and Fe^{+3} is reduced to Fe^{+2} through following reactions:

$$Fe^{+3} + H_2O_2 \longrightarrow Fe^{+2} + OH^- + HO^{\cdot} \quad \text{Eq. 12}$$

Decomposition rate of hydrogen peroxide and organic compounds oxidation rate are slow in

presence of Fe^{+3}/H_2O_2 in comparison of Fe^{+2}/H_2O_2 (Neyens & Baeyens, 2003) at pH 3. Fenton like process also generates peroxyl radicals.

$$Fe^{+3} + H_2O_2 \longrightarrow FeOOH^{+2} + H^+ \quad \text{Eq. 13}$$

$$FeOOH^{+2} \longrightarrow Fe^{+2} + HO_2^{\cdot} \quad \text{Eq. 14}$$

Homogeneous Fenton and Fenton like processes have been used widely to remove environmental contaminants because of ease of operation but these processes also have few disadvantages like production of sludge and limited operational pH values. To overcome this issue, Heterogenous Fenton oxidation processes was developed. In heterogeneous Fenton process, reaction occurs between hydrogen peroxide and Fe^{+3} in various forms (Fe_2O_3 or α-FeOOH). In a recent study nano-zerovalent iron activated with persulfate was couples with Fenton process (nZVI-PS-Fenton) and was used to remove different pharmaceutical contaminants from aqueous solution. The optimized molar ratio of nZVI-PS-H_2O_2 was found 4/2/1. Norfloxacin, tetracycline and paracetamol were degraded approximately 100% while sulfamethoxazole and sulfamethazine were degraded around 96%. Carbamazepine and phenacetin were not significantly removed, and abatement was around 77%. Sulphate and hydroxyl radicals play important role in degradation phenomena. Substitution of PS with hydrogen peroxide was done to reduce the operation cost and sulfates in water. In this process, the pseudo-first order kinetics was followed (J. Wu et al., 2020). Xie and his colleagues prepared MOF derived zero-valent iron embedded in the carbon matrix (FMC) which was synthesized through direct pyrolysis of Iron-based metal organic framework. FMC was utilized to degrade amoxicillin (AMX) as heterogeneous Fenton catalyst. The potential role of FMC/H_2O_2 was

determined and it was suggested that hydroxyl radicals attacked the amoxicillin and 60.41% degradation happened. Structure of carbon assisted the electrons passage and enhanced the contact of zero valent iron and Fe^{+2} species upon FMC surface with hydrogen peroxide giving enhanced generation of hydroxide radicals and great removal efficacy of amoxicillin (Figure 3) (Xie et al., 2021). Recently, heterogeneous catalyst δ-FeOOH)/MWCNTs nanocomposite was synthesized. The FeOOH/MWCNTs/H_2O_2 catalyst was used to remove ciprofloxacin through heterogeneous Fenton like process. Role of hydrogen peroxide concentration, pH, reaction times and dose of catalyst were investigated. Approximately 86.9 % CIP was removed through this phenomena (Salari, Rakhshandehroo, Nikoo, Zerafat, & Mooselu, 2021). Table 1 represents various reports for removal of pharmaceuticals through Fenton and Fenton like process.

Photo-Fenton process (The Fe^{2+}/H_2O_2/UV system)

UV radiations enhanced the Fenton process and accelerate the degradation of organic contaminants. Iron salts, H_2O_2 and UV radiations are included in photo-Fenton process. This process is well known for purification of polluted water (Xing et al., 2021). Photo-Fenton process has advantages over Fenton and Fenton like reagents as described following **(i)** photolysis of H_2O_2 generated as described in equation 4 providing a source of hydroxyl radicals, **(ii)** Reduction of Fe^{+3} to Fe^{+2} through utilization of UV radiations (Eq. 15) also generates hydroxyl radicals. Further this reaction assists the generation of Fe^{+2} which react with H_2O_2 to produce more hydroxyl radicals through conventional Fenton process (Eq. 10). So, this can be concluded that UV radiations improves the Fe^{+3}-Fe^{+2} cycle and assists the generation of hydroxyl radicals in both reactions (Eq 15, 10).

$$Fe(OH)^{+2} \xrightarrow{h\nu} Fe^{+2} + HO^{\cdot} \qquad \text{Eq. 15}$$

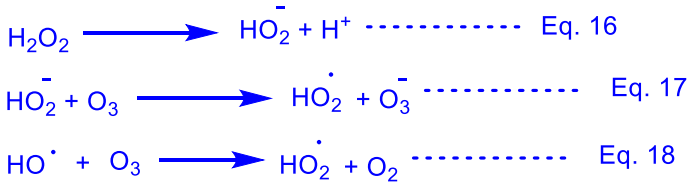
In a recent study, degradation of cephalexin was carried out by using homogeneous (Fe^{2+}/H_2O_2/UV) and heterogeneous (MoS_2@Fe/H_2O_2/UV) photo-Fenton processes. Photo-Fenton process play great role in degradation of pharmaceutical based contaminants. Higher degradation efficacy (73.10%) and pseudo first order degradation rate were obtained through heterogeneous catalytic system (MoS_2@Fe/H_2O_2/UV) in comparison of homogeneous system. Different degradation products were obtained in both homogeneous and heterogeneous pathways (Figure 4) (Gou et al., 2021). Davididou and colleagues reported the degradation of antipyrene in presence of ferrioxalate based

photo-Fenton reaction employing UVA light emitting diodes. Antipyrene was degraded in 2.5 minutes with 93% TOC removal in 60 minutes and also hydrogen peroxide amount reduced (Davididou, Monteagudo, Chatzisymeon, Durán, & Expósito, 2017). Recently Fe_3O_4@MIL-100(Fe) hybrid composites has been synthesized for promoting photo-Fenton process for degradation of levofloxacin. The composite showed higher degradation efficacy. The efficient reduction of Fe^{+3} to Fe^{+2} was observed. The developed composite removed levofloxacin from 77.90-85.50% for spiked wastewater treatment (He et al., 2021). In a recent study, photo-Fenton process was used to remove carbamazepine in presence of FeOCl. Hydroxyl radicals were generated. Hydrogen peroxide concentration, effects of UV radiations were evaluated and 92% carbamazepine was removed in presence of H_2O_2/UV/FeOCl system in half hour and various by-products were obtained (S. Sun et al., 2021) (Figure 5). Recently a study was carried out to degrade NSAIDS (ketoprofen, diclofenac, paracetamol) from aqueous system through photo-Fenton process mediated through ferrioxalate in UV-LED. Reaction conditions were optimized. Pseudo-first order kinetics were followed and 80% of all drugs was removed in 10 minutes (Marchetti & Bessa Azevedo, 2020). Pyrite is commonly used in Fenton process for pollutants degradation. Its efficacy is affected by extra hydrogen peroxide and pH adjustment. Pyrite based photo-Fenton process mediated through solar light, organic acids has been constructed for carbamazepine degradation. Incorporation of organic acids promotes the Fe^{+2} dissolution. Pyrite could generate the photoelectrons upon irradiation, which may reduce oxygen to form hydrogen peroxide facilitated through organic acids. Sunlight and organic acids enhanced the generation of H_2O_2 and Fe^{+2} species, supporting an effective Fenton process. Combination of pyrite with tartaric acid, citric acid and ascorbic acid degraded carbamazepine 70, 60 and 53% respectively in 30 minutes under solar light (Figure 6) (Guo et al., 2021). Few reports are presented in Table 1 regarding removal of pharmaceuticals through photo-Fenton process.

The O_3/H_2O_2 system

High molecular weight electron rich molecules are degraded directly through action of ozone, however during this process many low molecular weight by-products are produced which may further play role towards ozone oxidation or degradation via hydroxyl radicals pathways. And these low molecular by-products also show acute toxicity in comparison

of primary pollutants. The efficacy of ozonation process can be improved by incorporation of hydrogen peroxide which leads to formation of hydroxyl radicals. The O_3/H_2O_2 combined oxidation is known as peroxone which generates high conversion yields in comparison of ozonation in which direct reaction of ozone and pollutant follow slow kinetics. In such cases, the advanced oxidation process can be obtained through addition of little quantity of H_2O_2 in aqueous solution through which ozone is bubbled is easy. In the aqueous solution, the hydrogen peroxide is partially dissociated in its conjugate base called hydroperoxide ions (HO_2^-) (Eq. 16). These hydroperoxide ions reacts and decompose the ozone (Eq. 17) and giving rise to chain reactions in which hydroxyl radicals are involved. Furthermore, the reaction of ozone with hydroxyl radicals (Eq. 18) may produce more hydroperoxide ions that can react further with ozone and continue the process. In this way the dissolved organic pollutants in aqueous media undergo oxidation through two routes; The direct route which includes reaction of molecule with ozone or indirect route which includes reaction with hydroxyl radicals. Addition of hydrogen peroxide accelerated the decomposition of ozone and enhance the formation of hydroxyl radicals.



Recently, Pelalak and his colleagues reported the degradation of sulfasalazine (SSZ), sulfamethoxazole (SMX), sulfamethazine (SMT) and metronidazole (MNZ) under O_3/H_2O_2 processes. The synergistic effect of ozone and hydrogen peroxide was evaluated. At optimum conditions, the Sulfasalazine (SSZ), Sulfamethoxazole (SMX), Sulfamethazine (SMT) and Metronidazole (MNZ) were efficiently degraded (98.10%, 89.34%, 86.29% and 58.70%) respectively in O_3/H_2O_2 process. Through LC/MS and DFT calculations, the intermediates formed during degradation process were determined (Pelalak, Alizadeh, Ghareshabani, & Heidari, 2020). The O_3/H_2O_2 system has been utilized in degradation of various pharmaceuticals (Table 1) and this process proved highly effective, fast for wastewater treatment.

The O_3/H_2O_2/UV System

The ternary system including H_2O_2/O_3/UV system generates hydroxyl radicals. This ternary system has advantage that decomposition of ozone is enhanced in presence of UV and hydrogen peroxide which leads to enhanced production of hydroxyl radicals. Moreover, it can be employed in mild conditions as room temperature and atmospheric pressure etc. The three elements which are used in this system like ozone, hydrogen peroxide and UV are expensive, and this disadvantage limited the use of this process broadly. Thereof this ternary process is used for treatment of highly polluted wastewater to achieve efficient degradation and mineralization of pollutants. Various reports involving degradation of pharmaceuticals through O_3/H_2O_2/UV System have been presented in Table 1.

Conclusions and directions

Pharmaceutical compounds have recently been detected in the environmental compartments and their adverse impacts on living entities and the ecosystems have also been well documented. WWTP (primary and secondary) are generally not capable of removing these micropollutants, resulting in their introduction into drinking water systems. To deal with this issues, innovative bio-treatment processes are urgently required considering growing population at an accelerated rate and per capita increase in drug consumptions. AOPs has appeared as a robust approach for effective removal of pharmaceuticals from wastewaters and water systems. The detection and remediation of pharmaceutical compounds has become a subject of intensive research in recent years. Since a large number of new pharmaceuticals are introducing to the market every year, their associated ecological impacts and remediation approaches must be developed to deal with these new kinds of emerging contaminants. Some imperative future directions are given below.

1) Advanced and state-of-the-art strategies should be proposed and employed for precise and continuous recognition/monitoring of pharmaceutical substances in the environmental matrices particularly in rapidly emerging industrial countries like China.

2) Stringent regulatory guidelines should be followed and implemented for the release of effluents from hospital and industrial sources.

3) Greener and sustainable technologies are imperative to implement for pharmaceutical manufacture, development, and consumption.

4) Intensive research efforts are needed to gain comprehensive knowledge about chronic acquaintance and adverse impacts of pharmaceutical-based micropollutants on humans, and flora and fauna.

5) Standard operating procedures must be outlines and executed for limiting microcontaminants in water systems and wastewaters.

6) It is meaningful and urgent to track alternative technologies, which are essentially smart, greener, and environmentally competent.

7) Large-scale remediation of pharmaceutical pollutants by more efficient, low cost and affordable ways.

8) Equipment of WWTPs with innovative technologies for minimizing the release of pharmaceutical micropollutants.

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Conflict of interests

The author(s) declare no conflicting interests.

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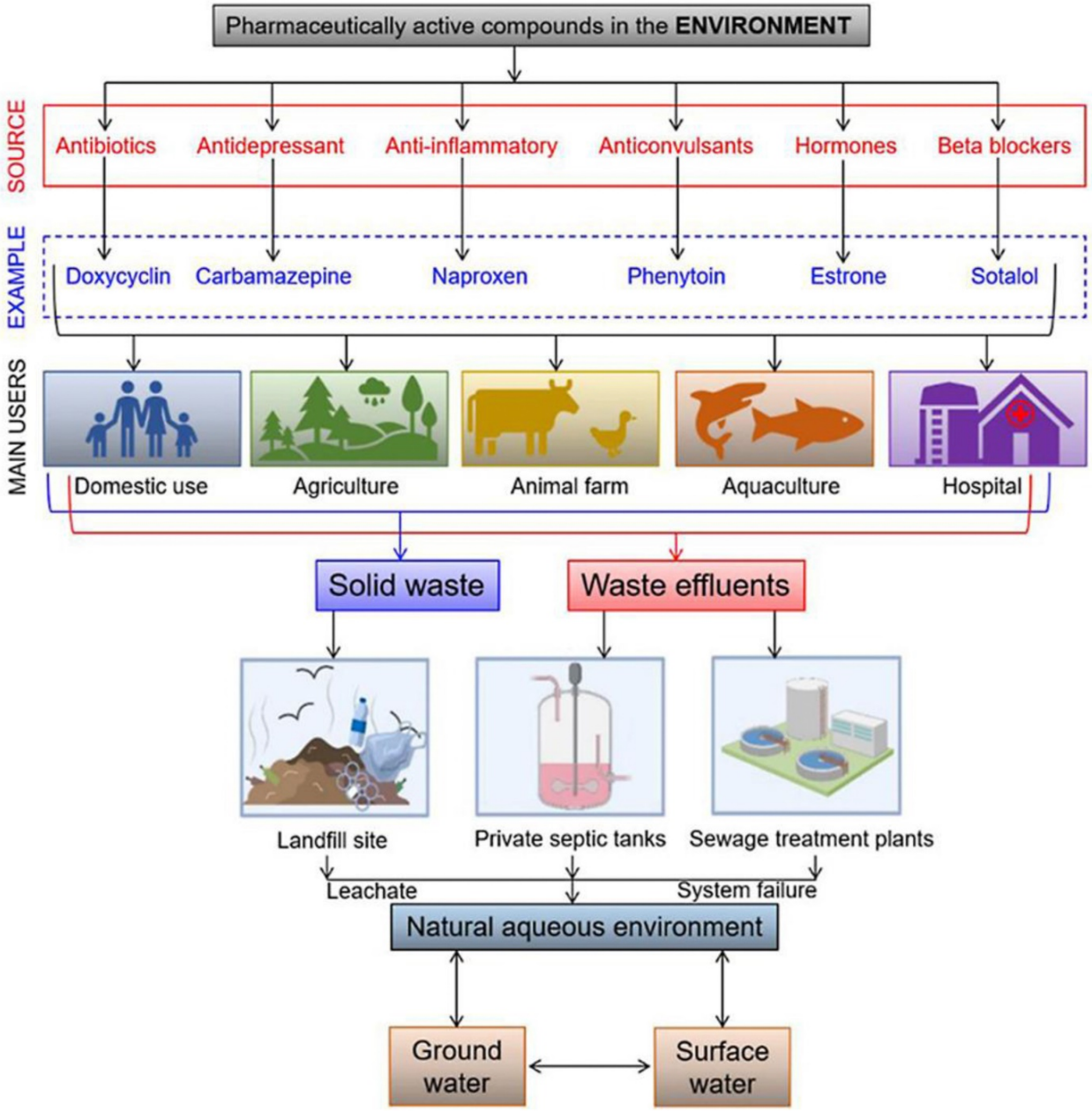
List of Figures



747

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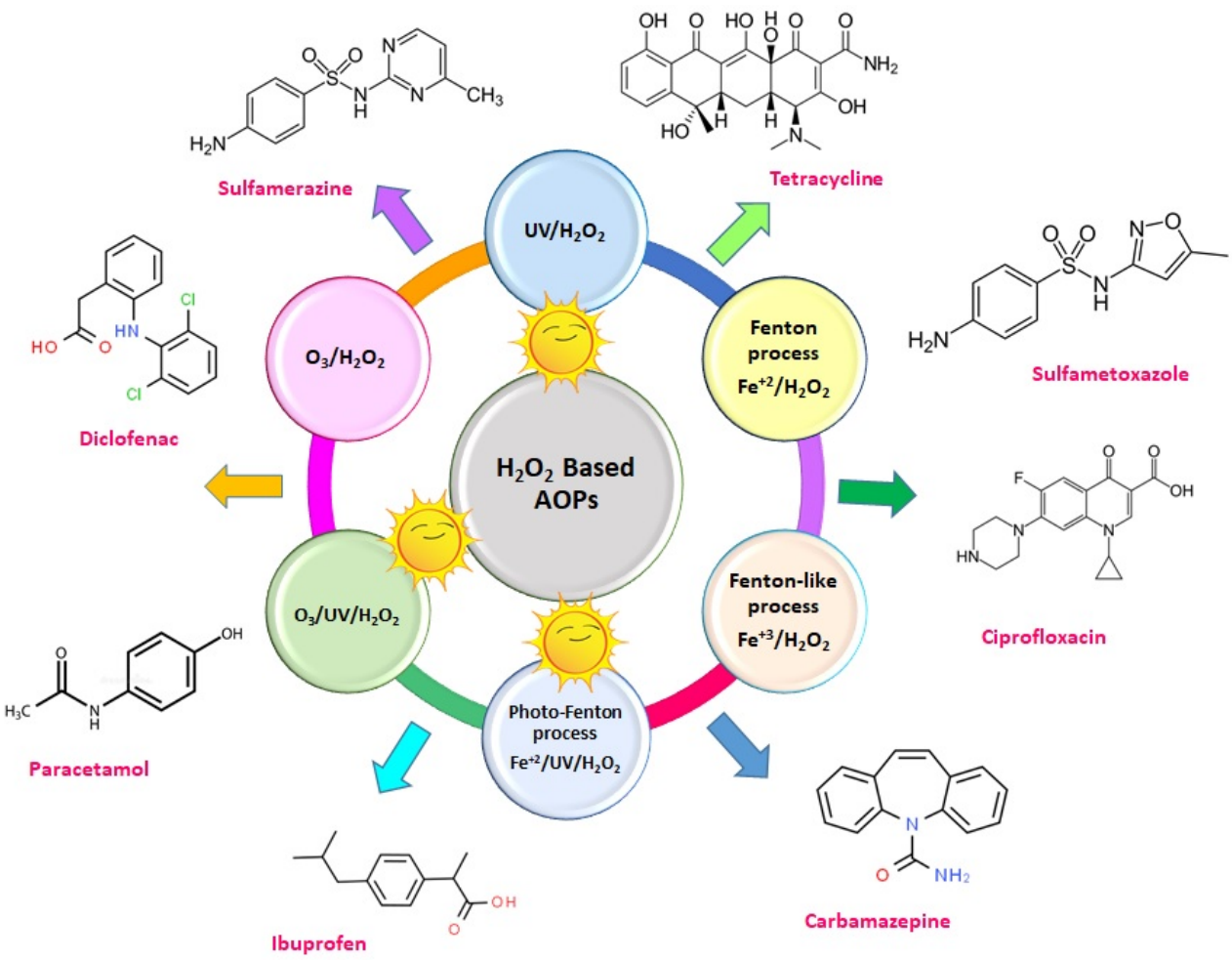

Figure 2 Hydrogen peroxide based advanced oxidation processes for degradation of pharmaceutical based contaminants.

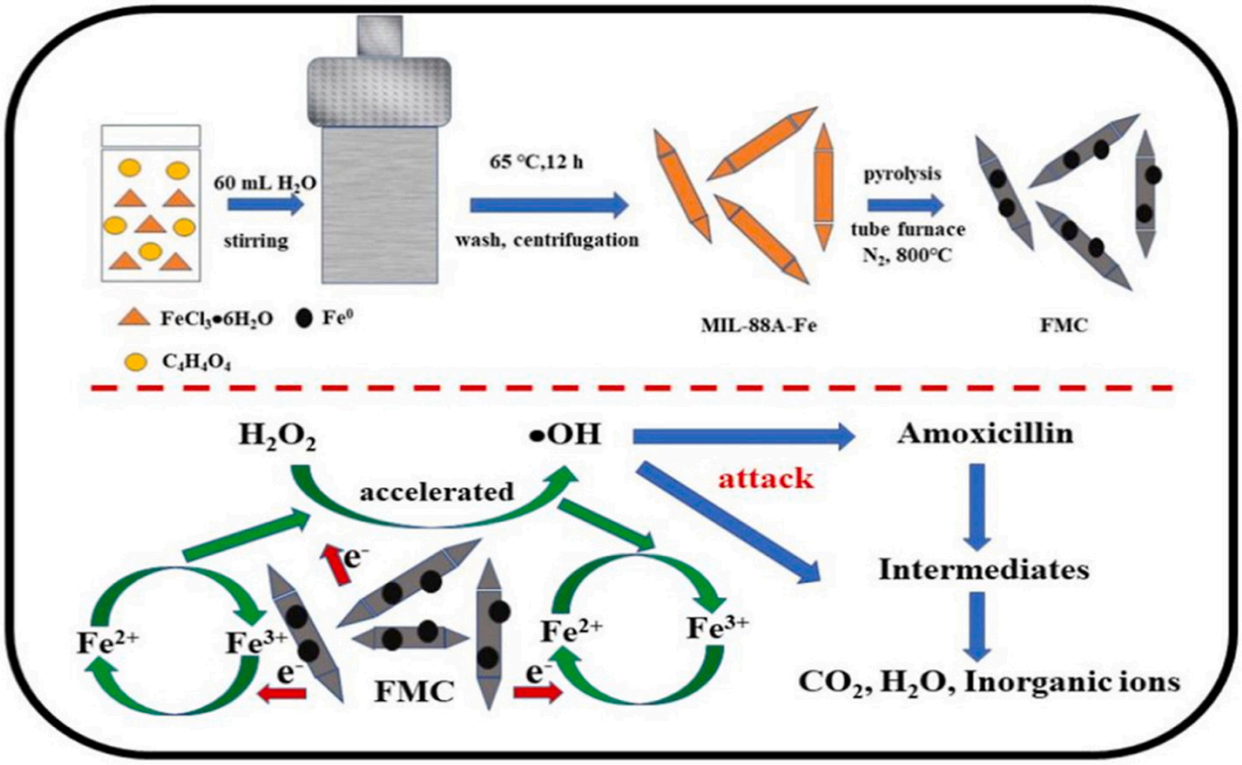

Figure 3 FMC/H_2O_2 as heterogeneous Fenton catalyst for degradation of amoxicillin. Reprinted from (Xie et al., 2021)) with permission from Elsevier. License Number: 5166570136177.

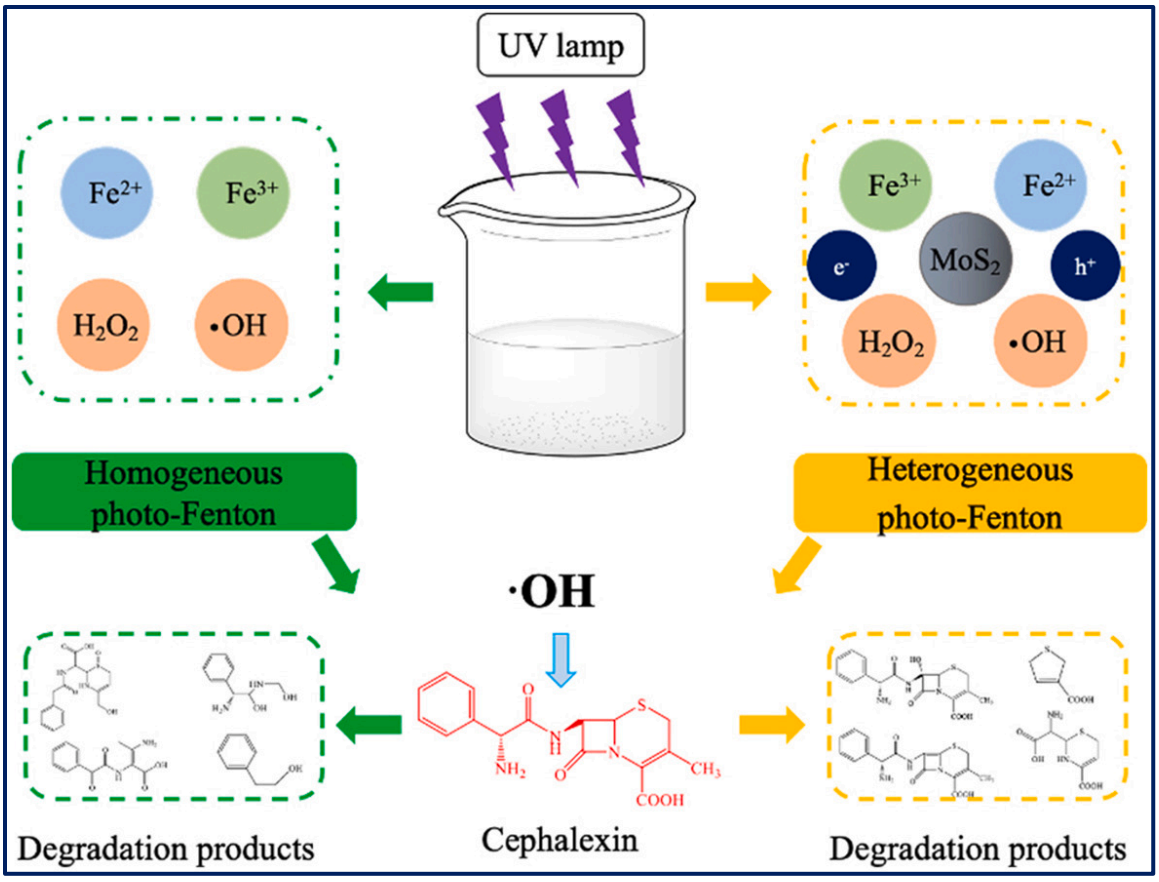

Figure 4 Degradation of cephalexin during homogeneous and heterogeneous photo-Fenton processes. Reprinted from (Gou et al., 2021) with permission from Elsevier. License Number: 5166570339411.

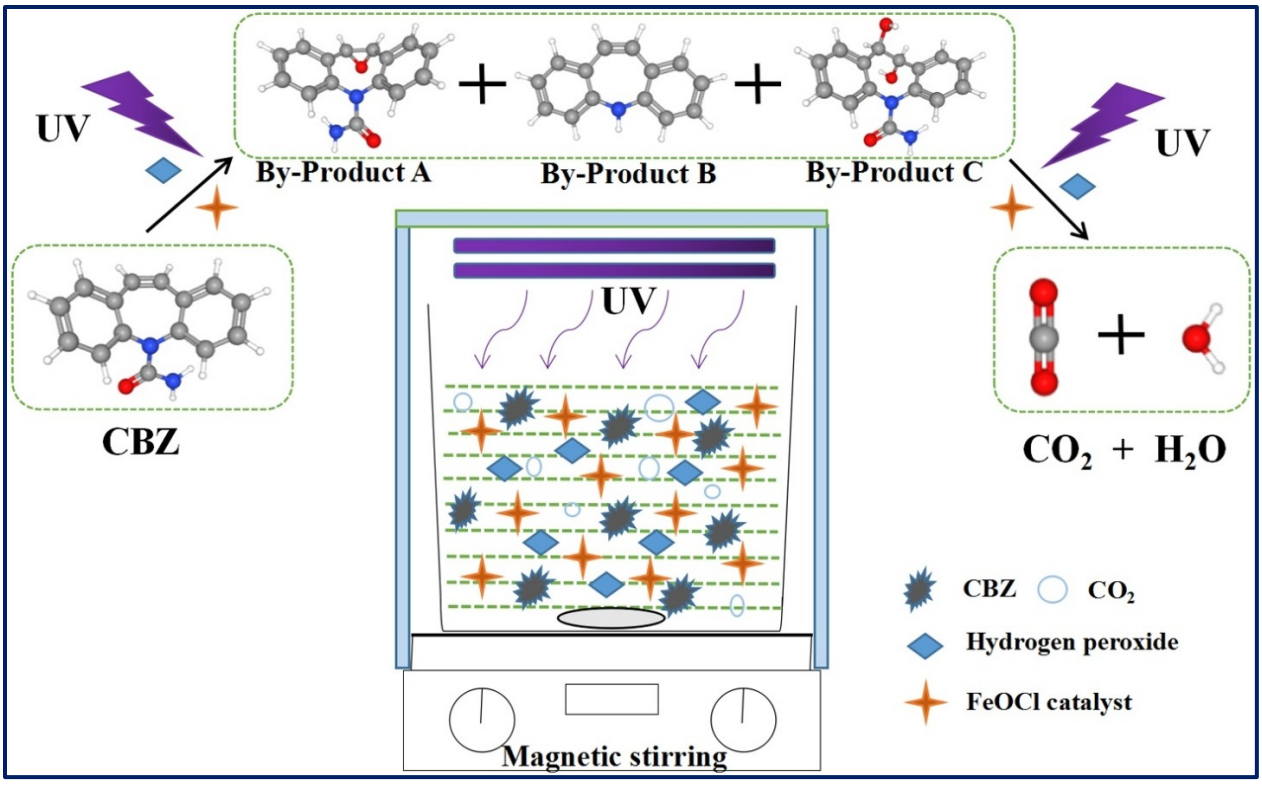

Figure 5 Degradation of carbamazepine in FeOCl based Photo-Fenton reaction. Reprinted from Sun et al., (2021) with permission from Elsevier. License Number: 5166570483714.

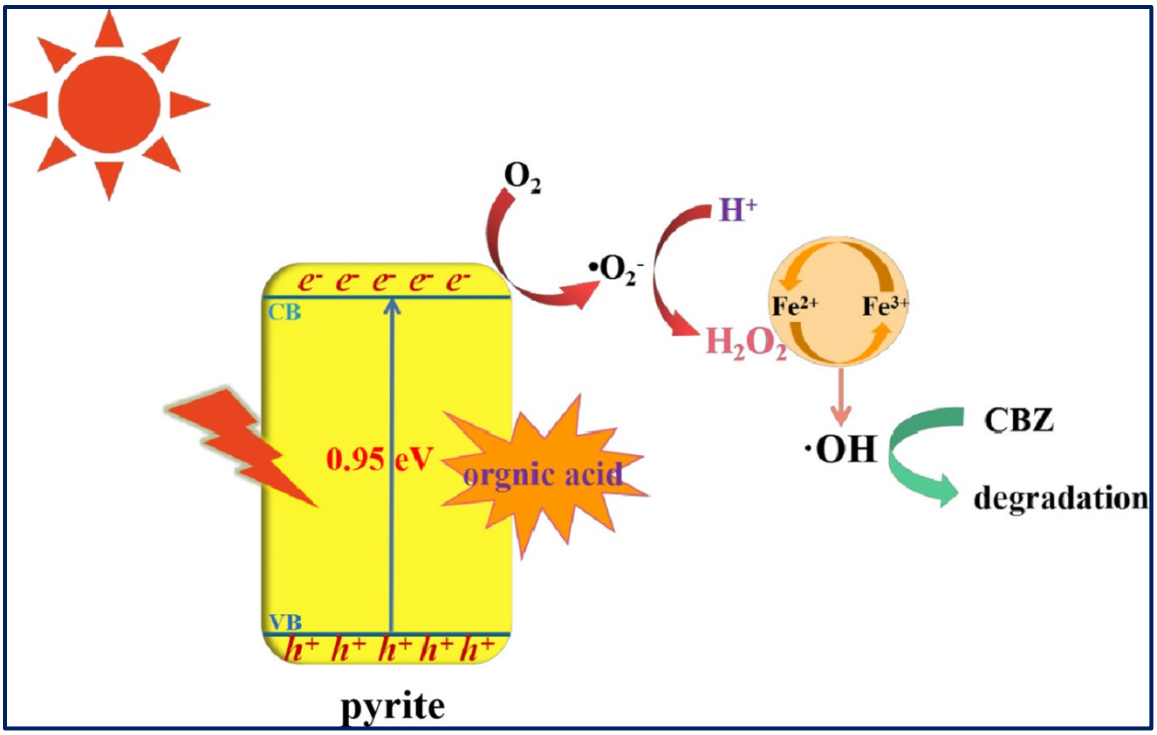

Figure 6 Degradation of Carbamazepine using Solar photo-Fenton process in presence of pyrite/organic acid. Reprinted from (Guo et al., 2021) with permission from Elsevier. License Number: 5166570483714.

831 **Table 1** Degradation of pharmaceutical based contaminants through various advanced oxidation processes (AOPs)
832 involving hydrogen peroxide-based systems.

Sr #	Matrix	Target pharmaceutical	AOPs Catalytic system	Removal efficiency	References
			UV/H_2O_2		
1	Aqueous solution	venlafaxine (VEN), sulfamethoxazole (SFX), fluoxetine (FLU), carbamazepine (CBZ)	UV/H_2O_2	Significant	(Hollman et al., 2020)
2	Surface water, deionized water and sewage treatment plant effluent	hydrochlorothiazide, naproxen and gemfibrozil	UV-C/H_2O_2	-	(Paniagua et al., 2019)
3	Aqueous solution	acetaminophen	UV/H_2O_2	75.6%	(Ghanbari et al., 2021)
4	Aqueous solution	metoprolol	UV/H_2O_2		(Gao, Zhang, Li, Tian, & Gao, 2020)
5	municipal wastewater effluents	carbamazepine erythromycin (ERY),	UV/H_2O_2	Significant	(Shi et al., 2021)

		atenolol (ATL) and clofibric acid (CA)			
6	Polluted water	Chloramphenicol	UV-LED/H_2O_2	95%	(M. Wu et al., 2020)
7	Tap water	Cyclophosphamide	UV/H_2O_2	100%	(Graumans, Hoeben, Russel, & Scheepers, 2020)
8	Ultrapure water and tap water	Cefalexin (CFL) Norfloxacin (NRF). Ofloxacin (OFX)	UV/ H_2O_2	~100% within 3-5 min	(Y. Sun et al., 2019)
9	Ultrapure water and tap water	Ceftriaxone (CFN)	UV/ H_2O_2	~100%	(Khorsandi et al., 2019)
10	Ultrapure water Secondary wastewater effluent	Roxithromycin (RXT)	UV/ H_2O_2	~100%	(W. Li et al., 2019)
11	Wastewater	Norfloxacin (NRF).	UV/ H_2O_2	72.56%	(Yang et al., 2020)
12	Wastewater	Ofloxacin, Levofloxacin	UV/ H_2O_2	94.49%, 97.48% respectively	(X. Liu et al., 2020)

13	Swine wastewater	Sulfamonomethoxine	UV/ H_2O_2	91%	(Y. Li, Yang, Chen, Han, & Cao, 2021)
14	Aq. system	Capecitabine	UV/ H_2O_2	99%	(Tang et al., 2021)
15	Aq. system	Albendazole	UVC/ H_2O_2	99%	(Ljubas et al., 2018)
Fenton (Fe^{+2}/H_2O_2)/ Fenton like process (Fe^{+2}/H_2O_2)					
16	Synthetic wastewater	Amoxicillin	Fe^{+2}/H_2O_2	83%	(Turkay & Kumbur, 2019)
17	Ultrapure water	Ciprofloxacin (CPR)	Fe^{+2}/H_2O_2	74%	(Salari, Rakhshandehroo, & Nikoo, 2018)
18	Ultrapure water	Ciprofloxacin	Fe^{+2}/H_2O_2	76%	(Rakhshandehroo, Salari, & Nikoo, 2018)
19	Spiked wastewater	Ciprofloxacin	Fe^{+2}/H_2O_2	70%	(Gupta & Garg, 2018)
20	Ultrapure water Synthetic wastewater	Trimethoprim (TRM)	Fe^{+2}/H_2O_2	100% in ultrapure water 36% in synthetic wastewater	(S. Wang & Wang, 2018)

21	Hospital wastewater	79 various pharmaceuticals	Fe^{+2}/H_2O_2	Reduced almost 99.8% load of pharmaceutical	(Segura et al., 2021)
22	Aqueous solution	indomethacin, norfloxacin, tetracycline, paracetamol sulfamethoxazole, sulfamethazine, carbamazepine phenacetin	nZVI/PS/H_2O_2	Indomethacin 100%, norfloxacin 100%, tetracycline 100%, paracetamol 100%, sulfamethoxazole ≥95%, sulfamethazine ≥95%, carbamazepine 77% phenacetin 77%	(J. Wu et al., 2020)
23	Ultrapure water	Ciprofloxacin	$NiCuO_2$, $MnCuO_2$ $FeCuO_2$, $CoCuO_2/H_2O_2$	90%	(Q. Wang, Ma, & Xing, 2018)
24	Ultrapure water	Ciprofloxacin	nZVI//H_2O_2	100%	(Mondal, Saha, & Sinha, 2018)
25	Ultrapure water	Ciprofloxacin	H_2O_2/Sludge Biochar	90%	(J. Li et al., 2019)

26	Ultrapure water	Tetracycline	$H_2O_2/Fe^0@CeO_2$	94%	(Zhang, Chen, Fang, & Tsang, 2019)
27	Ultrapure water	Tetracycline	H_2O_2/Fe^{+3}/WMoOx	86%	(Hu et al., 2019)
28	Ultrapure water Spiked wastewater	Tetracycline	H_2O_2/Fe substituted by a mixture of three biochars from corn stalks, bamboo, and pig manure	100%	(Huang et al., 2019)
29	Aqueous system	amoxicillin	MOF derived zero valent iron embedded in the carbon matrix (FMC)/H_2O_2	60.41%	(Xie et al., 2021)
30	Aqueous system	Ciprofloxacin	δ-FeOOH)/ MWCNTs/H_2O_2	86.9%	(Salari et al., 2021)
31	Hospital waste water	Cafazolin, imioenem, vancomycin	ZVI- H_2O_2-Fenton	Significant degradation obtained	(Furina et al., 2021)

32	wastewater	carbamazepine, clindamycin, gemfibrozil, ketoprofen, florfenicol, sulfamethazine	pelletized iron-modified diatomite/ H_2O_2	clindamycin 89.7 % gemfibrozil 100 %, ketoprofen 35.1 %, Carbamazepine 21.1 %, sulfamethazine 21.1 %, florfenicol 7.0%	(Ulloa-Ovares, Rodríguez-Rodríguez, Masís-Mora, & Durán, 2021)
33	Aqueous	sulfathiazole	CuMgFe- CO_3 layered double hydroxide	Approx. 100%	(de Melo Costa-Serge et al., 2021)
34	Aqueous system	sulfanilamide (SAM), sulfamerazine (SMR),sulfadimethoxine (SMX), sulfadiazine (SDZ), sulfamethazine (SMT), sulfametoxydiazine (SMD)	CNTs-Fe_3O_4/H_2O_2	Significant degradation obtained SAM < SMT < SDZ < SMR < SMD < SMX	(Y. Liu, Zhang, Deng, & Liu, 2021)
Photo-Fenton process (Fe^{+2}/H_2O_2/UV)					
35	Hospital wastewater	79 various pharmaceuticals	Fe^{+2}/H_2O_2/UV	Reduced almost 94.5% load of pharmaceutical	(Segura et al., 2021)

36	Aqueous system	Cephalexin	MoS_2@Fe/H_2O_2/UV Fe^{2+}/H_2O_2/UV	73.10%, 47.09%	(Gou et al., 2021)
37	Hospital waste water	Fluconazole	Solar photo Fenton	80%	(Della-Flora, Wilde, Lima, Lima, & Sirtori, 2021)
38	Spiked synthetic wastewater, spiked real water	Amoxicillin	H_2O_2 /Fe^{3+}/ Natural solar radiation	90%	(Guerra et al., 2019)
39	Spiked wastewater	Ampicillin	Solar photo-Fenton H_2O_2/Fe^{2+}	100%	(Ioannou-Ttofa, Raj, Prakash, & Fatta-Kassinos, 2019)
40	Spiked WWTP	Chloramphenicol	Black light lamps (350-400 nm)/or solar radiations/H_2O_2/Fe^{2+}	79%	(Ricardo, Paiva, Paniagua, & Trovó, 2018)
39	Spiked wastewater	levofloxacin	Natural photo-Fenton/ H_2O_2/Fe^{2+}	77.9-85.5%	(He et al., 2021)
40	Aq. systems	Carbamazepine	H_2O_2/UV/FeOCl	92%	(S. Sun et al., 2021)

41	Aq. system	cloxacillin	Photo-Fenton/VUV/Fe^{2+}	99%	(Moussavi, Rezaei, & Pourakbar, 2018)
42	wastewater effluents	Carbamazepine, crotamiton, ibuprofen	UVA/Fe^{III}-NTA/H_2O_2	92%	(Dong et al., 2019)
43	Aqueous system	ketoprofen, diclofenac, paracetamol	UV-LED/Ferrioxalate /H_2O_2	80%	(Marchetti & Bessa Azevedo, 2020)
44	Aqueous system	Carbamazepine	Solar light/pyrite-Tartaric acid/	70%	(Guo et al., 2021)
45	deionized water and hospital wastewater	Anastrozole	Fe^{2+}/H_2O_2/Solar light	DW matrix 95%, HWW 51%	(Sanabria, Scunderlick, Wilde, Lüdtke, & Sirtori, 2021)
O_3/H_2O_2					
46	Ultrapure water Spiked WWTP effluents	Sulfamethoxazole	O_3/H_2O_2	100%	(Gomes, Gando-Ferreira, Quinta-Ferreira, & Martins, 2018)
47	Aq. system	Sulfasalazine (SSZ), Sulfamethoxazole (SMX), Sulfamethazine	O_3/H_2O_2	SSZ = 98.10%, SMX = 89.34%, SMT =	(Pelalak et al., 2020)

		(SMT) and Metronidazole (MNZ)		86.29% and MNZ = 58.70%	
48	-	Carbamazepine	O_3/hydrodynamic cavitation/ H_2O_2	58.3%	(Thanekar, Panda, & Gogate, 2018)
49	Aq system	Carbamazepine, 17 thinylestradiol(EE2)	O_3/H_2O_2	CBZ = 80%; EE2 = Approx. 60%	(Z. Liu et al., 2019)
$UV/O_3/H_2O_2$					
50	Aq. system	Carbamazepine, 17 thinylestradiol (EE2)	$UV/O_3/H_2O_2$	CBZ = 80%; EE2 = Approx. 60%	(Z. Liu et al., 2019)
51	Spiked ultrapure and tap water	Sulfamethoxazole	UV-mercury lamp O_3/H_2O_2	100%	(Moradi & Moussavi, 2018)
52	Ultrapure water	Penicillin G	UV-mercury lamp/ O_3/H_2O_2	80%	(Luu, Minh, & Lee, 2018)
53		paracetamol	$UV/O_3/H_2O_2$	significant	(Bavasso, Poggi, & Petrucci, 2020)

54	urban wastewater	carbamazepine, diclofenac, ibuprofen, metoprolol, sulfamethoxazole,	O_3/UV/H_2O_2	Carbamazepine = 76.4%, diclofenac = 87.2%, Irbesartan = 79.9%, metoprolol = 24%, sulfamethoxazole = 53.5%	(Schoenell, Otto, Rodrigues, & Metzger, 2021)

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