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REVIEW **Open Access**

Environmental fate of tetracycline antibiotics: degradation pathway mechanisms, challenges, and perspectives

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Abstract

Tetracycline pollution is a growing global threat to aquatic and terrestrial biodiversity due to its unprecedented use in aquaculture, livestock, and human disease prevention. The influx of tetracycline may annihilate the microbial ecology structure in the environment and pose a severe threat to humans by disturbing the food chain. Although significant research data are available in the literature on various aspects of tetracycline, including detection techniques, degradation mechanisms, degradation products, and policy statements to curtail the issue, there is a scarcity of a report to compile the recent data in the literature for better analysis and comparison by the policymakers. To achieve this paucity in knowledge, the current study aims at collecting data on the available degradation strategies, mechanisms involved in biodegradable and non-biodegradable routes, the main factor affecting degradation strategies, compile novel detection techniques of tetracycline antibiotics in the environment, discuss antibiotic resistance genes and their potential role in degradation. Finally, limitations in the current bioremediation techniques and the future prospects are discussed with pointers for the decision-makers for a safer environment.

Keywords: Tetracycline, Degradation pathways, Biosensors, Mechanisms, Antibiotics

Background

Antibiotics are complex molecular compounds with extraordinary antimicrobial abilities. With the accidental discovery of penicillin back in 1928, an array of antibiotics has been developed afterward. Antibiotics are classified based on mechanism of action, bacterial spectrum, type of activity, and route of administration, but the most useful is chemical structure. However, antibiotics belonging to the same structural class share similar effectiveness and allergic or toxic potential [1, 2]. Antibiotics are being used as a therapeutic drug and have successfully been applied in animal farming as growth promoters and improving feed efficiency [3]. Though its use in feed to improve animal growth is banned in the European Union, its use is common in the USA, Canada, and China [4]. Antibiotics are the most successful drugs in the pharmaceutical industry for human and animal treatment alike. Global antibiotic consumption has increased immensely. An increase of 65% defined daily dose was recorded between 2000 and 2015, leading to an antibiotics consumption rate up to 39% [5]. China uses up to 180,000 tons of antibiotics for both human and agricultural purposes [6].

Tetracyclines (TCs) are the most common antibiotic drugs in the world. This broad-spectrum family of antibiotics is known to inhibit protein synthesis in bacteria besides combat a variety of bacterial infections. TCs are derived from various *Streptomyces* species, and a total of twenty compounds are introduced in the market as antibiotics [7]. The basic structural element is a tetracyclic ring system with various hydroxyl, methyl, keto, and dimethylamino functional groups [8]. TCs are divided into three classes based on their nature, dosage,

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and elimination time; oxytetracycline, chlortetracycline, and TC. The current study mainly focuses on TC unless otherwise stated. Structural comparison (Fig. 1) of several tetracyclines and mode of action is beyond the current study's scope. The readers are referred to the work of Chopra and Roberts [9]. TCs have widespread usage in human therapy, aquaculture, and animal husbandry because TCs have low production prices, high quality, and great purity. TCs is ranked second worldwide in production and usage while first in China [10].

Though tetracycline presents several benefits to human and animal health, its overuse is associated with allergic reactions in humans, bacterial resistance, and significant fluctuations in environmental microflora that detrimental to environmental health. It is linked to the difficult metabolization of TCs in the human and animal digestion system and, therefore, excreted into the environment by human feces and animal excreta up to 50–80% [11]. Hospitals, pharmaceutical industries, and livestock also add the share in the accumulation of TC in the wastewater systems [12]. Domestic wastewater contains low (1 µg L^{-1}), whereas hospital wastewater has a relatively higher TCs concentration, 100 µg L^{-1} [13, 14]. Figure 2 illustrates the aquatic and terrestrial routes of TCs in the environment. TCs are stable and difficult to oxidize in the environment but are unstable at extreme pHs, forming epi- and anhydro- products supported with their relatively low Henry's constant ($3.45 \times 10-24$ to $3.91 \times 10-26$ atm^3 mol^{-1}) that indicate the low volatility, ultimately describing lesser degradability as well. The conventional methods aimed at treating wastewater cannot effectively eliminate large quantities of tetracycline; besides, TCs easily make stable compounds due to their binding potential to Ca^{+2} and other ions [15, 16]. Therefore, a significant portion is detected in wastewater, surface water, groundwater, sludge, and sediments.

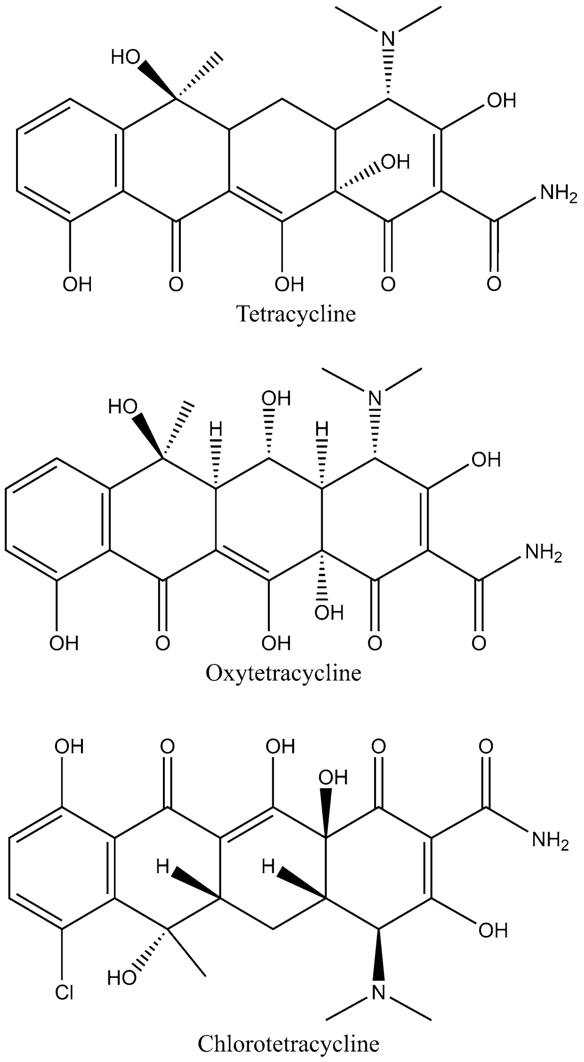

Fig. 1 Structural comparison of tetracycline, oxytetracycline, and chlortetracycline

Antibiotics like TC are becoming a serious threat to the environment due to their unaccounted use in subtherapeutic animal growth promotion and human treatment. The environmental fate of antibiotics has emerged as a research topic in the previous decade to address the issue. Long-term detrimental effects of TC would lead to ecological imbalance due to poor degradation of TC in the current treatment processes. It is of utmost importance to counter TCs linked to environmental pollution because it severely impacts human health due to the development of bacterial resistance. Non-efficient wastewater systems are the source of antibiotics in the food web that further ruining human health. Soil seepage is drastically affecting the soil microbial flora. Different removal strategies have been developed to degrade TCs from the environment. However, microbial biodegradation is the future of the removal strategies due to its low capital cost, effectiveness, and process simplicity. The literature is deficient in providing a specific review on tetracycline degradation strategies, proposed degradation pathways of TC in various microorganisms, and the role of resistant genes in TC degradation. Therefore, this review aims to collect data and discuss the merits and demerits of available TC degradation techniques, the impact of anti-resistant genes affecting the microbial biodegradation, new insights into the detection of antibiotics, and limitations and prospects of applying microbial degradation for TC degradation.

Degradation strategies of tetracycline

TCs in the environment can be degraded through several pathways. The degradation mechanism

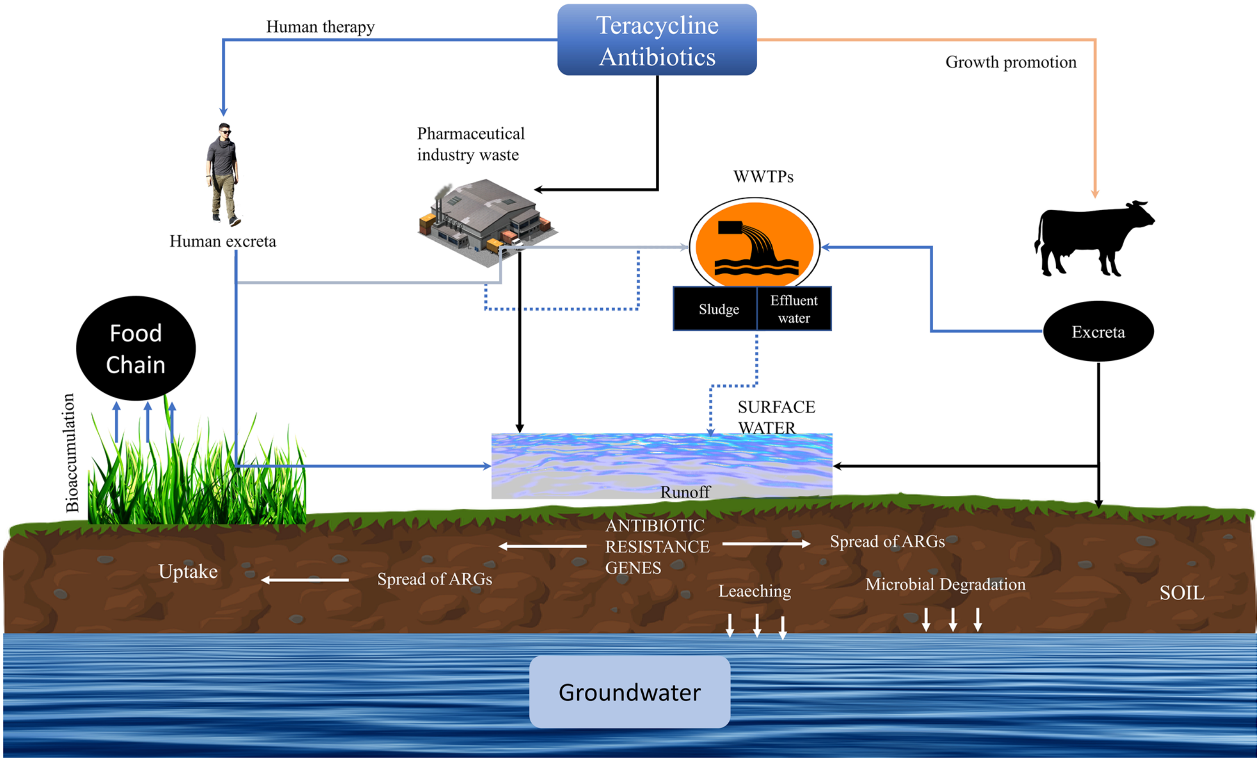

Fig. 2 Aquatic and terrestrial routes of tetracycline in the environment

breakdown macromolecules to smaller molecules that are relatively less harmful and non-hazardous. The degradation mechanism produces secondary metabolites that may cause pollution and are challenging to mineralize. The chemical structure of TCs (Fig. 1) is essential to understand its degradation route by different degradation techniques. Several removal strategies for TCs have been developed for TC degradation that can broadly be categorized as non-biodegradable and biodegradable. Each strategy has its own merits and demerits. However, the best strategy would be cost-effective, high degradation efficiency, environmentally benign, and up-scalable to the industry level. Non-biodegradable methods are expensive, energy-intensive, and environmentally less benign. Biodegradation is the cost-effective and most suitable approach to degrade TCs in the soil at the expense of microbial enzyme machinery. Understanding the degradation mechanism of different enzymes at the molecular level is crucial for further scale-up to pilot and industrial scale. However, the microbial degradation pathway of TC by different bacteria is not much explored, except some references for pure cultures are reported [17, 18].

Non-biodegradable route of TC removal

Advanced oxidative processes

The inefficiency of conventional methods of removing TC antibiotics from the wastewater streams resulted in developing advanced treatment technologies, including advanced oxidation processes (AOPs). AOPs are cost-effective as the processes operate with less energy than direct oxidation. The process is based on hydroxyl (•HO) radicals that react with the organic compounds. Hydroxyl radicals (•HO) were reported to have higher oxidative reactivity ($E° = 2.8$ V) than ozone and chlorine gas, but their selectivity is relatively poor [19]. These highly reactive •HO radicals are generated by H_2O_2 and ozone along with metal or semimetal catalysts. AOPs could produce low toxic intermediates, leading to complete mineralization. Advanced oxidation processes are further divided based on light, catalysts, and ultrasounds such as Fenton processes, ozonation, photocatalysis, UV photolysis, and sonolysis. These processes have been studied for wastewater treatment aiming to degrade micropollutants. Table 1 gives a quick overview of comparison on different non-biodegradable

Table 1 A comparison of non-biodegradable tetracycline methods

Non-biodegradable method	Advantages	Disadvantages	Influencing parameters
Ozonation	High process efficiency Lesser O_3 consumption Environmentally safe, i.e., no sludge production Improve efficiency by catalyst utilization	High cost Lesser solubility in water Possible production of carcinogenic by-product (bromate) Mass transfer limitation	Ozone dose pH and temperature of the reaction medium Type of catalyst Initial TC concentration
Fenton process	High performance Simplicity Non-toxic Environmentally safe end products generation, i.e., H_2O, O_2 Possibility of catalyst utilization to improve the efficiency Possibility of combination with other non-biodegradable methods to improve efficiency	Strict pH range High H_2O_2 consumption Ferric sludge generation	Operating pH and temperature Ferrous ion concentration H_2O_2 concentration Initial TC concentration
Photolysis/photocatalysis	Reaction conditions easily met Complete decomposition of organic matter Strong redox ability Low cost Long durability No adsorption saturation Potential upscale possibility	Inefficient visible light utilization Rapid degradation of photogenerated intermediate compounds Mass transfer limitations Incomplete mineralization	Intensity of radiation Type of catalysts Water hardness pH Redox conditions Initial TC concentration Humic acid concentration
Sonolysis/sonochemical oxidation	Green or safe technique No or negligible secondary pollution Ultrasound waves clean catalyst surface thereby increasing catalyst efficiency Low cost reactors In combination with Fenton process reduce sludge generation	Non-selective mechanism High energy consumption High maintenance cost	Ultrasonic power pH Initial TC concentration Reaction time Redox potential

The data for comparison are taken from the references [27, 32–36]

methods regarding advantages and disadvantages, applied for TC degradation.

Ozonation

Ozone is a well-known oxidizing agent that has been extensively studied for tetracycline degradation. It offers advantages over other technologies, such as no chemical sludge generated after ozonation of organic and inorganic pollutants, ozone decomposes quickly to oxygen in water [20]. Understanding the ozonation mechanism is pivotal in determining its role in TC degradation. Ozonation works by two mechanisms: direct reaction with liquefied ozone or indirect reaction by OH radicals formation [21]. Ozone primarily attacks the double bonds, aromatic ring, and amine functional groups of organic compounds like TC in an aqueous form. Ozone reacts via Direct 1,3-dipolar cycloaddition to C=C, C=N, N=N, and in situ generations of •HO. Highly reactive species are generated during the ozone decomposition, especially at alkaline pH [22]. Ozone reacts with TC in its protonated form $[H^+]$ and adds one and two oxygen atoms at C11a-C12 and C2-C3 locations, respectively [23]. C11a-C12 double bond is highly susceptible to ozone attack than C2-C3 double bond because it bears two carbonyl groups while the former contains only one carbonyl group. Unstable epoxide intermediate is generated during this process by the release of an O_2 molecule by transient ozonide. Epoxide quickly undergoes a rearrangement with hydroxyl groups at C12, resulting in an oxidized product of size 460 Da. Similarly, another product of size 476 Da was generated at double bond C2-C3 [23].

Several factors, including pH, tetracycline concentration, temperature, ozone generation rate, and catalyst dosage, if applied, play their role in effective TC degradation by ozonation. pH plays a crucial role in the ozonation mechanism. At low pH, the hydroxyl group (OH^-) at the ring I of TC was non-dissociated while the amide functional group (CO–NH) turns into protonated form. This results in a decrease in electron densities on C2-C3 double bond and amide and keto groups at C1 position via conjugation. The decreased electron densities lower the probability of ozone attack at C2-C3 position. Khan et al. [24] proposed an ozone-dependent TC degradation pathway based on TC chemistry, ozonation mechanisms, and the mass spectroscope (M.S.) spectra of TC products. Ozone complemented TC degradation, at a lower pH of 2.2, resulted in oxidized products of *m/z* value of 461, 477, 509, at C11a-C12 location, while a product of *m/z* value of 416 at C2-C3 location. Moreover, ozonation at the said locations gave products of *m/z* 432, 480, 448, 525, and 496. In comparison to lower pH, higher pH of 7 resulted in only three products. The authors speculated that at higher pH, free radicals non-selectively react with intermediate products of TC leading to low molecular weight final products that need advanced, sophisticated instrumentation to detect and quantify. Gulnaz and Sezer [25] found that 50% of TC was degraded within 10 min of Ozonation at pH 3 while complete removal was seen in 40 min ozonation. The authors further reported ozone efficiency for TC degradation follows the order of pH 3 > pH 7 > pH 11.

In contrast, TC degradation is also reported to be favored by higher pH. Wu et al. [26] studied TC degradation at pH values of 5, 7, and 9 for 5 min of Ozonation. The authors found a direct relation in degradation reaction rate constant with alkaline conditions due to hydroxyl radicals' contribution. Higher pH is responsible for a higher OH^- radicals concentration that is recognized as more reactive than ozone. The authors concluded a higher rate constant of 0.890 min^{-1} at pH 9 than pH 5 (0.592 min^{-1}). Ozonation is reported to promote TC degradation but does not lead to its mineralization. Several organic compounds are generated during ozonation, but their mineralization is slow [24].

Catalysts like metal oxides can enhance the ozonation process to remove antibiotics and their products. Catalytic ozonation is categorized as homogeneous and heterogeneous ozonation. Ozone decomposition is favored by transition metal ions in the former category while by solid catalysts in the latter category [27]. A comprehensive mechanism of homogeneous and heterogeneous catalytic ozonation is reviewed elsewhere [27]. Catalyst can easily be separated from the liquid and reuse in heterogeneous ozonation catalysis [20]. ZnO nanoparticles catalyzed ozonation potentially degrade TC due to high surface area and lesser production cost. ZnO-ozonation achieved 94% OTC removal at pH 7 after 5 min at ozone generation rate of 1.38 mg /s. [21]. In another study, 88.52% TC degradation efficiency was achieved by $ZnO/\gamma\text{-}Fe_2O_3$ nanocomposite [28]. Cobalt-modified silicate ore (CoSiO) catalyzed ozonation removed 93.2% TC [29]. Another catalyst, cerium-doped compound $Mn_3Gd_{7-x}Ce_x(SiO_4)_6O_{1.5}$ reported to increase the TC degradation up to 15% [30].

A load of research was published on ozonation and novel catalysts to improve the ozonation efficiency. In a recent study, Ostman et al. [31] reported Sweden's first full-scale ozonation treatment plant for removing antibiotics. However, the study did not mention about tetracycline removal. Ozonation mechanism still needs to be much explored regarding homogeneous and heterogeneous catalysis for optimum reaction parameters. Catalytic ozonation also faces issues like ozone adsorption on metal surfaces that need to be explored. A negative effect of inorganic ions typically presents in wastewater streams on the ozonation process due to their high affinity towards active catalytic sites should be addressed. Novel stable catalysts with enhanced ozonation efficiency should be developed to lower the ozone dose in the reaction process.

Fenton process

H.J. Fenton first reported the Fenton reaction in 1984 by describing that oxidative potential of H_2O_2 could be enhanced using Fe^{2+} as catalyst under acidic conditions [37]. The reactions involved in Fenton processes are presented in Eqs. 1–1d. Equation 1 is considered the core reaction involved in the Fenton chemistry. A detailed insight into the Fenton and Fenton-like reaction chemistry is already presented in a review by Babuponnusami and Muthukumar [35]. The importance of •OH-related reactions is overwhelming as seen by more than 1700 rate constants reported in the last few decades [38]. An in-depth overview of different Fenton processes, including single-Fenton and coupled-Fenton processes, reaction parameters optimization for wastewater treatment is reviewed by Zhang et al. [39]. Classical Fenton or coupled-Fenton processes have been successfully applied to degrade TC, including photo-Fenton [34], sono-Fenton [40], and electro-Fenton process [41].

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^- \quad (1)$$

$$\bullet OH + H_2O_2 \rightarrow HO_2 + H_2O \quad (1a)$$

$$Fe^{2+} + \bullet \mathrm{OH} \rightarrow \mathrm{Fe}^{3+} + \mathrm{OH}^- \quad (1b)$$

$$Fe^{3+} + HO_2\bullet \rightarrow Fe^{2+} + O_2 + H^+ \quad (1c)$$

$$\bullet \mathrm{OH} + \bullet \mathrm{OH} \rightarrow \mathrm{H_2O_2} \quad (1d)$$

Fenton reactions are pH-dependent regardless of the substrate. Optimum pH is reported for Fenton reactions is around 3 [42]. At higher pH, reaction efficiency is lesser due to lower generation of OH^- radicals, even auto-decomposition of H_2O_2 is noted [43]. Other influencing factors for classical Fenton reactions are Fe^{2+} concentration, initial concentration of the target organic compound, and temperature [35]. Fenton and Fenton-like processes have been applied to wastewater treatment plants to degrade anthropogenic compounds such as phenol, nitrophenol, chlorophenol, alkylbenzene sulfonate, etc. [44–47]. Photo-Fenton processes are mostly reported in the literature for TC degradation. Yamal-Turbay et al.

reported total TC remediation and 77% mineralization for 40 mg L^{-1} TC initial concentration at 71.5 mg L^{-1} H_2O_2 and 5 mg L^{-1} Fe^{2+} [48]. In another study, TC degradation was observed under black-light and solar irradiation with different concentrations of $Fe(NO_3)_3$ and H_2O_2. Total TC degradation was noted in the presence of $Fe(NO_3)_3$ after 1 min black-light irradiation [34].

Electro-Fenton is another environment-friendly process where •HO are generated either indirectly at the cathode or directly by anodic oxidation. The process requires lower pH conditions, i.e., pH 2–4. The following reaction sequence (2–4) occurs at the cathode to generate •HO radicals.

$$O_2 + 2H^+ \rightarrow H_2O_2(acidic) \tag{2a}$$

$$O_2 + 2H_2O + 2e \rightarrow H_2O_2 + 2OH^-(neutral, basic) \tag{2b}$$

$$H_2O_2 + 2e \rightarrow 2 \bullet \mathrm{HO} \tag{3}$$

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^- + \bullet\mathrm{HO} \tag{4}$$

The process is advantageous in terms of low cost; however, the main disadvantage is the production of $Fe(OH)_3$ sludge that could be avoided using heterogeneous reagents like metal oxides. H_2O_2 concentration plays a significant role in the degradation of TC, supported by Borghi et al. [49]. The authors conducted a rotational central composite design to investigate influencing parameters temperature, H_2O_2 concentration, and ferrous ion concentration on residual doxycycline concentration and total organic carbon (TOC) in the system. The authors concluded that only one parameter, H_2O_2 concentration showed a statistically significant effect with TOC reduction up to 30%. In another study, a comparison of UV irradiation, electro-Fenton, and photo-electro-Fenton processes was carried out. The authors demonstrated photo-electro-Fenton as the best TC degradation method following the order: photo-electro-Fenton > electro-Fenton > UV irradiation. Besides, Fe_3O_4-graphite cathode was reported to be stable during the degradation process and speculated to be reused, suggesting its valuable potential in TC wastewater treatment [50].

Several researchers studied novel heterogeneous catalysts to avoid $Fe(HO)_3$ sludge production. Zheng et al. [51] prepared a novel Fe@*Bacillus subtilis* heterogeneous catalyst by impregnating iron (iii) chloride hexahydrate and studied it as Fenton's reagent with H_2O_2 addition to degrade TC. The authors reported the complete elimination of TC with negligible iron leaching. Besides, the performance of the catalyst was found to be maintained after three consecutive runs. The ultrasound-assisted Fenton process using magnetite (Fe_3O_4) catalyst was found to remove 93.6% TC within 60 min of reaction with 31.8% removal efficiency of TOC [52]. Wang et al. reported more than 90.7% TC degradation when authors applied ultrasound to 0.2 mM Fe^{2+} and 2 mM H_2O_2 in a novel enhanced sonolysis process [40]. In a recent study, the mesoporous bimetallic Fe/Co catalyst was reported to degrade TC optimally (86% removal rate) at Fe to Co ratio of 2:1, pH 5–9, H_2O_2 30 mmol, and initial TC concentration of 30 mg L^{-1} [53]. Iron-loaded granular activated carbon (GAC-Fe) catalyst reported a limited removal of TC 4.94% [54]. The authors speculated that the lower TC removal rates in GAC-Fe are attributed to the limited surface area, poor structure, and functional groups in the two materials.

Though Fenton processes effectively remove recalcitrant organics in wastewater streams, the process has limitations that need to be removed before its application at the industrial level. Iron levels beyond the acceptable limit could result from the Fenton process that would need another expensive unit operation. Also, sludge generation is an oft-cited demerit of the Fenton process. Novel catalysts should be explored, developed, and tested to tackle the abovementioned issues before industrial application.

Photolysis

Photolysis (photodecomposition, photodissociation, or photodegradation) is the degradation of inorganic or organic compounds by solar irradiation. A comprehensive overview of chemical reactions during photolysis is referenced by [55]. It is an important antibiotic degradation way in the natural aquatic environment. Photocatalytic oxidation is a non-toxic, stable, and low-cost method to disintegrate TC. The photolysis behavior of antibiotic in an aquatic environment is reported to be influenced by dissolved organic matter and nitrate because humic acid in the organic matter upon irradiation results in the generation of various reactive oxygen species that influence antibiotic degradation [56, 57]. Photocatalysis of TC is a complex degradation mechanism resulting in numerous polar and non-polar intermediates during the process.

TC photolysis has been studied with several photocatalyst composites, including TiO_2, hydroxyapatite nanocomposite [58], zinc oxide–Bi_2O_3/TiO_2 heterostructure [59], CdS–TiO_2 heterostructure composite [60], In_2O_3@$ZnFe_2O_4$ heterojunctions [61], Ag–AgBr/AlOOH plasmonic [62], $ZnIn_2S_4$@PCN-224 [63], g-C_3N_4/TiO_2/CdS [64], and without catalysts presence [65]. Photocatalyst substantially increased TC degradation rate and overall degradation up to 90% in the case of In_2O_3@$ZnFe_2O_4$ heterojunctions [61]. Zhu et al. identified several intermediate compounds in TiO_2-assisted photocatalysis and proposed a TC degradation mechanism [66]. Humic acid may also reduce the photodegradation rate by inner filtering [67]. In addition to solar radiation, TC can also be degraded by UV irradiation [68].

The fate of antibiotics by photochemical is reported to be affected by humic substances [69]. It may enhance photolysis of organic compounds by the generation of reactive oxygen species like hydroxyl radicals, peroxyl radicals, superoxide, and single oxygen [69] or inhibit photolysis by acting as an inner filter and competitively absorb light and photons, thus causing loss to organic matter removal rate [70]. Photocatalyst TiO_2 was investigated for photodegradation of TC, emphasizing humic acid concerning reaction kinetics and TC's removal mechanism. The authors found a significant inhibition in TC loss by humic acid due to the surface deactivation of TiO_2 and hydroxyl radicals quenching. TiO_2-assisted photocatalysis is reported to significantly enhance the TC degradation efficiency in the presence of Cu^{2+} /Pb^{2+}, SO_4^{2-}/Cl^{-1}, and humic acid, while the presence of tannic acid, gallic acid, citric acid, Tween 80, salicylic acid significantly decreased the degradation efficiency [71]. Niu et al. observed a slight increase in TC photolysis rate at a low humic acid concentration [72]. It was further confirmed that humic acid could inhibit the oxidation pathways initiated by hydroxyl radicals. Jiao et al. reported that the photolysis of TC followed first-order kinetics, and the rate was dependent on the initial concentration of TC. Reaction rate decreased to 0.0014 min^{-1} when TC concentration was increased from 10 to 40 mg L^{-1} [73].

Visible light-driven photocatalysis has gained much attention recently in the remediation of environmental pollution. Novel photocatalysts are being developed to work in visible light spectra [74, 75]. AgI/$BiVO_4$ heterostructured photocatalyst was synthesized in situ that has shown excellent photoactivity for TC decomposition under visible light complemented with structure transformation from double type (AgI/$BiVO_4$) to sandwich-type (AgI/Ag/$BiVO_4$). The authors witnessed 94.91% TC degradation within 60 min while degradation efficiency was much higher than $BiVO_4$ (62.68%) and AgI (75.43%) under similar conditions. Besides, superior mineralization was recorded as 90.46%. Total organic carbon (TOC) was removed within 120 min [76]. The efficiency of a photocatalyst is highly dependent upon the spatial separation of photogenerated electron–hole pair. Therefore, the fabrication of heterogeneous photocatalysts with two different inorganic semiconductors seems an excellent strategy to improve the charge separation of electrons and holes. Luo et al. [77] developed a novel g-C_3N_4/Bi_3TaO_7 nanocomposite photocatalyst for superior TC degradation under visible-light spectra. The authors proposed a Z-scheme system reaction mechanism for TC degradation under visible light. In another study, 81.2% TC degradation was reported by BOC/BWO Z-scheme photocatalyst [78].

In brief, photolysis is an emerging technology with potential applications to treat wastewater at an industrial scale. Novel photocatalysts are being developed to improve the degradation efficiency and encounter the problems like visible light adsorption, fast electron–hole recombination, and bandgap energy. Photolysis for TC degradation is tested on the laboratory scale. Before its industrial application, the technology needs to be tested at a pilot scale to generate techno-economic data for the stakeholders.

Biodegradable route of TC removal

Microbial degradation of TC

Microorganisms could initiate the biodegradation of toxic compounds like TC by opening their loop structure or cutting the attached functional groups. However, a limited number of pure microbial strains are isolated with TC degrading potential (Table 2). Several putative biodegradation pathways of TC have been proposed by different researchers based on biodegradation metabolite products. Yin et al. [18] proposed three putative TC degradation pathways by *Klebsiella* sp. strain TR5 based on 8 metabolites: i) reduction of a hydroxyl group on C-3 of TC followed by successive dehydration reactions at C-12-a and C-6; ii) demethylation on C-4; iii) oxidization of TC on C-5 followed by removal of carbonyl group on C-1 (Fig. 3). In another study, *Klebsiella* sp. strain SQY5 is reported to start TC biodegradation by removing the methyl functional group. Once the hydrolysis opened the ring, the carbonyl group was removed, followed by removing the amine group that leads to successive removal of further two methyl and three hydroxyl groups. During this degradation process, the authors identified nine degradation products and proposed a new putative degradation mechanism [79]. Leng et al. [17] reported that bacterial strain *Stenotrophomonas maltophilia* DT1 initiates TC degradation by demethylation at C-4, followed by carbonyl and amine group removal. The authors identified six biotransformation products during TC degradation. In all the studies reported, it is common that N-methyl, carbonyl, and amine groups are removed from the parent compound during TC biodegradation.

Liao et al. [83] reported microbial degradation of chlortetracycline (CTC) by a mixed microbial community with and without acclimation. The acclimated microbial community showed more effective degradation efficiency. An increase in acclimated microbiota concentration increased biodegradation. Acclimated microbial community resulted in 48.7% and 84.9% CTC removal rate in 1 and 4 weeks, respectively, compared to 15.9% and 32.5% for the non-acclimated microbial community.

Table 2 Pure microbial strains degrading tetracycline

	Microbial strain	Initial TC concentration[1] (mg L^{-1})	pH	Temperature (°C)	% degradation	Degradation pathway	Reference
Pure bacterial cultures	*Stenotrophomonas maltophilia* DT1	50	9	30	89	Denitromethylation, decarbonylation, deamination	[17]
	Sphingobacterium sp. strain PM2-P1-29	20	7	30	50	Not reported	[80]
	Klebsiella sp. strain TR5	200	7	28	90	Oxidation, hydrolysis ring-opening, decarbonylation, deamination, demethylation	[18]
	Bacillus sp. TD-1 *Shewanella* sp. TD-4 *Shewanella* sp. TD-5	100	7.2	37	98.89 94.96 97.60	Not reported	[81]
Pure fungal cultures	*Trichosporon mycotoxinivorans* XPY-10	200–800	7	30	89.61	Epimerization, dehydration, proton-transfer pathway	[82]

The authors further reported a higher 89.8% removal rate at 45 °C while only 18.8% at 5 °C.

TC is found in reasonable quantities in wastewater streams, as stated earlier in this text. Many researchers have studied fate and TC's occurrence in activated sludge systems [16, 84]. TC has been reported non-biodegradable in sludge systems because it can easily sorb up to 90% of sludge by binding to Ca^{+2} and similar ions to form stable complexes [85]. Cetecioglu et al. [86] reported that > 80% TC introduced in the anaerobic reactor was fully or partially degraded. However, complete mineralization was not speculated. TC biodegradation showed a non-biodegradable behavior under nitrate-reducing and sulfate-reducing conditions, while a slightly biodegradable behavior was seen under methanogenic conditions [87]. In contrast, *Klebsiella* sp. SQY5 showed a maximum TC reduction rate and denitrification of 0.113 mg L^{-1} h^{-1} and 4.64 mg L^{-1} h^{-1}, respectively, after 32 and 92 h of inoculation.

Activated sludge is the prime source for novel microbial strain exploration. In a recent study, Yang et al. [88] explored sludge for TC degrading microbial strains and reported four antibiotic-degrading bacterial strain roots to *Pseudomonas, Bacillus,* and *Clostridium* genera. *Pseudomonas* strains showed increased biodegradation potential under aerobic while *Bacillus* and *Clostridium* strains under anaerobic conditions. The authors further suggested that sludge contains 24 bacterial genera with potential antibiotic-degrading capability.

Soil is the main harbor of microorganisms. Bacterial community has shown tolerance towards TC, OTC, and CTC and co-tolerance towards Cu indicating the metabolic potential of bacteria to further utilize these compounds leading to ultimate degradation [89]. Therefore, TC-contaminated soil could be a potential source for isolating bacterial strains capable of degrading TC, possibly employing novel degradation and bio-geo-chemical pathways. Wu et al. [90] isolated *Raoultella* sp. XY-1 and *Pandoraea* sp. XY-2 from TC-contaminated soil capable of degrading 81.72% TC within 12 days in Lysogeny broth medium. The evaluation of the microbial community structure of tested soil during TC degradation revealed four predominant phyla, including *Proteobacteria, Bacteroidetes, Acidobacteria,* and *Chloroflexi.* The nutrients available in the soil also affect the biotransformation potential of microorganisms. *Stenotrophomonas maltophilia* strain DT1 was tested against various nutrients, i.e., No background nutrient (N.B.), peptone (P), peptone plus citrate (P.C.), and peptone plus glucose (P.G.) for TC biotransformation. The strain showed the order of $PC > P > PG > NB = 0$ for biotransformation.

Membrane bioreactors (MBR) have been successfully tested for treating wastewater and are considered superior over conventional wastewater treatment. The impact of TC on semi-industrial MBR was tested for denitrification, coupled with TC biodegradation. No disturbance in MBR was recorded on the injection of TC to eliminate organic matter and nitrification. However, denitrification was affected slightly. It was further confirmed that the origin of activated sludge has a positive impact on MBR performance for TC removal. Activated sludge from a conventional reactor can withstand TC concentration up to 10–20 mg TOC L^{-1} [91].

In comparison, sludge from the MBR reactor can operate optimally up to TC concentration of 40 mg TOC L^{-1} with 90% of TC removal using acclimated sludge. The authors also verified a robust inhibitory effect on the microbial community by TC, but phylum *Proteobacteria*

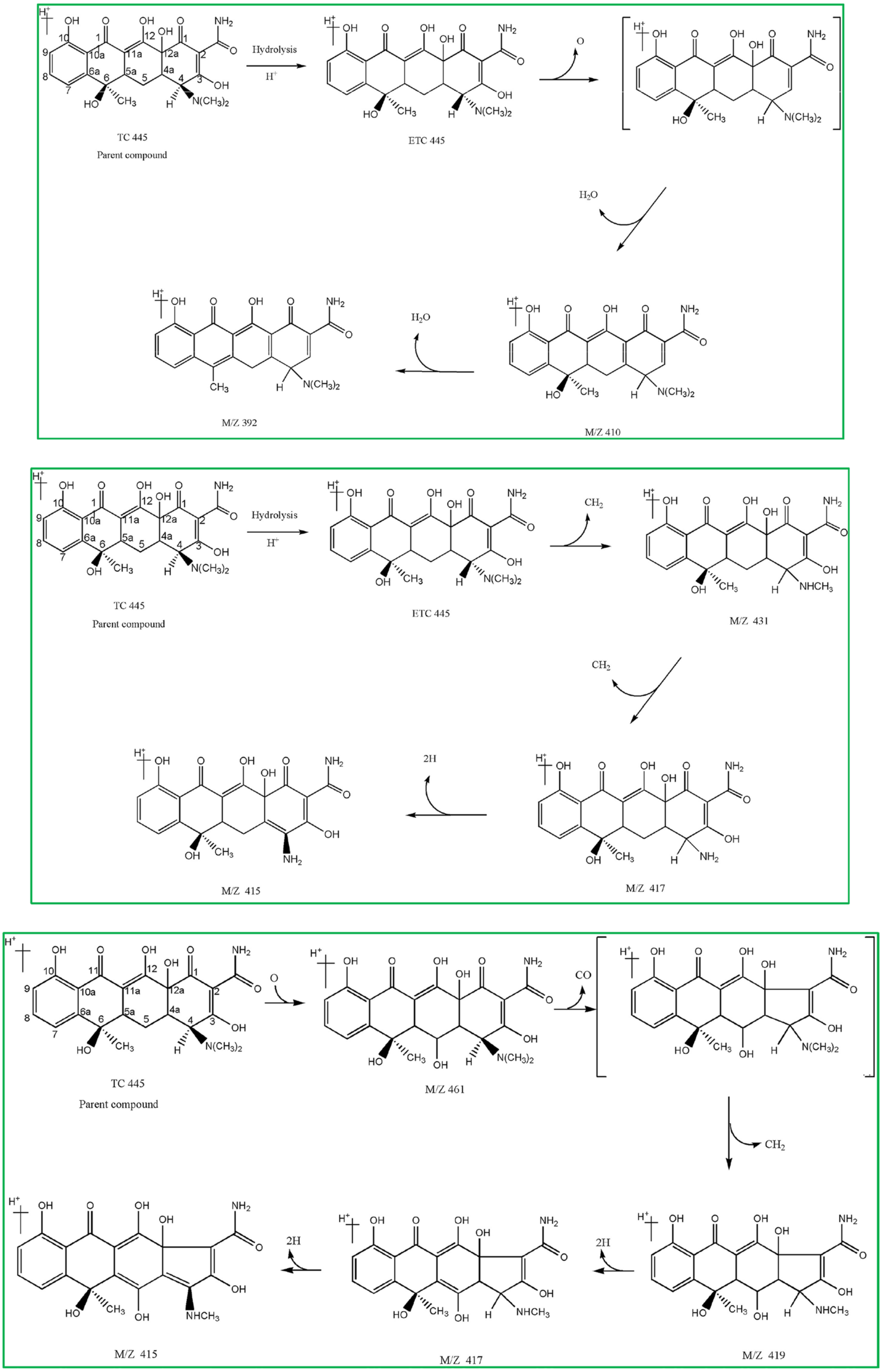

Fig. 3 TC biodegradation pathway proposed in *Klebsiella* sp. strain TR5 [18], reprinted with permission from Elsevier. Copyright [2020]

showed resistance up to 1–1000 µg L^{-1} [92]. Likewise, Tran et al. [93] showed a higher TC removal (83.3–95.5%) by MBR than the conventional process (44.3–87.6%). Sheng et al. [94] observed 100% TC removal for lower (≤ 1 mg L^{-1}) TC concentration in MBR utilizing nitrosifying sludge but low removal (40%) at higher (10 mg L^{-1}) concentration. The data indicated that MBR is a better option than conventional wastewater treatment plants for TC removal. It can further be affirmed that MBR can effectively remove TC in wastewater streams when in a lower concentration. However, to remove higher TC concentration, integration with other removal strategies like Ozonation would be helpful.

TC biodegradation is also studied in integration with other removal strategies. Simultaneous sorption and TC biodegradation were studied by nitrifying granular sludge [95]. The pseudo-second-order kinetic model was verified by the adsorption process, in addition to the complex mechanism of surface adsorption and intra-particle diffusion process. A successive increase in TC removal rate was noted up to 7.30 mg g^{-1} with an increase in TC initial concentration up to 30 mg L^{-1} with non-sterilized granules, but the maximum percent degradation verified was 51.76% at an initial concentration of 20 mg L^{-1}. The authors explained that the sorption of TC to nitrifying granular sludge occurred quickly and reached the maximum sorption capacity after 4 h. At the same time, biodegradation proceeds gradually and continues till 50 h of operation. However, Kim et al. [96] found no evidence for TC biodegradation in activated sludge and reported sorption as the principal TC removal mechanism.

Microbial fuel cell (MFC) is another approach in the primitive stage to biodegrade TC. MFCs offer the advantage of utilizing organic compounds from readily biodegradable to refractory organics and convert them into electricity. Electrodes in MFCs act as continuous electron acceptors for anaerobic microorganisms, resulting in enhanced organic matter degradation under anoxic conditions. Wang et al. [97] studied a novel approach of anaerobic degradation of TC by MFC using glucose-TC mixtures under gradient acclimation conditions. The authors reported 79.1% TC degradation within 7 days of operation, much higher than the conventional anaerobic method (14.9%). In another study, Wang et al. [98] reported 74.2% and 78% degradation rate of CTC and OTC, respectively, by MFC. Since MFCs could be open circuit and closed circuit, it was found that TC removal efficiency is higher in closed circuits MFCs than open circuit ones.

An MFC coupled constructed wetland was successfully tested for wastewater containing TC and sulfamethoxazole. Zhang et al. [99] reported significant decrease in TC and sulfamethoxazole concentration with the development of resistance genes. Another report found that the 3D-biofilm electrode reactor removed TC up to 95% [100]. Since TC degradation by MFCs is at a developmental stage, limited data is available in the literature that also points out research potential in this research area.

Factors affecting microbial TC biodegradation

Microorganisms thrive best at specific parameters for optimum growth and metabolic activities like temperature, pH, and nutrient conditions. To optimize the TC biodegradation by various bacteria, researchers have optimized the reaction conditions, including pH, initial TC concentration, and temperature. Leng et al. [17] studied *Stenotrophomonas maltophilia* DT1 at different pH conditions for optimum TC biodegradation. The authors verified the fastest TC hydrolysis rate at initial pH of 10; the hydrolysis rate was increased with an increase in pH. The highest TC biotransformation was visualized at pH 9. In comparison, a lag phase of 3 days was observed when pH was 6 at the reaction initiation.

The initial concentration of antibiotics like TC is vital in determining biodegradation potential and the rate of biodegradation by microbial communities. Degradation ratio of *Klebsiella* sp. SQY5 is reported to increase with an increase in initial TC concentration when tested from 10 to 100 mg/L. The maximum degradation ratio reached up to 89.66% for 80 mg/L initial TC concentration. However, the degradation ratio tends to decrease afterward, but it is interesting to know that since strain SQY5 can utilize TC as a carbon and energy source, it can withstand a selection pressure of 100 mg/L TC but with a lower degradation ratio [79].

Stenotrophomonas maltophilia DT1 is reported to show the Michaelis–Menten model of biotransformation kinetics of TC as a function of initial TC concentration. The degradation rate of DT1 strain increased to 75 mg/L initial concentration; afterward, it decreased [17]. *Klebsiella pneumonia* was identified from chicken manure that can degrade up to 90% TC within 36 h at an initial concentration of 200 mg/L under optimized conditions [18]. *Sphingobacterium* sp. PM2-P1-29 reported degrading TC with up to ~ 50% decrease in OD363 for a 27-h incubation period [80].

In addition to bacteria, yeast strain *Trichosporon mycotoxinivorans* XPY-10 was studied for TC biodegradation at a concentration of 600 mg/L. The strain managed to degrade TC up to 78% within 7 days [82]. Recombinant *E. coli* strain ETD-1 was reported to degrade 95% doxycycline within 48 h at an initial concentration of 50 mg L^{-1} [101].

As far as temperature is concerned, little info is available on this aspect. Shen et al. [102] noted that TC degradation rates increased in swine manure by an increment in temperature up to 55 °C where maximum TC degradation was recorded. During composting, thermal degradation and biodegradation work synergistically to improve TC degradation [103]. Ratasuk et al. [104] investigated the role of temperature, illumination, and pH on the degradation of OTC in swine manure and noted that 65% OTC was degraded after 100 h at 40 °C. Li et al. [105] also stated that temperature and pH are major factors degrading OTC. Limited literature is available on pure microbial strains able to degrade TC. Therefore, future research must be directed to isolate novel bacterial and/or fungal strains for TC degradation.

Enzymatic degradation of TC

Enzymatic preparation has been effectively utilized in removing TC from the environment. Laccase has been extensively used to catalyze the oxidation of a wide range of phenolic and non-phenolic compounds, including environmental pollutants. Therefore, laccase can offer a green alternative in bioremediation and wastewater treatment [106]. Laccases are the largest subgroup of multicopper oxidases widely found in bacteria, fungi, and insects [107]. Laccases are dimeric or tetrameric glycoproteins containing four Cu atoms organized into an active site [108], serving as a backbone for the catalysis process of various substrates, including tetracycline.

The laccase catalysis mechanism involves three steps: a) reduction of type I Cu; b) flow of electrons from type I Cu to type II and type III cluster; c) oxygen reduction to water [109]. The overall mechanism involves four-electron O_2 reduction to water. Initially, the enzyme is completely oxidized at the resting stage. Then at the T1 site, Cu centers reduction (Cu^{2+} to Cu^{+}) occurs by the substrate. After that, dioxygen reduction is initiated at T2/T3 cluster site, forming peroxide intermediates and their subsequent reduction to water molecules. In the final step, all the four Cu centers are oxidized with the release of O^{2-} as a second H_2O molecule. The net result is the oxidation of four substrate molecules to create four radicals while reducing one oxygen molecule to two water molecules [106]. In another study, Suda et al. [110] proposed that TCs biodegradation mechanism mainly involves the oligomerization of oxidized TCs via radical–radical coupling by laccase in the presence of 1-hydroxybenzotriazole (HBT). Crude lignin peroxidase from *Phanerochaete chrysosporium* degraded 95% of 50 mg L^{-1} TC and OTC at 40 U L^{-1} enzyme activity [111]

Enzyme immobilization techniques have been developed to improve enzyme stability, reusability, and lower the cost. Enzymatic membrane reactors have been developed based on laccase immobilized on ceramic membranes to degrade TC in wastewaters. Cazes et al. [112] reported 56% TC degradation with an enzymatic membrane compared to 30% for free laccase. In another report, laccase from *Trametes versicolor* was studied in relation to the pore diameter of the membrane and gelatin concentration for TC degradation. The authors reported a higher specific degradation rate of 175 mg h^{-1} m^{-2} at enzyme and gelatin concentration of 10 g L^{-1} and pore diameter of 1.4 µm [113]. The data indicated that improved reactivity and stability of immobilized enzymes have a positive impact on TC degradation.

Magnetic cross-linked enzyme aggregates (M-CLEAs) are a relatively new immobilization method where CLEAs are attached to amino-functionalized magnetic nanoparticles. Characteristic features of CLEAs are presented in the work of Sheldon [114]. To lower the cost of operation, M-CLEAs are utilized, which present easy separation and recycling of immobilized enzymes from the reaction mixture by the magnetic field [115]. Yang et al. [116] studied M-CLEAs prepared from *Cerrena* laccase for antibiotic treatment and observed effective degradation efficiency for TC, oxytetracycline (OTC) followed by ampicillin, sulfamethoxazole, and erythromycin. *Cerrena* laccase eliminated 100 µg ml^{-1} TC in 48 h at 25 °C. Though it is reported that *T. versicolor* laccase removed 78% of 100 mg L^{-1} TC in 18 h in the absence of a mediator [117], *Cerrena* laccase is proved to be more effective in TC degradation [116]. It is worth mentioning that the redox mediator ABTS was unable to improve the degradation of TC and OTC, although it is the best mediator for the decolorization of Coomassie Brilliant Blue by *C.* laccase.

Laccase oxidation system was coupled with soil adsorption to study the simultaneous removal and biodegradation of multiple antibiotics [118]. Laccase-hydroxybenzotriazole and laccase-syringaldehyde showed higher TC, OTC, CTC, and DC. (doxycycline) removal, while the only laccase showed poor removal efficiency comparable to the control reactor (no laccase). Laccase-mediated oxidation systems and soil adsorption systems resulted in 70% antibiotics removal in just 15 min of reaction while close to 100% in 180 min. In another study, Migliore et al. [119] reported the complete removal of OTC by extracellular laccase by fungus *Pleurotus ostreatus* in 14 days. Likewise, crude lignin peroxidase (40 U L^{-1}) was reported to degrade 95% of TC and OTC at an initial concentration of 50 mg L^{-1} in about 5 min.

Although enzyme-mediated TCs biodegradation is a practical approach with promising results, future research should focus on developing cost-effective sorbent materials, innovative immobilization techniques for multifunctional catalysts with higher catalytic potential. Novel enzymatic bioreactor configuration must be sought for higher degradability with minimum input on enzyme concentrations. Most of the research has been conducted at a lab scale. Therefore, enzyme-mediated degradation must be tested under real field conditions and scale-up to pilot scale. In this regard, bioreactor design, i.e., packed bed or membrane-based for continuous operation, must be carefully decided for optimum results.

Antibiotic resistance genes (ARGs) relation to tetracycline degradation

Antibiotics resistance refers to an increase in minimum inhibitory concentration (MIC) of antibiotics towards microorganisms. In this mechanism, microbes survive antibiotics stress [120]. ARGs are natural in the environment, but their increased prevalence by human activities has led them to consider ARGs as an emerging environmental contaminant [121]. ARGs transfer from environmental bacteria to human pathogens resulting in decreased antibiotic treatment efficiency, thereby causing severe health concerns. Global tetracycline-resistance was 8.7% and 24.3%, respectively, for methicillin-resistant *Staphylococcus aureus* and *Streptococcus pneumoniae* [122]. Tetracycline resistance (TC-resistance) is acquired in the following ways: acquiring some genetic material already carrying resistance genes, mutations at ribosomal binding sites, and chromosomal mutations resulting in overexpression of intrinsic resistance [123]. Resistance to TC is mainly conferred by 1 or more than 36 tet genes [124].

Molecular TC-resistance mechanisms include efflux, ribosome protection proteins, and enzymatic inactivation [125]. Seven efflux pump groups are identified, so far, conferring TC-resistance, most members lie into facilitator superfamily. Only three genes have been reported to inactivate TC [126], while only one enzyme Tet(X) demonstrated confirmed activity in vitro. Tet(X), a flavoprotein monooxygenase, utilizes monohydroxylation to inactivate TC followed by the non-enzymatic breakdown [127]. Nesme et al. [128] reported that tetracycline inactivation is rarely detected in environmental metagenomes. Monooxygenases like Tet(X) are commonly found in nature, catalyzing a range of chemical transformations, including aromatic modifications. Therefore, sequence diversity of flavoenzymes could result in the acquisition of new functions by horizontal gene transfer. So far, limited information is available in the literature on Tet(X) for environmental samples regarding TC biodegradation that warrants future research in this area because enzyme might have been under sampled and could be a potential source of undiscovered inactivating enzymes [129].

Novel antibiotics detection techniques

The conventional antibiotic detection methods are slow and do not provide quantitative data on the antibiotic residues in the environmental samples. Therefore, it is necessary to develop novel antibiotic detection techniques that are rapid, robust, cost-effective, time-saving, and easy to perform. Antibiotic residues in environmental samples are currently detected by high-performance liquid chromatography, gas chromatography–mass spectrometry, and liquid chromatography–mass spectrometry. Chromatography is the most reliable antibiotic detection technique, but it requires expensive instruments, trained personnel, and laborious pretreatment of samples.

Biosensors, in contrast, can circumvent these challenges for rapid and accurate on-site analysis. Biosensors are compact analytical devices with only two main components, a) target signal element, b) signal transducer element. Various biosensors have been developed, including electrochemical, mass-based, optical, enzyme-based, immunosensors, microbial biosensors, aptasensors, calorimetric, and molecularly imprinted polymer sensors. Biosensors selection criteria are based on the intended application. Each biosensor has its potential in a specific field with limitations. The working principle of these biosensors is beyond the scope of the review. The readers are referred to [130, 131]. Biosensors offer several advantages: high selectivity detection, high sensitivity, rapid identification, lesser inhibition to the solute, repeated biocatalyst usage, and applicability to a range of solutes from colorless to colored/turbid samples, portability, on-site pollutants detection, and detection of the targeted compound in complex matrices. Various biosensors have been studied for TC detection, including aptasensors [132–134], calorimetric [135, 136], electrochemical [137] immunosensor [138–140]. For an in-depth understanding of electrochemical and optical aptamer-based sensors, the readers are referred to Jalaian et al. [141]. Delgado et al. [142] developed an ultralow cost electrochemical sensor made of potato starch to detect trace amounts of TC (detection limit–1.15 μmol L^{-1}) in drinking water.

With the advancement in nanotechnology, new sensors are being developed. Nanofabrication on biosensors showed substantial advantages; a) improved optical and electrochemical measurement, b) high portability, and more practical applications. Zhang et al. [143] reported an aptamer nano-biosensor based on nanoporous silicon for the rapid detection of tetracycline. Electrochemical impedance spectroscopy determined a decrease in biosensor impedance with the specific binding of TC. The linear range reported for the sensor was 2.1–62.4 nM. A highly efficient nano-biochemical sensor was developed in a recent report to sense the ultralow concentration of TC (10^{-9} mol L^{-1}) using hot spot surface-enhanced Raman scattering (SERS). The sensor showed TC detection with an enhancement factor of 2×10^8. It was verified that the sensor works optimally at a pH range of 5 and 6 [144] that presents their limitation under harsh conditions.

Biosensors have been developed robustly in the current decade. Real-time, high sensitivity, selectivity, and easy-to-handle detection devices in environmental pollution detection and clinical diagnostics require ever-increasing demand for biosensors development. Much advances in biosensors for biomedical applications are sought, but, in comparison, environmental monitoring is still at the infancy stage due to limitations of inherent challenges in the environmental analysis [145]. In the future, biosensor technology should be focused on the development of microarray and nano-biosensors for multiplexed analyte detection for optimum results under field conditions. Electrochemical and enzymatic biosensors have been extensively used in environmental monitoring, but these biosensors work under a narrow range of optimum temperature and pH. Therefore, research efforts must be put in search of stable materials to improve the biosensor's detection capability under harsh conditions.

Limitation and prospects for bioremediation of tetracycline

Antibiotic contamination is a global threat that has increased the risk of antibiotic resistance in microorganisms. Following the limitations and proposed prospects for future research concerning the degradation of TC: A) conventional wastewater treatment plants should be upgraded with novel bioremediation techniques to treat higher concentrations of tetracycline in wastewater streams effectively; B) most of the research has been conducted on a laboratory scale. Therefore, it is necessary to put efforts towards pilot-scale or industrial-scale research to generate data for policymakers; C) TC degradation occasionally results in complete mineralization due to the toxicity of intermediate products and/or byproducts of the TC degradation pathway that needs more research in this area; D) single degradation processes are not viable for the complete removal of TC from the aqueous and terrestrial environment. Therefore, future research must be directed towards the integration of different degradation pathways like ozonation and adsorption, photocatalysis and ozonation, and most importantly, ozonation and biodegradation; E) activated sludge and contaminated soil have not been fully explored for their potential with respect to the discovery of novel degrading bacterial strains. Much research is needed to discover novel bacterial strains; F) future research should be focused on Omics technologies and recombineering to isolate genes responsible for TC degradation and the development of mutant strains with dedicated antibiotic degradation capacity; G) new cheap materials should be discovered for adsorption processes and biosensor fabrication to reduce the cost; H) novel modification processes should be sought to improve the oxidation at the anode in electrochemical oxidation during the photocatalysis process; I) new nano-sized photocatalysts should be developed that can work effectively in visible light.

Conclusion

Tetracycline antibiotic has widespread usage due to its low cost, effectiveness against bacterial infections, and as a growth promoter in livestock. However, a higher proportion of tetracycline is recovered in the waste stream due to lower biodegradability in human and livestock and poses a severe threat to environmental ecology and human health. Complete tetracycline mineralization is not possible in currently available biodegradable and non-biodegradable routes due to the formation of inhibitory intermediate products and byproducts during the degradation process. The identification of intermediate products is mandatory to propose the degradation pathways. Integration of ozonation and microbial biodegradation is the recommended process for effective removal of tetracycline from aqueous streams. Initial tetracycline concentration, pH, and temperature are found to be the critical factor affecting tetracycline biodegradation. The current study systematically compiled TC degradation strategies and identified pros and cons in each strategy. The study finally concluded with future perspectives and pointers for the decision-makers to work in association with the stakeholders to tackle tetracycline degradation, thereby providing a safer environment to live in.

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Authors' contributions
DZ conceived the idea; FA wrote the manuscript; DZ and JS revised and put additional input in finalizing the manuscript. All authors read and approved the final manuscript.

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None.

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References

1. Kümmerer K (2009) Antibiotics in the aquatic environment–A review–Part I. Chemosphere 75:417–434. https://doi.org/10.1016/j.chemosphere.2008.11.086
2. Mojica ERE, Aga DS (2011) Antibiotics Pollution in Soil and Water: Potential Ecological and Human Health Issues. In: Nriagu JO (ed) Encyclopedia of Environmental Health. Elsevier, Burlington, pp 97–110
3. Cowieson AJ, Kluenter AM (2019) Contribution of exogenous enzymes to potentiate the removal of antibiotic growth promoters in poultry production. Anim Feed Sci Technol 250:81–92. https://doi.org/10.1016/j.anifeedsci.2018.04.026
4. Sarmah AK, Meyer MT, Boxall ABA (2006) A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. Chemosphere 65:725–759. https://doi.org/10.1016/j.chemosphere.2006.03.026
5. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, Goossens H, Laxminarayan R (2018) Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci USA 115:E3463. https://doi.org/10.1073/pnas.1717295115
6. Zheng Q, Zhang R, Wang Y, Pan X, Tang J, Zhang G (2012) Occurrence and distribution of antibiotics in the Beibu Gulf, China: impacts of river discharge and aquaculture activities. Mar Environ Res 78:26–33. https://doi.org/10.1016/j.marenvres.2012.03.007
7. Granados-Chinchilla F, Rodríguez C (2017) Tetracyclines in food and feedingstuffs: from regulation to analytical methods, bacterial resistance, and environmental and health implications. J Anal Methods Chem. https://doi.org/10.1155/2017/1315497
8. Barker SA (1998) Chapter 17 - Antibiotics. In: Deyl Z, Mikšik I, Tagliaro F, Tesařová E (eds) Journal of Chromatography Library. Elsevier, pp 737–777
9. Chopra I, Roberts M (2001) Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev 65:232–260. https://doi.org/10.1128/MMBR.65.2.232-260.2001
10. Hou G, Hao X, Zhang R, Wang J, Liu R, Liu C (2016) Tetracycline removal and effect on the formation and degradation of extracellular polymeric substances and volatile fatty acids in the process of hydrogen fermentation. Biores Technol 212:20–25. https://doi.org/10.1016/j.biortech.2016.03.156
11. Chen A, Chen Y, Ding C, Liang H, Yang B (2015) Effects of tetracycline on simultaneous biological wastewater nitrogen and phosphorus removal. RSC Adv 5:59326–59334. https://doi.org/10.1039/C5RA08434B
12. Mahamallik P, Saha S, Pal A (2015) Tetracycline degradation in aquatic environment by highly porous MnO2 nanosheet assembly. Chem Eng J 276:155–165. https://doi.org/10.1016/j.cej.2015.04.064
13. Yang S, Cha J, Carlson K (2005) Simultaneous extraction and analysis of 11 tetracycline and sulfonamide antibiotics in influent and effluent domestic wastewater by solid-phase extraction and liquid chromatography-electrospray ionization tandem mass spectrometry. J Chromatogr A 1097:40–53. https://doi.org/10.1016/j.chroma.2005.08.027
14. Pena A, Paulo M, Silva LJG, Seifrtová M, Lino CM, Solich P (2010) Tetracycline antibiotics in hospital and municipal wastewaters: a pilot study in Portugal. Anal Bioanal Chem 396:2929–2936. https://doi.org/10.1007/s00216-010-3581-3
15. Gao P, Ding Y, Li H, Xagoraraki I (2012) Occurrence of pharmaceuticals in a municipal wastewater treatment plant: Mass balance and removal processes. Chemosphere 88:17–24. https://doi.org/10.1016/j.chemosphere.2012.02.017
16. Li B, Zhang T (2010) Biodegradation and adsorption of antibiotics in the activated sludge process. Environ Sci Technol 44:3468–3473. https://doi.org/10.1021/es903490h
17. Leng Y, Bao J, Chang G, Zheng H, Li X, Du J, Snow D, Li X (2016) Biotransformation of tetracycline by a novel bacterial strain *Stenotrophomonas maltophilia* DT1. J Hazard Mater 318:125–133. https://doi.org/10.1016/j.jhazmat.2016.06.053
18. Yin Z, Xia D, Shen M, Zhu D, Cai H, Wu M, Zhu Q, Kang Y (2020) Tetracycline degradation by Klebsiella sp. strain TR5: Proposed degradation pathway and possible genes involved. Chemosphere 253:126729. https://doi.org/10.1016/j.chemosphere.2020.126729
19. Khataee AR, Fathinia M (2013) Chapter 11 - Recent Advances in Photocatalytic Processes by Nanomaterials. In: Suib SL (ed) New and Future Developments in Catalysis. Elsevier, Amsterdam, pp 267–288
20. Gharbani P, Mehrizad A (2014) Heterogeneous catalytic ozonation process for removal of 4-chloro-2-nitrophenol from aqueous solutions. J Saudi Chem Soc 18:601–605. https://doi.org/10.1016/j.jscs.2012.07.013
21. Mohsin MK, Mohammed AA (2021) Catalytic ozonation for removal of antibiotic oxy-tetracycline using zinc oxide nanoparticles. Appl Water Sci 11:9. https://doi.org/10.1007/s13201-020-01333-w
22. Glaze WH (1987) Drinking-water treatment with ozone. Environ Sci Technol 21:224–230. https://doi.org/10.1021/es00157a001
23. Dalmázio I, Almeida MO, Augusti R, Alves TMA (2007) Monitoring the degradation of tetracycline by ozone in aqueous medium via atmospheric pressure ionization mass spectrometry. J Am Soc Mass Spectrom 18:679–687. https://doi.org/10.1016/j.jasms.2006.12.001
24. Khan MH, Bae H, Jung J-Y (2010) Tetracycline degradation by ozonation in the aqueous phase: Proposed degradation intermediates and pathway. J Hazard Mater 181:659–665. https://doi.org/10.1016/j.jhazmat.2010.05.063
25. Gulnaz O, sezer G, (2015) Ozonolytic degradation of tetracycline antibiotic: Effect of PH. Fresenius Environ Bull 25:2928–2934
26. Wu J, Jiang Y, Zha L, Ye Z, Zhou Z, Ye J, Zhou H (2010) Tetracycline degradation by ozonation, and evaluation of biodegradability and toxicity of ozonation byproductsPaper submitted to the Journal of Environmental Engineering and Science. Can J Civ Eng 37:1485–1491. https://doi.org/10.1139/L10-100
27. Nawrocki J, Kasprzyk-Hordern B (2010) The efficiency and mechanisms of catalytic ozonation. Appl Catal B 99:27–42. https://doi.org/10.1016/j.apcatb.2010.06.033
28. Semeraro P, Bettini S, Sawalha S, Pal S, Licciulli A, Marzo F, Lovergine N, Valli L, Giancane G (2020) Photocatalytic degradation of tetracycline by ZnO/γ-Fe2O3 paramagnetic nanocomposite material. Nanomaterials 10:1458. https://doi.org/10.3390/nano10081458
29. Luo L, Zou D, Lu D, Yu F, Xin B, Ma J (2018) Study of catalytic ozonation for tetracycline hydrochloride degradation in water by silicate ore supported Co3O4. RSC Adv 8:41109–41116. https://doi.org/10.1039/C8RA08402E
30. Fu J, Liu N, Mei L, Liao L, Deyneko D, Wang J, Bai Y, Lv G (2019) Synthesis of Ce-doped Mn 3 Gd 7−x Ce x (SiO 4) 6 O 1.5 for the enhanced catalytic ozonation of tetracycline. Sci Rep 9:18734. https://doi.org/10.1038/s41598-019-55230-7
31. Östman M, Björlenius B, Fick J, Tysklind M (2019) Effect of full-scale ozonation and pilot-scale granular activated carbon on the removal of biocides, antimycotics and antibiotics in a sewage treatment plant. Sci Total Environ 649:1117–1123. https://doi.org/10.1016/j.scitotenv.2018.08.382
32. Safari GH, Nasseri S, Mahvi AH, Yaghmaeian K, Nabizadeh R, Alimohammadi M (2015) Optimization of sonochemical degradation of tetracycline in aqueous solution using sono-activated persulfate process. J Environ Health Sci Eng. https://doi.org/10.1186/s40201-015-0234-7
33. Wammer KH, Slattery MT, Stemig AM, Ditty JL (2011) Tetracycline photolysis in natural waters: Loss of antibacterial activity. Chemosphere 85:1505–1510. https://doi.org/10.1016/j.chemosphere.2011.08.051
34. Bautitz IR, Nogueira RFP (2007) Degradation of tetracycline by photo-Fenton process—Solar irradiation and matrix effects. J Photochem Photobiol A 187:33–39. https://doi.org/10.1016/j.jphotochem.2006.09.009
35. Babuponnusami A, Muthukumar K (2014) A review on Fenton and improvements to the Fenton process for wastewater treatment. J

Environ Chem Eng 2:557–572. https://doi.org/10.1016/j.jece.2013.10.011

36. Huang ST, Lee SY, Wang SH, Wu CY, Yuann JMP, He S, Cheng CW, Liang JY (2019) The influence of the degradation of tetracycline by free radicals from riboflavin-5′-phosphate photolysis on microbial viability. Microorganisms. https://doi.org/10.3390/microorganisms7110500
37. Fenton HJH (1894) LXXIII.—Oxidation of tartaric acid in presence of iron. J Chem Soc, Trans 65:899–910. https://doi.org/10.1039/CT8946500899
38. Buxton GV, Greenstock CL, Helman WP, Ross AB (1988) critical review of rate constants for reactions of hydrated electrons, hydrogen atoms and hydroxyl radicals (·oh/·o— in aqueous solution. J Phys Chem Ref Data 17:513–886. https://doi.org/10.1063/1.555805
39. Zhang M, Dong H, Zhao L, Wang D, Meng D (2019) A review on Fenton process for organic wastewater treatment based on optimization perspective. Sci Total Environ 670:110–121. https://doi.org/10.1016/j.scitotenv.2019.03.180
40. Wang C, Jian J-J (2015) Degradation and Detoxicity of Tetracycline by an Enhanced Sonolysis. J Water Environ Technol 13:325–334. https://doi.org/10.2965/jwet.2015.325
41. Luo T, Feng H, Tang L, Lu Y, Tang W, Chen S, Yu J, Xie Q, Ouyang X, Chen Z (2020) Efficient degradation of tetracycline by heterogeneous electro-Fenton process using Cu-doped Fe@Fe2O3: Mechanism and degradation pathway. Chem Eng J 382:122970. https://doi.org/10.1016/j.cej.2019.122970
42. Babuponnusami A, Muthukumar K (2011) Degradation of phenol in aqueous solution by fenton, sono-fenton and sono-photo-fenton methods. CLEAN–Soil. Air, Water 39:142–147. https://doi.org/10.1002/clen.201000072
43. Szpyrkowicz L, Juzzolino C, Kaul SN (2001) A Comparative study on oxidation of disperse dyes by electrochemical process, ozone, hypochlorite and fenton reagent. Water Res 35:2129–2136. https://doi.org/10.1016/S0043-1354(00)00487-5
44. Siedlecka EM, Stepnowski P (2005) Phenols degradation by Fenton reaction in the presence of chlorides and sulfates. Pol J Environ Stud 14:823–828
45. Yalfani MS, Contreras S, Medina F, Sueiras J (2009) Phenol degradation by Fenton's process using catalytic in situ generated hydrogen peroxide. Appl Catal B 89:519–526. https://doi.org/10.1016/j.apcatb.2009.01.007
46. Lin SH, Lin CM, Leu HG (1999) Operating characteristics and kinetic studies of surfactant wastewater treatment by fenton oxidation. Water Res 33:1735–1741. https://doi.org/10.1016/S0043-1354(98)00403-5
47. Sedlak DL, Andren AW (1991) Oxidation of chlorobenzene with Fenton's reagent. Environ Sci Technol 25:777–782. https://doi.org/10.1021/es00016a024
48. Yamal-Turbay E, Jaén E, Graells M, Pérez-Moya M (2013) Enhanced photo-Fenton process for tetracycline degradation using efficient hydrogen peroxide dosage. J Photochem Photobiol, A 267:11–16. https://doi.org/10.1016/j.jphotochem.2013.05.008
49. Borghi AA, Silva MF, Al Arni S, Converti A, Palma MSA (2015) Doxycycline degradation by the oxidative Fenton process. J Chem 2015:1–9. https://doi.org/10.1155/2015/492030
50. Liu S, Zhao X, Sun H, Li R, Fang Y, Huang Y (2013) The degradation of tetracycline in a photo-electro-Fenton system. Chem Eng J 231:441–448. https://doi.org/10.1016/j.cej.2013.07.057
51. Zheng P, Bai B, Guan W, Wang H, Suo Y (2016) Degradation of tetracycline hydrochloride by heterogeneous Fenton-like reaction using Fe@Bacillus subtilis. RSC Adv 6:4101–4107. https://doi.org/10.1039/C5RA24155C
52. Hou L, Wang L, Royer S, Zhang H (2016) Ultrasound-assisted heterogeneous Fenton-like degradation of tetracycline over a magnetite catalyst. J Hazard Mater 302:458–467. https://doi.org/10.1016/j.jhazmat.2015.09.033
53. Li J, Li X, Han J, Meng F, Jiang J, Li J, Xu C, Li Y (2019) Mesoporous bimetallic Fe/Co as highly active heterogeneous Fenton catalyst for the degradation of tetracycline hydrochlorides. Sci Rep 9:15820. https://doi.org/10.1038/s41598-019-52013-y
54. Pan L, Cao Y, Zang J, Huang Q, Wang L, Zhang Y, Fan S, Tang J, Xie Z (2019) Preparation of iron-loaded granular activated carbon catalyst and its application in tetracycline antibiotic removal from aqueous solution. Int J Environ Res Public Health. https://doi.org/10.3390/ijerph16132270
55. Speight JG (2018) Chapter 7 - Redox Transformations. In: Speight JG (ed) Reaction Mechanisms in Environmental Engineering. Butterworth-Heinemann, pp 231–267
56. Andreozzi R, Raffaele M, Nicklas P (2003) Pharmaceuticals in STP effluents and their solar photodegradation in aquatic environment. Chemosphere 50:1319–1330. https://doi.org/10.1016/S0045-6535(02)00769-5
57. Zhan M, Yang X, Xian Q, Kong L (2006) Photosensitized degradation of bisphenol A involving reactive oxygen species in the presence of humic substances. Chemosphere 63:378–386. https://doi.org/10.1016/j.chemosphere.2005.08.046
58. Bekkali CE, Bouyarmane H, Karbane ME, Masse S, Saoiabi A, Coradin T, Laghzizil A (2018) Zinc oxide-hydroxyapatite nanocomposite photocatalysts for the degradation of ciprofloxacin and ofloxacin antibiotics. Colloids Surf A 539:364–370. https://doi.org/10.1016/j.colsurfa.2017.12.051
59. Sood S, Mehta SK, Sinha ASK, Kansal SK (2016) Bi2O3/TiO2 heterostructures: Synthesis, characterization and their application in solar light mediated photocatalyzed degradation of an antibiotic, ofloxacin. Chem Eng J C. https://doi.org/10.1016/j.cej.2016.01.017
60. Li W, Ding H, Ji H, Dai W, Guo J, Du G (2018) Photocatalytic degradation of tetracycline hydrochloride via a CdS-TiO2 heterostructure composite under visible light irradiation. Nanomaterials (Basel). https://doi.org/10.3390/nano8060415
61. Fei W, Song Y, Li N, Chen D, Xu Q, Li H, He J, Lu J (2019) Hollow In2O3@ZnFe2O4 heterojunctions for highly efficient photocatalytic degradation of tetracycline under visible light. Environ Sci Nano 6:3123–3132. https://doi.org/10.1039/C9EN00811J
62. Zhang S, Khan I, Qin X, Qi K, Liu Y, Bai S (2020) Construction of 1D Ag-AgBr/AlOOH plasmonic photocatalyst for degradation of tetracycline hydrochloride. Front Chem. https://doi.org/10.3389/fchem.2020.00117
63. Jin P, Wang L, Ma X, Lian R, Huang J, She H, Zhang M, Wang Q (2021) Construction of hierarchical ZnIn2S4@PCN-224 heterojunction for boosting photocatalytic performance in hydrogen production and degradation of tetracycline hydrochloride. Appl Catal B 284:119762. https://doi.org/10.1016/j.apcatb.2020.119762
64. Liu Y, Tian J, Wei L, Wang Q, Wang C, Xing Z, Li X, Yang W, Yang C (2021) Modified g-C3N4/TiO2/CdS ternary heterojunction nanocomposite as highly visible light active photocatalyst originated from CdS as the electron source of TiO2 to accelerate Z-type heterojunction. Sep Purif Technol 257:117976. https://doi.org/10.1016/j.seppur.2020.117976
65. Yun SH, Jho EH, Jeong S, Choi S, Kal Y, Cha S (2018) Photodegradation of tetracycline and sulfathiazole individually and in mixtures. Food Chem Toxicol 116:108–113. https://doi.org/10.1016/j.fct.2018.03.037
66. Zhu X-D, Wang Y-J, Sun R-J, Zhou D-M (2013) Photocatalytic degradation of tetracycline in aqueous solution by nanosized TiO2. Chemosphere 92:925–932. https://doi.org/10.1016/j.chemosphere.2013.02.066
67. Gao H, Zepp RG (1998) Factors Influencing Photoreactions of Dissolved Organic Matter in a Coastal River of the Southeastern United States. Environ Sci Technol 32:2940–2946. https://doi.org/10.1021/es9803660
68. Redelsperger IM, Taldone T, Riedel ER, Lepherd ML, Lipman NS, Wolf FR (2016) Stability of doxycycline in feed and water and minimal effective doses in tetracycline-inducible systems. J Am Assoc Lab Anim Sci 55:467–474
69. Caupos E, Mazellier P, Croue J-P (2011) Photodegradation of estrone enhanced by dissolved organic matter under simulated sunlight. Water Res 45:3341–3350. https://doi.org/10.1016/j.watres.2011.03.047
70. Zhou L, Ji Y, Zeng C, Zhang Y, Wang Z, Yang X (2013) Aquatic photodegradation of sunscreen agent p-aminobenzoic acid in the presence of dissolved organic matter. Water Res 47:153–162. https://doi.org/10.1016/j.watres.2012.09.045
71. Zhu X, Wang Y, Zhou D (2014) TiO2 photocatalytic degradation of tetracycline as affected by a series of environmental factors. J Soils Sediments 14:1350–1358. https://doi.org/10.1007/s11368-014-0883-7
72. Niu J, Li Y, Wang W (2013) Light-source-dependent role of nitrate and humic acid in tetracycline photolysis: Kinetics and mechanism. Chemosphere 92:1423–1429. https://doi.org/10.1016/j.chemosphere.2013.03.049

73. Jiao S, Zheng S, Yin D, Wang L, Chen L (2008) Aqueous photolysis of tetracycline and toxicity of photolytic products to luminescent bacteria. Chemosphere 73:377–382. https://doi.org/10.1016/j.chemosphere.2008.05.042
74. Wu S, Li X, Tian Y, Lin Y, Hang HuY (2020) Excellent photocatalytic degradation of tetracycline over black anatase-TiO2 under visible light. Chem Eng J. https://doi.org/10.1016/j.cej.2020.126747
75. Lan NT, Anh VH, An HD, Hung NP, Nhiem DN, Van Thang B, Lieu PK, Khieu DQ (2020) Synthesis of C-N-S-Tridoped TiO_2 from vietnam ilmenite ore and its visible light-driven-photocatalytic activity for tetracyline degradation. J Nanomater 2020:1–14. https://doi.org/10.1155/2020/1523164
76. Chen F, Yang Q, Sun J, Yao F, Wang S, Wang Y, Wang X, Li X, Niu C, Wang D, Zeng G (2016) Enhanced photocatalytic degradation of tetracycline by AgI/BiVO4 Heterojunction under visible-light irradiation: mineralization efficiency and mechanism. ACS Appl Mater Interfaces 8:32887–32900. https://doi.org/10.1021/acsami.6b12278
77. Luo B, Chen M, Zhang Z, Xu J, Li D, Xu D, Shi W (2017) Highly efficient visible-light-driven photocatalytic degradation of tetracycline by a Z-scheme g-C3N4/Bi3TaO7 nanocomposite photocatalyst. Dalton Trans 46:8431–8438. https://doi.org/10.1039/C7DT01250K
78. Wu Z, Yan X, Shen H, Li J, Shi W (2018) Enhanced visible-light-driven photocatalytic activity of Bi12O15Cl6/Bi2WO6 Z-scheme heterojunction photocatalysts for tetracycline degradation. Mater Sci Eng, B 231:86–92. https://doi.org/10.1016/j.mseb.2018.10.003
79. Shao S, Hu Y, Cheng C, Cheng J, Chen Y (2018) Simultaneous degradation of tetracycline and denitrification by a novel bacterium, Klebsiella sp. SQY5. Chemosphere 209:35–43. https://doi.org/10.1016/j.chemosphere.2018.06.093
80. Ghosh S, Sadowsky MJ, Roberts MC, Gralnick JA, LaPara TM (2009) Sphingobacterium sp. strain PM2-P1-29 harbours a functional tet(X) gene encoding for the degradation of tetracycline. J Appl Microbiol 106:1336–1342. https://doi.org/10.1111/j.1365-2672.2008.04101.x
81. Wang Q, Li X, Yang Q, Chen Y, Du B (2019) Evolution of microbial community and drug resistance during enrichment of tetracycline-degrading bacteria. Ecotoxicol Environ Saf 171:746–752. https://doi.org/10.1016/j.ecoenv.2019.01.047
82. Huang X, Zhang X, Feng F, Xu X (2016) Biodegradation of tetracycline by the yeast strain Trichosporon mycotoxinivorans XPY-10. Prep Biochem Biotechnol 46:15–22. https://doi.org/10.1080/10826068.2014.970692
83. Liao X, Zou R, Li B, Tong T, Xie S, Yuan B (2017) Biodegradation of chlortetracycline by acclimated microbiota. Process Saf Environ Prot 109:11–17. https://doi.org/10.1016/j.psep.2017.03.015
84. Prado N, Ochoa J, Amrane A (2009) Biodegradation and biosorption of tetracycline and tylosin antibiotics in activated sludge system. Process Biochem 44:1302–1306. https://doi.org/10.1016/j.procbio.2009.08.006
85. Alexy R, Kümpel T, Kümmerer K (2004) Assessment of degradation of 18 antibiotics in the Closed Bottle Test. Chemosphere 57:505–512. https://doi.org/10.1016/j.chemosphere.2004.06.024
86. Cetecioglu Z, Ince B, Gros M, Rodriguez-Mozaz S, Barceló D, Orhon D, Ince O (2013) Chronic impact of tetracycline on the biodegradation of an organic substrate mixture under anaerobic conditions. Water Res 47:2959–2969. https://doi.org/10.1016/j.watres.2013.02.053
87. Cetecioglu Z, Ince B, Azman S, Ince O (2014) Biodegradation of tetracycline under various conditions and effects on microbial community. Appl Biochem Biotechnol 172:631–640. https://doi.org/10.1007/s12010-013-0559-6
88. Yang CW, Liu C, Chang BV (2020) Biodegradation of amoxicillin, tetracyclines and sulfonamides in wastewater sludge. Water 12:2147. https://doi.org/10.3390/w12082147
89. Santás-Miguel V, Arias-Estévez M, Díaz-Raviña M, Fernández-Sanjurjo MJ, Álvarez-Rodríguez E, Núñez-Delgado A, Fernández-Calviño D (2020) Bacterial community tolerance to tetracycline antibiotics in cu polluted soils. Agronomy 10:1220. https://doi.org/10.3390/agronomy10091220
90. Wu X, Gu Y, Wu X, Zhou X, Zhou H, Amanze C, Shen L, Zeng W (2020) Construction of a tetracycline degrading bacterial consortium and its application evaluation in laboratory-scale soil remediation. Microorganisms. https://doi.org/10.3390/microorganisms8020292
91. Prado N, Ochoa J, Amrane A (2009) Biodegradation by activated sludge and toxicity of tetracycline into a semi-industrial membrane bioreactor. Biores Technol 100:3769–3774. https://doi.org/10.1016/j.biortech.2008.11.039
92. Xu R, Wu Z, Zhou Z, Meng F (2019) Removal of sulfadiazine and tetracycline in membrane bioreactors: linking pathway to microbial community shift. Environ Technol 40:134–143. https://doi.org/10.1080/09593330.2017.1380714
93. Tran NH, Chen H, Reinhard M, Mao F, Gin KY-H (2016) Occurrence and removal of multiple classes of antibiotics and antimicrobial agents in biological wastewater treatment processes. Water Res 104:461–472. https://doi.org/10.1016/j.watres.2016.08.040
94. Sheng B, Cong H, Zhang S, Meng F (2018) Interactive effects between tetracycline and nitrosifying sludge microbiota in a nitritation membrane bioreactor. Chem Eng J 341:556–564. https://doi.org/10.1016/j.cej.2018.02.013
95. Shi YJ, Wang XH, Qi Z, Diao MH, Gao MM, Xing SF, Wang SG, Zhao XC (2011) Sorption and biodegradation of tetracycline by nitrifying granules and the toxicity of tetracycline on granules. J Hazard Mater 191:103–109. https://doi.org/10.1016/j.jhazmat.2011.04.048
96. Kim S, Eichhorn P, Jensen JN, Weber AS, Aga DS (2005) Removal of antibiotics in wastewater: effect of hydraulic and solid retention times on the fate of tetracycline in the activated sludge process. Environ Sci Technol 39:5816–5823. https://doi.org/10.1021/es050006u
97. Wang J, He MF, Zhang D, Ren Z, Song T, Xie J (2017) Simultaneous degradation of tetracycline by a microbial fuel cell and its toxicity evaluation by zebrafish. RSC Adv 7:44226–44233. https://doi.org/10.1039/C7RA07799H
98. Wang J, Zhou B, Ge R, Song T, Yu J, Xie J (2018) Degradation characterization and pathway analysis of chlortetracycline and oxytetracycline in a microbial fuel cell. RSC Adv 8:28613–28624. https://doi.org/10.1039/C8RA04904A
99. Zhang S, Song H-L, Yang X-L, Yang Y-L, Yang K-Y, Wang X-Y (2016) Fate of tetracycline and sulfamethoxazole and their corresponding resistance genes in microbial fuel cell coupled constructed wetlands. RSC Adv 6:95999–96005. https://doi.org/10.1039/C6RA20509G
100. Zhang S, Song H-L, Yang X-L, Yang K-Y, Wang X-Y (2016) Effect of electrical stimulation on the fate of sulfamethoxazole and tetracycline with their corresponding resistance genes in three-dimensional biofilm-electrode reactors. Chemosphere 164:113–119. https://doi.org/10.1016/j.chemosphere.2016.08.076
101. Wen X, Huang J, Cao J, Xu J, Mi J, Wang Y, Ma B, Zou Y, Liao X, Liang JB, Wu Y (2020) Heterologous expression of the tetracycline resistance gene tetX to enhance degradability and safety in doxycycline degradation. Ecotoxicol Environ Saf 191:110214. https://doi.org/10.1016/j.ecoenv.2020.110214
102. Shen Y, Wei Y, Zheng J, Fang Y, Chen L (2009) Biodegradation of tetracycline antibiotics residues in swine manure. Chin J Process Eng 9:962–968
103. Ramaswamy J, Prasher SO, Patel RM, Hussain SA, Barrington SF (2010) The effect of composting on the degradation of a veterinary pharmaceutical. Biores Technol 101:2294–2299. https://doi.org/10.1016/j.biortech.2009.10.089
104. Ratasuk N, Boonsaner M, Hawker DW (2012) Effect of temperature, pH and illumination on abiotic degradation of oxytetracycline in sterilized swine manure. J Environ Sci Health Part A 47:1687–1694. https://doi.org/10.1080/10934529.2012.687274
105. Li Z, Qi W, Feng Y, Liu Y, Ebrahim S, Long J (2019) Degradation mechanisms of oxytetracycline in the environment. J Integr Agric 18:1953–1960. https://doi.org/10.1016/S2095-3119(18)62121-5
106. Wong DWS (2009) Structure and Action Mechanism of Ligninolytic Enzymes. Appl Biochem Biotechnol 157:174–209. https://doi.org/10.1007/s12010-008-8279-z
107. Giardina P, Faraco V, Pezzella C, Piscitelli A, Vanhulle S, Sannia G (2010) Laccases: a never-ending story. Cell Mol Life Sci 67:369–385. https://doi.org/10.1007/s00018-009-0169-1
108. Riva S (2006) Laccases: blue enzymes for green chemistry. Trends Biotechnol 24:219–226. https://doi.org/10.1016/j.tibtech.2006.03.006
109. Gianfreda L, Xu F, Bollag J-M (1999) Laccases: A Useful Group of Oxidoreductive Enzymes. Bioremediat J 3:1–26. https://doi.org/10.1080/10889869991219163
110. Suda T, Hata T, Kawai S, Okamura H, Nishida T (2012) Treatment of tetracycline antibiotics by laccase in the presence of 1-hydroxybenzotriazole.

Biores Technol 103:498–501. https://doi.org/10.1016/j.biortech.2011.10.041

111. Wen X, Jia Y, Li J (2009) Degradation of tetracycline and oxytetracycline by crude lignin peroxidase prepared from Phanerochaete chrysosporium–A white rot fungus. Chemosphere 75:1003–1007. https://doi.org/10.1016/j.chemosphere.2009.01.052
112. de Cazes M, Belleville M-P, Petit E, Llorca M, Rodríguez-Mozaz S, de Gunzburg J, Barceló D, Sanchez-Marcano J (2014) Design and optimization of an enzymatic membrane reactor for tetracycline degradation. Catal Today 236:146–152. https://doi.org/10.1016/j.cattod.2014.02.051
113. de Cazes M, Belleville M-P, Mougel M, Kellner H, Sanchez-Marcano J (2015) Characterization of laccase-grafted ceramic membranes for pharmaceuticals degradation. J Membr Sci 476:384–393. https://doi.org/10.1016/j.memsci.2014.11.044
114. Sheldon RA (2011) Characteristic features and biotechnological applications of cross-linked enzyme aggregates (CLEAs). Appl Microbiol Biotechnol 92:467–477. https://doi.org/10.1007/s00253-011-3554-2
115. Kumar VV, Sivanesan S, Cabana H (2014) Magnetic cross-linked laccase aggregates — Bioremediation tool for decolorization of distinct classes of recalcitrant dyes. Sci Total Environ 487:830–839. https://doi.org/10.1016/j.scitotenv.2014.04.009
116. Yang J, Lin Y, Yang X, Ng TB, Ye X, Lin J (2017) Degradation of tetracycline by immobilized laccase and the proposed transformation pathway. J Hazard Mater 322:525–531. https://doi.org/10.1016/j.jhazmat.2016.10.019
117. Llorca M, Rodríguez-Mozaz S, Couillerot O, Panigoni K, de Gunzburg J, Bayer S, Czaja R, Barceló D (2015) Identification of new transformation products during enzymatic treatment of tetracycline and erythromycin antibiotics at laboratory scale by an on-line turbulent flow liquid-chromatography coupled to a high resolution mass spectrometer LTQ-Orbitrap. Chemosphere 119:90–98. https://doi.org/10.1016/j.chemosphere.2014.05.072
118. Ding H, Wu Y, Zou B, Lou Q, Zhang W, Zhong J, Lu L, Dai G (2016) Simultaneous removal and degradation characteristics of sulfonamide, tetracycline, and quinolone antibiotics by laccase-mediated oxidation coupled with soil adsorption. J Hazard Mater 307:350–358. https://doi.org/10.1016/j.jhazmat.2015.12.062
119. Migliore L, Fiori M, Spadoni A, Galli E (2012) Biodegradation of oxytetracycline by Pleurotus ostreatus mycelium: a mycoremediation technique. J Hazard Mater 215–216:227–232. https://doi.org/10.1016/j.jhazmat.2012.02.056
120. Trinh TD, Zasowski EJ, Claeys KC, Casapao AM, Compton M, Lagnf A, Kidambi SD, Levine DP, Rybak MJ (2018) Role of vancomycin minimum inhibitory concentrations by modified population analysis profile method and clinical outcomes in high inoculum methicillin-resistant staphylococcus aureus infections. Infect Dis Ther 7:161–169. https://doi.org/10.1007/s40121-018-0187-0
121. Pruden A, Pei R, Storteboom H, Carlson KH (2006) Antibiotic resistance genes as emerging contaminants: studies in northern Colorado. Environ Sci Technol 40:7445–7450. https://doi.org/10.1021/es060413l
122. Mendes RE, Farrell DJ, Sader HS, Streit JM, Jones RN (2015) Update of the telavancin activity in vitro tested against a worldwide collection of Gram-positive clinical isolates (2013), when applying the revised susceptibility testing method. Diagn Microbiol Infect Dis 81:275–279. https://doi.org/10.1016/j.diagmicrobio.2014.12.011
123. Grossman TH (2016) Tetracycline antibiotics and resistance. Cold Spring Harb Perspect Med. https://doi.org/10.1101/cshperspect.a025387
124. Bryan A, Shapir N, Sadowsky MJ (2004) Frequency and distribution of tetracycline resistance genes in genetically diverse, nonselected, and nonclinical *Escherichia coli* strains isolated from diverse human and animal sources. Appl Environ Microbiol 70:2503–2507. https://doi.org/10.1128/AEM.70.4.2503-2507.2004
125. Markley JL, Wencewicz TA (2018) Tetracycline-inactivating enzymes. Front Microbiol. https://doi.org/10.3389/fmicb.2018.01058
126. Diaz-Torres ML, McNab R, Spratt DA, Villedieu A, Hunt N, Wilson M, Mullany P (2003) Novel tetracycline resistance determinant from the oral metagenome. Antimicrob Agents Chemother 47:1430–1432. https://doi.org/10.1128/AAC.47.4.1430-1432.2003
127. Volkers G, Palm GJ, Weiss MS, Wright GD, Hinrichs W (2011) Structural basis for a new tetracycline resistance mechanism relying on the TetX monooxygenase. FEBS Lett 585:1061–1066. https://doi.org/10.1016/j.febslet.2011.03.012
128. Nesme J, Cécillon S, Delmont TO, Monier J-M, Vogel TM, Simonet P (2014) Large-scale metagenomic-based study of antibiotic resistance in the environment. Curr Biol 24:1096–1100. https://doi.org/10.1016/j.cub.2014.03.036
129. Forsberg KJ, Patel S, Wencewicz TA, Dantas G (2015) The tetracycline destructases: a novel family of tetracycline-inactivating enzymes. Chem Biol 22:888–897. https://doi.org/10.1016/j.chembiol.2015.05.017
130. Mungroo NA, Neethirajan S (2014) Biosensors for the Detection of Antibiotics in Poultry Industry—A Review. Biosensors (Basel) 4:472–493. https://doi.org/10.3390/bios4040472
131. Kivirand K, Kagan M, Rinken T (2015) Biosensors for the detection of antibiotic residues in milk. Biosensors Micro and Nanoscale Appl . https://doi.org/10.5772/60464
132. Niazi JH, Lee SJ, Gu MB (2008) Single-stranded DNA aptamers specific for antibiotics tetracyclines. Bioorg Med Chem 16:7245–7253. https://doi.org/10.1016/j.bmc.2008.06.033
133. Hou H, Bai X, Xing C, Gu N, Zhang B, Tang J (2013) Aptamer-based cantilever array sensors for oxytetracycline detection. Anal Chem 85:2010–2014. https://doi.org/10.1021/ac3037574
134. Liu Y, Yan K, Zhang J (2016) Graphitic carbon nitride sensitized with CdS quantum dots for visible-light-driven photoelectrochemical aptasensing of tetracycline. ACS Appl Mater Interfaces 8:28255–28264. https://doi.org/10.1021/acsami.5b08275
135. Wang Y, Sun Y, Dai H, Ni P, Jiang S, Lu W, Li Z, Li Z (2016) A colorimetric biosensor using Fe3O4 nanoparticles for highly sensitive and selective detection of tetracyclines. Sens Actuators, B Chem 236:621–626. https://doi.org/10.1016/j.snb.2016.06.029
136. Duyen TTM, Matsuura H, Ujiie K, Muraoka M, Harada K, Hirata K (2017) Paper-based colorimetric biosensor for antibiotics inhibiting bacterial protein synthesis. J Biosci Bioeng 123:96–100. https://doi.org/10.1016/j.jbiosc.2016.07.015
137. Mohammad-Razdari A, Ghasemi-Varnamkhasti M, Rostami S, Izadi Z, Ensafi AA, Siadat M (2020) Development of an electrochemical biosensor for impedimetric detection of tetracycline in milk. J Food Sci Technol. https://doi.org/10.1007/s13197-020-04506-2
138. Pollap A, Kochana J (2019) Electrochemical immunosensors for antibiotic detection. Biosensors (Basel). https://doi.org/10.3390/bios9020061
139. Prusty AK, Bhand S (2020) A capacitive immunosensor for tetracycline estimation using antibody modified polytyramine-alkanethiol ultra-thin film on gold. J Electroanal Chem 863:114055. https://doi.org/10.1016/j.jelechem.2020.114055
140. Conzuelo F, Campuzano S, Gamella M, Pinacho DG, Reviejo AJ, Marco MP, Pingarrón JM (2013) Integrated disposable electrochemical immunosensors for the simultaneous determination of sulfonamide and tetracycline antibiotics residues in milk. Biosens Bioelectron 50:100–105. https://doi.org/10.1016/j.bios.2013.06.019
141. Jalalian SH, Karimabadi N, Ramezani M, Abnous K, Taghdisi SM (2018) Electrochemical and optical aptamer-based sensors for detection of tetracyclines. Trends Food Sci Technol 73:45–57. https://doi.org/10.1016/j.tifs.2018.01.009
142. Delgado KP, Raymundo-Pereira PA, Campos AM, Oliveira ON, Janegitz BC (2018) Ultralow cost electrochemical sensor made of potato starch and carbon black nanoballs to detect tetracycline in waters and milk. Electroanalysis 30:2153–2159. https://doi.org/10.1002/elan.201800294
143. Zhang J, Wu Y, Zhang B, Li M, Jia S, Jiang S, Zhou H, Zhang Y, Zhang C, Turner APF (2012) Label-free electrochemical detection of tetracycline by an aptamer nano-biosensor. Anal Lett 45:986–992. https://doi.org/10.1080/00032719.2012.670784
144. Alwan AM, Wali LA, Hasan KK (2020) A new route for developing highly efficient nano biochemical sensors for detecting ultra-low concentrations of tetracycline antibiotic residue in water. Gold Bull 53:39–46. https://doi.org/10.1007/s13404-020-00272-3
145. Shukla VKN, P, (2015) Enzyme based biosensors for detection of environmental pollutants-a review. J Microbiol Biotechnol 25:1773–1781. https://doi.org/10.4014/jmb.1504.04010

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