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Emerging Pharmaceutical Contaminants- Diclofenac: A Review

Kelechi E. Onwuka[1*], Jude C. Igwe[1], Chinonso F. Aaron[2], Chidi.I. Nosiri[2], OkechukwuC. Atasie[2], Chinedu Aguwamba[3], Nwabekee I Uzoamaka[1]

[1]Department of Pure and Industrial Chemistry, Abia State University Uturu, Nigeria. P.M.B. 2000
[2]Department of Biochemistry, Abia State University Uturu, Nigeria. P.M.B. 2000.
[3]Department of Chemical Sciences: Biochemistry Program, Clifford University, Owerrinta, Abia State Nigeria

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Abstract: Numerous studies on environmental remediation have been focused on water pollution by pharmaceuticals. Diclofenac (DCF) is regarded as an anti-inflammatory drug which is used globally. For more than 10 years now, intensive studies have shown the distribution of diclofenac in various environmental media at different concentrations worldwide. In this case, diclofenac behaviour in different environmental matrices especially soil and water were addressed, giving credence to modem remediation techniques. Toxicity issues as it concerns diclofenac in both soil and water as well as exposure to diclofenac metabolites via consumption and abiotic degradation route has also been discussed. Possible Mechanisms of diclofenac interactions with other contaminants, ranging from interactions with metals, other inorganic and organic matter, and with other emerging contaminants and diclofenac metabolites have been duly discussed.

Keywords: diclofenac, contaminants, metabolites, pharmaceuticals, phototransformation product, Wastewater

1.0. Introduction

There are large numbers of pharmaceutical industries present globally, making them one of the biggest and most prominent industries today. Varieties of drugs find application in the maintenance of both human and animal health [1]. Substances like drugs, hormones and antibiotics which find application in medicine biotechnology and agriculture are mostly constituents of pharmaceutical products [1]. In most developed countries, average pharmaceutical products consumption per capita could be found in the range of 50 to 150 grams, but on the approximate is 15 grams globally [2]. As part of a known kind of drugs, pharmaceutically active compounds (PhACs) penetrate both into terrestrial and/or aquatic environments as metabolites that are pharmacologically active or as parent compounds [3]. Yearly, about 100,000 tons or even more of active substances are consumed globally [4]. Drugs are mostly developed for the essence of providing a positive biological effect on the target organisms of interest, although such compounds somehow find their way into the environment

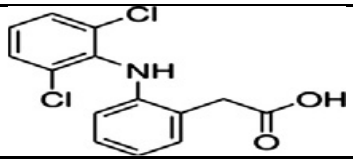
* Corresponding Author: onwukake@gmail.com

resulting in negative biological effects [3]. Globally the outbreak of PhACs and pharmaceuticals into the environment remain a matter of unknown implication. Numbers of studies have reported the presence of pharmaceutically active compounds and other pharmaceuticals in terrestrial and aquatic environments with both long and short-term effects still not better understood [5,6]. However, only quite recently pharmaceutically active compounds have gained attention by ecologists globally [7].

Non-steroidal anti-inflammatory drug (NSAID) among other pharmaceutical active compounds has found wide global application and has also been detected in various environmental matrices in a concentration range of nanograms per litre to milligrams per litre [3]. Additionally, non-steroidal anti-inflammatory drugs are frequently consumed, and this makes their presence in the environment highly noticeable especially in countries where they are sold as over-the-counter (OTC) drugs. Diclofenac has been reported as the most popular pain reliever worldwide which is widely consumed with a market share equivalent to those of its counterparts like naproxen, ibuprofen and mefenamic acid even in their combination [8]. A Swiss pharmaceutical company named Ciba-geigy which has currently merged with Novartis discovered diclofenac in 1973 with the name diclofenac derived from 2-(2,6-dichloroanilino) phenyl acetic acid, which represents its chemical name. diclofenac commonly finds application in disease conditions such as acute trauma and arthritis since they exhibit great pain-relieving and anti-inflammatory properties [1]. It can also serve as an anti-diuretic agent, and its application could be either dermal or oral.

Commercially, DCF has been distributed under various brand names. In Russia, France, Egypt, Portugal, Norway, Belgium, Sweden, Israel, New Zealand, South Africa, Argentina, Turkey and Australia diclofenac is sold as Voltaren; Canada (voltaren emugel), China (votalin), Nigeria (cataflam), Spain (Diclofenaco normon), Germany (Diclo-denk), India (Volini), United States and Korea (Diclofenac-Asteria) [1]. Table 1 displays the physicochemical properties of diclofenac.

Table 1. Physico-chemical properties of diclofenac (in unionized form).

Properties		**Reference**
Structure		[9, 10]
Molecular formula and molecular weight	$C_{14}H_{11}Cl_2NO_2$, 296.16 g mol^{-1}	[9, 11]
CAS no.	15307-86-5 15307-79-6 (disodium salt)	[9, 11]
Water solubility	2.37 mg L^{-1} (25 °C)	[10, 11]
Henry's law constant	4.79×10^{-7} Pa m^3 mol^{-1} (25 °C)	[9, 12]
Melting and boiling points	283–285 °C and 412 °C at 760 mm Hg (predicted) respectively	[10, 11]
pKa	4.15	[10, 11]

Log K_{ow} (logarithm of octanol-water partition coefficient	4.15	[9, 12]

During wastewater treatment, diclofenac is not completely removed while using wastewater treatment plants (WTPs) occasioned by its low degradation and its high usage [1, 13, 14]. However, this makes its presence in rivers and sediments inevitable [5, 6]. Because of its frequent occurrence in drinking water sources and its potential toxicity to organisms at high concentration, diclofenac has recently become a pharmaceutical of interest [15-17]. For better absorption and solubility diclofenac is mostly used in combined state as sodium or potassium salt. To date, dart information exists on the environmental concern and perspectives of diclofenac, although, some previously published studies [1, 18, 19] have emphasized on the Fate of diclofenac in wastewater treatment plants.

This review elaborates on the status of diclofenac in the environment with emphasis on its application, tolerability, occurrence, stability, metabolites and toxicity. Additionally, the hypothetical potential of diclofenac to interact with other emerging contaminants, inorganic and other organic contaminants, as well as their metabolites has been discussed. This review also appraises key research gaps in current knowledge, environmental fate of DCF and its Dynamics as well as its future research needs.

1.1. Legislation and global consumption

The presence of diclofenac has been reported to pose a health hazard to terrestrial organisms [1]. In Nepal, Pakistan and India the use of diclofenac on animals like cattle has endangered vulture population. Even though vultures do not consume diclofenac directly, diclofenac has been proven to be toxic to vultures, when they consume cattle carcasses. India was the first to introduce a regulation banning the production and veterinary application of diclofenac [20]. They even threatened a jail term for those who flaunt the regulation in 2008. In same year, Pakistan and Nepal also banned the application of veterinary drugs, and then Bangladesh in 2010 [21]. The European medicine agency (EMA) has given no approval for the Central market for the utilization of diclofenac for veterinary purposes, but approval is solely based on individual member states. A maximum residue limit has been established for pigs and cattle by the European medicine agency [1].

Spain and Italy began commercial production of DCF in 2013 and their products have been circulated among other countries in the European Union. A merger comprising the IUCN Vulture specialist group, birdlife and Royal Society for the Protection of Birds are continuously campaigning for a global/continental ban on the use of diclofenac for veterinary purposes following the ordeal in India [22]. Recently, diclofenac has been incorporated into the European environmental quality standard (EQS). The community standard documents (COM(2011)876) has reported an average

concentration of 0.1 microgram per litre for diclofenac as the annual quality assessment (QSM). Although this paper is subjected to further review after it has been watched listed and previously revised [23]. Among other pharmaceutical active compounds, diclofenac was incorporated into the European Union control list and adequate monitoring data was obtained to checkmate dangerous mitigation measures. According to the EQS document, the acceptable concentration of 0.1 microgram per litre and 0.01 microgram per litre is allowed. United Kingdom has also incorporated diclofenac into its priority list, thereby causing various water industries to employ newer and efficient techniques for the mitigation of diclofenac from industrial wastewater. A regulatory measure has been put in place against the use of diclofenac by handful of countries globally. On a global scale, other than very scanty regulation at a national or regional level, there are no strict regulations governing diclofenac consumption and production to enable control its presence in various environmental matrices. Unarguably, diclofenac has become an environmental pollutant of urgent concern since it is harmful to terrestrial organisms like vultures and eagles, effort has been made to quantify and assess the level of diclofenac in the environment and establish laws to regulate the drug usage. Setting out a maximum acceptable limit for the concentration of diclofenac in various environmental matrices can also serve as an appropriate guideline [1].

For numerous reasons such as variation in trade names for diclofenac, availability as a generic drug and its human and veterinary application, there is a high level of unattainability on estimating the total quantity of diclofenac consumed globally. However, based on the data obtained from international marketing services, Zhang et al. [18] reported an approximate value of 940 tons of diclofenac consumed globally every year. In 76 major countries globally, about 877 tonnes of diclofenac were sold in 2007, and this value corresponds to approximately 96% of diclofenac sold globally in the pharmaceutical market [18]. Diclofenac was in the 12th position of best seller in the world herzicer as of 2012, and as of 2011, about 1.66 billion dollars in diclofenac turnover equivalent of 15.5% annually was reported [24]. More than 1,000 tons of diclofenac is likely to be consumed yearly, consequence of the variations in sales information as well as previous assessment in quantity of consumption. Furthermore, emerging markets like Brazil, India and China consumes about 60 tons of diclofenac yearly, as addition to already developed markets like the United States [1, 25]. Occasioned by the absence of data for the consumption of diclofenac for veterinary purpose the estimated consumption of diclofenac excluded veterinary practice, this implies that consumption may not skyrocket if included. Emergency Medical Lists (EMLs) incorporates diclofenac in about 74 countries worldwide [1]. Notwithstanding the consistent rise in the market share of diclofenac in North America, no information exists for the exact yearly consumption of diclofenac. Henry [26] reported about 17% and 6% non-steroidal anti-inflammatory drugs representing diclofenac in Canada and the United States respectively.

There is an imminent probability that diclofenac consumption will continue to be on the high side in North America since arthritis and heart related diseases are prevalent among aging population, consequently making the consumption of pain relievers like diclofenac a common routine. Data on annual consumption and prescription of diclofenac is only available for very few countries. Annually, about 4 tons, 86 tons, 26.13 tons, 6.14 tons and 16 tons of diclofenac has been reported for Australia, Germany, Great Britain, Austria, and France respectively according to consumption estimation models [27-31]. However, a total of 179.8 tons per yearly consumption of diclofenac across the European continent has been reported [31]. No data is available for most African and Asian countries consequent upon unavailability of stock on sale as well as lack of survey relative to diclofenac consumption. One could imagine the enormous consumption of diclofenac in these countries, taking into account reported concurrent toxicological effects of diclofenac on birds especially eagles and vultures. A study in 2015 that is based on IMS health data involving 86 countries estimated an average value of 1443 ± 58 tons of diclofenac consumed globally [25]. Deduction from this study showed that about 28.7% and 39.5% of diclofenac is consumed in Europe and Asia respectively. Moreover, this data excludes diclofenac consumption for veterinary purposes. Current data for veterinary applications are not available, however, calculation of total annual global diclofenac consumption may not be realistic [1].

2.0 Environmental Fate of Diclofenac

Drugs are generally designed to cure and care for human and animals, but their presence in the environment at a reasonable concentration can be detrimental. Most pharmaceuticals act by following similar pathways in organisms with same cells, tissues or even target organs, when present in the environment [32]. The potential adverse environmental effect of diclofenac has been reported in numerous literatures [6, 15, 17, 33]. However, the need to understand the origin and Fate of diclofenac to design an efficient technology to monitor and control its presence in the environment remains indispensable. Pharmaceutical industries are responsible for the production of diclofenac which finds application in both humans and animals. Via veterinary or human pathways diclofenac finds its way into landfills or wastewater plants as its metabolites or as diclofenac itself. The tendency that pharmaceuticals directly find their way into wastewater treatment plants via improper disposal and mishandling of pharmaceutical waste can never be underestimated. For this reason, the adoption of wastewater treatment plant as traditionally used for diclofenac removal is not enough [13, 14] since it could allow for leaching of diclofenac into drinking water sources from surface water. Even at environmentally relevant conditions, diclofenac has been reported to pose severe health risks to living organisms. Many studies have reported the negative effect of diclofenac to aquatic organisms [26, 32-34]. A study in 2011 reported the concentration of 100 micrograms per litre no-effect concentration (NEC) of diclofenac from Japanese killifish and freshwater cladocerans

[34], and in another study 320 microgram per litre no observed effect concentration (NOEC) was reported for zebrafish an example of freshwater organism [35].

2.1. Presence in Soil and Aquatic Environment

Numerous literatures have reported the presence of diclofenac in soil. As identified in Ontario Canada, diclofenac may reach topsoil via application of sewage sludge or naturally as a nutrient provider to soil [36]. Study conducted by Scheytt et al. [37] showed low mobility of diclofenac in groundwater as displayed in its adsorption coefficient implying the importance of absorption in Sandy sediments. In the contrary, another study reported slow mobility in Soil rich in organic matter and high mobility in freshwater Column, which leached into surface and drinking water after precipitation [38, 39]. Similar possibilities have been reported in other literatures [40].

Scanty information exists on the toxicity effects of diclofenac in soil on plants and soil microorganisms. The fast degradation of diclofenac in soil as well as the high adsorptivity on soil rich in organic contents remains the only available information [36, 40]. Diclofenac shows no deleterious effects to plant growth and less toxicity to leguminous plants compared to other drugs such as sulfamethazine [41, 42]. However, moderate risk was reported after a portion of land was spread with sewage sludge containing diclofenac [43]. Dart information available on the toxicity and Fate of diclofenac in soil, implies mild tolerability and low toxicity. But in soils rich in organic matter, the adsorptivity of diclofenac into the soil is sacrosanct, thereby posing resistance to aerobic/anaerobic degradation and leaching into groundwater consequently resulting to high level of diclofenac toxicity [1]. There is a need to further investigate the behaviour of diclofenac in agricultural soil with respect to behaviour of underground aquifers. Numerous studies have reported the adverse effect of diclofenac in aquatic environment [1, 29, 32-34]. However, most of these investigations were carried out on laboratory-scale. The concentration of diclofenac was found in nanograms per litre and microgram per litre in surface water bodies and wastewater respectively. Natural processes such as photo transformation, biodegradation, soil retention as well as physicochemical processes employed during wastewater treatment in wastewater treatment plants account for reduced concentrations.

Recent occurrence of diclofenac in aquatic environment in many countries is displayed in table 2. Diclofenac contamination has occurred in lakes, estuaries and Rivers among all the surface water [44-47]. Rabiet et al. [48] and Benoti et al. [49] have reported the presence of diclofenac in drinking water and underground water. Detection of diclofenac has been mostly reported in Europe; however this does not imply that diclofenac is only detected in EU countries. The unavailability of systematic annual data in Asia accounts for the insufficient data to predict the environmental concentration of diclofenac. In North America, a low amount of diclofenac is consumed, consequently resulting to

scanty reports compared to Europe [46, 50]. 4900 ng/L of diclofenac was the highest concentration detected in River Pakistan. Lonappan et al. [1] attributed this high concentration to lack of advanced wastewater treatment plants in most Asian countries. In the United States and Germany, diclofenac has been detected in drinking water, and in Fresh water bodies globally. There are no effective measures to monitor and control diclofenac in the aquatic environment in most Asian countries. Very few studies conducted have shown that diclofenac is not properly treated before wastewater is discharged into surface waters. However, the dynamic discharge of diclofenac into the aquatic environment can be reduced by proper waste water treatment in this area.

Table 2. Occurences of DCF in aquatic environment

Country	Environmental medium	Concentration (ng L^{-1})/µgl^{-1}	Ref
Nigeria	Ground Water	13.48 µgL^{-1}	[51]
China	River	230 (max. observed)	[52]
Brazil	Seawater (subtropical coastal zone)	19.4	[53]
Argentina	River	34–145	[54]
Spain	Tap water	18	[55]
Sspain	River	49	[55]
South korea	River	15	[56]
Spain	River	260 (max. Observed)	[57]
Finland	River	2--3	[58]
Canada	River	21-90	[50]
Canada	River	18-50	[46]
UK	Estuary	195	[59]
Germany	River	6.2	[60]
Germany	River	1030	[61]
Mediterranean region	Ground water/wells	2	[62]
Spain	Aquifer	1.7	[63]
Spain	Well	3.1	[63]
Spain	River delta	29.5-380	[63]
US	Drinking water	1.2	[49]
Austria	River	15.8-35.5	[64]
China	River	7.8-64.8	[65]
Pakistan	Harbor lagoon	100	[66]
Germany	Well	590 (max. observed)	[67]
Switzerland	Lake	370	[44]
France	Well	0.9	[48]
France	River	0.7	[48]

2.2 Diclofenac Toxicity and Metabolites

Previously, the adverse effect of diclofenac on aquatic animals has been the centre of discuss for numerous studies on toxic effect of diclofenac. Again, most toxicological studies concerning diclofenac have been based on laboratory investigation, using model organisms. Oaks et al. [17] reported the first case of pharmaceutical causing major environmental hazard, which was the sudden collapse of vultures occasioned by consuming carcasses of cattle containing diclofenac. Thereafter, diclofenac gained widespread attention. The toxicity problem related with diclofenac in the aquatic environment, mostly in diclofenac toxicity events extends to terrestrial animals and freshwater environments.

2.2.1. Aquatic and terrestrial organisms

Globally, a lot of studies on evaluation of the toxicity of diclofenac in aquatic organisms have been carried out. Acute immobilization test remains one of the most rampant and highly standardized methods for evaluating toxicity. One of the tests on toxicity of diclofenac was first conducted in 2003 by Ferrari et al. [31]. In this study, the toxic effect of diclofenac on fish, micro crustaceans, bacteria and algae was assessed and it showed low toxic effects at ambient concentration. Although the potential toxicological effect of diclofenac has been reported in subsequent studies. According to reports from studies on risk assessment, there exist high potential ecological hazard of diclofenac in surface water [68]. According to the findings of Cleuver [16], based on ecotoxicity of diclofenac using algae and acute Daphnia, diclofenac was found to be toxic to aquatic organisms. In crustaceans like Daphnia Magna sp, at acute concentration in mg/L, high mortality results. At mild environmental concentration of 10-100 ng/L, a Canadian study reported that diclofenac poses higher risk [69]. Diclofenac has been reported to be lethal in some vertebrates like fish, resulting in gastro-intestinal tissue distortion and kidney failure. A study in 2009 has shown that exposure of fish population to diclofenac at environmentally relevant condition down to ng/L results in adverse chronic effects [70]. Reduction of growth during egg stage, hatching delay and reduced hatchability has been associated with negative effect of diclofenac on Japanese killifish (Oryzias Latipes) [34]. Similar results on zebrafish have also been reported by Hallare and co-workers [71].

The presence of diclofenac in rainbow trout even at acceptable concentration resulted to interference which biochemical functions causing tissue damage [72, 73]. Table 2 summarizes some cases of diclofenac in various aquatic environments. When mussels were exposed to diclofenac at lower concentration in mg/L, it resulted in tissue damage consequent of lipid peroxidation (LPO) [74]. Ericson et al. [75] has also reported negative effect of diclofenac on Baltic blue mussels, especially in their growth retardation and metabolism issues. The estimated 0.1 mg per litre non effect concentration of diclofenac is high compared to those reported in table 2. Diclofenac may be

less toxic at environmental concentrations comparative to order phototransformation products [76]. Evidently, only very few studies have investigated the negative effect of diclofenac metabolites. Futuristic investigations should be based on toxicity of diclofenac phototransformation products, as well as other additives. Presence of diclofenac in food web, should be investigated and, chronic exposure study should be carried out at environmental concentrations, since diclofenac residues increases dynamically as diclofenac has frequently been introduced into the environment.

Oaks et al. [17] and Taggat et al. [77] reported the first major environmental damage from pharmaceutical, which involved the collapse of vultures after ingesting cattle carcasses containing diclofenac, thereby endangering the vulture population. According to IUCN, Vulture population has been endangered in India because of sudden decline in population by 98% occasioned by diclofenac consumption [78]. The sudden catastrophic collapse of Indian Bald Eagle Gyps and long-billed eagle Gyps indicus as reported by A study in 2003 related it to an epidemic of an unknown cause [31, 79]. Oaks et al. (2004) attributed the sharp decline in the vulture population to diclofenac-induced vasoconstriction, while Naido and Swan (2009) related the sudden death of vultures to decrease in the excretion of uric acid. Some other studies have also reported diclofenac to pose a major risk of renal failure [80-82]. Generally, diclofenac has effects on the ecosystem community structure and not only the vulture population. Numerous negative effects on cultural and biodiversity as well as socio-economic implications are inevitable since carnivores remain a major target. For instance, vultures consume the same food as dogs-causing rabies therefore, the reduction in the vulture population consequently results to less food competition between available surviving vultures and predominant dog-causing rabies [83]. Thus, biological and social implication of reduction in Vulture population in specific areas has been reported by Lonappan et al. [1]. In Africa, the use of diclofenac for veterinary purposes has also posed a risk to vultures [84, 85]. In Kenya, death of other carrion-eating bird preys and also vultures have been connected to diclofenac consumption [86]. Studies have reported rising in population size of birds (vultures) as a result of banning of diclofenac for veterinary purposes in south Asian countries [87, 88]. However, it is highly paramount to investigate the presence of diclofenac residues in water and soil to avoid futuristic chronic toxicity to organisms. Also, there is need to investigate other terrestrial animals that consume cattle carcasses as source of food since they are intermediate carriers of diclofenac during veterinary usage

2.2.2. Diclofenac metabolites

In animals, hydroxyl and other derivatives are the byproduct of diclofenac breakdown. Diclofenac in the environment breaks down or biodegrades via photochemical or photo transformation by sunlight. Among other pharmaceuticals, diclofenac has been mostly studied [18, 19]. However, influence of

diclofenac metabolite on the environment (toxicity) and its occurrence has been understudied (Lonappan et al., 2016).

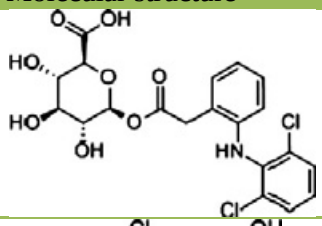
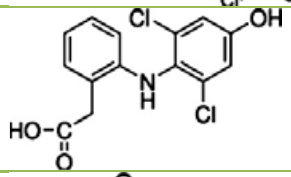
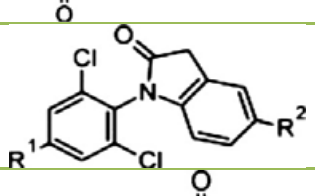
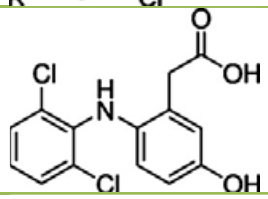
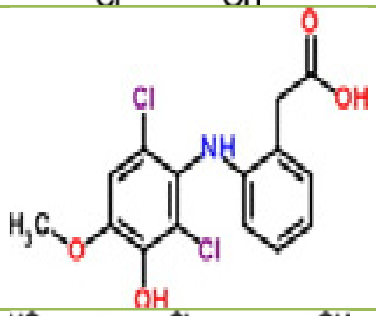
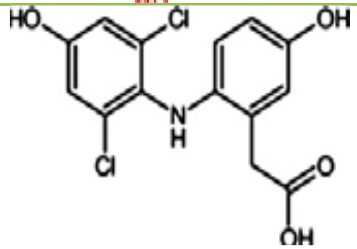
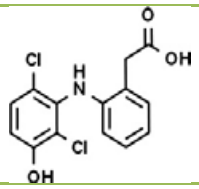
2.2.2.1. Via Consumption and Abiotic Channels

Human blood plasma and urine are major locations for diclofenac. Diclofenac could exist as glucuronide-bound form or as it's free form whether it is its methoxylated or hydroxylated derivative. In the late 70s, Stierlin et al. [90] investigated diclofenac metabolites in human and discovered 4′,5-dihydroxydiclofenac (2-[2,6-dichloro-4-hydroxyphenylamino]-5-hydroxyphenylethanoic acid) and (15%), 5′-hydroxydiclofenac (2-[2,6-dichlorophenylamino]-5-hydroxyphenylethanoic acid) (10%), and also 4′-hydroxydiclofenac (2-[2,6-dichloro-4 hydroxyphenylamino] phenylethanoic acid) (30%) which was dominant [90, 91]. Some other form of minor metabolite has also been found in humans [92]. Naisbitt et al. [93] and Kallio et al. [94] have also reported the discovery of hydroxylacyl glucuronide in fish and mice, along with other hydroxyl derivatives of diclofenac. Table 3 represents various identified human metabolite of diclofenac.

Further investigation on diclofenac metabolites is necessary, since the abundance of human metabolite of diclofenac in water share the same structural resemblance with diclofenac and they are both toxic. In the water cycle, diclofenac is very suitable to first order kinetics when it photodegrades in the presence of sun light at its half-life of 3.3 hours [76, 95]. About 90% of diclofenac was removed from lakes, adopting photodegradation technology. This identifies it as a major process/technique for diclofenac removal [44]. Numerous studies have reported different photo transformation products of diclofenac [93-95]. Erikson et al. [96] has also identified photolysis to corresponding mono halogenated carbazole as the most crucial process in phototransformation. 8-hydroxyl and 8-chloro carbazole and 2-chloro and 2,6-dichloro diphenyl amine are the two major obtain products from most photodegradation [94, 95].

Generally, diclofenac and its metabolites find their way into the aquatic environment. Diclofenac has been reported to be less toxic than its metabolites. Researchers [76, 96] have reported a six-fold increase in toxicity essays involving algal growth caused by phototransformation products of diclofenac. Since diclofenac metabolites are toxic to varieties of organisms, proper monitoring during environmental and pharmacotoxicological investigation is highly paramount [97]. However, there is a need to investigate the potential toxic effect of diclofenac in futuristic studies. Also, evaluating the photo transformation product of diclofenac can always be tasking. For example, accurate measure/evaluation of diclofenac transformation products is not feasible occasioned by unavailability of metabolite standards. Low concentration of diclofenac and its transformation products, mainly in nanogram per liter remains a major analytical challenge [1]. Appropriate methods and highly sensitive MS/MS instruments are required to measure these micro-contaminants.

Table 3. Human metabolites of diclofenac.

Metabolite	Molecular structure	Reference
1-O-acyl glucuronide (DCF-gluc)		[98]
4′-Hydroxydiclofenac		[89, 90, 97]
4′-Hydroxy diclofenac Dehydrate		[97]
5′-Hydroxydiclofenac		[89, 90, 97]
3′-Hydroxy-4′-methoxy Diclofenac		[90]
4′,5-Dihydroxydiclofenac		[89, 90]
3′-Hydroxydiclofenac		[89, 90]

2.3. Possible Interactions with Other Contaminants

One of the largest sinks for diclofenac is the Wastewater Treatment Plants. Possible interactions with other contaminants are worth looking into. Pollutants that are accepted by municipal water treatment due to their complexity are supplied by different sources. [1]. Included are nutrients such as phosphorus, nitrogen, and carbon (of a variety of sources), surfactants, pesticides, phenols, heavy

metals, pathogens, different classes of viruses, contaminants such as suspended solids and biodegradable organic substances which include carbohydrates, fats (usually hospital wastewater), and proteins. Also accepted are emerging contaminants such as pharmaceutical and personal care products (PPCPs) [1]. The quantification of these emerging contaminants is mostly carried out in minimum concentrations which are either in microgram per liter or nanogram per liter. In any case, the negative effect these trace contaminants can have on the environment cannot be overlooked. Additionally, contaminants might fuse with the same or different varieties of other contaminants. For example, drugs containing diclofenac has shown that if drug mixtures or all drugs are used at concentrations below the NOEC, a sufficient level of combination effect would occur. Various studies have compounded the toxicity issues affiliated with diclofenac in different environmental settings. It is to be noted that some research has been made concerning the issues of addictive toxicity to diclofenac and drug alike. Aristi et al. [99] suggested antagonistic interactions between emerging contaminants and nutrients including diclofenac. To demonstrate the real toxic effect of additives, it is essential to conduct free long-term exposure experiments. For future risk assessment studies to be realized, the focus of mixture toxicity studies should be concentrated on the toxicity of individual drug acting alone at low levels of concentration and also checkmating whether the ecotoxicity of a pharmaceutical mixture surpasses the toxicity of each individual substituents [100]. With the number of drugs in use and the continuous expansion of the pharmaceuticals industries, routine evaluation of the toxicity of diclofenac as well as other drugs needs to be carried out. Furthermore, these studies need the efforts of environmental exposure assessment studies to evaluate toxicity. Test organisms toxicokinetic interactions, ecological interactions and even ordinary toxicokinetics, among other forms of toxicological interactions should be adequately considered [100, 101].

2.3.1. Diclofenac Interactions with Metals, Other Inorganic and Organic Matter

Industrial, municipal, domestic, and even hospitals are among the various sources which wastewater treatment plants receive wastewater. Diclofenac treatment is always carried out in the wastewater treatment plant. Some researchers [102-104] suggested that metal, especially heavy metals are regular contaminants). The process can be set in motion by the different physicochemical conditions that are already existent in wastewater treatment plants. The structure of diclofenac is embodied with active groups such as carbonyl, amine and hydroxyl. The bonding properties/metals complexation of various metals can be greatly improved by these groups. There is a good chance of obtaining an organometallic complex of a drug in a wastewater treatment plant by chelation. From the works of Refat et al. [105], complexation of Sn (II), Pb(II) and Hg(II) with diclofenac displayed high potency to antimicrobial effect; and Cu(II)/DCF complex can also clave DNA [106]. Diclofenac through protonated functional groups can serve as a ligand with metal ions. The characteristics of diclofenac and other contaminants with the cellular and antibacterial intermediary are completely transformed during the interaction with the metal complex. The various studies on diclofenac metal complexes is

usually centered on the discovery of underlying mechanisms and new therapeutic values. . However, to our knowledge, dart information on the toxicity of DCF metal complexes and wastewater exists. As a matter of fact, considering diclofenac as an emerging contaminant with high potential toxicity on different organisms places DCF metal complexes as an emerging contaminant too. Occasioned by its antibacterial properties, it should be carefully handled. The toxicity of diclofenac metal complexes to organisms remains a matter of urgent concern since it adds another layer of chemical complexity. Diclofenac can replace or act as a ligand for other inorganic groups due to it structural characteristics. From a toxicological viewpoint, mostly in HCV, these characteristics are crucial. There are high tendencies of interaction via aggregation and complexation, with nitrates, chloride and sulfates and also with other organics in aqueous medium.

2.3.2. Diclofenac Interaction with Other Emerging Contaminants and Diclofenac Metabolites

Some studies have identified the toxic effect of combining diclofenac with other drugs (emerging contaminants), but there are worries about the toxicity of diclofenac metabolites. 5'-hydroxyl diclofenac, 4'-hydroxyl diclofenac and 3'-hydroxy diclofenac are the Major hydroxyl metabolites of diclofenac. When these metabolites are mixed, their toxic effects still remain unknown. When diclofenac is combined with other drugs, the toxic effects of this combination may be likened to that of combining diclofenac and its aforementioned metabolites. Wastewater treatment process in wastewater treatment plants can enhance combination of diclofenac and its metabolites which will eventually results to a new potential contaminant. Additionally, about 65% of diclofenac exists as metabolites, making diclofenac and all its metabolites remain in abundance [90]. Most metabolites of diclofenac reported in literatures contain OH groups at different positions in the diclofenac structure, with the basic molecular structure of diclofenac remaining unchanged. With the presence of OH-groups, π-π interaction with metals will be highly enhanced. This principle has been utilized to form DCF-Metal complex due to the presence of hydroxy group in the diclofenac molecule [107]. Diclofenac metabolite also contains some active groups like carbonyl, amino, carboxyl and hydroxyl, therefore possible interaction between these groups cannot be underestimated and this may consequently result in a new contaminant of interest. Similarly, order emerging contaminants can also interact with diclofenac. Surfactants, PPCPs, pesticides, among other ECs are mostly contained in wastewater [108]. These emerging contaminants often contain different active functional groups in their structures. However, during treatment, the ECs may interact with one another, with DCF or even with DCF metabolites. Osorio et al. [109] investigated the synergystic effect of combining diclofenac with sulfamethoxazole and nitrogen and these compounds displayed high toxicity. To carry out adequate toxicity studies and device appropriate risk assessment for diclofenac, experimental evidence of the above interaction is required. To further enhance ecotoxicological studies which highly involve number of contaminants, futuristic investigations based on DCF

compounds, proven or merely generated products, emerging contaminants, metals and even metabolites are highly necessary.

3.0 Conclusion

Diclofenac remains one of the most essential pharmaceutical products used every day across the globe. Its residues can be found in soil, drinking water and surface water. The utilization of natural processes like photodegradation is most of the time effective for DCF removal, although some toxic residue like diclofenac metabolite or sometimes diclofenac may be left behind. Information obtained from ecotoxicological data reveals that diclofenac is always detected in low concentration, mainly in nanogram/liter or microgram/liter which could likely result to acute toxic effect to most organisms. A prolonged environmental exposure of diclofenac through drug use in a year increases its residues in the environment, and chronic toxic effect is eminent after a long-term exposure to low concentration. Diclofenac is absorbed to high organic rich soil, exhibiting potential to resist anaerobic/aerobic degradation and on the other hand may leach into ground water resulting in toxic effects. However, there is still a lacuna in understanding the fate of diclofenal in soil. Various studies suggest that diclofenac metabolites might contain more toxic compounds than the parents' compound. Though there is insufficient knowledge available on the toxicity of diclofenac metabolites.

Conflict of interest

Authors declare no conflict of interest.

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