



REVIEW ARTICLE

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Ecopharmacovigilance: Perspectives, concepts, applications, and relationships in modern context

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Introduction: Environmental scientists have made great strides to regulate pharmaceutical waste. However, the monitoring of emerging environmental problems induced by drugs should attract the further interest of pharmacy and pharmacovigilance scientists. Ecopharmacovigilance (EPV) as a kind of pharmacovigilance for the atmosphere is widely recognized as essential to minimize the environmental impact of pharmaceutical toxins.

Methods: In efforts to answer the environmental issues created by medications, the constructive involvement of the pharmaceutical sector is essential. On a prioritized basis, EPV can target individual pharmaceuticals. For EPV deployment targeting pharmaceutical contamination, certain advice and management practice solutions are recommended. On administration certain drugs are metabolized throughout the bloodstream, being inert or becoming converted to metabolites, whereas others are excreted in the urine or liver and excreted in the sewage. The substances that are released into drainage can be processed into a number of chemicals by a sewage treatment process.

Results: The involvement of different drugs and their components have been found in the marine world, with the aquatic environment being the most researched to date. Nanostructure materials have been around for a long time, and their interactions with biological processes have been discussed in various applications to enhance the understanding and importance of environmental and health effects.

Conclusions: In order to regulate pharmaceutical residues in effluents, Technologies for sewage water management should be applied. In particular, the presence of pharmacy including pharmacovigilance professionals is also important for enhancing multidisciplinary collaboration.

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Introduction

The research of “Ecopharmacovigilance” (EPV) has become a recent subject of concern in the sense of the rise of pharmaceutical contamination. For the last 30 years,

multinational institutions and the pharmaceutical industry have come to recognize that pharmaceutical drugs have a negative global effect on the climate. Although it is a global issue, like other environmental issues,



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pharmaceutical pollution more directly and seriously affects those living near production plants whose water and food sources are contaminated with waste pharmaceutical products (**Figure 1**) (Wang and Hu, 2014). With the continued rapid development of the global pharmaceutical industry, increasing attention has been given to environmental issues caused by pharmaceutical pollutants. This is an increase in the consumption, occurrence, and persistence of pharmaceutical products in the environment with their diverse biological effects (Coetsier *et al.*, 2007). While not entirely, although to a great degree, medicines were a blessing for mankind in curbing the diseases (Medhi and Sewal, 2012). In the developed world, pharmacovigilance was well accepted and practiced, but decades were absorbed by emerging areas of the globe. India is also currently starting a national initiative to track the adverse effects of medications (Gupta, 2010). These environmental pharmaceutical pollutants include excretion of pharmaceuticals after human and veterinary therapeutic use. This dominates the global input of pharmaceuticals into the environment and are a much more difficult source to control; adding to the direct release into the wastewater system and terrestrial depositions from manufacturing or hospitals; and disposal of unused drugs (Holm *et al.*, 2013).

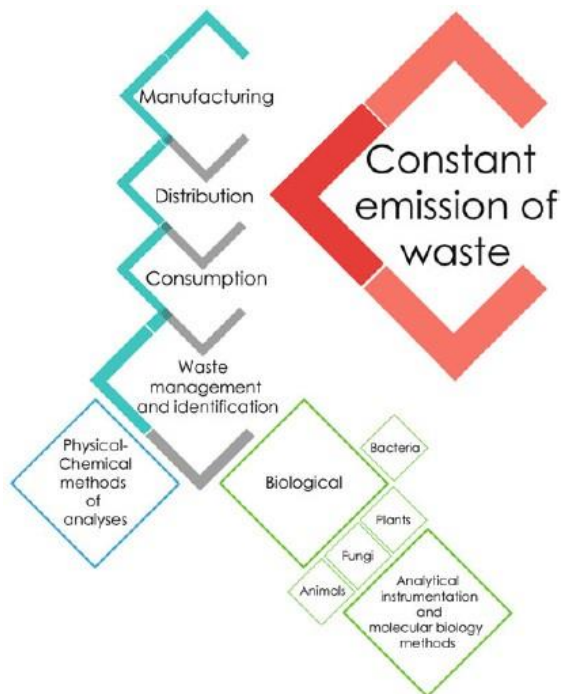


Figure 1: Life cycle of medicinal products. (Courtesy: Gomez-Olivan, 2018)

Ecopharmacovigilance refers to drug-related toxic reactions within the ecosystem and all effects on humans and other species in the environment. Drug use is escalating day by day in both the human and veterinary

communities. 100,000 tonnes of antimicrobials are used worldwide, according to one report (Silva *et al.*, 2011). More than 30 billion doses are consumed annually of non-steroidal anti-inflammatory drugs (NSAIDs) class. Nearly all households surveyed to dispose of prescription residuals are either thrown into the landfill or rinsed down the toilet or drain. In total, 7% did not dispose of their expired drugs, producing a possible household surplus that may contribute to injuries or be intentional violence (Kuspi and Krenzelok, 1996). The contamination of pharmaceutical drugs into the atmosphere may result in harmful effects to fish as well (**Figure 2**). Although these papers present the EPV principle and some EPV approaches, they appear to address a much wider field including all aspects of sustainable pharmacy, such as green drug design, green chemistry in the production of processes, minimization of pollution from processing, better prescription practices and handling of expired drugs. Furthermore, all of the EPV methods proposed to date have been predominantly preventive in nature and have concluded that the involvement in the ecosystem of pharmaceuticals would eventually lead to an adverse effect without taking into account the possibility of impact or damage (Velo, 2017). Only after modern scientific methods and instruments were developed were we able to understand that we are continuously subjected to a number of forms of chemicals which are the source of several different diseases. This review describes the general methods used currently to detect, identify, and quantify pharmaceutical compounds in water. Major toxic effects and risks associated with the presence of pharmaceuticals in water and environment.

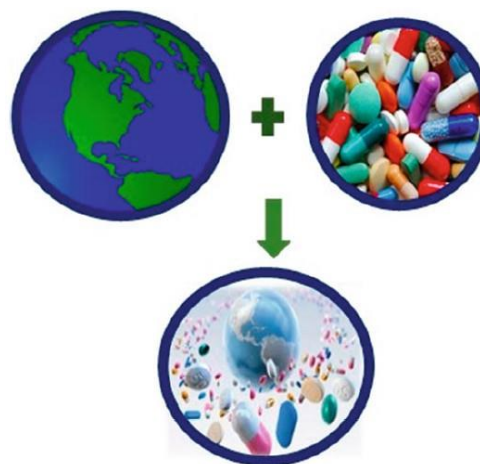


Figure 2: Pharmaceuticals as emerging contaminants. (Courtesy: Gomez-Olivan, 2018)

Decline in vulture population

The cause of the decline has been identified by thorough studies to be 'diclofenac', a non-steroidal anti-inflammatory drug (NSAID) used to treat livestock. Vultures are exposed to the substance as carcasses of animals infected with diclofenac are eaten shortly before death. Vultures, with post-mortem results with extensive

visceral gout, die from kidney damage within days of exposure to diclofenac infected tissues. Also unexplained and unforeseen was the intense vulnerability of Gyps vultures (Swan *et al.*, 2006). Acute symptoms were also found as a result of exposure to diclofenac in the African white-backed vulture (*Gyps africanus*) and the Eurasian griffon vulture (*Gyps fulvus*). However, owing to susceptibility to diclofenac, North American vulture species such as *Cathartes aura* tend to be less vulnerable than Gyps vultures (Figure 3).

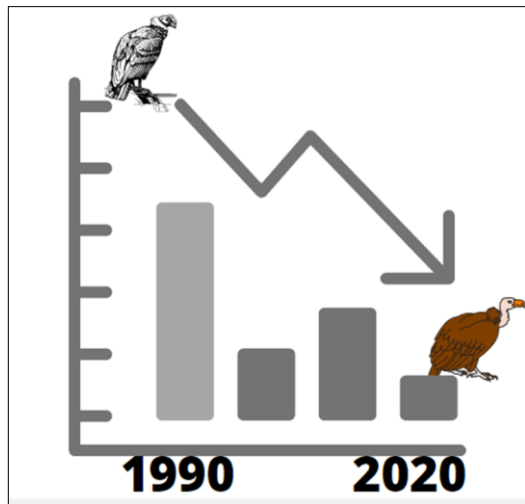


Figure 3: Decline in vulture population. (Courtesy: Gomez-Olivan, 2018)

Methods of extracting pharmaceuticals products

On administration certain drugs are metabolised throughout the bloodstream, being inert or becoming converted to metabolites, whereas others are excreted in the urine or liver and excreted in the sewage. The substances that are released into drainage can be processed into a number of chemicals by a sewage treatment process. In fact, studies show that the average current methods utilised by wastewater treatment plants are ineffective, and lead to inadequate removal of active pharmaceutical ingredients that lead to discharge into surface water (He *et al.*, 2017).

Unfortunately, certain drugs are washed into the toilet as they become ineffective. Additionally, pharmaceuticals were able to be incorporated into the ecosystem by the eventual leaching of cattle and poultry waste. This is certainly relevant of growth hormones, which are widely used as growth promoters in animal husbandry, the latter practice having been tagged as the highest user of this category of pharmaceutical drugs. Soil is cleaned and manure is put in a pit before it is leached out (Kummerer, 2003). Pharmaceuticals processed, medicinal or livestock and poultry supplies ultimately hit surface or ground water and eventually drinking water, closing the loop, and become a genuine hazard to human health, biodiversity, and the climate (Jones *et al.*, 2001). Figure 4 summarizes the origins and routes of medication releases.

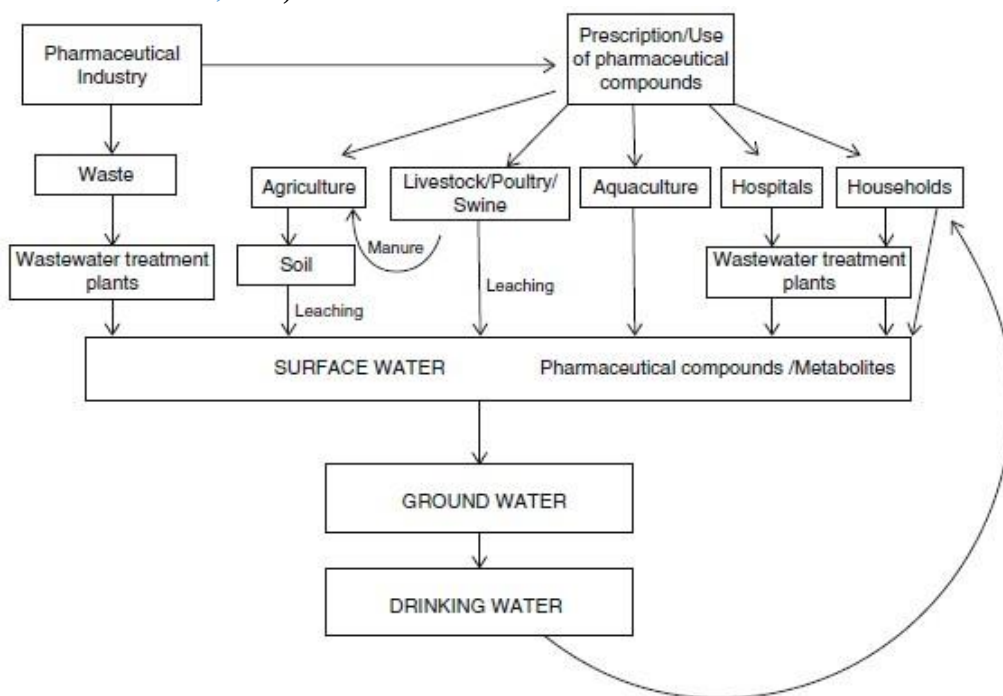


Figure 4: The origins and occurrence of pharmaceuticals in the environment. (Courtesy: Gomez-Olivan, 2018)

Studies on EPV has become possible to determine the life cycle of the pharmaceuticals in environment, and it recognized that due to its high use, pharmaceuticals are

increasingly manufactured by the company and then released into the atmosphere via various means. After administration, most pharmaceuticals are metabolized by

phase I and/or phase II reactions in the liver to allow them more water soluble than the initial parent drug (Alshakka *et al.*, 2016).

Subsequently, they may be extracted as unaltered type or as metabolites (active, inactive, or toxic) by urine and feces; in this manner, they enter the wastewater which enters the wastewater treatment plants (WWTP) which incompletely extract these compounds, contributing to the pollution of surface waters, seawaters, groundwater, and

some drinking waters (Halling-Sorensen *et al.*, 1998). Hospital wastewater is the other major source of pollution, but the dilution of hospital effluents by urban wastewaters can reduce the concentration of pharmaceuticals only marginally, since the latter often include pharmaceuticals from households and veterinary sources; other sources are disposal of discarded or expired pharmaceuticals from trash and the pharmaceutical industry discharges (**Figure 5**).

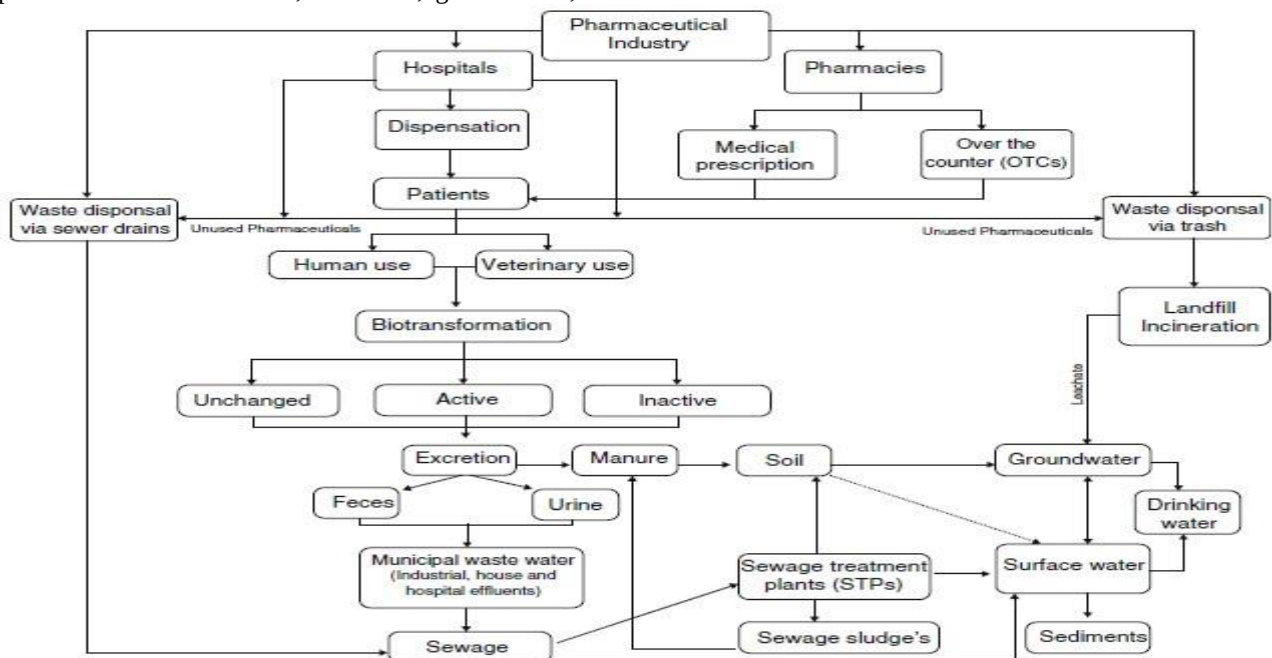


Figure 5: Life cycle of pharmaceuticals in environment. (*Courtesy: Gomez-Olivan, 2018*)

The involvement of different drugs and their components has been found in the marine world, with the aquatic environment being the most researched to-date. Such wastes originate primarily from clinics, pharmacy and tobacco companies, excretions from humans, industrial waste, or in the case of unused medications, are washed down the toilet. Residues, owing primarily to their physicochemical properties, withstand to a lesser or

greater degree to various forms of degradation (photochemical, nuclear, and biochemical), which allows them a longer environmental half-life (Figure 6) (Islas-Flores et al., 2017). The word "environmental half-life" implies the period it takes to deplete 50% of the amount of a material existing in the environment, and is used to calculate the pace at which the substance is dissipating over time.

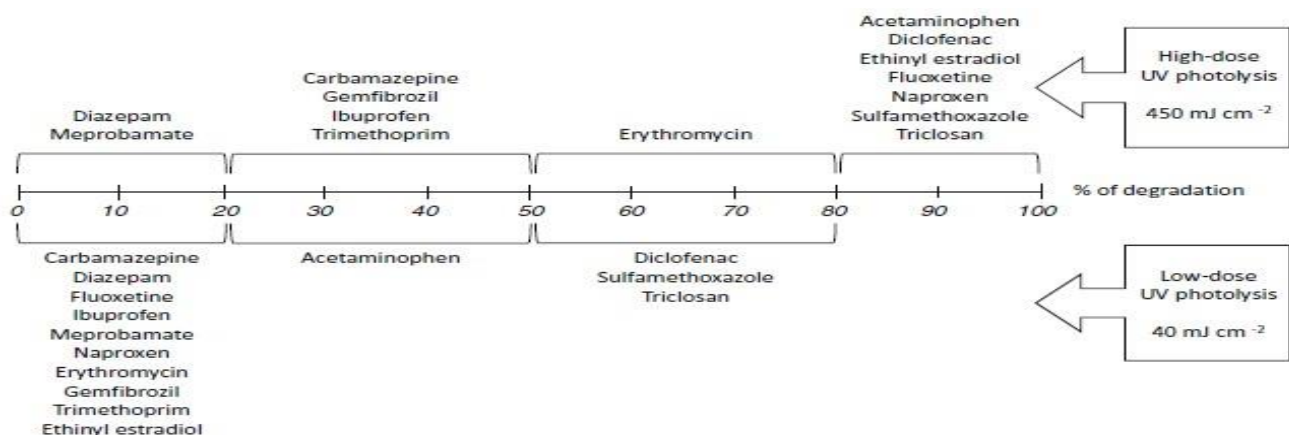


Figure 6: Drugs degraded by UV photolysis. (Courtesy: Gomez-Olivan, 2018)

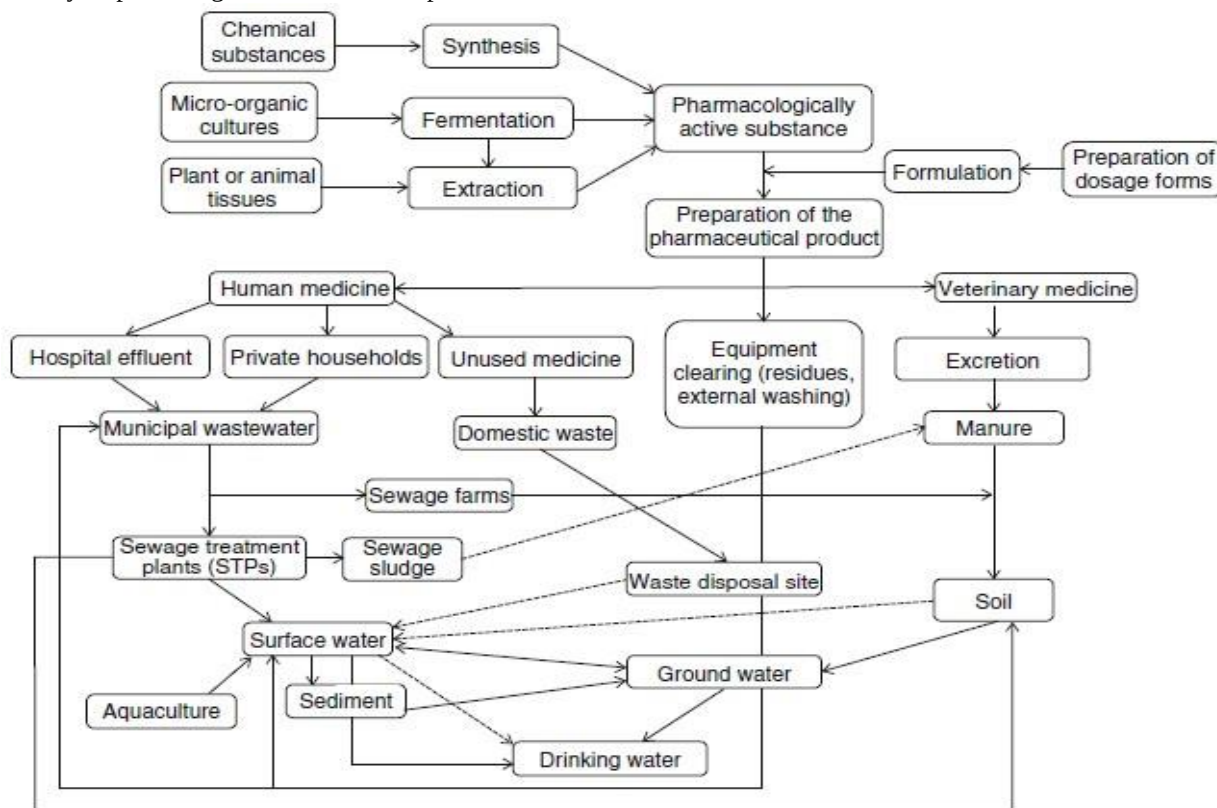
Establish the amount of time a material stays below those environmental levels. However, certain substances whose environmental half-life is comparatively small may also survive in the medium due to their sluggish decomposition.

Degradation, leading to a process known as pseudo-persistence, in which there is a constant substitution of the contaminant into the atmosphere and abiotic elements of the same, primarily by chemical deterioration through oxidation. The molecules vulnerable to this kind of chemical reactions are mainly ester, amides, amines, carbamates, nitriles, and alkyl halogens. Certain chemicals including acetylsalicylic acid, beta-lactam antibiotics, and clarithromycin, induce this form of reaction (Wang *et al.*, 2019). Hydrolysis is a very significant reaction involving photodegradation in groundwater, though not with photodegradation. Such reactions such as hydrolysis and photolysis take place in the aqueous compartment, although reactions such as aerobic and anaerobic biodegradation are triggered by microorganisms. Understanding the environmental degradation mechanisms are key to predicting the destination of pharmaceuticals in

sewage and the potential for them to be introduced into the world (Nieto *et al.*, 2010). The mechanisms by which a chemical is transformed will determine its environmental persistence.

Sources and routes of pharmaceuticals to the environment

The existence of pharmaceuticals in drinking water has resulted in public alarm because of their prevalence, persistent leakage into the atmosphere, and possibly ecotoxicological consequences (Patneedi and Prasadu, 2015). Of the 4,000 pharmaceuticals used in the medical industry, less than 300 were already found in water systems, because expensive and sufficiently responsive equipment is needed to calculate the concentrations that usually exist in aquatic environments, varying from ng/L to µg/L (Camacho-Munoz *et al.*, 2012). There are many diverse forms of prescription exposure (Figure 7). During administration of pharmaceuticals in humans and livestock, any quantity of the pharmaceutical and its metabolites will be excreted in the breath and urine (Rodil *et al.*, 2012).

**Figure 7:** Sources and entry routes of pharmaceuticals into the environment. (Courtesy: Gómez-Oliván, 2018)

Nanoscale materials: forms and properties

Nanostructured materials (with sizes in the range from 1 to 1,000 nm, but the most accepted concept limits

nanomaterials to the range in between 1 and 100 nm) have been around us for a long time, and their associations with biological processes have been explored in many applications to enhance our knowledge of the possible

environmental and health implications of their usage (Mendez-Rojas *et al.*, 2014). Multiple groups around the world are focusing on producing nanomaterials with regulated structure, form, and scale, which will, in turn, describe their specific physical properties and, as a consequence, their possible applications (Kharisov *et al.*, 2016). Although there are many kinds of nanomaterials, these products may be classified into many groups including carbon nanotubes, metal nanowires and nanoparticles, graphene, metal oxides, and nanocomposites (Figure 8).

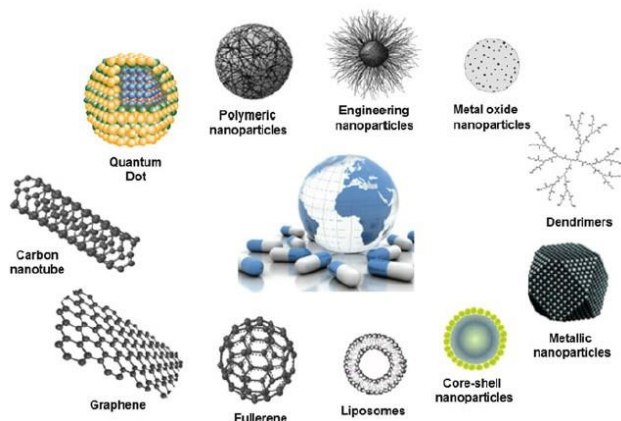


Figure 8: Potential nanomaterials for environmental remediation of some common pharmaceutical contaminants. (Courtesy: Gómez-Oliván, 2018)

The special properties of nanostructured material can be extended to a number of fields such as catalysis, medicine, environmental remediation, and energy production. The great surface/size ratios of nanomaterials provide them with the needs for enhancing catalytic activity or their capacity to extract contaminants through adsorption / absorption. The characteristics of a nanomaterial may not directly predict with that of a macroscopic equivalent, since they do not share the same material properties not only on its chemical composition, but also on its scale, dimension, and form. Due to their small scale, their wide surface and higher water solubility, many nanomaterials are useful for environmental applications, especially in improving the removal or deterioration of pharmaceutical compounds (Cerro-Lopez and Méndez-Rojas, 2017).

Conclusions

The usage of pharmaceuticals has been part of our regular lives, but everybody needs to bear in mind the effects of pharmaceutical contamination. We must be aware of the effects of whatever move we take on the world. Therefore, it is important that prescription drugs be tracked and controlled as quickly as possible considering their potential danger for the environment and biodiversity. Furthermore, efforts must be directed toward developing effective and green wastewater treatments which minimize the existence of xenobiotics and the wastewater from its source. Both forms of emissions must be regulated and

managed by government officials. It is critical that new pharmaceuticals and goods are checked for ecotoxicity before they can be sold or used.

Conflict of interest

Authors declare no conflict of interest for publication of this article.

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