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PPCP contamination in surface water: Emerging threats to human health and ecosystem stability

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Key words: PPCP compound, Surface water, Endocrine disrupting compounds (EDC), Human Health

Abstract

Pharmaceutical and personal care items are endangering human health and harming the environment. River and surface water bodies are the main contaminated resources as they include a variety of polluting residues, including those from antibiotics, synthetic hormones, analgesics, antimicrobials, and cosmetic items. Very high pharmaceutical concentrations (in the order of mg/l) have been found in industrial effluents in China, India, Israel, Korea, and the USA. India is also one of the top 5 pharmaceutical manufacturers in the world. As a result, these waste residues exist in freshwater in trace amounts and can enter our systems through drinking water or the food chain. By attaching to receptors, it has an impact on the endocrine system in both humans and animals, causing both agonistic and antagonistic effects. Numerous ailments and diseases have been reported in humans, animals, and aquatic species as a result. These compounds give birth to a new class of pollutants known as Emerging Contaminants (EC). Therefore, it is crucial to assess the effects of PPCP residue in surface water on human health.

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Introduction

Personal care products (PPCPs) are a class of organic compounds used to improve the quality of daily life, whereas pharmaceutical drugs are used to prevent or treat human and animal diseases (veterinary medicine) (Boxall *et al*., 2012). There is extensive use of PPCPs and veterinary medicine, which results in their continuous release into the environment (Nikolaou *et al.,* 2007). By 2020, there were 4.5 trillion doses of utilized medication consumed worldwide, with almost 50% of people taking more than one dose day (Quintiles IMS Global*,* 2020). According to Balakrishna *et al.* (2017), drugs used for human and veterinary applications are not completely absorbed by the body, and as a result, approximately 10 to 90 percent of administered doses are excreted from the human body, with the remainder being eliminated as metabolites or in conjugated forms. Ultimately, these unabsorbed residues end up in sewage water.

When sewage sludge is put as a fertilizer to agricultural land, the sewage effluent is utilized as irrigation for crops and landscaping (Ternes *et al*., 2004; Kinney *et al*., 2006). The conventional sewage /wastewater treatment has its limitations and cannot remove these organic compounds allowing them to re-enter the stream, river and water bodies to the food chain.

These contaminations mainly cause hormonal imbalance in animals and humans and called Endocrine-disrupting compounds. EDC are derived from during water disinfection processes, released from industry and livestock activity, or therapeutic drugs released into sewage (Andressa *et al.,* 2020). These byproduct compounds can bind with body receptors very easily and inhibits normal endocrine function (Sharma *et al.,* 2009*;* Zoeller *et al.,* 2012) and finally alter the product in the body. Therefore, it has become a major concern for water quality due to untreated effluent in many areas of the world (Nikolaou *et al.,* 2007).

To review pharmaceutical and personal care product and their residues in surface water and health impact on animals and humans.

Pharmaceutical industry in India

India is the second-largest populated country which has 1.38 billion human densities. It ranks world's 3rd largest pharmaceutical industry by volume and 14th largest in terms of value. It is also the largest provider of generic drugs globally (Annual Report 2020-21). According to the Federation of Indian Chambers of Commerce and Industry (2005 report), the Indian pharmaceutical industry is valued at approximately US $8 billion globally. The research and manufacturing of Indian drugs were estimated at US $532 million and Contract manufacturing was approximately 84%. In India, only 29% of wastewater is treated out of 38 billion litres of municipal wastewater.

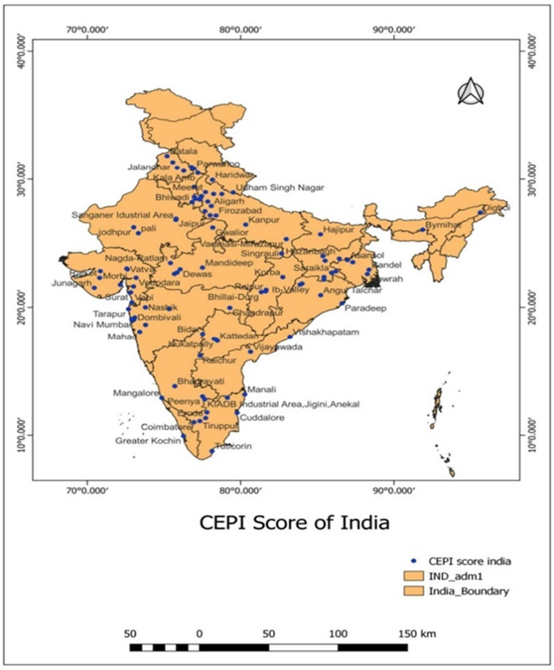

Fig. 1. CPCB; comprehensive environmental pollution index (CEPI) scores for industrial areas monitored in 2018

However, 80% of surface water is polluted in India. The central pollution control board use CEPI score to analyze the critically polluted industrial area in the context of air, water, land and health-related statistics. According to the central pollution control board in 2017-2018, 100 polluted industrial areas were identified of which 38 were critically polluted, 31 were severely polluted and remaining as other polluted areas (CPBC, 2018). Some critically water polluted industrial areas lie in Maharashtra, Delhi, Uttar Pradesh, Gujarat and Haryana (Fig. 1).

PPCP compounds

Pharmaceutical and personal care products are organic compounds in emerging environmental contamination. It includes a diverse group of compounds such as anti-biotic, hormones, anti-inflammatory drugs, antiepileptic drugs, blood lipid regulators, β-blockers, contrast media, and cytostatic drugs for pharmaceuticals; and antimicrobial agents, synthetic musk's, insect repellents, preservatives, and sunscreen UV filters for personal care products (Table 1).

Table 1. Common PPCPs categories (Liu and Wong, 2013)

PPCPs categories	Subcategory	Reference
Pharmaceuticals	Antibiotics	Sui *et al.*, 2015
	Analgesics	Oliveira *et al.*, 2015
	Antimalarial drugs	Tella *et al.*, 2018),
	Antiseptics & hormones	Peng *et al.*, 2014
	Steroid and endocrine-disrupting products	Yu *et al.*, 2011
	Anti-inflammatory &antifungal	Guerra *et al.*, 2014),
	Antiepileptic and antianxiety drugs	Kathleen, 2010.),
	Cytotoxic drugs	Al-Farsi *et al.*, 2017),
	Anticancer drugs	Xie, 2012
	Cytostatic drugs	Prasanna *et al.*, 2015
	Beta-blockers, oestrogen, lipid regulators	Zheng and Li, 2013
	Anticonvulsants	Cizmas *et al.*, 2015)
Personal care product	Moisturizers, hair colours, deodorants, toothpastes	Boxall *et al.*, 2012
	Sunscreen, detergents	Juliano and Magrini, 2017
	Disinfectants	Zhang *et al.*, 2014
	Preservatives	Archer *et al.*, 2017
	Fragrances and perfumes	Zheng and Li, 2013

Table 2. Common PPCPs compounds found in environment

PPCPs	Subgroup	Representative compounds	Reference
Pharmaceuticals	Antibiotics	Macrolides (e.g. erythromycin, roxithromycin), sulfonamides (e.g. sulfamethoxazole, sulfadimethoxine), and fluoroquinolones (e.g. norfloxacin, ciprofloxacin)	Heberer, 2002
	Hormones	Estrone (E1) Estradiol (E2) Ethinylestradiol (EE2)	Heberer, 2002
	Analgesics and anti-inflammatory drugs	Diclofenac and ibuprofen; blood lipid regulators (such as clofibrate and gemfibrozil)	Heberer, 2002
	Antiepileptic drugs	Carbamazepine and primidone)	Heberer, 2002
	Blood lipid regulators	Clofibrate and gemfibrozil	Heberer, 2002
	β-blockers	Metoprolol and propanolol)	Heberer, 2002
	Contrast media	Iopromide and diatrizoate)	Heberer, 2002
	Cytostatic drugs	Ifosfamide Cyclophosphamide	Heberer, 2002
Personal care products	Antimicrobial agents/Disinfectants	Triclosan Triclocarban	Heberer, 2002
	Synthetic musk's/Fragrances	Galaxolide (HHCB) Toxalide (AHTN)	Heberer, 2002
	Insect repellents	N,N-diethyl-m-toluamide (DEET)	Heberer, 2002
	Preservatives	Parabens (alkyl-p-hydroxybenzoates)	Heberer, 2002
	Sunscreen UV filters	2-ethyl-hexyl-4-trimethoxycinnamate (EHMC) 4-methyl-benzilidine-camphor (4MBC) s	Brausch and Rand, 2011

The Table 1 categorizes the PPCPs into two major groups i.e., pharmaceuticals and personal care products providing examples for each category. In the pharmaceuticals sector, antibiotics have special attention for their wide application in human health livestock agriculture. It has been reported that there will be an increase in the usage of antibiotic drugs by 67% in the livestock feed worldwide by 2030 (from

2015 levels) (Van Boeckel *et al.,* 2015). Continuous exposure to antibiotics can result in the emergence of resistant bacteria strains with public health concerns (Zhang *et al.,* 2009b). Synthetic steroid hormones are believed to be connected with the endocrine-disrupting effects of polluted water bodies (Lai *et al.,* 2002). Other pharmaceutical groups include analgesics and anti-inflammatory drugs (Table 2).

Table 2 lists out the various PPCPs detected in the environment, their subgroups and the representative compounds, which is important to assess the possible impact on the ecosystem and human exposure.

Route of entry of PPCPs into the environment

The major route of pharmaceutical residues entering the aquatic environment is probably by wastewater effluents from sewage treatment plants that contain the excreta of patients undergoing pharma treatments. Most of the medications or the pharmaceutical substances are unused in the body (not metabolised) which may be then excreted in biologically active form, usually via the urine or are washed off through bathing showers or sink drains (Dey *et al.,* 2019).

Furthermore, many pharmaceutical substances are not fully taken up by the intestine (following oral administration in patients) into their blood stream. The fraction not taken up into the blood stream will remain in the gut and eventually be excreted via the faeces. Hence, both urine and faeces from treated patients contain pharmaceutical residues. Between 30 and 90% of the orally administered dose is generally excreted as active substance via urine.

The improper disposal practice of dumping the expired or unused medicines and other personal care products along with the thrash onto open lawns and barren grounds or flushing down in the toilets all end up on the soil bed finally leached into the water bodies (Nikolaou *et al.,* 2007). Fig. 2 Depicts the PPCPs usage and their transport into the environment through wastewater, landfills, leachates and agriculture that may ultimately reach humans via drinking water and through food web. Understanding these pathways is vital for assessing the potential health risks and implementing mitigation strategies.

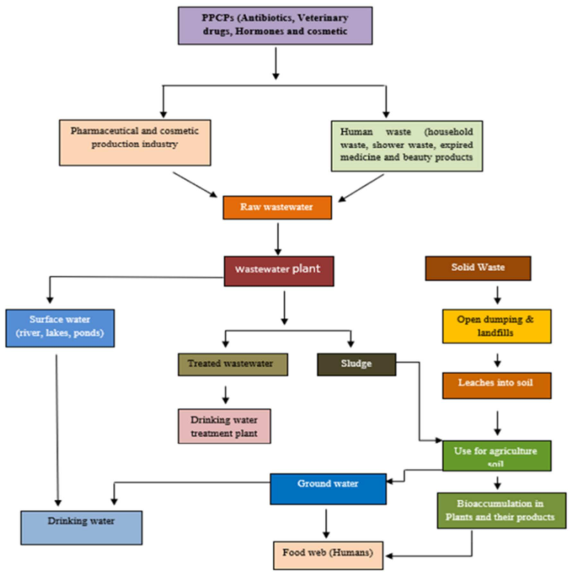

Fig. 2. Impact of PPCPs in surface water and human health

Surface water

PPCP residues have been detected in surface water, groundwater and the oceanic environment in the last 20 years (WHO, 2011; Klosterhaus *et al.*, 2013; Luo *et al.*, 2014). The concentration level of pharmaceutical chemicals found in nanometre in the lower organism and in lesser extent in drinking water but the presence of these compounds at low concentration has more concern regarding potential risks to living organism due to persistent nature in the water (Heberer *et al.,* 1998). It has been reported in UK, USA and Australia that pharmaceuticals compounds are mainly present in drinking water at high concentrations (More than -1000-folds). In several European countries and the United States pharmaceutical substances are more than 100 in an aquatic environment. Western Europe consisted of 30 pharmaceutical substances and Asia-Pacific Group, Africa Group, and Eastern Europe Group, 30 different pharmaceutical substances or fewer have been detected (Beek *et al.,* 2016).

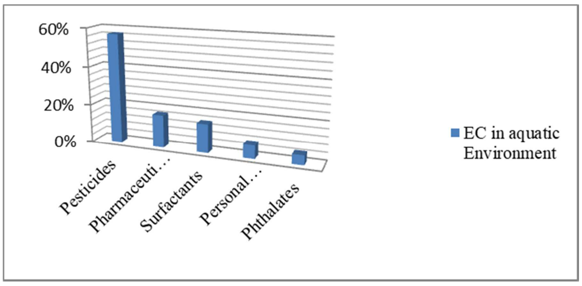

Fig. 3. Emerging contaminants in aquatic environment in India (Gani and Khazm,i 2016)

Emerging Contaminants (ECs) have been detected in many water bodies across India (Fig. 3). EC are present in surface water, groundwater, stormwater, treated wastewater, treated industrial effluent, and bottled water. Several studies have ascertained the presence of Active Pharmaceutical Ingredients (API), Personal Care Products (PCP), pesticides, Endocrine-Disrupting Chemicals (EDC) and Artificial Sweeteners (ASW) in surface water bodies.

PPCP contamination in Indian river

Most of the Indian rivers mainly contaminated by untreated sewage and industrial effluent which highly contain micro-polluting compounds. The Delhi-based non-profit Centre for Science and Environment (CSE) reports that 78 per cent of the sewage generated in India remains untreated and is discharged in rivers, groundwater or lakes (CSE, 2016). But here minor information and research is existed on the occurrence of PPCP in water bodies in India.

Fig. 3 graphically represents the presence of emerging contaminants in percentage in India's aquatic ecosystems. It highlights higher percentage of pesticides followed by pharmaceuticals, surfactants, personal care products and phthalates, indicating their distribution and impacts on India's water bodies; this shows the growing concern of these contaminants in the nation's aquatic environment.

Table 3. Predominate pharmaceutical and cosmetic residues in Indian river

Active pharmaceutical ingredients (API)	Class of drug	Conc. (µg/L)	Location	Reference
Carbamazepine (CBZ)	Antiepileptic	13.00	Kaveri, TN	Ramaswamy *et al.* (2011)
		15.14	Tamiraparani, TN	Ramaswamy *et al.* (2011)
		2.67	Vellar, TN	Ramaswamy *et al.* (2011)
		6.65	Pichavarom, TN	Ramaswamy *et al.* (2011)
		0.113	Ahar River, Udaipur	William *et al.* (2019)
		0.02	River Ganga, UP	Lapworth *et al.* (2018)
		0.016	Stretch of River Ganga	Sharma *et al.* (2019)
Sulfamethoxazole	Antibiotic	0.82	Ahar River, Udaipur	William *et al.* (2019)
		0.1	River Ganga, UP	Lapworth *et al.* (2018)
		0.028	Stretch of River Ganga	Sharma *et al.* (2019)
Trimethoprim	Antibiotic	0.05	Ahar River, Udaipur	William *et al.* (2019)
Azithromycin	Antibiotic	0.99	Ahar River, Udaipur	William *et al.* (2019)
Ampicillin	Antibiotic, Penicillin	13.75	Yamuna River, Delhi	Mutiyar and Mittal (2014)
Ciprofloxacin	Antibiotic fluoroquinolone	14000	Isakavagu-Nakkavagu River, Hyderabad	Fick *et al.* (2009)
		0.029	Stretch of River Ganga	Sharma *et al.* (2019)
Sparfloxacin	Antibiotic, fluoroquinolone	2.09	Yamuna River, Delhi	Mutiyar and Mittal (2014)
Cefuroxime	Antibiotic	1.7	Yamuna River, Delhi	Mutiyar and Mittal (2014)
Gatifloxacin	Antibiotic, fluoroquinolone	0.48	Yamuna River, Delhi	Mutiyar and Mittal (2014)
Naproxen	Non-Steroidal Anti-inflammatory drug (NASID)	0.24	Ahar River, Udaipur	William *et al.* (2019)
				Sharma *et al.* (2019)
		0.003	Stretch of River Ganga	Sharma *et al.* (2019)
Personal care product				
Triclosan,	Preservative in cosmetics, Antibacterial	0.04	Kaveri rivers	Ramaswamy *et al.* 2011
		0.009	Vellar	Ramaswamy *et al.* 2011
		0.14	Tamiraparani	Ramaswamy *et al.* 2011
		0.005	Stretch of River Ganga	Sharma *et al.* (2019)
Triclocarban	Antibacterial	1.12	Kaveri	Vimalkumar *et al.* (2018)
		0.17	Tamiraparani	Vimalkumar *et al.* (2018)
		0.10	Vellar	Vimalkumar *et al.* (2018)
		0.003	Stretch of River Ganga	Sharma *et al.* (2019)
Caffeine	Cosmetic, Psychoactive drug	37.5	Ahar river, Udaipur	Williams *et al.* (2019)
		0.743	Stretch of River Ganga	Sharma *et al.* (2019)

Table 4. Effluent showing pharmaceutical contamination (ng/L) in WTP, in India

Contaminants	Effluent (ng/L)	WTP Place	Reference
Antischizophrenics			
Quetiapine	20	Udupi, Karnataka	Subedi *et al.*, 2017
	5.2	Mangalore, Karnataka	Subedi *et al.*, 2017
	6.32	Beur, Bihar	Subedi *et al.*, 2015a
	16.6	Coimbatore, Tamil Nadu	Subedi *et al.*, 2015a
	22.4	Manipal, Karnataka	Subedi *et al.*, 2015a
Noquetiapine	4.04	Saidpur, Bihar	Subedi *et al.*, 2015a
	10.1	Coimbatore, Tamil Nadu	Subedi *et al.*, 2015a
	1.92	Udupi, Karnataka	Subedi *et al.*, 2015a
	6.50	Manipal, Karnataka	Subedi *et al.*, 2015a
Aripiprazole	71	Udupi, Karnataka	Subedi *et al.*, 2017
	0.4	Mangalore, Karnataka	Subedi *et al.*, 2017
Dehydroaripiprazole	2.20	Saidpur, Bihar	Subedi *et al.*, 2015a
Sedatives-hypnotics-anxiolytics			
Lorazepam	23	Udupi, Karnataka,	Subedi *et al.*, 2017
	12	Mangalore, Karnataka	Subedi *et al.*, 2017
	19.1	Saidpur, Bihar	Subedi *et al.*, 2015a
	27.4	Beur, Bihar	Subedi *et al.*, 2015a
Alprazolam	33	Udupi, Karnataka,	Subedi *et al.*, 2017
	25	Mangalore, Karnataka	Subedi *et al.*, 2017
	6.9	Saidpur, Bihar	Subedi *et al.*, 2015a
	5.72	Beur, Bihar	Subedi *et al.*, 2015a
	2.52	Manipal, Karnataka	Subedi *et al.*, 2015a
α-hydroxyalprazolam	8.48	Saidpur, Bihar	Subedi *et al.*, 2015a
Diazepam	36	Udupi, Karnataka,	Subedi *et al.*, 2017
	9.5	Mangalore, Karnataka	-
	8.20	Saidpur, Bihar	Subedi *et al.*, 2015a
	47.0	Beur, Bihar	Subedi *et al.*, 2015a
	24.6	Udupi, Karnataka	Subedi *et al.*, 2015a
	238	Manipal, Karnataka	Subedi *et al.*, 2015a
Oxazepam	85	Udupi, Karnataka,	Subedi *et al.*, 2017
	50	Mangalore, Karnataka	Subedi *et al.*, 2017
	38.2	Coimbatore, Tamil Nadu	Subedi *et al.*, 2015a
	17.0	Udupi, Karnataka	Subedi *et al.*, 2015a
	17.0	Manipal, Karnataka	Subedi *et al.*, 2015a
Nordiazepam	85	Udupi, Karnataka	Subedi *et al.*, 2017
	50	Mangalore, Karnataka	Subedi *et al.*, 2017
	10.5	Saidpur, Bihar	Subedi *et al.*, 2015a
	6.70	Beur, Bihar	Subedi *et al.*, 2015a
	8.56	Coimbatore, Tamil Nadu	Subedi *et al.*,2015a
	3.08	Udupi, Karnataka	Subedi *et al.*, 2015a
	5.96	Manipal, Karnataka	Subedi *et al.*, 2015a
Carbamazepine	580	Udupi, Karnataka	Subedi *et al.*, 2017
	480	Mangalore Karnataka	Subedi *et al.*, 2017
	88	Saidpur, Bihar	Subedi *et al.*, 2015a
	236	Beur, Bihar	Subedi *et al.*, 2015a
	900	Coimbatore, Tamil Nadu	Subedi *et al.*, 2015a
	147	Udupi, Karnataka	Subedi *et al.*, 2015a
	318	Manipal, Karnataka	Subedi *et al.*, 2015a
Antimicrobial			
Triclocarban	540	Udupi, Karnataka	Subedi *et al.*, 2017
	260	Mangalore, Karnataka	Subedi *et al.*, 2017
	22.4	Saidpur, Bihar	Subedi *et al.*, 2015a
	457	Beur, Bihar	Subedi *et al.*, 2015a
	5860	Coimbatore, Tamil Nadu	Subedi *et al.*, 2015a
	48.4	Udupi, Karnataka	Subedi *et al.*, 2015a
	375	Manipal, Karnataka	Subedi *et al.*, 2015a
Triclosan	3500	Nagpur	Archana *et al.*, 2016
	2500	Coimbatore, Tamil Nadu	Subedi *et al.*, 2015a
	202	Udupi, Karnataka	Subedi *et al.*, 2015a
Antibiotics/fungicides			
Trimethoprim	25	Mangalore, Karnataka	Subedi *et al.*, 2017
	8, 1, 3	Southern India	Prabhasankar *et al.*, 2016
	34.8	Beur, Bihar	Subedi *et al.*, 2015a

	38.0	Beur, Bihar	Subedi *et al*., 2015a
	103	Coimbatore, Tamil Nadu	Subedi *et al*., 2015a
	2080	Manipal, Karnataka	Subedi *et al*., 2015a
Sulfamethoxazole	260	Udupi, Karnataka	Subedi *et al*., 2017
	25	Mangalore, Karnataka	Subedi *et al*., 2017
	13,27,9	Southern India	Prabhasankar *et al*., 2016
	70.2	Beur, Bihar	Subedi *et al*., 2015a
	318	Coimbatore, Tamil Nadu	Subedi *et al*., 2015a
	228	Udupi, Karnataka	Subedi *et al*., 2015a
	296	Manipal, Karnataka	Subedi *et al*., 2015a
Ampicilin	12.68	Okhla, Delhi,	Mutiyar and Mittal, 2014
Ciprofloxacin	8	Okhla, Delhi,	Mutiyar and Mittal, 2014
	11676	Nagpur	Archana *et al*., 2016
Erythromycin	2, 1, 9	Southern India	Prabhasankar *et al*., 2016
Gatifloxacin	1.22	Okhla, Delhi,	Mutiyar and Mittal, 2014
Sparfloxacin	0.14	Okhla, Delhi,	Mutiyar and Mittal, 2014
Cefuroxime	0.22	Okhla, Delhi,	Mutiyar and Mittal, 2014
Ofloxacin	0–212	Southern India	Akiba *et al*., 2015
Clindamycin	25	Mangalore, Karnataka	Subedi *et al*., 2017
	48.0	Saidpur, Bihar	Subedi *et al*., 2015a
	6.96	Beur, Bihar	Subedi *et al*., 2015a
	17.5	Coimbatore, Tamil Nadu	Subedi *et al*., 2015a
	63.8	Udupi, Karnataka	Subedi *et al*., 2015a
	952	Manipal, Karnataka	Subedi *et al*., 2015a
Lincomycin	430	Udupi, Karnataka	Subedi *et al*., 2017
	130	Mangalore, Karnataka	Subedi *et al*., 2017
	53.0	Saidpur, Bihar	Subedi *et al*., 2015a
	17.5	Beur, Bihar	Subedi *et al*., 2015a
	3.92	Coimbatore, Tamil Nadu	Subedi *et al*., 2015a
	187	Udupi, Karnataka	Subedi *et al*., 2015a
	43.0	Manipal, Karnataka	Subedi *et al*., 2015a
Miconazole	8.0	Udupi, Karnataka	Subedi *et al*., 2017
	25	Mangalore, Karnataka	Subedi *et al*., 2017
	17.8	Saidpur, Bihar	Subedi *et al*., 2015a
	8.92	Beur, Bihar	Subedi *et al*., 2015a
	1020	Coimbatore, Tamil Nadu	Subedi *et al*., 2015a
	17.0	Manipal, Karnataka	Subedi *et al*., 2015a
Tiabendazole	79	Udupi, Karnataka	Subedi *et al*., 2017
	25	Mangalore, Karnataka	Subedi *et al*., 2017

Here it has been given the high levels of API in water matrices which is frequently detectable in Indian River (Table 3).

Carbamazepine (CBZ) concentration is high in Cauvery and Tamiraparani River. It uses as an anthropogenic indication of sewage contamination in freshwater bodies (Kumar *et al.,* 2016) and it is poorly removed by the conventional wastewater treatment plants (WWTP). It is often used to treat bipolar disorder, neurologists, and pain specialists by causing inhibition of sodium gated channel (VGSC) and decrease synaptic nerve (Gambeta *et al.,* 2020).

Caffeine is a xanthine alkaloid compound found in coffee, tea, or caffeinated soft drinks and also in condiments, tobacco and medications which stimulates the central nervous system. The average consumption of caffeine found to be between 80 and 400 mg per person per day globally (Gokulakrishnan *et al.,* 2005). In humans, it is metabolized by the liver and excreted about 0.5 to 10 % through urine and faeces (Berthou *et al*., 1992; Seiler *et al*., 1999; Knee *et al*., 2010; Rodriguez del Rey *et al*., 2012). Improper disposal of coffee into household drainage system contribute to hundreds of milligrams of caffeine to surface waters and thus flow to streams, rivers or ponds that finally deposits into the aquatic environment (Seiler *et al.,* 1999).

It also affects environmental parameters in the ocean such as a change in temperature, pH and bleaching of coral reefs (Pollack *et al.,* 2009). In this period, we have depended on antibiotic medicine or habituated to intake for fast response. In the world, consumption of antibiotic lies between 100,000 and 200,000 ton per annum in which nearly 50% used for veterinary drugs (Van Boeckel *et al.,* 2014). In the world, India was the fifth -largest consumer of antibiotics in food animals (poultry, pigs, and cattle) in 2010, after China, the United States, Brazil, and Germany, based on livestock density (Van Boeckel *et al.,* 2014).

The markets of India in Cosmetic and beauty products are increasing day by day which is categorized into five major categories - body care, face care, hair care, hand care and color cosmetics (Report on Indian Cosmetics Industry). The use of PCPs varies from geographical region, sex and age difference. It estimated that female uses approximately 12 products while male uses 6 product (Leonard, 2010) which contains 168 chemicals. As result female uses more personal product than male. In personal care products, various chemicals are prone to be such as UV filters, some preservatives (parabens, Phthalates, triclosan), and microplastics.

According to classification, cosmetics can be divided into leave-on (eg, perfumes, face cream and antiperspirants) and rinse-off products (shampoos, soaps, shower gels, and toothpaste). Some of these compounds are shown as bioactive, persistent and bioaccumulated in environment (Brausch *et al.,* 2011).

Therefore, some chemicals such as synthetic musks (Carballa *et al.,* 2004), perfluoroalkyl compounds (Campo *et al.,* 2014), some organic UV-filters (Ramos *et al.,* 2016) and microplastics (Browne *et al.,* 2004) do not always remove by wastewater treatment plants (WTP) because their efficiency of removal of pharmaceutical contamination through existing WTP is about 112.5% to 100% (Santos *et al.,* 2007*;* Luo *et al.,* 2014). Surface water contamination is mainly caused by wastewater treatment outlets (Daughton and Ternes, 1999). Various drugs have been detected at higher concentrations in wastewater from Indian WTPs such as Aripiprazole, Carbamazepine in Udupi WTP, Karnataka, Diazepam Manipal, Karnataka to treat anxiety and mental illness. For antimicrobial drugs, Triclocarban and Triclosan concentration is high in Udupi, Karnataka and Nagpur wastewater treatment plants.

Antibiotics such as Trimethoprim (Manipal, Karnataka), Sulfamethoxazole (Manipal, Karnataka), Lincomycin, Miconazole (Udupi, Karnataka) and Ofloxacin (Southern India) have been found in WTPs (Table 4).

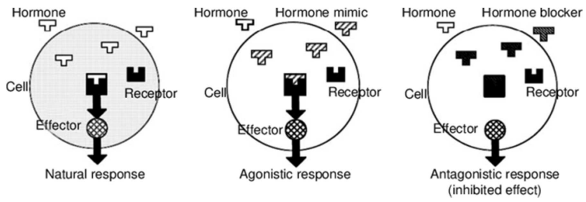

Fig. 4. Endocrine disruption process (Birklett, 2003)

Endocrine disrupting compounds (EDC)

The United States Environmental Protection Agency (USEPA) states that any agents or chemical that interfere the natural hormone in their 'interfere with the synthesis, secretion, transport, binding, or elimination of natural hormones in the body that are responsible for regulate biological process, maintain homeostasis, reproduction process, adulthood development and sexual behavior in the body (Birklett, 2003). A group of steroid hormones includes both natural and synthetic drug such as alkylphenols, pesticides, organic oxygen compounds, polyaromatic hydrocarbons (PAHs) and dioxins which comes under EDC (Fig. 4). These compounds may act as hormone mimics which binds to target cell to activate response is called agnostic response and also act as a blocker or no response termed as an antagonistic response. EDC and PPCPs compounds have an undesired effect, present in trace concentration in water. These compounds are almost ubiquitous in municipal sewage treatment plant (STP) effluents and finally, these residues go for drinking water treatment plants (Snyder *et al.,* 2005). Many studies have shown that conventional treatment systems perform poorly in removing these chemicals from drinking water (Snyder *et al*., 2003; Westerhoff, 2003; Stackelberg *et al*., 2004).

EDC occurrence in water

EDC includes pesticides, bisphenols, phthalates, synthetic and natural hormones, and polychlorinated biphenyls compounds (Gore *et al*., 2014). The waste residues of these compounds generally found in the water bodies (Table 5).

Table 5. Concentrations of main antibiotic and steroid hormone (EDC) in different water matrices

Water matrix	Types of EDC	Concentration	Country	Reference
Fresh water	Lamivudine	167,100	Kenya	Fekadu *et al.*, 2019
	Paracetamol	106,970	Kenya	Fekadu *et al.*, 2019
	Naproxen	59,300	South Africa	Fekadu *et al.*, 2019
	Sulfamethoxazole	53,828	Mozambique	Fekadu *et al.*, 2019
	Ibuprofen	17,600	South Africa	Fekadu *et al.*, 2019
		1440	Spain	Fekadu *et al.*, 2019
	Zidovudine	17,410	Kenya	Fekadu *et al.*, 2019
	Ciprofloxacin	14,331	South Africa	Fekadu *et al.*, 2019
	Trimethoprim	11,383	Kenya	Fekadu *et al.*, 2019
	Valsartan	6260	Spain	Fekadu *et al.*, 2019
	Erythromycin	5300	Croatia	Fekadu *et al.*, 2019
	Metformin	3100	Germany	Fekadu *et al.*, 2019
	Carbamazepine-10,11-epoxide	1670	Spain	Fekadu *et al.*, 2019
	Azithromycin	1500	Croatia	Fekadu *et al.*, 2019
	Sulfadiazine	1100	Croatia	Fekadu *et al.*, 2019
	Steroid hormone			
	Progesterone	1000	Croatia	Fekadu *et al.*, 2019
	Testosterone	0.23–13.7	Hungary	Fekadu *et al.*, 2019
	Estrone(E1)	2.6–3	Italy	Fekadu *et al.*, 2019
	Estrone(E1)	0.1–69	Europe	Fekadu *et al.*, 2019
	Estriol(E3)	1.5–7.2	Portugal	Rocha *et al.*, 2019
	Estriol(E3)	45,550	South Africa	Fekadu *et al.*, 2019
	Estriol(E3)	2.38	France	Fekadu *et al.*, 2019
	Estradiol(E2)	510–45,500	Africa	Fekadu *et al.*, 2019
	Estradiol(E2)	0.33–5	Hungary	Fekadu *et al.*, 2019
	Estradiol(E2)	15,700	South Africa	Fekadu *et al.*, 2019
	Ethinylestradiol (EE2)	0.8–1.7	Portugal	Rocha *et al.*, 2019
	Ethinylestradiol (EE2)	0.3–0.5	Portugal	Rocha *et al.*, 2019
Wastewater	Antibiotic			
	Nordiazepam	0.6	Greece	Papageorgiou *et al.*, 2016
	Carbamazepine	6822	Greece	Papageorgiou *et al.*, 2016
	9-OH risperidone	0.4	Greece	Papageorgiou *et al.*, 2016
	Octylphenol	1.9	Serbia	Papageorgiou *et al.*, 2016
	Indomethacine	297	Greece	Papageorgiou *et al.*, 2016
	Ketoprofen	793	Greece	Papageorgiou *et al.*, 2016
	Meloxican	648	Greece	Papageorgiou *et al.*, 2016
	Naproxen	3581	Greece	Papageorgiou *et al.*, 2016
	Diclofenac	4869	Greece	Papageorgiou *et al.*, 2016
	Nimesulide	2452	Greece	Papageorgiou *et al.*, 2016
	Paracetamol	27.7	Greece	Papageorgiou *et al.*, 2016
	Phenazone	44.9	Greece	Papageorgiou *et al.*, 2016
	Piroxicam	1192	Greece	Papageorgiou *et al.*, 2016
	Ampicillin	1805	Greece	Papageorgiou *et al.*, 2016
	Ciproflaxicin	591	Greece	Papageorgiou *et al.*, 2016
	Erythromycin	320	Greece	Papageorgiou *et al.*, 2016
	Lincomycin	281	Greece	Papageorgiou *et al.*, 2016

	Metronidazole	64.7	Greece	Papageorgiou *et al.*, 2016
	Moxifloxacin	773	Greece	Papageorgiou *et al.*, 2016
	Sulfadiazine	846	Greece	Papageorgiou *et al.*, 2016
	Sulfamethoxazole	507	Greece	Papageorgiou *et al.*, 2016
	Trimethoprim	200	Greece	Papageorgiou *et al.*, 2016
	Fluvoxamine	75.4	Greece	Papageorgiou *et al.*, 2016
Drinking water	Antibiotic			
	Erythromycin	11	Taiwan	Yang *et al.*, 2014
	Acetaminophen	7	Taiwan	Yang *et al.*, 2014
	Steroid hormone			
	E1	5.9	Serbia	Celi´c *et al.*, 2020
	E2	7.2	Serbia	Celi´c *et al.*, 2020
	E3	4.9	Serbia	Celi´c *et al.*, 2020
	E1-3-sulfate	.4	Serbia	Celi´c *et al.*, 2020
	E3-3-sulfate	6.6	Serbia	Celi´c *et al.*, 2020

Antibiotic concentration in WTP in India

One case has been reported that high level of pharmaceutical compounds was found in effluent treatment plant (ETP) in Patancheru in Medak district, Andhra Pradesh (Table 6).

Table 6. Active pharmaceutical ingredients (Larsson *et al.*, 2007)

Drug	Levels in µg/l
Ciprofloxacin	28,000-31,000
Losartan	2,400-2,500
Cetirizine	1,300-1,400
Metoprolol	800-950
Enrofloxacin	780-900
Citalopram	770-840
Norfloxacin	390-420
Lomefloxacin	150-300
Enoxacin	150-300
Ofloxacin	150-160
Ranitidin	90-160

In this given table Ciprofloxacin, Losartan and Cetirizine are present in very high level in wastewater. Ciprofloxacin is high spectrum fluoroquinolone antibiotic drug and it orally administrated to humans which is unmetabolized and excreted through urine (44.7%) and 25% in feces (Fassse, 2017). Losartan is an antihypertensive drug which decreases blood pressure. It shows high bio concentration in the aquatic organisms (US EPA, 2014). Cetirizine is used to seasonal allergic rhinitis and is orally administrated drug. It unmetabolized and 70 – 85% are excreted through urine and 10-13% in faces (NCBI, 2021). Furthermore, it has been estimated that about 30-90% oral pharmaceutical administrated drugs generally excreted via urine and faces as active substances (BIO Intelligence Service, 2013).

Table 7. Hormonal disruption in vertebrate species due to water contamination

Species	Health effect	Environmental exposure/PPCP contamination	References
Mosquito Fish	Masculinization	Exposure to androgenic Paper mill effluents	Howell *et al.* (1980), Sumpter (2005) and Orlando and Guillette (2007)
Rainbow trout	Feminization (male fish producing eggs and female hormones such as vitellogenin) and sterility	Ethinyl-estradiol (EE2) and alkylphenol ethoxylates present in sewage treatment plant (STP) effluents	Purdom *et al.* (1994)
Alligators	Reproductive tracts disorder including reduced penis size in males and population decrease	Organochlorines such as DDTs, DDEs	Guillette *et al.* (1994) and safe (2000)

Gulls, terns, herons and other predatory birds	Feminization and other sexual abnormalities, thin-walled eggshells	Polychlorinated biphenyls (PCBs), DDTs, DDEs	Safe (2000) and Fry (2005)
White-backed (*Gyps bengalensis*) and long-billed (*Gyps indicus*) vultures	Kidney failure leading to death. These species are on the verge of extinction in South Asia	Veterinary use of diclofenac	Proffitt and Bagla (2004)
Snails	Imposex (altered sexual orientation)	Exposure to tributyltin (TBT) in marine environment near ports	Lintelmann *et al.* (2003); Sharpe and Irvine (2004) ; Sumpter (2005)
Daphnia pulex	Impaired reproduction	Simazine	Falconer *et al.* (2006)
Ewes/sheep	Infertility	Observed in sheep that were grazed in clover pastures rich in phytoestrogen. Formononetin in clovers is primarily held responsible	Adams (2000)

Impact of EDC in animals

EDCs interferes with the hormonal control of developing humans and wildlife. It adversely affects the normal endocrine system functioning in wildlife animals. Synthetic endocrine chemicals act like natural hormones and reduce their production (Table 5). It controls organism development, behavior and metabolism. Hermaphroditism (both male and female reproductive organs in a single organism) and impaired offspring survival and development have been reported in frogs, salmon, oysters, newts, trout and turtles expose to EDCs (Gilbert and Wendall, 2013). Estrogenic compounds like 17 beta-estradiol (natural female hormones) and ethinylestradiol (analogy of 17 beta-estradiol) have been shown to cause reproductive and developmental effects in fish and amphibians (Kavlock and Daston, 1996). Ethinylestradiol is a bioactive chemical that bioaccumulates within an organism and 0.1 ng/L is enough to produce vitellogenin (female egg protein) in male trout (Purdom and Randall, 1998; Larsson *et al.*, 1999) (Table 7).

Table 8. Emergence compounds and their health effect in Humans

ED compound	Product	Health effect	References
Diethylstilbestrol		Reproductive disorders, cognitive impairment and miscarriage	Birnbaum, 1994; Damgaard *et al.*, 2002; Falconer *et al.*, 2006; Inadera, 2006
Industrial chemicals and organochlorine pesticides		Early onset of puberty in girls, delayed puberty in boys and impaired fertility in men	Colon *et al.*, 2000; Sharpe and Irvine, 2004; Snyder *et al.*, 2005).
DDT		Declined sperm counts, sperm quality and sex ratios in Canada and the United States	Allan *et al.*, 1997; Safe, 2000; Mackenzie *et al.*, 2005
High levels of phthalate esters	Beauty and skin care products (such as shampoos, lotions, makeup, and perfume)	Puerto Rican girls with premature breast development (premature thelarche). Prolonged or permanent neurological injuries including cognitive impairment and behaviour abnormalities may occur in children, particularly to the foetus if exposed to dioxins and PCBs	Falconer *et al.*, 2006
		Phthalate esters (PE) may have an aetiological association with endometriosis.	Reddy *et al.*, 2006
Triclosan	Broad-spectrum antimicrobial agent		(APUA) January 2011
	Toothpastes, Antiseptic soaps, Mouthwash , Deodorant ,Hair products ,Detergents, Cosmetics	Impact male and female hormones like testosterone and estrogen, and may also affect thyroid systems	Calafat *et al.*, 2008; Gee *et al.*, 2008
Triclocarban	Antibacterial,	Associated with lower levels of thyroid	UC Davis, 2014

Parabens	soaps, deodorants, detergents, cleansing lotions, Personal care products, cosmetics, pharmaceutical products and food.	hormone and testosterone, which could result in altered behaviour, learning disabilities, or infertility Presence of Butylparaben in low concentration cause breast tumors.84	Goswami *et al.*, 2013

Human health

According to Kasprzyk-Hordern *et al.* (2009), the primary way that humans develop contact with PPCP is through bioaccumulation in animals or in naturally occurring freshwater resources (Table 8). These compounds are hazardous even at ppb doses. Numerous studies are being conducted to examine the impact of their PPCPs on aquatic life, human health, and all other associated living things (Boxall *et al.*, 2012). The widespread usage of PPCP has led to an increase in human-related diseases and disorders. UNEP, WHO (2012) Science of Endocrine Disrupting Chemicals reports that up to 40% of young males have reduced semen production. Over the past few decades, there has been a rise in certain nations in the number of children affected by neurobehavioral disorders linked to disruptions of the thyroid. Over the past 40–50 years, there has been an increase in endocrine-related malignancies, including those of the breast, endometrial, ovarian, prostate, testicular, and thyroid. Worldwide rates of obesity and type 2 diabetes have skyrocketed in the previous 40 years.

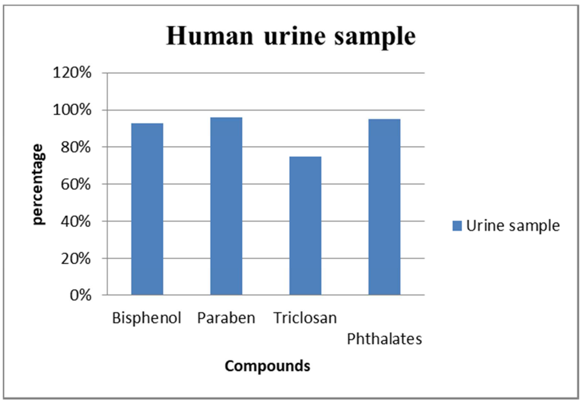

Fig. 5. PCPs concentration in human urine sample

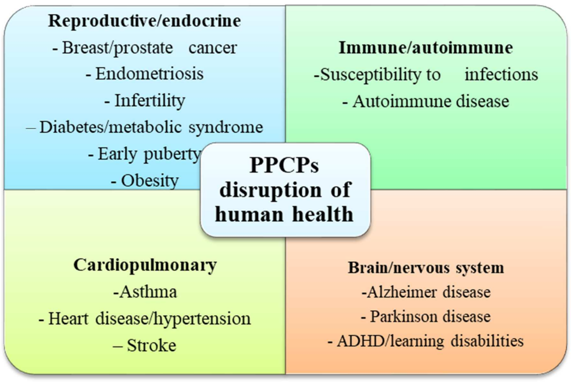

Fig. 6. Diseases induced by exposure to EDCs during development in animal model and human studies (UNEP, WHO; 2012)

A WHO analysis estimates that between 1980 and 2008, the number of adults worldwide with type 2 diabetes grew from 153 million to 347 million and that 1.5 billion persons worldwide are overweight. While cosmetic items mostly contain bisphenol B, triclosan, triclocarban, and parabens, personal care products also contain phthalates. When these compounds are used, they are absorbed by the body and may, with minimal exposure, accumulate in bodily tissues. For example, methylparaben builds up in human breast tissues (Darbre *et al.*, 2004). According to a report, the following PCPs were found in high concentrations in human urine: bisphenol (Calafat *et al.*, 2008), triclocarban (Antonia *et al.*, 2008), phthalates (Ying *et al.*, 2011), and parabens (Ye *et al.*, 2006) (Fig. 5 &6).

Pharmaceutical by-products excreted by usage of ethinylestradiol (birth control pill), menopause treatments, thyroid replacements, and cancer therapies which leads hormonal disruption. Significant relations have been identified between endocrine disrupters and prostate and breast cancer (Cizmas *et al.,* 2015)

Conclusion

In nature, PPCPs are abundant and have the ability to linger, bioaccumulate, and contaminate freshwater resources. There is a possible risk of drinking water pollution since PPCP is not entirely removed by the sewage treatment system, particularly in metropolitan locations where there are high sewage wastewater outputs and low surface water inputs. We need multiple wastewater treatment methods, which likely require water treatment goals since there isn't a single treatment technique that can remove all toxins from water. Developing nations have a markedly increased risk of endocrine disruption from chemical exposure. We know India is fast growing in the pharmaceutical industry and has ranked under the top five globally but there is limited research and data for the presence of PPCP contamination in Indian water. In this review we conclude result that pharmaceutical compounds such as carbamazepine, ciprofloxacin, erythromycin and cetirizine are used extensively in India as well as their waste residues found in high concentration in wastewater treatment plant and rivers also. Wherein personal care products phthalate, triclosan, triclocarban and parabens are found in high concentrations in Indian water. So therefore' emission of PPCP residues in surface water can be an imminent threat to the freshwater resources and increase human health burden. With concern to the scientific knowledge and awareness on the potential adverse impact of EDCs and their handling technologies.

Future research and measurement needs for PPCPs

To effectively address the challenges posed by Pharmaceuticals and Personal Care Products (PPCPs), future research and policy measures should focus on the following key areas:

1. Appropriate attention from the government and other concerned agencies regarding PPCP.
2. Establishment of concerted international as well as local policies to ensure minimal exposure to EDCs, and also their limited and appropriate usage.
3. Appropriate drug disposal practices, minimizing the overuse and inappropriate use of pesticides and drugs.
4. Manufacturing herbal drug-like estrogens to replace synthetic steroid hormones.
5. Collaborative research should be undertaken to monitor high-risk groups to identify the pathways of exposure and potential adverse impacts.
6. Establishment of minimum permissible limits of pharmaceuticals in wastewater and implementation of new policy in India.
7. Sustainable and cost-effective research for pharmaceutical removal strategies in wastewater treatment plants.

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