Environmental hazards of common over-the-counter drugs on aquatic life: A systematic review

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ABSTRACT

INTRODUCTION Over-the-counter (OTC) pharmaceuticals are increasingly detected in aquatic environments due to widespread use and incomplete removal during wastewater treatment. Their persistence and bioactivity can adversely affect aquatic organisms through biochemical, behavioral, and reproductive disruptions. The aim of the study was to systematically evaluate and summarize existing evidence on the ecotoxicity of commonly used OTC drug classes in aquatic organisms, highlighting research trends, data gaps, and potential implications for human and environmental health.

METHODS A comprehensive literature search was conducted in PubMed, Cochrane CENTRAL, EBSCO, and CINAHL databases up to December 2024. Eligible studies included original experimental studies assessing the toxicity of over-the-counter (OTC) drugs (intervention) on aquatic organisms (population), reporting ecotoxicological outcomes (outcomes). Studies limited to analytical detection or environmental concentration measurements without toxicity assessment were excluded. Data on drug class, test species, exposure conditions, and reported ecotoxicological outcomes were narratively synthesized and descriptively analyzed. Where available, key quantitative outcome measures reported in the included studies were summarized. Formal risk-of-bias assessment was not undertaken due to heterogeneity in study designs and outcome measures.

RESULTS Of 1127 studies screened, 116 met the inclusion criteria. Most were *in vivo* (n=59), followed by in vitro (n=52) and combined studies (n=5). Research activity has increased markedly over the past decade. 17α-ethinylestradiol was the most frequently tested compound (n=43). Fish were the most studied taxa (n=63), with Danio rerio as the predominant model species. Common endpoints included biochemical alterations (20.1%), mortality (17.9%), genotoxicity (14.4%), and reproductive behavior changes (12.5%). Diclofenac, levonorgestrel, ibuprofen, and clotrimazole also showed notable toxicity, while data for naproxen, omeprazole, vitamin C, and chloroxylenol were limited at environmentally relevant concentrations (≤1 µg/L).

CONCLUSIONS OTC pharmaceuticals, especially hormonal and analgesic compounds, exhibit measurable toxic effects on aquatic organisms even at trace levels. More chronic and mixture-toxicity studies are needed to improve ecological risk assessments and guide regulatory policies.

INTRODUCTION

The world is facing a growing climate crisis[1], and a similar environmental threat is emerging from pharmaceutical contamination, with drugs increasingly entering ecosystems and food chains[2]. Awareness is increasing worldwide about the ecological harm caused by pharmaceuticals and their by-products[3]. Many drugs are persistent and resistant to degradation, allowing them to accumulate in the environment

and potentially re-enter the human population[4,5]. After therapeutic use in humans and animals, many pharmaceuticals enter the environment, where long-term exposure can cause chronic toxicity, endocrine disruption, microbial resistance, growth inhibition, cytotoxicity, mutagenicity, teratogenicity, and other adverse effects in plants and animals[6].

Pharmaceutical quantities between ng/L and µg/L are routinely reported in aquatic bodies, and sewage treatment plants have been identified as a primary pathway for this release[7,8]. Pharmaceuticals are effective at very low concentrations and can therefore disrupt the biochemical and physiological functions of aquatic organisms throughout their life cycle, underscoring the urgent need to assess environmentally relevant compounds despite limited data on their occurrence, bioaccumulation and ecological effects[9]. Aquatic organisms rely on waterborne infochemicals for communication, feeding, reproduction, and predator avoidance[10]. Pharmaceutical residues can interfere with these signals even at low concentrations, and these contaminants are difficult to remove during wastewater treatment; they persist and accumulate in aquatic ecosystems[10]. Growing environmental contamination has led to increased research on the behavioral effects of pharmaceuticals, which pose a significant risk to aquatic species by accumulating in their tissues and altering their behavior[11].

According to previous studies, painkillers (NSAIDs), antimicrobials, antiepileptics, antidepressants and anticancer agents have been researched the most in relation to environmental pollution[12-14]. A few studies are also collating data on cardiovascular and anti-diabetic medications[13]. However, other potentially ecotoxic therapeutic classes which are sold as 'over-the-counter (OTC) drugs' (i.e. medications that are directly sold to an individual without a prescription) have not received much attention, despite being extensively utilized worldwide[15-19].

Although different countries have formulated their own guidelines for classification, regulation and use of OTC drugs, some classes commonly utilized by majority of the countries include analgesics and antipyretics, antidiarrheals, antacids and indigestion remedies, antiemetics, anti-allergics, cough and cold remedies, vitamins and minerals, topical steroids, laxatives, hormonal contraceptives, antiseptics and disinfectants, topical antifungals, skincare products, piles and warts remedies, and ophthalmic products[15-19]. As a general rule, an OTC drug is proven to be reasonably safe and well tolerated for human consumption[16]. Unfortunately, these drug classes are also implicated in rampant self-medication (and even self-dosing) globally, thereby exacerbating the problem of their potential bioaccumulation[20]. Long-term bioaccumulation of such drugs in tissues of organisms may lead to unpredictable consequences on ecosystems[9,16]. Therefore, the aim of this research study was to conduct a systematic review and summarize the characteristics of toxicity caused by common over-the-counter drug classes on aquatic organisms.

METHODS

Study design

This was a systematic review of all original studies evaluating the environmental toxicity of one or more OTC drugs.

Study registration

A preliminary literature search was conducted in MEDLINE via PubMed, Cochrane CENTRAL and PROSPERO to look for any review with the same research question and objectives. After ensuring no such publications or registrations, a systematic review protocol was written and registered in Open Science Framework as it was not eligible for registration on PROSPERO due to lack of clear relevance to human health[21]. The standard PRISMA checklist was followed for the design, implementation, and reporting of this study.

Study population

The inclusion criteria were defined using the PICO framework: Population (P) - any aquatic species used in experimental toxicity assessments; Intervention (I) - exposure to one or more OTC pharmaceutical drugs; Comparison (C) - unexposed or control conditions, or baseline toxicity measurements where applicable; and Outcomes (O) - any reported ecotoxicological effects attributable to OTC drug exposure. Accordingly, original research articles published in English up to December 2024 that investigated the toxicity of OTC pharmaceutical drugs in aquatic organisms were included in the study.

Studies were excluded if they focused solely on the presence or environmental concentrations of pharmaceutical contaminants without evaluating or describing toxicity characteristics in aquatic organisms, as they did not address relevant biological endpoints. In addition, drug classes that may be sold as OTC medications in certain regions but do not represent conventional allopathic OTC drugs, namely herbal products, traditional medicines, and homeopathic remedies, were excluded from this review to ensure pharmacological and regulatory consistency with conventional OTC drugs. Furthermore, non-primary research and non-full-text publications, including book chapters, conference abstracts, commentaries, editorials, expert opinions, narrative reviews, and perspective articles, as well as studies not published in the English language, were also excluded due to a lack of original data and challenges in standardized quality assessment, respectively.

Search strategy

A systematic search of the literature was conducted in MEDLINE via PubMed, Cochrane CENTRAL (Central register of controlled trials), EBSCO, and CINAHL (Cumulative Index to Nursing and Allied Health Literature to find relevant articles published to date. Regional databases (e.g. IndMed), clinical trial registries (e.g. CTRI), hand-searching of non-indexed journals, conference proceedings, and unpublished (grey) literature were also attempted by the reviewers.

Authors were contacted via e-mail and ResearchGate in case the full text was not available. The databases were last searched in December 2024. For each search result, search keywords included: aquatic organisms, toxicity, and one of the following OTC class names – analgesics & antipyretics, antidiarrheals, antacids & indigestion remedies, antiemetics, laxatives, anti-allergics, cough and cold remedies, vitamins & minerals, topical steroids, hormonal contraceptives, antiseptics & disinfectants, topical antifungals, topical antimicrobials, skincare products, piles and warts remedies, ophthalmic products. The search terms were combined with the logical operator AND. In case the yield with a particular class name was found to be low, a standardized list of drugs belonging to that class was available with the authors conducting the search (Supplementary file Table 1), and the class name was replaced by the individual drug name. Exposure/intervention classes (and drug names) were chosen according to previous studies identifying these drugs as commonly used OTC medicines[15,16,18-20].

Study selection

The results of the searches were screened for relevance, and eligible studies were selected for inclusion according to the predefined inclusion and exclusion criteria. Two reviewers then independently and in a blinded fashion screened the titles and abstracts of articles. Duplicates were removed using manual verification, and no automated software was used.

Data extraction and synthesis

Subsequently, each reviewer independently extracted data from the selected studies, and the third reviewer cross-checked the data. Disagreement was resolved through discussion with the third author or consensus. Once the study was included, the following data were collected and tabulated: Title, author, year of publication, country in which the study was conducted, compound tested, source of the sample, organism in which the compound was tested or determined, dose or concentration at which the compound was tested, environmental association with the dose used, duration of exposure, toxicity tests conducted and their findings. If any study observed direct environmental toxicity in any organism without conducting any laboratory tests or simulations, such data were also collected and highlighted. Authors of the original studies were contacted in case of incomplete information in the published article included in the review. A detailed narrative synthesis of the results was done for each drug tested against different aquatic organisms.

RESULTS

Sample characteristics

We identified 1127 articles through our literature review. After de-duplicating the sample, we screened 1121 articles for relevance, finding 137 eligible for full text review, 116 of which were included in our full analysis[22-137] (Figure 1; and Supplementary file Table 2).

The number of articles published on the environmental toxicity of OTC drugs has grown over time, especially over the last decade. The highest number of studies were available for hormonal contraceptives[22-78], followed by analgesics[79-95] and topical antifungals[96-108] (Table 1). The search yield was low for antidiarrheals, laxatives, topical steroids, skincare products, and ophthalmic products, and no relevant studies could be selected from these drug classes.

Overall, the highest number of studies included

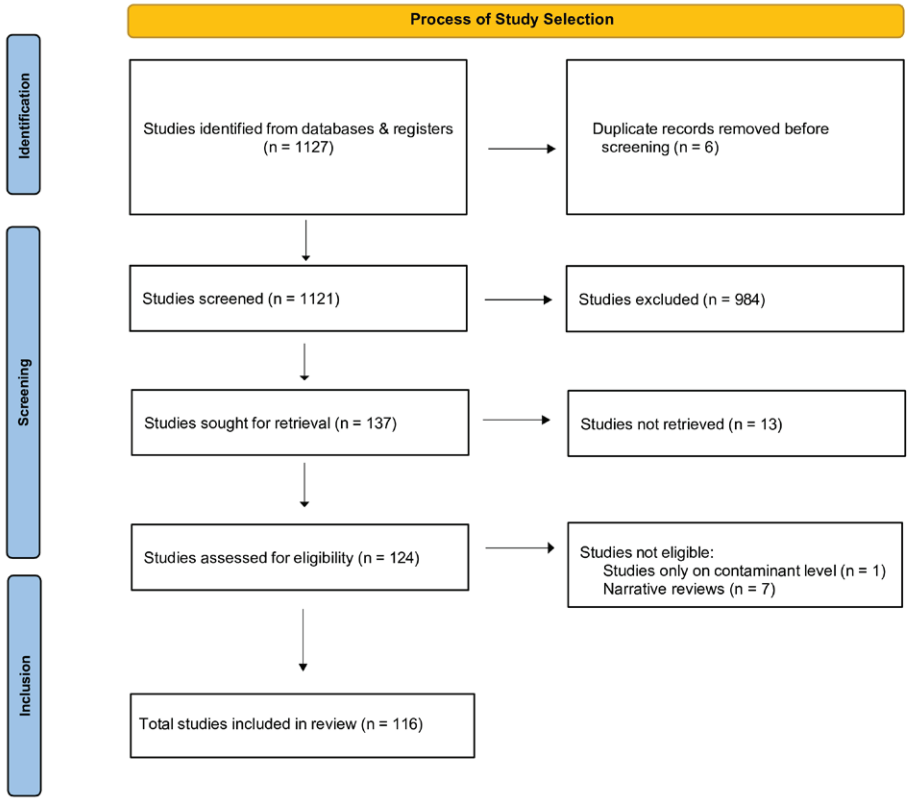
Table 1. Time-wise distribution of included experimental studies (N=116) assessing the environmental toxicity of over-the-counter (OTC) drug classes on aquatic organisms. Data are grouped by decade (1990–2000, 2001–2010, 2011–2020, 2021–December 2024)

Over-the-counter drug class	1990–2000	2001–2010	2011–2020	2021–present	Total
Overall[22-137]	1	12	86	18	116
Analgesics[79-95]	0	1	12	4	17
Antacids[122,128]	0	1	1	0	2
Antiemetics[123]	0	1	0	0	1
Antiallergics[109,113,114,120,124]	0	0	5	0	5
Cough and Cold[129,137]	0	0	2	0	2
Vitamins & Minerals[125]	0	0	1	0	1
Hormonal Contraceptives[22-78]	1	6	41	9	57
Antiseptics[110-112,126,127,130,131]	0	0	5	2	7
Topical Antifungals[96-108]	0	1	11	1	13
Topical Antimicrobials[121,132]	0	1	1	0	2
Piles and Wart Remedies[115-119,133-136]	0	0	7	2	9

Table 2. Test drugs used in the included experimental studies (N=116) evaluating toxicity of over-the-counter (OTC) drugs on aquatic organisms (numbers in parentheses indicate the number of studies in which each drug was tested)

Over-the-counter drug class	Drugs studied
Analgesics	Diclofenac (n=9)[60,79,83,86,90,91,95,99,116], Paracetamol (n=7)[80,82,87,92,94,95,128], Ibuprofen (n=6)[78,80,88,89,93,128], Naproxen (n=3)[33,81,85], Aspirin (n=2)[37,84], Diclofenac-Ibuprofen mixture (n=1)[86], 4-Hydroxydiclofenac (n=1)[91]
Antacids	Ranitidine (n=1)[122], Omeprazole (n=1)[128]
Antiemetics	Cyclizine (n=1)[123], Prochlorperazine (n=1)[123]
Antiallergics	Diphenhydramine (n=2)[109,120], Cetirizine (n=2)[113,114], Loratadine (n=1)[124], Desloratadine (n=1)[124]
Cough and Cold	Codeine (n=1)[129], Ephedrine (n=1)[137]
Vitamins & Minerals	Vitamin C (n=1)[125]
Hormonal Contraceptives	17α-ethinylestradiol (n=43)[22-68,70,97], Levonorgestrel (n=10)[30,68-76], 17β-Estradiol (n=4)[32,51,68,106], Norethindrone (n=3)[74,77,78], Drosperinone (n=3)[46,72,74], Desogestrel (n=1)[72], Gestodene (n=1)[72], Cyproterone acetate (n=1)[74]
Antiseptics	Triclosan (n=4)[100,110,111,128], Povidone-iodine (n=2)[126,127], Phenol (n=1)[130], Chloroxylenol (n=1)[131], Chlorhexidine (n=1)[112]
Topical Antifungals	Clotrimazole (n=9)[96-104], Ketoconazole (n=5)[96,105-108], Econazole (n=1)[96], Miconazole (n=1)[96]
Topical Antimicrobials	Neomycin (n=2)[99,121]
Piles and Wart Remedies	Salicylic acid (n=8)[115-119,134-136], Zinc sulphate (n=1)[133]

Figure 1. Flow diagram showing study identification, screening, eligibility assessment, and inclusion of experimental studies evaluating the environmental toxicity of over-the-counter (OTC) drugs on aquatic organisms. Total included studies: n = 116 (Search conducted up to December 2024)



were found to be conducted in the USA (n=23)[30,31,35.36,38-40,54,57,58,61,63,65.67,70,73,75,76,78,109-112], followed by Portugal (n=18)[27,29,45,47,69,87,92,94,95,98,103,113-119] and China (n=12)[25,26,32,62,77,80,85,93,106,107,120,121]. In all the mentioned countries, most of the studies belonged to hormonal contraceptives class[22-78] (Supplementary file Table 3).

Nearly all the studies included in the analysis were found to be experimental in nature, with the majority of them being *in vivo* (n=59)[22-24,26,27,29-31,34,36,39,42,47,48,54,56,58,63,66,67,69-72,77,79,80,82-95,97,101,102,104,106,107,109,113,114,117,119,120,122-127], followed

Table 3. Concentration ranges of drugs tested in included experimental studies and assessment of effects at environmentally relevant concentrations (N=116)

Drug	Concentration range across studies	Whether the effects of ng/L or µg/ L concentrations investigated in studies
Diclofenac[60,79,80,83,86,90,91,95,99,116]	0.1–100 mg/L	Yes
Naproxen[33,81,85]	42.5–115.2 mg/L	No
Paracetamol[80,82,87,92,94,95,128]	0–150 mg/L	Yes
Aspirin[37,84]	5 µg/L–500 mg/L	Yes
Ibuprofen[78,80,86,88,89,93,128]	0–80 mg/L	Yes
Ranitidine[122]	0–100 mg/L	Yes
Omeprazole[128]	80–140 mg/L	No
Cyclizine[123]	2–100 mg/L	Yes
Prochlorperazine[123]	2–100 mg/L	Yes
Diphenhydramine[109,120]	0.8 µg/L–10 mg/L	Yes
Cetirizine[113,114]	0–12 µg/L	Yes
Loratadine[124]	0.09–100 mg/L	Yes
Codeine[129]	1–2500 µg/L	Yes
Ephedrine[137]	0–1000 mg/L	Yes
Vitamin C[125]	100–400 mg/L	No
17α-ethinylestradiol[22-68,70,97]	1 ng/L–100 mg/L	Yes
Levonorgestrel[30,68-76]	0.06–125 ng/L	Yes
17β-Estradiol[32,51,68,106]	0.1–10 µg/L to 5 mg/L	Yes
Norethindrone[74,77,78]	0–398.6 ng/L	Yes
Drosperinone[46,72,74]	100 ng/L	Yes
Desogestrel[72]	1–100 ng/L	Yes
Gestodene[72]	1–100 ng/L	Yes
Cyproterone acetate[74]	500 µM	Yes
Triclosan[100,110,111,128]	1–200 µg/L	Yes
Povidone-iodine[126,127]	0–240 mg/L	Yes
Phenol[130]	11.38 and 22.76 µM	Yes
Chloroxylenol[131]	50 mg/L	No
Chlorhexidine[112]	900 µg/L	Yes
Clotrimazole[96-104]	0–14.63 µg/L	Yes
Ketoconazole[96,105-108]	0–10 µg/L	Yes
Econazole[96]	4.8–20.1 ng/L	Yes
Miconazole[96]	7.9–16.7 ng/L	Yes
Neomycin[99,121]	11.2 µmol/L	Yes
Salicylic Acid[115-119,134-136]	5–125 µg/L	Yes
Zinc Sulphate[133]	0.6–619 µmol/L	Yes

Table 4. Drug-wise outcome patterns reported in included experimental studies (N=116) assessing the toxicity of over-the-counter (OTC) drugs in aquatic organisms (number displayed in parenthesis is the number of studies in which the corresponding outcome pattern was observed)

Drug	Outcome patterns
Diclofenac[60,79,80,83,86,90,91,95,99,116]	· Mortality – Nasturtium officinale[79], Callitriche platycarpa[79], Dreissena polymorpha[79], Gasterosteus aculeatus[79], Daphnia magna[80], Cyprinus carpio (2)[86,90], Mytilus trossulus[91] · Biochemical alterations – Azolla filiculoides[83], Xanthoria parietina[83], Cyprinus carpio (2)[86,90], Mytilus trossulus[91], Daphnia magna[95], Lemna minor[116] · Morphological changes – Daphnia magna (2)[60,80], Mytilus trossulus[91] · Immunological changes – Nasturtium officinale[79], Callitriche platycarpa[79], Dreissena polymorpha[79], Gasterosteus aculeatus[79] · Genotoxicity changes – Nasturtium officinale[79], Callitriche platycarpa[79], Dreissena polymorpha[79], Gasterosteus aculeatus[79], Cyprinus carpio[86] · Changes in population structure – Nasturtium officinale[79], Callitriche platycarpa[79], Dreissena polymorpha[79], Gasterosteus aculeatus[79], Mytilus trossulus[91] · Reproductive behavior changes – Daphnia magna (2)[60,80], Mytilus trossulus[91] · Bioaccumulation – Hydropsyche sp., Erpobdella octoculata[99]
Naproxen[33,81,85]	· Mortality – Hydra magnipapillata[81], Danio rerio[85] · Biochemical alterations – Hydra magnipapillata[81] · Morphological changes – Hydra magnipapillata[81], Danio rerio[85] · Immunological changes – Harbor seal lymphocytes[33] · Genotoxicity changes – Hydra magnipapillata[81] · Physiological changes – Danio rerio (delayed hatching, lower heart rate, pericardial edema)[85] · Reproductive behavior changes – Danio rerio[85]
Paracetamol[80,82,87,92,94,95,128]	· Mortality – Daphnia magna[80], Nostoc muscorum[82], Anguilla anguilla[94], Tetraselmis suecica128 · Biochemical alterations – Nostoc muscorum[82], Ruditapes philippinarum[87], Hediste diversicolor[92], Anguilla Anguilla[94], Daphnia magna[95], Tetraselmis suecica[128] · Morphological changes – Daphnia magna[80] · Reproductive behavior changes – Daphnia magna[80]
Aspirin[37,84]	· Mortality – Daphnia magna[84,] Artemia sp., Mysidopsis juniae, Echinometra lucunter[37] · Physiological changes – Daphnia magna[84] · Behavioural Changes – Daphnia magna (altered swimming speed)[84]
Ibuprofen[78,80,86,88,89,93,128]	· Mortality – Daphnia magna (2)[80,89], Cyprinus carpio[86], Chironomus riparius[88], Pimephales promelas[78], Tetraselmis suecica[128] · Biochemical alterations – Daphnia magna[89], Cyprinus carpio[86], Chironomus riparius[88], Tetraselmis suecica[128] · Morphological changes – Daphnia magna (3)[80,89,93], Pimephales promelas[78], Tetraselmis suecica[128] · Immunological changes – Chironomus riparius[88] · Genotoxicity changes – Daphnia magna[89], Cyprinus carpio[86], Chironomus riparius[88] · Changes in population structure – Daphnia magna (2)[89,93] · Physiological changes - Tetraselmis suecica[128] · Reproductive behavior changes – Daphnia magna (3)[80,89,93]
Ranitidine[122]	· Mortality –Rotifiers, Crustaceans[122] · Genotoxicity changes – Rotifiers, Crustaceans[122]
Omeprazole[128]	· Growth inhibition – Tetraselmis suecica[128] · Biochemical alterations – Tetraselmis suecica[128]
Cyclizine[123]	· Mortality – Balanus amphitrit[123]
Prochlorperazine[123]	· Mortality – Balanus amphitrit[123]
Diphenhydramine[109,120]	· Mortality – Lemna gibba[109], Daphnia magna[109], Pimephales promelas[109] · Biochemical alterations – Carassius auratus[120] · Behavioural changes – Lemna gibba[109], Daphnia magna[109], Pimephales promelas[109], Carassius auratus[120] · Reproductive behaviour changes – Lemna gibba[109], Daphnia magna[109], Pimephales promelas[109] · Bioaccumulation – Carassius auratus[120]

Continued

Table 4. Continued

Drug	Outcome patterns
Cetirizine[113,114]	· Mortality – Ruditapes philippinarum[114] · Biochemical alterations – Ruditapes philippinarum[114], Mytilus galloprovincialis[113] · Physiological changes – Ruditapes philippinarum[114], Mytilus galloprovincialis[113]
Loratadine[124]	· Mortality – Pseudokirchneriella subcapitata[124], Brachionus calyciflorus[124], Thamnocephalus platyurus[124], Ceriodaphnia dubia[124]
Codeine[129]	· Biochemical alterations – Lemna minor[129] · Morphological changes – Lemna minor[129] · Physiological changes – Lemna minor[129]
Ephedrine[137]	· Mortality – Daphnia magna[137], P. subcapitata[137], T. thermophila[137] · Immobilization – Daphnia magna[137], P. subcapitata[137], T. thermophila[137]
Vitamin C[125]	· Biochemical alterations – Juvenile Rockfish[125] · Morphological changes – Juvenile Rockfish[125] · Bioaccumulation – Juvenile Rockfish[125]
17α-ethinylestradiol[22-68,70,97]	· Mortality – Dicentrarchus labraxc[23] Daphnia magna (2)[29,51], Artemia sp.[37], Mysidopsis juniae[37], Echinometra lucunter[37], Heterandria Formosa[39], Danio rerio (2)[26,35], Pimephales promelas[54], Clarias gariepinus[56], Gobiocypris rarus[62] · Immobilization - Chlorella vulgaris[68], Scenedesmus armatus[68] · Biochemical alterations – Mytilus galloprovincialis[24], Chlorella pyrenoidosa[25], Ruditapes philippinarum[27], Daphnia magna (2)[29,51], Dunaliella salina[43], Danio rerio liver cells[57], Gobiocypris rarus[62] · Behavioral changes - Dicentrarchus labrax[23], Gasterosteus aculeatus[58] · Morphological changes – Dicentrarchus labrax[23], Chlorella pyrenoidosa[25], Danio rerio (3)[26,28,35], Daphnia magna (2)[29,51], Oryzias latipes testis[31], Heterandria Formosa[39], Clarias gariepinus[56], Pimephales promelas[54], Gobiocypris rarus[62] · Immunological changes – Danio rerio larvae[26], Harbor seal lymphocytes[33] · Genotoxicity changes – Dicentrarchus labrax[23], Mytilus galloprovincialis[24], Chlorella pyrenoidosa[25], Danio rerio (4)[26,28,34,35], Daphnia magna[29,51], Oryzias latipes testis[31], Japanese medaka male larvae[38], Sardinops sagax[40], Scomber japonicus[40], Poecilia reticulata[42], Dunaliella salina[43], Gadus morhua liver[44], Oncorhynchus mykiss hepatocytes[49], Gasterosteus aculeatus testis[58], Clarias gariepinus[56], Potamopyrgus antipodarum[59], Pimephales promelas (2)[54,61] · Changes in population structure – Daphnia magna[29,51], Danio rerio (3)[26,34,35] · Physiological Changes - Mytilus galloprovincialis[24], Chlorella pyrenoidosa[25], Daphnia magna[29,51], Dunaliella salina[43], Clarias gariepinus[56], Pimephales promelas[54] · Reproductive behavior changes – Daphnia magna[29,51], Artemia sp.[37], Mysidopsis juniae[37], Echinometra lucunter[37], Heterandria formosa[39], Mytilus galloprovincialis[41], Paracentrotus lividus[41], Sparus aurata larvae[41], Danio rerio (3)[26,34,35], Daphnia magna (2)[29,51], Clarias gariepinus[56], Potamopyrgus antipodarum[59], Gobiocypris rarus[62] · Histopathological Changes – Clarias gariepinus[56], Gobiocypris rarus[62] · Bioaccumulation – Japanese flounder vitellogenin (Vtg)[32], Desmodesmus subspicatus[53]
Levonorgestrel[30,68-76]	· Mortality – Menidia beryllina[30], Pimephales promelas (2)[72,73], Gambusia holbrooki[76] · Biochemical alterations – Danio rerio hepatocytes[69], Pimephales promelas (2)[72,73], Cyprinus carpio[74] · Morphological changes – Menidia beryllina (2)[30,70], Pimephales promelas[73], Gambusia holbrooki[76] · Immunological changes – Menidia beryllina (2)[30,70] · Genotoxicity changes – Menidia beryllina (2)[30,70], Pimephales promelas (2)[72,73], Gambusia holbrooki[76] · Changes in population structure – Menidia beryllina[70] · Reproductive behaviour changes – Menidia beryllina (2)[30,70], Pimephales promelas (2)[72,73], Danio rerio[69]
17β-Estradiol[32,51,68,106]	· Mortality – Daphnia magna[51] · Biochemical alterations – Male Carassius auratus[106] · Genotoxicity changes – Male Carassius auratus[106] · Reproductive behaviour changes – Daphnia magna[51] · Immobilization - Chlorella vulgaris[68], Scenedesmus armatus[68] · Bioaccumulation – Japanese flounder vitellogenin (Vtg)[32]

Continued

Table 4. Continued

Drug	Outcome patterns
Norethindrone[74,77,78]	· Mortality – Pimephales promelas[78] · Biochemical alterations – Cyprinus carpio[74], Danio rerio[77] · Behavioral changes – Danio rerio[77] · Morphological changes – Pimephales promelas[78] · Genotoxicity changes – Danio rerio[77] · Reproductive behaviour changes – Danio rerio[77] · Histopathological changes – Danio rerio[77]
Drosperinone[46,72,74]	· Mortality – Daphnia magna[46] · Biochemical alterations – Daphnia magna[46], Pimephales promelas[72], Cyprinus carpio[74] · Genotoxicity changes – Danio rerio[46] · Morphological changes – Pimephales promelas[72] · Reproductive behaviour changes – Pimephales promelas[72]
Desogestrel[72]	· Biochemical alterations – Pimephales promelas[72] · Morphological changes – Pimephales promelas[72] · Reproductive behaviour changes – Pimephales promelas[72]
Gestodene[72]	· Biochemical alterations – Pimephales promelas[72] · Morphological changes – Pimephales promelas[72] · Reproductive behaviour changes – Pimephales promelas[72]
Cyproterone acetate[74]	· Biochemical alterations – Cyprinus carpio[74]
Triclosan[100,110,111,128]	· Mortality – Danio rerio[110] · Biochemical alterations – Danio rerio[110], Phytoplankton[111], periphyton[100] , Tetraselmis suecica[128] · Morphological changes – Danio rerio[110] · Physiological changes – Danio rerio[110] · Reproductive behavior changes – Danio rerio[110] · Growth inhibition – Tetraselmis suecica[128]
Povidone-iodine[126,127]	· Histopathological changes – Cyprinus carpio[126] · Histopathological changes – Carassius auratus[127]
Phenol[130]	· Biochemical alterations – Lemna paucicostata[130] · Morphological changes – Lemna paucicostata[130]
Chloroxylenol[131]	· Biochemical alterations – Cunninghamella elegans IM 1785/21GP[131], Trametes versicolor IM 373[131] · Genotoxicity changes – Cunninghamella elegans IM 1785/21GP[131], Trametes versicolor IM 373[131]
Chlorhexidine[112]	· Mortality –Vibrio fischeri[112], Pseudokirchneriella subcapitata[112], Daphnia magna[112], Danio rerio[112] · Biochemical alterations – Vibrio fischeri[112], Pseudokirchneriella subcapitata[112], Daphnia magna[112], Danio rerio[112]
Clotrimazole[96-104]	· Biochemical alterations – Xenopus tropicalis[97], Lemna minor[98], Lemna gibba[98], periphyton[100], Oncorhynchus mykiss[101], Clarias gariepinus[102], Daphnia Magna[96,103] · Morphological changes – Oncorhynchus mykiss[101], Clarias gariepinus[102] · Physiological changes – Oncorhynchus mykiss[101], Clarias gariepinus[102] · Genotoxicity changes – Cyprinus carpio[104] · Changes in population structure – Xenopus tropicalis[97] · Reproductive behavior changes – Xenopus tropicalis[97] · Histopathological changes – Xenopus tropicalis[97], Oncorhynchus mykiss[101] · Bioaccumulation - Hydropsyche sp.[99], Erpobdella octoculata[99], Oncorhynchus mykiss[101], Cyprinus carpio[104]
Ketoconazole[96,105-108]	· Biochemical alterations – Daphnia similis[105], Carassius auratus (2)[106,107] · Genotoxicity changes – Carassius auratus (2)[106,107] · Reproductive behavior changes – Daphnia similis[105] · Growth inhibition – Pseudokirchneriella subcapitata[108] · Bioaccumulation – Carassius auratus[106]

Continued

Table 4. Continued

Drug	Outcome patterns
Salicylic Acid[115-119,134-136]	· Biochemical alterations – Dunaliella salina[135], Gibbula umbilicalis[115], Lemna minor[116], Hediste diversicolor[118], Mytilus galloprovincialis (3)[117,119,134] · Immobilization - Pseudokirchneriella subcapitata[136] · Genotoxicity changes – Mytilus galloprovincialis (2)[117,134] · Physiological changes – Mytilus galloprovincialis (2)[119,134] · Histopathological Changes – Mytilus galloprovincialis[134] · Bioaccumulation – Mytilus galloprovincialis[134]
Zinc Sulphate[133]	· Genotoxicity changes – Danio rerio larva[133]

by *in vitro* (n=52)[25,32,33,35.37,38,40,41,43-45,49-53,55,57,59-62,64,65,68,73-75,78,96,98,100,103,105,108,110-112,115,116,118,121,128-136] and a few both *in vivo* and *in vitro* (n=5)[28,46,76,81,137]. One study was found to be observational[99].

Drugs studied

Most studies were conducted using 17α-ethinylestradiol as the test drug (n=43)[22-68,70,97]. Drugs studied under each OTC class are listed in Table 2.

Sample utilized

Most studies utilized artificially created aquatic test drug exposure to organisms (n=109)[1-21,23-50,53-95,97,98,100-128,130-136]. However, some studies used serial dilutions of samples taken from wastewater treatment plants (WWTP), i.e. wastewater effluent (n=4)[52,96,99,129], river water (n=2)[51,137], and groundwater (n=1)[22].

Organisms studied

Overall, a total of 147 organisms were studied in the 116 included studies. Of these, fish were used as the test organism most number of times (n=63)[23,26,28,30-32,34-36,38-42,44-50,54-58,61-67,69-79,85,86,90,94,96,109,101,102,104,106,107,110,120,125-127,132,133], followed by crustaceans (n=23)[29,37,51,60,80,84,89,93,95,96,103,105,109,122-124,132,137], algae (n=19)[25,43,52,53,68,96,100,108,111,112,124,128,135-137], molluscs (n=13)[24,27,41,59,79,87,91,113-115,117,119,134], aquatic plants (n=10)[79-83,98,109,116,129,130], aquatic insects (n=3)[83,99,120], fungi (n=1)[131], bacteria (n=4)[82,112,121,132], aquatic worms (n=4)[22,92,99,118], echinoderms (n=2)[37,41], and some other organisms like Tetrahymena, Hydra, leech, eel, frog, and harbor seal (n=8)[33,81,83,96,97,122,124,137].

Organisms frequently tested are mentioned below. Among fish, the commonly studied species included *Danio rerio*/ Zebrafish (n=19)[26,28,34,35,45-48,57,63-65,69,71,77,85,110,133], *Pimephales promelas*/ Fathead minnow (n=8)[54,61,67,72,73,75,78,109], *Cyprinus carpio* (n=5)[74,86,90,104,126], *Carrasius auratus* (n=4)[106,107,120,127], *Gasterosteus aculeatus* (n=2)[50,58], *Menidia beryllina* (n=3)[30,36,70], *Oncorhynchus mykiss* (n=3)[49,66,101], *Oryzias latipes* (n=2)[31,38], *Clarias gariepinus* (n=2)[56,102]. Among crustaceans, *Daphnia* species (*D. magna* and *D. similis*) were most frequently used (n=16)[29,51,60,80,84,89,93,95,96,103,105,109,112,131,132,137]. Algal models included *Pseudokirchneriella subcapitata* (n=5)[108,112,124,136,137] and *Dunaliella salina* (n=2)[43,135]. Molluscs comprised *Mytilus* species (*M. galloproviancialis* and *M. trossulus*; n=7)[24,41,91,113,117,119,134] and *Ruditapes philippinarum* (n=3)[27,87,114]. Aquatic plants studied were *Lemna* species (*L. minor, L. gibba* and *L. paucicostata*; n=5)[98,109,116,129,130]. Bacterial assays employed *Vibrio fischeri* (n=2)[112,132] and *Vibrio qinghaiensis* (n=1)[121], while aquatic worms included *Hediste diversicolor* (n=2)[92,118].

Zebrafish (*Danio rerio*) was the most frequently studied organism in *in vivo* studies (n=9)[26,34,48,63,69,71,77,85,133], *in vitro* studies (n=8)[35,43-45,57,64,65,110] and in studies following both *in vitro* and *in vivo* design (n=2)[28,46]. *Daphnia sp.* were next to zebrafish in being the most frequently studied organism in *in vivo* (n=7)[29,80,84,89,93,95,109] and *in vitro* (n=8)[51,60,96,103,105,112,131,132] studies and in studies following both *in vitro* and *in vivo* design (n=1)[137].

Drug concentration range

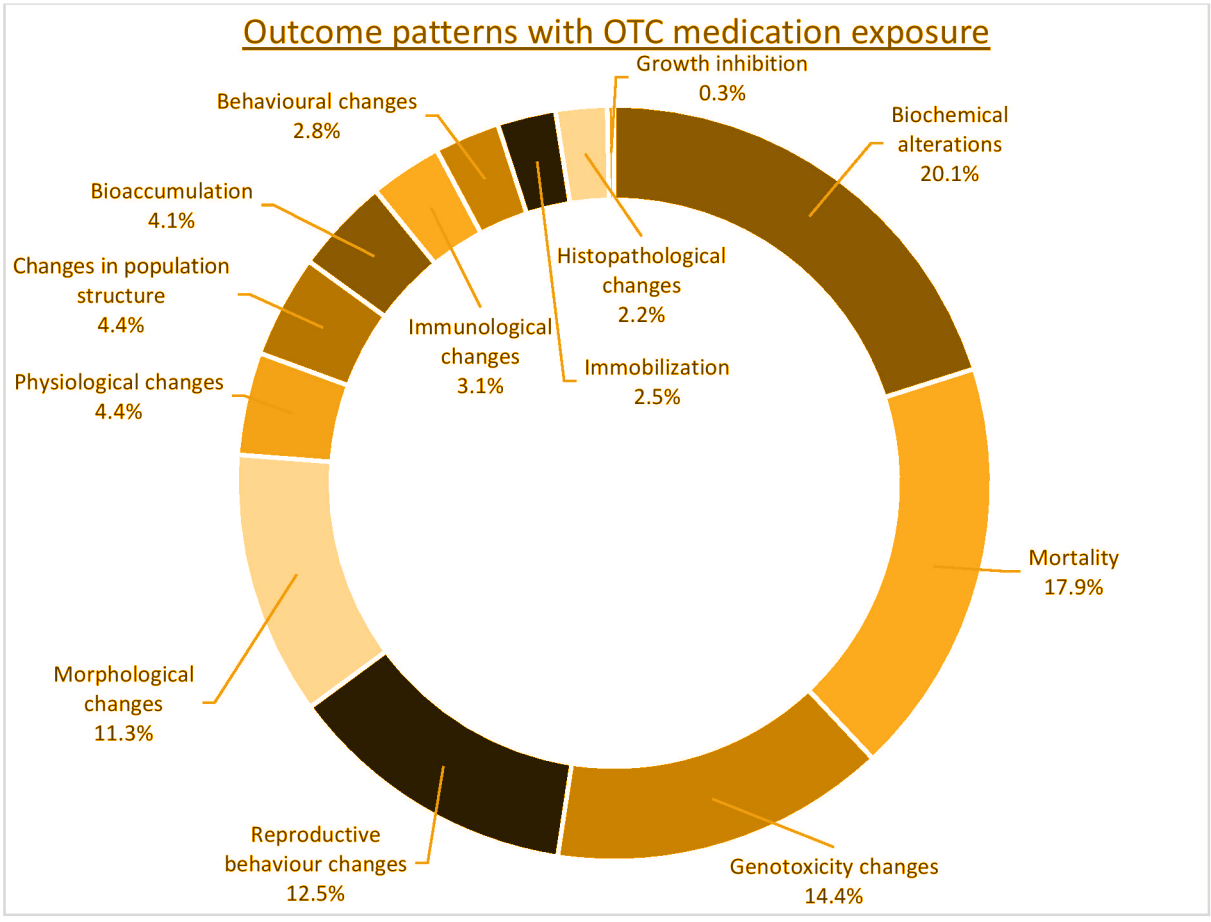
The concentration ranges of various drugs used for exposure to organisms have been listed in Table 3 after compiling the data used in the included studies.

It was also documented whether the effects of environmentally relevant concentrations, which are usually in the range of ng/L or µg/ L, were investigated in these studies. A paucity of studies investigating environmentally relevant dose effects was observed for naproxen, omeprazole, vitamin C, and chloroxylenol. In these drugs, higher concentrations in the range of mg/L were investigated (Table 3).

Outcome patterns

Analysis revealed a total of 319 outcome patterns. Of these, the most frequently observed outcome with OTC medication exposure was biochemical alteration (20.1% of all reported outcomes, n=64)[24,25,27,29,43,46,51,57,62,69,72-74,77,81-83,86-92,94-98,100-103,105-107,110-114-120,125,128-131,134,135]. Mortality (17.9%; n=41)[23,26,29,30,35,37,39,46,51,54,56,62,72,73,76,78-82,84-86,88-91,94,96,109,110,112,114,122-124,128,137], genotoxicity changes (14.4%; n=37)[23-26,28-31,34,35,42-44,46,49,51,54,56,58,59,61,70,72,73,76,77,79,81,86,88,89,104,106,107,117,122,131,133,134], morphological changes (13.2%; n=33)[23,25,26,28-31,35,39,51,54,56,60,62,70,72,73,76,78,80,81,85,89,91,93,101,102,110,125,128-130], reproductive behavior changes (11.3%; n=27)[26,29,30,34,35,

Figure 2. Distribution of included experimental studies (n = 116) by study design assessing the toxicity of over-the-counter (OTC) drugs in aquatic organisms



[37,39,41,51,56,59,60,62,69,70,72,73,77,80,85,89,91,93,97,105,109,110], physiological changes (10.1%; n=18)[24,25,29,43,51,54,56,84,85,101,102,110,113,114,119,128,129,134], bioaccumulation (n=9)[32,53,99,101,104,106,120,125,134], changes in population structure (n=9)[26,29,34,35,51,70,89,93,97], histopathological changes (n=8)[56,62,77,97,101,126,127,134], immunological changes (n=6)[26,30,33,70,79,88] , behavioral changes (n=6)[23,58,77,84,109,120], immobilization (n=3)[68,136,137], and growth inhibition (n=2)[108,128] were other notable outcomes. Outcomes observed have been depicted in Figure 2.

Highest number of outcome patterns were reported with 17α-ethinylestradiol (28.2% of all reported outcomes, n=90)[22-68,70,97]. Details of drug-wise effects observed are presented in Table 4.

DISCUSSION

This systematic review highlights the current landscape of environmental toxicity research concerning OTC medications, emphasizing the growing global attention toward their ecological impact, particularly over the last two decades. This is in keeping with the rise in the use of medications by the general population however, without an association to overall better health of the community. This increased demand corroborates with the surge in global sales of OTC pharmaceuticals in recent times of COVID and post COVID era[16]. With 116 studies included, our review demonstrates an increasing body of literature focusing on hormonal contraceptives, analgesics, and topical antifungals, while exposing a significant paucity of studies in other common OTC drug classes such as antidiarrheals, laxatives, topical steroids, and skincare and ophthalmic products.

The reported global statistics of OTC market at an estimate of US$ 157 billion in 2021, which is expected to increase at a 5.8% compound annual growth rate (CAGR) to reach US$ 233 billion by 2028 supports the growing usage[138]. In past sales reports have suggested that countries like the United States, Japan, Germany, and the United Kingdom followed by Asian countries, Middle East and Africa contribute maximally to the worldwide OTC sales[139].

Overall, the USA had the greatest number of included studies, followed by Portugal and China. This is probably

because despite the global coverage, pronounced regional patterns in the intensity of environmental monitoring efforts prevail. According to a previous study, roughly 3 out of 4 database entries originate from western Europe[140].

We noticed an imbalance in the types of OTC medications being studied. Classes such as antidiarrheals, laxatives, antacids, and antihistamines remain significantly underexplored despite their widespread use and excretion into wastewater systems. These classes yielded a low search rate in our review. This is despite the fact that the cough and cold remedies segment lead the sales, followed by analgesics, and vitamins and minerals segment. The digestive and intestinal remedies, skin treatments and other segments are expected to pick up the pace[141]. Moreover, there is an unmet need of good quality ecotoxicity studies with respect to topical steroids, skin care products, ophthalmic medications, cough and cold remedies and vitamins and minerals even as they hold a significant chunk of market share.

Previously, a few narrative and systematic reviews have focused on a single class of drugs affecting the environment[13,14]. The present study could be considered as one of the first attempts to systematically review the impact of several classes of common over-the-counter drugs on aquatic organisms. The highest number of studies in the present review were available for hormonal contraceptives, followed by analgesics and topical antifungals. The analgesics segment, as we are aware, is among the classes of OTC drugs that have been researched the most in relation to environmental pollution and this may also be related to its significant global market share [12,141].

We found that there has been a sharp increase in studies based on environmental pollution by pharmaceuticals, including OTC drugs, since 2011, suggesting rising environmental and scientific concern around the ecological footprint of pharmaceutical residues, especially those found in wastewater effluents. The predominance of studies from the USA, Portugal, and China, all with a focus on hormonal contraceptives, may reflect both the research infrastructure in these countries and the global prioritization of endocrine-disrupting compounds like 17α-ethinylestradiol, which was the most commonly studied drug. However, there is an evident underrepresentation of other hormonal agents like levonorgestrel, norethindrone, and cyproterone acetate, which also demonstrated presence in environmental matrices. This suggests a potential research bias and highlights the need for broader exploration across a range of hormonal compounds. Few reports have also suggested that a mixture of drugs, including hormonal compounds, poses a greater threat to the aquatic environment via drug synergism[142]. Likewise, while antiseptics like triclosan have received substantial attention, other compounds, such as chloroxylenol, have not been studied at environmentally relevant concentrations, raising concerns about knowledge gaps in evaluating their true ecological risk.

Most included studies utilized experimental designs, primarily *in vivo*, with a wide array of aquatic organisms serving as bioindicators. Zebrafish (*Danio rerio*) and *Daphnia spp*. were the most frequently used organisms, underscoring their established utility in ecotoxicological assessments due to their sensitivity, ease of use, and relevance to aquatic ecosystems. However, the ecological representation could be broadened with further inclusion of microbial and plant species, which were comparatively underrepresented.

Importantly, although many studies assessed drug exposures at environmentally relevant concentrations (ng/L or µg/L), some drugs such as naproxen, omeprazole, vitamin C, and chloroxylenol were often tested only at mg/L levels, which may not reflect realistic environmental exposure scenarios. This gap underscores the need for future studies to include dose ranges that more accurately simulate actual aquatic contamination levels to assess chronic low-dose effects, especially considering the bioaccumulation and mixture toxicity potential of these compounds.

Strengths and limitations

While our review has several strengths, such as following a rigorous systematic approach to extract and analyze data across several classes of drugs for the first time, there are also a few limitations we identify with this study. As for a systematic review, data for only published studies could be taken, negative or neutral; the likely unpublished studies could not be taken into account, resulting in a publication bias. Owing to the heterogeneity of aquatic species taken in this study, we did not include the extraction of data pertaining to test design, test substance, and statistical design of individual studies in our methodology protocol. Hence, we refrain from reporting on the quality assessment of the studies included in our review. This review did not search for articles in languages other than English, and this may have resulted in a language bias. Conference abstracts were excluded due to insufficient extractable data. Additionally, information on the characteristics we were abstracting about drug abandonment and repurposing may not have been published in the medical or pharmaceutical peer-review literature and may have been missed.

CONCLUSIONS

Overall, the findings of this systematic review point toward the necessity of expanding the scope of ecotoxicological assessments for OTC drugs, both in terms of drug classes and environmental realism. This review shows that aquatic life is surely at risk for exposure to pharmaceuticals as they come directly in contact with waste water effluents for prolonged periods and we cannot ignore the entry of such chemicals into the food chain. Most commonly studied OTC pharmaceuticals, like hormonal and analgesic compounds, exhibit measurable toxic effects on aquatic organisms even at trace levels. Biochemical alterations (20.1%), mortality (17.9%), genotoxicity (14.4%), reproductive behavior changes (12.5%), morphological and immunological

variations have been noted with a variety of pharmaceuticals. There is a need of greater focus on inclusion of mixture toxicity studies to evaluate synergistic or antagonistic effects of multiple drugs concurrently present in aquatic environments. Only a handful of studies actually sampled wastewater and river water samples. Future research should also consider regional variations in drug usage, wastewater treatment infrastructure, and ecological vulnerability to develop more locally relevant environmental risk assessments. ultimately informing regulatory frameworks and wastewater management practices.

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CONFLICTS OF INTEREST
The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY
The data supporting this research are available from the authors on reasonable request.

AUTHORS' CONTRIBUTIONS
SK: conceptualization, writing of the original draft, formal analysis. VS: data curation, project administration. NM: formal analysis. AN: data curation. All authors: reviewing and editing of the manuscript. All authors read and approved the final version of the manuscript.

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