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First evidence of metformin detected in Jakarta waters

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Abstract
Pharmaceutically active compounds have been considered contaminants of emerging concern, in response to evidence that these substances may adversely affect non-target organisms. The pharmaceutical metformin is the most commonly prescribed anti-diabetes medicine throughout the world. Metformin has been detected in numerous freshwater systems as well as in seawater at a number of sites around the world over the last few years, but has never been reported in the Indonesian capital city Jakarta. Several recent studies have highlighted various ecotoxicological effects of this medicine on aquatic organisms. Here we report the first evidence of metformin's presence in Jakarta waters. Samples from the Angke river, one of the main rivers in Jakarta, were collected from six sites. Metformin was detected at three sites in concentrations ranging from 27 ng/L to 414 ng/L. Metformin is one of the most detected APIs (active pharmaceutical ingredients) in aquatic environments worldwide, and there is increasing concern regarding its impact on the health of wildlife and humans. However, this is the first report of metformin contamination in Jakarta waters, adding to the evidence of potentially increased pollution with pharmaceuticals, as noted in our previous studies. With no natural degradation processes, these chemical compounds can be easily reintroduced to the food chain and impact human health.

Keywords Emerging contaminants · Metformin · Pharmaceuticals · Jakarta · Water pollution

1 Introduction

Water pollution caused by emerging contaminants such as pharmaceuticals is of growing concern worldwide [1]. The presence of these contaminants in water sources has been shown to have adverse effects on aquatic life and human health [2]. Indonesia, the world's fourth most populous country, has faced its share of significant environmental challenges, including water pollution [3]. Indeed, recent studies have shown the presence of pharmaceuticals in surface waters in Indonesia, including rivers and lakes [4–6].

Jakarta, the capital city of Indonesia, is one of the most populated cities in the world, with a population of over 10 million people [7]. Like many other cities in developing countries, Jakarta is facing a number of environmental challenges, with water contamination among the most pressing. The Angke River is one of Jakarta's major water courses,

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and receives numerous sources of pollution, including untreated domestic sewage, industrial wastewater, and solid waste [8], all of which may contain a variety of pharmaceuticals and their active metabolites.

Metformin is an antidiabetic drug that has been widely prescribed for the treatment of type 2 diabetes, with its use increasing rapidly worldwide [9]. In 2030, the World Health Organization estimates that almost 400 million people will be diagnosed with diabetes, and that consequently metformin will see a spike in production. Unlike many pharmaceutical drugs, metformin is not metabolized by humans but passes through the body unchanged. Entering aquatic compartments, it can be bacterially transformed into its metabolite, guanylurea [10]. As a result of its widespread use, metformin has been detected in various environmental matrices in recent years [11], including surface waters [12], sediments [13], and soils [14], raising concerns about its potential environmental impact.

In Europe, metformin has been recorded at concentrations as high as 325 ug/L—the level detected in wastewater influent in Portugal [15]. In Asia, the highest recorded concentration is 53.6 ug/L, detected by Yan et al. [16] in wastewater treatment plant influent in China. In North America, a concentration of 107 ug/L was recorded in Mexican groundwater by Lesser et al. [17]. Meanwhile, Archer et al. [18] recorded the highest level of metformin detected so far in Africa, with a concentration of 9.3 ug/L in South African wastewater influent. Despite this growing global body of evidence for its occurrence, metformin has never been reported in the environment in Jakarta, Indonesia.

In aquatic animals, several significant negative impacts of metformin exposure have been reported, such as severe gonadal tissue pathologies, destabilization of lysosomal membranes in hemocytes, and altered mRNA expression in the mussel *Mytilus edulis* after short exposure [19, 20]. Ussery et al. [21] showed that exposure of medaka fish *Oryzias latipes* to metformin at early stages of development led to negative effects on growth metrics, metabolomes, and transcriptomes, including an increased production of some steroid hormones in adult female medaka. Interestingly, a recent study by Nielsen et al. [22] suggested that wild embryos of fathead minnow (*Pimephales* sp.) are more sensitive to environmentally relevant concentrations of metformin, than their lab spawned counterparts.

This study reports for the first time the presence of metformin in Angke River in Jakarta, providing the first evidence of the occurrence of this pharmaceutical in Jakarta waters. The findings of this study will contribute to a better understanding of the extent of pharmaceutical contamination of Jakarta's rivers, and their bioavailability for the aquatic biota, therefore supporting the development of new strategies to tackle water pollution.

2 Materials and methods

2.1 Water sample collection

Surface water samples were collected in June 2022 from six different sites along the Angke River in Jakarta, Indonesia, as depicted in Fig. 1. The comprehensive descriptions of these sampling sites, including the location names, coordinates, and environmental conditions at the time of sample collection, are provided in Table 1. Prior to the sampling process, all containers and equipment were cleaned and treated with methanol to ensure sterility and prevent contamination. Aluminum foil and other consumables were discarded immediately after use, and each container was used for one sample only.

During the sampling process, a 2 L bucket was used to collect the water, which was then transferred into 25 ml sample bottles and 2 L water containers. To maintain consistency and accuracy in the results obtained, duplicate samples were collected from each site using grab sampling techniques as recommended by Wang et al. [23]. The plastic bucket was thoroughly cleaned before and after each use. To preserve the integrity of the samples, they were placed in pre-cooled cool boxes with ice, minimizing any potential biological or chemical alterations that could occur during transportation.

The samples were promptly transported to the laboratory for comprehensive analysis. The collection, storage, and preparation of samples were conducted in accordance with good laboratory practice standards, following guidelines provided by the United States Environmental Protection Agency (US-EPA) [24] and the American Public Health Association (APHA) [25]. Adhering to these guidelines ensured that the data gathered would provide valuable insights into the water quality of the Angke River and identify any potential environmental issues that may need to be addressed.

Fig. 1 Map of sampling sites along the Angke River, Jakarta. Inset map shows the location of Jakarta within Indonesia

2.2 Sample processing and preparation

Upon arrival at the laboratory, the surface water samples were processed immediately to ensure the integrity of the analytes. The analyses of the physicochemical parameters were conducted following the procedures referenced in Supplementary Table S1, which includes Standard Methods for Examination of Water and Wastewater published by the American Public Health Association [25], Indonesian National Standards (SNI) [26], and the standardized protocols from the Jakarta Regional Health Laboratory. All analyses were conducted at the Jakarta Regional Health Laboratory, a testing laboratory accredited by ISO/IEC 17025:2017, ISO 45001:2018, and ISO 15189:2012, indicating its compliance with recognized international standards.

For the metformin analysis, the sample preparation process started with the filtration of a 15 mL aliquot using a filter disc (Sartorius, Grade: 390, diameter 125 mm) and silanized glassware, eliminating potential interferences due to particulate matter. From the filtered sample, a 3 mL volume was taken and supplemented with 10 µL of a 10 ppm internal standard (ISTD) mefruside for quantitation purposes. This sample was subsequently loaded onto a Sep-Pak C18 solid-phase extraction (SPE) cartridge (Nexus, 200 mg, 6 mL), which had been preconditioned with 3 mL of methanol and 3 mL of water to ensure proper retention of the analytes. Samples were loaded at a flow rate of 3 mL min−1, followed by a washing step with two sequential 1 mL aliquots of water to remove any matrix interferences. The SPE sorbent was dried under vacuum at room temperature, and the analytes were subsequently eluted from the column using 3 × 1 mL aliquots of methanol at a flow rate of 1 mL min−1, ensuring optimal recovery of the compounds of interest. The methanol eluate was evaporated to dryness at 40 °C using a Turbovap under a gentle stream of nitrogen. The dried residue was then reconstituted in 150 µL of a methanol:water (1:1) solution and subsequently injected into the LC-MS/MS system for analysis.

Table 1 Description of sampling sites along Angke River, Jakarta, Indonesia

ID	Location name	Coordinates	Distance from preceding location	Description
1	Duri Kosambi, West Jakarta	– 6.187045, 106.720453	NA	Near Kembangan power plant; characterized by swift, turbid brown water; accessed through an area with tall grass and numerous large trees; rapid flow conditions and potential influence from the power plant
2	Rawa Buaya, West Jakarta	– 6.165606, 106.748331	3.89 km	Located beside Kembangan Baru road; presence of a fish feed vendor; calm, light brown water with significant amounts of trash visible; likely impacted by nearby human activity and waste disposal
3	Kedaung Kali Angke, West Jakarta	– 6.158201, 106.7599355	1.52 km	Situated beside Daan Mogot road; active bridge construction site; calm, shallow water conditions; possible construction-related impacts on water quality
4	Wijaya Kusuma, West Jakarta	– 6.145298, 106.775080	2.20 km	Densely populated area; calm water conditions; the river splits into two channels here, potentially affecting water flow and dispersion of pollutants
5	Kapuk Muara, Penjaringan, North Jakarta	– 6.123370, 106.774228	2.43 km	Located beside a highway bridge; moderately swift water flow with substantial amounts of trash; presence of people and goods ferries, possibly influencing water quality due to increased human activity and resuspension of sediments
6	Pluit, Penjaringan, North Jakarta	– 6.110076, 106.774421	1.47 km	Positioned at the Angke dock under a bridge; calm, turbid water conditions; significant amounts of trash and a line of moored boats; potential impacts from boat-related activities and waste disposal

2.3 Metformin quantification and quality control

We quantified metformin using the method described by Afonso-Olivares et al. [27] in their study on pharmaceutical compounds, ensuring accurate and validated results. Chromatographic analysis was performed on an Agilent 6470 series Triple Quad LC-MS/MS system coupled with a 1260 Infinity II HPLC (Agilent Technologies, USA) using positive electrospray ionization. Analytes were separated using an Infinity C18 column (150 × 2.1 mm; 2.7 µm particle size) with a 0.2 µm pre-filter. The mobile phase consisted of 20% acetonitrile (solvent A) and 80% of 0.1% formic acid in water (solvent B). A flow rate of 0.2 mL/min was applied, and the column temperature was maintained at 40 °C. The injection volume was 10 µL, with a stop time of 18 min and a post-time of 2 min. The gradient used in this procedure, consisting of six steps with varying proportions of solvents A and B, ensures optimal separation and peak resolution of the target analytes, as presented in Table 2.

The system was set up with specific source and ionization parameters to ensure optimal sensitivity, selectivity, and accurate quantification. The source parameters included a capillary voltage of 3500 V, desolvation temperature of 350 °C, gas temperature of 300 °C, nitrogen gas flow rate of 11 L/min, nebulizing pressure of 45 psi, sheath gas temperature of 350 °C, and sheath gas flow of 11 L/min. Nitrogen gas was employed as the nebulizing, desolvation, and collision gas. Two multiple reaction monitoring (MRM) transitions were monitored for each analyte, allowing for efficient ionization of the analytes and maximizing signal intensity. Additional quality criteria, such as pre-determined ion ratio and retention time tolerances, were employed to ensure the reliability of the data. Supplementary Table S2 provides more details on the instrumental parameters employed in the ESI-MS analysis, and the analytical parameters for each analyte.

To ensure the accuracy and reliability of the analysis, analytical reference standards of metformin (99.60% purity, MT20231219, Pharma Metric Labs) and mefruside (CAS No. 7195-27-9, TRC-M205150-50MG, LGC Standards) as an internal standard were employed. The standards were prepared at concentrations of 0.1 and 1.0 mg/mL in methanol and stored at − 20 °C in darkness. HPLC grade methanol and acetonitrile were obtained from Merck, while ultrapure water with a quality of 18.2 MΩ cm−1 was used.

To maintain the reliability of the metformin analysis, quality controls were integrated within the method development and during the analysis of river water samples. This included the calibration linearity range for each compound, method detection limits, and analysis of reagent blanks. Reproducibility was verified by processing duplicates of each sample, and the method accuracy was validated through spike recoveries in reagent water and river water samples, aiming for a standard recovery rate of 90–110%. Moreover, at least one method blank (ultrapure water), one duplicate, and one spiked sample were processed with each batch of river water samples analyzed, ensuring the precision and accuracy of the LC-MS/MS detection process. A 10 L river water sample was employed for the development and validation of the analytical method within the sample matrix. Table 3 provides essential information on the validation parameters and ensures that the method used is reliable and reproducible.

3 Results

3.1 The physicochemical properties of the water samples

Table 4 presents water quality data from all sampling sites along the Angke river, with measurements for parameters in Attachment 1 Chapter II Point A of the Regulation of the Minister of Health of the Republic of Indonesia No. 32 of 2017

Table 2 Gradient mobile phase program

Step	Time	Solvent A (acetonitrile) %	Solvent B (0.1% formic acid in water) %	Flow rate
1	1 min	40	60	0.2 mL/min
2	4 min	90	10	0.2 mL/min
3	5 min	40	60	0.2 mL/min
4	7 min	50	50	0.2 mL/min
5	9 min	20	80	0.2 mL/min
6	13 min	20	80	0.2 mL/min

Table 3 Quality control of metformin validation using LC-MS/MS method

Parameter	Result	Acceptance criteria
Repeatability	0.4 ng/L = 2.71%	< 2/3 CV Horwitz < 12.24%
	0.8 ng/L = 1.85%	< 2/3 CV Horwitz < 11.03%
	0.2 ng/L = 2.59%	< 2/3 CV Horwitz < 9.61%
Recovery/trueness	96.66%–116.81%	80–120%
MDL (method detection limit)	0.10 ng/mL SD = 18.15%	SD < 20%
MQL (method quantitation limit)	0.23 ng/mL	–
Measurement range	0; 0.2; 0.4; 0.6; 0.8; 1.0; 2.0; 5.0 ng/mL	–
Linearity	$R^2 = 0.9985$	Df–2 (confidence 95%) = 0.811
Specificity/selectivity	Specific measurement of metformin based on retention time in blank standard, negative sample, and spiked sample	Specific measurement based on the absence of peaks and ion m/z with the same RT in negative and spiked samples

Table 4 The water quality parameters in selected sampling sites, compared with the Indonesian government regulation limits^{+++}

No	Parameter	Unit	Site						Maximum allowable concentration^{+++}	Method reference
			1	2	3	4	5	6		
1	Turbidity	NTU scale	41.15	31.7	26.8	16.4	126.5	7.245	25	IK02/PP16.5-Air-17025/Labkesda
2	Color	TCU scale	412.5	325.5	272.5	275	439	473.5	50	SNI 6989.80:2011
3	Dissolved solids	mg/L	123	164	202	167	99.5	2602	1000	IK.01/PP16.5-Air-17025/Labkesda
4	Temperature (Ex situ)$^{++}$	°C	26.85	26.95	26.7	26.45	26.6	26.45	–	IK.03/PP16.5-Air-17025/Labkesda
6	Odor	–	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless	SNI 3554:2015
7	pH (Ex situ)$^{++}$	–	6.965	7.055	7.045	6.99	6.86	7.195	–	SNI 6989.11:2019
8	Iron	mg/L	0.02905	0.0145	0.04875	0.01655	0.0234	0.0021	1	Std Met. APHA 3120B/23/2017;3030B/23/2017
9	Fluoride	mg/L	0.075	0.2	0.165	0.24	0.075	1.6	1.5	SNI 06–6989.29–2005
10	Hardness (as $CaCO_3$)	mg/L	68.135	108.935	95.055	82.02	61.83	5320.5	500	SNI 06–6989.12–2004
11	Manganese	mg/L	0.0567	0.0027	0.2514	0.08245	0.0077	0.0027	0.5	Std Met. APHA 3120B/23/2017;3030B/23/2017
12	Nitrate as N	mg/L	1.03	0.905	0.016	0.45	1.36	0.016	10	Std Met. APHA 4110C/23/2017
13	Nitrite as N	mg/L	0.478	4.075	0.016	0.145	0.075	0.016	1	Std Met. APHA 4110C/23/2017
14	Cyanide^{+}	mg/L	0.0015	0.0015	0.0015	0.0015	0.0015	0.0015	0.1	IK.15/PP16.5-Air-17025/Labkesda
17	Mercury^{+}	mg/L	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.001	IK.21/PP16.5-Air-17025/Labkesda
18	Arsenic	mg/L	0.0085	0.0085	0.0085	0.0085	0.0085	0.0085	0.05	Std Met. APHA 3120B/23/2017;3030B/23/2017
19	Cadmium	mg/L	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.005	Std Met. APHA 3120B/23/2017;3030B/23/2017
20	Chromium Hexavalent^{+}	mg/L	0.005	0.005	0.005	0.005	0.005	0.005	0.05	Std Met. APHA 3500-Cr.B/23/2017
21	Selenium	mg/L	0.002	0.002	0.002	0.002	0.002	0.002	0.01	Std Met. APHA 3120B/23/2017;3030B/23/2017
22	Zinc	mg/L	0.0099	0.0099	0.0099	0.0099	0.0099	0.0099	15	Std Met. APHA 3120B/23/2017;3030B/23/2017
23	Sulfate	mg/L	14.47	26.58	21.71	15.14	12.94	2226.57	400	Std Met. APHA 4110C/23/2017
24	Lead	mg/L	0.0017	0.0017	0.0017	0.0017	0.0017	0.0017	0.05	Std Met. APHA 3120B/23/2017;3030B/23/2017
26	Organic Matter ($KMnO_4$)	mg/L	7.225	12.22	11.405	10.365	15.265	39.39	10	SNI 06–6989.22–2004

$^{+}$Parameter is not yet accredited

$^{++}$The examination of Ex Situ temperature and pH cannot be compared to the Maximum Quality Standard

$^{+++}$In accordance with Attachment 1 Chapter II Point A of the Regulation of the Minister of Health of the Republic of Indonesia No. 32 of 2017 regarding Standard Quality of Environmental Health and Health Requirements for Hygiene, Sanitation, Swimming Pools, Per Aqua Solutions, and Public Baths[28] regarding Standard Quality of Environmental Health and Health Requirements for Hygiene, Sanitation, Swimming Pools, Per Aqua Solutions, and Public Baths [28]. Water samples were analyzed using various methods and standard references as shown in Table 4. In general, the water samples demonstrated varying degrees of compliance with maximum allowable concentrations.

Site 6 shows particularly concerning results, with several parameters exceeding their respective maximum allowable concentrations. Dissolved solids (2602 mg/L), hardness (as $CaCO_3$, 5320.5 mg/L), fluoride (1.6 mg/L), and sulfate (2226.57 mg/L) levels all surpass the limits. Additionally, the organic matter ($KMnO_4$) levels at this site (39.39 mg/L) are significantly higher than the maximum allowable concentration (10 mg/L). Turbidity at Site 5 also exceeds the limit, with a measured value of 126.5 NTU. The remaining sites display parameter levels mostly within acceptable ranges, with some sites showing elevated nitrite as N (Site 2), manganese (Site 3), and organic matter ($KMnO_4$) levels (Sites 2, 3, 4, and 5). The water samples were generally odorless, tasteless, and within acceptable temperature ranges.

3.2 The concentration of metformin in the water samples

The results show that metformin was present at 3 sites, with concentrations ranging from 27 to 414 ng/L (Fig. 2). To the best of our knowledge, this is the first time metformin has been detected in Jakarta waters. The concentration of metformin at site 3 is considerably higher than at site 2. The range of values between replicates is larger for site 3 than for site 2, suggesting greater variability in the metformin concentration at site 3.

Figure 3 shows the metformin levels detected in this study, relative to other reported concentrations from around the world. Our lowest concentration detected at Site 2 (27 ng/L) falls within the 5th percentile. This indicates that the metformin concentration at Site 2 is relatively low compared to the global range of metformin concentrations in surface water. The highest concentration in this study (414 ng/L) falls within the 40th percentile. This indicates that the metformin concentration at Site 3 is higher than 40% of the global range of metformin concentrations in surface water but still lower than the remaining 60%. More detail on the concentration ranges detected in these studies can be found in Supplementary Table S3.

4 Discussion

4.1 The comparative analysis of metformin concentrations in Indonesia's Angke river with global data

Our study reports data on the presence of metformin, a common antidiabetic drug, in the Angke River, a significant waterway in Jakarta, Indonesia. We detected metformin concentrations ranging from 27 ng/L to 414 ng/L.

These findings, while considered relatively moderate in a global context, represent an important step in understanding pharmaceutical pollution in Indonesia's aquatic environments. Our highest recorded concentration of 414 ng/L is comparable to ranges observed in German surface waters, which vary between 35 ng/L and 643 ng/L [10]. Turkey recorded lower metformin concentrations in surface water, ranging from 0.14 ng/L to 14.1 ng/L [29]. In contrast, Canada reported significantly higher concentrations, with a range of 145 ng/L to 10,100 ng/L [30].

Other countries with notable metformin concentrations in surface water include Vietnam [31] with a range of 10 ng/L to 8247 ng/L, Saudi Arabia [32] with a concentration of 4801 ng/L in the Red Sea, and South Africa [18] with a range of 65 ng/L to 316 ng/L.

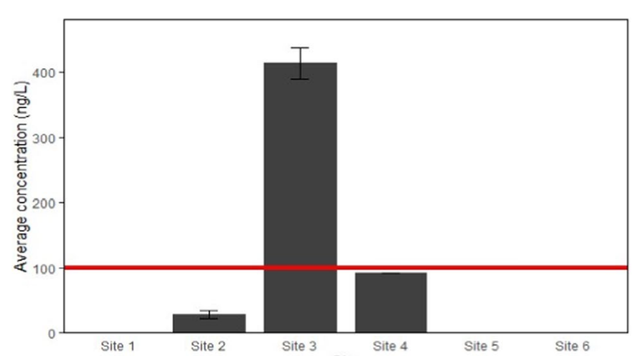

Fig. 2 Mean metformin concentrations detected in Angke river. Error bars depict maximum and minimum values (two samples were collected per site). The red line is the limit of detection (LOD) at 100 ng/L

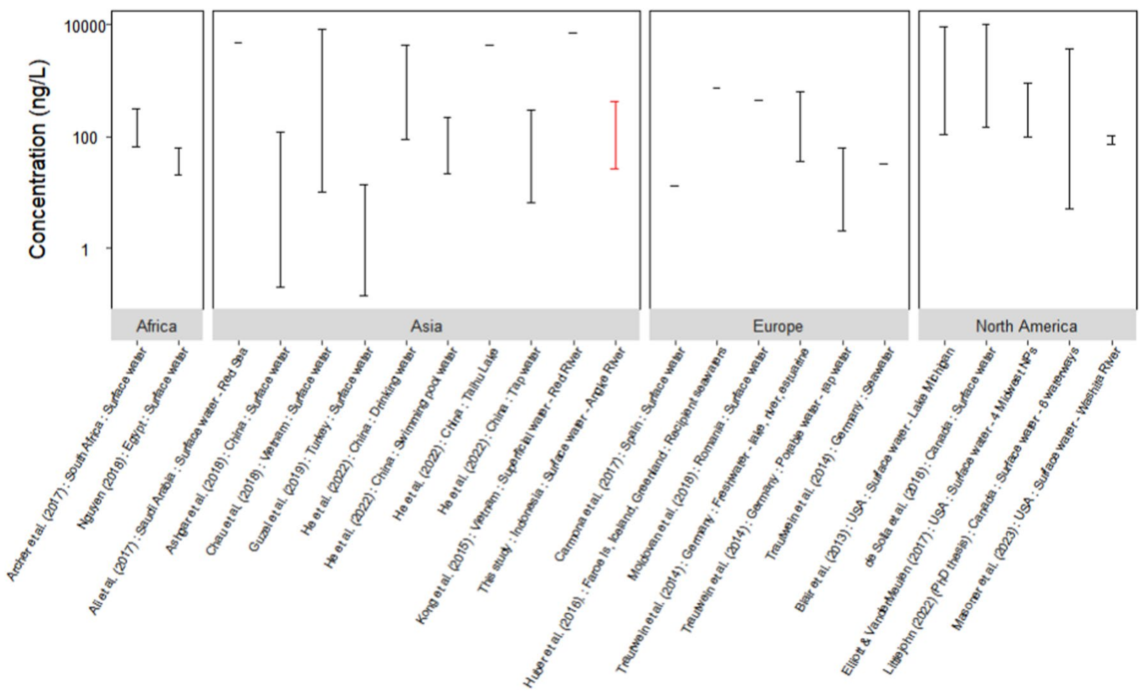

Fig. 3 The concentrations of metformin reported in surface waters around the world. Bars depict the range of concentrations detected in each study. Studies that only provided a single concentration value are represented by a horizontal line. The red bar shows the data from this study

The prevalence of diabetes in Indonesia's adult population stands at 6.2%, a figure significantly lower than the global average of 9.3% as recorded in the International Diabetes Federation (IDF) Atlas [33]. This may partially account for the relatively reduced traces of metformin observed in our study. However, current global trends suggest an accelerating adoption of metformin due to its proven efficacy, advantageous safety profile, and economic affordability as supported by Ahmad et al. [34]. Given these contributing factors and the projected escalation in diabetes prevalence in Indonesia—the adult diabetic population is anticipated to rise from 10.7 million in 2019 to an estimated 16.6 million by 2045 [33]—it is reasonable to predict a subsequent surge in metformin levels within the country's aquatic environments in the forthcoming years.

The Angke River, already facing significant pollution from sources such as domestic sewage discharge and industrial effluents, could be increasingly impacted by this trend. While the precise contribution of these sources to metformin levels is unclear in the absence of direct data, the combined influence of industrial and domestic waste is likely substantial.

Our work underscores the necessity for more comprehensive research on the occurrence and impacts of pharmaceuticals in Indonesian water bodies. As metformin use is likely to rise rapidly, proactive measures to minimize pharmaceutical pollution are essential. Comprehensive understanding requires consideration of factors such as evolving drug prescription practices, changing population health trends, waste management systems, and specific environmental conditions. Future studies should focus on the potential impacts on aquatic ecosystems and public health, with the goal of informing pollution management strategies and contributing to the global understanding of pharmaceutical pollution.

4.2 Associations between physicochemical parameters and metformin concentrations in the Angke river, Jakarta: a comparative analysis of polluted sites

Based on the water quality parameters presented in Table 4, we can analyze the potential links and connections between the physicochemical properties and the metformin concentrations detected at the various sampling sites. The presence of metformin in the Angke River, particularly at Sites 2, 3, and 4, raises questions about the potential factors influencing its concentrations in the water. A comprehensive analysis of the physicochemical parameters of the water quality needs to be taken into consideration when discussing the transport and behavior of metformin in the river. In this context, it is essential to consider the local context, land use, and nearby pollution sources when interpreting these findings.

Turbidity, color, and organic matter content appear to be the most likely parameters related to metformin concentrations in the Angke River. High turbidity levels at Site 2 (31.7 NTU) and Site 3 (26.8 NTU), both exceeding the maximum allowable concentration (25 NTU), indicate the presence of suspended particles, which can contribute to the adsorption and transport of metformin in the water [35]. Additionally, high color values at all three sites (Site 2: 325.5 TCU, Site 3: 272.5 TCU, Site 4: 275 TCU) suggest an elevated organic matter content or the presence of other pollutants, which could affect metformin concentrations. Boyd [35] elucidates that water turbidity, color, and organic matter significantly affect the transport, adsorption, and degradation of pharmaceuticals in water, with turbidity enhancing surface area for sorption and sedimentation, color impacting solubility and photodegradation, and organic matter competing for sorption sites or aiding in biodegradation. Additionally, the organic matter, which can be derived from both natural and anthropogenic sources, plays a critical role in determining water's biological, chemical, and physical properties such as oxygen demand, pH, and conductivity.

The manganese concentration at Site 3 was observed to be significantly high at 0.2514 mg/L, notably surpassing the values recorded at Site 2 (0.0027 mg/L) and Site 4 (0.08245 mg/L). Intriguingly, this pattern mirrors the distribution of metformin levels across these sites. Elevated manganese concentrations may serve as a potential marker for pollution, often resulting from processes such as erosion of geological substrates, discharge of industrial waste, or leaching from landfills [36]. These findings suggest the possible presence of industrial waste and/or landfill leaching activities in the vicinity of Site 3, thereby warranting a more detailed investigation into potential sources of contamination in this area.

The pH and temperature of the water samples from the three sites do not show variations that could account for the differences in metformin concentrations. The pH values at Site 2 (7.055), Site 3 (7.045), and Site 4 (6.99) are close to neutral, which should not significantly impact the metformin concentrations, as metformin is more stable and soluble at neutral pH levels [37, 38]. Similarly, temperature varies only by no more than 0.5 °C among the sampling sites, making it unlikely that temperature variations contribute to the observed metformin concentrations, as suggested by Sharma et al. [39].

Although metformin levels were undetectable, site 6 presented the most concerning water quality profile, with multiple parameters exceeding the defined limits, suggestive of potential water contamination. Notably, dissolved solids exhibited an extreme deviation at 2602 mg/L, more than double the allowable limit of 1000 mg/L, indicative of potential pollution. Moreover, fluoride and hardness (expressed as $CaCO_3$) levels were over the set limits, suggesting the presence of industrial contaminants and high levels of dissolved minerals [40], respectively. The sulfate concentration at site 6 was markedly high, further pointing to possible runoff of industrial or household waste, particularly detergent and cleaning products [41, 42]. Additionally, organic matter, measured using $KMnO_4$, was considerably over the limit, indicative of a potential influx of organic waste [43]. These alarming findings underscore the need for a thorough investigation into the source of these exceedances to devise appropriate remedial measures, in consideration of the intended water usage in this area.

4.3 Implications of the study

The detection of metformin in the Angke River in Jakarta, Indonesia, brings attention to an often overlooked aspect of water pollution—pharmaceuticals. Despite concentrations in this study falling within the lower 40% of the global range, the potential ecological and human health impacts must not be underestimated, given the projected expansion of the number of diabetes diagnoses, both in Indonesia and globally. In addition, metformin's use as an ovulation induction agent for polycystic ovarian syndrome [44] suggests its global use could further increase with increasing demand for fertility treatments. Metformin's adverse effects on aquatic organisms have been documented, even at low concentrations. In invertebrates, metformin has been shown to potentially alter reproduction and morphological traits, cause immobilization, and induce oxidative stress [19, 20, 45, 46]. These factors may, over time, affect population dynamics and alter the balance within these ecosystems.

In fish, exposure to metformin has been found to induce endocrine disruption and intersex in males, affect embryogenesis, and reduce overall growth [47–49]. These factors may potentially lead to reduced fitness and survivability, contributing to population declines and, over extended periods, could lead to local extinctions. The potential ecological ramifications are profound, as they can ripple through food webs and alter biodiversity across trophic levels, with potential impacts on ecosystem functions and services.

The presence of metformin in surface waters, moreover, poses potential risks to human health, as these waters serve various purposes such as irrigation, recreation, and drinking water sources. With this study acting as a key stepping stone in understanding pharmaceutical pollution in Indonesian waters, it underscores the urgency for enhanced wastewater treatment and management practices, alongside increased monitoring and assessment of pharmaceutical pollutants. This includes the need for well-established regulatory frameworks and public awareness campaigns promoting responsible drug disposal practices.

Pharmaceutical pollution poses a global threat to environmental and human health [50, 51], as well as to the delivery of the United Nations Sustainable Development Goals, especially SDGs 3 (Good health and well-being), 6 (Clean water and sanitation), 12 (Responsible consumption and production) and 14 (Life below water). Further research is required to comprehensively evaluate the extent of contamination and the potential risks associated with exposure to metformin and other emerging contaminants in Indonesian waters. This would enable the development of informed strategies to address this urgent concern.

5 Conclusion

This study represents the first detection of metformin in the waters of Jakarta, and thus highlights the intersection of pharmaceutical consumption, particularly due to growing diabetes prevalence, and environmental health in Indonesia. In addition to illuminating the extent of this issue, the study provides valuable insights into the parameters influencing metformin's prevalence in water bodies, including turbidity, color, organic matter content, and manganese levels. The environmental and public health concerns presented here support the growing need for extensive monitoring and assessment of pharmaceutical pollutants, improved wastewater treatment methods, and enhanced public awareness of responsible drug disposal practices. The development and implementation of appropriate regulatory frameworks will be vital in safeguarding both public health and the environment. Finally, this research underscores the need for a more thorough understanding of the potential risks associated with exposure to metformin and other pharmaceutical pollutants. This knowledge is crucial for developing effective strategies to address this issue, which not only impacts Indonesia's aquatic ecosystems but also has far-reaching implications for global environmental health and the achievement of the United Nations Sustainable Development Goals.

Author contribution Wulan Koagouw: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing—Original Draft (main contributor). Erna Simanjuntak: Methodology, Writing—Original Draft. Richard J. Hazell: Formal analysis, Investigation, Resources, Writing—Original Draft. Riyana Subandi: Methodology, Writing—Original Draft. Corina Ciocan: Resources, Writing—Original Draft, Supervision. All authors read and approved the final manuscript.

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Availability of data and materials All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate Ethical approval was not necessary for this study as it did not involve human or animal subjects. Not applicable, as the study does not involve human or animal participants, but all procedures were conducted ethically and responsibly.

Consent for publication All authors listed have reviewed the final version of the manuscript and unanimously consent to its publication.

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