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АНАЛИТИЧЕСКИЕ МЕТОДЫ ДЛЯ ОЦЕНКИ ФАРМАЦЕВТИЧЕСКОГО ЗАГРЯЗНЕНИЯ РЕК МИРА; ОБЗОР

Джасим. М.С. Джамур

Джасим. М.С. Джамур (ORCID 0000-0001-5558-5075)

Факультет химии, Педагогический колледж чистой науки (Ибн Аль-Хайсам), Багдадский университет, Ирак
E-mail: jasim.m.s@ihcoedu.uobaghdad.edu.iq

Недавние сообщения о новых проблемах загрязнения, вызванных присутствием лекарств в водной среде, вызвали большой интерес к исследованиям, направленным на анализ и смягчение связанных с этим экологических рисков, а также степени этого загрязнения. Основными источниками фармацевтических загрязнителей в природных озерах и реках являются сточные воды клиник, сточные воды фармацевтического производства и сточные воды жилых домов, загрязненные экскрементами потребителей лекарств. При оценке состояния рек фармацевтические загрязнители были определены как одни из новых загрязнителей. Предыдущие исследования показали, что примесями в широко используемых фармацевтических препаратах являются нестероидные противовоспалительные препараты, антибиотики, антиретровирусные и противораковые препараты. Кроме того, этот обзор демонстрирует использование аналитических методов для изучения этих загрязнителей в различных видах речной воды. Из-за их чрезвычайно низких концентраций в водной среде (примерно в диапазоне от нг/л до г/л) для идентификации и количественного определения этих продуктов необходимо применять методику высокочувствительного и селективного многокомпонентного одновременного анализа. Этот аналитический метод обеспечивает гибкие и надежные средства для выявления и оценки фармацевтических загрязнителей в пробах речной воды путем сочетания твердофазной экстракции и масс-спектрометрических методов. SPE-LC/MS/MS – основной метод оценки уровня загрязнения.

Ключевые слова: аналитические методы, фармацевтическое загрязнение, реки

ANALYTICAL TECHNIQUES IN PHARMACEUTICAL POLLUTION OF THE WORLD’S RIVERS; A REVIEW

Jasim. M.S. Jamur

Jasim. M.S. Jamur (ORCID 0000-0001-5558-5075)

Department of Chemistry, College of Education for Pure Science (Ibn Al- Haitham), University of Baghdad, Iraq
E-mail: jasim.m.s@ihcoedu.uobaghdad.edu.iq

Recent reports of new pollution issues brought on by the presence of medications in the aquatic environment have sparked a great deal of interest in studies aiming at analyzing and mitigating the associated environmental risks, as well as the extent of this contamination. The main

sources of pharmaceutical contaminants in natural lakes and rivers include clinic sewage, pharmaceutical production wastewater, and sewage from residences that have been contaminated by drug users' excretions. In evaluating the health of rivers, pharmaceutical pollutants have been identified as one of the emerging pollutants. The previous studies showed that the contaminants in pharmaceuticals that are widely used are non-steroidal anti-inflammatory drugs, antibiotics, antiretrovirals, and anticancer drugs. Additionally, this review demonstrated the use of analytical techniques to examine these contaminants in various kinds of River water. Due to their extremely low concentrations in the aqueous environment (about in the range of ng/L to g/L), it is necessary to apply a technique for highly sensitive and selective multicomponent simultaneous analysis to identify and quantify these products. This analytical technique provides a flexible and reliable means to identify and evaluate pharmaceutical contaminants in river water samples by combining solid phase extraction and hyphenated mass spectrometric techniques. SPE-LC/MS/MS is the main method for estimating the level of pollution.

Key words: analytical techniques, pharmaceutical pollution, rivers

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INTRODUCTION

Wastewater pollution adversely affects community water sources and may have detrimental effects on health [1]. Emerging pollutants (EPs), as defined by the United States Geological Survey, are those that can infiltrate the environment and have identified or suspected negative effects on the natural world, toxicology, and health of humans. Even though these toxins have been extensively spread throughout the environment, they are now being identified thanks to the advancement of modern detection techniques. New sources of emerging pollutants may be produced by by modifications to the usage and. EPs are divided into six main kinds according to their origins and several physiochemical traits: Endocrine-disrupting substances (EDCs), pharmaceutical pollutants (PPs), persistent organic pollutants (POPs), artificial sweeteners (ASs), and microplastics (MPs) are just examples of the contaminants found in products for personal use. Numerous classes of EPs are being consumed at a significantly higher rate as a result of population and economic growth. Over 700 EPs have previously been found in the environment of water in Europe [2].

A challenge for the environment has been the detection of EPs in several surface water bodies worldwide [3-7] including pharmaceutical and personal care products, polycyclic aromatic hydrocarbons [8], and phenols [9]. Though their low concentrations have harmed routine monitoring of them, it is now being done seriously since data suggests that these contaminants affect the biological function of rivers and other bodies of water [10, 11]. In addition, another main environmental problem is metals in soils from wastewater [12].

Nowadays, pharmaceuticals and pharmaceutically active substances are classified as new environmental pollutants as a result of their inevitable increase in consumption and expanding presence in a range of environmental compartments [13]. Pharmaceuticals and personal care products (PPCPs) are acknowledged as environmental toxins of worldwide significance due to their biological activity, their prevalence in global ecosystems [14], and more recently, their role as drivers of global change [15]. For pharmaceutical products to be more stable and to ascertain whether the degradation products and contaminants are harmful, more information about the structure of the degradation process is needed [16]. PPs are substances utilized in both agricultural products and human health care to support the well-being or growth of farm animals. The production and use of pharmaceutical items have both increased substantially in recent decades as medicine has advanced. A few hundred tons of chemicals are manufactured annually, and about 3.000 are required to prepare medicines [17, 18]. The three classes of pharmaceuticals that are used the most frequently worldwide are analgesics, antibiotics, and anti-inflammatory treatments. On farms all around the world. These medications are widely used in the medical field for the prevention and treatment of animal diseases as well as to boost financial rewards in industrial the production of livestock. Every day, people use a range of different medications for their health [19-22].

Medication is eliminated from the body as active ingredients, or metabolites, through the urine and feces after intake [23]. On the other hand, these medicines are also present in freshwater ecosystems and marine settings due to wastewater effluents created under regenerate circumstances [24-30]. The primary problem is that some of these emerging contaminants (ECs) are challenging to remove using traditional treatment facilities; therefore, new approaches are being sought after and investigated to entirely eradicate them [31]. Studying pharmaceuticals is essential because of the dramatic increase in pharmaceutical usage worldwide and the associated environmental implications, particularly their. Pharmaceutical compounds are categorized as ECs in the settings of wastewater and biological degradation attributed to the lack of standards for their environmental discharge and impacts on the environment [32-35]. Marketing of some medications without a prescription from a doctor or prior registration, so are commonly consumed globally, indicating that they spread over the environment [36].

Pharmaceutical substances enter bodies of water, on both surfaces. There were numerous sources of surface and groundwater. Urban wastewater is the first of these, and it contains a significant amount of medications in human feces, as well as insufficient drug disposal caused by the failure to have little management control. Another significant source of pharmaceuticals is livestock and agricultural waste, particularly the latter, as animals are kept in vast farms for intensive livestock, are frequently given feed supplements that contain medicines, and excreta is frequently utilized as soil additives in agriculture, reaching the water table through leaching [37, 38]. Despite stringent monitoring of pharmaceutical products in Europe and the United States, substantial amounts of medicines have been identified in discharges from companies in Asia, Europe, and America, making pharmaceutical sector effluents another significant source [39-44].

Pharmaceutical wastewater contents change on a weekly and daily basis as a result of commuter, usage, and activity patterns [45-50]. Pharmaceutical concentrations in rivers may be extremely dynamic when leaking infrastructure is the main source of the drugs because of changes in loading and stream flow over time [51]. Wastewater treatment plants can greatly minimize the temporally unpredictable nature of human use and discharge patterns [50]. Although the treated effluent is often a steady point source, changes in stream flow and stream attenuation could eventually lead to changes in the concentrations of downstream pharmaceuticals [52-54]. Since leaks have the potential to transport temporal trends in human usage to receiving waterways, it may expect a lot more unpredictability if sewage infrastructure leaks are the main source of pharmaceuticals entering waterways. The amount of pollution that enters and affects recipient water bodies is determined by time-integrated mass, often known as a load. Load is essential for calculating the quantity transported to the seas downwind and the possible buildup in the sediments. Understanding pharmaceutical concentrations and their temporal fluctuation is crucial for assessing these levels, as well as the hazards to aquatic life [55, 56].

According to several studies that examined the microbiome of wastewater, hospitals tend to have a lot of anaerobes that pose a hazard to patients' health, including Bifidobacteriales, Bacteroidales, and Clostridiales [57-59]. They also noted that medical facility wastewater, in comparison to wastewater from other sources, contains bacteria with higher proportional levels of antibacterial and resistance to antibiotics genes [57]. A considerable overhaul of current water treatment techniques is necessary in order to comply with the principles of sustainable development and "green" technologies [60].

LITERATURE REVIEW

Commonly used groups of pharmaceutical pollutants

Non-steroidal anti-inflammatory drugs (NSAIDs)

With a variety of chemical compositions and related therapeutic effects, non-steroidal anti-inflammatory medicines (NSAIDs) and analgesics are among the most significant classes of medical products in the world, with an estimated yearly output of several hundred tons [61]. Humans require significant doses of anti-inflammatory drugs when prescribed, but far larger quantities are often sold over-the-counter [62]. In the field of veterinary medicine, antibiotics, and NSAIDs are regularly used to treat conditions such as pain, inflammation, fever, osteoarthritis, arthritic illness, and stress [63, 64]. Unfortunately, these two classes of drugs have a variety of detrimental consequences on patients, including asthma, exceedingly rare allergic reactions, ulcers, gastrointestinal problems, and renal failure with an increased risk of postoperative bleeding [65-68]. These drug concentrations are currently being checked in effluents all over the world, and various studies have shown that both NSAIDs and analgesics are frequently found in water sources [69, 70]. The most important NSAIDs in various environmental samples were measured using a variety of methodologies because drug contamination and environmental risk assessment are widespread issues [71].

NSAIDs are often used throughout the world and can cure joint inflammation, fever, and muscle pain in both people and animals [72]. The highest concentration of ibuprofen (2.32 μg/L) in natural water systems has been recorded in India, Ketoprofen (1.07 μg/L) and acetaminophen (1.56 μg/L) were found in the Ganga River close to Sahibganj, Bihar [73, 74]. The contaminants found in river water have been determined to be posing an intermediate to high ecological risk [75]. In Cuernavaca (Mexico), samples taken at different times over the years have revealed high concentrations of diclofenac (258-1.398 ng/L) and naproxen (732-8.889 ng/L), as well as influent and wastewater from a WWTP, are found in the Apatalco River surface waters. [76]. Additionally, drugs such as d diclofenac (10.221 ng/L maximum concentration reported) were found in wastewater from the Red Sea (Saudi Arabia) [77]. Various quantities of diclofenac (19.4 ng/L) and acetaminophen (17.4-34.6 ng/L) were found in Brazilian surface and bottom water samples collected from Santos Bay [78]. Because of increased tourism, the same drugs were also found in surface water in the northern Antarctic Peninsula region, with acetaminophen and diclofenac concentrations of 48.74 and 15.09, ng/L, respectively [79].

Antibiotics

Antibiotics, which have been used to stop or reduce the growth of bacteria, are the most potent medication now on the market [80]. Antibiotics work in a variety of ways, one of which is by inhibiting the formation of peptidoglycan and nucleic acids, which has a detrimental effect on cell division [81]. Aquatic organisms are chronically exposed to antibiotics as a result of their constant introduction into the environment [82, 83]. They are hazardous to organisms and have a synergistic impact when combined with other medications and/or xenobiotic substances since they function in extremely low quantities [84]. Antibiotics hurt algae and aquatic plants [85, 86]. Due to their ability to obstruct photosystem II's electron chain and enhance oxidative stress, several of them have been reported to be photosynthesis inhibitors [87]. The primary issue is that antimicrobial resistance genes (ARGs), which are genes that provide bacterial antibiotic resistance and can spread through horizontal gene transfer are present in the environment and are consequently regarded as contaminants [88, 89]. Despite research showing that the plasmids that conjugate might increase the levels of ARGs in lakes and rivers down of wastewater treatment facilities, and integrons as wastewater that have been treated still contain considerably fewer ARGs than untreated wastewater regardless of this [90-94].

Based on the type of reservoir, different quantities of antibiotics are used overall; for instance, they may range from 0.0013 to 0.0125 μg/mL in wastewater, from 0.0005 to 0.0214 μg/mL in drinking water, and from 0.0003 to 0.0039 μg/mL in river water [95-97]. Antibiotic resistance among microbes to antimicrobials is projected to significantly increase human morbidity and mortality shortly [98]. Several rivers exist around the world, including those in Spain, Italy, South Korea, Taiwan, France, the United States, Sweden, and China have been observed to contain antibiotics [99-102].

Antiretrovirals

Antiretrovirals are commonly found in wastewater, but they are not as closely monitored as other drugs [103-107]. According to the studies by Hawkins [108], Ncube et al. [109], and Mlunguza et al. [110], these drugs offer significant ecotoxicological dangers to human health by entering drinking water sources after being treated with wastewater in WWTPs. The biggest worry at the moment is that exposure to water polluted with these medications could result in the development of resistant HIV strains in the body [109, 111].

Anticancer drugs

Annual cancer cases are predicted. In excess of 20 million in the ensuing decades, which would cause the usage of anticancer drugs to increase exponentially and their consequent discharge into wastewater [112]. The majority of these substances are insufficiently absorbed and digested by the human body, which results in their excretion in urine and feces. The most often used anti-cancer medications include, among others, cyclophosphamide, tamoxifen, ifosfamide, and methotrexate. Surface water, influents and effluents from WWTPs, and hospital effluents have all had these medicines found in them. According to the study by Nassour et al., the concentrations of cyclophosphamide, ifosfamide, methotrexate, and tamoxifen that were detected ranged from 0.05 to 22.100 ng/L, 0.14 to 86.200 ng/L, and 0.01 to 740 ng/L, respectively [113]. These drugs have been found in water masses in several investigations, demonstrating that current water treatment systems cannot break them down [114, 115]. To lessen the negative environmental impact of medications, regulations for their handling and preservation have been developed by a number of international bodies [116]. One of the primary issues is that these medications could experience biomagnification [117].

Application of analytical techniques in the pharmaceutical analysis of Rivers

In the study by Madureira and co-workers [118], solid-phase extraction (SPE) and high-performance liquid chromatography with diode array detection (HPLC-DAD) were used to determine six diverse pharmaceuticals in estuarine surface waters. The calibration curves' linearity consistently revealed a correlation of better than 0.99, and the validation parameters showed that this technique had good specificity (> 99%) for all substances tested. Recovery rates for the majority of the target compounds were more than 70%, and the limits of detection (LOD) were in the ng/L range. This method can therefore be used to efficiently filter pharmaceuticals in contaminated estuarine areas, it can be concluded.

Liquid chromatography (LC), a UV-Vis diode array detector, and a Thermo Scientific C18 (250 mm × × 2.1 mm, i.d.: 5 m) column in negative ion mode were used to evaluate some pharmaceuticals in surface water. Using a 0.1% mobile phase, they were taken out of the column. For mass spectrometry, time of flight (TOF) equipment was utilized. For the linearity range of 5-500 ng/mL, all compounds have a determination coefficient (R2) > 0.99. The LOD in the river water varied from 65 to 136 ng/L, while the recovery was between 45 and 111.2% [119].

Fick and co-authors have studied how environmental exposure to active pharmaceutical compounds occurs in a crucial area for the production of bulk medications. At an effluent treatment plant, samples of water were collected that is shared and located close to Hyderabad, India. This facility receives process water from roughly 90 bulk pharmaceutical manufacturers. When all of the wells were analyzed using the LC-MS method, the following drugs were all detected in significant amounts: citalopram, cetirizine, enoxacin, ciprofloxacin, and terbinafine. Antibiotic resistance is becoming a serious concern, and producers and regulatory organizations confront a challenging task in their efforts to address the issue [120].

In Turkey's Ceyhan River, the presence of 91 pharmaceutically active chemicals from several drug classes-including painkillers, antimicrobials, cardiovascular medications, hypolipidemic medications, CNS medications, and stimulants was examined. Pharmaceutically active substances were inspected periodically between September 2013 and August 2014 at 9 stations. SPE was employed for the pharmaceutically active molecule analysis, and liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to assess the results. The two pharmaceuticals that were most frequently found in the river water were carbamazepine and lidocaine [121].

It was simple, quick, and affordable to identify 38 PPCPs, including 19 antibiotics, in surface water samples using lyophilization and LC-MS/MS. The volume of the water sample, its components, and the extraction solvent were all altered one at a time. After lyophilizing 80 mL of water samples to concentrate the analytes, 2 mL of each of acetonitrile, acetone, and ultrapure water were employed as the eluents to successfully elute the analytes. The LOD was present in the range of 0.02 ng/ L to 0.17 mg/L. The range for 30 different analytes was 40.0% to 124.4%, whereas the recovery rate for sulfaguanidine was 40.0%. (flumequine). All of the analytes exhibited relative standard deviations under 21% besides ciprofloxacin (29%) in this study. water, especially river surfaces [122].

The four biggest hydrographic basins' principal rivers, as well as a commercial water treatment facility in Curitiba, Brazil, were evaluated for the presence of 25 pharmaceuticals using a multiclass analytical technique that was developed and validated. The medicines were evaluated using SPE-HPLC-MS/MS. 10-100 ng/L and 20-200 ng/L, respectively, were the LOD and LOQ values. Sulfamethoxazole has the highest concentration of any antibiotic. Antibiotics, psychiatric drugs, anti-inflammatories, analgesics, antiretrovirals, and diabetes medicines were additionally often discovered and measured. The study's findings show that humans have had a significant impact on the Iguaçu basin, which is primarily supported by the area's high proportion of residential rubbish [123].

The HPLC approach with DAD detection was suggested for the simultaneous study of 15 pharmaceuticals from different therapeutic classes in surface water and wastewater. Dexamethasone and prednisolone, two corticosteroids, were among the medications, along with NSAIDs such as paracetamol, metamizole, aspirin, salicylic acid, diclofenac, and naproxen. The pre-concentration of water samples using solid-phase extraction (SPE) columns from Oasis HLB, NEXUS, and Bond Elut ENV was examined. Water samples that had been spiked with an amount of 0.2 g/L were used to assess the validity of each method. The highest rate of recovery was generated by the Oasis HLB column. Various HPLC columns were examined to achieve the best separations in the shortest period. The recommended method can be used as a quick and inexpensive analytical instrument for screening. It was used to examine water samples, especially from rivers. The optimistic findings should be supported by MS methods, though [124].

For the majority of analytes, high recoveries were obtained for extraction from both water and sediment samples using LC/MS-MS. Low limits of detection were attained for all substances under investigation in both the silt (1-3 ng/g) and the water sample (1-5 ng/L). Environmental samples contained samples that contained 60% of the target chemicals. Pesticides dimethoate and atrazine were the most commonly observed analytes in river sediments [125].

With the help of SPE and GC-MS, Togola and colleagues have developed an analytical technique for identifying medicinal chemicals in various aqueous samples (wastewater and surface water). Depending on the type of chemical, samples were filtered, extracted, and concentrated using C18 or HLB cartridges. To ensure the preservation of the medicinal ingredient, sample storage conditions were assessed and adjusted while environmental sampling circumstances were taken into account. For the bulk of the medicines studied, LOD ranged from 0.4 to 2.5 ng/L depending on the chemical, with recovery between 53 and 99% and variability under 15% throughout the entire operation [126].

A variety of analytes, including small pharmaceutical compounds and polymers, have been investigated using ionization mass methods [127]. The liquid chromatography/electrospray ionization/tandem mass spectrometry (LC-ES/MS-MS) technology was developed, validated, and utilized by Hao and colleagues to investigate pharmaceutical inputs in the Grand River watershed, Ontario, Canada. 27 antibiotics and neutral medicines were extracted from aqueous ambient samples and evaluated by LC/MS-MS. The method's recoveries ranged from 51 to 130%, and its detection limits for the targeted substances were 20 to 1,400 ng/L [128].

LC-MS spectroscopy was used to investigate weekly samples from a network of urban streams in Baltimore, Maryland, for the presence of 92 pharmaceuticals because the network lacked wastewater treatment effluents. 37 distinct chemicals were present in the network, and streams with higher population densities had higher chemical concentrations. It shows that between 0.05 and 42% of the medications people in this watershed use are discharged to surface waterways. Varying substances offer diverse channels with different weights. These findings highlight the significance of creating, preserving, and enhancing sewage infrastructure to safeguard water resources from pharmaceutical contamination [51].

The influence of these pharmaceuticals on surface rivers receiving treated wastewater is the main subject of this study by Torres-Palma and co-workers, which is the first to look at the removal of pharmaceutical drugs in wastewater treatment plants. To do this, samples from surface water at the junction of the rivers in Juliaca (Peruvian Highlands), Cusco, Puno, and Lima (Peruvian Coast) were examined. In this investigation, a total of 38 target drugs were identified using LC-MS/MS. Surface water and MWWTPs, respectively, contained 60% and 75% of the target medications. Acetaminophen, which was found in all samples of treated wastewater in the Puno department and had average amounts of more than 100 g/ L, was the pharmaceutical with the greatest concentration. Data from this study indicated that the MWWTP Cusco was more effective than the MWWTP Lima in terms of removing drugs. The quantities of some medicines (about 50% of the chemicals examined) in treated wastewater, however, were either equal to or greater than those in influent wastewater. The Risk quotient, which was determined from the concentration information in the samples was used to evaluate the environmental and ecological risks of medicines. Our results demonstrated that the aquatic ecosystem was exposed to a high environmental risk (RQ 1) from the analgesic acetaminophen and three antibiotics (clindamycin, ciprofloxacin, and clarithromycin). Except for norfloxacin, all antibiotics as well as the painkillers acetaminophen and diclofenac posed a high environmental risk (RQ 1) in the river. It may be concluded that the wastewater treatment techniques employed in the country's largest cities are insufficiently successful in eliminating pharmaceuticals based on information that was uncovered. MWWTPs should therefore include additional treatment techniques for the more efficient removal of these chemical compounds [129].

Wan-Ching Lin and colleagues have modified the procedure for analyzing particular pharmaceutical compounds in water samples. Investigations were conducted on various solid-phase extraction cartridges. The analytes were derivatized in real-time in the injection port of the GC-MS, which enabled the identification and quantitative analysis of the analytes. The injection volume was considerable (10 μl), and TBA salts were utilized. As the quantitation ions, a mix of molecular ions and a few identifying ions were used to obtain the best detection sensitivity and specificity. In samples of 500 ml tap water. The range of these substances' quantitation limits was 1.0 to 8.0 ng/L. Between 50 and 108% of these residues were recovered from spiked water samples, while the RSD ranged from 1 to 10%. The specified analytes were identified in river water and wastewater treatment plant effluent samples in concentrations ranging from 30 to 420 ng/L [130].

Spectrophotometric methods can be useful for identifying environmental samples because they are simple and affordable [131]. It is shown how time-domain NMR (TD-NMR) analysis can be used to detect the water content of medicinal components. In the initial stages of the investigation, samples of a variety of disintegrants, including croscarmellose sodium, maize starch, low-substituted hydroxypropyl cellulose, and crospovidone, were used. These disintegrants had additional water in predefined amounts (between 0 and

30% of the total weight). Partial least squares (PLS) regression was used to analyze the samples' T2 relaxation curves after they had been collected by TD-NMR measurements. The investigation showed that trustworthy and precise PLS models were developed, allowing precise estimation of the samples' water content [132].

CONCLUSION

Pharmaceutical contamination in aquatic environments is a major concern, with sewage from production facilities, hospitals, and homes being the main sources. Studies are being conducted to reduce this contamination. The current review has studied the literature on using extremely sensitive and highly selective analytical technology (hyphenated chromatography-mass-techniques) to identify pharmaceuticals that are causing new environmental contamination problems. SPE-LC/MS/MS is the main method for figuring out the extent of this contamination. This review also defined and arranged the information gleaned from published analytical instances and discussed the future potential of this environmental analysis technique. According to recent studies using this methodology, these pharmaceutical pollutants include NSAIDs drugs, antibiotics, antiretrovirals, and anticancer medications that may hasten the growth of bacteria that are resistant to antibiotics in the aquatic environment.

The authors declare the absence a conflict of interest warranting disclosure in this article.

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