Sustainable Chemistry and Pharmacy 33 (2023) 101127

Contents lists available at ScienceDirect

Sustainable Chemistry and Pharmacy

journal homepage: www.elsevier.com/locate/scp

Developing a smart and clean technology for bioremediation of antibiotic contamination in arable lands

Farhad Mahmoudi Jalali [a], Benyamin Chahkandi [b], Mohammad Gheibi [c], Mohammad Eftekhari [d], Kourosh Behzadian [e, f, *], Luiza C. Campos [f, **]

[a] *Department of Civil Engineering, Faculty of Engineering, Islamic Azad University, Tabriz Branch, Iran*
[b] *School of Civil Engineering, University of Tehran, Tehran, Iran*
[c] *Association of Talent Under Liberty in Technology (TULTECH), 10615, Tallinn, Estonia*
[d] *Department of Chemistry, Faculty of Sciences, University of Neyshabur, Neyshabur, Iran*
[e] *School of Civil Engineering, University of West London, London, UK*
[f] *Department of Civil, Environmental and Geomatic Engineering, University College London, Gower St, London, WC1E 6BT, UK*

A R T I C L E I N F O

Handling Editor: Borhane Mahjoub

Keywords:
Azithromycin
Bioremediation
Machine learning
Penicillium simplicissimum
Taguchi design

A B S T R A C T

This study presents a smart technological framework to efficiently remove azithromycin from natural soil resources using bioremediation techniques. The framework consists of several modules, each with different models such as *Penicillium Simplicissimum* (PS) bioactivity, soft computing models, statistical optimisation, Machine Learning (ML) algorithms, and Decision Tree (DT) control system based on Removal Percentage (RP). The first module involves designing experiments using a literature review and the Taguchi Orthogonal design method for cultural conditions. The RP is predicted as a function of cultural parameters using Response Surface Methodology (RSM) and three ML algorithms: Instance-Based K (IBK), KStar, and Locally Weighted Learning (LWL). The sensitivity analysis shows that pH is the most important factor among all parameters, including pH, Aeration Intensity (AI), Temperature, Microbial/Food (M/F) ratio, and Retention Time (RT), with a p-value of <0.0001. AI is the next most significant parameter, also with a p-value of <0.0001. The optimal biological conditions for removing azithromycin from soil resources are a temperature of 32 °C, pH of 5.5, M/F ratio of 1.59 mg/g, and AI of 8.59 m^3/h. During the 100-day bioremediation process, RP was found to be an insignificant factor for more than 25 days, which simplifies the conditions. Among the ML algorithms, the IBK model provided the most accurate prediction of RT, with a correlation coefficient of over 95%.

1. Introduction

Managing soil health is a significant challenge in agriculture. Moreover, it is a complex issue that is difficult to address using traditional methods (Mohammad et al., 2021). With the increasing prevalence of new diseases worldwide, people especially in low-income countries are resorting to antibiotics to treat infections (Klein et al., 2021). This trend can have adverse health effects due to the carcinogenic properties of antibiotics (Llor and Bjerrum, 2014). Recent studies have also shown that the widespread use of antibiotics in

* Corresponding author. School of Civil Engineering, University of West London, London, UK.
** Corresponding author.
E-mail addresses: farhadmahmoudijalali@gmail.com (F. Mahmoudi Jalali), Beniaminch@gmail.com (B. Chahkandi), mohamadgheibi@ymail.com (M. Gheibi), meftekhari85@yahoo.com (M. Eftekhari), kourosh.behzadian@uwl.ac.uk (K. Behzadian), l.campos@ucl.ac.uk (L.C. Campos).

https://doi.org/10.1016/j.scp.2023.101127
Received 25 January 2023; Received in revised form 1 May 2023; Accepted 14 May 2023
Available online 28 May 2023

natural resources such as air, soil, water, and humans can lead to health risks as microorganisms develop drug resistance (Zhang et al., 2015).

Azithromycin (AZ) is one of the most widely used antibiotics for treating bacterial infections. According to the Food and Drug Administration (USFDA), AZ (Zithromax or Zmax) can disrupt the electrical processes of the heart, leading to a potentially fatal irregular heartbeat (Patel et al., 2020). Due to the persistent nature of antibiotics, their recalcitrance, and the emergence of resistance genes, their widespread presence in natural resources can cause a global environmental problem, making their remediation essential (Cycoń et al., 2019).

Azithromycin is classified as an Endocrine Disrupting Compound (EDC), which can pose unprecedented health risks due to pollutant emissions in soil and water (Lau et al., 2020). Soil pollution by EDCs can occur when pharmaceutical and industrial solid wastes are released into the environment without adhering to regulations and landfill standards (Hu et al., 2010). According to a survey conducted by SOM-institute[1] in Sweden in 2020, environmental pollution and antibiotic resistance are considered significant concerns by the public. The release of azithromycin in soil exacerbates both issues and increases public concerns. Therefore, reducing the concentration of azithromycin in soil would alleviate these problems and increase public satisfaction.

Addressing antimicrobial resistance (AMR) requires clear global guidelines and regulatory options, but this has been challenging due to the diversity and dynamic nature of healthcare and regulatory systems across different countries (Chokshi et al., 2019). As a result, the World Health Organisation (WHO) has made policies and recommendations, but it is up to each nation to regulate antibiotic resistance. To tackle AMR, individuals, healthcare professionals, policymakers, the healthcare industry, and the agricultural sector all need to act.

The WHO recommends that individuals use antibiotics only with a prescription, follow infection prevention guidelines, and practice safe food preparation according to the WHO Five Keys to Safer Food (FKSF). Policymakers can develop a national action plan to reduce antibiotic resistance, improve surveillance systems of antibiotic use, regulate the proper use and disposal of medicine, and educate the public on antibiotic resistance. Healthcare professionals can prevent infections by maintaining a clean and sterile working environment, prescribing antibiotics only when necessary, reporting antibiotic-resistant infections to surveillance systems, and educating patients on the risks of antibiotic misuse and how to prevent infections. The healthcare industry should invest in research and development of new antibiotics, diagnostics, and vaccines. The agricultural sector must use antibiotics in animals only under the supervision of a veterinarian, avoid using antibiotics to prevent diseases, and use vaccines instead. Fine practices can help reduce infections and improve biosecurity on farms (WHO, 2019).

In 2015, the World Health Assembly established a global action plan on AMR, consisting of 5 key policies: 1) enhancing public awareness about AMR, 2) promoting stewardship of antibiotics, 3) reducing and preventing infection, 4) improving surveillance systems and research, and 5) ensuring sustainable investment in combating AMR. The Assembly also urged each country to develop its own national action plan (NAP) to combat AMR (Anderson et al., 2020). In response, Iran created its own NAP (IRI-NAP) in 2016 in five sections (summarised in Table 1) aligned with the main policies outlined in the global action plan (Moradi et al., 2018).

Among the most common types of antibiotics (e.g., *β-lactams*, *Macrolides*, *Fluoroquinolones*, *Tetracyclines*, *Sulfonamides*, *Diaminopyrimidines*, *Lincosamides*, and their degradation products), according to the reports, Fluoroquinolones, Tetracyclines, and Sulfonamides have the highest concentration in soil samples mostly caused by manure and wastewater irrigation (Yang et al., 2021). Table 2 shows the concentration data of some of the frequently found antibiotics in soil.

Various techniques are available for degrading antibiotics in different environments such as water, wastewater, soil, and solid waste. These techniques include adsorption (Gheibi et al., 2023), integrated biological treatment with membranes (Zhao et al., 2021), permeable reactive barriers (Zhao et al., 2018), fungus-based bioremediation (Mohammadi et al., 2021), and electrochemical systems (Bicudo et al., 2021). However, each technique has its strengths and weaknesses and is applicable in specific real field situations. For example, permeable reactive barriers, membranes, biofilm membranes, and adsorption processes provide an acceptable efficiency of more than 95%, but they have limited capacity for decontamination and may require regeneration or recovery of the system in a short time (Zhang et al., 2020). On the other hand, coagulation and electrocoagulation procedures have high efficiency but involve chemical material addition and unusual energy consumption (Bicudo et al., 2021). Bioremediation, which involves living organisms such as fungi, algae, bacteria, plants, and animals, is a process that removes or detoxifies pollutants in the environment (Jagtap, 2020). It is environmentally friendly, requires low capital investment, and has minimal energy consumption, making it a popular method for degradation (Irshad et al., 2021). Bioremediation is particularly suitable for removing antibiotic compounds that are sensitive to pH and temperature (Liu et al., 2017).

Mycoremediation is a type of bioremediation that involves the use of fungi as the decomposer of pollutants (Schmit and Mueller, 2007). Fungi are a diverse group of microorganisms with unique characteristics, including the ability to form extensive mycelial networks, low specificity of their catabolic enzymes, and their independence from using pollutants as a growth substrate (Harms et al., 2011). Fungi are known to be capable of degrading and mineralising recalcitrant antibiotics due to their non-specific, non-stereoselective enzymatic systems based on free-radical levels (Čvančarová et al., 2015). Over the past two decades, fungi have been widely used for the treatment of waste and wastewater as well as for the degradation of hazardous compounds (Khatoon et al., 2021). Fungi have multiple strategies to cope with toxic compounds, such as antibiotics, including *bioadsorption*, *biomineralisation* (bioprecipitation) as well as biotransformation and biodegradation mediated by enzymatic systems (Olicón-Hernández et al., 2017).

Fungi have been found to play a critical role in removing heavy metals and mineralising various types of pollutants, including phenols, halogenated phenolic compounds, petroleum hydrocarbons, and polycyclic aromatic compounds (Singh, 2006). They are known

[1] Source(s): SOM-institute; ID 909223.

Table 1
Selected policies of the national action plan in Iran against Antimicrobial resistance.

Goal	Policy
Enhance public awareness of AMR	- Conduct education courses for specific groups such as children and elders - Run awareness campaigns for people working in related fields - Initiate targeted activities
Optimise the use of antibiotics	- Strategic purchases of antimicrobial medicines to improve the quality - Empowering medical institutions to create guidelines and manuals for antimicrobial stewardship of their own
Prevent and control infections	- Promotion of vaccines - Support NGO activities in coordination with hospitals to prevent and control infection - Control antimicrobial residue in food productions - Sending AMR experts all over the country to respond quickly while outbreaks happen
Improve surveillance system	- Create a monitoring system of prescriptions and antibiotics - Update and monitor prescription criteria for antibiotics - Increase the capacity of laboratories dealing with AMR - Research the AMR surveillance systems
Guarantee sustainable investment and research in combating AMR	- Promote research to clarify the necessity of AMR - Create a database of resistant genes - Conduct more research to deeply investigate the impact of AMR on health - Reconsidering the microbial diagnosis, treatment, and prevention approaches - Promote research and industry with the international collaboration

Table 2
The highest concentrations of some major antibiotics reported in the soil environment.

Type	Antibiotic	Concentration (ng/g)	Reference
β-lactams	*Amoxicillin*	200	Braschi et al. (2013)
Fluoroquinolones	Ciprofloxacin	350	Al Masud et al. (2023); Martínez-Carballo et al. (2007); Karcı and Balcıoğlu, 2009; Hu et al. (2010); Van Doorslaer et al. (2014); Pan and Chu, 2017b
	Difloxacin	21.5	
	Enrofloxacin	1347.60	
	Norfloxacin	5610	
	Ofloxacin	898	
Quinolone	*Sarafloxacin*	5.92	Ren et al., 2021
Macrolides	*Enrofloxacin*	22.93	Thiele-Bruhn (2003); Li et al., 2012; Tasho and Cho (2016); Pan and Chu (2017), 55
	Erythromycin	100	
	Tylosin	1250	
	Azithromycin	1000	Tasho and Cho, 2016
	Total macrolides	1.471	Li et al. (2023)
Sulfonamides	*Sulfachloropyridazine*	52.9	Thiele-Bruhn (2003); Dolliver et al. (2007); Karcı and Balcıoğlu, 2009; Hu et al. (2010); Carter et al. (2014); Pan and Chu (2017)
	Sulfadiazine	85.5	
	Sulfadimethoxine	40.4	
	Sulfadoxine	9.1	
	Sulfamethoxazole	54.5	
	Sulfamethazine	200–25,000	
	Sulfamonomethoxine	5.37	
	Sulfapyridine	5.11	
	Total sulfonamides	18.497	Li et al. (2023)
Tetracyclines	*Chlortetracycline*	12,900	Hamscher et al. (2002); Thiele-Bruhn (2003); Karcı and Balcıoğlu, 2009; Hu et al. (2010); Liu et al. (2016); Tasho and Cho (2016); Pan and Chu (2017); Łukaszewicz et al. (2018)
	Doxycycline	728	
	Oxytetracycline	50,000	
	Minocycline	32	
	Tetracycline	2683	

to excrete enzymes for the decomposition of carbohydrates without prior hydrolysis, making them highly effective in degrading a vast number of pollutants (Bellaouchi et al., 2021). Fungi have several advantages such as being easy to grow in fermenters and having a filamentous structure that allows for easy separation of fungal biomass (Akhtar and Abdullah, 2014). *Penicillium* strains are popular among all other fungi species as they can live in saline environments and have been reported to treat heavy metals, polycyclic aromatic hydrocarbons, phenol and its derivatives, wastewater, and wastes (Leitão et al., 2007). Among these species, *Penicillium simplicissimum* (PS) has been selected as the decomposer in this study to learn the effectiveness of this specie in the removal of AZ in soil (Sidhu et al., 2021).

The performance of microorganisms is mainly dependent on the cultural conditions (Khayati and Barati, 2017). The efficiency of biodegradation processes relies on several factors such as pH, temperature, soil properties and substrate (Oliveira et al., 2020). Conventional optimisation methods take a lot of time and cost due to numerous variables, which can be overcome by using multi-factor methods such as Taguchi orthogonal design (Carraro et al., 2022). This approach helps to investigate parameters, obtain more data, and reduce time and cost by suggesting effective adjustments to control factors. Taguchi has been used for myco-synthesis of nano-silver, wastewater treatment processes, and bioremediation and biodegradation process optimisation.

The use of Machine Learning (ML) approaches has significantly helped in modelling biodegradation procedures with high accuracy and non-limited applicability (Sodhi and Singh, 2022). Several studies have been conducted on the bioremediation of various pollutants by fungi, and ML algorithms such as Random Forest (RF), Adaptive Neuro-Fuzzy Inference System (ANFIS), Random Tree (Mohammadi et al., 2021), Support Vector Machine (SVM) (Liu et al., 2022), M5 Pruned model tree, Gaussian Processes (GP), and Sequential Minimal Optimisation (SMOreg) (Akbarian et al., 2022) have been applied to predict the biodegradation efficiency and cultural conditions.

The fate and remediation of antibiotic pollutants in the environment have been extensively researched. Vermillion Maier and Tjeerdema (2017) studied the degradation kinetics of AZ under aerobic and anaerobic conditions. Sidhu et al. (2019) used Continuous Stirred-Tank Reactors (CSTRs) to remediate *ciprofloxacin* and AZ with soil-based biomaterials, while Li et al. (2019) used electrokinetic remediation for tetracycline-polluted soil. Zhan et al. (2021) evaluated heat treatment for the decontamination of *tetracycline* and *roxarsone*. Mohammadi et al. (2021) proposed a fungus-based purification method for *amoxicillin*, while Sidhu et al. (2021) assessed AZ resistance in biosolids. Zelt et al. (2021) emphasised the importance of purifying antibiotics from agricultural soil to ensure food chain health.

To evaluate the research on bioremediation process for decontamination of antibiotics from soil, the library assessment was carried out using the VOSviewer software, where more than ten documents (Fig. 1a) and over 100 repetitions of keywords (Fig. 1b) related to soil, bioremediation, and antibiotics were filtered (Fig. 1). The results showed that China, India, and the United States have conducted most of the investigations on this topic. The research on this subject in Iran was challenging due to the limitation of facilities and equipment. The bioremediation subject is associated with soil pollution, antibiotics, soil microbiology, and biodegradation issues, and it is regarded as a pressing issue, essential for scientific communities, which is the aim of this study. The figures generated by the software represent different ranges of time series and show the accumulated published documents based on different subjects and the focus of the country's contributions.

Table 3 provides an overview of research that has used fungi for the removal of antibiotics. The authors argue that a sustainable system for soil quality management is necessary to reduce the impact of biomagnification, epidemiological disease, and immunological issues (Fasihi et al., 2021), but previous studies have not considered a smart system for controlling bioremediation structures. Therefore, this study aims to develop a smart framework for optimal control and degradation of AZ in soil using *Penicillium Simplicissimum* (PS) bioactivities, the Taguchi design method for optimisation, and three lazy machine learning models to predict bioremediation behaviour. The study also aims to design a control system for the bioremediation system based on decision tree

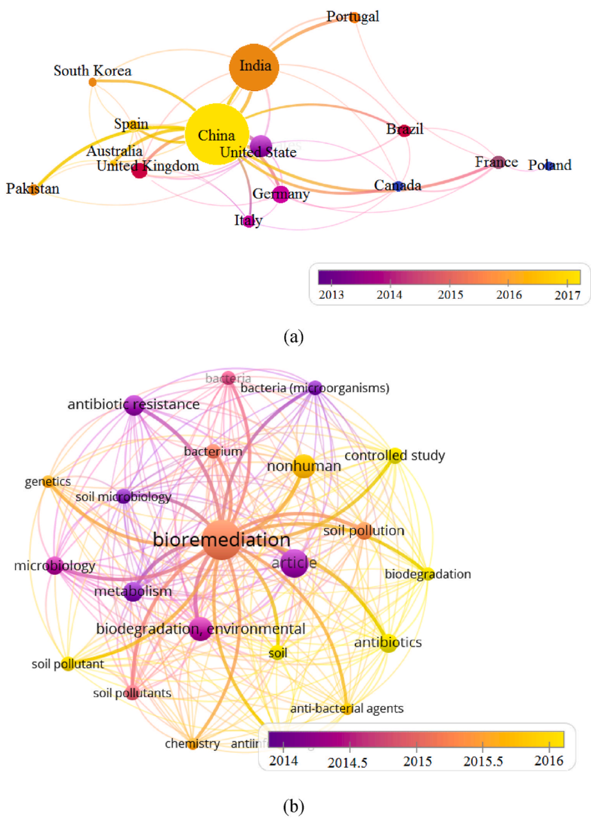

Fig. 1. Scientometry analysis of antibiotic bioremediation from soil resources through (a) country, and (b) occurrence of keywords aspects.

Table 3
Bioremediation studies using fungus for antibiotic removal.

Fungal name	Antibiotic contamination	Mechanism	Reference
Trametes versicolor	Azithromycin	Bio-oxidation	Del Álamo et al. (2022)
Ganoderma lucidum	20 different antibiotics	Biodegradation	Salandez et al. (2022)
Penicillium oxalicum RJJ-2	Erythromycin	Biodegradation	Ren et al. (2021)
Penicillium commune *Epicoccum nigrum* *Trichoderma harzianum* *Aspergillus terreus* *Beauveria bassiana*	Oxytetracycline	Biodegradation	Ahumada-Rudolph et al. (2021)
Penicillium restrictum	Sulfamethoxazole, Erythromycin, Tetracycline	Biodegradation	Fakhri et al. (2021)
Aspergillus flavus	Amoxicillin	Biodegradation	Mohammadi et al. (2021)
Trametes versicolor	Azithromycin	Biodegradation	Tormo-Budowski et al. (2021)
Pleurotus ostreatus	Sulfonamides Tetracyclines	Biodegradation	Camacho-Arévalo et al. (2021)
Trametes polyzona	Amoxicillin	Biodegradation	Lueangjaroenkit et al. (2019)
Pycnoporus sanguineus, Phanerochaete chrysosporium	Ciprofloxacin	Biodegradation	Gao et al. (2018)
Pleurotus ostreatus	Ciprofloxacin	Biodegradation	Sidhu et al. (2019)
Aspergillus terreus FZC3	Gentamicin	Biosorption and biodegradation	Liu et al. (2016)
Trichoderma harzianum	Clarithromycin	Biodegradation	Buchicchio et al. (2016)
Trametes versicolor	*Cefalexin, Ciprofloxacin, Etracycline*	Biodegradation	Badia-Fabregat et al. (2016)
Irpex lacteusb, Trametes versicolor	*Ciprofloxacin, Norfloxacin, Ofloxacin*	Biodegradation	Čvančarová et al. (2015)
Trametes versicolor	*Ofloxacin*	Biodegradation	Gao et al. (2018)
Trametes versicolor	*Erythromycin, Ciprofloxacine, Azithromycin, Cefalexine*	Biodegradation	Cruz-Morató et al. (2013)
Trametes versicolor	*Norfloxacin Ciprofloxacin*	Biodegradation	Patel et al. (2020)
Cunninghamella elegans	*Flumequine*	Biotransformation	WHO (2019)
Trichoderma viride	*Ciprofloxacin Norfloxacin*	Identification of degraded products	Picariello et al. (2022)
Pestalotiopsis guepini	*Ciprofloxacin Norfloxacin*	Biotransformation	Pan and Chu (2017)
Mucor ramannianus	*Enrofloxacin*	Biotransformation	Picariello et al. (2022)
Gloeophyllum striatum	*Ciprofloxacin, Enrofloxacin*	Biodegradation and metabolite identification	WHO (2019, 1999)

modelling and evaluate a sustainable industry using conceptual models. The authors argue that this study will address a knowledge gap related to optimising decontamination of AZ by considering optimisation, system performance prediction, and process control through conceptual modeling at the same time.

2. Materials and methods

2.1. Methodology

This investigation proposes a new smart framework for the bioremediation of AZ in soil, which includes lab-scale tests and a prediction system. The study highlights the need for sustainable and nature-based approaches to manage Emerging pollutants (EPs) such as AZ. The proposed framework involves setting up a lab-scale bioremediation system and optimising control factors and designing a prediction system for AZ bioremediation. The study also presents a flow cycle of AZ in the environment as illustrated in Fig. 2 that emphasises the carcinogenic effects of EPs on human health, highlighting the urgency of managing them with sustainable and nature-based approaches (Abubakr et al., 2020). The study emphasises the importance of smart, sustainable systems for environmental purification and highlights the use of bioremediation techniques with a decision support system as a no-chemical and sustainable method for the decontamination of soil from AZ. The soil samples were collected in the Industrial Centre of Mashhad, Iran for the purpose of investigating the soil properties and preparing the experimental setup.

2.2. Experimental techniques

Fig. 3 provides a list of materials and reagents used in the experiments, including measurement procedures, soil evaluation, and field practices. The PS seed was obtained from the Iranian Genetic Bank (IGB), while all other materials were purchased from Merck, Darmstadt, Germany. Distilled water was used throughout the experiments, and the soil sample was collected from the Quchan road region in Mashhad, Iran, where a pharmaceutical complex is located. The purpose of the experiments was to mitigate the adverse effects of polluted effluent on the surrounding soil. As the AZ concentration was synthesised in the laboratory, all soil samples were planted deep to ensure the absence of AZ.

The study collected soil samples from three points in a polluted district for lab-scale experiments and field performance assessment. AZ solutions were prepared using a 1000 mg/g stock standard solution from Merck, Germany, and the concentrations of AZ in

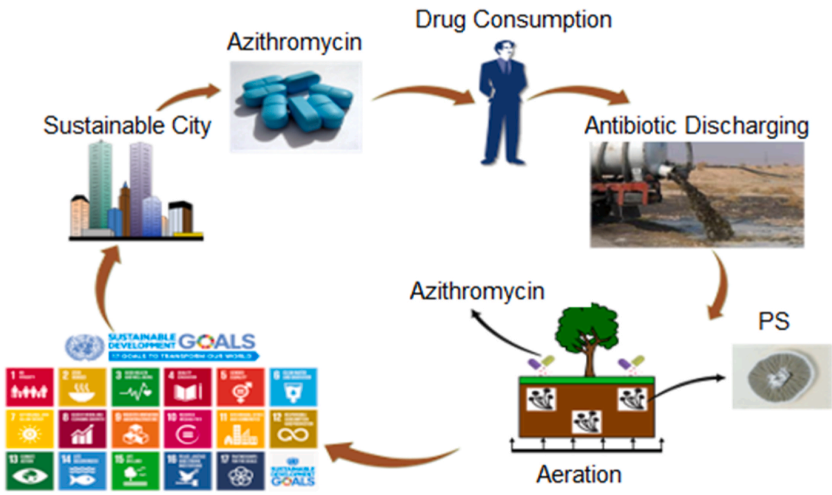

Fig. 2. Schematic plan of sustainable antibiotic bioremediation cycle in the study
PS: *Penicillium Simplicissimum*.

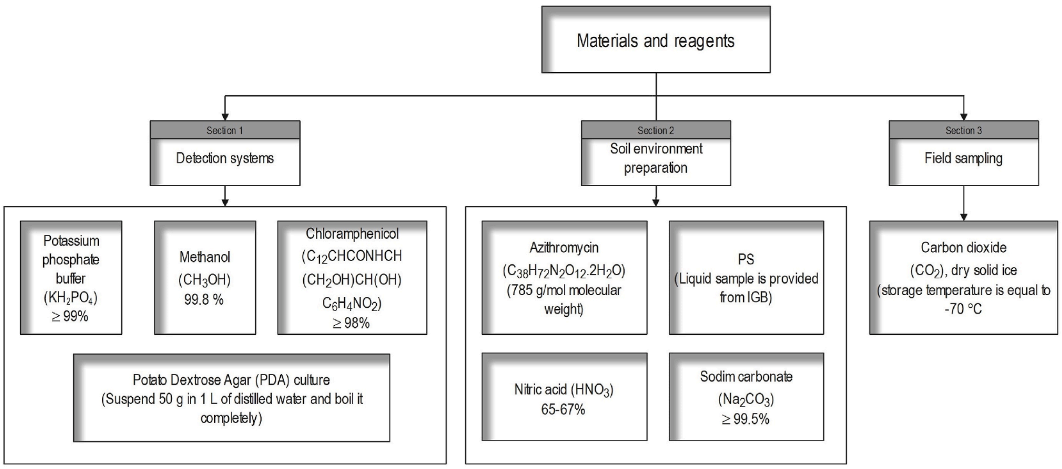

Fig. 3. Materials and regents used in the experiments.

the samples were measured at five points (12, 9, 3, 7, and 1.5 mg/g) with a mean amount of 6.5 mg/g, representing the simulated concentrations of the real accumulated pollution condition in the field.

The detection system used in the experiment includes several instruments from different manufacturers, such as the Waters Alliance 2695 HPLC from the USA, a pH and EC meter from Switzerland, an autoclave, and an incubator by WTW from Germany, and a temperature meter by HTC Instrument from India. Other equipment used includes a belt-driven air compressor1.5–7.5 kW made by REMEZA Co. from Germany, a plastic batch reactor by Kisker Co. from Germany, steel electrothermal elements by Element Co. from Iran, a sterile steel vessel by Kisker Co., from Germany, and a steel soil sampling device by Gilson Co. from USA. The study's controlling system uses Arduino hardware and adjusts temperature by coordinating thermal sensors and elements. The mobile phase for AZ measurement is adjusted with a concentration on isocratic flow, and the AZ detector is set on UV (210 nm) and fluorescence with corresponding emission (435 nm) and excitation wavelengths (365 nm). Fig. 4 elaborates on the information (including model numbers) of the instruments used to detect AZ, preparation of the soil medium, and samples from different points of the soil (Hussain et al., 2021).

Selective isolates of PS in Petri dishes with three repetitions for each sample containing Potato Dextrose Agar (PDA) were placed in a growth chamber at 28 °C and under light cycle conditions (12:12) for two weeks for insemination and transfer. After inoculation, spore suspension using distilled water sterile containing 0.1% Tween 80 was prepared. Purification of isolates was done by single spore method on a water-agar culture medium (WA) (Babaahmadi et al., 2018).

Fig. 5 provides a diagram of the key elements and sensors utilised in the laboratory-scale experiments, which were based on bioreactor design principles and environmental regulations. The lab-scale setup consists of two parts: online and offline systems. The offline system includes a fungal seedling, a pH meter (Metrohm 827, Metrohm AG, Switzerland), and manually adjusted air pressure (using piston compressor, Belt driven 1.5–7.5 kW, REMEZA Co., Germany). The soil layers used in the experiment are uniform and

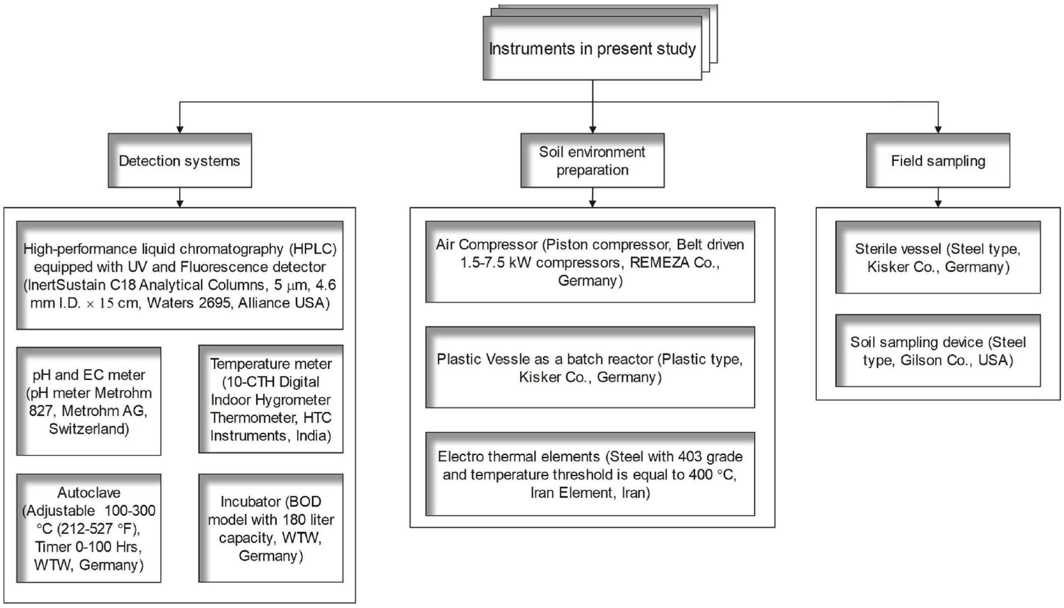

Fig. 4. Instruments and their specifications used in the experiments.

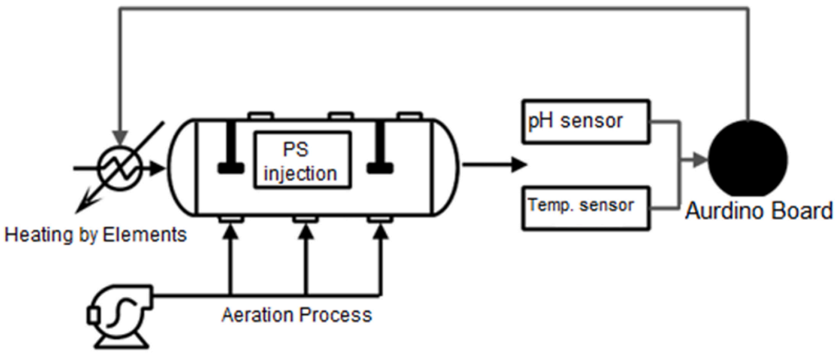

Fig. 5. Schematic layout of the lab-scale set up in the study.

have the same characteristics. Heating is controlled by solid elements and the temperature is monitored using an Arduino controller. The experiment package size 10 × 15 × 30 cm with a soil mass of 6.750 kg.

This study involves measuring AZ and culturing PS. The stages for the determination of AZ and PS culturing are described by Mohammadi et al. (2021). To measure AZ, the HPLC instrument (InterSustain C1 Analytical Columns, 5 µm, 4.6 mm I.D. × 15 cm, Waters 2695, Alliance, USA) must be adjusted with specific settings for the detector wavelengths, oven column temperature, and flow rate equal to 210 nm, 40 °C, and 0.8 mL/min, respectively and adding 50 mm Methanol-phosphate buffer 0.02 M (90:10, v/v).

To reach pH 8, phosphate acid was used, and the injection volume was set to 50 µL. A calibration curve was plotted with 5 data points resulting in an R^2 greater than 0.96. By 1 mg/g spiked concentration, the value of AZ is equal to 0.005 mg/g (the limit of AZ is equal to 0.005 mg/g). To culture the PS for seeding into the bio-engine, several steps are required. These include obtaining PS seeds from the IGB, creating a suspension of initial seeds with sterilised water under laboratory conditions, mixing the provided suspension with WA culturing environment in a sterilised hood, transferring the created seedlings to normal laboratory conditions after 12–18 h, and charging the seedlings onto PDA Petri dishes with suitable slops for complete growth in the incubator for 4–5 days. Finally, the cultivated PS can be stored in the laboratory's refrigerator at 4 °C for future experimental tests.

2.3. Optimisation and numerical models

2.3.2. Taguchi design

Taguchi is a useful tool for designing complex systems and finding the best set of designs for quality parameters, despite noise factors. Experiments are conducted using an experimental matrix known as the orthogonal array, and quality loss values are calculated for each quality characteristic. The quality loss function is categorised into three types, and the values are transformed into a signal-to-noise (S/N) ratio that shows the dispersion around the desired value. The larger S/N ratio indicates better quality, and it is calculated using Eq. (1) as:

$$S/N = -10 \log\left(\frac{1}{n}\sum_{i=1}^{n}\frac{1}{y_i^2}\right) \quad \text{Eq. 1}$$

where y_i = ith observed response value, n = the number of observations in a trial. The S/N ratio is a measure of the effect of control factor levels on the response quality. A higher S/N ratio corresponds to better performance of the response. Therefore, the optimal levels of parameters can be obtained by identifying the levels that result in the highest S/N ratios.

The Taguchi model is used to design experiments by determining parameter characteristics, defining levels, designing the orthogonal matrix, and inspecting results by desirability and S/N ratio (Klein et al., 2021). This study's experimental parameters include Temperature (*T*) (°C), Retention Time (*RT*) (day), pH, Aeration Intensity (*AI*) (m^3/h), and Microorganism to Food weight ratio (*M/F*) (mg/g) as influential parameters according to the literature. The Taguchi design method in MiniTab16 software is used to obtain the most efficient range of parameters, and the primary levels are set in Table 4. All experiments are initially conducted for 20 days, and AZ concentration is measured in both influent and effluent every five days from day five to day 100. The PS used in the bio-engine for AZ decontamination is fed by local agricultural waste from the municipal waste centre in Mashhad.

2.3.3. Response surface methodology (RSM)

RSM is a statistical tool used to predict the interactions between factors that may be difficult to observe or too complex to test experimentally. RSM provides a way to investigate the relationship between variables and a response variable or performance characteristic of a system under control. The relationship between the controlling variables ($X_1, X_2, \ldots, X_n$) and the response (Z) is represented by a function f, as shown in Eq. (2). In this equation, ε represents other sources of variables that are not included in the function f, which is assumed to have a normal distribution with a mean of zero and variance of σ^2. Therefore, the expected value of the response function is the f function.

$$Z = f(X_1, X_2, \ldots, X_n) + \varepsilon \quad \text{Eq. 2}$$

To simplify the estimation of the complicated f function, a polynomial equation based on experimental data can be used. This polynomial equation can estimate the response of the variables in points where there is insufficient experimental data. A second-order polynomial function, represented by Eq. (3) is commonly used as an estimation of the actual response surface around a desired point. This approach is known as response surface methodology and can help researchers understand the relationship between variables and the response (Sodhi and Singh, 2022).

$$Z = a_0 + a_1X_1 + a_2X_2 + \ldots + a_nX_n + a_{12} \times 1 \times {}_2 + a_{13} \times 1 \times {}_3 + \ldots + a_{1n}X_1X_n + a_{23} \times 2 \times {}_3 + a_{24} \times 2 \times {}_4 + \ldots + a_{2n}X_2X_n + \ldots + a_{(n-1)\ nXn-1}X_n + a_{11}X^2{}_1 + \ldots + a_{nn}X^2{}_n \quad \text{Eq. 3}$$

The ANOVA test is used to determine the significance of the regression (Salandez et al., 2022). Using RSM, researchers can predict the values of culture parameters at points where experimental data is lacking. In this study, the efficiency of the reactor in Fig. 5 is evaluated on a lab-scale setup using optimal conditions, and the resulting data is used in Design Expert 7 software to predict data for other points. These predicted values can be considered as the desired set of control variables based on the operating situation.

2.3.4. Machine learning algorithms

Prediction models based on ML are used in the study to estimate AZ degradation in soil. The performance of ML models can vary depending on the dataset and the specific problem being addressed. Therefore, it's recommended to evaluate multiple algorithms and compare their performance before selecting the most appropriate one for a specific application. As such, several factors were considered for selecting the most effective ML algorithms for this study, including the nature of the problem, available data, and prior experience. After careful consideration, IBK, Kstar, and LWL were selected for their suitability for classification and regression tasks with complex decision boundaries and non-linear relationships. The prediction models of these algorithms are developed using WEKA 3.9 software by training based on 70% of the experimental data and then validating based on the remaining 30% of the data. The main objective is to compare the performance of these methods for application to bioremediation processes. More details of modelling with these algorithms are outlined below.

2.3.3.1. Instance-based K (IBK) algorithm. The IBK algorithm with the *K* parameter falls into the category of regression and classification lazy algorithms. The IBK algorithm works by identifying similarities between instances and specifying the number of nearest neighbours to use when classifying a test instance. It can select the most suitable value of *K* by using cross-validation and distance

Table 4
The primary data of Taguchi design for being optimised.

Parameter	1	2	3
Temperature (°C)	24	28	32
Retention time (day)	20	40	60
pH	3	6	9
Aeration intensity (m^3/h)	8	14	20
Microbial/Food ratio (mg/g)	1	4	7

weighting, (Moayedi et al., 2019). Note that in WEKA software, IBK is based on cross-validation, which helps find the best value for K's nearest neighbour.

2.3.3.2. K-star algorithm. Kstar, another lazy learning algorithm, selects the most relevant features for classification using statistical methods based on the K nearest neighbour method and is suitable for datasets with many features. Unlike other instance-based learners, K-Star attempts to divide n data points into k clusters using an entropic distance measure. This involves computing the probability of transforming one instance into another, which requires measuring the distance between instances. To achieve this, the algorithm determines a finite set of transformations that map an instance into another and transforms an instance using a limited series of transformations starting at point 'a' and ending at 'b'. The K-Star computation is as follows:

$$K\left(y_i, n\right) = -\ln \acute{P}\left(y_i, n\right) \quad \text{Eq. 4}$$

where n = new data points attached to the most expected class y_i and $P' =$ the probability of the point i reaching point j through a random path.

2.3.3.2. Locally Weighted Learning algorithm. LWL, a non-parametric regression algorithm, assigns weights to training instances based on their distance from the query point and is suitable for regression tasks with non-linear relationships. prediction in LWL is based on local functions using a subset of data to replace a global function that result in faster predictions. More specifically, a local model is created for each point of interest based on the neighbouring data of the query point instead of a global model for the entire dataset. To satisfy this, each data point becomes a weighting factor that represents its influence on the prediction. This means that the closer a point is to the query point, the more weight it receives, making this method very accurate and allowing new training points to be added easily. If there is a continuous function f with noise ε, then the LWL cost function is as follows:

$$y = f(x) + \varepsilon \quad \text{Eq. 5}$$

$$G = \frac{1}{2} \sum w_i x_q \left(y_i - x_i \beta_q\right)^2 \quad \text{Eq. 6}$$

where x_q is the point of interest (or query point) which is the point where we want the prediction y_q. Labelled training data $D = \left\{\left(x_i, y_i\right) \middle| i = 1, 2, \ldots, n\right\}$ where each data point of x_i belongs to a corresponding y_i. w_i represents the weight of the corresponding set of (x_i, y_i) for the current prediction which is computed through a weighting function. β describes the regression coefficient of the linear model.

The algorithm aims to find the β in a way that minimises the G function for the current point of interest x_q. It is one of the main differences of this method to global least functions where β is dependent on the x_q and finding w_i through two these steps: (1) The distance function $d(x_i, x_q)$; $d = \sqrt{(x-q)\,D\,(x-q)}$, measures the relevance of the training points in the current prediction. This function receives two inputs and gives one number. D describes the distance metric which is an important parameter expressing the size and shape of the receptive field; and (2) The Kernel function $K(d)$; $K(d) = \exp(-d^2)$ gives out a weight for each distance value.

These three algorithms (IBK, Kstar, and LWL) are also specifically suitable for the AZ decontamination process due to a range of factors that are difficult to capture in a simple model. For example, the process may have many factors influencing the performance of fungi for which K-star is a suitable algorithm while other algorithms such as SVM and RF may be inappropriate for problems with complex decision boundaries or many input features.

2.3.5. Decision tree

After identifying the optimal conditions for the experiments, a decision tree (DT) is created to develop a smart control system (Amini et al., 2021; Gheibi et al., 2019). In this context, the DT serves as a dashboard for the decision support system. DTs are a simple modelling technique that represents a sequence of interventions over a period as a graphical tree-like structure. The tree has branches and leaves representing options between alternatives and outcomes, respectively. It consists of three parts (Fig. 6): the root node, which is the starting point of the tree; branches, which represent possible answers; and leaf nodes, where each branch ends and are shown in three types: decision nodes, chance nodes, and terminal nodes.

The DT structure produces a series of rules that explain the path from the root to a leaf of the DT. Each path represents a rule, and the leaf is labelled with the class in which the correct value of records is assigned. DTs have limitations in modelling decision problems but provide several advantages, such as visual aid that requires no further explanation and is easy to understand. They can also cover both quantitative and qualitative data and consider data sets that may contain errors or missing values. DTs are also convenient to draw and free of complicated computations.

3. Results and discussion

3.1. Mechanism of the bioremediation process

Fig. 7 illustrates the biodegradation mechanism of AZ through the *Penicillium Simplicissimum* (PS) bioremediation process and other fundamental concepts. The PS fungal cell walls are negatively charged due to the presence of various functional groups, such as carboxylic, phosphate, amine, or sulfhydryl, in different wall components such as hemicelluloses, pectin, and lignin (Fomina et al., 2007). The decomposition process is carried out through the transfer of electrons between O_2 and organic matter by fungus activities (Bell et al., 2011). The PS decomposes AZ compounds using hydrolase and free radical enzymes via the oxidation-reduction process (Dias et al., 2021).

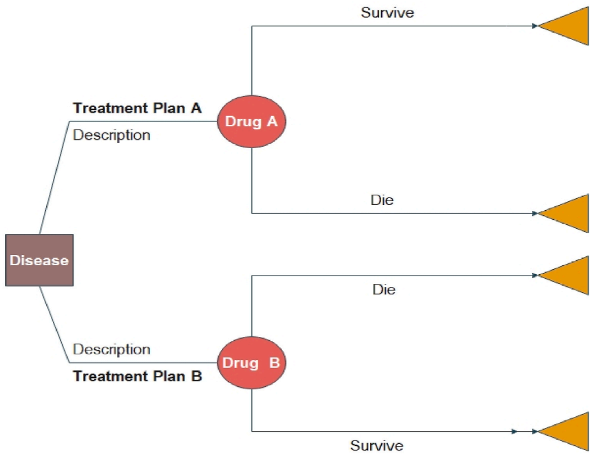

Fig. 6. A simple example of a decision tree.

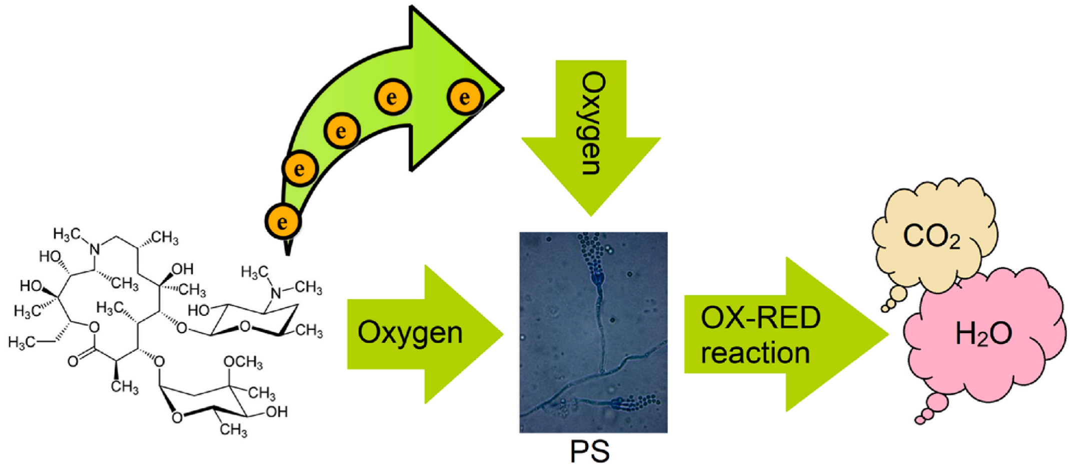

Fig. 7. The mechanism of azithromycin biodegradation by fungus activities in this study.

The degradation process of AZ involves a reduction half-reaction and an oxidation half-reaction catalysed by enzymes secreted by PS. The reduction half-reaction involves the transfer of a hydride from the substrate to the reactant, resulting in a binary complex between the two-electron reduced enzyme and the p-quinone methide of the substrate. In the oxidation half-reaction, the reduced AZ is oxidised by molecular oxygen with the concomitant hydration of the quinone methide intermediate. This process continues until CO_2 and H_2O are the final products of the reaction, which is called mineralisation. The main compounds generated during the degradation process of AZ are safe intermediate materials containing CO_2 and H_2O (Deblonde et al., 2011) while some degradation products are also potential to be created under aerobic conditions (Fig. 8).

The bioremediation of AZ by PS involves the formation of a binary complex between the enzyme and the substrate, which could be an important step in breaking down the antibiotic into less harmful forms (Fleming, 1946). Enzymes play a critical role in bioremediation, and PS may use them to break down AZ which is an antibiotic that can accumulate in the environment and potentially lead to negative effects on ecosystems (Clarke, 2015). Therefore, the input of the clean technology was AZ as a hazardous material in nature, and the outputs were CO_2 and H_2O as safe materials for the environment. Hence, the bioremediation process of AZ by PS can be assumed as a clean and green technology for soil protection.

3.2. Optimisation and mathematical modelling

3.3.2. Taguchi design analysis

The Taguchi model was used to determine the optimal parameters for bioremediation of AZ by PS. The result of the experiments designed by Taguchi method as illustrated in Fig. 9 and Table 5 shows that the best temperature range was 28 °C, and lower temperatures resulted in a steeper reduction in RP due to the increase in the hydrolysis rate of AZ. Retention time also affected RP, with a RT of 40 days resulting in the highest RP. The pH of the soil was critical for both antibiotic stability and fungus activity, with an acidic environment being better for removing AZ from the soil. Aeration intensity performed optimally at around 14 m^3/h, while the degradation rate improved as the M/F ratio increased.

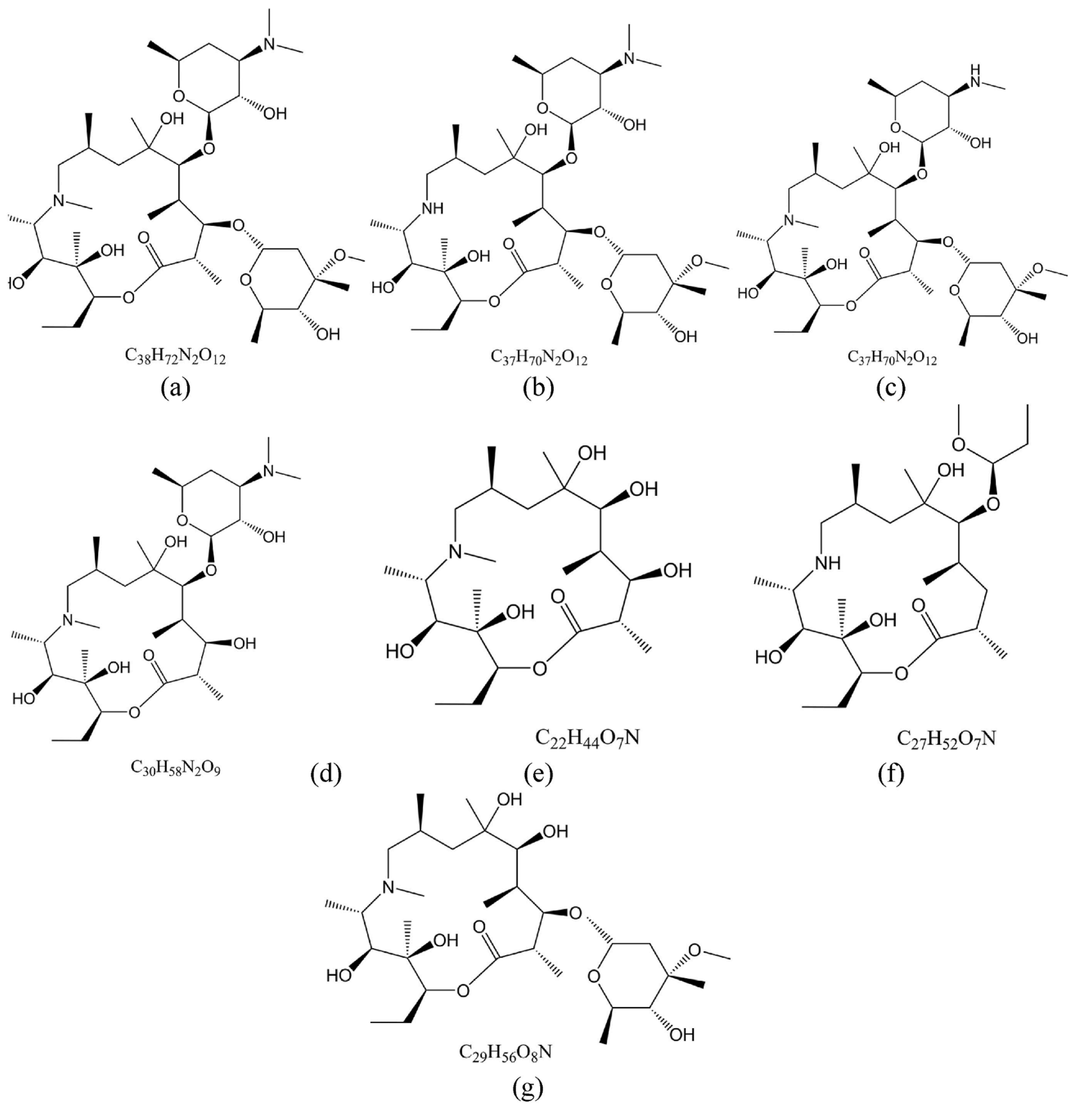

Fig. 8. (a) Azithromycin and the potential degradation products, (b) 9a-N-desmethyl azithromycin, (c) Desclandose azithromycin, (d, e, f) resulted from the removal of some other groups from azithromycin, (g) N-desmethyl azithromycin.

The Taguchi Orthogonal Array approach is designed to isolate the effects of selected variables, and adding extraneous variables outside the orthogonal array can introduce confounding effects that bias the results. Careful selection of variables is important, and if additional variables are included, a larger orthogonal array can be used for comparison. In such cases, a comparison can be made between the original orthogonal array and the expanded orthogonal array to assess the impact of the additional variables on the prediction model. However, adding variables outside the orthogonal array can make the process more complex and may not lead to better results. In this study, important features were extracted from the literature review (Mohammadi et al., 2021), and the optimisation process is done as per the operational optimum condition.

3.3.3. Response surface methodology

The RSM used the historical data analysis to determine the maximum degradation rate of AZ and the impact of various cultural conditions on the rate of degradation. As such, the Design-Expert 7.0.0 software was used to predict the response of AZ degradation rate to cultural conditions including temperature, retention time, aeration intensity, pH, and M/F ratio. Therefore, a quadratic polynomial equation was obtained based on the above parameters to predict the response of the AZ degradation rate. This equation considers the interactions between the different cultural conditions to provide a more accurate prediction of the degradation rate as follows:

$$P = 54.70 + 4.08A - 2.39B - 31.83C - 23.94D + 5.5E - 33.22AB - 12.61AC - 1.58AE + 1BC + 0.083BE - 2CE - 0.33DE - 5.81A^2 - 0.22E^2 \quad \text{Eq. 7}$$

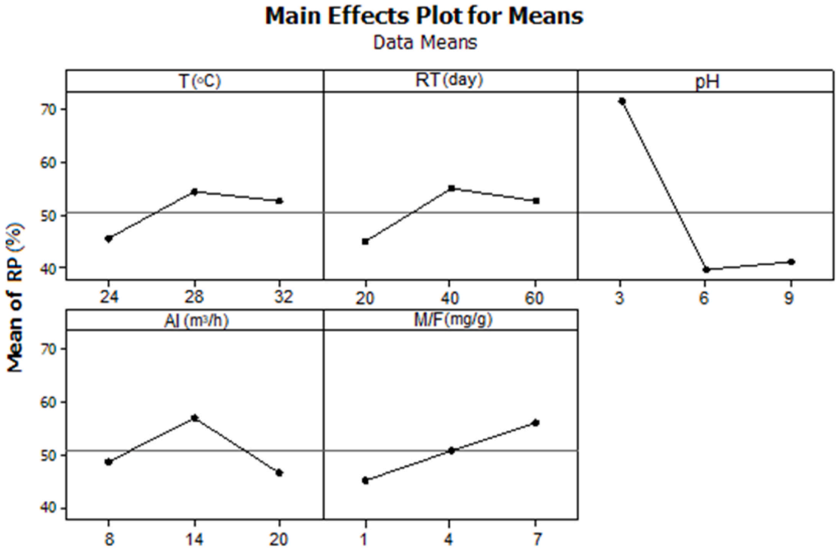

Fig. 9. Results of Taguchi design optimisation for Temperature (T), Retention time (RT), pH, Aeration intensity (AI) and Microbial/Food (M/F) ratio.

Table 5
Results of experimental trials based on the Taguchi design method.

T (°C)	RT (day)	pH	AI (m^3/h)	M/F (mg/g)	Performance RP (%)
24	20	3	8	1	48
24	20	3	8	4	57
24	20	3	8	7	69
24	40	6	14	1	38
24	40	6	14	4	45
24	40	6	14	7	51
24	60	9	20	1	27
24	60	9	20	4	34
24	60	9	20	7	39
28	20	6	20	1	31
28	20	6	20	4	32
28	20	6	20	7	36
28	40	9	8	1	42
28	40	9	8	4	48
28	40	9	8	7	50
28	60	3	14	1	76
28	60	3	14	4	84
28	60	3	14	7	89
32	20	9	14	1	40
32	20	9	14	4	44
32	20	9	14	7	45
32	40	3	20	1	66
32	40	3	20	4	73
32	40	3	20	7	81
32	60	6	8	1	38
32	60	6	8	4	41
32	60	6	8	7	45

Where P = the predicted value of AZ removal percentage and A, B, C, D, and E = coded factors of temperature, retention time, pH, aeration intensity, and M/F ratio, respectively. The statistical data of the quadratic polynomial equation indicates this is a significant equation ($p < 0.0001$ and $R^2 = 0.9887$). The regression data also demonstrate that temperature (A), pH (C), aeration intensity (D), M/F ratio (E), and the square term of temperature (A^2) were significant ($p < 0.0002$), whereas the square term of M/F and retention time (B) were insignificant. It is also evident that pH with the $p < 0.0001$ and the highest F-value is the most influential factor followed by aeration intensity. Table 6 also shows the result of the ANOVA analysis including interactions and the squared effects.

In other words, Eq. (7) represents a mathematical formula that can be used to predict the removal percentage (RP) of AZ in a bioremediation process using PS, based on certain operational factors. These factors include the initial concentration of AZ, the size of the fungi inoculum, and the duration of the process. This equation can be particularly useful for optimising bioremediation processes for AZ or similar pollutants. By incorporating the variables described in the equation, it can help predict the removal percentage of AZ

Table 6
Results of ANOVA analysis in this study.

Source	*Sum of Squares*	*Mean Square*	*F-Value*	*P-value Prob > F*
Model	7904.03	564.57	163.10	< 0.0001
Temperature (T)	92.34	92.34	26.67	0.0002
Retention time (RT)	25.68	25.68	7.42	0.0185
pH	4560.12	4560.12	1317.41	< 0.0001
Aeration intensity (AI)	1474.29	1474.29	425.92	< 0.0001
Microbial/Food ratio (M/F)	544.50	544.5	157.30	< 0.0001
T × RT	1655.57	1655.57	478.29	< 0.0001
T × pH	238.56	238.56	68.92	< 0.0001
T × AI	0.00			
T × M/F	30.08	30.08	8.69	0.0122
RT × pH	2.00	2.00	0.58	0.4619
RT × AI	0.00			
RT × M/F	0.08	0.08	0.02	0.8793
pH × AI	0.00			
pH × M/F	48.00	48.00	13.87	0.0029
AI × M/F	1.33	1.33	0.39	0.5464
T^2	115.56	115.56	33.38	< 0.0001
$(RT)^2$	0.00			
$(pH)^2$	0.00			
$(AI)^2$	0.00			
$(M/F)^2$	0.30	0.30	0.09	0.7748

without having to conduct time-consuming and expensive experimental trials. Moreover, this equation can be applied in various settings beyond the bioremediation process discussed in this study. It can be adapted to fit different experimental designs or operational factors, or it can be used as a foundation for developing more sophisticated models of bioremediation processes.

Fig. 10 depicts the results of some statistical tests according to the ANOVA computation as variance analysis for effective factors used in the prediction model. The sensitivity analysis reveals that the maximum efficiency occurs at a pH of approximately 3 when the retention time (RT), aeration intensity (AI), and M/F ratio are fixed. The plots show that the slope of pH and AI are

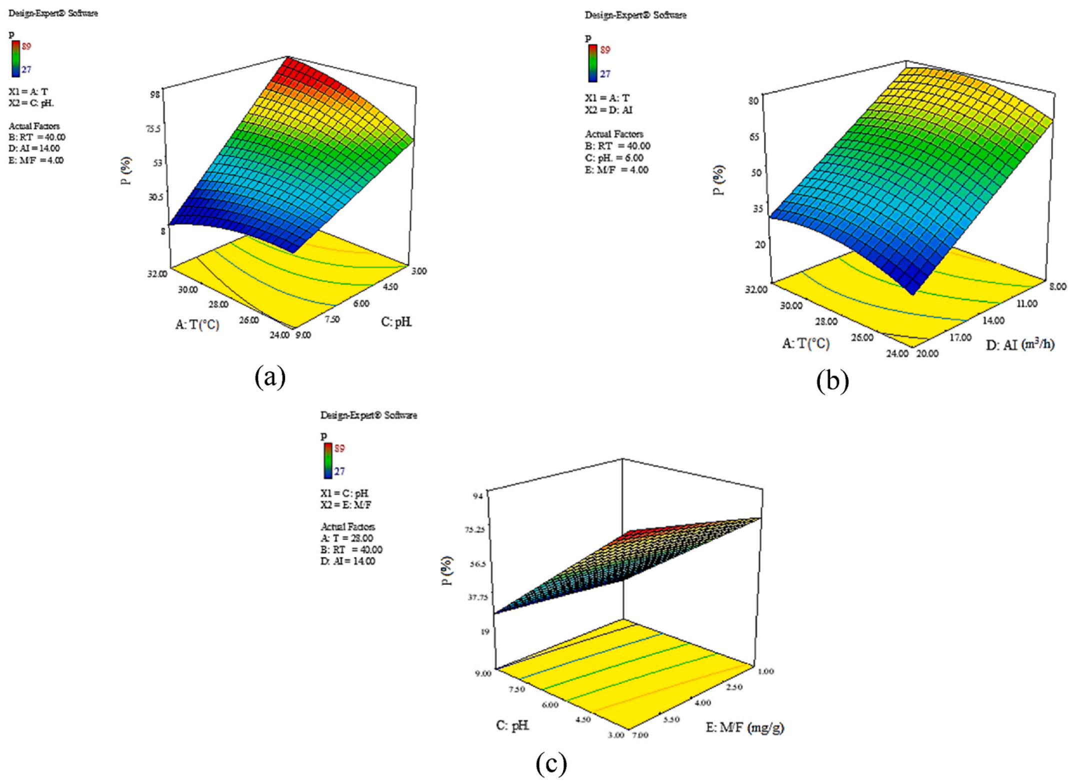

Fig. 10. The dual sensitive analysis of AZ bioremediation factors in this study a) Temperature (T) against pH, b) T against Aeration Intensity (AI) c) pH against Microbial/Food (M/F) ratio.

higher than the other parameters, indicating that the removal percentage (RP) is more sensitive to changes in these factors. These results are consistent with the outcome predicted by the RSM analysis. Table 7 provides some of the data resulting from the prediction model by the RSM analysis. Based on Fig. 10, it is evident that the aeration volume and pH control should receive constant attention during the operation of the system, and the operator should adjust them to optimal conditions with high precision under different conditions.

The data in Table 7 indicates that the best performance for AZ removal is achieved at a pH lower than 4. However, it is also possible to achieve high efficiency at higher pH levels, which are more practical to achieve in real-world settings due to the complexity of the test for reaching the pH of 3. Studies on AZ biodegradation in soil environments are limited, but Li et al. (2012) found that microbiomes in soil are most efficient at pH levels between 6.5 and 8.5 and temperatures between 25 and 45 °C. They also noted that the optimum pH for tetracycline degradation was around 6.5. Ding et al. (2016) investigated the simultaneous removal of 14 different antibiotics from soil using laccase oxidation and soil adsorption processes. They achieved over 70% efficiency in the first 15 min at pH 6 and a temperature of approximately 25 °C.

The optimum temperature range for AZ bioremediation under fungal activity is between 28 and 32 °C, which is consistent with expectations from Taguchi modelling. Retention time (RT) does not significantly affect the optimum cultural conditions and is effective for periods of more than 25 days. Anaerobic degradation of AZ is ineffective, according to Vermillion Maier and Tjeerdema (2017), who found that biotic degradation in aerobic environments leads to higher levels of AZ removal.

Based on the research findings, the suggested operating conditions for AZ bioremediation under fungal activity are outlined in the fifth row of Table 7. While the removal efficiency may not be the highest, it is at a desirable level, and the recommended cultural conditions, such as pH, are more practical to achieve. The pH level is closer to the natural pH of the soil, and AI is at a low level, reducing power usage and associated costs including the energy cost and depreciation/operating costs. The low M/F ratio means that cheap and abundant agricultural waste can be used as a food source, reducing waste and costs (El-Ramady et al., 2022). Finally, the low RT range reduces waiting time and allows for early response of the system.

The degradation of AZ by fungi in the soil can be represented by the following:

$$AZ + H_2O \rightarrow \text{Degradation products}$$

It should be mentioned that the moisture percentage of the examined soil in this study is kept between 30% and 45% which is enough for completing the reactions. The range of moisture percentage is related to the type of agriculture and land curing process in the case study. To accurately evaluate the effect of increasing the concentration of AZ on the rate of degradation, a comprehensive experimental study should be conducted that considers all the relevant factors and monitors the degradation process over time. This would involve measuring the concentration of AZ and its degradation products at different time intervals and under different operational conditions. The results of such a study could be used to optimise the bioremediation process and develop more efficient strategies for treating contaminated soils.

If the reaction is first order concerning AZ, the rate of the reaction is given by $rate = k[AZ]$, where k is the rate constant, and $[AZ]$ is the concentration of AZ. If the concentration of AZ is increased, the rate of the reaction will also increase proportionally, because the new $rate = k[2AZ] = 2k[AZ] = 2(old\ rate)$. This shows that the reaction rate is directly proportional to the concentration of AZ when the reaction is first ordered with respect to AZ. If the reaction is second order concerning water, the rate of the reaction is given by $rate = k\ [H_2O]^2$. If water concentration is increased, the rate of the reaction will increase proportionally to the square of the concentration of water, because the new $rate = k\ [(2H_2O)^2] = 4k\ [H_2O]^2 = 4(old\ rate)$. This shows that the reaction rate is proportional to the square of the concentration of water when the reaction is second order concerning water. Changes in the concentration of azithromycin and water can have a significant effect on the rate of degradation of azithromycin by fungi in soil. In this reaction, the rate of degradation is directly proportional to the concentration of azithromycin and proportional to the square of the concentration of water. However, it should be noted that the degradation of AZ by fungi is a complex process that may involve multiple reactions and intermediates. Therefore, the kinetics of the degradation process may not always follow a simple first-order or second-order rate law. The actual rate of degradation may depend on various factors, including the type of fungus used, the initial concentration of AZ, the pH, temperature, moisture content, and the presence of other pollutants or organic matter in the soil. It is important to note that the specific reaction mechanism and the environmental conditions in the soil may also play a role in determining the rate of the reaction. Therefore, changing in concentrations of different elements in the reaction, the rate is changed, and operational features are considered constant approximately because they are related to the origin of the applied fungi and its interactions with AZ.

Table 7
The optimisation results obtained from the RSM analysis.

No.	T (°C)	RT (day)	pH	AI (m^3/h)	M/F (mg/g)	RP (%)
1	29.44	25.88	3.03	13.64	4.63	100
2	31.53	25.83	4.02	14.47	2.13	99.79
3	28.98	45.1	3.42	8.73	1.74	97.96
4	30.95	41.78	3.1	13.76	5.91	96.67
5	31.1	28.21	5.52	8.55	1.59	95.39
6	31.98	25.71	6.39	8.04	1.09	92.28

3.3. Machine learning prediction modelling

The results of the ML models (IBK, KStar, and LWL algorithms) for predicting the bioremediation of AZ under PS degradation are presented in Table 8. All the ML models have correlation coefficients above the acceptance range. However, the IBK with a correlation coefficient of 0.95 outperforms the other two models with high accuracy and more confidence. Furthermore, a correlation coefficient of 0.94 has been achieved through the KStar model which means a close accuracy to the IBK simulation. This suggests that IBK and KStar algorithms may be more suitable for predicting the bioremediation of AZ under PS degradation, while LWL may not be as accurate with a correlation coefficient of 0.89. The value of these prediction models is better understood by looking at the complexity, cost, and time of conducting the experiments. However, it is important to conduct further testing and validation to confirm the reliability and generalisability of these models as well as considering other factors such as interpretability, scalability, and computational efficiency when selecting an ML algorithm for a specific application.

Several studies have used various ML algorithms to predict the behaviour of bio-engine systems. For example, Mohammadi et al. (2021) used RF, ANFIS, and RT algorithms to predict amoxicillin removal efficiency from soil, achieving correlation coefficients of 0.97, 0.95, and 0.99, respectively. Amiri et al. (2022) employed an M5 tree model to predict AZ removal efficiency from aqueous solutions, achieving a correlation coefficient of 0.946 and RMSE of 9.89%. Mojiri et al. (2020) used an artificial neural network to predict the removal efficiency of ciprofloxacin in wastewater, achieving $R^2 > 0.99$. Zhu et al. (2021) investigated the adsorption capacity of antibiotics on carbon-based adsorbents, finding that random forest-based algorithms performed better than other models, with the specific surface area of adsorbents being highly important. Lastly, Arab et al. (2022) used ANN and ANFIS approaches to predict the experimental data for removing cephalexin from the water and found these models with high accuracy, achieving accuracy of 88.21% and 93.87%, respectively, at a pH of 6.14.

The study highlights the benefits of using AI in predicting the performance of a system accurately without conducting costly and time-consuming tests. In other words, if this system undergoes changes in operation for any reason; Using the methods of *AI* and the performance of the operator to adjust the parameters, the soft ML-based system forecasted the removal efficiency of AZ. The ML algorithms used in this study collected data via the results of optimised solutions from Taguchi runs. The size of the data entered in ML modelling is the same as the data derived from Taguchi simulations. However, the ML algorithms may not perform well when used to make predictions outside of that range mainly because the model may not be able to accurately capture the underlying relationships between the variables being modelled when applied to data within the training range. This should be considered as a constraint of *ML* models. Note that as experiments are based on Taguchi's design, the optimal situation is necessarily among the experiments that have taken place.

Furthermore, RSM prediction modelling may outperform ML algorithms due to its ability to model complex relationships between variables and response variables, and its capacity to optimise the system being studied. RSM can also provide a clear understanding of the underlying mechanisms driving the system, making it easier to identify the most important variables and interactions. In contrast, ML algorithms may struggle to capture complex interactions and can be opaque, making it difficult to understand why a particular prediction is made.

3.4. Bioremediation control system

The DT modelling in Fig. 11 shows the influential parameters for the bioremediation process and how they should be controlled. The bioremediation process can be maintained at a high-efficiency level by adjusting the parameters to their optimised values using the dashboard. The four most important parameters are M/F, pH, T, and AI, which are adjusted in parallel based on the ANOVA analysis. Reaction time is then controlled at the optimum value of 25 days, followed by other effective factors organised in the DT. The DT is based on a linear control system and can help maintain the process at high efficiency.

The process of AZ bioremediation involves two types of factors: significant and insignificant. The insignificant factor, which is RT, does not require specific optimisation and only needs to be more than 25 days. On the other hand, the significant factors need to be adjusted accurately. According to ANOVA analysis, pH is the most influential factor that needs to be monitored consistently. The optimised range for pH is 5.5, and if the pH is below this level, alkaline compounds should be added to the soil. Conversely, acidic compounds should be added to raise the pH if it is too high. The modification can be calculated through the error functions f_1 and f_2. Once the optimum pH is achieved, the system moves on to adjust AI. Functions f_3 and f_4 are used to calculate the difference in current aeration intensity and adjust AI to achieve optimum degradation. The condition is being constantly checking and further passes to the next cultural parameter which is the M/F ratio. The same process is repeated for M/F ratio and temperature, and functions f_5, f_6, f_7, and f_8 are used to amend the specified parameters respectively. This whole process is constantly repeated to ensure that the optimum condition is maintained throughout the project.

Table 8
The outcomes of prediction models through IBK, KStar, and LWL algorithms.

Parameters of ML algorithm	IBK	KStar	LWL
Correlation coefficient	0.95	0.94	0.89
Mean absolute error	4.07	4.45	6.28
Root mean squared error	5.099	5.55	8.04
Relative absolute error (%)	28.23	30.83	43.50
Root relative squared error (%)	28.85	31.40	45.46

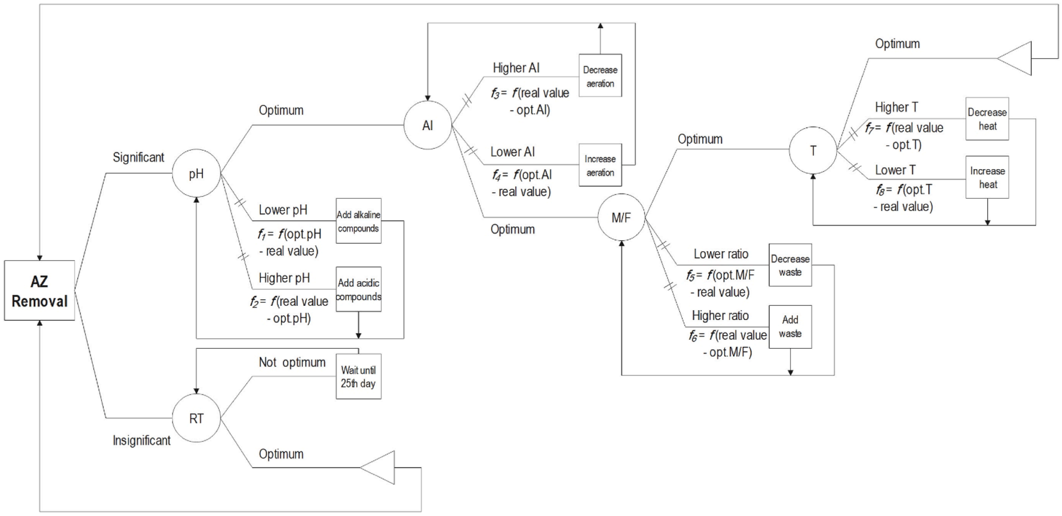

Fig. 11. The decision tree based on RSM analysis.

3.5. Economic evaluation of the system

To implement the bioremediation process for the degradation of AZ in soil in real-world scenarios, it is important to consider its economic evaluation. The process can be assessed using frameworks for smart sustainable operation of systems, although there is no specific framework for the exact economic assessment of biological methods. Scientific knowledge and experiences can be employed to help with the real field operation of the process.

The economic evaluation of the bioremediation process for AZ degradation in soil as illustrated in Fig. 12 indicates that operational costs (37%) are more significant than investment costs (63%). Therefore, the bioremediation approach is appropriate for treating antibiotic contamination in soil, with a focus on operational costs. It should be noted that the main challenge of biological decontamination is related to operational costs, and this challenge is addressed by the investigated bioremediation process, as shown by the outcomes of other studies (Ghadami et al., 2021; Gheibi et al., 2021; Gheibi et al., 2021, 2021; Mirabi et al., 2019). The investment costs for the bioremediation process include a fee for transference, cost of experimental tests, setup preparation, and organisational costs. On the other hand, the operational costs consist of the cost of human resources, sampling practices, energy price, and material consumption.

By using the obtained costs provided for lab scale and assuming a scale-up factor of 10, an estimation of the costs involved in the full-scale implementation of the bioremediation technology can be obtained based on calculations given in the appendix. Based on these calculations, the total estimated cost for full-scale implementation is $23,865. However, it is important to note that these costs are based on the financial conditions of the case study in Iran, where human resource and energy costs are much lower than in similar cases in Western countries.

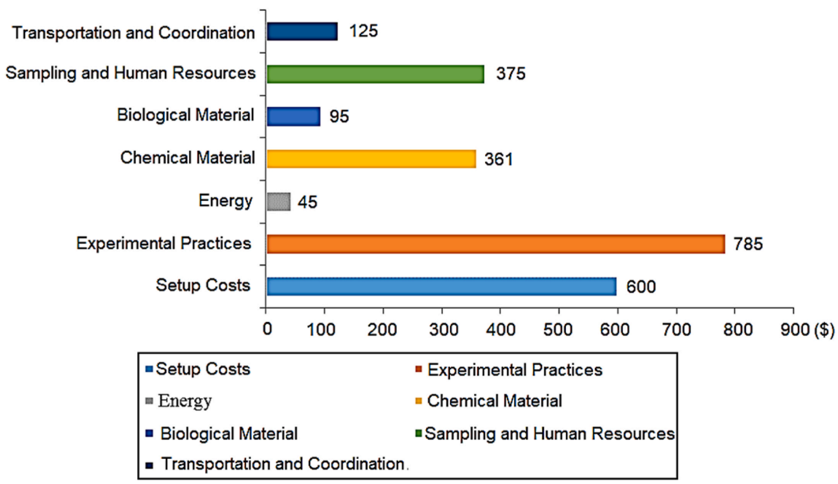

Fig. 12. Cost-effective analysis Economic value in $ for different stages of the experiment in this study.

Table 9
The mechanism of azithromycin contamination decomposition by different strains of Penicillium.

Strain type	Description	Decontamination mechanism	Reference
Penicillium chrysogenum	It is commonly found in soil, and it is applied as a source of penicillin.	Breaking down the β-lactam ring structure of azithromycin by β-lactamases enzyme. It also decomposes molecules by extracellular enzymes, such as proteases and lipases.	Leitão et al. (2007)
Penicillium roqueforti	It is used to produce different types of cheese widely.	Breaking down the complex organic molecules in azithromycin	Chang et al. (1996)
Penicillium notatum	It is the main source of penicillin and, it is used for the production	Breaking down the complex organic molecules in azithromycin by enzymes	Bujacz et al. (1995)
Penicillium camemberti	It is used to produce soft cheeses.	Changing the structure of azithromycin by using proteases and lipases enzymes	Lessard et al. (2014)
Penicillium glaucum	It is utilised due to the product's hard cheeses.	Applying proteases and lipases enzymes due to the degraded structure of azithromycin	Hugo (1991)
Penicillium candidum	It is applied to produce blue cheese	Using both proteases and lipases and extracellular enzymes for changing the formulation of azithromycin	Lessard et al. (2014)

According to fundamental equations and models, the bioremediation project is expected to generate an annual profit of $237,163 and a total revenue of $250,000 per year. The net present value (NPV) and internal rate of return (IRR) of the project will depend on the discount rate used and the actual costs and revenues incurred during the project's lifetime. It is worth noting that the total annual cost of the project is higher than the annual operational costs alone, which supports the notion that investment costs are higher than operational costs in environmental bioprocesses.

Finally, it should be mentioned that a comparison with another research on the decontamination of *amoxicillin* by *Aspergillus Flavus* fungi in the soil environment (Mohammadi et al., 2021) reveals differences in energy values (AI difference), experimental practices (difference in protocols), and chemical materials (difference in roadmap of both studies), which contribute to cost differences.

Moayedi et al. (2019) evaluated AZ biodegradation and sorption by considering the effects of operational parameters. The study conveyed that aerobic bioremediation is the best option between aerobic degradation, anaerobic decomposition, and sorption procedures. However, the bioremediation reaction time in their study is much slower (about 150 days) than PS fungi (at least 25 days) as per the achievements of this study. Another study by Hanamoto and Ogawa (2019) presented a smart system for predicting the sorption of AZ onto organic and inorganic compounds in sediments. They evaluated both ion exchange and adsorption processes. However, the main disadvantage of their achievements is related to regeneration essentially after completing the surface capacity. However, this study continuously conducts antibiotic decontamination with the application of bioremediation.

The bioactivities of various strains of *Penicillium* in the process of decontamination are similar, and their characteristics and decontamination mechanisms summarised in Table 9. It is worth noting that all strains can produce enzymes such as proteases and lipases, which break down the complex organic molecules in azithromycin, and they also produce extracellular enzymes that can degrade the molecule. However, the biodegradation mechanism of *Penicillium chrysogenum* differs slightly. Therefore, based on theoretical evaluations, the ML computations, and optimum operational conditions developed in this study, it is possible to apply them to other strains. However, experimental practices and verification are necessary to confirm this hypothesis.

4. Practical applications and prospects

To improve the efficiency of decontaminating antibiotics from soil, the study recommends a combination of adsorption and bioremediation techniques, with bio-adsorption being considered as a potential alternative to conventional adsorption methods. Further research could be conducted to determine the individual contributions of biodegradation, adsorption, aeration, and heating in the decontamination process. Furthermore, studying the kinetics of fungal activity could provide more precise insights into the bioremediation mechanism. Although the study focused on the decontamination of azithromycin by *Penicillium* fungus, future research should also evaluate the competitive effects of co-existing antibiotics such as *amoxicillin* and *azithromycin*, to determine which antibiotic exhibits greater affinity for degradation in soil. In other words, these measures would improve the sustainability of decontaminating antibiotics from soil resources.

5. Conclusions

This study focused on developing a sustainable and eco-friendly approach for removing antibiotics from soil samples using bioactivities, without the need for any hazardous chemicals. The study also explored the potential of ISWM as a novel approach for purifying hazardous materials in the environment. The study found that the M/F ratio was the most significant factor in removing AZ from soil samples and identified the optimal temperature, pH, AI, and M/F ratio for AZ removal. The study found that the IBK model had the highest accuracy in predicting optimal conditions for AZ removal. The study also conducted an economic evaluation of the system and found that 63% of the cost was associated with the investment, while 37% was associated with the operation. The study recommended integrating adsorption and bioremediation techniques for the purification of antibiotics from soil resources, with bio-adsorption being evaluated as an alternative to simple adsorption processes.

CRediT authorship contribution statement

Farhad Mahmoudi Jalali and Mohammad Gheibi devised the project, the main conceptual ideas and proof outline. **Farhad** and **Benyamin Chahkandi** worked out almost all of the experiments, technical details, mathematical formulation and performed the simulations. **Benyamin** contributed to do comparison of this study's outcomes with other researches. **Kourosh Behzadian and Mohammad Gheibi** supervised the designing the methodology, findings of this work and they worked out the validation, editing and reviewing of paper. **Mohammad Eftekhari** was in charge of supervising experiments and experimental analytical methods and **Luiza Campos** was the supervisor and proof reader of the whole work. All authors discussed the results and contributed to the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scp.2023.101127.

References

Abubakr, M., Abbas, A.T., Tomaz, I., Soliman, M.S., Luqman, M., Hegab, H., 2020. Sustainable and smart manufacturing: an integrated approach. Sustainability 12 (6), 2280.

Ahumada-Rudolph, R., Novoa, V., Becerra, J., Cespedes, C., Cabrera-Pardo, J.R., 2021. Mycoremediation of oxytetracycline by marine fungi mycelium isolated from salmon farming areas in the south of Chile. Food Chem. Toxicol. 152, 112198.

Akbarian, H., Jalali, F.M., Gheibi, M., Hajiaghaei-Keshteli, M., Akrami, M., Sarmah, A.K., 2022. A sustainable Decision Support System for soil bioremediation of toluene incorporating UN sustainable development goals. Environ. Pollut. 119587.

Akhtar, M.S., Abdullah, S.N.A., 2014. Mass production techniques of arbuscular mycorrhizal fungi: major advantages and disadvantages: a review. Biosci Biotechnol Res Asia 11, 1199–1204.

Al Masud, M.A., Annamalai, S., Shin, W.S., 2023. Remediation of ciprofloxacin in soil using peroxymonosulfate activated by ball-milled seaweed kelp biochar: performance, mechanism, and phytotoxicity. Chem. Eng. J. 465, 142908.

Amini, M.H., Arab, M., Faramarz, M.G., Ghazikhani, A., Gheibi, M., 2021. Presenting a soft sensor for monitoring and controlling well health and pump performance using machine learning, statistical analysis, and Petri net modeling. Environ. Sci. Pollut. Res. 1–17.

Amiri, M.J., Bahrami, M., Rajabi, S., 2022. Assessment of M5 model tree for prediction of azithromycin antibiotic removal by multi-wall carbon nanotubes in a fixed-bed column system. AQUA—Water Infrastructure, Ecosystems and Society 71 (4), 533–545.

Anderson, M., Schulze, K., Cassini, A., Plauchoras, D., Mossialos, E., 2020. Strengthening implementation of antimicrobial resistance national action plans. Eur. J. Publ. Health 30 (Suppl. ment_5). . ckaa165-1200.

Arab, M., Faramarz, M.G., Hashim, K., 2022. Applications of computational and statistical models for optimizing the electrochemical removal of cephalexin antibiotic from water. Water 14 (3), 344.

Babaahmadi, G., Mehrabi-Koushki, M., Hayati, J., 2018. Allophoma hayatii sp. nov., an undescribed pathogenic fungus causing dieback of Lantana camara in Iran. Mycol. Prog. 17 (3), 365–379.

Badia-Fabregat, M., Lucas, D., Pereira, M.A., Alves, M.A., Pennanen, T., Fritze, H., Rodríguez-Mozaz, S., Barceló, D., Vicent, T., Caminal, G., 2016. Continuous fungal treatment of non-sterile veterinary hospital effluent: pharmaceuticals removal and microbial community assessment. Appl. Microbiol. Biotechnol. 100, 2401–2415.

Bell, K.Y., Wells, M.J., Traexler, K.A., Pellegrin, M.L., Morse, A., Bandy, J., 2011. Emerging pollutants. Water Environ. Res. 83 (10), 1906–1984.

Bellaouchi, R., Abouloifa, H., Rokni, Y., Hasnaoui, A., Ghabbour, N., Hakkou, A., Bechchari, A., Asehraou, A., 2021. Characterization and optimization of extracellular enzymes production by Aspergillus Niger strains isolated from date by-products. Journal of Genetic Engineering and Biotechnology 19 (1), 1–8.

Bicudo, B., van Halem, D., Trikannad, S.A., Ferrero, G., Medema, G., 2021. Low voltage iron electrocoagulation as a tertiary treatment of municipal wastewater: removal of enteric pathogen indicators and antibiotic-resistant bacteria. Water Res. 188, 116500.

Braschi, I., Blasioli, S., Fellet, C., Lorenzini, R., Garelli, A., Pori, M., et al., 2013. Persistence and degradation of new b-lactam antibiotics in the soil and water environment. Chemosphere 93, 152–159. https://doi.org/10.1016/j.chemosphere.2013.05.016.

Buchicchio, A., Bianco, G., Sofo, A., Masi, S., Caniani, D., 2016a. Biodegradation of carbamazepine and clarithromycin by Trichoderma harzianum and Pleurotus ostreatus investigated by liquid chromatography – high-resolution tandem mass spectrometry (FTICR MS-IRMPD). Sci. Total Environ. 55, 733–739. https://doi.org/10.1016/j.scitotenv.2016.03.119.

Buchicchio, A., Bianco, G., Sofo, A., Masi, S., Caniani, D., 2016b. Biodegradation of carbamazepine and clarithromycin by Trichoderma harzianum and Pleurotus ostreatus investigated by liquid chromatography–high resolution tandem mass spectrometry (FTICR MS-IRMPD). Sci. Total Environ. 557, 733–739.

Bujacz, B., Wieczorek, P., Krzysko-Lupicka, T., Golab, Z., Lejczak, B., Kavfarski, P., 1995. Organophosphonate utilization by the wild-type strain of Penicillium notatum. Appl. Environ. Microbiol. 61 (8), 2905–2910.

Camacho-ArÃ© valo, R., Eymar, E., GÃ³mez, A., Mayans, B., AntÃ³n-Herrero, R., GarcÃa-Delgado, C., 2021,. Spent mushroom substrates as biofilter to reduce antibiotics (tetracyclines and sulfonamides) from wastewaters to be used in hydroponic cultures. InIII International Symposium. on Soilless Culture and Hydroponics: Innovation and Advanced Technology for Circular Horticulture 1321, 63–70.

Carraro, C.D.F.F., Loures, C.C.A., de Castro, J.A., 2022. Microalgae bioremediation and CO_2 fixation of industrial wastewater. Cleaner Engineering and Technology 8, 100466.

Carter, L.J., Harris, E., Williams, M., Ryan, J.J., Kookana, R.S., Boxall, A.B.A., 2014. Fate and uptake of pharmaceuticals in soil-plant systems. J. Agric. Food Chem. 62, 5955–5963. https://doi.org/10.1021/jf404282y.

Chang, S.C., Yeh, S.F., Li, S.Y., Lei, W.Y., Chen, M.Y., 1996. A novel secondary metabolite relative to the degradation of PR toxin by Penicillium roqueforti. Curr. Microbiol. 32, 141–146.

Chokshi, A., Sifri, Z., Cennimo, D., Horng, H., 2019. Global contributors to antibiotic resistance. J. Global Infect. Dis. 11 (1), 36.

Clarke, H.T. (Ed.), 2015. Chemistry of Penicillin, vol. 2167. Princeton University Press.

Cruz-Morató, C., Ferrando-Climent, L., Rodriguez-Mozaz, S., Barceló, D., Marco-Urrea, E., Vicent, T., Sarrà, M., 2013. Degradation of pharmaceuticals in non-sterile urban wastewater by Trametes versicolor in a fluidizedbed bioreactor. Water Res. 47, 5200–5210.

Čvančarová, M., Moeder, M., Filipová, A., Cajthaml, T., 2015. Biotransformation of fluoroquinolone antibiotics by ligninolytic fungi–metabolites, enzymes, and residual

antibacterial activity. Chemosphere 136, 311–320.
Cycoń, M., Mrozik, A., Piotrowska-Seget, Z., 2019. Antibiotics in the soil environment—degradation and their impact on microbial activity and diversity. Front. Microbiol. 10, 338.
Deblonde, T., Cossu-Leguille, C., Hartemann, P., 2011. Emerging pollutants in wastewater: a review of the literature. Int. J. Hyg Environ. Health 214 (6), 442–448.
Del Álamo, A.C., Pariente, M.I., Molina, R., Martínez, F., 2022. Advanced bio-oxidation of fungal mixed cultures immobilized on rotating biological contactors for the removal of pharmaceutical micropollutants in a real hospital wastewater. J. Hazard Mater. 425, 128002.
Dias, R., Sousa, D., Bernardo, M., Matos, I., Fonseca, I., Cardoso, V.V., Carneiro, R.N., Silva, S., Fontes, P., Daam, M.A., Maurício, R., 2021. Study of the potential of water treatment sludges in the removal of emerging pollutants. Molecules 26 (4), 1010.
Ding, H., Wu, Y., Zou, B., Lou, Q., Zhang, W., Zhong, J., Lu, L., Dai, G., 2016. Simultaneous removal and degradation characteristics of sulfonamide, tetracycline, and quinolone antibiotics by laccase-mediated oxidation coupled with soil adsorption. J. Hazard Mater. 307, 350–358.
Dolliver, H., Kumar, K., Gupta, S., 2007. Sulfamethazine uptake by plants from manure-amended soil. J. Environ. Qual. 36, 1224. https://doi.org/10.2134/jeq2006.0266.
El-Ramady, H., Brevik, E.C., Bayoumi, Y., Shalaby, T.A., El-Mahrouk, M.E., Taha, N., Elbasiouny, H., Elbehiry, F., Amer, M., Abdalla, N., Prokisch, J., 2022. An overview of agro-waste management in light of the water-energy-waste nexus. Sustainability 14 (23), 15717.
Fakhri, H., Shahi, A., Ovez, S., Aydin, S., 2021. Bioaugmentation with immobilized endophytic Penicillium restrictum to improve quorum quenching activity for biofouling control in an aerobic hollow-fiber membrane bioreactor treating antibiotic-containing wastewater. Ecotoxicol. Environ. Saf. 210, 111831.
Fasihi, M., Tavakkoli-Moghaddam, R., Najafi, S.E., Hajiaghaei-Keshteli, M., 2021. Developing a Bi-objective mathematical model to design the fish closed-loop supply chain. Int. J. Eng. 34 (5), 1257–1268.
Fleming, A., 1946. Penicillin. Its Practical application.*Penicillin. Its Practical application.*Fleming, A., 1946. Penicillin. Its Practical Application. Penicillin. Its Practical Application.
Fomina, M., Charnock, J., Bowen, A.D., Gadd, G.M., 2007. X-ray absorption spectroscopy (XAS) oftoxic metal mineral transformations by fungi. Environ. Microbiol. 9, 308–321.
Gao, N., Liu, C.X., Xu, Q.M., Cheng, J.S., Yuan, Y.J., 2018. Simultaneous removal of ciprofloxacin, norfloxacin, sulfamethoxazole by co-producing oxidative enzymes system of Phanerochaete chrysosporium and Pycnoporus sanguineus. Chemosphere 195, 146–155.
Ghadami, N., Deravian, B., Pouresmaeil, H., Aghlmand, R., Gheibi, M., 2021a. Smartening the movement path of municipal garbage trucks using genetic algorithm with emphasis on economic-environmental indicators. Ann Environ Sci Toxicol 5 (1), 80–85.
Ghadami, N., Gheibi, M., Kian, Z., Faramarz, M.G., Naghedi, R., Eftekhari, M., Fathollahi-Fard, A.M., Dulebenets, M.A., Tian, G., 2021b. Implementation of Solar Energy in Smart Cities Using an Integration of Artificial Neural Network, Photovoltaic System, and Classical Delphi Methods. Sustain Cities Soc, 103149.
Gheibi, M., Chahkandi, B., Behzadian, K., Akrami, M., Moezzi, R., 2023. Evaluation of ceramic water filters' performance and analysis of managerial insights by SWOT matrix. Environmental Industry Letters 1 (1), 1–9.
Gheibi, M., Chahkandi, B., Kian, Z., Takhtravan, A., Aghlmand, R., 2021a. Sensitivity analysis of parameters affecting suspended growth in industrial wastewater treatment plants; with emphasis on economic performance criteria. Ann Environ Sci Toxicol 5 (1), 38–44.
Gheibi, M., Dandansaz, H.K., Kian, Z., Aghlmand, R., 2021b. Economic evaluation of different biological municipal wastewater treatment systems and implementation of AHP method based on operating costs. Ann Sys Biol 4 (1), 21–25.
Gheibi, M., Emrani, N., Eftekhari, M., Akrami, M., Abdollahi, J., Ramezani, M., Sedghian, A., 2019a. Experimental investigation and mathematical modeling for microbial removal using potassium permanganate as an oxidant—case study: water treatment plant No. 1, Mashhad, Iran. Environ. Monit. Assess. 191 (3), 141.
Gheibi, M., Karrabi, M., Eftekhari, M., 2019b. Designing a smart risk analysis method for gas chlorination units of water treatment plants with combination of Failure Mode Effects Analysis, Shannon Entropy, and Petri Net Modeling. Ecotoxicol. Environ. Saf. 171, 600–608.
Gheibi, M., Pouresmaeil, H., Akrami, M., Kian, Z., Takhtravan, A., Mohammadi, M., 2021c. Presenting a novel approach for designing chlorine contact reactors by combination of genetic algorithm with non-linear condition functions, simulated annealing algorithm, pattern search algorithm and experimental efforts. Ann Environ Sci Toxicol 5 (1), 12–17.
Hamscher, G., Sczesny, S., Höper, H., Nau, H., 2002. Determination of persistent tetracycline residues in soil fertilized with liquid manure by highperformance liquid chromatography with electrospray ionization tandem mass spectrometry. Anal. Chem. 74, 1509–1518. https://doi.org/10.1021/ac015588m.
Hanamoto, S., Ogawa, F., 2019. Predicting the sorption of azithromycin and levofloxacin to sediments from mineral and organic components. Environ. Pollut. 255, 113180.
Harms, H., Schlosser, D., Wick, L.Y., 2011. Untapped potential: exploiting fungi in bioremediation of hazardous chemicals. Nat. Rev. Microbiol. 9, 177–192.
Hu, L., Wu, X., Liu, Y., Meegoda, J.N., Gao, S., 2010a. Physical modeling of air flow during air sparging remediation. Environ. Sci. Technol. 44 (10), 3883–3888.
Hu, X., Zhou, Q., Luo, Y., 2010b. Occurrence and source analysis of typical veterinary antibiotics in manure, soil, vegetables and groundwater from organic vegetable bases, northern China. Environ. Pollut. 158, 2992–2998. https://doi.org/10.1016/j.envpol.2010.05.023.
Hugo, W.B., 1991. The degradation of preservatives by microorganisms. Int. Biodeterior. 27 (2), 185–194.
Hussain, A., Afzal, O., Altamimi, A.S., Ali, R., 2021. Application of green nanoemulsion to treat contaminated water (bulk aqueous solution) with azithromycin. Environ. Sci. Pollut. Res. 1–11.
Irshad, S., Xie, Z., Mehmood, S., Nawaz, A., Ditta, A., Mahmood, Q., 2021. Insights into conventional and recent technologies for arsenic bioremediation: a systematic review. Environ. Sci. Pollut. Res. 1–23.
Jagtap, U.B., 2020. Bioremediation strategies for removing antibiotics from the environment. In: In*Antibiotics and Antimicrobial Resistance Genes*. Springer, Cham, pp. 319–337.
Karcı, A., Balcıoğlu, I.A., 2009. Investigation of the tetracycline, sulfonamide, and fluoroquinolone antimicrobial compounds in animal manure and agricultural soils in Turkey. Sci. Total Environ. 407 (16), 4652–4664.
Khatoon, H., Rai, J.P.N., Jillani, A., 2021. Role of fungi in bioremediation of contaminated soil. In: InFungi Bio-Prospects in Sustainable Agriculture, Environment and Nano-Technology. Academic Press, pp. 121–156.
Khayati, G., Barati, M., 2017. Bioremediation of petroleum hydrocarbon contaminated soil: optimization strategy using Taguchi design of experimental (DOE) methodology. Environmental Processes 4 (2), 451–461.
Klein, E.Y., Milkowska-Shibata, M., Tseng, K.K., Sharland, M., Gandra, S., Pulcini, C., Laxminarayan, R., 2021. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: an analysis of pharmaceutical sales data. Lancet Infect. Dis. 21 (1), 107–115.
Lau, C.H.F., Tien, Y.C., Stedtfeld, R.D., Topp, E., 2020. Impacts of multi-year field exposure of agricultural soil to macrolide antibiotics on the abundance of antibiotic resistance genes and selected mobile genetic elements. Sci. Total Environ. 727, 138520.
Leitão, A.L., Duarte, M.P., Oliveira, J.S., 2007. Degradation of phenol by a halotolerant strain*Penicillium chrysogenum*. Int. Biodeterior. Biodegrad. 59, 220–225.
Lessard, M.H., Viel, C., Boyle, B., St-Gelais, D., Labrie, S., 2014. Metatranscriptome analysis of fungal strains Penicillium camemberti and Geotrichum candidumreveal cheese matrix breakdown and potential development of sensory properties of ripened Camembert-type cheese. BMC Genom. 15 (1), 1–13.
Li, B., Zhang, Z., Ma, Y., Li, Y., Zhu, C., Li, H., 2019. Electrokinetic remediation of antibiotic-polluted soil with different concentrations of tetracyclines. Environ. Sci. Pollut. Res. 26 (8), 8212–8225.
Li, W., Bao, Y., Zhou, Q., 2012. Progress in the degradation pathways and main degradation products of tetracycline antibiotics. J. Appl. Ecol. 23, 2300–2308.
Li, M., Yang, L., Yen, H., Zhao, F., Wang, X., Zhou, T., Feng, Q., Chen, L., 2023. Occurrence, spatial distribution, and ecological risks of antibiotics in soil in urban agglomeration. J of Environ Sciences 125, 678–690.
Liu, J., Jia, H., Mei, M., Wang, T., Chen, S., Li, J., 2022. Efficient degradation of diclofenac by digestate-derived biochar catalyzed peroxymonosulfate oxidation: performance, machine learning prediction, and mechanism. Process Saf. Environ. Protect. 167, 77–88.
Liu, L., Liu, Y.-H., Liu, C.-X., Huang, X., 2016. Accumulation of antibiotics and tet resistance genes from swine wastewater in wetland soils. Environ. Eng. Manage. J. 15, 2137–2145. https://doi.org/10.30638/eemj.2016.231.
Liu, Y., Chang, H., Li, Z., Feng, Y., Cheng, D., Xue, J., 2017. Biodegradation of gentamicin by bacterial consortia AMQD4 in synthetic medium and raw gentamicin sewage. Sci. Rep. 7 (1), 11004.

Llor, C., Bjerrum, L., 2014. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf 5 (6), 229–241.

Lueangjaroenkit, P., Teerapatsakul, C., Sakka, K., Sakka, M., Kimura, T., Kunitake, E., Chitradon, L., 2019. Two manganese peroxidases and a laccase of Trametes polyzona KU-RNW027 with novel properties for dye and pharmaceutical product degradation in redox mediator-free system. MYCOBIOLOGY 47, 217–229.

Łukaszewicz, P., Białk-Bielinska, A., Dołzonek, J., Kumirska, J., Caban, M., Stepnowski, P., 2018. A new approach for the extraction of tetracyclines from soil matrices: application of the microwave-extraction technique. Anal. Bioanal. Chem. 410, 1697–1707. https://doi.org/10.1007/s00216-017-0815-7.

Martínez-Carballo, E., González-Barreiro, C., Scharf, S., Gans, O., 2007. Environmental monitoring study of selected veterinary antibiotics in animal manure and soils in Austria. Environ. Pollut. 148, 570–579. https://doi.org/10.1016/j.envpol.

Mirabi, M., Karrabi, M., Gheibi, M., 2019. An economic analysis of industrial wastewater treatment systems using multi-attribute decision-making methods (case study: toos Industrial Estate, Mashhad, Iran). Desalination Water Treat. 146, 131–140.

Moayedi, H., Tien Bui, D., Kalantar, B., Kok Foong, L., 2019. Machine-learning-based classification approaches toward recognizing slope stability failure. Appl. Sci. 9 (21), 4638.

Mohammadi, M., Gheibi, M., Fathollahi-Fard, A.M., Eftekhari, M., Kian, Z., Tian, G., 2021a. A hybrid computational intelligence approach for bioremediation of amoxicillin based on fungus activities from soil resources and aflatoxin B1 controls. J. Environ. Manag. 299, 113594.

Mohammadi, M., Gheibi, M., Fathollahi-Fard, A.M., Eftekhari, M., Kian, Z., Tian, G., 2021b. A hybrid computational intelligence approach for bioremediation of amoxicillin based on fungus activities from soil resources and aflatoxin B1 controls. J. Environ. Manag. 299, 113594.

Mojiri, A., Zhou, J., Vakili, M., Van Le, H., 2020. Removal performance and optimisation of pharmaceutical micropollutants from synthetic domestic wastewater by hybrid treatment. J. Contam. Hydrol. 235, 103736.

Moradi, G., Gouya, M.M., Eshrati, B., Mohraz, M., Molaei, L., Piroozi, B., 2018. National action plan of the Islamic Republic of Iran for combating antimicrobial resistance during 2016–2021. Med. J. Islam. Repub. Iran 32, 82.

Olicón-Hernández, D.R., González-López, J., Aranda, E., 2017. Overview on the biochemical potential of filamentous fungi to degrade pharmaceutical compounds. Front. Microbiol. 8, 1792.

Oliveira, J., Belchior, A., da Silva, V.D., Rotter, A., Petrovski, Ž., Almeida, P.L., Lourenço, N.D., Gaudêncio, S.P., 2020. Marine environmental plastic pollution: mitigation by microorganism degradation and recycling valorization. Front. Mar. Sci. 7, 567126.

Pan, M., Chu, L.M., 2017. Fate of antibiotics in soil and their uptake by edible crops. Sci. Total Environ. 599, 500–512. https://doi.org/10.1016/j.scitotenv.2017.04.214. –600. .

Patel, H., Calip, G.S., DiDomenico, R.J., Schumock, G.T., Suda, K.J., Lee, T.A., 2020. Prevalence of cardiac risk factors in patients prescribed azithromycin before and after the 2012 FDA warning on the risk of potentially fatal heart rhythms. Pharmacotherapy 40 (2), 107–115.

Picariello, E., Baldantoni, D., De Nicola, F., 2022. Investigating natural attenuation of PAHs by soil microbial communities: insights by a machine learning approach. Restor. Ecol. e13655.

Ren, J., Wang, Z., Deng, L., Niu, D., Huhetaoli, Li Z., et al., 2021. Degradation of erythromycin by a novel fungus,*Penicillium oxalicum* RJJ-2, and the degradation pathway. Waste Biomass Valorization 12, 4513–4523. https://doi.org/10.1007/s12649-021-01343-y.

Salandez, V., Emami, S., Taha, A.Y., La Saponara, V., 2022. Use of Ganoderma lucidum grown on agricultural waste to remove antibiotics from water. bioRxiv. https://doi.org/10.1101/2022.08.07.503092.

Schmit, J.P., Mueller, G.M., 2007. An estimate of the lower limit of global fungal diversity. Biodivers. Conserv. 16, 99–111. https://doi.org/10.1007/s10531-006-9129-3.

Sidhu, H., Bae, H.S., Ogram, A., O'Connor, G., Yu, F., 2021. Azithromycin and ciprofloxacin can promote antibiotic resistance in biosolids and biosolids-amended soils. Appl. Environ. Microbiol. 87 (16). . AEM-00373.

Sidhu, H., D'Angelo, E., O'Connor, G., 2019. Retention-release of Ciprofloxacin and azithromycin in biosolids and biosolids-amended soils. Sci. Total Environ. 650, 173–183.

Singh, H., 2006. Mycoremediation: Fungal Bioremediation. John Wiley & Sons.Sing H. *Mycoremediation*.John Wiley & Sons, Inc, New Jersey, USA.

Sodhi, K.K., Singh, C.K., 2022. Recent Development in the Sustainable Remediation of Antibiotics: A Review. Total Environment Research Themes, 100008.

Tasho, R.P., Cho, J.Y., 2016. Veterinary antibiotics in animal waste, its distribution in soil and uptake by plants: a review. Sci. Total Environ. 563–564, 366–376. https://doi.org/10.1016/j.scitotenv.2016.04.140.

Thiele-Bruhn, S., 2003. Pharmaceutical antibiotic compounds in soils - a review. J. Plant Nutr. Soil Sci. 166, 145–167. https://doi.org/10.1002/jpln.200390023.

Tormo-Budowski, R., Cambronero-Heinrichs, J.C., Durán, J.E., Masís-Mora, M., Ramirez-Morales, D., Quirós-Fournier, J.P., Rodriguez-Rodriguez, C.E., 2021. Removal of pharmaceuticals and ecotoxicological changes in wastewater using Trametes versicolor: a comparison of fungal stirred tank and trickle-bed bioreactors. Chem. Eng. J. 410, 128210.

Van Doorslaer, X., Dewulf, J., Van Langenhove, H., Demeestere, K., 2014. Fluoroquinolone antibiotics: an emerging class of environmental micropollutants. Sci. Total Environ. 500–501, 250–269. https://doi.org/10.1016/j.scitotenv.2014.08.075.

Vermillion Maier, M.L., Tjeerdema, R.S., 2017. Azithromycin sorption and biodegradation in a simulated California river system. Chemosphere. https://doi.org/10.1016/j.chemosphere.2017.10.008.

WHO, 2019. available online at;. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance.

Zelt, M., Staley, Z., Li, X., Wang, B., Miller, D.N., Schmidt, A., 2021. Antibiotic Resistance in Manure-Amended Agricultural Soils.

Zhan, L., Xia, Z., Xu, Z., Xie, B., 2021. Study on the remediation of tetracycline antibiotics and roxarsone contaminated soil. Environ. Pollut. 271, 116312.

Zhang, J., Gao, D., Li, Q., Zhao, Y., Li, L., Lin, H., Bi, Q., Zhao, Y., 2020. Biodegradation of polyethylene microplastic particles by the fungus Aspergillus flavus from the guts of wax moth Galleria mellonella. Sci. Total Environ. 704, 135931.

Zhang, Q.Q., Ying, G.G., Pan, C.G., Liu, Y.S., Zhao, J.L., 2015. Comprehensive evaluation of antibiotics emission and fate in the river basins of China: source analysis, multimedia modeling, and linkage to bacterial resistance. Environ. Sci. Technol. 49 (11), 6772–6782.

Zhao, K., Kang, S.X., Yang, Y.Y., Yu, D.G., 2021. Electrospun functional nanofiber membrane for antibiotic removal in water. Polymers 13 (2), 226.

Zhao, P., Yu, F., Wang, R., Ma, Y., Wu, Y., 2018. Sodium alginate/graphene oxide hydrogel beads as permeable reactive barrier material for the remediation of ciprofloxacin-contaminated groundwater. Chemosphere 200, 612–620.

Zhu, X., Wan, Z., Tsang, D.C., He, M., Hou, D., Su, Z., Shang, J., Abubakr, M., 2021. Machine learning for the selection of carbon-based materials for tetracycline and sulfamethoxazole adsorption. Chem. Eng. J. 406, 126782.