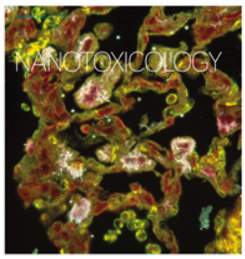

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REVIEW ARTICLE

Predicting the toxicity of nanoparticles using artificial intelligence tools: a systematic review

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ABSTRACT

Nanoparticles have been used extensively in different scientific fields. Due to the possible destructive effects of nanoparticles on the environment or the biological systems, their toxicity evaluation is a crucial phase for studying nanomaterial safety. In the meantime, experimental approaches for toxicity assessment of various nanoparticles are expensive and time-consuming. Thus, an alternative technique, such as artificial intelligence (AI), could be valuable for predicting nanoparticle toxicity. Therefore, in this review, the AI tools were investigated for the toxicity assessment of nanomaterials. To this end, a systematic search was performed on PubMed, Web of Science, and Scopus databases. Articles were included or excluded based on pre-defined inclusion and exclusion criteria, and duplicate studies were excluded. Finally, twenty-six studies were included. The majority of the studies were conducted on metal oxide and metallic nanoparticles. In addition, Random Forest (RF) and Support Vector Machine (SVM) had the most frequency in the included studies. Most of the models demonstrated acceptable performance. Overall, AI could provide a robust, fast, and low-cost tool for the evaluation of nanoparticle toxicity.

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KEYWORDS
Nanoparticles; nanomaterials; artificial intelligence; toxicity; safety

1. Introduction

Nanoparticles (NPs), as particles with the size of 1–100 nm, have been employed extensively in the food industry, physics, engineering, electronics, biosensors, and biomedicine (Bhatia 2016; Xiao-Ming et al. 2018; Chellaram et al. 2014; Nadeem et al. 2021). Nanomedicine, as a developing field of nanotechnology, could offer novel opportunities for diagnosing and treating diseases (Bhatia 2016; Singh et al. 2022). NPs are applied in the size of 5–100 nm for biomedical applications, which are preferred to overcome physiological barriers. These particles have exhibited wide efficacies in the nanomedicine fields due to their unique electronic, magnetic, and optical characteristics, which arise from their high surface-to-volume ratio (Yin and Zhong 2020; Bahadar et al. 2016).

Nano-scale drug delivery systems could incorporate drugs and improve solubility, bioavailability, stability, and blood circulation time, and reduce their adverse effects. Furthermore, nanoparticles, as the carrier of imaging agents, provide a platform for more sensitive and specific molecular imaging (Yin and Zhong 2020; Kesharwani et al. 2019).

Despite the engrossing and promising applications of nanoparticles in various scientific fields, their toxic effects have become a main concern, especially in clinical studies (Zoroddu et al. 2014). Nano-scaled systems could target a specific tissue after administration and penetrate the tissues due to their size. Thus, it is essential to assess the toxicological effects of nanoparticles (Aydın et al. 2012; Kakoty et al. 2022). Moreover, the toxicity of nanoparticles in non-target cells is a paramount concern due to their use in humans. A desirable nanocarrier should possess low toxicity at the prescribed dose (Elsaesser and Howard 2012; Fadeel and Garcia-Bennett 2010).

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The toxicity of nanoparticles could be classified into environmental and biological toxicity regarding adverse effects on the environment and human health. The biological toxicity of nanoparticles can lead to oxidative stress and inflammatory responses, allergies, neurotoxicity, fibrosis, hematological toxicity, toxic effect on heart function, prethrombotic effects, pulmonary toxicity, carcinogenicity, genotoxicity, teratogenicity, and toxicity to the brain (Rothen-Rutishauser et al. 2007; Mühlfeld 2008; Kakoty et al. 2022; Maynard et al. 2006; Nel et al. 2006).

Although the toxicity of bulk materials is determined mostly by the chemical composition, physicochemical properties such as particle size and surface area, structure, surface charge, and chemical composition could affect the toxicity of nanoparticles (Gatoo et al. 2014).

The toxicity of nanoparticles could be evaluated by the determination of the physicochemical properties, biodistribution, and in vitro and in vivo toxicity assessment. In vitro assessment includes proliferation (MTT), apoptosis, necrosis, and oxidative stress assays, and in vivo assessment includes oral toxicity test, dermal toxicity test, and eye irritation test (Fard et al. 2015; Kakoty et al. 2022). These in vitro and in vivo assessments are time-consuming and costly techniques owning to chemical diversity and heterogenicity in size, shape, and biological behaviors of various nanoparticles (Concu et al. 2017; Jones et al. 2016).

Artificial intelligence (AI) approaches, as an additional strategy, could be served to alleviate these limitations for the toxicity evaluation of nanoparticles. AI methods have been used for the prediction of nanomaterial toxicity in both academic and industrial fields (Chen et al. 2018; Mamoshina et al. 2016).

AI deals with the tools and techniques to give the machine the ability to mimic human behavior (Mintz and Brodie 2019). Machine learning models as a subfield of AI learn automatically instead of being programed explicitly (Olczak et al. 2021). Data mining refers to the process of extracting knowledge and identifying patterns from the data (Yang et al. 2020). Deep learning is a subcategory of machine learning that utilize a large amount of data and neural networks to build models (Olczak et al. 2021).

In the case of nanomaterials, toxicity assessment along with AI tools has not been widely reviewed. Herein, we reviewed the AI tools, including machine learning, data mining, and deep learning, for the safety and risk assessment of nanomaterials.

2. Materials and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009).

2.1. Search strategy

A systematic search was conducted using the following databases: PubMed, Web of Science, and Scopus. These databases were searched from inception to 7 September 2022 for select relevant articles. Medical Subject Headings (MeSH) were used to determine the keywords. The keywords used for the search included “Artificial Intelligence”, “Toxicity” and “Nanoparticle.” Search strategy for PubMed database is presented in Table 1. The search strategy is provided in Supplementary file 1.

2.2. Selection criteria

Based on the following inclusion and exclusion criteria, a decision was made regarding including studies in this systematic review:

The inclusion criteria were (1) studies retrieved from databases using the search strategy that (2) studies published in the English language.

Table 1. Search strategy for PubMed database.

Domain	Keywords
Artificial Intelligence	("AI"[Title/Abstract] OR "Artificial Intelligence"[Title/Abstract] OR "Deep Learning"[Title/Abstract] OR "Machine Learning"[Title/Abstract] OR "Data Mining"[Title/Abstract])
Toxicity	("cytotoxicity"[Title/Abstract] OR "toxicity"[Title/Abstract] OR "safety"[Title/Abstract])
Nano	("nanoparticles"[Title/Abstract] OR "nano"[Title/Abstract] OR "nanoparticle"[Title/Abstract] OR "nanomaterials"[Title/Abstract])

Exclusion criteria were (1) reviews, meta-analyses, conference abstracts, commentaries, editorials, protocols, expert opinions, and letter to the editor, (2) full text not published in English, (3) unavailability of full text for data extraction, (4) duplicate studies, and (5) studies unrelated to the purpose of the research (focused on AI and its application to predicting the toxicity of nanoparticles).

2.3. Study Selection

All studies identified were imported into EndNote X9 citation management software (Thomson Reuters, Toronto, Ontario, Canada). After removing duplicates by Endnote X9, the articles were imported to the Rayan platform, which is a systematic review web application designed to help reviews in the systematic review blind screening process (Ouzzani et al. 2016). Through this platform, three authors (ABY, HM, and MA) independently screened the titles and abstracts of all studies identified by the search criteria. Full texts of the remaining relevant studies were obtained, and three authors (ABY, HM, and SMA) read the full-text papers and made a final selection of relevant studies. Any disagreements were resolved by discussion and consensus between the authors. The full text of review articles that did not meet inclusion criteria was removed, and reasons for exclusion were noted.

2.4. Data extraction

Three reviewers performed data extraction independently (ABY, HM, and MA) using a designed form in Microsoft Excel. Any disagreement was resolved through discussion with SMA and MA. The extracted data consisted of the first author, publication year, country, aim of the study, type of NPs, Cell/Tissue/Animal, Dataset size (rows), Model validation, Dataset type, and AI methods were tabulated. In addition, AI methods, and the performance of each model (in the form of measurements and values) were tabulated in a separate table.

2.5. Quality assessment

We investigated the quality assessment of studies according to the quality assessment criteria presented by Kitchenham et al. (2009). The quality assessment criteria contain eight questions: 1) Are the aims of the study clearly stated?; 2) Are the scope and context of the study clearly defined?; 3) Is the proposed solution clearly explained and validated by an empirical study?; 4) Are the variables used in the study likely to be valid and reliable?; 5) Is the research process documented adequately?; 6) Are all study questions answered?; 7) Are the negative findings presented?; 8) Are the main findings stated clearly in terms of creditability, validity, and reliability? Each question was rated as "No = 0", "Partial = 1", or "Yes = 2" based on standardized criteria.

2.6. Data analysis

The results of this study were reported descriptively. The countries of the authors were plotted on a map using Microsoft Excel. AI models mentioned in the papers were harmonized (e.g. C4.5 assumed the same as the Decision Tree) and the frequency of each model was represented in a figure form. Most utilized AI methods were identified in this step. In the next step, Nanoparticles mentioned in the papers were categorized and shown in a sunburst figure. Due to the enormous variety of nanoparticles, only those with a frequency of more than two (papers) were shown. Finally, the most common performance measurements for each model were shown by a range figure using the range plot module of the Datawrapper platform (https://app.datawrapper.de/).

3. Results

3.1. Search output

A total of 775 potentially relevant articles were initially identified from the three databases; 312 articles were removed due to duplication, and the remaining 463 studies were screened. We excluded 432 articles due to low relevance based on the title and abstract, and 31 full-text articles were screened. The characteristics of the excluded studies are shown in the PRISMA diagram. After all the eligibility criteria were applied, 26 articles were included in this study (Figure 1).

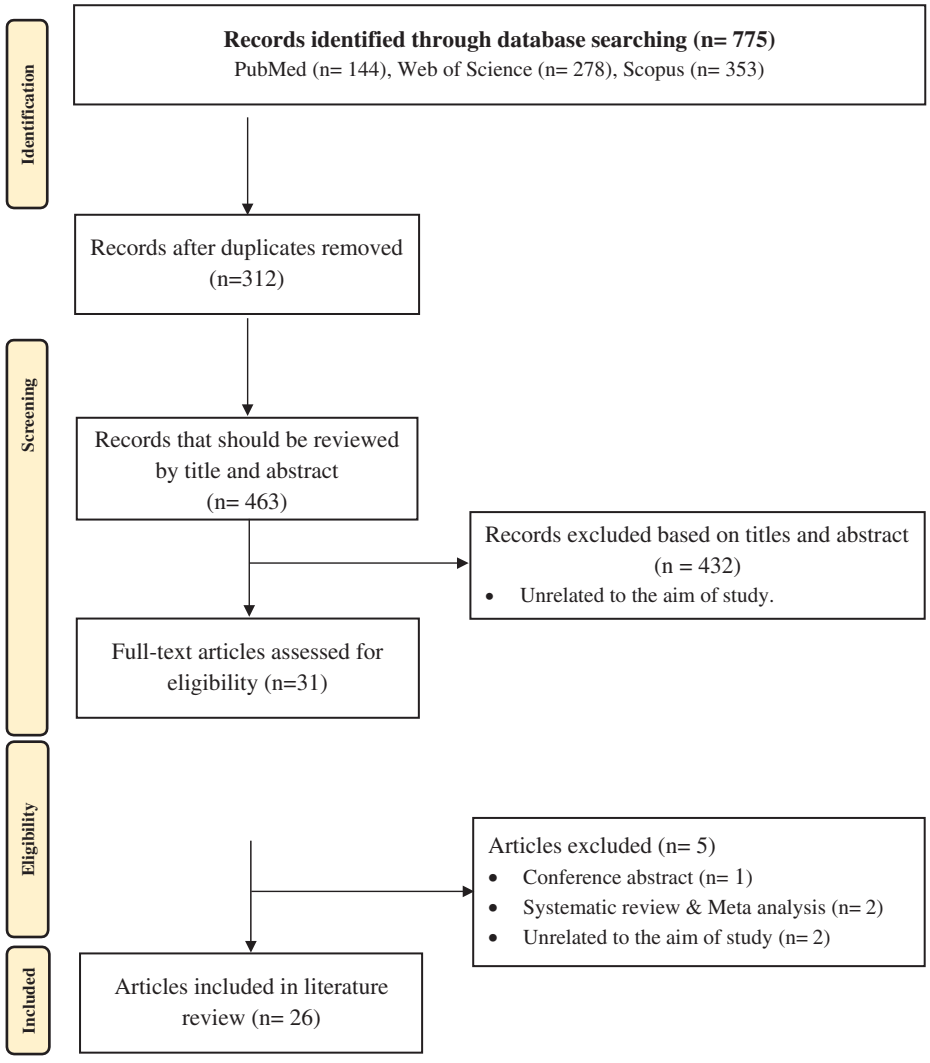

Figure 1. PRISMA flow diagram indicating results of identification and screening process for included and excluded papers.

3.2. Characteristics of the included studies

The characteristics of the 26 studies are shown in Table 2. The oldest and newest studies were published in 2011 and 2022, respectively. Most studies used metal oxide and metallic nanoparticles. The most common model validation method was K-Fold cross-validation (Table 2). Ten studies were from the United States ($n = 5$; 19.23%), and China ($n = 5$; 19.23%), four from Ireland (15.38%), two from Greece (7.69%), two from Italy (7.69%), and one from Cyprus, India, Poland, Portugal, Republic of Korea, Russia, Turkey, and Ukraine (Figure S1).

Table 3 shows the performance analysis of AI methods with measurement and value detail.

Figure 2 shows that most of the models used in the studies are Random Forest (RF) and Support Vector Machine (SVM).

Most of the nanoparticles used for the prediction of toxicity of nanoparticles in the studies belong to the metal oxide and the metallic categories. In the metal oxide category, iron oxide and TiO2, and in the metallic category, Au and Ag were the most used (Figure S2).

Figure 3 shows the accuracy of the models. The accuracy of the BN model has the largest variety, ranging from 0.38 to 1. In addition, the Decision Table (0.96–0.97) and PTML-QSTR (0.97–0.98) had the least variety of accuracy.

Figure 4 shows the sensitivity of the models. The sensitivity of the SVM model had the maximum possible variety, ranging from 0.0 to 1. The sensitivity of the ANN and RF models varied from 0.0 to 0.99. In addition, the sensitivity of the BN model varied from 0.1 to 1. The

Table 2. Characteristics of the 26 studies.

Source	Country	Aim of Study	Type of NPs	Cell/Tissue/Animal	Dataset Size (rows)	Model validation	Dataset Type	AI Method
Pyrgiotakis et al. (2011)	USA	to predict the toxicity of titania NPs	Anatase titanium dioxide	A549 lung epithelia cells	40	Leave-one- out cross-validation method	Table	SVM
Gernand et al (2013)	USA	to predict the toxicity of metal oxide NPs	metal oxide nanoparticles.	Lung (bronchoalveolar lavage (BAL) fluid)	100	Not mentioned	Table	RF
Liu et al. (2014)	USA	to predict different biological responses (signaling pathway activities and cytotoxicity effects) of metal and metal oxide NPs	Ag, Au, Pt, Al2O3, ZnO, and SiO2	Macrophage (RAW264.7), and Bronchial epithelial (BEAS-2B) cell line	Not mentioned	Not mentioned	Table	ARM
Toschi et. al. (2016)	Italy	to predict cytotoxicity of NPs	Ag, Au, Co, Fe, Fe3O4, Ni	A549, SK-OV-3, U- 87-MG cells	Not mentioned	A nested 10- fold cross- validation	Table	Two different nonlinear regressors (SVR with polynomic al kernels and RBF regressors)
Papa et al. (2016)	Italy	to predict the biological activity of gold NPs	surfaced- modified Au-nanoparticles	A549 human lung epithelial carcinoma cells	84	leave-one- out cross- validation	Table	k-NN, GRegNN, RBFNN, CPANN, SVM- radial, SVM-linear, PLS, MLR, PPR, EARTH, RF-6, RF- 150
Gernand et al. (2016)	USA	to predict the toxicity of NPs	CNT, TiO2, SiO2, ZnO, MgO	Rodent animal (bronchoalveolar lavage (BAL) fluid)	135	simple validation	Table	RF
Helma et al. (2017)	China	to predict the toxicity of metal NPs	Gold, silver	A549 human lung epithelial carcinoma cells	121	10-fold cross- validation	Table	RF, PLS, WA
Concu et al. (2017)	Russia	to predict the toxicity of NPs	Nanoparticles (NPs) solely metal-based to metallic oxide NPs, including silica-based NPs	RAW 264.7 cell line, Danio rerio (embryos), Pseudokirchneriella subcapitata	54371	Train-test split, Y-randomization (Y = 10)	Table	ANN
Trinh et. al. (2018)	Republic of Korea	to predict cytotoxicity of metallic NPs	Metallic NPs such as Au and Ag.	Normal and cancer cells	2005	10-fold cross- validation	Table	RF, SVM
Sizochenko et al. (2018)	Poland	to predict the toxicity of metal oxide NPs	Metal oxide nanoparticles	bacteria, algae, protozoa, and mammalian cell lines (Escherichia coli, Photobacterium phosphoreum, Vibrio fischeri, human keratinocyte cell line, HaCaT, epithelial cell line A549, human epithelial colorectal cell line Caco2, murine fibroblast cell line Balb/c 3T3, microalga Pseudokirchneriella subcapitata, and protozoan Tetrahymena thermophile)	184	Not mentioned.	Table	SOM
Kovalishyn et al. (2018)	Ukraine	to predict the toxicity of metal and metal oxide NPs	metallic NPs (Ag,spherical; Pt2+; Au3+; Zn2+; Ni, quasi-spherical; Co; Cu, Au spherical, Fe spherical) metal oxide NPs (TiO2, anatase, rutile, P25 Degussa; ZnO; CuO, spherical; ZnO, rhomboid, spherical and shortrod shape; AgNO3; Al2O3; CeO2, Fe3O4, ZrO2, GdO2, Dy2O3, Ho2O3, Sm2O3, Er2O3)	Bacteria such as Staphylococcus aureus, and Escherichia coli, Aquatic organisms such as Zebra fish embryos, Daphnia magna	964	five-fold cross- validation	Table	ASNN, RF, KNN
Jha et al. (2018)	China	to predict the toxicity of metal oxide NPs	Al2O3, CeO2, Co3O4, TiO2, ZnO, CuO, SiO2, Fe3O4, and WO3	Dataset I: BEAS-2B (bronchial epithelial) cells, Dataset II: BEAS-2B, and rat alveolar macrophage (RAW 264.7) cell lines Dataset III: endothelial, vascular muscle, monocyte, hepatocyte cell lines Dataset IV: human keratinocyte cell lines (HaCaT)	83	Visual validation	Table	PCA

(*continued*)

Table 2. Continued.

Source	Country	Aim of Study	Type of NPs	Cell/Tissue/Animal	Dataset Size (rows)	Model validation	Dataset Type	AI Method
Furxhi et.al. (2019b)	Ireland	to predict NP-induced cellular effects	Ag, Au, Polymeric NPs, CuO, ZnO, TiO2, SiO2, Fe2O3, Polystyrene NPs, CoFe2O4 NPs.	Organs: Kidney, Brain, Lung, Intestinal, Skin, Prostate, Liver,Colon, Cardiovascular, Breast, Cervix, Blood Cell lines: SH-SY5Y, 293 T, A549, CACO-2, HDF, PC3, THP-1, HEPG2, VSMC, HACAT, HMDM, JURKAT-T, MDDC, MCF-7, IMR-90, U251, HELA, HMEC 184, EAHY926, SAE, RKO, SK MEL-28	243	10-fold cross- validation	Table	BNs, BN- K2
Sizochenko et. al. (2019)	USA	to predict genotoxicity of metal oxide NPs	Metal oxide nanoparticles	A549, A531, BEAS- 2B, and HEC293, blood cells	Not mentioned	Not mentioned.	Table	SVM, NB, KNN, DT, SOM
Furxhi et.al. (2019a)	Ireland	to predict the toxicity of oxide NPs	seven oxide NPs	Normal and cancer cells	722	10-fold cross- validation for internal validation	Table	Ensemble (voting using BN, SMO, LR, NN, RF, LWL, IBk, DT, DIR, and LIR)
Ban et al. (2020)	China	to predict the cell response of NPs	Metalic/Liposo me/Carbonaceo us/Other (SiO2, PS, Zeolite, and Si)	RAW264.7, human leukemic cell line [THP-1], and dendritic cell line [DC2.4]	652	10-fold cross- validation	Table	RF
Papadiamantis et al. (2020)	Cyprus	to predict the toxicity of metal oxide NPs	metal oxide (MexOy) nanoparticles	"Human bronchial epithelial (BEAS-2B), and murine myeloid (RAW 264.7) cell lines"	1488 datapoints	Train-test split, leave-many-out cross- validation	Table	EnaloskN N
Furxhi & Murphy (2020)	Ireland	to predict the toxicity of NPs	metal (Ag), metal oxides (ZnO, CuO, SiO2, etc.) and carbon-based NPs (SWCNT).	HCMEC, BMEC, primary, ALT, D384, SHSY5Y, N9, BV2, PC12, N2a, CGC, RSC96, N27 cell lines	1588	10-fold cross- validation	Table	RF
Kotzabasaki et al. (2020)	Greece	to predict the toxicity of SPIONs	superparamagn etic iron oxide NPs	Stem cells	16	3-fold cross- validation	Table	LR
Spyropoulos et al. (2020)	Greece	to predict the toxicity of NPs	Not mentioned	A549 human cancer cells	229	K-Fold cross validation	Table	GLM, DT, SVM
Halder et al. (2020)	Portuga l	to predict the genotoxicity of metal oxide NPs	metal oxide NMs (Al2O3, Bi2O3, Co3O4, CuO, Fe2O3, Fe3O4, NiO, SiO2, SnO2, TiO2, V2O3, V2O5, ZnO, and ZrO2)	BMSC, HEK293, HepG2, NCIH441, BJ, CaCo-2, MDCK, HMM cells	6084	5-fold cross-validation	Table	PTML- QSTR
Bogdanska et al. (2021)	Ireland	to predict SPION biodistribution and toxicity in liver, lung, and kidney histological samples	Superparamagn etic Iron Oxide	BALB/c mice (lung, liver, kidney)	Not mentioned	10-fold cross- validation	Image	TWS, FRF
Gul et. al. (2021)	Turkey	to predict cytotoxicity of metallic NPs	Inorganic, organic and carbon-based NPs	MBMC, SIRC, SHSY5Y, HUVEC, HCMEC cells	4111	Not mentioned.	Table	ARM
Yu et. al. (2021)	China	to predict immune responses and pharmacokinetics of NPs	Various NPs[a]	Lung, liver, BALF (Bronchoalveolar lavage fluid)	1620	10-fold Shuffle Split cross- validation	Table	RF, ANN, SVM
Subramanian & Palaniappan (2021)	India	to predict toxicity of metal oxide NPs	Metaloxide nanoparticles: Al2O3, CuO, Fe2O3, TiO2, ZnO	NA	483	Train-test split	Table	LR, RF, SVM, NN
Huang et al. (2022)	China	to predict the genotoxicity of metal oxide NPs	MeONPs	THP-1 cells	240	10-fold cross- validation	Table	C4.5, LGR, RF, kNN, DT*, LWL, Bayesnet, SVM

[a]TiO2, MWCNT, Ag, Fe2O3, GO, rGO, CB, NiO, CNF, ZnO, CNP, Co3O4, Cr2O3, CuO, CeO2, SiO2, polystyrene, SWCNT, MgO, Au, C60, Cd, QD705, CoO, In2O3, Lipid, PVA, Cu, BaSO4, BN, DEP, Bi2Se3, Fe-TiO2, Pt, Fe3O4, AlO, AlCeO3, AlOOH, graphene, QD-CdSe-ZnS, EPOXY-REF, EPOXY-CNT, EPOCYL, DWCNT, C60(OH)24, cellulose nanocrystals, diesel exhaust particle, paint particle(TiO2), paint particle(Ag), paint particle(SiO2), Rosette nanotubes, SWGe-imogolite, DWGe-imogolite, Co, Nd2O3, Carbonly iron, Yb2O3, Ni

Abbreviation: SVM = Support vector machines; RF = Random Forests; ARM = Association Rule Mining; SVR = Support VectorRegressors; RBF = Radial Basis Function; PLS = Partial Least Squares Regression; WA = Weighted Average; ANN = Artificial NeuralNetworks; SOM = Self-Organizing Maps; ASNN = Associative Neural Network; KNN = k-nearest neighbors; PCA = Principalcomponent analysis; BNs = Bayesian networks; BN-K2 = Bayesian network-automated constructed using K2-algorithm; NB = NaïveBayes; DT = Decision Tree; DT* = Decision Table; SA = Simulated Annealing; GRBF = Generalized Radial Basic Function; AutoML = automated machine learning; GLM = Generalized linear model; PTML-QSTR = Perturbation Theory Machine Learning (PTML) basedQSTR approach; TWS = Trainable WEKA segmentation (TWS) plugin used for pixel classification and segmentation, FRF = FastRandom Forest classifier; LR = Logistic Regression; NN = Neural Network; C4.5 = C4.5 decision tree; LGR = Logistic Regression;DT = Decision Table; LWL = Locally Weighted Learning;

Table 3. Performance analysis of AI methods.

Sources	AI Method	Measurement	Value
Pyrgiotakis et al. (2011)	SVM	Accuracy	1
Gernand et al (2013)	RF	Error	∼[0.05,1450]
Liu et al. (2014)	ARM	Support	[0.100,0.183]
		Confidence	[0.818,1.000]
Toschi et. al. (2016)	SVR	R2	[0.640-0.818]
		r	[0.803,0.906]
	RBFreg	R2	[0.388,0.845]
		r	[0.703,0.922]
Papa et al. (2016)	k-NN	R2	[0.73,0.88]
		RMSE	[0.81,1.17]
	GregNN	R2	[0.74,0.93]
		RMSE	[0.63,1.18]
	RBFNN	R2	[0.74,0.87]
		RMSE	[0.82,1.1]
	CPANN	R2	[0.82,0.92]
		RMSE	[0.66,1.25]
	SVM-radial	R2	[0.76,0.94]
		RMSE	[0.59,1.09]
	SVM-linear	R2	[0.78,0.87]
		RMSE	[0.82,1.04]
	PLS	R2	[0.76,0.87]
		RMSE	[0.81,1.07]
	MLR	R2	[0.76,0.87]
		RMSE	[0.81,1.07]
	PPR	R2	[0.79,0.91]
		RMSE	[0.69,1.01]
	EARTH	R2	[0.8,0.9]
		RMSE	[0.73,1.1]
	RF-6	R2	[0.8,0.95]
		RMSE	[0.62,1.29]
	RF-150	R2	[0.8,0.95]
		RMSE	[0.63,1.43]
Gernand et al. (2016)	RF	Error	<0.1
Helma et al. (2017)	RF	R2	[0.45–0.69]
		RMSE	[1.51–2.1]
	PLS	R2	[0.27–0.67]
		RMSE	[1.55–2.16]
	WA	R2	[0.19–0.7]
		RMSE	[1.44–2.07]
Concu et al. (2017)	ANN	Accuracy	[0.595,0.64]
		Specificity	[0.014,1]
		Sensitivity	[0,0.986]
Trinh et. al. (2018)	RF	Mean RF-PChem score	[2.9,4.5]
		Accuracy	[0.851,0.88]
		Specificity	[0.995,1]
		Sensitivity	[0.0,0.593]
		F1	[0.0,0.727]
	SVM	Mean SVM-PChem score	[2.9,4.5]
		Accuracy	[0.802,0.87]
		Specificity	[0.816,1]
		Sensitivity	[0.0,0.822]
		F1	[0.0,0.727]
Sizochenko et al. (2018)	–	–	–
Kovalishyn et al. (2018)	ASNN	Accuracy	[0.67–0.84]
		Specificity	[0.69–0.93]
		Sensitivity	[0.60–0.85]
	RF	Accuracy	[0.76–0.88]
		Specificity	[0.74–0.89]
		Sensitivity	[0.70–0.88]
	KNN	Accuracy	[0.65–0.83]
		Specificity	[0.6–40.88]
		Sensitivity	[0.60–0.85]
Jha et al. (2018)	–	–	–
Furxhi et.al. (2019b)	BN	Accuracy	∼[0.38,1]
		Sensitivity	∼[0.1,1]
		MCC	∼[-0.3,1]
	BN-K2	Accuracy	∼[0.68,0.99]
		Sensitivity	∼[0.38,0.99]
		MCC	∼[-0.1,0.9]
Sizochenko et. al. (2019)	DT	Accuracy	[0.75,1]
		Specificity	[0.5,1]
		Sensitivity	[0.86,1]

(*continued*)

Table 3. Continued.

Sources	AI Method	Measurement	Value
		Error	[0,0.25]
	SVM	–	–
	NB	–	–
	KNN	–	–
	SOM	–	–
Furxhi et.al. (2019a)	Ensemble (Voting using BN, SMO, LR, NN, RF, LWL, IBk, DT, DIR, and LIR)	Specificity	[0.91,0.99]
		Sensitivity	[0.83,0.99]
		F1	[0.79,0.99]
		DP	[0.99,2.20]
Ban et al. (2020)	RF	R2	[0.61–0.88]
		RMSE	[1.3%–10.4%]
Papadiamantis et al. (2020)	EnaloskNN	R2	0.91
Furxhi et al. (2020)	RF	Accuracy	[0.962,0.992]
		Precision	[0.962,0.992]
		Sensitivity	[0,0.986]
		Specificity	[0.961,0.993]
		Sensitivity	[0.962,0.992]
		F1	[0.96,0.99]
		MCC	[0.92,0.98]
		ROC	[0.97,1]
Kotzabasaki et al. (2020)	Auto-ML	Accuracy	[0.91,1]
		Precision	[0.93,1]
		Recall	[0.91,1]
		F1	[0.91,1]
Spyropoulos et al. (2020)	SVM	Accuracy	[0.833,1]
		Specificity	[0.894,1]
		Sensitivity	[0.662,1]
	DT	Accuracy	[0.92,1]
		Specificity	[0.932,1]
		Sensitivity	[0.899,1]
	GLM	Accuracy	[0.694,1]
		Specificity	[0.704,1]
		Sensitivity	[0.674,1]
Halder et al. (2020)	PTML-QSTR	TP	{1374,3211}
		TN	{411,915}
		FN	{20,75}
		FP	{20,58}
		Accuracy	{96.87,97.81}
		Specificity	{94.04,95.35}
		Sensitivity	{97.71,98.56}
Bogdanska et al. (2021)	TWS, FRF	TPR	[0.841,0.996]
		FPR	[0.000,0.006]
		Precision	[0.939,1]
		Recall	[0.841,0.996]
		F1	[0.888,0.993]
		MCC	[0.889,0.991]
Gul et. al. (2021)	ARM	Support	[0.010,0.172]
		Confidence	[0.70,1.000]
		Lift	[1.37,1.95]
Yu et. al. (2021)	RF	R2	∼[0.12,1]
	ANN	R2	∼[0.1,0.9]
	SVM	R2	∼[0.05,0.9]
Subramanian & Palaniappan (2021)	LR	Accuracy	[0.91–0.95]
	RF	Accuracy	[0.94–0.98]
	SVM-Linear	Accuracy	[0.9–1]
	SVM-Radial	Accuracy	[0.86–1]
	SVM-Poly	Accuracy	[0.84–1]
	NN	Accuracy	[0.94–0.97]
Huang et al. (2022)	C4.5	Accuracy	[0.93,0.98]
		Specificity	[0.96,0.98]
		Sensitivity	[0.5,0.97]
		MCC	[0.46,0.95]
		F1	[0.66,0.98]
		AUC	[0.51,0.97]
	RF	Accuracy	[0.95,0.98]
		Specificity	[0.98,0.98]
		Sensitivity	[0.6,0.99]
		MCC	[0.64,0.96]
		F1	[0.74,0.98]
		AUC	[0.98,1]

(*continued*)

Table 3. Continued.

Sources	AI Method	Measurement	Value
	LGR	Accuracy	[0.8,0.82]
		Specificity	[0.83,0.94]
		Sensitivity	[0.11,0.81]
		MCC	[0.07,0.63]
		F1	[0.2,0.82]
		AUC	[0.57,0.87]
	kNN	Accuracy	[0.91,0.96]
		Specificity	[0.97,1]
		Sensitivity	[0.44,0.94]
		MCC	[0.63,0.91]
		F1	[0.62,0.96]
		AUC	[0.95,0.96]
	DT	Accuracy	[0.96,0.97]
		Specificity	[0.96,0.96]
		Sensitivity	[0.98,1]
		MCC	[0.69,0.94]
		F1	[0.97,0.98]
		AUC	[0.87,0.98]
	LWL	Accuracy	[0.89,0.94]
		Specificity	[0.98,1]
		Sensitivity	[0.4,0.91]
		MCC	[0.59,0.88]
		F1	[0.57,0.94]
		AUC	[0.95,0.97]
	Bayesnet	Accuracy	[0.96,0.96]
		Specificity	[0.96,0.98]
		Sensitivity	[0.94,1]
		MCC	[0.69,0.92]
		F1	[0.96,0.98]
		AUC	[0.93,0.99]
	SVM	Accuracy	[0.8,0.82]
		Specificity	[0.87,0.96]
		Sensitivity	[0.18,0.78]
		MCC	[0.21,0.64]
		F1	[0.31,0.82]
		AUC	[0.66,0.82]

[a–b]: reported performance range from a to b in paper.
[a,b]: multiple performances reported that range between a and b.
∼[a,b]: approximately value of performance inferred from figures.
{a,b}: performance value reported has the values of a and b.
Abbreviation: MCC: Matthews correlation coefficient; DP: Discriminative Power.

PTML-QSTR (0.98–0.99) had the least variety of sensitivity.

Figure 5 shows the specificity of the models. The ANN model specificity fluctuates from 0.1 to 1. In contrast, the PTML-QSTR and BN had the least variety of specificity with the range of (0.94–0.95) and (0.96–0.98), respectively.

4. Discussion

According to our results emerging artificial intelligence have the potential and capacity to predict the toxicity of nanomaterials. The main objective of this review was to identify and analyze the studies conducted on AI tools, including machine learning, data mining, and deep learning, for the safety and risk assessment of nanomaterial. In this research according to the search strategies, our inclusion criteria, we found that most articles on the predictions of nanoparticle toxicity through artificial intelligence models were from the United States and China.

The results of this study showed that metal oxide and the metallic categories are the most common nanoparticles for the prediction of toxicity. In the metal oxide category, iron oxide and TiO2, and in the metallic category, Au and Ag were the most popular. Metal/metal oxide nanoparticles (M/MO NPs), in different areas of solid-state chemistry, have gained significant momentum due to their physical and chemical properties (Chaudhary et al. 2019). Sawicki et al. (2019) in their study found that metal/metal oxide nanoparticles are also used extensively for disease diagnosis, drug delivery, gene delivery, and antimicrobial agent delivery

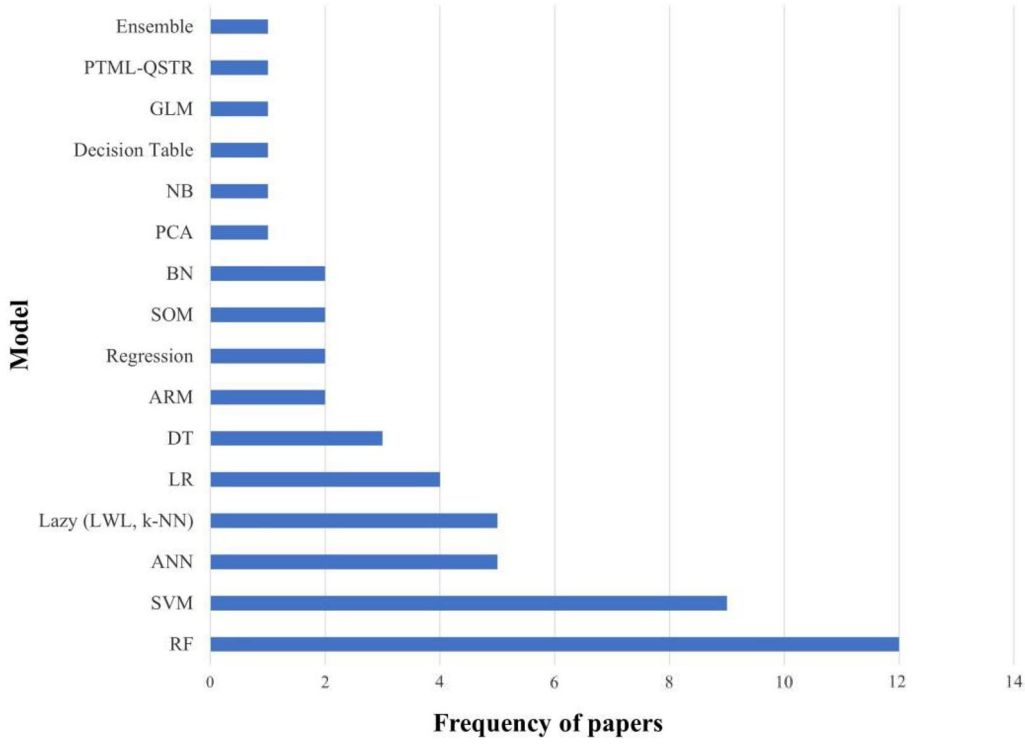

Figure 2. Frequency of models in the papers.

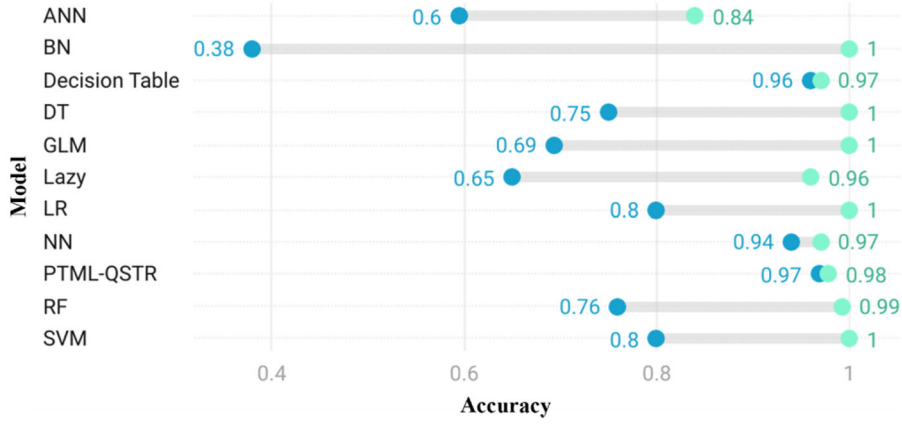

Figure 3. Accuracy of models.

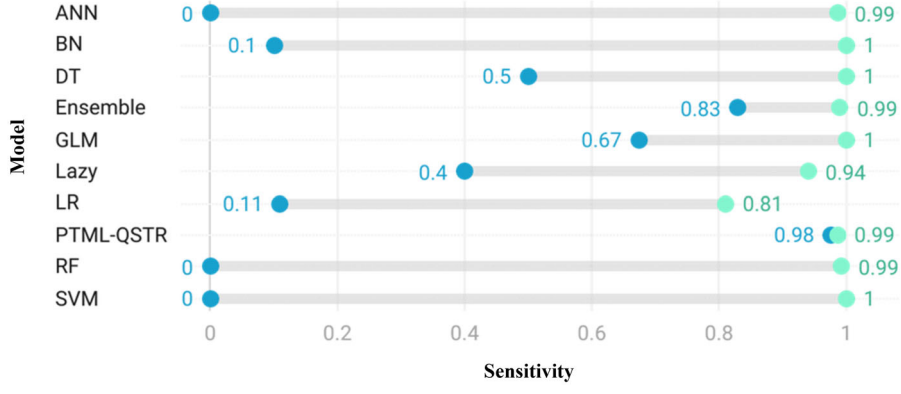

Figure 4. Sensitivity of models.

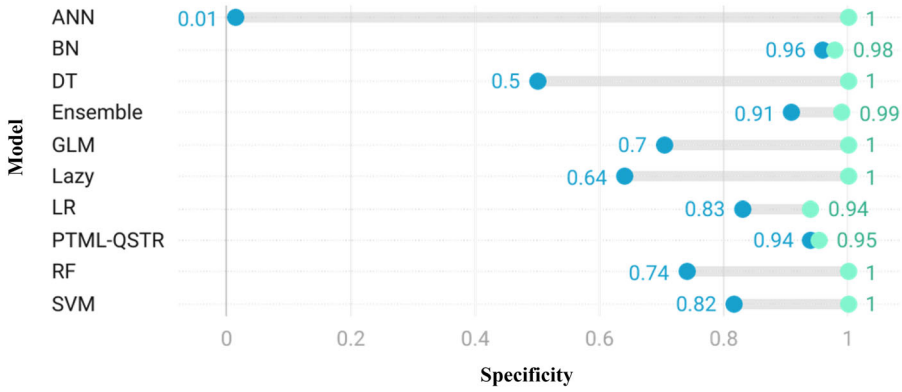

Figure 5. Specificity of models.

The other NPs, from the category of metal oxide, is TiO^2, which is medically used in bone and tissue engineering due to its reliability in inducing cell adhesion, cell migration, and healing (Nikolova and Chavali 2020; Ahn et al. 2018). On the other hand, these nanoparticles are used in health products in different markets and can block ultraviolet rays, causing concern about the dangers of this substance for health, safety, and the environment in the environment due to their dispersion (Ajdary et al. 2018). Nikolova et al. (2020) found that these nanoparticles are utilized as a strong carrier for the delivery of vaccines with the therapeutic application. In addition, Iron oxide nanoparticles have valuable biomedical applications and are one of the most vital nanoparticles (Vakili-Ghartavol et al. 2020; Sangaiya and Jayaprakash 2018). Au NPs, effectively protect against bacterial culture and prevent their growth (Chaudhary et al. 2019, Pourali et al. 2017). Sani et al. (2021) found that one of the things that increase the toxicity of AuNPs compared to larger particles is due to the physicochemical characteristics that internalize them into cells, which is not possible with larger particles. In addition, these nanoparticles have a high level of aggregation within the liver and spleen, which lead to more damage to the organism. Silver nanoparticles (Ag NPs) from the metallic category are also used as antimicrobial agents to treat burns and infections and are employed in personal care products (Chaudhary et al. 2019, Tortella et al. 2020). These nanoparticles are toxic to nerve cells that cause cell death (Sawicki et al. 2019). Tortella et al. (2020) found that silver nanoparticles are one of the most widely utilized metal nanoparticles that, due to their small size, pass through the biological membrane, and by entering into the cells of the damaged organisms cause toxicity at different levels. The studies above and the present research try to predict the toxicity of these nanoparticles.

SVM has a great ability to learn data classification patterns with balanced accuracy and repeatability (Pisner and Schnyer 2020). Raj and Ananthi (2019) revealed SVM provides a globally optimal solution, which makes it especially powerful. On the other hand, SVM performs better compared to advanced yielding features such as the traditional multi-layer perceptron model, radial basis function, and others (das Chagas Moura et al. 2011). Therefore it seems a powerful method (Pisner and Schnyer 2020). We also found SVM has been used more extensively in studies.

Another algorithm that has been commonly used in our findings is Random Forest which helps predict prognosis for clinical decision support, which makes it popular (Li et al. 2020). Touw et al. (2013) in their study, found that another reason that has made this algorithm popular is pattern recognition in omics data. On the other hand, due to attention to this model and its ability to manage highly linear data, it is suitable for forecasting tasks. Moreover, RF gives a perfect solution for solving high-dimensional issues and is considered an effective feature selection algorithm of choice (Li et al. 2020). The above findings verify why the importance of these models is high.

Also, studies included in this review indicated that the decision table model had the least variety of accuracy. The PTML-QSTR model had the least variety of specificity, sensitivity, and accuracy. BN had the least variety of specificity but the most variety in accuracy. ANN model had the most variety in sensitivity and specificity. Only one study (Concu et al. 2017) used ANN to predict the toxicity of nanoparticles. The researchers used ten Y-Randomization methods to evaluate their proposed model. The evaluation of the proposed ANN model showed high variation in specificity (ranging from

1.40% to 100%) and sensitivity (ranging from 0 to 98.6%). These following articles are examples of using PTML-QSTR model that is in line with our results. Kleandrova et al. (2014) develop a QSAR-perturbation model to anticipate diverse ecotoxicological profiles of nanoparticles. This model was determined from a database containing 5520 cases (nanoparticle– nanoparticle sets), and it displayed accuracies of ca. 99% in both training and prediction sets. In addition, Luan et al. (2014) developed a QSTR-perturbation model to predict the cytotoxicity of nanoparticles against mammalian cell lines. The model exhibited an accuracy higher than 93% for both training and prediction sets. In addition, Alejandro Speck-Planche et al. (2015) developed a QSAR irritation model that is given to the concurrent prediction of the distinctive antibacterial activities of NPs by considering the physicochemical/structural changes. The model showed an accuracy rate of around 98% for classifying NPs as dynamic or inactive. SVM and RF had the most variety of specificity. Sidharta and Sano (2018) indicated that, by comparing the decision tree, naïve Bayes and K-NN on web phishing models. The best predictor model with execution in terms of accuracy in this data set is the decision tree model, with a precision performance of 90.1% and a standard deviation of ±2.35%. Rodriguez-Galiano et al. (2015) in their systematic review studies comparing different machine learning methods, found that SVM models were less accurate than other methods and reached the highest average MSE errors (mean 0.19, standard deviation 0.03). However, the RF model was robust and stable, with the lowest mean and standard deviation of MSE values (mean 0.12, standard deviation 0.01). Zheng et al. (2017) in their study by comparing different machine learning models to work on diagnosis, diagnosis and medication cases of T2DM electronic health records (EHR) data using feature engineering and machine learning, concluded that SVM and RF models have the highest performance index and provide more than 95% accuracy, sensitivity, and specificity.

This study had several strengths, including searches on various databases: PubMed, Web of Science, and Scopus. We also did not filter the results for a time. The limitation of this study was to exclude non-English language studies.

Conclusion

Prediction of the possible toxic effects of nanoparticles in the environment and biological systems is necessary for safety purposes for humans, animals, and the environment. However, toxicity assessment of nanomaterials tends toward a more effortless and faster approach due to the difficulties of experimental methods. The use of AI classifiers has shown great potential to predict the toxicity of nanoparticles. Therefore, AI tools provide an opportunity to detect of harmful effects of nanomaterials which can help to prevent and manage the negative effects of nanomaterials on the ecosystem and biological systems. More research should be conducted to obtain more data regarding the toxicity of nanoparticles to train AI models in future studies.

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Ethics approval and consent to participate

Not applicable.

Author contributions

ABY, SMA and MA conceived the idea for the review. ABY, SMA, HM, and MG were involved in the study selection, quality assessment, and data extraction. ABY, and SMA conducted the statistical analysis. ABY, SMA, HM, MA, and NM wrote the first draft of the manuscript. All authors reviewed the manuscript, contributed to critical changes, and approved the final version of the manuscript for submission.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

All data generated or analyzed during this study are included in this published article.

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