

Drug toxicity refers to the chemical molecule's adverse effect on an organism or on any part of the organism due to the compound's mode of action or metabolism. The extended scope of AI has the potential to predict the off-target and on-target effects of drug molecules along with in vivo safety analysis of chemical compounds before their synthesis has fascinated the scientists associated with the drug development process. The involvement of AI has reduced drug development time, cost, attrition rates, and human resources. For this different web-based tools have been developed such as LimTox (<http://limtox.bioinfo.cnio.es/>) [321], pkCSM (<http://biosig.unimelb.edu.au/pkcsm/>) [322], admetSAR (http://lmmd.ecust.edu.cn/admet_sar2/) [323], and Toxtree (<http://toxtree.sourceforge.net/>) [324]. Srivastava et al. 2020 used admetSAR to evaluate the toxicity of Withania somnifera as a therapeutic compound against COVID-19, whereas Uygun et al. 2021 incorporated pkCSM for the identification of the therapeutic effect and toxicological properties of pyrazolo[1,5-a]pyrazine-4(5H)-one derivative on lung adenocarcinoma cell line [325, 326]. Advancements in AI-based approaches led to the development of different toxicity prediction software and web-based tools such as Tox21 (<https://ntp.niehs.nih.gov/whatwestudy/tox21/index.html>) [327], SEA (<http://sea.bkslab.org/>) [328], eToxPred (<https://www.brylinski.org/etoxpred-0>) [329], and TargeTox (<https://github.com/artem-lysenko/TargeTox>) [330]. Tox21 evaluates the toxicity of 12,707 environmental compounds and drugs, whereas SEA forecasts the toxicity of 656 marketed drugs against 73 unintended targets. TargeTox predicts toxicity risk based on the target-drug biological network. In 2016, Huang et al. predicted the in vivo toxicity profile and mechanism characterization of more than 10,000 chemical compounds through modeling Tox21, whereas, in the same year, Zhou et al. predicted the cancer-relevant proteins using an improved molecular SEA [331, 332]. Further, Gupta and Rana. 2019 employed eToxPred to predict the toxicity of small molecules of androgen receptor. The authors incorporated 1444 characteristics features of small molecules on 10,273 drugs in which 461 are considered as active and 9812 are inactive [333]. DeepTox (<http://bioinf.jku.at/research/DeepTox/tox21.html>) [334] and ProCTOR (<https://github.com/kgayvert/ProCTOR>) [335], are used for prediction of toxicity of new compounds and prediction of the toxicity probability in clinical trials, respectively. For example, Robledo-Cadena et al. 2020 predicted the effect of non-steroidal anti-inflammatory drugs on cisplatin, paclitaxel, and doxorubicin efficacy against cervix cancer cells using ProCTOR, whereas Gilvary et al. 2020 identified the novel indications for 2,576 small molecules incorporated with 16 different drug features for PD and Type 2 diabetes [336, 337]. Similarly, using DeepTox, Simm et al. 2018 analyzed and repurposed high-throughput imaging assay data to predict the biological activity of different chemical compounds that were targeting alternative biological pathways and processes [338]. Furthermore, DeepTox was used for the development of several ML and DL algorithms, which predicts the toxicity properties and chemical characteristics features of drug compounds such as SMILES2Vec (predicts chemical properties) [339], Chemception (DNN-based prediction of chemical properties) [245], DeepSynergy (prediction of anti-cancer drug synergy with DL) [340], and deepAOT (prediction of compound acute oral toxicity) [341]. However, the accuracy and precision of DeepTox and ProCTOR could be increased by using large and refined data sets, which could be achieved with the pharmaceutical industry's involvement. Recently, other ML-based tools such as SPIDER [342] and read-across structure-activity relationships (RASAR)

[343] were developed, which are capable of analyzing μ -lapachone targets and linking molecular structures and toxic properties of an unknown compound, respectively. Zhang et al. [344] developed different toxicity predictive models for drug-induced liver toxicity based on five ML algorithms combined with MACCS or FP4 fingerprinting. The results demonstrated that the best model yielded an accuracy rate of 75% against an external validation data set [344]. Similarly, several toxicity evaluation algorithms were constructed based on ML methods such as relevance vector machine (RVM), regularized-RF, C5.0 trees, eXtreme gradient boosting (XGBoost), AdaBoost, SVM boosting (SVMBoost), RVM Boosting (RVMBost). The constructed models were used to evaluate rat oral acute toxicity, respiratory toxicity, and urinary tract toxicity [345–348]. In recent years, the execution of deep-learning algorithms has led to novel approaches for the molecular representation of chemical compounds, making DL methods suitable for predicting compound toxicity. Further, the potential for DL algorithms for toxicity prediction depends on the quality and quantity of data sets. In short, more research should be done to make AI-based algorithms reliable for toxicity prediction. However, the current ML-based predictors remain inappropriate to replace biological systems, but they are sufficient to extend the medicinal chemistry principles in the right direction, which reduces the number of synthesis cycles. Further, the detailed description of toxicity prediction AI-based algorithms and tools is discussed in Table 2.