I. Supplementary Data

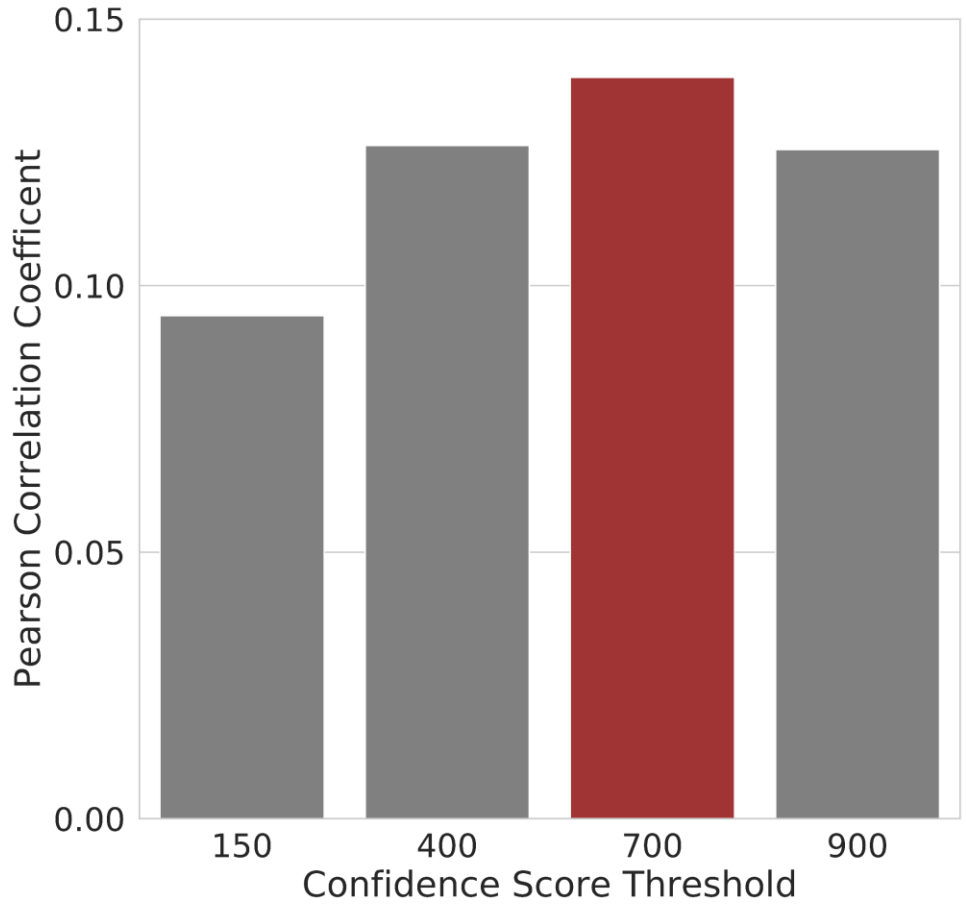

Fig. S1. Pearson correlation coefficient between ADR similarity and target similarity of drug pairs according to threshold of confidence score for protein-protein interactions and drug-protein interactions. Threshold of confidence score is divided into 4 categories suggested by the author of the database; low confidence(150), medium confidence(400), high confidence(700), highest confidence(900). Jaccard similarity between target vector and ADR vector were used for compute ADR similarity and target similarity.

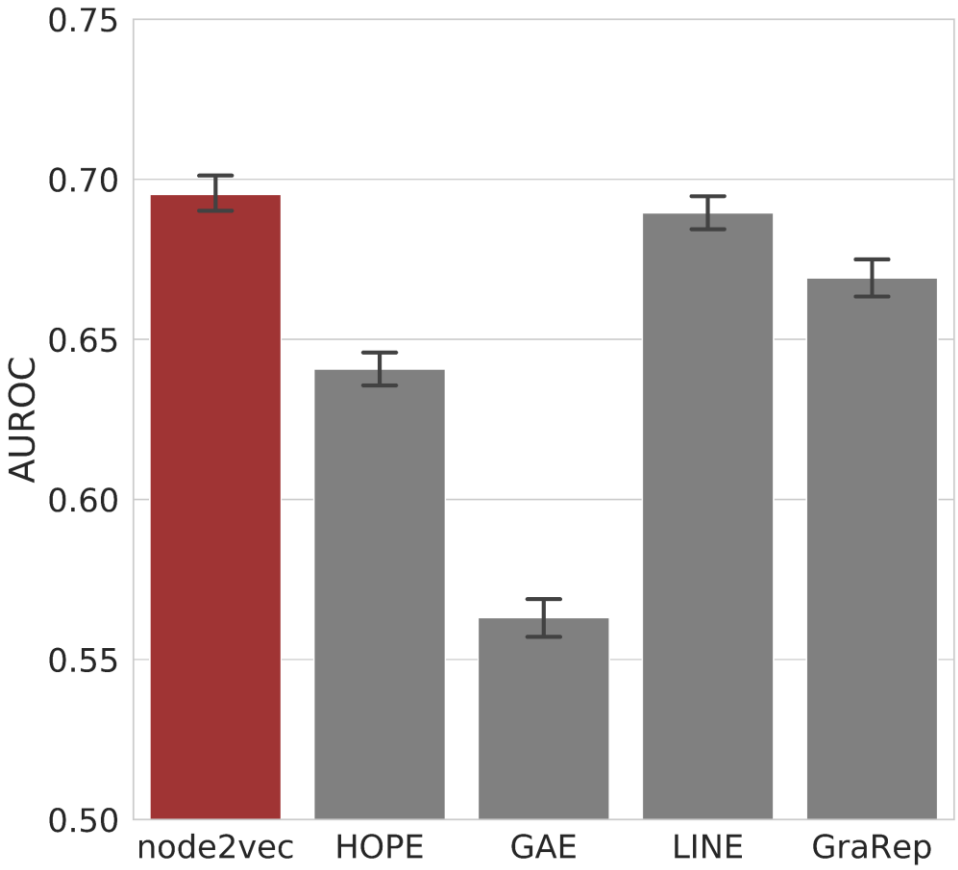

Fig. S2. Effects of graph embedding methods on ADR predictions. Performance of ADR predictions measured with 10-fold cross-validation. The error bar indicates the 95% confidence interval over cross-validation.

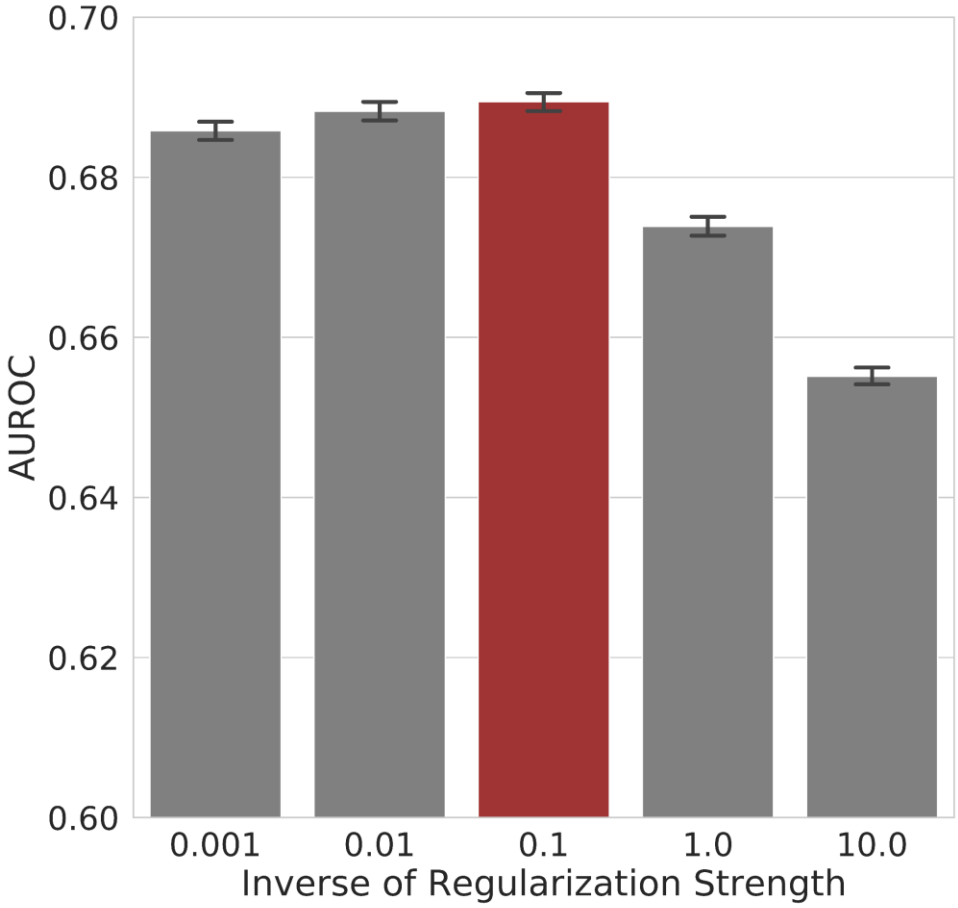

Fig. S3. Effects of regularization strength of logistic regression on ADR predictions. Performance of ADR predictions measured with 10-fold cross-validation. The error bar indicates the 95% confidence interval over cross-validation.

	Drug binds to the protein	Drug not binds to the protein
Drug has the ADR	True positive (TP)	False negative (FN)
Drug has not the ADR	False positive (FP)	True negative (TN)

Fig. S4. Confusion matrix of drugs categorized by the related ADR and binding protein. Using binding to a specific protein as a test for whether a drug has ADR, all drugs can be classified into one of four cases in the confusion matrix (TP, FN, FP, TN).

Table S1. Effects of hyperparameter (p, q) of node2vec on ADR predictions.

log(p)	log(q)	AUROC
-2	-2	0.6904±0.0057
-2	-1	0.6901±0.0057
-2	0	0.6876±0.0059
-2	1	0.688±0.0059
-2	2	0.6858±0.0059
-1	-2	0.6906±0.0058
-1	-1	0.6888±0.0058
-1	0	0.6888±0.0058
-1	1	0.6872±0.0059
-1	2	0.6895±0.0058
0	-2	0.6907±0.0059
0	-1	0.6885±0.0057
0	0	0.6914±0.0057
0	1	0.6890±0.0058
0	2	0.6883±0.0058
1	-2	0.6903±0.0058
1	-1	0.6947±0.0057
1	0	0.6906±0.0058
1	1	0.6857±0.0058
1	2	0.6838±0.0058
2	-2	0.6890±0.0058
2	-1	0.6953±0.0057
2	0	0.6920±0.0057
2	1	0.6913±0.0057
2	2	0.6889±0.0057

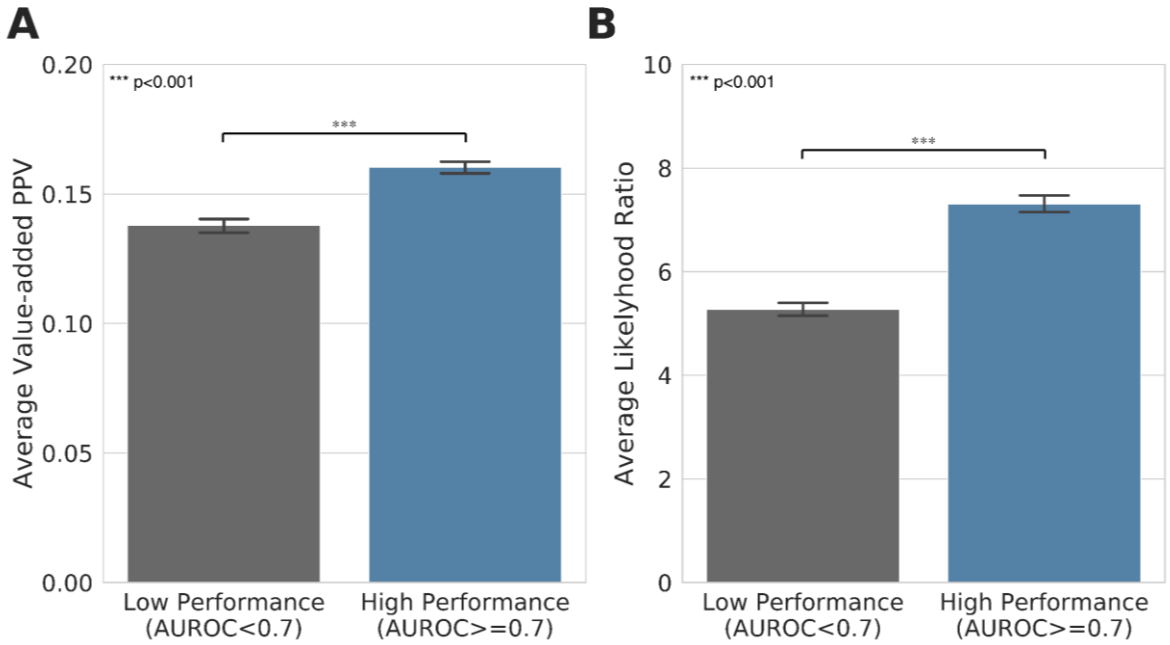

Fig. S5. Effect of ADR prediction model performance on VAPPV and LR of top 50 predictive proteins for the ADR. (A, B) Bar plots showing the average VAPPV and LR of the top 50 predicted proteins for two ADR groups according to the performance of their prediction models. The error bar indicates the 95% confidence interval of the average.

Table S2. Common pharmacological property of the top 10 drug pairs with the highest similarity in low-dimensional representation with low ADR similarity (0.0~0.2).

Drug A	Drug B	Representation similarity	ADR similarity	Common pharmacological property
Epinephrine	Norepinephrine	0.936	0.115	catecholamine family
Flurazepam	Quazepam	0.930	0.155	benzodiazepines
Quazepam	Temazepam	0.929	0.070	benzodiazepines
Bromazepam	Quazepam	0.929	0.107	benzodiazepines
Bromazepam	Estazolam	0.927	0.186	benzodiazepines
Flumazenil	Quazepam	0.918	0.060	benzodiazepines
thiothixene	Iloperidone	0.917	0.140	antipsychotic drugs
Chloramphenicol	Papaverine	0.914	0.095	-
Pramipexole	Iloperidone	0.913	0.182	dopamine agonist, antagonist
Dorzolamide	Hydroflumethiazide	0.909	0.076	hypertension teatment

Table S3. Top 10 predictive proteins for epilepsy

Rank	Symbol	VAPPV	LR	Reference
1	**HTR3A**	0.330	3.979	Zhao *et al*., 2018
5	**HTR3E**	N/A	N/A	
2	KATNAL2	0.124	1.658	Kurul *et al*., 2021
3	CD27	0.374	4.969	Rubio *et al*., 2016
4	CD70	N/A	N/A	
6	**SLC7A11**	0.290	3.316	Robert *et al*., 2015; Sørensen *et al*., 2018
7	SLC6A4	0.358	4.591	Cárdenas-Rodríguez *et al*., 2020
8	ABCC1	0.327	3.937	Van Vliet *et al*., 2005; Dombrowski *et al*., 2001
9	**MVP**	N/A	N/A	Sisodiya *et al*., 2003; Liu *et al*., 2011; Aronica *et al*., 2003
10	**CASP3**	0.190	2.162	Henshall *et al*., 2005

*Proteins in bold have direct causal evidence for ADR

Table S4. Top 10 KEGG pathways enriched by the top 50 predictive proteins for epilepsy

Rank	Name	P-value	Reference
1	**Serotonergic synapse**	3.6e-10	Richerson and Buchanan, 2011
2	**Apoptosis**	6.4e-08	Henshall and Engel, 2013
3	**Taste transduction**	5.5e-05	Heckmann *et al*., 2003
4	Drug metabolism	1.5e-04	Hedges *et al*., 2003
5	Legionellosis	3.5e-04	Johnson *et al*., 1984
6	Pentose and glucuronate interconversions	3.3e-03	-
7	MicroRNAs in cancer	6.6e-03	You *et al*., 2012
8	**Cocaine addiction**	6.7e-03	Kopppel *et al*., 1996
9	**Alcoholism**	1.0e-02	Hillborm *et al*., 2003
10	**Amphetamine addiction**	q.3e-02	Alldredege *et al*., 1989

*KEGG pathways in bold have direct causal evidence for ADR

Table S5. The summary of previous ADR-protein relation prediction studies

Name	Method	#Protein	#ADR	Score type	Supervised learning***
Khun et al., 2013	Fisher's exact test	296	1,428	q-value	No
Chen et al., 2016	Random walk with restart	1,153	4,192	probability	Yes
Letswaart et al., 2020	Random forest	184	321*	Gini score	No
Smit et al., 2021	Fisher's exact test	100	3,278	corrected p-value	No
Galletti et al., 2022	Ensemble model**	13,090	84	probability	Yes
LAPINE (our method)	Logistic regression	13,633	4,085	z-score	No

* ADR defined with the high level group term (HLGT)
** SVM, Neural network, Random forest
*** The method used known ADR-protein relations to learn the prediction model

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