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Safety Prediction for Pre 1988 Permitted Fixed Dose Combinations Using Artificial Intelligence - In Silico Approach

Ajay **Singh**[1], Deepika[2], and Shiwank **Rana**[1*].

[1] Dreamz College of Pharmacy, Sundernagar, Mandi, Himachal Pradesh, 175036, India

***Corresponding Author**: Shiwank Rana Assistant Professor, Dreamz College of Pharmacy, Sundernagar, Mandi, HP (India). Pin: 175036
Email: shiwankrana@gmail.com

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ABSTRACT

Background: Since the Drug Controller General of India (DCGI) approved more than 130 FDCs, the usage of fixed dose combinations (FDCs) has become more popular. FDCs are medications that contain more than one active component, aiming to enhance adherence, reduce adverse effects, and improve effectiveness. In a recent development, the Central Drug Standard Control Organisation (CDSCO) issued a notice on January 11, 2024, calling for the evaluation of pre-1988 permitted FDCs.

Objective: This study aimed to determine whether AI algorithms could predict the safety of FDCs by examining their pharmacokinetic properties.

Methods: In order to assess pharmacokinetic properties and verify the safety of pre-1988 permitted fixed dose combinations that were approved by The Central Drug Standard Control Organisation, India (CDSCO), this study used a range of AI tools, including ADMET.AI, SwissADME, vNN-ADMET, and AERSMine.

Results: The results made by these tools were giving dissimilar properties in the same drug combinations. So, these tools are presently needs to be developed to have more accurate and precise results.

Conclusion: This research contributes to the ongoing discourse surrounding FDCs, pharmaceutical innovation, and regulatory practices, providing valuable insights that can shape future approaches in drug development and patient care with the help of artificial intelligence and data-based analysis tools. Additionally, this work helps to strengthen the credibility of the current A.I. development for in-silico pharmacokinetic predictions.

KEYWORDS: Awareness and Attitudes, Cross-Sectional Studies, Off-Label Drugs, Pharmacists, and Parents.

INTRODUCTION

Fixed dose combinations (FDCs) are a type of medication that has many active ingredients and refers to a particular dosage. These can be given as single product or given in a synchronous way to the patient. The definition of a FDC drug could differ by the means of different regulatory bodies. The goal of these regulatory authorities but the rationale in making of FDCs is to improve adherence of multiple drugs added to be given together. FDCs tend to be useful against multiple chronic disorders often co-exist; reduce the adverse effects and cost, increase the efficacy and action of drug [1-9]. Over 130 FDCs have been approved by the Drug Controller General of India (DCGI) in the last three years. This shows the Fixed Dose Combinations are easily accessible and engaging for a broad audience and gradually increasing this engagement in every age group [10-16]. This factor also contributes to the growth of the Indian pharmaceutical market, enhancing its overall size, according to the IBEF (India Brand Equity Foundation) the Indian pharmaceutical size is 50 billion US Dollars in present time and by the end of the decade the total market size is expected to reach 130 billion US dollars [17-19]. Earlier this year on 11 January 2024 CDSCO (Central Drug Standard Control Organization) released a notice for the Evaluation of some pre-1988 permitted Fixed Dose Combination, to be stated their safety and efficacy data by conducting the phase 4 trials of the drug under the time of one year [20].

MATERIALS AND METHODS

Inclusion Criteria

The oral FDCs were chosen from the early 2024 public notice from CDSCO enlisted 5 oral FDCs, as shown in Table I. In order to assess pharmacokinetic properties and verify the safety of pre-1988 permitted fixed dose combinations that were approved by The Central Drug Standard Control Organisation, India (CDSCO), this study used a range of AI tools, including ADMET.AI, SwissADME, vNN-ADMET, and AERSMine.

Table I: Fixed dose combinations that are permitted before 1988 included in CDSCO notice of evaluation

Sr. no.	FDCs	Application	Adverse Drug Reactions (ADRs)
i.	Tablets containing 500 mg of paracetamol IP, 10 mg of phenylephrine hydrochloride IP, and 32 mg of caffeine anhydrous IP	Anti-pyretic, analgesic, common cold	Glossodynia, irritable bowel syndrome, liver injury, hypercholesterolemia
ii.	Tablets containing 15 mg & 30 mg of caffeine anhydrous IP; 500 mg & 650 mg of paracetamol; 5 mg & 10 mg of phenylephrine hydrochloride IP; and 2 mg & 4 mg of chlorpheniramine maleate IP	Common cold, watery eyes, runny nose	Sinusitis, lower respiratory tract infection, liver injury
iii.	Tablets with 250 mg of paracetamol IP, 150 mg of propyphenazone, and 30 mg of caffeine	Headache, toothache, postoperative pain	Hepatic enzyme increased, liver injury, hypercholesterolemia, analgesic drug level increased

iv.	Tablets containing 25 mg of imipramine hydrochloride IP and 2 mg & 5 mg of diazepam IP	Depression, nerve pain	Agitation, coma, depressed level of consciousness, hallucination
v.	Syrup containing 2 mg & 2.5 mg of chlorpheniramine maleate IP; 100 mg & 125 mg of ammonium chloride IP; and 50 mg/5ml & 55 mg/5ml sodium citrate IP	Cough, congestion with mucus	Abdominal pain, somnolence, chronic kidney disease, dry mouth, toxic epidermal necrolysis

Exclusion Criteria

The Drugs are excluded such as herbal, cosmetics, nutraceutical, parenteral and topical products; only oral fixed dose combinations are included.

1. ADMET.AI

The assessment of toxicity and pharmacokinetics is essential for developing novel drug discovery strategies. Generative AI and *in silico* virtual assets produce enormous amounts of molecules, which need to be whittled down to a manageable amount for synthesis and experimental verification. Assessing potential chemicals according to their Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) characteristics serves as an efficient primary filter. ADMET.AI is the command line tool, which is based on the python module; the generative predictions from the ADMET.AI gives in three different types in which first one is radial p lot for each molecule predicted five different properties (blood brain barrier, human ether-a-go-go-related gene (hERG) safe, bioavailability, solubility, and non-toxic). Second one is the distribution of ADMET predictions for each input molecule is displayed in a summary figure in relation to the drug bank reference set. Any two ADMET attributes can be displayed by adjusting the x- and y-axis. ADMET.AI provides a tabular prediction for every molecule (8 physiochemical properties, 41 ADMET properties). The units drive the regression properties, while the likelihood of the molecule having (blood brain barrier penetration) is the projected value for the classification properties [21, 26].

2. AERSMine

With its robust multi-cohort analysis tool that mines large amounts of information collected by the FDA's adverse event reporting system, AERSMine is at the forefront of pharmacovigilance. The platform gives researchers, clinicians, and regulatory professionals access to hundreds of thousands of clinical reports, currently totaling 20,346,289, enabling them to perform focused group comparisons (patients X medications), multidimensional subset-based correlation evaluations, along with view differential reporting patterns to identify a high-risk demographics segments. This goes beyond simple analysis; it seeks to reveal hidden connections among massive clinical impact data sets, gaining fresh perspectives on adverse events and demographic groupings. We revolutionize pharmacovigilance by identifying potential safety signals and producing testable hypotheses based on risk-altering interactions. This leads to

better therapeutic strategies and increased therapeutic efficacy, which ultimately assure safer healthcare procedures and better patient outcomes [27, 32].

3. vNN-ADMET

The vNN-ADMET web server is a publicly available web application that is intended to predict important pharmacokinetic characteristics, and to make it easier for new models to be built using our unique variable nearest neighbor (vNN) approach. This platform provides fifteen carefully constructed ADMET prediction models, all of which are intended to help users quickly and confidently assess a wide range of important attributes. These include interactions between drugs, Cell toxicity, genetic mutation, cardiac toxicity, microsomal stability, and drug-induced injury to the liver. They offer priceless information about the safety and effectiveness profiles of pharmacological substances. Through our user-friendly interface, researchers and practitioners alike can harness the power of predictive analytics to streamline drug development processes and prioritize compounds with the highest potential for success in clinical settings [33, 38].

4. SwissADME

With the help of a set of tools available on this web-based platform, users can calculate a broad range of physicochemical descriptors, forecast crucial ADME parameters, pharmacokinetic parameters, evaluate drug-likeness properties, and determine whether one or more small molecules are suitable for medicinal chemistry purposes. These features are strategically designed to provide robust support throughout the drug discovery process, empowering researchers, and practitioners with valuable insights into the molecular properties and potential efficacy of compounds under investigation. Whether exploring novel drug candidates or optimizing existing molecules, our platform serves as an indispensable resource, facilitating informed decision-making and accelerating the journey from drug discovery to clinical application [39-45].

5. Drug Bank

Drug bank online is a useful tooling that provides free access to a wide range of information about drugs structure and their targets. It's popular among professionals like drug industry experts, chemists, pharmacists, doctors, students, and the public. By offering detailed data on drugs and their targets, drug bank helps drive progress in data-driven medicine [46-51].

RESULT AND DISCUSSION

1. Tablets containing 500 mg of paracetamol IP, 10 mg of phenylephrine hydrochloride IP, and 32 mg of caffeine anhydrous IP

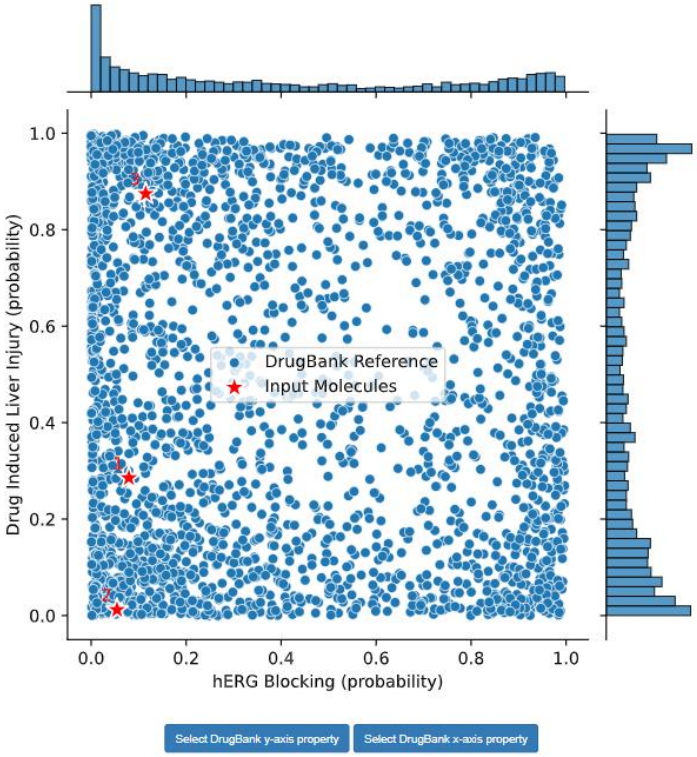

Figure. 1: Summary plot of drug molecule 1 (paracetamol) + molecule 2 (phenylephrine) hydrochloride + molecule 3 (caffeine anhydrous) between two different properties (drug induced liver injury [DILI] and hERG blocking)

i. ADMET.AI predictions

This combination is observed between the two properties of drug induced liver injury and hERG blocking (probability), the observation was that the molecule 3 (caffeine anhydrous) was having probability of affecting the liver most than the other drugs. Whereas the molecules 2 (phenylephrine hydrochloride) is partially having an effect on liver, and very low effect on the potassium channel (Figure. 1).

ii. SwissADME predictions

The observation made under the human intestinal absorption of the molecule 2 (phenylephrine hydrochloride) and molecule 3 (caffeine anhydrous), whereas the molecule 1 (paracetamol) is observed to cross the blood brain barrier.

iii. vNN-ADMET predictions

The prediction of this FDC is observed as the molecule 1 (paracetamol) is predicted to induce liver injury but do not affect in any other properties, on the other hand molecule 3 (caffeine anhydrous) does have effect on potassium channel by blocking it.

iv. AERSMine

According to the reports of AERSMine analysis tool the cases of the cases of the liver injury in total are the 19,682 and other adverse reactions are drug dependence, glossodynia, irritable bowel syndrome, and hypercholesterolemia, as depicted in Table II.

Table II: AERSMine reports for the combination paracetamol + phenylephrine hydrochloride + caffeine anhydrous

Sr. no.	Adverse reaction	Adverse reaction total reports	Absolute count of paracetamol	Absolute count of caffeine	Absolute count of phenylephrine
i.	Drug dependence	173,114	70,542	5,585	236
ii.	Glossodynia	22,827	5,453	1,523	354
iii.	Irritable bowel syndrome	25,224	5,496	968	225
iv.	Liver injury	19,682	4,396	838	168
v.	Hypercholesterolemia	11,877	2,206	368	65

2. Tablets containing 15 mg & 30 mg of caffeine anhydrous IP; 500 mg & 650 mg of paracetamol; 5 mg & 10 mg of phenylephrine hydrochloride IP; and 2 mg & 4 mg of chlorpheniramine maleate IP

i. ADMET.AI predictions

This FDC is observed between the two properties of drug induced liver injury and hERG blocking (probability), the observation was that the molecule 4 (caffeine) was having the probability of affecting the liver most and molecule 3 (paracetamol) have probability of affecting the liver partially as well. Whereas the molecule 1 (chlorpheniramine) is partially having no effect on liver and show highest probability of affecting on the potassium channel (blocker).

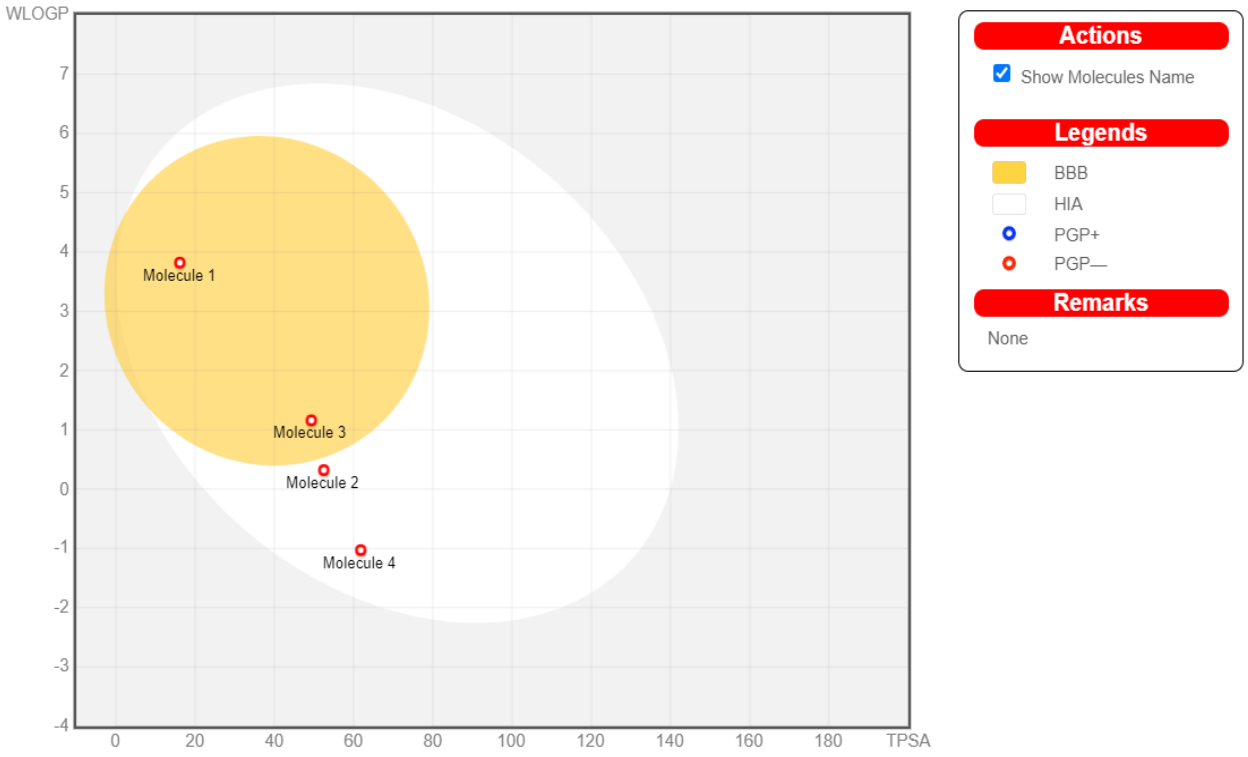

Figure. 2: Boiled egg plot of drug molecule 1 (chlorpheniramine) + molecule 2 (phenylephrine) + molecule 3 (paracetamol) + molecule 4 (caffeine) between two different properties (blood brain barrier and human intestinal absorption)

ii. SwissADME predictions

The observation made under the human intestinal absorption of the molecule 2 (phenylephrine) and 4 (caffeine), whereas the molecule 1 (chlorpheniramine) and 3 (paracetamol) is observed to penetrate the blood brain barrier, as shown below in the boiled egg diagram (Figure. 2).

iii. vNN-ADMET predictions

The prediction of this FDC is observed as the molecule 3 (paracetamol) is predicted to induce liver injury but do not affect in any other properties, on the other hand molecule 4 (caffeine) does have effect on potassium channel by blocking it.

iv. AERSMine

According to the reports of AERSMine analysis tool the cases of the cases of the liver injury in total are the 19,682 and other adverse reactions are drug dependence, sinusitis, lower respiratory tract infection, and drug abuse, as depicted in Table III.

Table III: AERSMine reports for the FDC combination chlorpheniramine + phenylephrine+ paracetamol + caffeine

Sr. no.	Adverse reaction	Adverse reaction total reports	Absolute Count of chlorpheniramine	Absolute Count of phenylephrine	Absolute count of paracetamol	Absolute count of caffeine
i.	Drug dependence	173,114	70,542	5,585	236	278
ii.	Sinusitis	119,574	20,151	1,991	475	479
iii.	Lower respiratory tract infection	49,156	9,285	985	179	535
iv.	Drug abuse	77,442	13,978	2,422	85	462
v.	Liver injury	19,682	4,396	838	168	55

3. Tablets with 250 mg of paracetamol IP, 150 mg of propyphenazone, and 30 mg of caffeine

i. ADMET.AI predictions

This FDC combination is observed between the two properties of drug induced liver injury and hERG blocking (probability), the observation was all the molecules were having very least probability of affecting the liver (50-52). Whereas the molecule 3 (caffeine) have very high effect on the potassium channel by blocking it and partial effect of molecule 1 (paracetamol) on potassium channel.

ii. SwissADME predictions

The observation made under the human intestinal absorption of the molecule 3 (caffeine), whereas the molecule 2 (propyphenazone) and 1 (paracetamol) is observed to penetrate the blood brain barrier.

iii. vNN-ADMET predictions

The prediction of this FDC is observed as the molecule 1 (paracetamol) is predicted to induce liver injury but do not affect in any other properties and molecule 2 (propyphenazone) is partially affect the

liver, on the other hand molecule 3 (caffeine) does have effect on potassium channel by blocking it (Figure. 3).

iv. AERSMine

According to the reports of AERSMine analysis tool the cases of the liver injury in total are the 19,682 and other adverse reactions are drug abuse, hepatic enzyme increased, hypercholesterolemia, and analgesic drug level increased, as depicted in Table IV

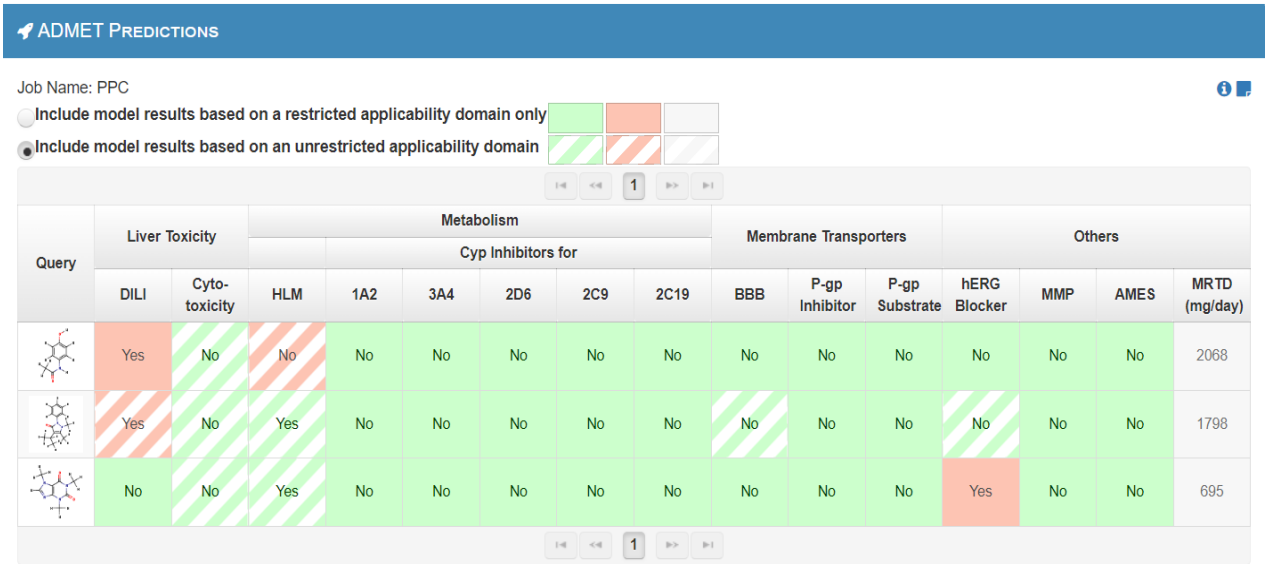

Figure. 3: vNN-ADMET predictions of drug molecule 1 (paracetamol) + molecule 2 (propyphenazone) + molecule 3 (caffeine) on different properties (liver toxicity, metabolism, membrane transporters).

Table IV: AERSMine reports for the FDC combination paracetamol + propyphenazone + caffeine

Sr. no.	Adverse reaction	Adverse reaction total reports	Absolute count of paracetamol	Absolute count of propyphenazone	Absolute count of caffeine
i.	Drug abuse	77,442	13,978	60	2,422
ii.	Hepatic enzyme increased	71,326	10,860	18	1,839
iii.	Liver injury	19,682	4,396	2	838
iv.	Hypercholesterolemia	11,877	2,206	2	368
v.	Analgesic drug level increased	1,283	1,074	2	26

4. Tablets containing 25 mg of imipramine hydrochloride IP and 2 mg & 5 mg of diazepam IP

i. ADMET.AI predictions

This FDC combination is observed between the two properties of blood brain barrier penetration and hERG blocking (probability). Where the molecule 1 (imipramine hydrochloride) is having high probability of penetrating the brain and partial effect of molecule 2 (diazepam) on potassium channel (Figure. 4).

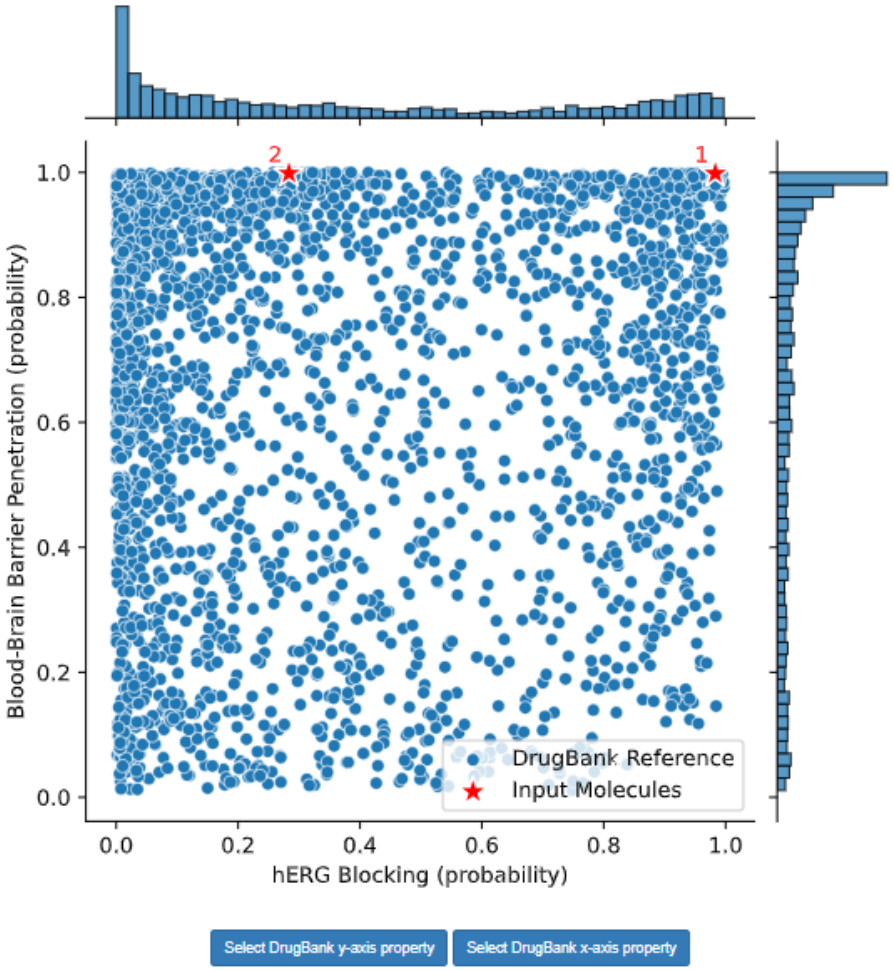

Figure. 4: Summary plot of drug molecule 1 (imipramine hydrochloride) + molecule 2 (diazepam) between two different properties (blood brain barrier penetration and hERG blocking)

ii. SwissADME predictions

The observation made under the human intestinal absorption and penetration of the blood brain barrier. It was observed as both the molecules (imipramine hydrochloride, diazepam) can penetrate the blood brain barrier.

iii. vNN-ADMET predictions

The prediction of this FDC is observed as the molecule 1 (imipramine hydrochloride) is predicted to induce liver injury, penetrates blood brain barrier, 2D6 inhibitor, P-gp inhibitor, hERG blocker and molecule 2 (diazepam) can also penetrates the blood brain barrier and have effect on potassium channel by blocking it.

iv. AERSMine

According to the reports of AERSMine

analysis tool the cases of the depressed level of consciousness in total are 43,921 in which for the FDC combination for the ADR events agitation, suicide attempts, coma, hallucination, and auditory defects, as depicted in Table V.

Table V: AERSMine reports for the FDC combination imipramine and diazepam

Sr. no.	Adverse reaction/ cases	Adverse reaction total reports	Absolute count of imipramine	Absolute count of diazepam
i.	Agitation	79,137	127	3,123
ii.	Suicide attempts	64,773	135	3,283
iii.	Coma	50,974	82	3,020
iv.	Depressed level of consciousness	43,921	115	1,893
v.	Hallucination, auditory defects	16,674	98	565

5. Syrup containing 2 mg & 2.5 mg of chlorpheniramine maleate IP; 100 mg & 125 mg of ammonium chloride IP; and 50 mg/5ml & 55 mg/5ml sodium citrate IP

i. ADMET.AI predictions

This FDC combination is observed between the two properties of blood brain barrier penetration and drug induced liver injury (probability), the observation was the molecule 3 (sodium citrate) is having partial effect on liver and partially penetrates the blood brain barrier. Whereas the molecule 1 (chlorpheniramine) and 2 (ammonium chloride) is having high probability of penetrating the blood brain barrier.

ii. SwissADME predictions

The observation made under the human intestinal absorption and penetration of the blood brain barrier. It was observed as both the molecules (chlorpheniramine, ammonium chloride) can penetrate the blood brain barrier. The molecule 3 (sodium citrate) was exempted as shown in the boiled egg diagram (Figure. 5).

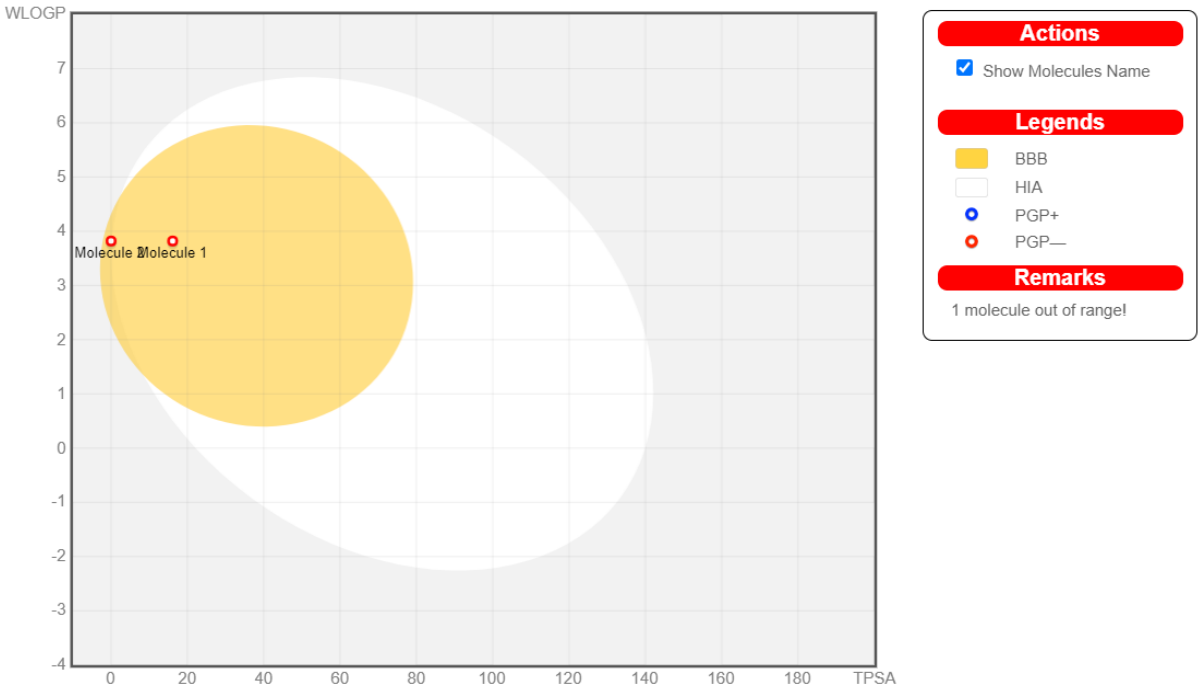

Figure. 5: Boiled egg plot of drug molecule 1 (chlorpheniramine) + molecule 2 (ammonium chloride) + molecule 3 (sodium citrate) between two different properties (blood brain barrier and human intestinal absorption)

iii. vNN-ADMET predictions

The FDC's prediction is seen in molecule 1's (chlorpheniramine) ability to partially incite liver damage, as well as molecule 3's (sodium citrate) ability to partially breach the blood brain barrier and P-gp substrate and P-gp inhibitor.

iv. AERSMine

According to the reports of AERSMine analysis tool the cases of the cases of the chronic kidney disease in total are 122,958 in which the for the FDC combination for the ADR events abdominal pain, somnolence, dry mouth, and toxic epidermal necrolysis, as depicted in Table VI.

Table VI: AERSMine reports for the FDC combination chlorpheniramine + ammonium chloride + sodium citrate

Sr. no.	Adverse reaction	Adverse reaction total reports	Absolute count of chlorpheniramine	Absolute count of ammonium chloride	Absolute count of sodium citrate
i.	Abdominal pain	259,222	1,099	172	878
ii.	Somnolence	207,296	984	143	249
iii.	Chronic kidney	122,958	1,583	275	329

	disease				
iv.	Dry mouth	82,551	365	136	174
v.	Toxic epidermal necrolysis	16,446	228	-	33

CONCLUSION

This study contributes to the ongoing discourse surrounding FDCs, pharmaceutical innovation, and regulatory practices, offering valuable insights that can inform future research. The various AI or data-based analysis and prediction tools can provide insights to the new drugs combinations by predicting the ADMET properties and by previously detected adverse reactions. The results made by these tools were giving dissimilar properties in the same drug combinations. So, these tools are presently needs to be developed to have more accurate and precise results.

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Ethical Statement: No experimental animal were used in whole study.

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