Research Article

Drug Metabolism: Pharmacoinformatics Efforts

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Cytochromes P450 are oxidizing enzymes, and among many subfamilies of cytochromes, a few play a significant role in drug metabolism. When a drug undergoes metabolism, cytochromes carry out many biochemical transformations like (i) conversion of prodrug to a drug, (ii) conversion into polar metabolites for easy excretion, or (iii) production of those metabolites which may be reactive and cause toxic effects in the body. Various experimental methods, such as mass spectral analysis, NMR, and in vitro analysis, can be utilized to determine the mechanisms involved in generating reactive metabolites that may cause toxicity. Pharmacoinformatic methods provide detailed atomic-level information, which is challenging to acquire from experimental studies, and this complementary information is essential in modern-day science. Methods like molecular dynamics, molecular docking, quantum chemical methods, and AI methods have become available in pharmacoinformatics to do in silico studies. This review aims to explore the use of quantum chemical studies and chemoinformatics, as well as the application of artificial intelligence, in investigating drug metabolism.

1. Introduction to drug metabolism

Drug metabolism is a pharmacokinetic process that transforms hydrophobic regions of drugs into hydrophilic regions through biotransformation.[1] The purpose of drug metabolism is to promote the drug's effectiveness in the body and ensure safe elimination from the body.[2] This involves the enzymatic breakdown of drugs or xenobiotics, such as by the CYP450 family of enzymes. This process is essential because the fat-soluble nature of drugs can prolong their stay in the body and cause unwanted side effects.

Drug metabolism can be classified into two main reactions: phase I and II. Phase I reactions involve modifying the drugs through oxidation, reduction, and hydrolysis, making it easier to eliminate from the body. However, these metabolized drugs may not be readily excreted from the body. Drugs require further modifications, which take place during phase II metabolism involving conjugation reactions.[3] In some instances, prior to undergoing phase II reactions, the drug metabolism process can generate reactive metabolites that may cause harm or toxicity.

Various factors can affect drug metabolism.[4] At the molecular level, the 3D structure of a drug and electronic structure play a crucial role. The active site of cytochrome enzymes, including their size, shape, exit channel and entry channel and amino acid composition, determines. The physiological and pathological conditions, diet, and environment influence the path and rate of biotransformation. Often, different organisms influence these biochemical reactions differently.[5]

Reactive metabolites (RMs) are produced due to drug metabolism and are highly electrophilic.[6] They can interact with biomolecules such as proteins, lipids, and nucleic acids, ultimately leading to cellular dysfunction. They can form covalent bonds with macromolecules, causing oxidative stress, protein malfunction, DNA damage, and cell death.[7]

The intricate details of the biotransformation happening in the body can be easily known using the in silico tools. These methods help us understand chemical interactions at the atomic scale, surface properties, reaction coordinate diagram of the biotransformation, hydrophobicity vs hydrophilicity balance,[8] the complete set of three-dimensional structures depicting the pathways of the reaction, charge distribution at various atoms of the drugs, are corresponding to the results emerging from experimental methods. Several in silico predictive tools became available that employ the physiochemical descriptors of drugs. Artificial intelligence (AI) methods are also becoming practical in evaluating drug metabolism and associated

toxicity. A few details are presented in this review.

2. Studies utilizing quantum chemistry to investigate drug metabolism and toxicity

Quantum chemistry involves use of Schrodinger wave equation to solve for the wavefunction of every electron in a chemical substance, including drugs and their metabolites. Various methods can be used to perform quantum chemical calculations. The method depends upon the type of system (small or large molecules). The most commonly used method for modelling CYP450-catalyzed metabolic reaction is density functional theory (DFT). B3LYP hybrid functional is the widely used density functional in which Hartree-Fock exact exchange[9] and Lee-Yang-Parr correlation functional[9] are mixed. The most realistic and economical approach for obtaining atomistic details of the enzyme catalytic environment is achieved using the two components: quantum mechanics and molecular mechanics (QM/MM) method, as the pure quantum chemicals method, take lots of computational time.[10]

Two case studies in this review are discussed in which the quantum chemical techniques were used. The results gave atomistic details of all the drugs and their metabolites. Energy values found using QC calculations were further used to determine the potential energy surface. In contrast, HOMO and LUMO values and shapes were used to predict the toxicity of the drugs and their metabolites.

2.1 Mechanistic details of metabolic conversion of remdesivir

Remdesivir (GS-5734) is an antiviral nucleoside analogue that showed positive findings against the Ebola virus. It was developed by Gilead Sciences in 2015.[11, 12] US FDA approved this drug for emergency use for potential COVID-19 treatments.[12] Despite initial hopes for its efficacy, the results of a randomized clinical trial indicated that remdesivir is not effective enough in reducing the mortality rate of hospitalized patients.[13]

Mackman et al. synthesized remdesivir that metabolized into active triphosphate inside the body.[14] Gotte et al. (2020) reported on the termination of RNA synthesis that inhibits the coronavirus replication cycle with the help of enzyme kinetic studies. The active triphosphate form of remdesivir effectively inhibits the replication cycle of the coronavirus by incorporating it into the virus's RdRp (nsp12) enzyme.[15] The old literature studies hinted at the metabolic activation pathway of remdesivir. Several enzymes were involved in the mechanism for protides proposed by McGuigan et al., which was based on experimental studies examining the metabolic conversion of 2′,3′-didehydro-2′,3′-dideoxythymidine monophosphate (d4T-MP) to its active metabolite (d4T-TP).[16] Furman et al. proposed a similar biotransformation pathway for PSI-7851, a phosphoramidate prodrug of 2′-deoxy-2′-α-fluoro-α-C-methyluridine-5′-monophosphate and its diastereomer PSI-7977.[16] Warren et al. performed *in vitro* metabolism studies of remdesivir. The concentrations inside the cell of various metabolites at various periods were also reported.[11]

Computational studies have also been performed to explore the drug's action. According to Zhang et al., the binding affinity of the triphosphate metabolite of remdesivir to SARS-CoV-2 RdRp was higher than that of ATP.[17] Jung et al. also investigated the binding site of remdesivir, and its monophosphate metabolite (GS-441524) on several non-structural proteins of SARS-CoV-2.[18] Wang and co-workers studied the mechanism of inhibition of SARS-CoV-2 RdRp.[19]

Our group utilized quantum chemical analysis to obtain atomic-level information about remdesivir metabolism.[20] Since the mass spectroscopy reports provided information on metabolites but no information on the three-dimensional (3D) conformations of the metabolites and the intermediates, the quantum chemical methods were employed to explore the drug metabolism mechanisms with 3D structures of each. A model system of remdesivir (MSR, MeOC(O)C(Me)NHP(O)(OMe)OPh) was built to study the biotransformation pathway of ProTide type prodrugs involving a pentacoordinate phosphorus intermediate, a cyclic anhydride intermediate and various P-N and P-O bond hydrolysis steps.

DFT calculations using the Gaussian09 software package were employed in the study. All the 3D structure optimizations were performed using hybrid functionals with Becke 3 Lee Yang Par (B3LYP) method. The X-Ray diffraction structure of remdesivir (CCDC No. 1525840) has been employed as an initial coordinate to maintain similar 3D geometry between MSR and remdesivir. The saddle points of the structures were established using the analytical frequencies estimated for the optimized structures. These computational studies gave an insight into the complete biotransformation pathway.

The critical function of phospharamidase enzyme in P-N bond hydrolysis of alanine metabolite of remdesivir (**R_M2**) was reported through the utilization of a combined approach involving molecular docking and quantum mechanics. The reaction involved the conversion of remdesivir into a

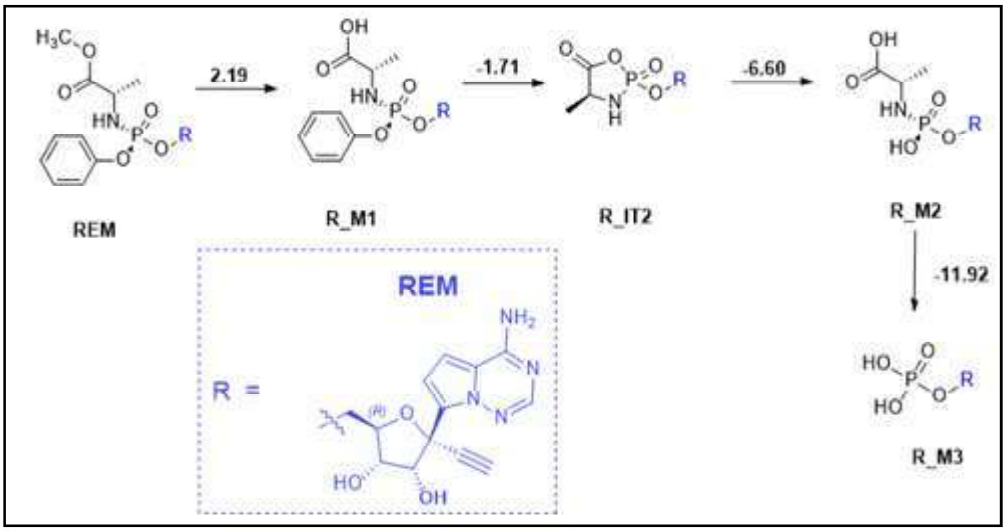

Figure 1. Metabolic pathway of remdesivir. Relative energy values (in kcal/mol) on the arrow marks represent ΔG values.

monophosphate derivative via four steps, i.e., hydrolysis of the ester bond to give free carboxylic acid metabolite followed by the intramolecular reaction of the carboxylic group at the phosphate centre and removal of phenol to yield **R_IT2** to give alanine metabolite **R_M2**. Further, the P-N bond hydrolysis of **R_M2** gave the **R_M3** metabolite (Figure 1). The formation of monophosphate metabolite of remdesivir **R_M3** through P-N bond hydrolysis in phosphoramidate metabolite **R_M2** required an energy of 41.78 kcal/mol which indicated the importance of an enzyme in P-N bond cleavage since this energy barrier is very high. The nucleoside phosphoramidase enzyme, human histidine triad nucleotide-binding protein 1 (hHint1), is responsible for cleaving the P-N bond in ProTide prodrugs. The calculations and analysis showed that the barrier was reduced by 27.52 kcal/mol. This analysis indicated the indispensable role of an enzyme in the P-N bond cleavage of phosphoramidate metabolite of remdesivir **R_M2**.

2.2 Biotransformation and toxicity prediction of drugs containing thiazole ring using quantum analysis

The biotransformation of drugs by cytochrome P450s (CYPs) can form electrophilic reactive metabolites (RMs), which can covalently bind with essential cellular macromolecules. The reactive metabolites can disrupt biological functions, leading to drug-drug interactions or idiosyncratic adverse drug interactions.[21,22,23] Reactive metabolites (RMs) are known to be generated by drugs that contain thiazole and aminothiazole groups. Several drugs containing thiazole rings, including sudoxicam, thiabendazole, and ritonavir, have been reported to be toxic. Sudoxicam, for example, is transformed through epoxidation, followed by a ring-opening reaction, which results in the formation of thioamides that can form covalent adducts.[22,24,25] The reactive metabolites from thiazole and thiabenzadole formed in mice were reported by Mizutani et al.[26,27] In their study, Kalgutkar and colleagues demonstrated that a 2-amino-4-aryl-thiazole functional group could undergo bioactivation in human liver microsomes. They also characterized the resulting GSH adducts using LC-MS/MS and NMR techniques.[28] Subramanian and colleagues also studied the cytochrome-mediated epoxidation of AKT inhibitors based on 2-aminothiazole.[29] Our group focussed on obtaining molecular details and explored the reaction coordinate diagram of drugs containing thiazole and aminothiazole rings using the model systems.[30]

Subramanian et al. utilized molecular docking studies with the Glide software in the Schrodinger suite of programs to investigate the site of metabolism for drugs containing thiazole.[31] They visually examined the highest-ranked poses and analyzed their interactions with active site residues and the heme Fe=O centre. Additionally, the authors used DFT (B3LYP(SCRF)/6-311++G(d,p)//6-31+G(d)) through the Gaussian 09 suite of programs to study the mechanisms associated with four crucial biotransformation pathways (epoxidation, S-oxidation, N-oxidation, and oxaziridine formation) of the model compounds thiazole (TZ) and aminothiazole (ATZ).

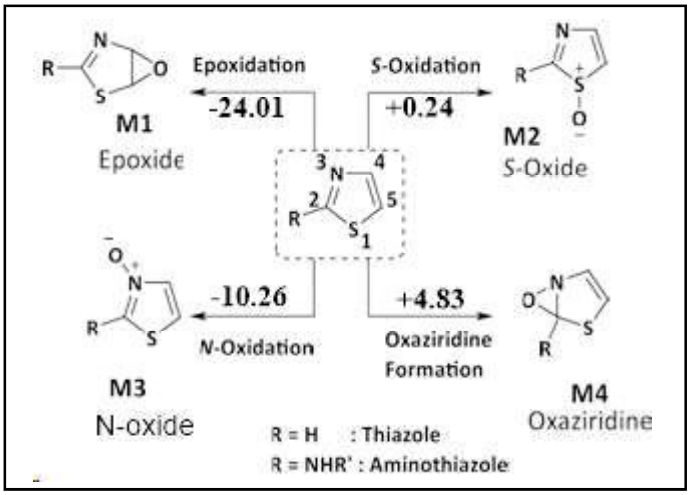

Figure 2. Biotransformation pathways of drugs containing thiazole rings include ΔG values, expressed in units of kcal/mol, indicated on the arrow as relative energy values.

The epoxidation reaction was found to be more favourable as this reaction is exergonic by 24.01 kcal/mol and requires a small energy barrier. The process begins with the attack of the Fe-O oxygen centre by the C5 carbon of the thiazole ring. The presence of the amine group at the C2 position enhances the favourability of the epoxidation reaction; that is, epoxidation at aminothiazole (ATZ) is more favourable by 7.92 kcal/mol compared to epoxidation at the thiazole group.

It was found that four reactive metabolites (M1-M4) of thiazoles could rearrange to an additional ten isomers via simple chemical rearrangements, as shown in Figure 3. The global electrophilicity indices of these 14 reactive metabolites were also calculated. The calculations suggested that **I10** and **I11** are highly electrophilic, and hence, they cause toxicity.

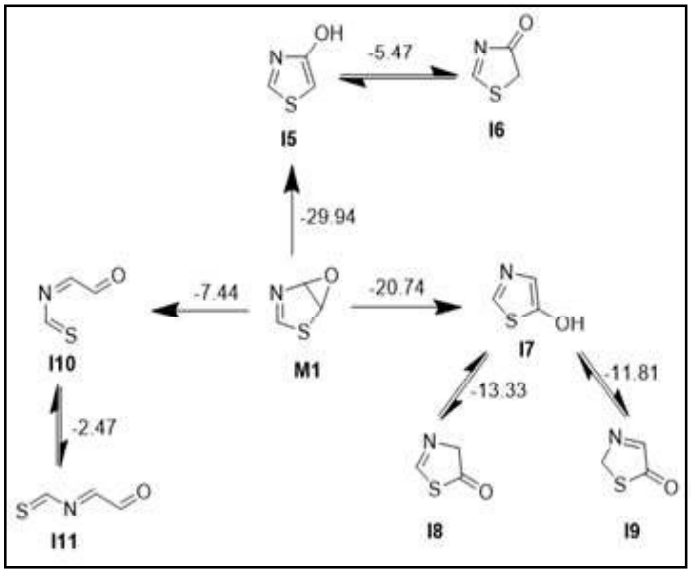

Figure 3. Isomeric forms of thiazole epoxide metabolite (M1) with rearrangeable processes and energy values in kcal/mol.

3. Artificial Intelligence in drug metabolism

Swamidas and coworkers[32] trained machine learning models using deep learning techniques to estimate quantum chemical properties. Transfer learning technology was used to conclude quantum chemical properties and to analyze chemical behaviour at the site level. This approach was employed in predicting the site of epoxidation and the site of covalent reactivity. The authors demonstrated that such a machine-learning approach could help explore the drug's metabolism.

Deep learning is one of the growing methods of artificial intelligence.[33] It can be applied to predict several aspects of the drug (i) toxicity, (ii) metabolism, (iii) bioactivity, (iv) mechanism of action, and thus valuable for drug design.[34] It has been established that very accurate quantum chemical properties can be estimated using deep learning methods. Quantum chemical studies are time-consuming because they involve the Schrodinger equation to solve the wavefunction to estimate the electronic structure of drugs and achieve a highly accurate level of prediction from quantum chemistry. Swamidas et al. adopted a two-stage machine learning approach. The deep learning method was used in the first stage, and in the second stage, the transfer learning method was used. In this approach, the deep neural network learns the observable properties of molecules similar to that of the wave function. Those calculated values can be transferred to another deep neural network to estimate drug metabolism and site-specific reactivity. The authors suggested that the deep learning approach using a small set of quantum chemical properties helps predict many more properties which are not employed in training.

The data set of epoxidation and reactivity were collected from previously published work by Hughes et al. Graph-based deep learning model was employed to compute quantum chemical representations. A message-passing neural network was constructed and trained using the PubChem QC project to predict the QC properties. Graph-based representations were computed for each atom in data sets collected for each model after training of PubChem QC data set. Two neural network models were developed used to perform transfer learning from quantum chemistry (TLQC) for both the reactivity data set and the epoxidation data set. The neural network was used to predict atomic level reactivity labels which had three layers incorporated into it. The first layer as input contained the information from the deep learning model, i.e., atom encodings, and this was passed to two hidden layers of 32 and 16 units and tanh activation. Finally, the information was passed through the output layer with four units and sigmoid activation. The next step performed by the authors was a comparison of models, topological descriptors (Top) or quantum chemical descriptors (QC). These models were used to predict both epoxidation and reactive sites. The 'neighbourhood convolution method' was used to construct the input details of the Top and QC models. The models were selected based on their highest overall accuracy across all tasks. The top-2 metric was chosen as the primary accuracy metric. Statistical tests like the McNemar test paired Z-test and Welch's t-test were also performed to validate the top-2 scores, AUCs and Z-scores.

By utilizing intermediate representations constructed through deep learning, transfer learning was

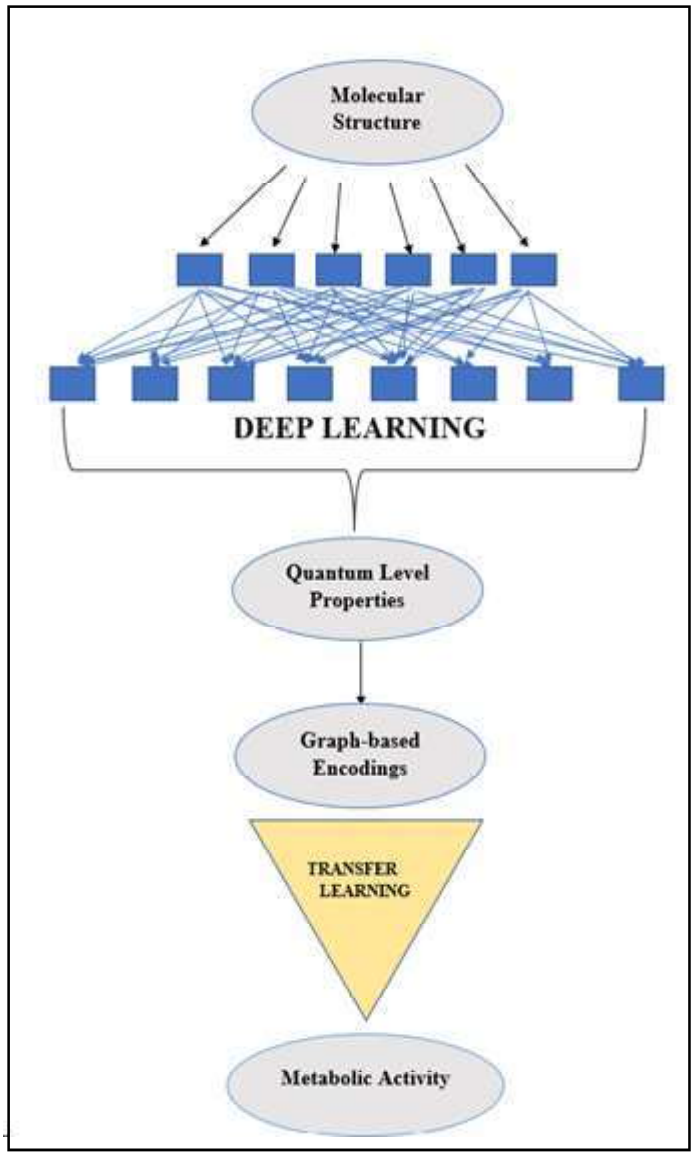

Figure 4. Flowchart depicting the steps involved in deep learning and transfer learning.

employed to accurately predict site-level chemical behaviours and compute additional quantum chemical properties. The prediction of the site of epoxidation was found to be more accurate for TLQC models than topological models. TLQC also showed better accuracy in three out of four reactivity tasks: cyanide, GSH, and protein covalent reactivity with the molecules. The results suggested that quantum representations may be generalizable to check the reactivity of other molecules apart from the properties of the QC set used to construct these representations. In comparison to topological models, TLQC yielded more accurate predictions for locations on an aromatic compound where epoxidation reactions can take place. Hence, this work suggested that transferring knowledge from the QC domain is fruitful in gaining reliable results and improving the models. In this way, a link was established by connecting the theory of quantum mechanics with chemical behaviours that are relevant to medicinal chemistry.

4. Chemoinformatics in drug metabolism

With the assistance of bacterial enzymes, drug metabolism has helped discover more than 50 drugs so far. Bacteria found in the human gut can activate, inactivate and reactivate drugs. This metabolism can show desirable or undesirable effects. It has been found that there are only a few computational tools for screening drugs that are metabolized by bacterial enzymes. Altman et al. designed a method to predict the metabolites of drugs using chemoinformatics descriptors and vector embedding techniques.[35] The significant obstruction for in-depth drug metabolism studies is analyzing time-consuming experiments like mass spectrometry. Mass spectrometry (MS) offers a quantitative analysis of metabolites with high sensitivity, selectivity, and the potential to identify metabolites. Traditional QSAR is also can be used to achieve this. It cannot depict the relationship between pairs of drugs and metabolites. It only focuses on an individual molecule. The metabolism of a drug molecule is defined over a pair of molecules. Hence, Altman et al. developed a novel computational approach for specifying the properties of molecular transformation. The central concept behind this approach is that there is a slight difference between metabolite and drug as the drug undergoes a well-defined transformation. For example, the hydroxylation of the drug upon getting catalyzed by CYP3A4, drug and metabolite forms matched molecular pairs. Many different approaches have been used for the matched molecular pair analysis (MMPA) method, like fragment indexing-based methods, structural and physiochemical approaches, etc. These approaches may fail to recognize multi-site transformations. The transformations are also considered independent of the surrounding atoms in these approaches.

Altman et al. tried to overcome these challenges by using the representations of chemical transformations as algebraic expressions of chemical structure vectors. The authors hypothesized that

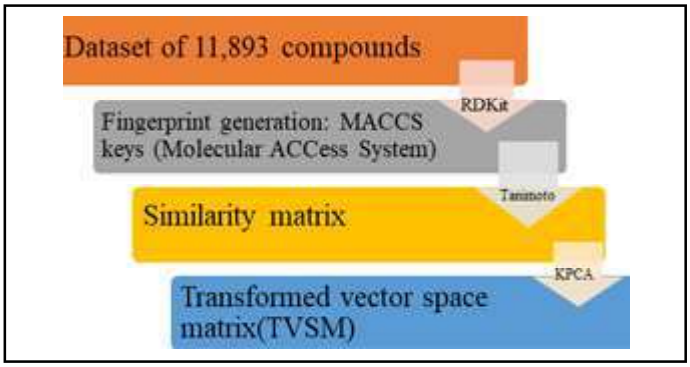

Figure 5. Schematic flow of vector space construction from a dataset

molecules in chemical reactions could form matching pairs with molecules of other reactions.

The data on compounds and chemical reactions were taken from the MetaCyc metabolic pathway database. The SMILES, reaction name, primary substrate compound, direction and immediate product were taken from the data collected. In total, 11,893 unique compounds were selected, which were included in a databank named compound_dataset with size num_compounds. The molecular vector space was generated after the selection of the compound dataset. The SMILES were taken as input that generated molecular fingerprints using kernel principal component analysis (KPCA). MACCS (Molecular ACCess System) key was used to encode molecular structure in a condensed bit vector form. Using molecular fingerprints, the Tanimoto similarity (Jaccard index) has been used as the kernel function for kernel PCA.

Further, the molecular-level and reaction-level analyses were done. K-means and enrichment analysis were used to find groups of given chemical types. Subsequently, the enriched molecule types for each cluster were determined using hypergeometric enrichment analysis with a Bonferroni correction. Kmeans clustering to reaction vectors formed using MetaCyc reactions was used to find the types of chemical reactions. Further enrichment was done to characterize clusters by enzymes that catalyze the reactions.

Queries were performed on metabolite-drug pairs inside a vector landscape. Similar reaction and drug-metabolite vectors were identified, which was a first step towards drug metabolism modelling using vector space. For example, one of the clusters contained a specific type of oxidoreductases and another group was enriched for glucosyltransferases. Hence, the authors discovered a method to compute similarities between the biotransformation of drugs and chemical reactions.

5. Conclusions

This assessment is centred on establishing the value of pharmacoinformatics efforts to understand the molecular mechanism of drug metabolism. Predicting the drug metabolism using AI and chemoinformatics tools prior to the in vitro experiments and the detailed molecular mechanism using quantum chemical studies can save time and resources. In this review, three case studies have been discussed, which show the importance of i) Quantum chemical studies, ii) Artificial intelligence iii) Chemoinformatics tools.

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