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Research article

Abbreviated Profile of Drugs (APOD): modeling drug safety profiles to prioritize investigational COVID-19 treatments

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HIGHLIGHTS

- Drugs with only strong and moderate safety profiles can be repurposed for COVID-19 or any other disease targets.
- The existing effective drugs with weak safety profiles can be modified into effective drugs with moderate/strong profiles.
- Unification, uniformity, and integration of drug properties by the APOD method represents an advancement in drug discovery.

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ABSTRACT

Safe and effective oral formulation of a drug, that is easy to store, transport, and administer, is imperative to reach the masses including those without adequate facilities and resources, in order to combat globally transmitted coronavirus disease 2019 (COVID-19). In this decision analytic modeling study, the safety of investigational COVID-19 drugs in clinical trials was assessed using the Abbreviated Profile of Drugs (APOD) methodology. The method was extensively tested for various unbiased datasets based on different criteria such as drugs recalled worldwide for failing to meet safety standards, organ-specific toxicities, cytochrome P450 inhibitors, and Food and Drug Administration (FDA) approved drugs with remarkable successes. Experimental validation of the predictions made by APOD were demonstrated by comparison with a progression of multiparametric optimization of a series of cancer drugs that led to a potent drug (GDC-0941) which went into the clinical development. The drugs were classified into three categories of safety profiles: strong, moderate and weak. A total of 3556 drugs available in public databases were examined. According to the results, drugs with strong safety profiles included molnupiravir (EIDD-2801), moderate safety profiles included dexamethasone, and weak safety profiles included lopinavir. In this analysis, the physicochemical-pharmacokinetic APOD fingerprint was associated with the drug safety profile of withdrawn, approved, as well as drugs in clinical trials and the APOD method facilitated decision-making and prioritization of the investigational treatments.

1. Introduction

An oral formulation, like a tablet or a capsule, is preferred to an injectable because it is durable, cost-effective, and easy to administer when considering the global pandemic such as coronavirus disease 2019 (COVID-19), where availability of adequate facilities and resources in certain parts of the world could be a challenge. COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Infection prevention and control are at the forefront of public health response efforts. Presently, there are no drugs approved by the U.S Food and Drug Administration (FDA) to treat COVID-19. Numerous therapeutics are currently being tested in clinical trials to evaluate the safety and effectiveness against COVID-19.

An ideal oral drug is one that is rapidly and completely absorbed from the alimentary canal, explicitly distributed to its site of action in the body, metabolized in a way that does not instantly remove its activity, and eliminated suitably, without causing any harm (Hodgson, 2001). It is estimated that nearly half of the drugs in the development fail to make it to the market due to poor safety (Hodgson, 2001). The laboratory techniques used to determine drug safety are time-consuming. The tell-tale signs of drug safety are in the actual makeup of the drug itself. Finding these characteristics requires a careful and exhaustive search of strong

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experimental evidence reported in scientific literature. Applying this critical information is yet another challenge.

An ideal drug also has a strong safety profile and high biological activity (Singal et al., 2014). The safety profile is usually determined using pharmacokinetics by studying the movement of the drug in the body including in the processes of absorption, distribution, metabolism, and excretion of drugs. Drugs with a strong safety profile have fewer side effects. An example is penicillin, which is virtually nontoxic, even in large doses (Wilkowske, 1977). Drugs with a weak safety profile have adverse side effects. An example is mibefradil (posicor), which was a drug used for the treatment of hypertension and was withdrawn from the market within a year after it was first released following a spate of dangerous/lethal effects (CDER, 2004). Drugs can produce physicological effects by initiating, inhibiting, modulating, or enhancing the basal biological activity in cells. Drug activity relates to its pharmacodynamics, the ability to bind to its target, and its dose. In this sense, a highly effective drug can cause a change in the behavior of the cell in a given tissue with only a small amount of the drug. On the other hand, an ineffective drug does not change the behavior of the cell or a large amount of the drug may be required to see a comparable change. A risky drug with adverse side effects has a weak safety profile, no matter how effective the drug is. An undesirable drug has a weak safety profile and low biological activity. Naturally, undesirable drugs should be identified early and eliminated promptly in the drug discovery process.

Laboratory techniques routinely used in the evaluation of the safety profiles of drugs are the major cause of slowdown in the evaluation process. These techniques include enzyme assays, cell culture, translocation, immunoblotting, and phosphoprotein immunoassay on cell lines, among others (Raynaud et al., 2009). They should be limited to as small a number as possible of promising drugs.

The APOD method allows a rapid evaluation of drug safety in a unified and cohesive way. It has been described in detail in an earlier article (Hiremath, 2007). Lipinski's rule of five (Ro5) with four conditions (Lipinski et al., 1997) was not adequate in revealing the drug-like characteristics of compounds. In the spirit of number five, Hiremath's rule (Hiremath, 2007) included the fifth condition with comprehensive polar surface area less than 150 $Å^2$ to Ro5. Briefly, APOD uses the drug's chemical properties for a mathematical model to predict its pharmacokinetic properties. In this approach, all the properties – physicochemical, biological, pharmacokinetic – were on the same scale from 0 to 9, thereby making any direct comparison possible. Analogous to the identification of high blood pressure as a significant risk factor for heart disease, this method relies on the vast number of proven studies and a comprehensive knowledge base (Lipinski et al., 1997; Lombardo et al., 2003; Pajouhesh and Lenz, 2005; Stenberg et al., 2001; Waterbeemd et al., 2001). For example, it is known that higher lipophilicity of compounds leads to increased metabolism and poor absorption, along with an increased probability of binding to undesired hydrophobic macromolecules, thereby increasing the potential for toxicity (Pajouhesh and Lenz, 2005). Such interplay of chemical and pharmacokinetic properties has been integrated into the APOD approach.

Currently, the ADMET-related in silico models predict tens to thousands of descriptors in different representations and units leaving a user in a maze of properties with ambiguous and indecisive outcomes (Gola et al., 2006). Machine learning-based methods, such as PrOCTOR and TargeTox, that are target-driven drug toxicity prediction methods rely on biological interaction networks which can limit their effectiveness due to incomplete information about all possible bound proteins (Gayvert et al., 2016; Lysenko et al., 2018). The challenges of applying machine learning lie primarily with the lack of interpretability and repeatability of its results, which may limit their application (Vamathevan et al., 2019). With machine learning algorithms prediction, there is always a concern with overfitting or underfitting (Patel et al., 2020). On the other hand, the wider knowledge-based APOD methodology uses the most critical properties and provides a clear verdict (Hiremath, 2007). Holistically, APOD provides biological insight not only into absorption, distribution, metabolism, excretion, and toxicity of a drug but also its exact placement in the spectrum of drug safety profiles.

SwissADME is a web tool to predict physicochemical properties, pharmacokinetics and drug-likeness (Diana, Michielin and Zoete, 2017). It provides easy input and interpretation but it does not predict toxicity. Additionally, APOD is easy to use and allows for prediction of all ADMET properties and prioritization of molecules.

There are numerous commercial computational tools available to predict ADMET behavior (Wu et al., 2020). Quantitative structure–activity relationship (QSAR) employs mathematical models to describe relationships between molecular structures and their biological activities. Although the use of QSAR models has made considerable progress in ADMET prediction, it is limited by its model expansion capability, and large experimental data are always needed for model construction; the narrow data distribution may induce over fitting and lead to inaccurate prediction results (Wu et al., 2020). On the contrary, APOD only uses readily available physicochemical data of the drug and it also offers model expansion capability.

This decision analytical model study explores the association of physicochemical-pharmacokinetic fingerprint with the drug safety profile for the COVID-19 related drugs in clinical trials and assesses whether Abbreviated Profile of Drugs (APOD) method can facilitate decision-making and prioritization of the investigational treatments. The molecular mechanisms of action and pharmacodynamics are beyond the scope of this study.

2. Theory

2.1. APOD knowledge base

The Hiremath "rule of five" are a set of five rules that the properties of a compound should satisfy to be drug-like (Hiremath, 2007). First, the molecular weight (W) should be less than 500 Da. Second, the number of hydrogen-bond acceptors/receivers (R) should be less than 10. Third, the number of hydrogen-bond donors/givers (G) should be less than 5. Fourth, the value of octanol-water partition coefficient (L) should be less than 5. Fifth, the comprehensive polar surface area (S) should be less than 150 $Å^2$.

Presently, the physicochemical knowledge base X as a function of the modifiable property limits is given by the Hiremath's rule

$$X = \begin{bmatrix} & lower & upper \\ W & 0 & 500 \\ R & 0 & 10 \\ G & 0 & 5 \\ L & 0 & 5 \\ S & 0 & 150 \end{bmatrix} \quad [1]$$

where, W is the molecular weight, R is hydrogen-bond acceptors (receivers), G is the hydrogen-bond donors (givers), L is the octanol-water partition coefficient, and S is the comprehensive polar surface area. The lower limit for most properties is zero because the values for properties such as molecular weight, hydrogen-bond acceptors and donors, and comprehensive polar surface area cannot be negative. However, for some compounds the partition coefficient can be negative.

Based on the physicochemical knowledge base, each property is expressed in A-POD format by dividing the actual value of the compound property by its upper limit and then multiplying by the number ten. In order to obtain a single number, the normalized value must then be rounded off ("abbreviated") to the lowest integer.

The pharmacokinetic knowledge base Y as a function of the physicochemical properties is best represented by

$$Y = \begin{bmatrix} & W & R & G & L & S \\ A & -2 & 0 & 0 & -2 & +1 \\ D & 0 & 0 & 0 & -2 & +1 \\ M & +1 & +1 & +1 & +1 & 0 \\ E & -1 & 0 & 0 & -1 & 0 \\ T & 0 & 0 & 0 & +1 & -1 \end{bmatrix} \quad (2)$$

where, A is the absorption, D is the distribution, M is the metabolism, E is the excretion, and T is the toxicity. The number represents the weight assigned to the property, and the positive and negative signs indicate direct and inverse correlations, respectively.

Empirically, the APOD pharmacokinetic estimation based on the pharmacokinetic knowledge base Y is performed by the equation

$$\Pi(\Gamma) = \frac{\sum \beta_i \left[9(2 - \alpha_i) + \Gamma_i(-1)^{\alpha_i} \right]}{\sum \beta_i} \quad (3)$$

where, Π is the APOD pharmacokinetic property, Γ is the APOD chemical property, i is the number of chemical properties, α is the favorability factor (2 if favorable, 1 if unfavorable), β is the weighting factor, and Σ is summation.

The APOD indicator knowledge base Z as a function of the pharmacokinetic properties is currently represented by

$$Z = \begin{bmatrix} & Benefit & Risk \\ A & +1 & 0 \\ D & +1 & 0 \\ M & 0 & 0 \\ E & 0 & -1 \\ T & 0 & +1 \end{bmatrix} \quad (4)$$

Empirically, the APOD score is computed using the equation

$$\Omega(\Pi) = \frac{\sum \beta_k \left[9(2 - \alpha_k) + \Pi_k(-1)^{\alpha_k} \right]}{\sum \beta_k} \quad (5)$$

where, Ω is the APOD indicator, Π is the APOD pharmacokinetic property, k is the number of pharmacokinetic properties, α is the favorability factor (2 if favorable, 1 if unfavorable), β is the weighting factor, and Σ is summation.

It is important to note that the knowledge base can be easily modified at any time to update, improve, and evolve.

The pharmacokinetic knowledge base can be customized to specific needs, such as intravenous route, organ-specific toxicities, etc. The immediate goal for any pharmaceutical formation is to get the absorbed drug into the bloodstream. For an oral route, the drug should be able to first survive the low pH of the gastrointestinal tract, and then diffuse across the cell membrane (lipid bilayer) which limits the molecular size. When a drug is intravenously administered, the customization of the knowledge base could involve allowing for lower lipophilicity and higher molecular size with appropriate weights based on their relative importance, for example. The power of the rule-based APOD method is due to the fact that it captures such knowledge of human experts in a specialized domain, through solid demonstrated scientific literature, in the form of explicitly stated and static model of a domain. From this practical perspective, since we do not need to simulate intelligence, the statistical and probabilistic methods are not necessary here.

An interactive web tool with easy input and interpretation of results is freely available through the website https://apodvision.com/apod/apod.pl.

2.2. APOD methodology

In the APOD approach (Hiremath, 2007), the physicochemical properties are normalized with respect to the upper limit of the corresponding properties. The resulting value for each property is multiplied by the number ten and then rounded off ("abbreviated") to the lowest integer. The property values that are violated are set to the upper limit 9 in the APOD representation.

The biological activity (B) is the concentration of the drug needed to produce a biological effect on a specific target. These values are different in various targets such as humans, rats, mice, rabbits, and monkeys. The input for biological activity is in nanomolar units, accepting values from 0 to 9999. So, the highest value in biological activity correspond to lowest efficacy and the lower values in biological activity correspond to higher efficacy of drug. In contrast, the increase in the APOD value represents the increase in biological activity or efficacy of the drug. The inverse relationship is converted into a direct relationship by considering the one-minus-activity values. In order to easily identify the activity ranges, two groups with 5 values were implemented; the micro-molar concentrations corresponding to APOD values from 0 to 4, and the nano-molar concentrations corresponding to APOD values from 5 to 9.

2.3. Numerical-APOD

The numerical representation (N-APOD) is concatenation of all property values as a single entity in terms of a fingerprint (WRGLSBADMET).

2.4. APOD score

The benefit and risk associated values for the drug are determined separately based on the individual APOD values associated with pharmacokinetic properties. The APOD score is a pair of APOD values that represents benefit and risk presented by a drug and indicates whether the drug would be suitable as a therapeutic.

3. Materials and methods

For analysis, the needed drugs were downloaded as a 2D Structure Data Format (SDF) file using PubChem, an open chemistry database at the United States National Institutes of Health (NIH). The SDF file was input into the online APOD program to calculate the APOD score of the drug. The market drugs recalled for failing to meet safety standards, cytochrome P450 inhibitors, as well as the FDA approved drugs, were used as controls and analyzed using the A-POD approach first. Then, COVID-19 related drugs in clinical trials were analyzed.

3.1. Data sources

Using FDA approved drugs (Drugs@FDA), the drugs were searched and a list was created. The Center for Drug Evaluation and Research, 2004 Report to the Nation was downloaded from the U.S. Department of Health and Human Services, Food and Drug Administration. The list of safety-based New Molecular Entity (NME) withdrawals comprised of 24 drugs from 1976 to 2005 (CDER, 2004). All drugs were included. Using the National Institute of Health (NIH), U.S. National Library of Medicine, the COVID-19 drugs were searched and a list of drugs was created.

3.2. Drug chemical properties data

First, using PubChem, the drug name was entered into the search field (PubChem). After browsing through the output, the relevant drug was selected. The default drug data available in the 2D Structure Data Format (SDF) was downloaded to the local computer. The chemical-data file contains a large number of associated data. The only associated data needed for analysis are: pubchem_molecular_weight, pubchem_cactvs_hbond_acceptor, pubchem_cactvs_hbond_donor, pubchem_xlogp3, and pubchem_cactvs_tpsa. The pubchem_compound_cid, a unique drug ID

Table 1. Data sets.

	PubChem Search	Counts (*n*)	Safety Profiles			Success (%)
			Strong	Moderate	Weak	
1	Withdrawn, worldwide	152	11	27	114	75.0
2	Withdrawn, used in other countries	71	4	13	54	76.1
3	Withdrawn, FDA historic	24	4	0	20	83.3
4	Liver toxicity, FDA (withdrawn)	52	2	12	38	73.1
5	Cardiotoxicity, severe (withdrawn)	30	2	6	22	73.3
6	Hepatotoxicity, US (withdrawn)	14	0	4	10	71.4
7	Hepatotoxicity, non-US (withdrawn)	24	0	5	19	79.2
8	Nephrotoxicity, acute	10	2	0	8	80.0
9	Cytochrome P-450 inhibitors	40	1	0	39	97.5
10	FDA approved	808	170	261	377	53.3
11	COVID-19	1474	558	427	489	*
12	COVID-19 clinical trials	401	81	78	242	*
13	FDA COVID-19 clinical trials (early)	49	8	13	28	*
14	FDA COVID-19 clinical trials	273	55	57	161	*
15	Promising EIDD-2801, similar structures	134	121	11	2	98.5*
	Total compounds analyzed	3556				

* No oral COVID-19 related drugs have been approved or withdrawn by FDA or other agencies.

was available. Since the name of the drug was not available in the associated data, pubchem_common_name was added and the drug name was entered manually by editing the SDF text file and saved; pubchem_bioactivity was also added. Even though, it was not required for the pharmacokinetic analysis, if the experimental information for bioactivity was available in the "Biological Test Results" section of PubChem entry or literature, it was entered as well. This was repeated for all the necessary drugs for the study. Datasets were created after excluding duplicates, synonyms, and monoclonal antibodies such as bevacizumab, eculizumab, mavrilimumab, meplazumab, sarilumab, siltuximab, and tocilizumab.

3.3. Datasets

For a specific dataset, text searches with the drug name in PubChem was first performed. Then a list of PubChem identifiers (CIDs) was used as input to PubChem search to view and download records as a SDF.

Table 2. Withdrawn, FDA historic.

	PubChem (CID)	Category and drug	APOD Score (Benefits-Risks)	N-APOD (WRGLSBADMET)
		Strong/moderate safety profile		
1	4369359	Azaribine	7–2	79209069450
2	72474	Grepafloxacin	6–3	77404957452
3	4474062	Flosequinan	5–3	45023055264
4	60021	Temafloxacin	5–4	89414046543
		Weak safety profile		
5	2099	Alosetron	4–4	52233045354
6	5090	Rofecoxib	4–4	64044044344
7	119607	Valdecoxib	4–5	65256044434
8	60726	Bromfenac	3–5	64465033535
9	4528	Nomifensine	3–5	42251033346
10	5359	Soprofen	3–5	54265033435
11	5733	Zomepirac	3–5	53253033345
12	39941	Benoxaprofen	2–6	64284022526
13	446156	Cerivastatin	2–6	97676023715
14	2769	Cisapride	2–6	97465023615
15	3337	Fenfluramine	2–6	44260032447
16	38409	Ticrynafen	2–6	65286022525
17	48041	Encainide	1–7	73282011517
18	5591	Troglitazone	1–7	86497012605
19	15130	Levomethadyl	1–8	73081011418
20	2247	Astemizole	0–8	95292000608
21	5282375	Etretinate	0–8	73092010418
22	60663	Mibefradil	0–8	96294901607
23	5311399	Rapacuronium	0–8	95093901507
24	5405	Terfenadine	0–8	93492000608

3.4. Safety profile analysis

All the drug files were stored together in a sub directory where the program resided. Using APOD, a specific drug or dataset was selected and submit button was clicked.

3.5. Outcomes

The primary outcome were the physicochemical-pharmacokinetic fingerprint and drug safety profile, numerical-APOD (N-APOD) and APOD score, respectively. The individual values in the N-APOD were interpreted based on the PubChem entries or scientific literature if available.

3.6. Success criteria

Two separate success criteria were used. For withdrawn drugs, the ratio of the number of weak drugs predicted to the number of drugs in a specific data set was multiplied by 100. Similarly, for approved drugs, the ratio of the number of strong/moderate drugs predicted to the number of drugs in a specific data set was multiplied by 100.

4. Results and discussion

4.1. Association of physicochemical-pharmacokinetic fingerprint and drug safety profile

The numerical APOD (N-APOD) included individual physicochemical and pharmacokinetic indicators. The independently determined APOD score was the sole indicator of drug safety. Based on the APOD score, a drug was classified into one of three categories: strong, moderate and weak. For a drug with a strong or moderate safety profile, the APOD value associated with the benefit (first number) was greater than the APOD value associated with the risk (second number). When the difference between the two indicators was large (greater than 4), the drug was categorized as strong; and when the difference was small (less than or equal to 4), it was categorized as moderate. On the contrary, for a drug with a weak safety profile, the risk indicator (second number) was greater than the benefit indicator (first number) in the APOD score, irrespective of the difference between the two indicators.

A total of 3556 compounds from PubChem (https://pubchem.ncbi.nlm.nih.gov/) comprising of various unbiased datasets were analyzed based on different criteria such as drugs withdrawn, toxicity, approved, and clinical trials (Table 1).

4.2. Withdrawn drugs

For the recalled drugs shown in Figure 1, such as nefazodone and troglitazone, it was evident that the predicted APOD values (indicated by arrows) for absorption (A), distribution (D), and excretion (E) were smaller than those for toxicity (T). For these drugs, the APOD score (of 1–8) indicates that it was alarmingly risky. Justly, these drugs were withdrawn due to the risk of hepatotoxicity. This pattern of the benefit indicator dwarfed by the risk indicator was mostly consistent for the recalled drugs, categorized under weak safety profile in Table 2. The reasons to withdraw the drug from the market for safety reasons were reported to be stroke, liver toxicity, fatal allergic reaction, hemolytic anemia, flank pain syndrome, fatal arrhythmia, kidney failure, increased deaths, heart value disease, severe constipation, breathing difficulty, birth defects, and skin disease (CDER, 2004). Besides, manufacturers or distributors usually implement voluntary recalls in order to carry out their responsibilities to protect the public health when they need to remove a marketed drug product that presents a risk of injury to consumers or to correct a defective drug product (CDER, 2004). Out of 24 historic FDA withdrawn drugs, only 4 drugs - azaribine, grepafloxacin, flosequinan, and temafloxacin - indicated false positives (categorized under strong/moderate safety profile in Table 2). This indicates that the APOD method had a success rate of 83.33 %.

Interestingly, the false positives for the 4 withdrawn drugs could be due to that fact they seem to be non-ADMET related issues. Azaribine is a prodrug, a biologically inactive compound which must be converted into the pharmacologically active agent (that would usually have issues such as poor aqueous solubility, instability, and other adverse effects or toxicities) by metabolic transformation (Wu, 2009). The most common adverse events with grepafloxacin were gastrointestinal, such as nausea, vomiting, and diarrhea (Lode et al., 1999). Flosequinan increased the heart rate and neurohormonal activation (Packer et al., 2017).

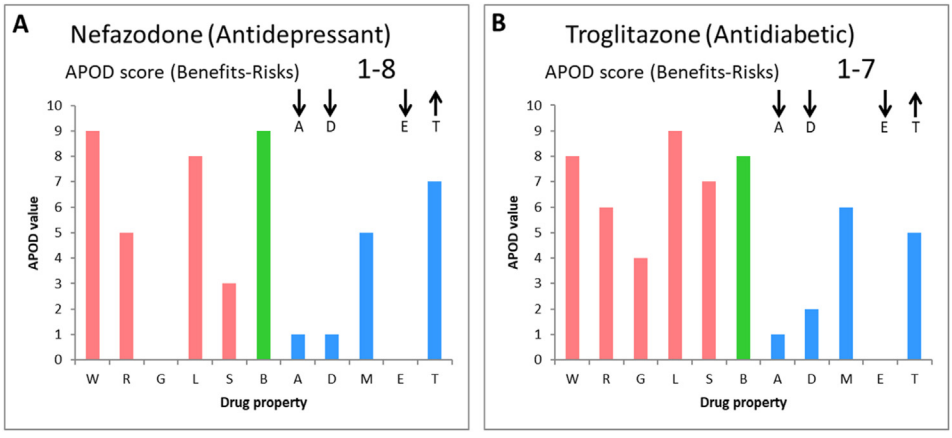

Figure 1. Graphical-APOD (G-APOD) representation of recalled drugs. (A) Nefazodone (B) Troglitazone. The bars in red correspond to the APOD values associated with chemical properties comprising of molecular weight (W), hydrogen-bond acceptors (R), hydrogen-bond donors (G), octanol-water partition coefficient (L), and comprehensive polar surface area (S). The bar in green in the middle corresponds to the APOD value associated with the biological activity property (B). The bars in blue correspond to the predicted APOD values associated with pharmacokinetic properties comprising of absorption (A), distribution (D), metabolism (M), excretion (E), and toxicity (T). The numerical representation (N-APOD) is the height of the bars for each of the properties as a single entity in terms of a fingerprint (WRGLSBADMET). The two drugs have the N-APOD of 95083911507 and 86497812605, respectively. The benefit and risk associated values for the drug are determined separately based on the pharmacokinetic properties and represented in the APOD score. The two drugs have the APOD-score of 1–8 and 1–7, respectively.

Temafloxacin was withdrawn due to immune hemolytic anemia (Blum et al., 1994).

4.3. Adverse effects

Ninan and Wertheimer compared the drugs banned in the U.S. versus the drugs banned in other prominent countries and showed that drug withdrawal is an important task that involves continued surveillance and pharmacovigilance and is as important as the process of drug discovery and production (Ninan and Wetheimer, 2012). Based on this expanded list of 152 drugs withdrawn worldwide, the APOD success rate was 75.0 %.

The World Health Organization (WHO) recommends that the countries carefully select the medicines to be included in their national essential medicines lists. Charles and others studied essential medicines list and found countries still use medicines that have been withdrawn worldwide (Charles et al., 2019). These 71 drugs indicated the APOD success rate of 76.1 %.

Drug-induced liver injury (DILI) is one of the major safety concerns for drug developer, regulators and clinicians. Chen and others have created a reference drug list with sufficient number of drugs that are well annotated based on their DILI risk in humans (Chen et al., 2016). Based on the 52 withdrawn drugs in the FDA drug induced liver injury rank (DILIrank) dataset (fda.gov), the APOD success rate was 73.1 %.

Bayzigitov and others have compiled a list of drugs belonging to various drug categories such as histamine antagonists, antipsoriatic agent, peripheral vasodilator, anorectic and hypolipidaemic agent, sympathomimetics, cough suppressant, antiobesity agents, and anthelmintic that have been withdrawn from market because of unexpected severe side effects on cardiovascular system (Bayzigitov et al., 2016). These 30 drugs (Table 3) indicated the APOD success rate of 73.3 %.

Guengerich has listed withdrawn drugs due to hepatotoxicity (Guengerich, 2011). The 14 US and 24 non-US withdrawn drugs have the APOD success rate of 71.4 % and 79.2 %, respectively.

Drugs are a common source of acute kidney injury, also known as nephrotoxicity. Naughton has published the list of drugs withdrawn due to nephrotoxicity (Naughton, 2008). These 10 FDA withdrawn drugs have the APOD success rate of 80.0 %.

4.4. Cytochrome P450 inhibitors

Cytochrome P450 enzymes are essential for the metabolism of many medications. These enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures (Lynch and Price, 2007). All 40 drugs on the list of strong cytochrome P450 CYP3A4 inhibitors (Table 4) at the DrugBank (https://go.drugbank.com/categories/DBCAT002647) yielded the APOD success rate of 97.5 %.

Table 3. Withdrawn drugs due to severe cardiovascular effects.

	PubChem (CID)	Category and drug	APOD Score (Benefits-Risks)	N-APOD (WRGLSBADMET)
		Strong safety profile		
1	16574	Azaribine	7–2	79209069450
2	135413539	Tegaserod maleate	7–2	87909059650
		Moderate safety profile		
3	71329	Dofetilide	5–4	88438046532
4	72474	Grepafloxacin	6–3	77404057452
5	39371	Levomethadyl acetate HCl	5–4	73201046354
6	60662	Mibefradil dihydrochloride	5–3	96604047542
7	4086	Orciprenaline	6–3	44814066463
8	60464	Sparfloxacin	6–2	79606058551
		Weak safety profile		
9	2247	Astemizole	0–8	95292000608
10	2467	Buflomedil	3–5	65043034345
11	2318	Benfluorex	0–8	76292010618
12	10007	Chlorphentermine	3–5	31251043256
13	6917698	Cisapride monohydrate	2–6	97465023615
14	26602	Cloforex	2–6	52272022437
15	26937	Clobutinol	2–6	52261032337
16	66265	Dexfenfluramine	2–6	44260032447
17	5702697	Dithiazanine iodide	2–6	94064023415
18	48040	Encainide HCl	3–5	73432034445
19	3337	Fenfluramine	2–6	44260032447
20	47811	Pergolide mesylate	1–7	62282021427
21	9801	Prenylamine	0–8	61290010419
22	10100	Propoxyphene	1–7	63081011428
23	5090	Rofecoxib	4–4	64044044344
24	77999	Rosiglitazone	3–5	76266034524
25	60149	Sertindole	1–7	83282011517
26	5210	Sibutramine	0–8	51090010329
27	5405	Terfenadine	0–8	93492000608
28	23480	Terodiline	0–8	51290010429
29	5452	Thioridazine	1–7	74093011517
30	119607	Valdecoxib	4–5	65256044434

Interestingly, methimazole is a small molecule with 13 atoms and all its chemical properties are at the lower end.

4.5. FDA approved drugs

For the FDA approved drugs (Drugs@FDA) shown in Figure 2, such as tylenol and cipro, the trends were opposite. For these drugs, the APOD score of 6–2 indicates that these drugs had a moderate safety profile. This pattern of the benefit indicator outweighing the risk indicator was consistent for the FDA approved drugs (partial list) shown in Table 5.

For a total of 808 FDA approved drugs in PubChem, the number of drugs with strong, moderate, and weak safety profiles were 170, 261, and 377, respectively, yielding a success rate of 53.3 %. At first glance, it may seem that FDA approved drugs represent uniform number of drugs across the safety spectrum. These compounds bring to attention the importance of context when considering toxicity events. In general, more frequent and serious side effects will be acceptable for drugs that are used to treat severe and otherwise untreatable conditions, such as cancer (Gayvert et al., 2016). If we consider human disease as an imbalance in the system with increased or decreased effects, then we need every tool in the arsenal of approved drugs to correct or cure by inhibiting or inducing changes to bring the system back into balance. After all, the ultimate goal in finding a cure to a disease is maximizing benefits with minimal or no adverse effects. Naturally, focusing more on the analysis of withdrawn drugs is justified here.

4.6. Sensitivity

The APOD approach demonstrates remarkable sensitivity as well. As indicated in Table 5, penicillin G, which was a commonly used penicillin

Table 4. Cytochrome P450 CYP3A4 inhibitors.

	PubChem (CID)	Category and drug	APOD Score (Benefits-Risks)	N-APOD (WRGLSBADMET)
		Strong safety profile		
1	1349907	Methimazole	7–2	21203077183
		Weak safety profile		
2	71616	Voriconazole	4–4	68235045443
3	3002190	Telithromycin	2–6	99289023704
4	456201	Ketoconazole	1–7	96084012506
5	4449	Nefazodone	1–8	95083011507
6	3793	Itraconazole	1–7	99096012606
7	84029	Clarithromycin	4–5	99869035813
8	441243	Saquinavir	2–6	97989023804
9	213039	Darunavir	4–4	99659035722
10	468595	Posaconazole	1–7	99297012705
11	92727	Lopinavir	1–7	95898012705
12	3010818	Telaprevir	2–6	98889023804
13	11625818	Idelalisib	2–6	87476023615
14	25151504	Cobicistat	2–6	99699013804
15	5311454	Stiripentol	2–6	43272032437
16	969516	Curcumin	3–5	76466034524
17	392622	Ritonavir	2–6	99899013804
18	151171	Conivaptan	1–7	93495011606
19	202225	Troleandomycin	2–6	99089023604
20	64139	Efavirenz	1–7	65282021527
21	148192	Atazanavir	2–6	99999013904
22	54682461	Tipranavir	1–7	99497012705
23	5284596	Naloxone	4–4	65444044444
24	644241	Nilotinib	1–7	99496012706
25	5625	Delavirdine	4–5	97647035623
26	3955	Loperamide	0–8	93292000508
27	44631912	Ribociclib	4–4	87446035533
28	11285588	Danoprevir	4–5	99669035713
29	5277135	Elvitegravir	1–7	87495011706
30	9829523	Midostaurin	1–7	94295011606
31	5405	Terfenadine	0–8	93492000608
32	8223	Ergotamine	4–5	96647035623
33	3198	Econazole	0–8	72091010418
34	8987	Ditiocarb	4–4	22232054265
35	5362440	Indinavir	4–5	97857035723
36	64143	Nelfinavir	1–7	96898012805
37	10324367	Boceprevir	4–5	95869035713
38	28417	Danazol	2–6	63273022426
39	39186	Diltiazem	2–6	86065023525
40	148195	Lonafarnib	1–7	93295011506

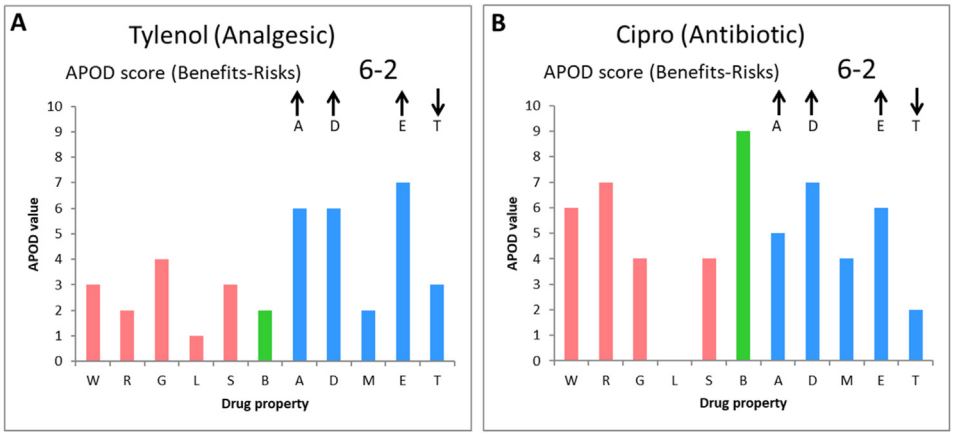

Figure 2. G-APOD representation of FDA approved drugs. (A) Tylenol (B) Cipro.

Table 5. FDA approved drugs as a positive control.

	PubChem (CID)	Category and drug	APOD Score (Benefits-Risks)	N-APOD (WRGLSBADMET)
		Strong safety profile		
1	2088	Alendronate	8–1	48909079570
2	3639	Hydrochlorothiazide	8–1	57609079460
3	6249	Ampicillin	7–1	66609069460
4	27661	Isosorbide Mononitrate	7–1	36206078271
5	4091	Metformin	7–1	21606078281
6	60773	Valacyclovir	7–1	66609069460
7	33613	Amoxicillin	7–2	77809069550
8	6915944	Cefdinir	7–2	79809069650
9	27447	Cephalexin	7–2	66619068450
10	54671203	Doxycycline	7–2	89909059650
11	3001055	Ranitidine	7–2	67407068461
		Moderate safety profile		
12	23664709	Penicillin G	6–2	75217957351
13	5904	Penicillin (Parent)	5–3	65437956442

derivative (sodium or potassium salts) on the market, had an APOD score of 6–2, whereas the parent, penicillin, had an APOD score of 5–3, matching with comparatively lower benefit and higher risk.

4.7. Experimental validation with series of cancer drugs

Raynaud and others showed a progression in multiparametric optimization of a series of cancer drugs from PI-103 through PI-540 and then to GDC-0941 (Raynaud et al., 2009). Based on the pharmacokinetic methods such as enzyme assays, cell culture, translocation, immunoblotting, and phosphoprotein immunoassay on cell lines, it was successfully shown that their data support the development of an improved drug GDC-0941 as a potent drug which went into the clinical development (Raynaud et al., 2009). Their optimized derivatives exhibited improvements in antitumor efficacy, solubility, bioavailability, and metabolism with high tissue distribution in mice; the fast plasma and tissue clearance were attributed to the rapid glucuronidation of phenol group. GDC-0941 showed limited microsomal metabolism, resulting in 78 % oral bioavailability (Raynaud et al., 2009). The APOD scores in Table 6 indicate a consistent improvement in benefits-indicator and reduction in risks-indicator, providing a real-world practical application of the APOD methodology. The APOD scores for PI-103, PI-540, and GDC-0941 are 3–5, 4-4, and 5–3, respectively. The APOD values for the two compounds, PI-103 and GDC-0941 as shown in Figure 3, there is increase in APOD values associated with absorption (A) by 1 and distribution (D) by 3, as well as decrease in APOD value associated the toxicity (T) by 3. The changes in chemical properties that led to the changes in pharmacokinetic properties is depicted by difference APOD (D-APOD) in Figure 3C. The patterns and consistencies between the experimental evidence and the independent APOD results are striking.

Table 6. Progression of the series of cancer drugs.

	PubChem (CID)	Category and drug	APOD Score (Benefits-Risks)	N-APOD (WRGLSBADMET)
		Weak safety profile		
1	9884685	PI-103	3–5	67255934534
2	11669062	PI-540	4–4	88246935533
		Moderate safety profile		
3	17755052	GDC-0941	5–3	99239947531

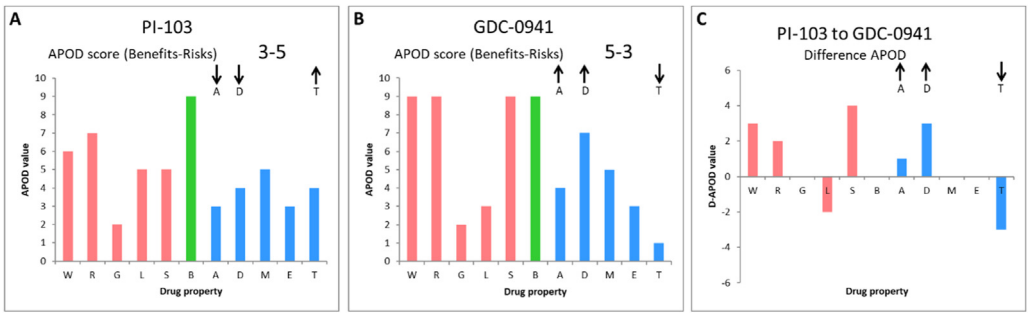

Figure 3. Comparison of the starting drug and the improved drug using APOD. (A) PI-103 (B) GDC-0941 (C) Difference APOD (D-APOD).

4.8. APOD guided optimization of drug safety profile

The improvement in the safety profile of the widely used penicillin G is due to the potassium salt penicillin derivative. The progression of the series of cancer drugs from PI-103 to clinical development candidate GDC-0941 is due to the shift in the safety profile favorably (Figure 3C) by increasing the polar surface area through rearrangement of the oxygen atoms in the structure and addition of hydrogen-bond acceptors while staying within the ideal property boundaries. This implies that the existing effective drugs with weak safety profile can be modified into effective drugs with moderate/strong profiles through the insights from the APOD fingerprint and difference APOD, even before the molecule is synthesized.

4.9. Analysis of COVID-19 related drugs in clinical trials worldwide

Since COVID-19 is an emerging, rapidly evolving situation, the number of COVID-19 drugs in clinical trials also keeps evolving. At any time, one can only get a snapshot. There are over 400 drugs being repurposed for COVID-19 around the world. However, an analysis of curated list of 68 investigational drugs related to COVID-19 in the worldwide clinical trials (Table 7) showed that 11 drugs including molnupiravir (also known as EIDD-2801) had strong safety profiles, 12 drugs including dexamethasone had moderate safety profiles, and 45 drugs including lopinavir had weak safety profiles. For the representative drugs in the three categories, if we consider the drug profile spectrum going from strong to weak, evidently the APOD values associated with absorption, distribution and excretion decrease whereas the APOD value associated with toxicity increases (Figure 4). By sorting the APOD score in the descending order for benefits and ascending order for risks, it is possible to prioritize drugs on the basis of their APOD score (Table 7).

4.10. Strong safety profiles

A representative in the category of strong safety profiles is molnupiravir which includes avigan, aviptadil, azvudine, baricitinib, deferoxamine, emtricitabine, galidesivir, riamilovir, ribavirin, and tenofovir with their APOD scores ranging from 8–1 to 7–2.

Molnupiravir, previously EIDD-2801 or MK-4482, is a broad-spectrum antiviral currently in phase III clinical trials. Recently, Wahl and others have shown that molnupiravir dramatically inhibited human coronavirus (SARS-CoV-2) replication in vivo and thus has significant potential for the prevention and treatment of COVID-19 (Wahl et al., 2021). Their results indicate that molnupiravir did not cause significant mitochondrial toxicity. Molnupiravir has an APOD score of 7–1. Based on its N-APOD, the APOD values associated with absorption, distribution and toxicity were 6, 9 and 0, respectively. With improved oral bioavailability in non-human primates, it is hydrolyzed in vivo, and distributes into tissues where it becomes the active 5′-triphosphate form (PubChem).

For tenofovir, based on its N-APOD, the APOD values associated with metabolism and toxicity were 4 and 0, respectively. Tenofovir has been shown to be highly effective in patients that have never had an antiretroviral therapy and it seemed to have lower toxicity than other antivirals such as stavudine. In phase 3 clinical trials, tenofovir presented an efficacy profile similar to efavirenz in treatment-naive HIV patients. In hepatitis B infected patients, after one year of tenofovir treatment, the viral DNA levels were undetectable. Tenofovir presents minimal metabolic processing and it does not appear to be a significant cause of drug induced liver injury (PubChem).

4.11. Moderate safety profiles

A representative in the category of moderate safety profiles is dexamethasone which includes AT-527, alpha lipoic acid, anakinra, apremilast, camostat, colchicine, dexamethasone, methylprednisolone, oseltamivir, remdesivir, suramin, and thalidomide with their APOD scores ranging from 6–2 to 5–4.

For remdesivir, based on its N-APOD, the APOD values associated with metabolism and toxicity were 7 and 1, respectively. In a study, 537 patients hospitalized for severe COVID-19 who were treated intravenously with compassionate-use remdesivir, clinical improvement was observed and appears to have a favorable clinical safety profile (Grein et al., 2020). However, it has also been reported that remdesivir was not suitable for oral delivery as its poor hepatic stability, because it was extensively metabolized, would likely result in almost complete first-pass clearance; there were no liver changes in rats or monkeys; remdesivir was non genotoxic in a standard battery of in vitro and in vivo studies (Grein et al., 2020).

4.12. Weak safety profiles

A representative in the category of weak safety profiles is lopinavir which includes abivertinib, acalabrutinib, arbidol, atorvastatin, atovaquone, azithromycin, baloxavir marboxil, bemcentinib, chloroquine, cholecalciferol, ciclesonide, clopidogrel, cobicistat, danoprevir, darunavir, dihydroartemisinine, ebastine, fingolimod, glucocorticoid, glycyrrhizinate, hydroxychloroquine, ifenprodil, imatinib, leflunomide, levamisole, losartan, naproxen, nintedanib, omeprazole, piperaquine, pirfenidone, prasugrel, RBT-9, ritonavir, rivaroxaban, ruxolitinib, selinexor, simvastatin, tetrandrine, tofacitinib, tradipitant, triazavirin, valsartan, and vidofludimus with their APOD scores ranging from 4-4 to 0–8.

Liponavir is an antiretroviral protease inhibitor. Based on its N-APOD, the APOD values associated with absorption, metabolism and toxicity were 1, 7 and 5, respectively. Lopinavir has exceptionally low oral bioavailability, undergoes extensive oxidative metabolism by hepatic cytochrome P450, and can cause serious adverse effects (PubChem). Researchers reported that liponavir/ritonavir caused significant liver damage (Cao et al., 2020).

Table 7. Worldwide clinical trials related to COVID-19 treatments.

	PubChem (CID)	Category and drug	APOD Score (Benefits-Risks)	N-APOD (WRGLSBADMET)	Country
		Strong safety profile			
1	10445549	Galidesivir	8–1	57909079560	US
2	3113817	Riamilovir	8–1	46209079370	US
3	37542	Ribavirin	8–1	47809079470	CN, US
4	464205	Tenofovir	8–1	58609079460	CN, US
5	24769759	Azvudine	7–1	57608068460	CN
6	60877	Emtricitabine	7–1	45407078371	CN, US
7	145996610	Molnupiravir	7–1	67809069560	US
8	492405	Avigan	7–2	34405077272	JP
9	16132300	Aviptadil	7–2	99909059640	EU, US
10	44205240	Baricitinib	7–2	77208068450	CA, EU, US
11	2973	Deferoxamine	7–2	99909059640	US
		Moderate safety profile			
12	5426	Thalidomide	6–2	54205067262	US
13	2536	Camostat	6–3	76429057441	JP, US
14	122527270	AT-527	5–3	99839047731	EU
15	864	Alpha lipoic acid	5–3	44235055353	CN
16	139595263	Anakinra	5–3	99629047631	AU, EU, US
17	65028	Oseltamivir	5–3	65426056452	US
18	121304016	Remdesivir[a]	5–3	99839047731	AU, EU, US, WHO
19	5361	Suramin	5–3	99939047731	CN
20	11561674	Apremilast	5–4	97238046532	EU, US
21	6167	Colchicine	5–4	76225046443	US
22	5743	Dexamethasone	5–4	76636046543	UK, US
23	6741	Methylprednisolone	5–4	75636046543	US
		Weak safety profile			
24	213039	Darunavir	4–4	99659035722	US
25	26879	Levamisole	4–4	42032044255	US
26	4594	Omeprazole	4–4	66246045443	US
27	40632	Pirfenidone	4–4	31031054165	CN
28	25126798	Ruxolitinib	4–4	64245045444	CA, CN, US
29	9926791	Tofacitinib	4–4	65235045443	US
30	11285588	Danoprevir	4–5	99669035713	CN, EU
31	9875401	Rivaroxaban	4–5	86257035523	US
32	107770	Dihydroartemisinine	3–5	55253033445	CN
33	3495	Glycyrrhizinate	3–5	99979024813	CN
34	3899	Leflunomide	3–5	56253033445	CN
35	156391	Naproxen	3–5	43263033346	US
36	71481097	Selinexor	3–5	89466024624	US
37	52947239	Triazavirin	3–5	59499033624	CN
38	71226662	Acalabrutinib	3–6	96467024614	EU
39	124081896	Baloxavir Marboxil	3–6	99078024614	CN
40	9820008	Vidofludimus	3–6	75465033525	US
41	447043	Azithromycin	2–6	99989023804	AU, UK, US
42	60606	Clopidogrel	2–6	64073022426	CA, US
43	25151504	Cobicistat	2–6	99699013804	US
44	107970	Fingolimod	2–6	63684022526	US
45	3652	Hydroxychloroquine	2–6	64473022526	AU, UK, US, WHO
46	5291	Imatinib	2–6	97475013615	US
47	3961	Losartan	2–6	85486022615	US
48	6918456	Prasugrel	2–6	76074022526	CA
49	154731616	RBT-9	2–6	98476023715	EU
50	392622	Ritonavir	2–6	99899013804	AU, CN, UK, US, WHO
51	60846	Valsartan	2–6	86487023615	US
52	3689	Ifenprodil	2–7	63472022527	US
53	72734520	Abivertinib	1–7	98686012705	US
54	131411	Arbidol	1–7	95285012606	CN, US
55	60823	Atorvastatin	1–7	96897012805	US

(*continued on next page*)

Table 7 (*continued*)

	PubChem (CID)	Category and drug	APOD Score (Benefits-Risks)	N-APOD (WRGLSBADMET)	Country
56	74989	Atovaquone	1–7	73293011517	US
57	46215462	Bemcentinib	1–7	97496012706	US
58	6918155	Ciclesonide	1–7	97296012606	US
59	11502129	Glucocorticoid	1–7	77694011717	CN
60	92727	Lopinavir	1–7	95898012705	AU, CN, UK, US, WHO
61	135423438	Nintedanib	1–7	97486012705	US
62	54454	Simvastatin	1–8	85294011607	CA
63	2719	Chloroquine	0–8	63291010518	AU, CN, EU, US, WHO
64	5280795	Cholecalciferol	0–8	71291010418	CA
65	3191	Ebastine	0–8	93091000508	CN
66	122262	Piperaquine	0–8	96092000608	CN
67	73078	Tetrandrine	0–8	98094001607	US
68	9916461	Tradipitant	0–8	99094001607	US

Drugs are oral formulations unless indicated.
[a] Injection.

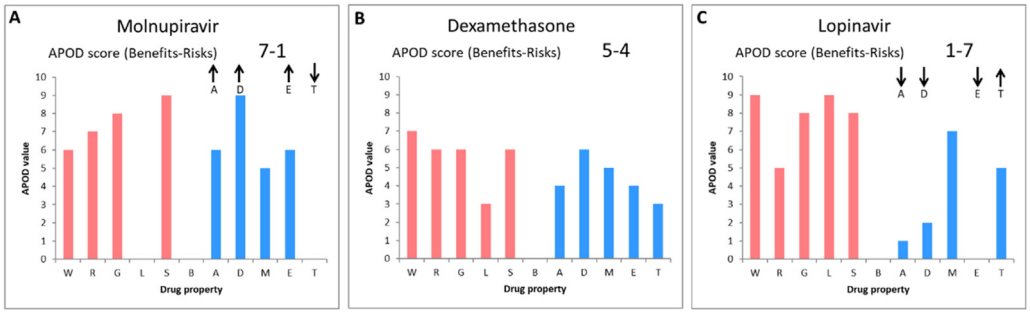

Figure 4. G-APOD representation of COVID-19 related drugs in clinical trials. (A) Molnupiravir (B) Dexamethasone (C) Lopinavir. The drugs were classified into three categories of safety profiles: strong, moderate and weak.

4.13. Success rate

In this study, a mathematical model was used to investigate whether the physicochemical-pharmacokinetic fingerprint was associated with the drug safety profile for investigational treatments of COVID-19. The model was specific for oral formulations of a drug and relies on the best-known scientific data available on a large number of property-safety relationships to predict the pharmacokinetic outcome of a drug. The APOD method encapsulates these associations in a fingerprint of drug and the APOD score reveals the drug safety. For a variety of 417 recalled drugs for failing to meet safety standards demonstrated that the physicochemical-pharmacokinetic fingerprint was associated with the drug safety profile, with an average success rate of 78 %. The classification of a large number of investigational treatments of COVID-19 into three categories of drug safety profiles, namely strong, moderate, and weak, was also achieved.

4.14. Global trials

World Health Organization (WHO) had announced a large global trial called Solidarity for the 6 (Table 7) promising coronavirus drugs to find out whether they could treat infections with the new coronavirus for the dangerous respiratory disease. As presented here, remdesivir had a moderate safety profile; hydroxychloroquine, chloroquine, and lip-onavir/ritonavir had a weak safety profile. These safety profiles were consistent with the observations reported (Cao et al., 2020).

4.15. Repurposing

FDA approved drugs comprise of safe as well as weak drugs. Drugs with weak safety profiles cannot be repurposed. The safety is an inherent characteristic of the drug, arising purely from the chemical property. Hence, the APOD score is independent of the disease target. Drugs with strong and moderate safety profiles can be repurposed for other disease targets.

4.16. APOD screening

High throughput screening (HTS) involves the screening of a large compound library directly against the drug target using a cell-based essay. Currently, all compounds are screened for all diseases in the early stages of drug discovery. Due to the iterative nature of the drug discovery process, this has a risk of starting with a set of unsafe drugs with weak safety profiles, thereby wasting precious time and resources. In future, it is recommended that the large compound library databases are screened using the APOD method and a small subset are created for initial screening against a new disease target. This sets a path with much greater success of drug for human therapeutics use.

4.17. Limitations of the study

As demonstrated, the APOD methodology predicts cardiotoxicity, hepatotoxicity, and nephrotoxicity with remarkable successes. However,

the limitation of APOD seems to be in predicting adverse effects arising from thromboembolism, hypoglycaemia, skin reactions, hypersensitivity reaction, heartburn, lactic acidosis, birth defects, severe constipation, diarrhea, neurohormonal activation, immune hemolytic anemia, and breathing difficulty.

5. Conclusion

In this analysis, the physicochemical-pharmacokinetic fingerprint was associated with the drug safety profile of withdrawn, approved and COVID-19 related drugs. The pharmacokinetic modeling for drug safety was solely focused on the oral formulation of a drug due to the global aspiration of a durable, cost-effective, and easy to administer treatment that can reach everyone including those lacking facilities and resources. The APOD method provides an advancement in the field of drug discovery by unifying all properties in the fingerprint, making any property comparisons possible with uniform representation, and integrating pharmacokinetic insights into drug design. APOD is sensitive and easy to use. The strengths of APOD are interpretability and repeatability of results. APOD provides biological insight not only into absorption, distribution, metabolism, excretion, and toxicity of a drug but also its exact placement in the spectrum of drug safety profiles. The prioritization of drugs based on their safety profiles allows for the acceleration of the pace of drug discovery. The five physicochemical properties needed for drug safety analysis are already available as online compound data, making the instantaneous extraction of the pharmacokinetic properties to produce an APOD score, which is independent of the disease target, highly convenient. Future work will focus on making the APOD score available routinely for all drugs that are part of public databases.

Declarations

Author contribution statement

Chaitanya N Hiremath: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed materials, analysis tools and data; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

Chaitanya N. Hiremath is inventor on patent held by the United States Patents and Trademark Office that covers the methodology (US8392166B2).

Additional information

No additional information is available for this paper.

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