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REVIEW

Prediction of drug–drug interaction potential using physiologically based pharmacokinetic modeling

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Abstract The occurrence of drug–drug interactions (DDIs) can significantly affect the safety of a patient, and thus assessing DDI risk is important. Recently, physiologically based pharmacokinetic (PBPK) modeling has been increasingly used to predict DDI potential. Here, we present a PBPK modeling concept and strategy. We also surveyed PBPK-related articles about the prediction of DDI potential in humans published up to October 10, 2017. We identified 107 articles, including 105 drugs that fit our criteria, with a gradual increase in the number of articles per year. Studies on antineoplastic and immunomodulatory drugs (26.7%) contributed the most to published PBPK models, followed by cardiovascular (20.0%) and anti-infective (17.1%) drugs. Models for specific products such as herbal products, therapeutic protein drugs, and antibody–drug conjugates were also described. Most PBPK models were used to simulate cytochrome P450 (CYP)-mediated DDIs (74 drugs, of which 85.1% were CYP3A4-mediated), whereas some focused on transporter-mediated DDIs (15 drugs) or a combination of CYP and transporter-mediated DDIs (16 drugs). Full PBPK, first-order absorption modules and Simcyp® software were predominantly used for modeling. Recently, DDI predictions associated with genetic polymorphisms, special populations, or both have increased. The 107 published articles reasonably predicted the DDI potentials, but further studies of physiological properties and harmonization of in vitro experimental designs are required to extend the application scope, and improvement of DDI predictions using PBPK modeling will be possible in the future.

Keywords Physiologically based pharmacokinetic modeling · Drug–drug interaction · Prediction

Introduction

Outstanding achievements in the pharmaceutical industry have led to the approval of numerous drugs for use in clinical settings, and consequently, patients are frequently exposed to polypharmacy to treat concurrent diseases or to treat a single disease effectively (Hajjar et al. 2007). Co-administration of multiple drugs increases the prevalence of drug–drug interactions (DDIs), and clinically significant DDIs are mainly mediated by pharmacokinetic (PK) mechanisms. PK DDIs are caused by changes in the absorption, distribution, metabolism, and excretion (ADME) properties of a drug due to co-administered drugs, which often involve inhibition or induction of drug metabolizing enzymes, transporters, or both (Varma et al. 2015b). The occurrence of DDIs can reduce the efficacy or safety of a drug. Furthermore, rare but fatal adverse reactions could result from DDIs and be a major cause of the withdrawal of a drug from the market (Zhang et al. 2009). Therefore, understanding and assessing PK DDIs are essential for rational therapeutics and have traditionally been investigated by conducting clinical trials. However, the high expense and potential risks related to conducting clinical trials have necessitated the introduction of alternative approaches to studying DDIs (Von Moltke et al. 1998). Therefore, efforts to develop models that utilize drug parameters for the in vitro prediction DDIs in humans are increasing, and specific detailed information about

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these approaches are available in previously published studies (Einolf 2007; Boulenc and Barberan 2011; Bohnert et al. 2016).

Briefly, the approaches are generally classified into three categories, simple static, mechanistic static and mechanistic dynamic models. For simple static models, quantification of the DDI potential is mainly based on a single constant inhibitor concentration and inhibition constant derived from in vitro data. The model assumes that the concentration of the inhibitor does not change over time. In addition, the substrate drug is assumed to be metabolized only in the liver, and the fraction metabolized (f_m) for the substrate drug is 100%. Hence, the simple static model represents the worst-case scenario, and the DDI magnitude could be overestimated (Einolf 2007). The mechanistic static model includes additional information, and the substrate drug is assumed to be metabolized not only in the liver but also the intestines. The f_m of substrate drugs are considered, and the net effect of competitive or mechanism-based inhibition and induction can be incorporated into the model (Fahmi et al. 2008). Nevertheless, the model is not capable of describing the complete dynamic characteristics of drug metabolism in humans because a single constant inhibitor concentration is used and the DDI magnitude difference between staggered and simultaneous dosing cannot be described (Fowler et al. 2017). Above all, the greatest weakness of both simple and mechanistic static models is the associated challenges in applying the most relevant inhibitor concentration, and therefore the DDI magnitude could differ based on the inhibitor concentration (e.g., the maximum concentration [C_{max}], average concentration [$C_{average}$], and hepatic inlet concentration) (Boulenc and Barberan 2011; Cho et al. 2014).

Unlike other approaches, mechanistic dynamic models such as the PBPK model aim to explain all PK characteristics of a drug and describe time-variable concentrations of the substrate and inhibitor drug in different organs (Jones et al. 2015). Therefore, temporal profiles of inhibition procedure are defined, and the model has been shown to be more predictive than static models are generally (Einolf 2007). For example, the prediction of the DDI potential of AZD2066 as a perpetrator using the simple static model indicated that the occurrence of clinically significant DDIs is possible (area under the curve [AUC] ratio > 1.1) (Nordmark et al. 2014). However, the likelihood of DDIs occurring in vivo was low when the same in vitro data were analyzed using the PBPK model. The in vivo study also indicated no or low risk for clinically significant DDIs, and this improved accuracy may be partially attributable to the ability of the PBPK model to use time-variable drug concentrations instead of a single inhibitor concentration (Nordmark et al. 2014).

In addition, the PBPK model considers inter-individual variabilities such as the age, sex, ethnicity, and genetic polymorphisms and can assess individual PK variability. Hence, the magnitude and range of DDIs in the virtual population that reflects individual variability can be investigated using the PBPK model (Einolf 2007). Furthermore, the effect of factors such as the dosing regimen and population on changes on DDI potentials can be explored. Overall, the PBPK model is a more powerful strategy for predicting the DDI potential than existing methods, and regulatory agencies have approved DDI studies using PBPK models to replace clinical trials. Consequently, the application of PBPK modeling for DDI prediction has increased widely in recent years, and numerous articles have been published (Huang et al. 2013).

However, the PBPK model has limitations because abundant input data related to the PK characteristics of the drug are required for successful DDI prediction. Thus, it is a time-consuming process compared to static approaches and generally more preferably used in the late drug development stage. In addition, input parameters derived from in vitro assay or in silico prediction methods are highly variable, and uncertainty exists. Therefore, continuous refinement of the model is required as the drug-related knowledge accumulates. In addition, precise input parameter values related to the human physiology are currently lacking, and further studies are necessary for more accurate PBPK modeling (Boulenc and Barberan 2011; Varma et al. 2015b).

Nevertheless, the utility of PBPK modeling has recently been expanded to drug development, and clinical practice and the investigation of DDI potentials accounts for the highest application (Zhang et al. 2009). However, the systemic evaluation of PBPK modeling articles focused on DDI potentials has not been reported yet. In this review, we briefly described the concept of PBPK modeling and its use in predicting DDI potentials, and we examined 107 published articles on PBPK modeling for predicting DDI potentials up to October 10, 2017.

PBPK modeling: concept and methodology

Concept of PBPK modeling

PBPK modeling is a mathematical modeling technique that uses a series of mass balance differential equations to predict the ADME characteristics of drugs in humans and other animal species. The solutions to these differential equations are typically concentrations of a drug in each organ or tissue as a function of time. Indeed, the concept of PBPK modeling is not new. The use of multi-compartmental models that incorporate physicochemical and

physiological components in the simulation of PK data was first adapted by Teorell as early as 1937 (Teorell 1937). Despite the long history of PBPK modeling, the expansion of its use has been limited due to its mathematical complexity. However, for several decades, efforts have been made to refine PBPK models so they can be used in drug development and environmental toxicology (Rowland et al. 2011 and references therein). Currently, with the advancements in computing power, improvements in silico/in vitro tools, and knowledge of physiology coupled with the availability of user-friendly software, PBPK modeling is rapidly becoming a powerful tool for predicting human PK (Khalil and Laer 2011; Rowland et al. 2011; Rowland-Yeo et al. 2013; Jones et al. 2015; Zhuang and Lu 2016). Thus, PBPK modeling is becoming increasingly popular and can be used to (1) predict preclinical/clinical PK profiles; (2) determine oral absorption characteristics including food or formulation effects, or both; (3) select the first-in-human dose; (4) predict clinical DDI potentials; (5) predict special population PK characteristics such as pediatric, geriatric, pregnancy, obstetric, and profiles of patients with concurrent disease states; and (6) predict large molecule PK during the drug discovery and development process (Khalil and Laer 2011; Rowland et al. 2011; Baneyx et al. 2012; Wagner et al. 2015). Of these applications, the highest portion was related to the prediction of DDIs (Huang et al. 2013), and a recent literature review reported that DDI-related articles accounted for the highest percentage (28%) of a total of 366 PBPK-related studies (Jones et al. 2013; Vieira et al. 2014; Sager et al. 2015). Presently, PBPK modeling and simulation is recommended by regulatory agencies, e.g., the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Ministry of Health Labor and Welfare of Japan to inform DDI study design and estimate the magnitude (Huang et al. 2013; Jones et al. 2015; Sager et al. 2015).

The full (whole-body) PBPK model consists of a number of compartments that represent different body organs or tissues, connected by the systemic circulation, e.g., the arterial and venous blood. Each organ is generally identified as either perfusion or permeability rate limited (Jones et al. 2006). The perfusion rate limited model is assigned under the assumptions that the tissue membrane is present without a barrier and that the blood flow rate is the rate-limiting factor. In the permeability rate limited model, drug-specific permeability rather than the blood flow rate is the rate-limiting factor. For example, if drugs cross the tissue membrane by an active transport process, the permeability rate limited model incorporating efflux- or influx-related parameters is used to describe the active transport process (Jones et al. 2013; Sager et al. 2015). In contrast, the minimal PBPK model construct reduces the number of compartments to no more than five, and other organs with comparable blood flow rates are grouped as one compartment to simplify the model (Jones et al. 2013; Sager et al. 2015).

Construction of PBPK models

Input parameters included in the PBPK model can be divided into three categories: system, drug, and the study design (Jamei et al. 2009a). System-dependent parameters are related to the physiological properties of the body and are defined by organ volume, mass, blood flow rate, enzyme or transporter abundance, plasma protein abundance, hematocrit, or genetic polymorphisms (Rowland et al. 2011). Information on these physiological properties of humans or other species are now available in the literature, and PBPK modeling also enables the incorporation of the altered physiological properties in different disease states or population groups (Jones et al. 2013).

Drug-dependent parameters consist of physicochemical parameters as well as ADME related parameters of the drug determined from a variety of in vitro, in silico, or in vivo data, or a combination of these (Tsamandouras et al. 2015). To explain the absorption process, mechanistic absorption models are required and rely on various drug-specific parameters including molecular weight, lipophilicity, solubility, and pKa values. Initially, a first-order absorption model was developed based on one-compartment kinetics. In addition, a compartmental absorption and transit (CAT) model, which divided the gastrointestinal tract into nine compartments (the stomach, seven small intestinal compartments, and the colon), has been introduced. Recently, advanced compartmental absorption and transit (ACAT) and advanced dissolution, absorption, and metabolism (ADAM) models have also been developed to supplement the CAT model (Jamei et al. 2009b). Distribution of the drug in each organ is generally described by either a perfusion or permeability rate limited model, as mentioned above. Clearance, which is a key parameter of the PBPK model, has a considerable effect on the PK behavior of the drug. Several approaches have been introduced for the characterization of in vivo clearance, and the in vitro–in vivo extrapolation (IVIVE) method, which was developed to predict the PK profiles of humans before the first dosing, is coupled with PBPK modeling to describe whole-organ clearance. In addition, the retrograde approach, which is a back-calculation method from oral clearance to in vitro intrinsic clearance, or direct incorporation of in vivo clearance could be used. Parameter estimation, which is the estimation of an in vitro intrinsic clearance parameter from observed PK profiles, can also be used when essential in vitro data and scaling factors are not available (Tsamandouras et al. 2015). For hepatic

clearance, the application of IVIVE has been well studied, and in vitro data derived from experiments with recombinant enzymes, microsomes, or hepatocytes have been extrapolated to whole-liver clearance using scaling factors (Chen et al. 2012). For non-hepatic clearance, such as renal or biliary excretion, other approaches can be used to predict in vivo organ clearance. When a single approach is insufficient to characterize the in vivo clearance, any combination of the abovementioned information can be used to compensate for the missing clearance details.

Finally, information on the study design such as dose, route, and frequency of administration, the effect of concomitant drugs and food, and formulation properties is required to define a PBPK modeling and simulation.

PBPK modeling software

In the last step, the PBPK model equations and integration algorithms can be written and solved using specific programming languages, simulation software, or spreadsheet programs to simulate the PK profile of a drug in the plasma and tissues (Khalil and Laer 2011). The open and designed software are two main types of software currently used for PBPK modeling and simulation (Khalil and Laer 2011; Bouzom et al. 2012). The open software packages for PBPK modeling such as MATLAB®, NONMEM®, Berkeley Madonna®, SAAM II®, and acslX® require the modeler to write and code their model equations and functions. Thus, they are less suitable for novice modelers (Khalil and Laer 2011; Bouzom et al. 2012). The designed software comprises Simcyp®, GastroPlus®, PK-Sim®, Cloe PK ®, and MoBi®, which have made PBPK modeling more accessible to those without extensive modeling and programming experience. These user-friendly software packages include physiological databases of predefined species and populations that are combined with compound-specific information and are used to parameterize a whole-body PBPK model (Bouzom et al. 2012; Kuepfer et al. 2016). The availability of user-friendly software has broadened the use of PBPK models in the drug discovery and development process (Khalil and Laer 2011; Bouzom et al. 2012; Jones et al. 2015; Kuepfer et al. 2016).

PBPK model verification

A newly developed PBPK model is used to simulate PK profiles of predefined populations and actual clinical trials using the aforementioned user-friendly software packages. The performance of the PBPK model is subsequently verified by comparing the simulated PK parameters (AUC and C_{max}) with the observed clinical data and using the visual inspection approach for the concentration–time profiles (Kuepfer et al. 2016). The predictive performance of PBPK models is evaluated using the mean observed/predicted ratio of the AUC and C_{max}, and is considered acceptable when the ratios fall within the predefined success range (e.g., 1.25-, 1.5-, or 2-fold) (Guest et al. 2011; Abduljalil et al. 2014; Wagner et al. 2015; Ke et al. 2016). In addition, the visual inspection checks were deemed acceptable if the clinically determined plasma concentrations are within the 5th and 95th percentiles of the predicted profile (Zhou et al. 2016). Although there appears to be a lack of consistency in the acceptance criteria for model verification, it was recently reported that the criteria should be predefined by considering various factor and should be appropriate (Jones et al. 2015). This PBPK model should also adequately predict independent clinical data (e.g., different dose levels, population, and route of administration) that are not used in the model construction, if possible. The PBPK model is refined during this step by parameter optimization and sensitivity analysis is mandatory for model optimization. Sensitivity analysis is informative for identifying key parameters that are likely to affect the model performance. The identified sensitive parameters should be reflected in the model (Zhou et al. 2016; Zhuang and Lu 2016). The verification/modification step is essential for the subsequent use of the model, and afterward, the verified PBPK model can be used to simulate other uninvestigated clinical scenarios or DDI predictions.

PBPK modeling for predicting DDI potentials

The DDI prediction study using PBPK modeling involves the development of PBPK models for both the victim and perpetrator drugs. The developed models are subsequently verified based on clinical data obtained using the dosage regimen planned for the study where possible, followed by model refinement. Then, the DDI prediction is carried out by simulating the substrate-inhibitor interaction according to the study design.

PBPK modeling articles on predicting DDI potentials

Journal search

Journal articles were selected using the PubMed search engine. The search terms were "Physiologically based pharmacokinetic modeling" and "drug–drug interaction," and 214 articles were identified for the period up to October 10, 2017. Among the articles, a review article and a study on the application of PBPK modeling in animals were excluded, whereas articles on the PK of DDI using PBPK modeling in humans were analyzed. Finally, we identified 107 articles, including 105 involving different

drugs that fit our scope and were further categorized by publication year (Fig. 1). The first article on PBPK modeling for DDI prediction was reported in 2008 (Chenel et al. 2008; Hyland et al. 2008), and the number of related articles has consistently increased since then to more than 20 articles per year (Fig. 1). Although most of the articles studied CYP-mediated DDIs, transporter-mediated DDIs were first reported in 2012. Similarly, articles on PBPK modeling for predicting complex DDI potentials that considered the effects of both CYP- and transporter-mediated DDIs have also been reported since 2012 (Fig. 1). The increase in the number of articles on DDI-related PBPK modeling may be attributable to the development of user-friendly software, and the regulatory authorities' approval of the application of PBPK modeling in the drug development process. The increased knowledge of the body's physiology and the advancement of in vitro experimental techniques for investigating drug properties and providing improved drug PK profiling are anticipated to increase the number of articles on predicting DDIs using PBPK modeling. Detailed information on DDI mechanisms, PBPK model description, and interactive predictions of DDIs of the 105 classified drugs are summarized in Tables 1, 2, 3, 4, 5, 6, along with references.

Classification of selected drugs from articles on DDI-related PBPK modeling

A total of 105 drugs were categorized according to the first level of the Anatomical Therapeutic Chemical (ATC) classification system, which groups drugs according to their main anatomical group, as developed by the World Health Organization (http://www.whocc.no/atcddd/). The developed PBPK models for the drugs were found in the following therapeutic categories at the indicated proportions: antineoplastic and immunomodulatory had the highest contribution (28 drugs, 26.7%), followed by the cardiovascular system (21 drugs, 20.0%), systemic anti-infective (18 drugs, 17.1%), alimentary tract and metabolism (11 drugs, 10.2%), nervous system (11 drugs, 10.5%), blood and blood-forming organs (six drugs, 5.7%), respiratory system, anti-parasitic (three drugs, 2.9%, each), musculoskeletal system (two drugs, 1.9%), systemic hormonal, and various other categories (one drug, 1.0%, each) (Fig. 2).

Among the antineoplastic and immunomodulatory agents, 24 drugs were antineoplastic with the highest contribution. Antineoplastic drugs are highly toxic and have a narrow therapeutic index. In addition, chemotherapy regimens include at least one or more antineoplastic drugs (Chabner and Roberts 2005). Thus, the DDI risk is increased in patients with cancer and, therefore, the evaluation of DDI potential is important under such conditions. However, volunteer recruitment is challenging for clinical trials and, consequently, the use of PBPK modeling for determining antineoplastic DDIs has increased (Table 1). However, this strategy is limited because most simulations were performed in healthy populations and the altered physiological properties in patients with cancer were not incorporated in the models. Nevertheless, it is encouraging

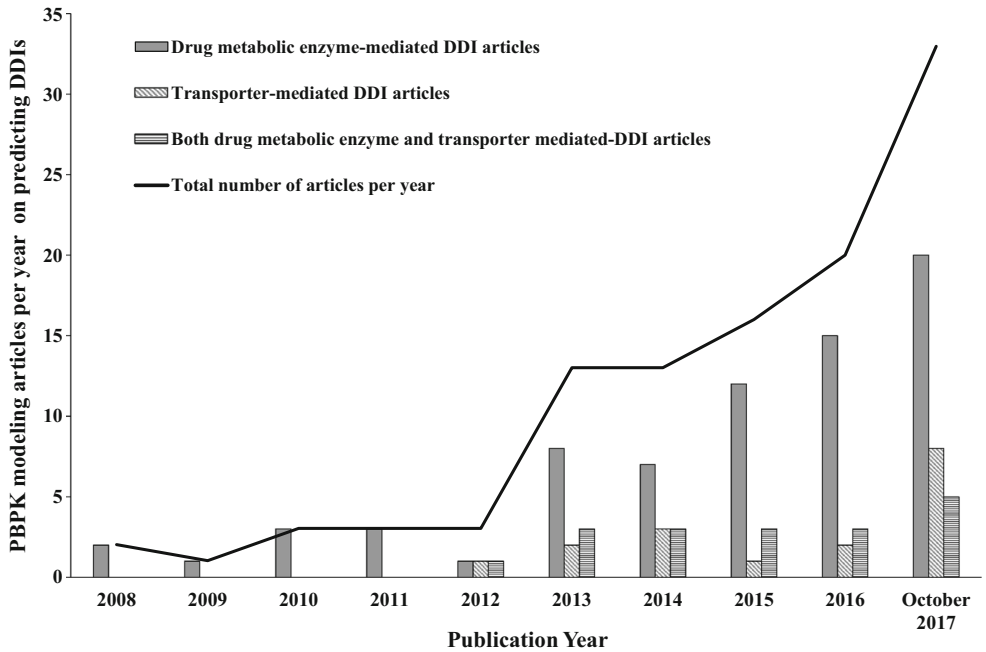

Fig. 1 PBPK modeling articles per year for predicting DDIs

Table 1 List of drugs classified as antineoplastic and immunomodulatory agents that used in DDI prediction by PBPK modeling

	Mediator Mechanism	PBPK models	Modules Absorption	 Elimination	Predicting drugs	References
Antineoplastic agents						
All-*trans*-Retinoic-Acid	CYP2C8, 3A4, 26A1 Inducer, Substrate	Full	First-order	IVIVE	Ketoconazole, Liarozole	Jing et al. (2017)
Baricitinib	BCRP, OAT3, P-gp, MATE2-K Substrate	Full	First-order	IVIVE and in vivo	Diclofenac*, Ibuprofen*, Probenecid	Posada et al. (2017)
Blinatumomab[a]	CYP1A2, 2C9, 3A4 Reverse supression	Minimal	ND	In vivo	Caffeine*, Midazolam*, Simvastatin*, Theophylline*, (S)-Warfarin*	Xu et al. (2015)
Bosutinib	CYP3A4 Substrate	Full	First-order	Retrograde	Ketoconazole, Rifampicin, Erythromycin*, Fluconazole*, Fluvoxamine*, Verapamil*	Ono et al. (2017)
Brentuximab Vedotin[b]	CYP3A4 Inhibitor, Substrate	Minimal	ND	IVIVE and Retrograde	Ketoconazole, Midazolam, Rifampicin	Chen et al. (2015b)
Cobimetinib	CYP3A4 Substrate	Full	First-order	Retrograde	Diltiazem, Efavirenz, Erythromycin, Fluvoxamine, Itraconazole, Rifampicin	Budha et al. (2016)
Crizotinib	CYP3A4 Inducer, Inhibitor, Substrate	Full	First-order	Retrograde	Ketoconazole, Rifampicin, Diltiazem*, Erythromycin*, Fluconazole*, Fluvoxamine*	Yamazaki et al. (2015)
Dasatinib	OATP1B1/3 Inhibitor	Minimal	First-order	In vivo	Pravastatin	Pahwa et al. (2017)
Enzalutamide	CYP3A4 Inducer	Full	First-order	In vivo	Midazolam	Rangaraj et al. (2016)
Erlotinib	CYP3A4 Substrate	Full	CAT	IVIVE	Darunavir/Ritonavir, Efavirenz, Etravirine	Moltó et al. (2017)
Gefitinib	CYP3A4 Substrate	Full	CAT	IVIVE	Darunavir/Ritonavir, Efavirenz, Etravirine	Moltó et al. (2017)
Ibrutinib	CYP3A4 Substrate	Full	ADAM	IVIVE, in vivo and Retrograde	Ketoconazole, Rifampicin, Azithromycin*, Carbamazepine*, Clarithromycin*, Diltiazem*, Efavirenz*, Erythromycin*, Itraconazole*, Fluvoxamine*, Voriconazole*	de Zwart et al. (2016)
Icotinib	CYP3A4 Substrate	Full	ADAM	IVIVE	Ketoconazole*, Rifampicin*	Chen et al. (2015a)
Ixazomib	CYP3A Substrate	Full	ADAM	In vivo and Retrograde	Clarithromycin, Ketoconazole, Rifampicin	Gupta et al. (2017)
LCL161	CYP3A Inducer, Inhibitor	Full	First-order	In vivo	Midazolam	Dhuria et al. (2013)
LY2603618	CYP2D6 Inhibitor	Minimal	ND	In vivo	Desipramine, Dextromethorphan	Hynes et al. (2015)

Table 1 continued

	Mediator Mechanism	PBPK models	Modules		Predicting drugs	References
			Absorption	Elimination		
Orteronel	CYP1A2, 2C8, 2C9, 2C19 Inhibitor	Minimal	First-order	In vivo	Omeprazole, Repaglinide, Theophylline,Warfarin	Lu et al. (2014)
Palbociclib	CYP3A Inhibitor, Substrate	Full	First-order	Retrograde	Diltiazem, Itraconazole, Rifampicin, Efavirenz*, Fluoxetine*, Fluvoxamine*, Midazolam*, Verapamil*	Yu et al. (2016)
Panobinostat	CYP3A Inhibitor, Substrate	Minimal	First-order	IVIVE, in vivo and Retrograde	Dexamethasone, Ketoconazole, Midazolam*, Rifampicin*	Einolf et al. (2017b)
Pemetrexed	OAT3/4 Substrate	Full	ND	IVIVE	Ibuprofen	Posada et al. (2015)
Ruxolitinib	CYP2C9, 3A4, P-gp Inhibitor, Substrate	Full	ACAT	IVIVE and in vivo	Erythromycin, Ketoconazole, Rifampicin, Digoxin*, Fluconazole*	Shi et al. (2015)
Antineoplastic agents						
Sonidegib	CYP3A Substrate	Full	First-order	Retrograde	Ketoconazole, Rifampicin, Efavirenz*, Erythromycin*	Einolf et al. (2017a)
Veliparib	CYP2D6, OCT2 Substrate	Full	First-order	IVIVE and Retrograde	Cimetidine*, Quinidine*	Li et al. (2014)
Venetoclax	CYP3A Substrate	Minimal	ADAM	IVIVE	Ketoconazole, Rimfampicin, Diltiazem*, Efavirenz*, Erythromycin*, Fluconazole*, Fluoxetine*, Fluvoxamine*, Itraconazole*, Prednisone*, Verapamil*	Freise et al. (2017)
Immunomodulatory agents						
Cyclosporine A	CYP3A4, OATP1B1/3 Inhibitor	Full	CAT	IVIVE	Repaglinide	Gertz et al. (2013)
Cyclosporine A	OATP1B1/3 Inhibitor	Full	First-order	IVIVE	Pitavastatin	Shitara and Sugiyama (2017)
G2917	CYP3A Inducer	Full	First-order	IVIVE	Midazolam*	Mao et al. (2017)
Sirolimus	CYP3A4 Substrate	Full	ADAM	IVIVE	Diltiazem*	Emoto et al. (2013)
Sirukumab[a]	CYP1A2, 2C9, 2C19, 3A Reverse supression	Minimal	ND	In vivo	Caffeine, Midazolam, Omeprazole, Warfarin	Jiang et al. (2016)

ACAT advanced compartmental absorption and transit, *ADAM* advanced dissolution, absorption, and metabolism, *CAT* compartmental absorption and transit, *First-order* first order absorption model according to one compartment kinetics, *IVIVE* in vitro-in vivo extrapolation method, *In vivo* in vivo clearance, *MATE* multidrug and toxin extrusion protein, *Retrograde* retrograde calculation from in vivo clearance parameter, *ND* not determined, *OAT* organic anion transporter, *OATP* organic anion-transporting polypeptide, *OCT* organic cation transporter

[a]Cytokine modulating therapeutic protein drug

[b]Antibody drug conjugate

* Prospective DDI prediction to simulate unstudied scenarios

Table 2 List of drugs classified as cardiovascular system that used in DDI prediction by PBPK modeling

	Mediator Mechanism	PBPK models	Modules Absorption	 Elimination	Predicting drugs	References
Amiodarone[c]	CYP2C9, 2D6, 3A Inhibitor	Full	First-order	Retrograde	Metoprolol, Simvastatin, Warfarin	Chen et al. (2015b)
Atorvastatin[c]	CYP3A4, OATP1B1 Substrate	Full	ADAM	IVIVE and in vivo	Cimetidine, Clarithromycin, Itraconazole, Phenytoin, Rifampicin	Zhang (2015)
Atorvastatin	CYP3A4, OATP1B1, BCRP Substrate	Full	ADAM	IVIVE and Retrograde	Cyclosporine A, Erythromycin, Gemfibrozil, Itraconazole, Rifampicin	Duan et al. (2017)
Bosentan	OATP1B1/3, CYP3A Substrate	Full	First-order	IVIVE	Itraconazole, Rifampicin	Yoshikado et al. (2017)
Digoxin	P-gp Substrate	Full	ADAM	Retrograde	Rifampicin, Verapamil	Neuhoff et al. (2013)
Diltiazem[c]	CYP3A4 Inhibitor	Minimal	First-order	IVIVE and in vivo	Midazolam	Zhang et al. (2009)
Diltiazem[c]	CYP3A4 Inhibitor	Minimal	First-order	IVIVE and in vivo	Triazolam	Rowland-Yeo et al. (2010)
Dronedarone	CYP3A4 Substrate	Minimal	First-order	In vivo	Ketoconazole	Mano et al. (2015)
Eplerenone	CYP3A4 Substrate	Minimal	First-order	In vivo	Erythromycin, Fluconazole, Ketoconazole	Mano et al. (2015)
Fluvastatin	OATP1B1/3 Substrate	Full	First-order	IVIVE and in vivo	Cyclosporine A	Yoshikado et al. (2016)
Gemfibrozil[c]	CYP2C8, OATP1B1 Inhibitor	Minimal	First-order	IVIVE	Cerivastatin, Repaglinide, Rosiglitazone, Pioglitazone	Varma et al. (2015a, b)
Macitentan[c]	CYP3A4 Substrate	Full	First-order	IVIVE and Retrograde	Cyclosporine A, Ketoconazole, Rifampicin, Sildenafil, Warfarin, Carbamazepine*, Clarithromycin*, Diltiazem*, Erythromycin*, Itraconazole*, Phenytoin*, Ritonavir*, Saquinavir*, Verapamil*	de Kanter et al. (2016)
Pitavastatin	CYP2C8, OATP1B1/3 Substrate	Full	ADAM	IVIVE, in vivo and Retrograde	Cyclosporine A, Gemfibrozil, Rifampicin	Duan et al. (2017)
Pitavastatin	OATP 1B1/3 Substrate	Full	First-order	IVIVE and in vivo	Cyclosporine A	Yoshikado et al. (2016)
Pravastatin	OATP1B1 Substrate	Full	First-order	IVIVE and in vivo	Cyclosporine A, Gemfibrozil, Rifampicin	Varma et al. (2012)
Quinidine[c]	CYP2D6 Inhibitor	Minimal	First-order	IVIVE and in vivo	Dextromethorphan, Metoprolol, Nifedipine	Marsousi et al. (2017)
Rosuvastatin	BCRP, NTCP, OATP Substrate	Full	ADAM	IVIVE, in vivo and Retrograde	Cyclosporine A	Jamei et al. (2014)
Rosuvastatin	BCRP, NTCP, OAT3, OATP Substrate	Full	ADAM	IVIVE and Retrograde	Cyclosporine A, Gemfibrozil, Rifampicin	Wang et al. (2017)
Sacubitril/ Varsartan	OATP1B1 Inhibitor	Minimal	First-order	In vivo	Atorvastatin, Simvastatin	Lin et al. (2017)

Table 2 continued

	Mediator Mechanism	PBPK models	Modules Absorption	 Elimination	Predicting drugs	References
Simvastatin	CYP3A Substrate	Full	ACAT	IVIVE	Diltiazem, Itraconazole	Fenneteau et al. (2010)
S44121	OAT1, OCT1 Substrate	Full	First-order	IVIVE	Ciprofloxacin, Probenecid, Tenofovir	Ball et al. (2017)
Telmisartan	BCRP, OATP1B1/3 Inhibitor	Full	First-order	In vivo	Rosuvastatin	Bae et al. (2017)
Tolvaptan	CYP3A4 Substrate	Minimal	First-order	In vivo	Ketoconazole	Mano et al. (2015)
Vardenafil	CYP3A4 Substrate	Minimal	First-order	In vivo	Erythromycin, Indinavir, Ketoconazole	Mano et al. (2015)
Verapamil[c]	CYP3A Inhibitor	Minimal	ACAT	IVIVE and in vivo	Cyclosporine A, Midazolam, Simvastatin	Wang et al. (2013)

ACAT advanced compartmental absorption and transit, *ADAM* advanced dissolution, absorption, and metabolism, *First-order* first order absorption model according to one compartment kinetics, *IVIVE* in vitro-in vivo extrapolation method, *In vivo* in vivo clearance, *Retrograde* retrograde calculation from in vivo clearance parameter, *BCRP* breast cancer resistance protein, *OATP* organic anion-transporting polypeptide, *NTCP* sodium-taurocholate co-transporting polypeptide, *P-gp* P-glycoprotein

[c]Integrated PBPK models for both parent-metabolite(s)

* Prospective DDI prediction to simulate unstudied scenarios

that recent articles have included the physiological conditions of patients with cancer and this additional detailed information is required for more reliable prediction (Ono et al. 2017; Einolf et al. 2017a). Cardiovascular drugs had the second highest proportion of agents investigated using PBPK models (Table 2). It has been reported that patients with cardiovascular diseases often present with a higher incidence of DDI that those without these conditions do (Mendel et al. 2011). This observation occurs possibly because these conditions are mainly associated with old age, multiple drug regimens, and the nature of the cardiovascular drug (Mendel et al. 2011). Among the cardiovascular drugs, statins were the most investigated, and PBPK models of atorvastatin (Zhang et al. 2015; Duan et al. 2017), fluvastatin (Yoshikado et al. 2016), pitavastatin (Yoshikado et al. 2016; Duan et al. 2017), pravastatin (Varma et al. 2012), rosuvastatin (Jamei et al. 2014; Wang et al. 2017), and simvastatin (Fenneteau et al. 2010) have been developed (Table 2). The statins were shown to be substrates of CYP3A4 (simvastatin), organic anion-transporting polypeptide 1/3 (OATP1B1/3; fluvastatin, pravastatin, and rosuvastatin), or both CYP isoforms and OATP1B1/3 (atorvastatin and pitavastatin). Furthermore, the inhibitory effects of the statins were simulated using PBPK modeling (Table 2).

Articles on PBPK modeling of DDI for specific products

Of the 105 drugs included in our dataset, two herbal products, silibinin, a semi-purified milk thistle seed extract, and Wuzhi capsule, consisting of *Schisandra sphenanthera* ethanol extract, were included. Recently, the PBPK models of the individual constituents (silybin A and B) of silibinin were developed (Brantley et al. 2014; Gufford et al. 2015; Table 4). In humans, the inhibitory effects of silibinin on intestinal glucuronidation of raloxifene and the substrates of CYP2C9 (warfarin) and CYP3A4 (midazolam) were accurately predicted using the PBPK modeling and simulation approach (Brantley et al. 2014; Gufford et al. 2015). The PBPK models of two main active components (schisantherin A and schisandrin A) for Wuzhi capsule were also established (Zhang et al. 2017; Table 4). The developed PBPK models adequately predicted the PK of tacrolimus-associated DDIs mediated by CYP3A4 inhibition (Zhang et al. 2017). These studies showed the feasibility of using the PBPK modeling and simulation approach to predict of herb–drug interaction potentials. However, the limited human PK data available for herbal constituents, combined with a lack of herbal product standardization, continues to challenge the development of PBPK models for the prediction of herb–drug interaction potentials (Brantley et al. 2014; Gufford et al. 2015).

Table 3 List of drugs classified as anti-infectives for systemic use that used in DDI prediction by PBPK modeling

	Mediator Mechanism	PBPK models	Modules		Predicting drugs	References
			Absorption	Elimination		
Alisporivir	CYP3A4 Inhibitor, Substrate	Minimal	First-order	Retrograde	Ketoconazole, Rifampicin	Xia et al. (2014)
Atazanavir	CYP1A2, 2C9, 2C19, 2D6, 3A4 Inducer, Inhibitor	Minimal	First-order	IVIVE	Citalopram*, Fluoxetine*, Mirtazapine*, Sertraline*, Venlafaxine*	Siccardi et al. (2013a)
Ciprofloxacin	CYP1A2 Inhibitor	Full	ACAT	Parameter estimation	Caffeine	Park et al. (2017)
Ciprofloxacin	CYP1A2 Inhibitor	Minimal	First-order	In vivo and Retrograde	Caffeine, Theophylline	Marsousi et al. (2017)
Clarithromycin	CYP3A Inhibitor	Minimal	First-order	IVIVE, in vivo and Retrograde	Midazolam, Triazolam, Repaglinide	Marsousi et al. (2017)
Clarithromycin	CYP3A4 Substrate	Full	First-order	IVIVE	Itraconazole, Rifampicin	Yoshikado et al. (2017)
Clarithromycin	CYP3A4, P-gp Inhibitor	Full	ND	IVIVE and in vivo	Digoxin, Midazolam	Moj et al. (2017)
Darunavir	CYP1A2, 2C9, 2C19, 2D6, 3A4 Inducer, Inhibitor	Minimal	First-order	IVIVE	Citalopram*, Fluoxetine*, Mirtazapine*, Sertraline*, Venlafaxine*	Siccardi et al. (2013a)
Darunavir	CYP3A4 Substrate	Minimal	First-order	Retrograde	Carbamazepine, Clarithromycin, Ketoconazole, Omeprazole, Paroxetine, Ritonavir, Saquinavir	Wagner et al. (2017)
Dasabuvir	CYP2C8 Substrate	ND	ND	IVIVE and in vivo	Clopidogrel, Gemfibrozil, Ketoconazole, Ritonavir, Trimethoprim	Shebley et al. (2017a)
Dasabuvir[c]	BCRP, P-gp Inhibitor	Minimal	First-order	In vivo	Digoxin, Ritonavir, Paritaprevir, Pravastatin, Rosuvastatin	Shebly et al. (2017b)
Efavirenz	CYP1A2, 2C9, 2C19, 2D6, 3A4 Inducer, Inhibitor	Full	First-order	IVIVE	Bupropion, Desipramine, Maraviroc, Midazolam, Sildenafil, Tolbutamide, Citalopram*, Fluoxetine*, Mirtazapine*, Sertraline*, Venlafaxine*	Siccardi et al. (2013a)
Efavirenz	CYP2B6, CYP3A4 Inducer	Full	First-order	IVIVE	Rifampicin	Rekić et al. (2011)
Efavirenz	CYP2B6, 3A4 Inducer	Minimal	First-order	Retrograde	Alfentanil, Atazanavir, Bupropion, Clarithromycin, Maraviroc	Ke et al. (2016)

Table 3 continued

	Mediator Mechanism	PBPK models	Modules Absorption	 Elimination	Predicting drugs	References
Efavirenz	CYP2C8, 3A4 Inducer, Inhibitor	Full	CAT	IVIVE	Montelukast*, Paclitaxel*, Pioglitazone*, Repaglinide*	Marzolini et al. (2017)
Fluconazole	CYP2C9, 2C19 Inhibitor	Minimal	First-order	In vivo and Retrograde	Omeprazole, Phenytoin, Warfarin	Marsousi et al. (2017)
Itraconazole[c]	CYP3A4 Inhibitor	Minimal	First-order	IVIVE and in vivo	Alprazolam, Midazolam, Quinidine, Simvastatin, Triazolam, Zolpidem	Marsousi et al. (2017)
Itraconazole[c]	CYP3A4 Inhibitor	Minimal	First-order	Parameter estimation	Midazolam	Chen et al. (2016)
Ketoconazole	CYP3A Inhibitor	Minimal	First-order	In vivo	Midazolam	Han et al. (2013)
Ketoconazole	CYP3A Inhibitor	Minimal	First-order	IVIVE and in vivo	Alprazolam, Midazolam, Simvastatin, Triazolam	Marsousi et al. (2017)
Lopinavir	CYP3A Substrate	Minimal	First-order	In vivo	Ketoconazole, Omeprazole, Rifampicin, Ritonavir	Wagner et al. (2017)
Maraviroc	CYP3A4 Substrate	Minimal	First-order	IVIVE and in vivo	Atazanavir, Ketoconazole, Ritonavir, Saquinavir	Hyland et al. (2008)
Paritaprevir	BCRP, OATP, CYP2C9 Inhibitor	Minimal	First-order	in vivo	Dasabuvir, Digoxin, Pravastatin, Ritonavir, Rosuvastatin	Shebly et al. (2017b)
Rifampicin	CYP3A4 Inducer	Full	ACAT	IVIVE and in vivo	Alfentanil, Midazolam, Nifedipine, Triazolam	Baneyx et al. (2014)
Rifampicin	CYP3A4 Inducer	Full	ADAM	In vivo	Alprazolam, Itraconazole, Midazolam, Nifedipine, Quinidine, Repaglinide, Simvastatin, Triazolam, Zolpidem	Marsousi et al. (2017)
Rifampicin	CYP3A4 Inducer	Minimal	First-order	Parameter estimation	Alprazolam, Atorvastatin, Buspirone, Cyclosporine A, Gefitinib, Imatinib, Mefloquine, Midazolam, Nifedipine, Prednisolone, Simvastatin, Telithromycin, Triazolam, Zolpidem, Zopiclone	Yamashita et al. (2013)
Rifampicin	CYP3A4 Inducer	Minimal	First-order	In vivo	Alfetanil, Alprazolam, Midazolam, Nifedipine, Simvastatin, Triazolam, Zolpidem	Almond et al. (2016)
Ritonavir	CYP2B6, 2C9, 2D6, 3A4 Inducer, Inhibitor	Minimal	First-order	IVIVE	Bupropion, Desipramine, Maraviroc, Midazolam, Sildenafil, Tolbutamide, Citalopram*, Fluoxetine*, Mirtazapine*, Sertraline*, Venlafaxine*	Siccardi et al. (2013a)
Ritonavir	CYP3A4 Inducer	Minimal	First-order	In vivo	Dasabuvir, Digoxin, Paritaprevir, Pravastatin, Rosuvastatin	Shebly et al. (2017b)
Simeprevir	CYP3A4, OATP1B1/3 Substrate	Full	First-order	IVIVE and Retrograde	Azithromycin, Carbamazepine, Clarithromycin, Cyclosporine A, Darunavir, Diltiazem, Efavirenz, Eryrhromycin, Rifampicin, Ritonavir	Yoshikado et al. (2017)

Table 3 continued

	Mediator Mechanism	PBPK models	Modules Absorption	 Elimination	Predicting drugs	References
Simeprevir	CYP3A4, OATP1B1/3 Substrate	Full	First-order	IVIVE	Itraconazole, Rifampicin	Snoeys et al. (2016)
Telithromycin	CYP3A4 Inhibitor	Full	ADAM	In vivo and Retrograde	Midazolam	Vieira et al. (2012)
Voriconazole	CYP2C9, 2C19, 3A4 Substrate	Full	ACAT	IVIVE	Omeprazole*, Esomeprazole*, Lansoprazole*, Rabeprazole*	Qi et al. (2017)
Voriconazole	CYP2C19 Substrate	Full	First-order	IVIVE	Fluconazole	Damle et al. (2011)

ACAT advanced compartmental absorption and transit, *ADAM* advanced dissolution, absorption, and metabolism, *CAT* compartmental absorption and transit, *First-order* first order absorption model according to one compartment kinetics, *IVIVE* in vitro-in vivo extrapolation method, *In vivo* in vivo clearance, *Parameter estimation* estimation of in vitro intrinsic clearance parameter from observed pharmacokinetic profiles, *Retrograde* retrograde calculation from in vivo clearance parameter, *ND* not determined, *OATP* organic anion-transporting polypeptide, *P-gp* P-glycoprotein

[c]Integrated PBPK models for both parent-metabolite(s)

* Prospective DDI prediction to simulate unstudied scenarios

PBPK models for cytokine-modulating protein drugs such as blinatumomab and sirukumab have been reported to quantitatively predict the potential clinical DDI between the therapeutic protein and a small-molecule drug in disease states associated with significantly elevated levels of the cytokine, interleukin (IL)-6 (Xu et al. 2015; Jiang et al. 2016; Table 1). The increased level of cytokines such as IL-6, IL-1β, tumor necrosis factor-α, and interferon-α in some inflammatory disease states can downregulate the drug-metabolizing CYP enzymes, decreasing the clearance of co-administered small-molecule drugs that are substrates of the affected CYP enzymes (Xu et al. 2015; Jiang et al. 2016). Cytokine-modulating protein drugs could reverse (or normalize) the suppression of CYP expression and a subsequent increase in the clearance of concomitant small-molecule drugs, referred to as disease-related protein DDIs (Aitken et al. 2006; Xu et al. 2015; Jiang et al. 2016). The alteration of IL-6 levels and its suppression of CYPs before and after therapeutic protein drug treatment in patients were investigated, and the developed PBPK models successfully predicted the perpetuating role of IL-6 (Xu et al. 2015; Jiang et al. 2016).

In addition, a PBPK model of brentuximab vedotin, an antibody–drug conjugate (ADC), has been reported, and the DDI potentials were investigated (Chen et al. 2015c; Table 1). ADCs are monoclonal antibodies attached to cytotoxic small molecules by a chemical link and designed as a targeted therapy to treat cancer. The conversion of the antibody-conjugated cytotoxic small molecules to unconjugated forms was described in the model, and the predicted DDI potential between the unconjugated cytotoxic small molecule and other drugs was comparable to that observed in previous data (Chen et al. 2015c).

PBPK modeling for predicting CYP- or transporter-mediated DDIs or both

The mechanisms of the DDIs associated with the classified drugs were further characterized. Most PBPK models of the drugs were used to simulate CYP-mediated DDIs (74 drugs, 70.5%), whereas some focused on transporter-mediated DDIs (15 drugs, 14.3%), or a combination of CYP and transporter-mediated DDIs (16 drugs, 15.2%).

Among the 74 drugs used to simulate CYP-mediated DDIs, 85.1% (63 drugs) were CYP3A4-mediated (Tables 1, 2, 3, 4, 5). CYP3A4 is the major enzyme involved in drug metabolism, which explains the increased susceptibility to CYP3A4-mediated DDIs (Lynch and Price 2007). The PBPK models for 18 drugs associated with multiple CYP isoforms, which revealed substrates (3/74 drugs), inhibitors (6/74 drugs), and both inducers and inhibitors (5/74 drugs), or both substrate and inducers (2/74 drugs) have been published (Tables 1, 2, 3, 4, 5). As mentioned previously, the PBPK models for two therapeutic protein drugs (2/74 drugs), blinatumomab and sirukumab, reasonably explored the reverse suppressions of multiple IL-6-induced CYP isoform levels and predicted their modulatory effects on the PK of small-molecule drugs metabolized by the multiple CYP isoforms (Table 1). Recently, the PBPK model of all-*trans*-retinoic acid, which

Table 4 List of drugs classified as alimentary tract and metabolism, nervous system, and blood and blood-forming organs that used in DDI prediction by PBPK modeling

	Mediator Mechanism	PBPK models	Modules		Predicting drugs	References
			Absorption	Elimination		
Alimentary tract and metabolism						
Aprepitant	CYP3A4 Substrate	Minimal	First-order	In vivo	Ketoconazole	Mano et al. (2015)
Canagliflozin	CYP3A4 Inhibitor	Full	ADAM	In vitro and in vivo	Simvastatin, Warfarin, Bupropion*, Repaglinide*	Mamidi et al. (2017)
Domperidone	CYP3A4 Substrate	Full	ADAM	In vivo and Retrograde	Erythromycin, Itraconazole, Ketoconazole	Templeton et al. (2016)
Glibenclamide	CYP2C9, 2C19, 3A4 Substrate	Minimal	First-order	IVIVE	Clarithromycin, Rifampicin, Fluconazole*	Greupink et al. (2013)
Glyburide	CYP3A4, OATP1B1 Substrate	Full	ADAM	IVIVE	Clarithromycin, Erythromycin, Rifampicin, Verapamil	Varma et al. (2014)
Metformin	MATE, OCT2 Substrate	Full	First-order	IVIVE and Retrograde	Cimetidine	Burt et al. (2016)
Milk thistle[d]	CYP2C9, 3A4 Inhibitor	Full	First-order	Parameter estimation	Midazolam, Warfarin	Brantley et al. (2014)
Milk thistle[d]	UGT1A1, 1A8, 1A10 Inhibitor	Full, Minimal	First-order	IVIVE	Raloxifene	Gufford et al. (2015)
Naloxegol	CYP3A4, P-gp Substrate	Full, Minimal	First-order	In vivo and Retrograde	Dilitazem, Ketoconazole, Quinidine, Rifampicin, Alprazolam*, Amlodipine*, Atorvastatin*, Cimetidine*, Efavirenz*, Ciprofloxacin*, Erythromycin*, Fluconazole*, Fluoxetine*, Verapamil*	Zhou et al. (2016)
Repaglinide	CYP2C8, CYP3A4, OATP1B1 Substrate	Full	ADAM	IVIVE	Cyclosporine A, Gemfibrozil, Itraconazole	Varma et al. (2013)
Alimentary tract and metabolism						
Repaglinide	CYP2C8, CYP3A4, OATP1B1 Substrate	Full	Full	IVIVE	Cyclosporine A, Gemfibrozil	Kim et al. (2017)
Repaglinide	CYP3A, OATP Substrate	Full	First-order	IVIVE	Itraconazole, Rifampicin	Yoshikado et al. (2017)
Repaglinide	CYP2C8, CYP3A4, OATP1B1 Substrate	Minimal	First-order	In vivo	Gemfibrozil, Itraconazole	Kudo et al. (2013)
Teneligliptin	CYP3A4 Substrate	Minimal	ADAM	IVIVE and in vivo	Ketoconazole, Diltiazem*, Fluvoxamine*	Nakamaru et al. (2015)
Wuzhi Capsule[d]	CYP3A4 Inhibitor	Full	First-order	IVIVE	Tacrolimus*	Zhang et al. (2017)
Nervous system						
Alprazolam	CYP3A Substrate	Full	ACAT	IVIVE	Ketoconazole	Fenneteau et al. (2010)

Table 4 continued

	Mediator Mechanism	PBPK models	Modules		Predicting drugs	References
			Absorption	Elimination		
Atomoxetine	CYP2D6, 3A4 Inhibitor, Substrate	Full	First-order	IVIVE and in vivo	Desipramine, Fluoxetine, Midazolam, Paroxetine	Huang et al. (2017)
AZD2066	CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A4 Inhibitor	Minimal	First-order	In vivo	Bupropion, Caffeine, Metoprolol, Tolbutamide	Nordmark et al. (2014)
AZD2327[c]	CYP3A4 Inhibitor	Full	First-order	Retrograde	Midazolam	Guo et al. (2015)
Lanicemine	CYP3A4 Inhibitor	Minimal	ND	Parameter estimation	Midazolam	Bui et al. (2015)
Midazolam	CYP3A4 Substrate	Full	ND	IVIVE	Clarithromycin*, Fluconazole*, Rifampicin*	Johnson and Rostami-Hodjegan (2011)
Nervous system						
Midazolam	CYP3A Substrate	Full	First-order	IVIVE	Itraconazole	Yoshikado et al. (2017)
Midazolam	CYP3A Substrate	Full	First-order	IVIVE and in vivo	Azithromycin, Cimetidine, Clarithromycin, Diltiazem, Estradiol, Fluconazole, Ketoconazole, Pleconaril, Rifampicin	Cherkaoui-Rbati et al. (2017)
Midazolam	CYP3A Substrate	Full	ACAT	IVIVE	Itraconazole, Saquinavir	Fenneteau et al. (2010)
Midazolam	CYP3A4 Substrate	Full	CAT	IVIVE	Ketoconazole, Verapamil	Perdaems et al. (2010)
Midazolam	CYP3A4 Substrate	Minimal	CAT	IVIVE	SX (a phase I compound)	Chenel et al. (2008)
Midazolam	CYP3A4 Substrate	Minimal	First-order	IVIVE and in vivo	Fluconazole, Fluvoxamine, Itraconazole, Amiodarone*	Rougee et al. (2017)
Modafinil	CYP1A2, 2C9, 2C19, 2D6, 3A4 Inducer, Inhibitor	Minimal	First-order	Retrograde	Caffeine*, Dextromethorphan*, Losartan*, Midazolam*, Omeprazole*	Rowland et al. (2016)
Oxycodone[c]	CYP2D6, 3A Substrate	Minimal	First-order	Retrograde	Clarithromycine, Itraconazole, Ketoconazole, Paroxetine	Marsousi et al. (2014)
Paroxetine	CYP2D6 Inhibitor	Minimal	First-order	IVIVE, in vivo and Retrograde	Desipramine, Imipramine, Metoprolol	Marsousi et al. (2017)
Perampanel	CYP3A Substrate	Full	ND	Retrograde	Itraconazole, Ketoconazole	Gidal et al. (2017)
Triazolam	CYP3A Substrate	Full	ACAT	IVIVE	Ketoconazole	Fenneteau et al. (2010)
Blood and blood forming organs						
Clopidogrel[c]	CYP3A4 Substrate	Full	First-order	IVIVE	Dronedarone	Djebli et al. (2015)

Table 4 continued

	Mediator Mechanism	PBPK models	Modules Absorption	 Elimination	Predicting drugs	References
Clopidogrel acyl-β-D-glucuronide[c]	CYP2C8, 3A4, OATP1B1 Inhibitor	Minimal	First-order	IVIVE and Retrograde	Repaglinide	Tornio et al. (2014)
Dabigatran etexilate[c]	P-gp Substrate	Full	CAT	IVIVE	Amiodarone, Clarithromycin, Dronedarone, Quinidine, Rifampicin, Verapamil, Captopril*, Carvedilol*, Conivaptan*, Diltiazem*, Felodipine*, Itraconazole*, Lopinavir/Ritonavir*, Mibefradil*, Nifedipine*, Ranolazine*, Ritonaivr*, Saquinavir/Ritonavir*, Telaprevir*, Telmisartan*, Ticagrelor*, Tipranavir/Ritonavir*	Zhao and Hu (2014)
Rivaroxaban	CYP3A4, P-gp Substrate	Minimal	First-order	In vivo	Erythromycin	Grillo et al. (2012)
Sarpogrelate[c]	CYP2D6 Inhibitor	Full	ADAM	IVIVE and Retrograde	Metoprolol, Desipramine*, Dextromethorphan*, Imipramine*, Tolterodine*	Min et al. (2016)
Warfarin	CYP2C9 Substrate	Minimal	First-order	IVIVE and in vivo	Amiodarone, Fluconazole, Clozapine*, Fluvoxamine*	Rougee et al. (2017)
Ticagrelor	CYP3A4 Substrate	Minimal	First-order	In vivo	Ketoconazole	Mano et al. (2015)

ACAT advanced compartmental absorption and transit, *ADAM* advanced dissolution, absorption, and metabolism, *CAT* compartmental absorption and transit, *First-order* first order absorption model according to one compartment kinetics, *IVIVE* in vitro-in vivo extrapolation method, *In vivo* in vivo clearance, *Parameter estimation* estimation of in vitro intrinsic clearance parameter from observed pharmacokinetic profiles, *Retrograde* retrograde calculation from in vivo clearance parameter, *ND* not determined, *MATE* multidrug and toxin extrusion transporters, *OATP* organic anion-transporting polypeptide, *OCT* organic cation transporters, *P-gp* P-glycoprotein, *UGT* uridine diphosphate glucuronyltransferase

[c]Integrated PBPK models for both parent-metabolite(s)

[d]Herbal product

*Prospective DDI prediction to simulate unstudied scenarios

is both a substrate and inducer of CYP26A1, the main all-*trans*-retinoic acid hydroxylase in human liver, has been developed and published (Jing et al. 2017; Table 1). The developed model was used to quantitatively predict the interaction between all-*trans*-retinoic acid and liarozole, an inhibitor of CYP26A1 (Jing et al. 2017; Table 1).

In contrast, only one drug, silibinin, was used for a non-CYP-mediated DDI prediction, and the inhibitory effects of silibinin on uridine diphosphate glucuronyltransferase 1A1 (UGT1A1) were evaluated (Gufford et al. 2015; Table 4).

Seven drugs were used to predict OATP1B1/3-mediated DDIs, which accounted for most of the 15 drugs evaluated for transporter-mediated DDI predictions (Tables 1, 2, 3, 4, 5). The OATP family is a well-characterized family of uptake transporters, and, particularly, the subfamily of OATP1B transporters has been reported to be involved in clinically significant DDIs (Koenen et al. 2011). The prediction of OATP1B1/3-mediated DDIs was 42.9 and 57.1% for the substrate and inhibitor, respectively.

Sixteen drugs were used to assess combined CYP- and transporter-mediated DDIs (Tables 1, 2, 3, 4, 5). The developed PBPK models could describe the DDI potentials when the drugs acted as inhibitors or substrates of both CYP isoforms and uptake (OATPs, OATs, OCTs, or MATEs) or efflux (P-glycoprotein [P-gp] or breast cancer resistance protein [BCRP]) transporters simultaneously in the kidney and liver. In contrast to the PBPK model, the simple static model considers the inhibitory or inductive effects on enzymes or transporters separately (Einolf 2007). It has been reported that most drugs act simultaneously as substrates or inhibitors of a specific CYP enzyme and transporter, and the PBPK modeling approach is useful for revealing combinatorial effects of enzymes and transporters (Shugarts and Benet 2008).

Table 5 List of drugs classified as respiratory system, antiparasitic products, musculoskeletal system, systemic hormonal preparations, and various that used in DDI prediction by PBPK modeling

	Mediator	PBPK models	Modules		Predicting drugs	References
	Mechanism		Absorption	Elimination		
Respiratory system						
Montelukast	CYP2C8, OATP1B1 Substrate	Full	ADAM	IVIVE	Clarithromycin, Fluconazole, Gemfibrozil, Itraconazole, Cyclosporine A*, Rimfampicin*	Varma et al. (2017)
Theophylline	CYP1A2 Substrate	Full	CAT	IVIVE	Caeffein*, Ciprofloxacin*	Navid et al. (2016)
Terfenadine	CYP3A4 Substrate	Full	ADAM	IVIVE	Clarithromycin, Erythromycin, Fluconazole, Fluoxeinte, Itraconazole, Ketoconazole, Paroxetine	Wisniowska and Polak (2016)
Antiparasitic products						
Artemether	CYP2B6, 3A4 Substrate	Full	CAT	IVIVE	Efavirenz	Siccardi et al. (2013b)
Artemether	CYP3A4 Substrate	Full	ADAM	IVIVE	Ketoconazole, Lumefantrine, Rifampicin	Olafuyi et al. (2017a)
Lumefantrine	CYP3A4 Substrate	Full	ADAM	Retrograde	Artemether, Ketoconazole, Rifampicin	Olafuyi et al. (2017a)
Piperaquine	CYP3A4 Substrate	Full	First-order	Retrograde	Efavirenz, Ritonavir	Olafuyi et al. (2017b)
Musculoskeletal system						
Diclofenac	CYP2C9 Substrate	Minimal	First-order	IVIVE and in vivo	Amiodarone*, Clozapine*, Fluconazole*, Fluvoxamine*	Rougee et al. (2017)
Probenecid	Kidney transporters Inhibitor	Full	First-order	IVIVE, in vivo and Retrograde	Cidofovir, Cefuroxime, Oseltamivir	Hsu et al. (2014)
Systemic hormonal preparations						
Prednisone[c]	CYP3A4 Inducer	Minimal	First-order	Retrograde	Midazolam, Odanacatib	Marcantonio et al. (2014)
Various						
Tc-Mebrofenin	ND Substrate	Minimal	Parameter estimation		MRP2 Ritonavir*	Pfeifer et al. (2013)

ADAM advanced dissolution, absorption, and metabolism, *CAT* compartmental absorption and transit, *First-order* first order absorption model according to one compartment kinetics, *IVIVE* in vitro-in vivo extrapolation method, *In vivo* in vivo clearance, *Parameter estimation* estimation of in vitro intrinsic clearance parameter from observed pharmacokinetic profiles, *Retrograde* retrograde calculation from in vivo clearance parameter, *ND* not determined, *MRP* multidrug resistance-associated protein, *OATP* organic anion-transporting polypeptide

[c]Integrated PBPK models for both parent-metabolite(s)

* Prospective DDI prediction to simulate unstudied scenarios

PBPK modeling was used to predict DDIs between inhibitory parent–metabolite pairs for 15 of the 105 drugs (14.3%, Tables 1, 2, 3, 4, 5). This integrated PBPK approach for both parent and metabolite(s) based on the availability of in vitro and in vivo metabolite data may increase the accuracy of predictions of all DDIs compared with the predictions based on the parent compounds alone (Chen et al. 2015b).

The limitation of the articles published to date is that the investigations were restricted to a small number of well-known drug metabolizing enzymes or transporters. This may have resulted from the lack of information about the

Table 6 List of drugs that used in PBPK modeling for the DDI prediction associated with genetic polymorphisms

Drugs	Mediated CYPs	Phenotypes	References
Efavirenz	CYP2B6	EM, PM	Rekić et al. (2010)
Clopidogrel	CYP2C19	EM, IM, PM, UM	Djebli et al. (2015)
Voriconazole	CYP2C19	EM, PM	Damle et al. (2011)
Oxycodone	CYP2D6	EM, PM	Marsousi et al. (2014)
Veliparib	CYP2D6	EM, PM, UM	Li et al. (2014)

EM extensive metabolizer, *IM* intermediate metabolizer, *PM* poor metabolizer, *UM* ultrarapid metabolizer

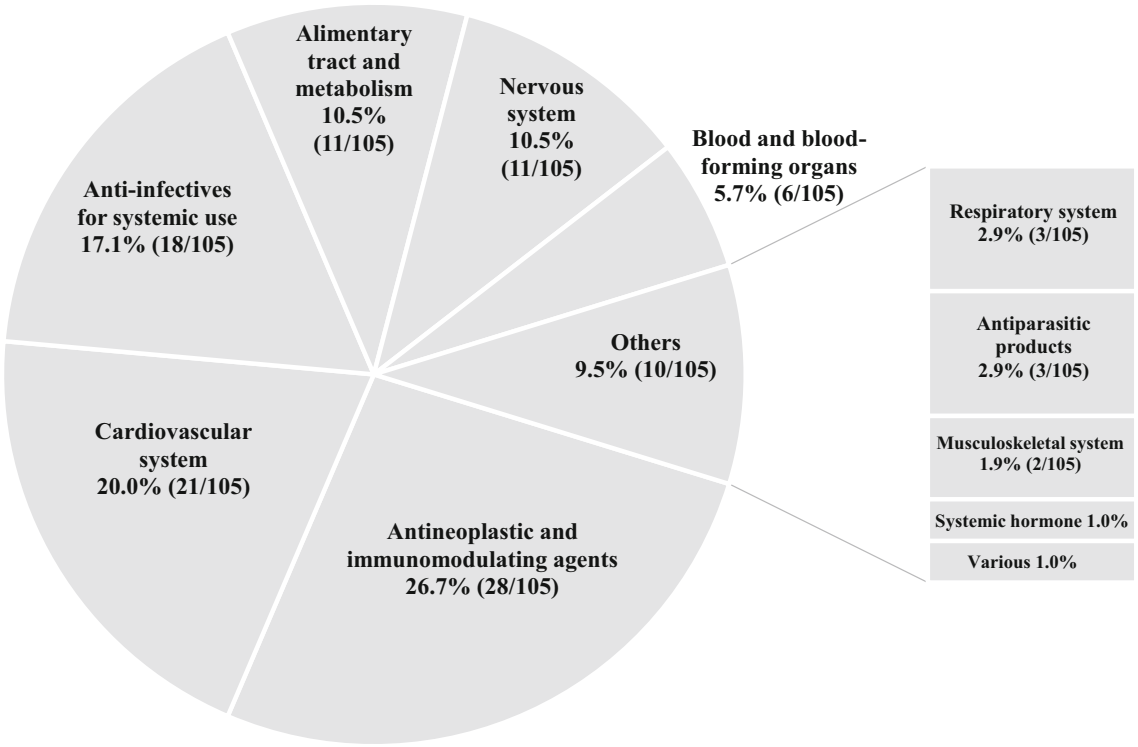

Fig. 2 Classification of 105 drugs selected in the DDI-related articles using PBPK modeling according to the first level of the Anatomical Therapeutic Chemical (ATC) classification system, which groups drugs according to their main anatomical group, as developed by the World Health Organization (http://www.whocc.no/atcddd/)

physiological properties of the body such as the absolute abundance of non-CYP enzymes or transporters. This may have consequently led to the unsuccessful use of the IVIVE approaches (Varma et al. 2012). Thus, further investigations are needed to broaden the application scope of PBPK modeling to studies of potential DDIs.

PBPK modeling strategies to predict DDI potentials

The full PBPK model was more commonly constructed (54 drugs, 51.4%) than the minimal PBPK model was (42 drugs, 40.0%), and the PBPK models of nine drugs (8.6%) were constructed using both full and minimal models (Tables 1, 2, 3, 4, 5). To describe the absorption process, the first-order absorption model was predominantly selected (63 drugs, 64.3%), followed by the ADAM model (17 drugs, 17.3%), CAT (three drugs, 3.1%), and ACAT model (5 drugs; 5.1%). The remaining 10.2% involve cases of multiple absorption models in different articles. The elimination process was mainly described using of multiple strategies (41 of 105 drugs, 39.0%), followed by IVIVE (26 of 105 drugs, 24.8%), in vivo clearance parameters (19 of 105 drugs, 18.1%), and retrograde approaches (17 of 105 drugs, 16.2%). The remaining 1.9% were parameter estimation (2/105 drugs). However, it was reported that the in vitro inhibition potencies differed among various literature reports and, thus, the harmonization of in vitro experimental designs is needed for the construction of more precise PBPK model (Gertz et al. 2013). For the clinical trial design, the oral dosing route was more predominant (94 drugs, 89.5%) than the intravenous administration was (seven drugs, 6.7%). Additionally, four drugs

(3.8%) were investigated using both oral and intravenous administration routes. As mentioned earlier, several criteria are used for the verification of successful PBPK models. The most frequently used the criteria for evaluating the predictive performance of PBPK, and the most commonly used was values within a two-fold range of the ratio of the predicted to the observed mean AUC or C_{max} (49 of 105 drugs, 46.7%). In addition, other criteria determined were values within a 1.25- or 1.5-fold range or 5th and 95th percentiles. However, numerous PBPK models of some drugs (38 of 105 drugs, 36.2%) did not use the specific criteria for the predictive performance. Of the commercially available software packages for PBPK modeling, the most commonly used software to predict DDI potentials was the Simcyp® (76 of 105 drugs, 72.4%).

PBPK modeling articles on effects of body physiology on DDIs

Most of the PBPK modeling articles predicted DDI potentials only in healthy adult populations, which is a limitation of this approach because the magnitude of DDI potentials can be altered by the different physiological properties of various population groups or patients. However, some recent articles have included the effects of physiological properties on the prediction of DDI potentials and examples of these articles are discussed below.

Genetic polymorphisms

Among the 105 drugs on PBPK modeling of DDIs, five (clopidogrel, efavirenz, oxycodone, veliparib, and voriconazole) investigated the effect of genetic polymorphisms associated with DDIs (Table 6). It has been reported that CYP2B6, CYP2C9, CYP2C19, and CYP2D6 polymorphisms account for the most frequent variations in phase I metabolic enzymes, and the identified genetic polymorphisms affect enzyme activities (Zhou et al. 2009). Thus, additional considerations of the effect of gene polymorphism would be required in the evaluation of potential DDIs mediated by these CYPs. Information on genetic polymorphisms of clinically important drug transporters is scarce, in contrast to that on genetic polymorphisms of drug-metabolic CYPs, although several genetic polymorphisms have been identified in efflux (P-gp) and uptake (OATPs) transporters (Sissung et al. 2010). The effects of CYP2B6, CYP2C19, or CYP2D6 polymorphism, or a combination of any of these on the PK behaviors of their substrates with or without inhibitors, were evaluated using PBPK modeling, which captured both the inhibitory potency of the perpetrator and the effect of genetic polymorphisms on the PK properties of the substrate drug (Table 6).

Special populations

Physiological properties such as organ weight, blood flow, plasma binding, and drug metabolic enzyme or transporter activity are dependent on the species or population considered. For example, in the case of special populations (e.g., children, pregnant women, or disease-specific population), these physiological properties differ between the special and the healthy adult population (Hartmanshenn et al. 2016). Previous studies of the altered physiological properties of special populations are insufficient and, therefore, the use of PBPK modeling to predict DDI potentials in special population is limited. However, 12 articles supporting such modeling were found in our dataset (Tables 1, 2, 3, 4, 5); these included patients with impaired renal or hepatic function (Emoto et al. 2013; Lu et al. 2014; Nakamaru et al. 2015; Ono et al. 2017; Wagner et al. 2017), patients who were immunocompromised or had rheumatoid arthritis (Xu et al. 2015; Jiang et al. 2016), patients with cancer (Einolf et al. 2017a; Jing et al. 2017; Ono et al. 2017), pediatrics (Johnson and Rostami-Hodjegan 2011; Jing et al. 2017; Olafuyi et al. 2017a), and a pregnant population (Olafuyi et al. 2017b). The simulated results were comparable to clinical observations in special populations, and further investigations of disease- or age-related physiological properties in humans would be helpful.

Conclusion

The importance of predicting DDI potential has been discussed in many review articles, and PBPK modeling has been increasingly used for DDI predictions. This review provides a brief overview of PBPK model development and its application for DDI predictions. In addition, 107 PBPK modeling articles on the prediction of DDI potentials were identified, and the advantages of PBPK modeling, including capturing time-variable changes and inter-individual variability, have increased the number of articles published yearly. Although the articles reasonably predicted the DDI potentials in humans, investigation of DDI potentials using PBPK modeling was restricted to a limited number of drug metabolizing enzyme-mediated and transporter-mediated DDIs. In addition, the simulations were performed mostly in healthy adult populations. To widen the application scope of PBPK modeling in DDI predictions, more information on the physiological properties of the body and the incorporation of pathophysiological conditions in disease states are required. In addition, a harmonized in vitro experimental design is required for proper PBPK model building, and precise acceptance criteria should be set up for the validation process. Nevertheless, the outstanding

achievements and progress in life sciences and computer technologies will soon solve these problems, and DDI predictions will be improved by the incorporation of in vitro data into PBPK models.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflict of interest.

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