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PBPK Modeling: Empowering Drug Development and Precision Dosing in China

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ABSTRACT

Physiologically based pharmacokinetic (PBPK) modeling, a cornerstone of model-informed drug development and model-informed precision dosing, simulates drug disposition in the human body by integrating physiological, biochemical, and physicochemical parameters. While PBPK modeling has advanced globally since the 1970s, China's adoption of this technology has followed a distinctive path, characterized by accelerated growth over the past 2 decades. This review provides a comprehensive analysis of China's contributions to PBPK modeling, addressing knowledge gaps in publication trends, application domains, and platform preferences. A systematic literature search yielded 266 original PBPK research articles from PubMed up to August 08, 2024. The analysis revealed that drug disposition and drug–drug interaction studies constitute the largest proportion of PBPK analyses in China. Chinese universities and hospitals emerge as the leading contributors to PBPK research among institutions in China. Although established commercial PBPK platform such as GastroPlus and Simcyp remain popular within the Chinese pharmaceutical industry, open-source platforms like PK-Sim are gaining significant traction in PBPK applications across China. This review underscores the transformative potential of PBPK modeling in drug development within China, offering valuable insights into future directions and challenges in the field.

1 | Background

Model-informed drug development (MIDD) integrates and quantifies real-world data on physiology, pharmacology, and disease processes using advanced modeling and simulation techniques to facilitate critical decision-making in drug development [1]. Complementing this approach, model-informed precision dosing (MIPD) represents a significant advancement in personalized medicine, tailoring drug dosing to individual patient characteristics for optimized treatment outcomes [2]. These approaches leverage quantitative pharmacology to enhance decision-making throughout the drug development process and advance precision medicine. By integrating diverse computational and statistical methods, MIDD and MIPD enable researchers and clinicians to predict drug behavior, efficacy, and safety with unprecedented accuracy, thereby streamlining the path from discovery to clinical application and optimizing patient outcomes. Within this paradigm, physiologically based pharmacokinetic (PBPK) modeling has gained prominence as a powerful tool for simulating drug systemic absorption and disposition in the human body [3].

PBPK models incorporate physiological, biochemical, and physicochemical parameters to predict drug concentration–time

Dongsheng Yang and Jian Li contributed equally to this manuscript.

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profiles across different tissues and organs (Figure 1). These models have found widespread applications in drug–drug interaction (DDI) assessments, pediatric drug development, and the optimization of dosing regimens for special populations. The utility of PBPK modeling in regulatory decision-making has also grown significantly, with major health authorities increasingly accepting PBPK data in drug submissions [4, 5].

Despite the global advancements in PBPK modeling since its inception in the 1970s [6], China's engagement with this technology has followed a unique trajectory, marked by rapid growth over the past 2 decades [7]. The integration of PBPK modeling into drug development in China not only aligns with global trends but also addresses specific local needs, such as optimizing drug dosing in diverse populations and enhancing the safety and efficacy of both modern pharmaceuticals and traditional Chinese medicines (TCMs).

Despite these advancements in PBPK modeling, there remains a gap in the literature regarding China's contributions to this field. This review aimed to fill this gap by providing a comprehensive analysis of China's engagement with PBPK modeling. It explores publication trends, research domains, and platform preferences, offering insights into the significant role played by Chinese universities, hospitals, and regulatory bodies in advancing PBPK research. Furthermore, the review highlights the challenges and future directions for PBPK modeling in China, emphasizing the potential for this approach to transform drug development practices and contribute to the advancement of precision medicine.

As China continues to invest in innovative drug research and development, the role of PBPK modeling is expected to expand further. The increasing collaboration between Chinese regulatory authorities and international organizations, alongside the growing adoption of open-source PBPK platforms, underscores China's potential to influence global drug development practices. This review not only sheds light on the current state of PBPK modeling in China but also offers a roadmap for future research and development in this dynamic field.

2 | Literature Sources and Screening

A systematic literature search was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [8]. An extensive search of both

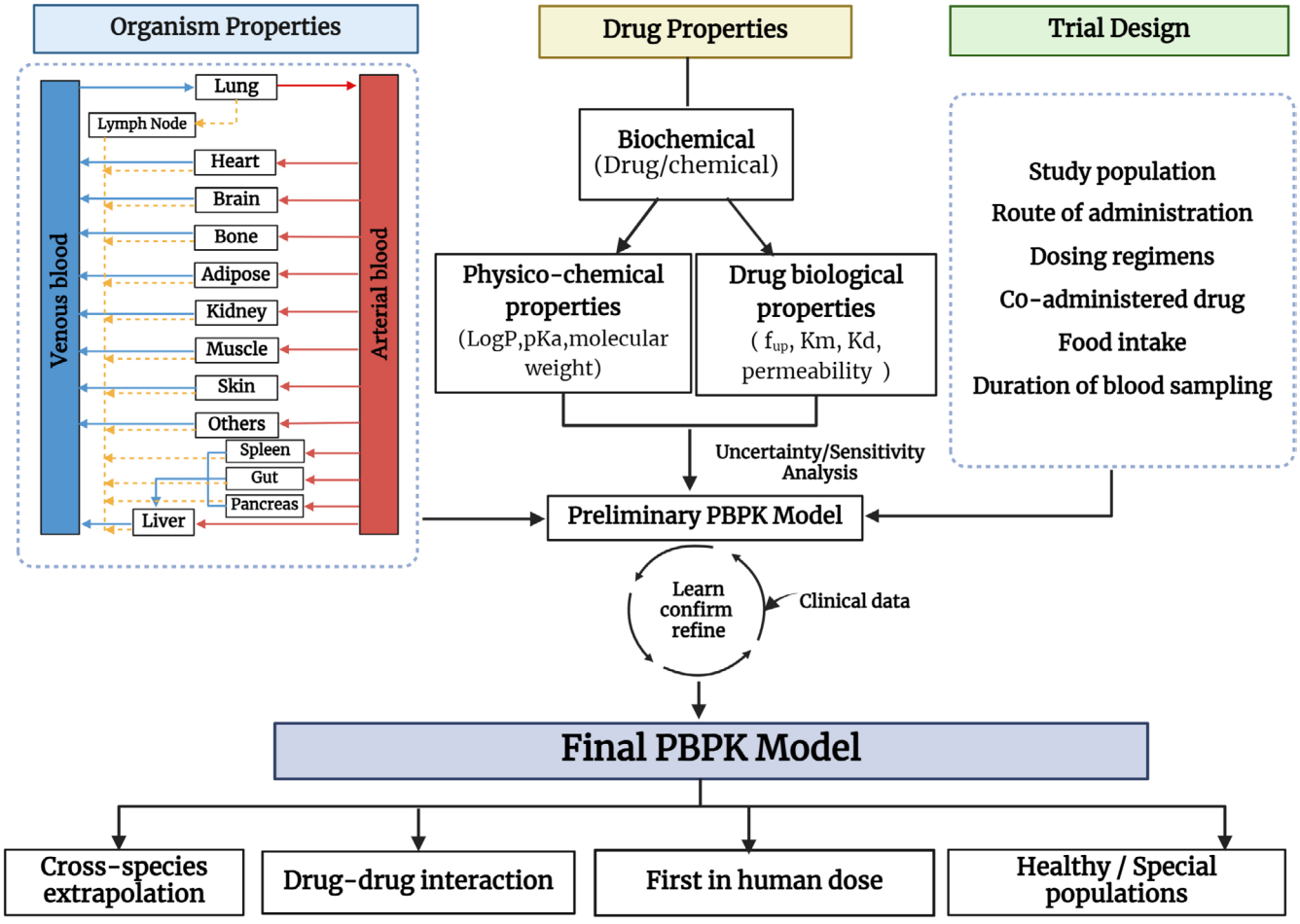

FIGURE 1 | Schematic overview of PBPK modeling workflow. This workflow illustrates the development of a PBPK Model, which integrates information from three primary components: organism properties includes key physiological compartments with arterial and venous blood flows interconnecting them; drug properties includes physicochemical properties and biological properties that influence drug kinetics; trial design encompasses variables like study population, route of administration, and blood sampling schedules. LogP: partition coefficient in oil and water. pKa: acid dissociation constant. f_{up}: unbound fraction in plasma. Km: michaelis constant. Kd: dissociation constant.

PubMed (National Center for Biotechnology Information) and Web of Science (Clarivate Analytics) was performed up to August 08, 2024 (publishing time), using the following search terms: (PBPK [Title/Abstract]) AND (China [Title/Abstract]); (PBPK [Title/Abstract]) AND (China [Affiliation]); (Drug–Drug interaction [Title/Abstract]) AND (PBPK [Title/Abstract]) AND (China [Title/Abstract]); (Drug–Drug interaction [Title/Abstract]) AND (PBPK [Title/Abstract]) AND (China [Affiliation]); (Traditional Chinese medicine [Title/Abstract]) AND (PBPK [Title/Abstract]) AND (China [Title/Abstract]); (Traditional Chinese medicine [Title/Abstract]) AND (PBPK [Title/Abstract]) AND (China [Affiliation]).

We implemented a systematic, four-stage screening process to identify relevant PBPK modeling studies. Starting with the combined search results from PubMed and Web of Science, the duplicate entries were first eliminated through manual verification in Excel. In the second stage, review articles were excluded based on document classification metadata from the databases. The third stage involved screening titles and abstracts to remove studies focusing on veterinary pharmaceuticals or environmental risk assessments. In the final stage, we conducted a detailed examination of methods and results sections to exclude papers that lacked original PBPK model construction. Through this process, only primary research articles describing PBPK models for human pharmaceutical applications were retained (Figure 2).

Our systematic search of two electronic databases identified 381 PBPK-related articles published between September 1, 2005 (the first PBPK publication in China) and August 8, 2024. The screening process excluded 115 articles: 41 reviews, 69 articles focused on veterinary drugs or hazardous substances, and 5 articles that lacked PBPK model construction. The final analysis included 266 original PBPK research articles, with the complete dataset available in Table S1.

3 | Evolution of PBPK Publications in China

The first PBPK-related article in China was a review authored by Chen et al. in 2005 [9], followed by the first original research publication on PBPK by Gao et al. in 2009 [10]. Since then, the number of original PBPK research publications in China has grown significantly, with annual output increasing exponentially over the years (Figure 3).

We conducted an extensive statistical analysis of the author's affiliation for 266 PBPK studies featured in this research (Table S1). Our findings revealed that these studies were predominantly published by universities (117 publications, 43.98%), hospitals (108 publications, 40.60%), industries (21 publications, 7.89%), scientific research institutes (19 publications, 7.14%), and regulatory agencies (1 publication, 0.38%). This distribution highlighted that universities and hospitals are the leading contributors to PBPK research in China.

In the university sector, China Pharmaceutical University and Fudan University emerged as the leading contributors to PBPK research, with 25 and 21 publications, respectively. Remarkably, 21 publications (84%) from China Pharmaceutical University were produced by the Center of Drug Metabolism and Pharmacokinetics. At Fudan University, all PBPK studies were conducted by the Department of Clinical Pharmacy and Drug Administration. This highlighted the focused areas of PBPK research within Chinese universities, indicating a concentration of expertise and resources in specific departments that drive advancements in this field.

In terms of hospitals, the First Affiliated Hospital of Fujian Medical University (18 publications) and Peking University Third Hospital (17 publications) led in output. Articles from the former were primarily from its department of pharmacy, while those from the latter were from its clinical trial center. Notably, our statistical analysis indicated that clinical trial centers (50 publications, 46.30%) were the predominant departments for PBPK research publications in Chinese hospitals (Table S1). This trend was likely influenced by the surge in generic drug research and development in China, particularly following the 2016 guidance from the National Medical Products Administration (NMPA), which encouraged 289 drug varieties to complete consistency evaluations by the end of 2018 [11]. This requirement led to the establishment of numerous clinical trial centers, primarily within hospitals, to address the growing demand for pharmacometric studies, including PBPK research [12].

4 | Research Domains and Specific Populations in PBPK Studies in China

We categorized these PBPK studies based on their primary research objectives into the following groups: "drug disposition," "DDI," "TCM," "dose optimization," "formulation," "investigational new drug (IND)," and "others" as depicted in Figure 4. Among these categories, drug dispositions emerged as the most prominent, accounting for 76 studies (28.57%), followed closely by DDI with 73 studies (27.44%) and dose optimization with 39 studies (14.66%). This distribution highlighted the focus of PBPK research in China. Notably, these findings aligned with previously published global reports, which also indicated that DDI and drug dispositions were the most frequently studied domains in published PBPK models [13–15].

To examine the inclusion characteristics of specific populations across various PBPK research fields in China, we analyzed and categorized the specific populations represented in the relevant literature (Figure S1). The results indicated that the pediatric population was more frequently included in dose optimization studies, likely due to the challenges associated with drug administration in pediatric clinical practice. Meanwhile, patients with hepatic and renal impairments were more commonly featured in dose optimization, drug disposition, and IND studies, as these domains prioritize understanding drug metabolism mechanisms directly related to liver and kidney functions. Additionally, preclinical animals were notably included in TCM, IND, and drug formulation studies, highlighting the essential role of preclinical studies in the drug development process, particularly in addressing uncertainties regarding drug toxicity.

5 | Drug–Drug Interactions

To predict DDIs using a DDI-PBPK model, a complex workflow must be followed (Figure 5). This workflow includes the

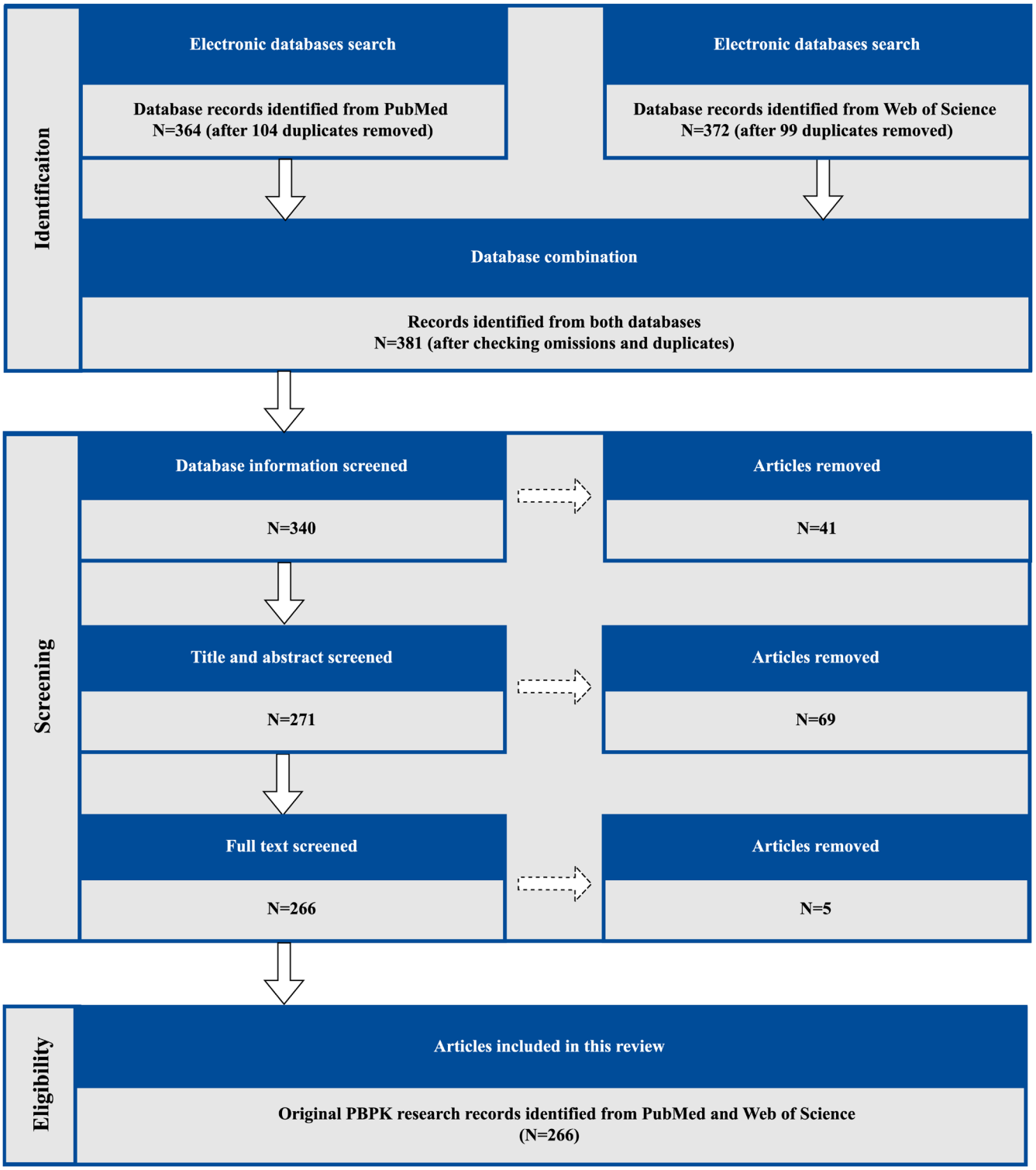

FIGURE 2 | Flowchart of the PBPK publication screening process for this study. A total of 381 records were identified after combing through the records of PubMed and Web of Science. After screening the title and abstract or reviewing the full text, 115 articles were manually removed. Ultimately, 266 research articles related to PBPK modeling were included in this study.

development of PBPK models for both victim drug and perpetrator drug, the integration of these models (known as DDI-PBPK model bridging), and the application of the DDI-PBPK model. The critical step in this process is bridging the primary PBPK models to create a cohesive DDI-PBPK model. This phase requires in-depth knowledge of the biochemical and physiological interactions between the two drugs. Once validated, the DDI-PBPK model can be applied to various practical and regulatory scenarios to predict drug interactions.

In this review, we found that the first DDI study in China was published by Liu et al. in 2011 [16], which investigated the potential DDI effects of theophylline and antofloxacin using a PBPK model. Since then, the number of DDI studies in China has

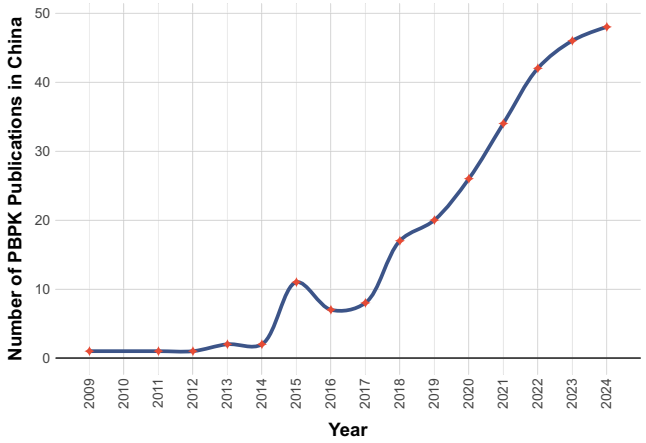

FIGURE 3 | Publication of PBPK literature in China over the years (2009–2024). The number of PBPK publications has generally been on an upward trend in China, especially in the past decade.

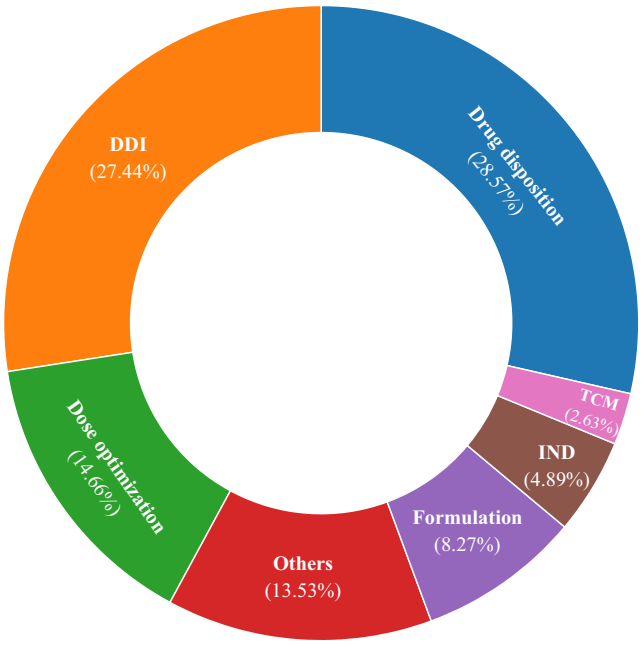

FIGURE 4 | Distribution of PBPK study domains in China. DDI: drug–drug interaction. IND: investigational new drug. TCM: traditional Chinese medicine. Others: food effect, race specificity, and pharmacogenomic, etc.

increased annually, in line with the overall rise in PBPK studies (Figure S2). Starting in 2021, approximately 15 original research articles involved DDI-PBPK model have been published each year in China.

We categorized the DDI studies based on the mechanisms involved, such as metabolic enzymes, transporters, and pH alterations. Among the 91 articles that constructed DDI-PBPK models, 67 (73.63%) focused on metabolic enzymes, 9 (9.89%) investigated the role of transporters, and 12 (13.19%) explored the interplay between metabolic enzymes and transporters (Table S1). This distribution aligned with prior research indicating that enzyme-based DDIs represent nearly 90% of DDI-PBPK studies [14, 15]. Notably, among the enzyme-DDI studies, 54 (68.35%) specifically examined CYP3A4, establishing it as the most frequently studied enzyme in DDI-PBPK applications within China (Figure 6). This observation was further supported by global reports highlighting CYP3A4's common involvement in published PBPK studies, relevant for both P450-sensitive substrates and those with narrow therapeutic indices [13, 17].

6 | PBPK Platform Distribution and Publication Trend in China

Our study summarized the annual publication trends of popular PBPK platforms in China, totaling 238 publications (Figure 7). MATLAB was the first platform used in PBPK studies in China, with its debut publication in 2011 [16]. Following this, pharmacometric platform such as GastroPlus, Simcyp, and PK-Sim gradually became integral to Chinese PBPK modeling and analysis.

Over the past 2 decades, publication trends for PBPK modeling platform in China have shown distinct patterns. GastroPlus and Simcyp initially experienced rapid growth, followed by a gradual decline. In contrast, PK-Sim has demonstrated a steep upward trajectory in adoption for PBPK modeling within the country. As of 2023, PK-Sim has emerged as the predominant PBPK modeling platform in China (Figure 7), with its popularity continuing to rise at an unprecedented rate. These findings aligned with Bayer's statistics indicating that China has emerged as the largest user of PK-Sim globally [18]. The rapid adoption of PK-Sim can be attributed to its open-source nature and versatility in accommodating diverse, customized application scenarios. We contend that the use of PBPK applications on open-source platforms like PK-Sim has significantly increased and is poised to challenge the dominance of traditional commercial PBPK platform in China.

Additionally, we assessed the overall proportions of PBPK platforms and their associated publishing institutions in China. Our findings revealed that Simcyp (81 publications, 30.45%) was the most frequently used platform in Chinese PBPK modeling studies, followed by GastroPlus (72 publications, 27.07%) and PK-Sim (62 publications, 23.31%) (Figure S3).

Notably, Simcyp and PK-Sim were more commonly employed by universities and hospitals (Figure 8). This trend could be attributed to Simcyp's academic bonus license program and PK-Sim's open-source nature, which enhance accessibility for university researchers and hospital clinicians working under budget constraints. However, PK-Sim had minimal industry adoption, accounting for only 4.76% of its total applications (figure not shown). This limited industrial use may reflect PK-Sim's relatively small footprint in IND/NDA applications for novel drugs [19].

Meanwhile, GastroPlus was predominantly used in scientific research institutes and industry (Figure 8), despite its generally high licensing costs. This prevalence can be attributed to two key factors: These institutions' focus on novel drug development, and the comprehensive support system provided by GastroPlus's Chinese distributor, *PharmoGo*, which includes extensive training programs and detailed application guidance [20]. Taking

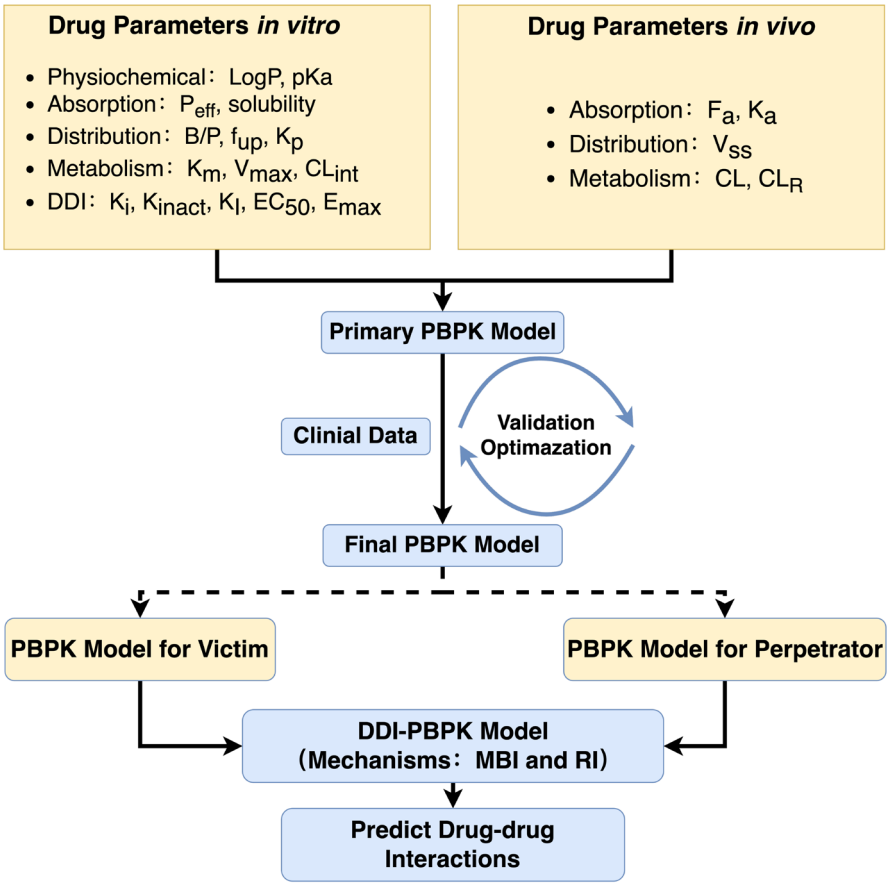

FIGURE 5 | Mechanistic workflow of DDI-PBPK model construction. LogP: partition coefficient in oil and water. pKa: acid dissociation constant. P_{eff}: effective human intestinal permeability. B/P: blood/plasma partition ratio. f_{up}: unbound fraction in plasma. K_p: tissue/plasma partition coefficient. Km: michaelis constant. Vmax: maximum rate of reaction. CL_{int}: intrinsic clearance. Ki: concentration of inhibitor that supports half inhibition. Kinact: inactivation rate of the enzyme. KI: concentration of mechanism-based inhibitor associated with half maximal inactivation rate. EC_{50}: drug concentration to reach 50% of maximal drug effect. E_{max}: maximal drug effect. Fa: fraction of drug absorbed. Ka: drug absorption rate. Vss: volume of distribution at steady-state: CL_R: renal clearance.

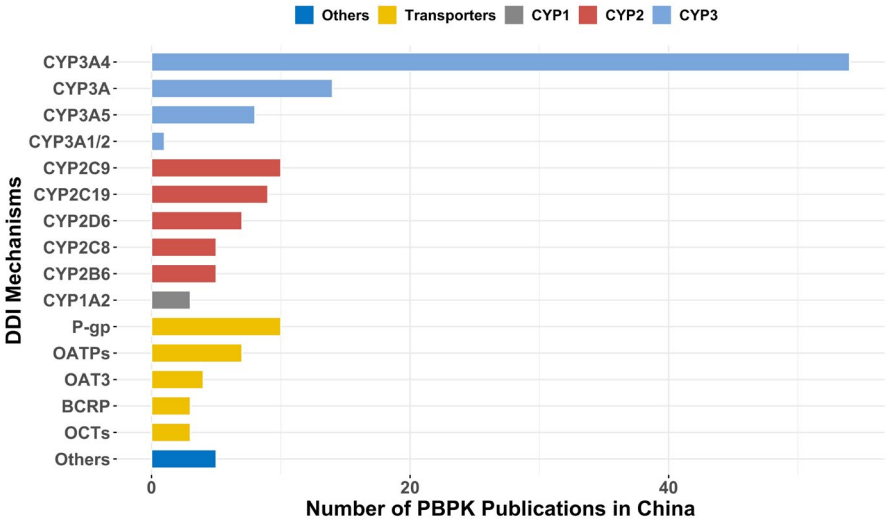

FIGURE 6 | Mechanisms taken into account in DDI studies in China. CYP: cytochrome P450. P-gp: P-glycoprotein. OATPs: organic anion-transporting polypeptides. OAT3: organic anion transporter 3. BCRP: breast cancer resistance protein. OCTs: organic cation transporters. Others: tubular transporter transport, UGTs, and PH, etc.

inspiration from this successful approach, several academic centers in Beijing, Changsha, and Shanghai launched PBPK modeling workshops in 2024, focusing on the open-source platform PK-Sim [21–23]. These online and in-person workshops are expected to significantly boost both the adoption of PK-Sim and the overall quality of PBPK applications in China.

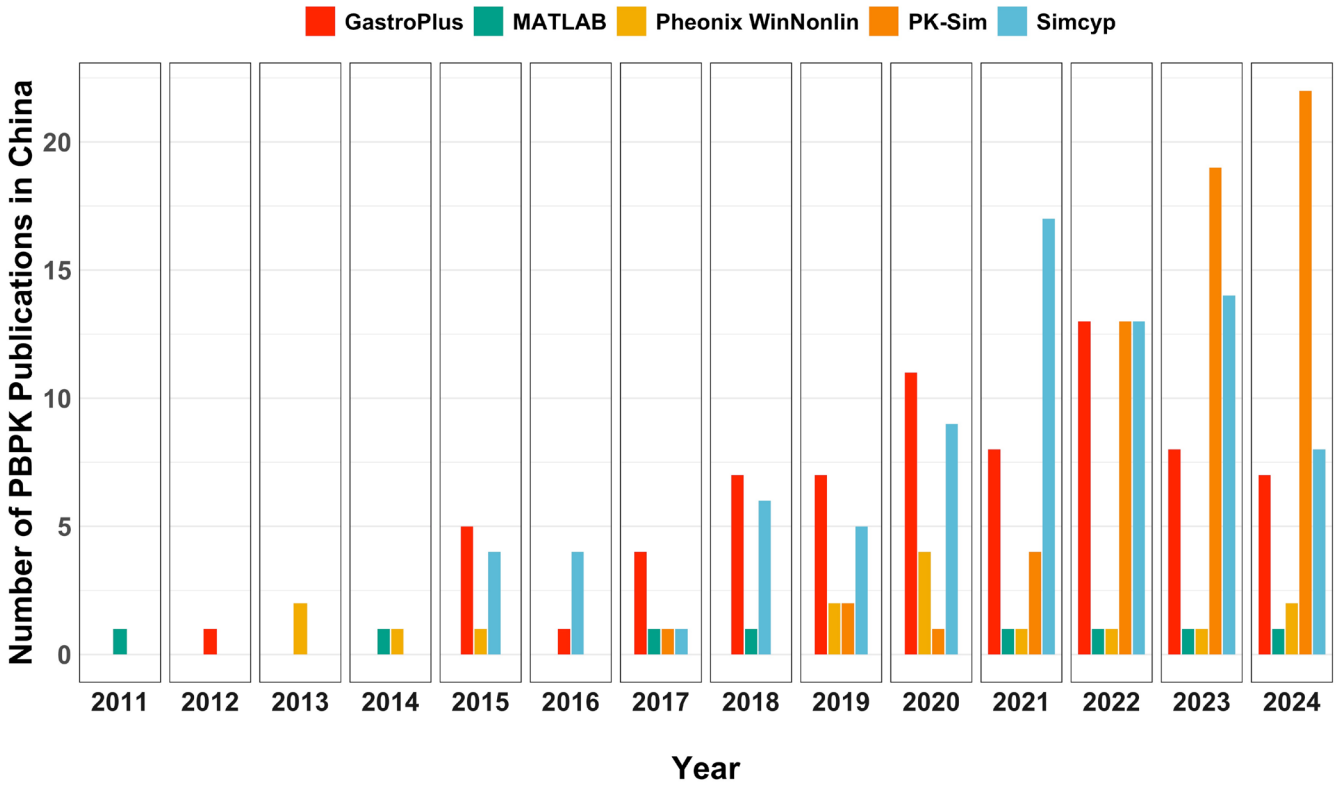

FIGURE 7 | Temporal trends in PBPK platform utilization in China. Only the five most popular PBPK platforms (GastroPlus, Simcyp, PK-Sim, Phoenix WinNonlin, and MATLAB) in China were shown.

7 | Distribution of PBPK Platforms Across Research Domains in China

We investigated platform selection trends across various PBPK research domains in China. Six pie charts (Figure S4) illustrate the usage of PBPK platforms across the categories of "drug disposition," "DDI," "TCM," "dose optimization," "formulation," and "IND." The results revealed that Simcyp was predominantly favored for DDI analysis (43.84%), IND applications (38.46%), and drug disposition (30.26%) within China. These findings aligned with previous studies highlighting Simcyp's significant role in DDI research within PBPK modeling [24, 25]. GastroPlus emerged as the preferred choice for formulation studies (45.45%) and IND applications (38.46%), corroborated by one earlier report indicating that GastroPlus was extensively used for formulation research (54% of its total usage) [25]. Meanwhile, PK-Sim demonstrated substantial usage for dose optimization studies (53.85%). This trend may be attributed to the fact that dose optimization studies were predominantly (89.74%) conducted by universities and hospitals in China (Table S1), where PK-Sim was the commonly used platform. These results illustrated the platform preferences among Chinese PBPK modelers across diverse research contexts.

Subsequently, we categorized the drugs in this study into large molecules (> 900 Da) and small molecules (< 900 Da) based on their molecular weight [26, 27]. Our findings revealed that the majority of China's PBPK studies (95.86%) focused on small molecules, with only 11 studies involving large molecules (Table S1). One possible explanation is the dominance of small molecule drugs in the market [28, 29]. Additionally, large molecule PBPK modeling requires extensive in vivo tissue distribution data to characterize how these drugs distribute throughout the body, which has limited its application [30]. Interestingly, the development of PBPK models for large molecules in China has increased significantly over the past 3 years and PK-SIM was the primary modeling platform used in 45.45% of these studies, suggesting the role of PK-SIM in advancing large molecule PBPK modeling in China.

Furthermore, we revealed distinct patterns in model types and their applications across research domains and modeling platforms. This review identified 22 studies that explicitly used whole-body PBPK models, while only four studies specifically employed minimal PBPK models [31–34]. The remaining studies did not specify their model category but were considered to use whole-body PBPK approaches (Table S1). Despite its limited adoption in China, minimal PBPK modeling has made significant contributions to pharmacometrics. The concept was first introduced by Henthorn et al. in 1992 [35] and was further developed by Cao, Jusko, and Mavroudis et al. [36–38].

Minimal PBPK models distinguish themselves by focusing exclusively on plasma and target organ pharmacokinetic distribution while excluding less relevant organs and tissues. This approach offers several key advantages: (1) Minimal PBPK models are more straightforward to construct and compute compared with whole-body models. This simplification reduces the burden of verification and calibration when dealing with numerous parameters. (2) The model parameters, such as fractional

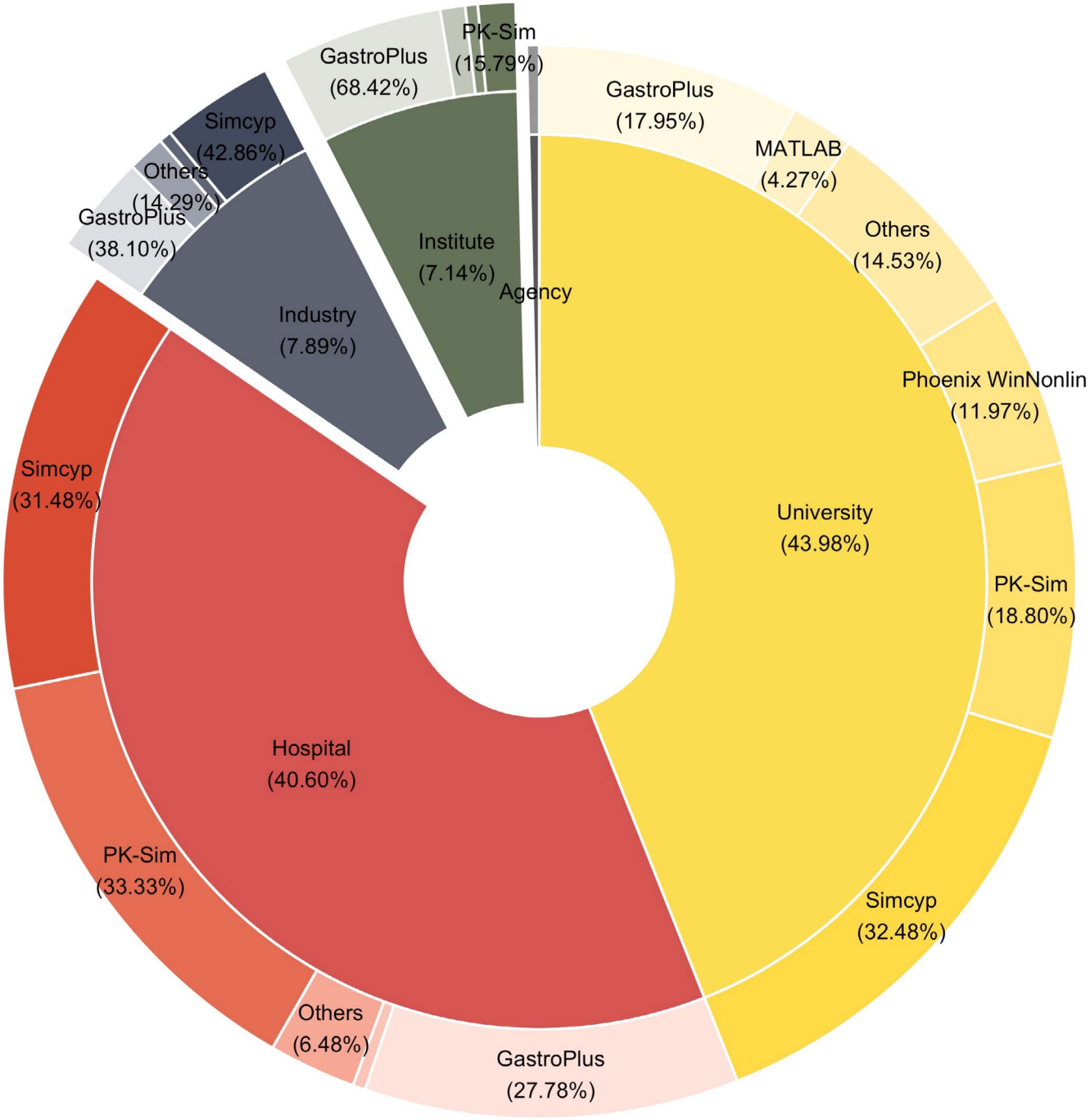

FIGURE 8 | Pie–Donut chart of BPBK platforms and publishing units in China. Institute: scientific research institute. Agency: regulatory agency. Others: NONMEM, Monolix, and Berkeley Madonna, etc.

distribution (f_d) and permeability/surface area coefficient (*PS*), provide more physiologically meaningful insights than conventional mammillary models [36]. (3) This approach requires less extensive tissue and organ distribution data, making them particularly valuable in scenarios with limited in vivo data availability. (4) Minimal PBPK models can be effectively integrated with pharmacodynamic approaches, including target-mediated drug disposition (TMDD) and quantitative systems pharmacology (QSP) models [39, 40]. Notably, the minimal PBPK approach has proven particularly effective for drugs targeting specific organs, such as monoclonal antibodies targeting the liver and antituberculosis medications targeting the lung [41, 42]. Given these advantages, there is significant potential for expanded application of minimal PBPK modeling in future Chinese pharmaceutical research.

8 | Chinese Research and Development (R&D) Drugs

This study included 31 Chinese R&D drugs (Table S2). Among them, 11 drugs (35.48%) were in the IND stage, including HSK3486 (Hisco Pharmaceutical Group Co. Ltd.) [43], PB-201 (PegBio Co. Ltd.) [44], and XZP-5610 (Xuanzhu Biotechnology

Co. Ltd.) [45], etc. These studies primarily utilized PBPK models in Simcyp and GastroPlus to translate preclinical experimental results into clinical contexts. Additionally, 10 approved drugs (31.25%) were investigated for DDIs, such as anlotinib (Chia Tai Tianqing Pharmaceutical Group Co. Ltd.) [46], icotinib (Beida pharmaceutical co. Ltd.) [47], and pyrotinib (Jiangsu Hengrui Pharmaceuticals Co. Ltd.) [48]. The remaining 10 drugs (31.25%) were evaluated for various purposes, including dose optimization, formulation development, and drug disposition studies.

Among the PBPK publications (34 in total) concerning Chinese R&D drugs, there are 11 publications (32.35%) dedicated to MIDD for IND drugs and 23 publications (67.65%) on MIPD for approved drugs (Table S2). Our analysis revealed that MIDD studies were predominantly conducted in scientific research institutes and hospital clinical trial centers (8 publications, 72.73%), whereas MIPD studies were mostly found in universities or other hospital departments (14 publications, 60.87%). This distribution clearly illustrated the institutional landscape and developmental trends of MIDD and MIPD studies for innovative drugs in China. Significantly, the PBPK platforms used in these studies predominantly rely on traditional commercial platform, such as GastroPlus and Simcyp, which were employed in 72.73% of MIDD studies and 82.61% of MIPD studies, respectively (Table S2). This trend highlighted a preference for established commercial PBPK platform within China's novel drug development sector, aligning with global reports [19, 25].

The Office of Statistics and Clinical Pharmacology, established by the Center for Drug Evaluation (CDE) in 2016 [49], has played a pivotal role in shaping clinical pharmacology practices for innovative drug development in China. The office's emphasis on pharmacometric modeling has significantly influenced the CDE's review process, prompting pharmaceutical companies to increasingly incorporate these approaches in their IND/NDA submissions in China [49]. A notable example of regulatory impact can be seen in pediatric PBPK modeling. While no pediatric PBPK models were published in China before 2023 [50, 51], the landscape changed following the CDE's release of the "Technical Guidelines for the Application of Physiological Pharmacokinetic Models in Drug Development for Pediatric Populations" in 2023. These developments underscored the crucial role of regulatory authorities in advancing PBPK research and applications in China.

9 | Traditional Chinese Medicines in PBPK Studies

There were 14 articles related to TCMs included in this research, among which 9 articles constructed the first PBPK model of targeted TCM (Table S3), and the remaining 5 articles were DDI studies of Wuzhi Capsule (Table S4).

Although China is the main producer and user of TCMs [52, 53], PBPK modeling for TCMs in China was relatively scarce. There are four main challenges: (1) *Multicomponent complexity of TCMs*, PBPK models typically simulate one or several main active ingredients, whereas TCMs often contain hundreds or even thousands of ingredients, many of which are not fully elucidated in terms of structure and properties. (2) *Variability in TCM ingredient content*, the content of ingredients in TCMs varies greatly due to factors such as origin, growth environment, and harvest time, leading to significant batch-to-batch differences. (3) *Internal interactions within TCMs*, TCM ingredients may interact with each other through competitive metabolism, synergistic effects, etc. These complex interactions are difficult to model accurately in PBPK frameworks. (4) *Lack of preclinical or clinical data*, compared to chemical drugs, TCMs often lack comprehensive pharmacokinetic research data, particularly human data, which hinders parameter fitting and model validation in PBPK studies.

To overcome these challenges, some Chinese researchers focused on comprehensive data collection. They measured the physicochemical and physiological parameters of the main TCM components through preclinical in vitro and in vivo experiments before incorporating these findings into PBPK modeling [10, 54, 55]. Simultaneously, researchers enhanced predictive capabilities by integrating advanced computational methods into TCM PBPK modeling. A notable example is the work by Li et al. [56], who combined a support vector machine classifier with PBPK modeling to predict the hepatotoxicity of 17 TCM ingredients. Their optimized approach successfully predicted safe dosing regimens for oxymatrine that aligned closely with clinical recommendations, demonstrating the potential of hybrid modeling approaches. These methodological advanced represent promising steps toward improving the precision and applicability of PBPK models for TCMs, despite the inherent complexities of these multicomponent therapeutic agents.

10 | Highly Frequent Drugs Included in Chinese PBPK Studies

In the literature reviewed for this study, certain drugs appeared frequently in PBPK modeling. Rifampicin was the most frequently modeled compound, appearing in more than 21 studies, followed by itraconazole and ketoconazole, which were featured in over 17 and 13 studies, respectively (data not shown). The prevalence of these specific drugs stemmed from their strong modulatory effects on cytochrome P450 (CYP) enzymes, making them essential probe compounds for DDI studies.

Several other drugs featured prominently in the PBPK modeling literature, with levetiracetam, tacrolimus, and Wuzhi capsules each appearing in more than five studies (Table S4). *Levetiracetam*, a widely prescribed antiepileptic drug known for its favorable safety profile, was the subject of multiple PBPK modeling studies. These investigations focused on bioequivalence assessments across various formulations, dose optimization strategies, and drug disposition patterns in specific patient populations [57–61]. These models provided crucial quantitative support for the clinical use of levetiracetam in various scenarios. *Tacrolimus*, a critical immunosuppressant used to prevent organ rejection in transplant recipients, was extensively modeled to predict DDI and dose optimization across different patient populations [62–66]. These PBPK models offered valuable guidance for personalizing tacrolimus therapy in diverse transplant populations. *Wuzhi Capsule*, a Traditional Chinese Medicine with hepatoprotective properties, also functions as a CYP enzyme

inhibitor. PBPK modeling of Wuzhi Capsule primarily focused on predicting potential interactions with CYP-metabolized drugs, such as tacrolimus and cyclosporine A [67–71]. These models provided important insights into herb–drug interactions in transplant patients and inform dosing strategies when combining Traditional Chinese and Western medicines.

11 | Prospect

The statistical data from this study underscores the commitment of quantitative pharmacologists in China to advancing PBPK models across diverse research fields and clinical scenarios. Over the past decade, China has emerged as a significant player in the drug development landscape, evidenced by a marked increase in the introduction of novel drugs. The rise of open-source quantitative pharmacology platform and the establishment of international forums have significantly facilitated and strengthened communication among PBPK modelers worldwide. With the guidance and support of the CDE and NMPA, PBPK models have become integral to the successful development of innovative pharmaceuticals in the country. To further enhance the clinical application of TCMs, Chinese researchers are actively integrating PBPK models for quantitative analysis. Additionally, they are exploring the synergy of advanced technologies, such as AI and machine learning, with PBPK modeling to boost the global applicability of TCMs. These innovative efforts not only demonstrate China's growing influence in quantitative pharmacology but also signal promising directions for the field's future development.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.