Journal of Applied Pharmaceutical Science Vol. 13(04), pp 001-010, April, 2023
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2023.87792
ISSN 2231-3354

Application of *in silico* methods in clinical research and development of drugs and their formulation: A scoping review

Luciana Ferreira Mattos Colli*, Lúcio Mendes Cabral, Guacira Correa Matos, Carlos Rangel Rodrigues, Valeria Pereira de Sousa
Department of Faculty of Pharmacy, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

ARTICLE INFO

Received on: 24/10/2022
Accepted on: 29/01/2023
Available Online: 28/03/2023

Key words:
Drug discovery, *in silico* clinical trial, computational methods, drug development, virtual patients.

ABSTRACT

The drug regularization process involves many steps that are complex and time-consuming. The demand for new drugs has prompted researchers and regulatory authorities to search for predictive methods that can streamline the development process. Current studies point to innovative computational techniques in a drug's study phases. This study aims to carry out a scoping review of research involving the application of computational methods and *in silico* studies in the clinical research and development of new drugs. A scoping review was conducted according to the eferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. Online databases from 2001 to 2021 in English were used and the trial registration was 10.17605/OSF.IO/USXCM. The development of protocols and the application of a computational method for researching new drugs and their formulation, published in a peer-reviewed journal, were included. The data extraction and analysis were performed by two independent reviewers. In this study, 312 articles were retrieved, of which 6 were duplicates. After the title was read, only 101 remained for analysis. After the abstracts were read, 34 papers were considered for the scoping review. The use of *in silico* methodologies has been expanding in terms of research into the development of new drugs and the improvement of existing products.

INTRODUCTION

The efficacy and safety of a drug are basic concepts of health surveillance adopted by regulatory agencies around the world (ANMAT, 2022; ANVISA, 2021; European Medicine Agency (EMA), 2019; FDA, 2018; PMDA, 2022). One of the main tools for drug regulation is the clinical trial, which, for new drugs, can take up to 12 years or more and cost millions of dollars (Berndt *et al*., 2015; Dimasi *et al*., 1995; Jensen, 1987). To circumvent such factors, over the years, major technological advances have been made, and new methodologies have been developed to streamline the process of evaluating a new molecular entity (Ji *et al*., 2017; Kar and Leszczynski, 2017).

**Corresponding Author*
Luciana Ferreira Mattos Colli, Department of Faculty of Pharmacy, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.
E-mail: colli.luciana @ gmail.com

The clinical trial protocols aimed at registering a drug were standardized with the Common Technical Document, a publication of the International Council of Harmonization (ICH), in which guidelines for the quality, safety, and efficacy of drugs were postulated. In the safety guide (M4S (R2)), the ICH prescribes the pharmacological evaluation of the drug, the pharmacodynamic (PD) study, and the interaction with other drugs. In addition, assessments of absorption, distribution, metabolism, excretion, and toxicity are applied (ICH, 2004).

In line with international practices, the Food and Drug Administration (FDA) divides clinical trials for drug registration into interventional and observational studies, the first being more common and the second obtained through researchers' observation of outcomes after the use of a particular drug (FDA, 2019).

The structure of clinical studies involving new drugs is agreed upon worldwide as having four phases. The application of *in silico* studies, especially the well-known physiologically based pharmacokinetic (PBPK) studies that now already have guides published by the FDA and EMA, can be a strategy to compose the regulatory dossier, shortening the time of its elaboration (EMA, 2016; FDA, 2016).

The discussion that predominates in the area is the development of a set of strategies to shorten the long years of research. One possibility to speed up clinical trials is the application of *in silico* studies, with the use of digital resources, aiming to assess the effect that a particular drug can have on the human body (Clermont *et al*., 2004; Mancini *et al*., 2018; Pappalardo *et al*., 2019; Sinisi *et al*., 2020).

This scoping review aims to provide an overview of the specialized scientific literature on the use of digital technologies in clinical trials, with the application of *in silico* trials in the evaluation of new drugs, and the improvement of already regularized drugs and their formulations, to anticipate events in a traditional *in vivo* clinical trial involving humans.

METHODS

A scoping review was carried out to identify the conditions for the application of *in silico* studies in the current context of clinical research with new drugs. A request was made to register the research in the Open Science Framework (OSF) with the number 10.17605/OSF.IO/USXCM.

The research was conducted in March 2022, using the databases Latin American and Caribbean Health Sciences Literature (Lilacs), National Library of Medicine (PubMed), MEDLINE, Web of Science, and Scopus, in English. The report of the present scoping review was prepared by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) checklist (Page and Moher, 2018; Peter *et al*., 2020, 2022). Studies that applied *in silico* methods to evaluate new or already registered drugs, improvements in formulation, evaluation of drug interaction, and pharmacometrics were considered. The specific keywords/descriptors that are Health Science Descriptors addressed drug discovery, *in silico* clinical trials, computational methods, drug development, and virtual patients. Publications in English between 2001 and 2021 were adopted.

After the selected articles were read, a form was filled out with collected data, which were compared in an infographic. Data analysis sought (a) the virtual and *in vivo* patient; (b) the protocols adopted in the studies; (c) a comparison with a traditional clinical study, in cases where it was observed; and (d) the observed outcomes.

RESULTS

The literature search strategy took place in the MEDLINE/PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Lilacs databases; the terms used in the search were ((*in silico*) AND (clinicaltrials) AND (drugtrials)); ((computationalmethods) AND (drugdevelopment)); ((computationalmethods) AND (drugdiscovery)); ((model-informeddrugdiscoveryanddevelopment)); and ((Virtual PhysiologicalHuman) and (drugdevelopment)), with a total of 312 articles retrieved. Of these, six were duplicates; therefore, they were disregarded.

The first phase of the study was carried out by reading the titles and abstracts of the articles. Those that were within the scope and met the inclusion criteria proceeded to the second stage, in which the text was read in full. Two researchers performed the complete reading of 70 articles. In total, 34 articles were considered for the scoping review and 36 were eliminated because they used multiple methods or tools or their methodology did not specify the software used. The selection flowchart can be seen in Figure 1.

PKs and PDs simulation: PK/PB using software

GastroPlus™

Simulation models are increasingly used in drug development studies and formulation improvement. Their application seeks to speed up the process and guide the conduct in the design of a new drug, with the GastroPlus™ software being directed to this. The development of a drug has complex factors that are difficult to adjust, such as physical-chemical, physiological, and formulation factors. It is necessary to employ tools to support the process. In the scoping review, six studies were identified as involving the use of the GastroPlus™ PK simulator. The results of the scoping review with GastroPlus™ are summarized in Table 1.

In approaches to PK studies, the study conducted by Jereb *et al*. (2021) evaluated delayed-release tablet pantoprazole compared to dolutegravir and its impact on the patient's gastrointestinal tract after a meal and in the fasted state. This study used virtual models, with pantoprazole performing better than dolutegravir in terms of bioavailability.

In the application of the method in the study of formulations in the comparison of different formulations, Kato *et al*. (2020) evaluated three formulations, A, B, and C, and their PK in oral use. They noted differences between the developed batches, including those that were not bioequivalent. In a similar objective, the study by Xia *et al*. (2013) used *in silico* techniques to evaluate the PK of developed formulations and the effect of feeding. In this study, the drug in the experimental phase NVS123, of basic character and with pH-dependent solubility, was evaluated.

The occurrence of changes in gastric pH is a biopharmaceutical event that can impact the bioavailability of several drugs. The study by Samant *et al*. (2018) evaluated the pH and its consequences on the absorption of ribociclib, finding that PK had no impact on the elevation of gastric pH. Similarly, this occurred in the evaluation of alectinib (Parrott *et al*., 2016).

Regarding the evaluation of formulations, GastroPlus™ proved to be a possibility in a generic candidate drug study [Biopharmaceutics Classification System (BCS) class 2] compared to the reference. Additionally, a clinical study and dissolution test were conducted. An additional concern was assessing the impact of food and fasting, with the tests supporting the construction of the regulatory dossier (EMA, 2016; FDA, 2016; Rebeka *et al*., 2019).

NONMEM®

NONMEM® is an acronym that stands for "NON-linear Mixed-Effects Modeling," which is a software developed in the early 1980s, with an application in *in silico* studies involving the PKs of several drugs. The results of the scoping review with NONMEM® are summarized in Table 2.

In cases of patient exposure, the work by Li *et al*. (2015) used abiraterone and nilotinib to determine mock PK assays. The parameters adopted for the PK study were obtained from

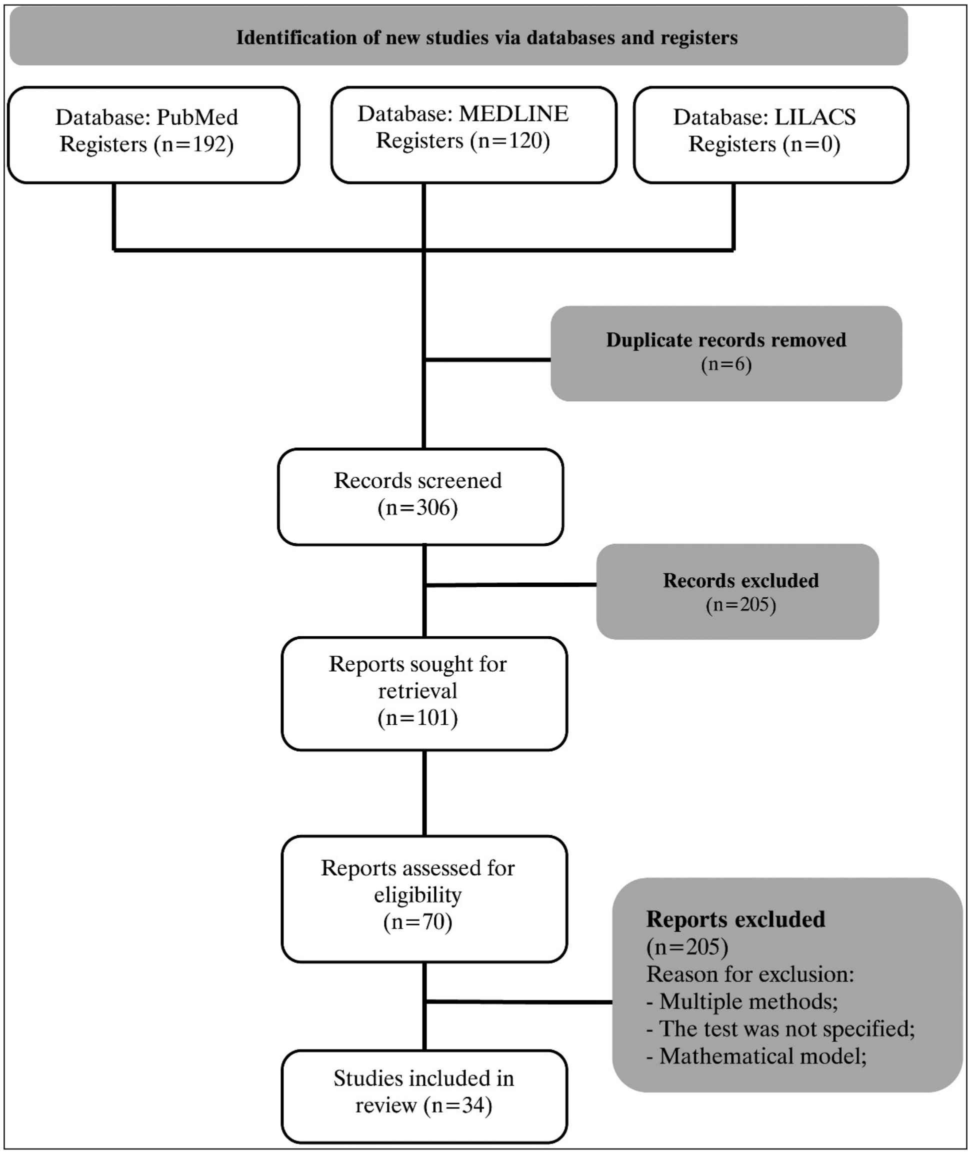

Figure 1. Flowchart for selecting articles for the scoping review, using the PRISMA methodology.

Table 1. Scoping review studies involving PK simulators using GastroPlus™ software.

References	Objective	Medicine	Result
Jereb *et al*. (2021)	Assess bioavailability with variations in the gastrointestinal tract.	Delayed-release pantoprazole and dolutegravir	In pantoprazole, the result with altered physiology was superior to dolutegravir.
Kato *et al*. (2020)	Develop a relevant technical specification for an oral drug.	Comparison between formulations A, B, and C	The *in silico* method was able to discriminate between a bioequivalent batch and a nonbioequivalent batch.
Samant *et al*. (2018)	Investigate the influence of changes in gastric pH and PKs.	Ribociclib	It did not indicate an effect of gastric pH on changes in PKs.
Xia *et al*. (2013)	Describe various *in silico*/*in vitro*/ *in vivo* tools to support formulation development.	NVS123	An investigation of the new formulation and the practical application of PBPK modeling were carried out.
Parrott *et al*. (2016)	Understand the impact of gastric pH changes on alectinib absorption.	Alectinib	Simulations with this model supported the development of alectinib aiding in the design and interpretation of pharmacology studies.
Rebeka *et al*. (2019)	To evaluate a generic formulation compared *in vitro* and *in vivo* with a reference drug.	BCS 2 drug	The model was able to capture the difference between the two drugs containing different forms of drugs (amorphous and crystalline).

Table 2. Scoping review studies involving PK simulators using NONMEM® software.

Reference	Objective	Medicine	Result
Albers *et al*. (2008)	To investigate the PKs of carvedilol in children.	Carvedilol	PKs of carvedilol in pediatric patients depends on age and weight.
Fransson and Gréen (2008)	Studied the PKs of two types of formulations for paclitaxel.	Paclitaxel	Both formulations performed satisfactorily.
Li *et al*. (2015)	PK assay simulation.	Abiraterone and nilotinib	Assess the characteristics of drugs with highly variable PKs.
Ma *et al*. (2014)	To assess the responsiveness to the treatment of RA.	Metotrexate	The study may collaborate in future clinical trials for the treatment of RA.
Wang *et al*. (2013)	Assess MEDI-546 using a biomarker.	MEDI-546	There were phase I study and a phase II randomized multiple-dose study.
Cardozo *et al*. (2010)	Develop predictive models to describe the dose response of fesoterodine.	Fesoterodine	A consistent dose response to fesoterodine has been demonstrated for overactive bladder outcomes.
Friberg *et al*. (2009)	Modeling to characterize the response to asenapine in schizophrenia.	Asenapine	Analyses have shown that asenapine doses of 5 and 10 mg twice daily are effective.
Nathan *et al*. (2008)	Identify optimal dosing time using two surrogate markers of glucocorticoid action.	Budesonide and fluticasone propionate	Dosage simulations as an antiasthmatic observing cortisol suppression.
Kowalski *et al*. (2008)	Test the dose of SC-75416.	SC-75416, rofecoxib, valdecoxib, and ibuprofen	The 360 mg SC-75416 dose achieved superior results compared to 400 mg of ibuprofen.
Van Hest *et al*. (2005)	To evaluate the PKs of fixed-dose and multiple-dose Mycophenolate sodium.	Mycophenolate sodium	The results of this simulation resulted in prospective studies comparing a concentration-controlled regimen with a fixed dosage.

the mean and standard deviation of several published studies (Ryan *et al*., 2010; Tanaka *et al*., 2010; Zytiga, 2013 apud Li *et al*., 2015). The simulation is applied to evaluate possible results in a clinical trial in different dosing regimens looking at new treatments compared to methotrexate, with the possibility of understanding the endpoints for rheumatoid arthritis (RA) trials and clarifying confounding factors; the method was also applied with fesoterodine (Cardozo *et al*., 2010; Ma *et al*., 2014).

In an evaluation of the sublingual route, the response to the dose of asenapine in patients with schizophrenia was characterized. The analysis enabled an understanding of the results of six placebo-controlled trials in which responses and dropout rates varied. Although the simulations indicated that the post hoc probability of success of the performed trials was low to moderate, these analyses demonstrated that asenapine doses of 5 and 10 mg twice daily have similar efficacy (Friberg *et al*., 2009).

Additionally, one study evaluated another route of administration, testing inhaled glucocorticoids in the work by Nathan *et al*. (2008) as a first-line therapy in asthma. The study sought to identify the optimal timing of dosing using two surrogate markers of glucocorticoid action. A previously published study (Mollmann *et al*., 2001 *apud* Nathan *et al*., 2008) on the PK and PD (blood cortisol and lymphocyte suppression) of the glucocorticoids budesonide and fluticasone propionate was reanalyzed using a population PK approach allowing established dosage. This can be applied in pediatric dose-setting cases, such as carvedilol for children (Albers *et al*., 2008) (Table 2).

Clinical trial simulations and PK/PD models were conducted to recommend a study design to test the dose of the compound SC-75416, a selective inhibitor of cyclooxygenase-2, in pain relief compared to 400 mg of ibuprofen in a model of pain after oral surgery. Study results confirmed the hypothesis that 360 mg of SC-75416 achieved superior pain relief compared to 400 mg of ibuprofen and demonstrated the predictive performance of PKPD models (Kowalski *et al*., 2008). In a biomarker approach, the PD of another MEDI-546 test compound, a monoclonal antibody, was characterized by modeling and simulation (Wang *et al*., 2013).

Application in therapeutic drug monitoring can also be performed using *in silico* methods. Studies with mycophenolate mofetil (MMF) in a fixed-dose regimen and another regimen of a controlled concentration of mycophenolic acid exposure were developed. Estimates for oral clearance of MMF were used to calculate values in the area under the curve (Van Hest *et al*., 2005).

Simcyp™ simulator in drug interaction

Bioequivalence and bioavailability studies can also be conducted with the Simcyp™ Simulator software, which is the PBPK model platform for determining human dosing, optimizing the design of clinical studies, evaluating new drug formulations, defining the dose in untested populations, and performing virtual analyses of bioequivalence and drug interactions (Certara, 2022). The data of the scoping review with Simcyp™ are summarized in Figure 2.

The Simcyp™ ADME Simulator can also be a database for simulation modeling of oral absorption, tissue distribution, drug metabolism, and excretion, and drug development studies in certain populations predicting the extent of action and drug–drug interaction (Jamei *et al*., 2009).

The drug interaction studies were observed using Simcyp™. In one of them, models of interaction between the target drug nemiralisib and itraconazole were used; additionally,

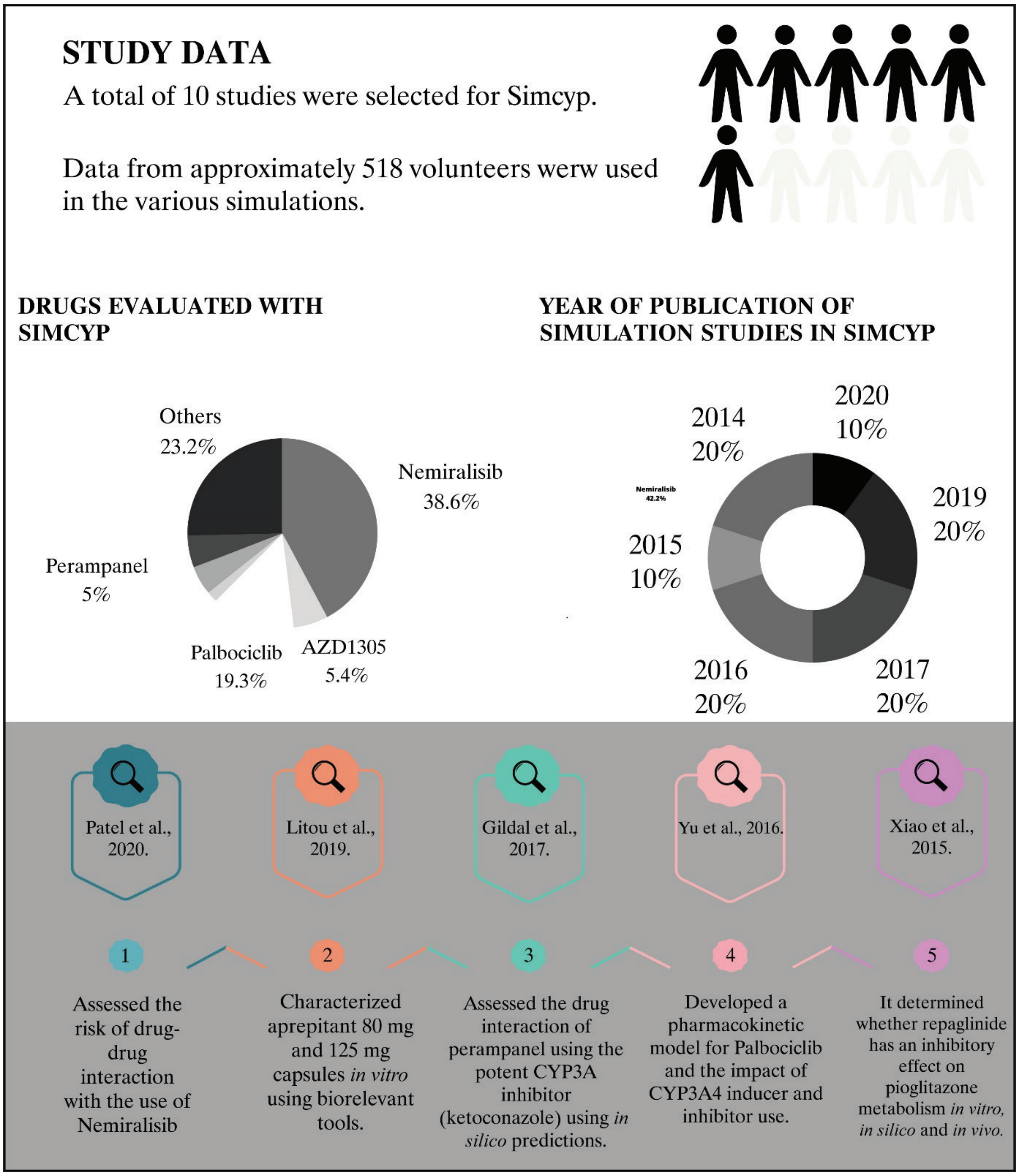

Figure 2. Infographic illustrating studies mapped to Simcyp™, with key data, drugs, and authors.

midazolam and clarithromycin were evaluated (Patel *et al*., 2020; Yu *et al*., 2017).

Another study evaluated enzyme inhibitors, with concomitant application of *in vitro*, *in silico*, and *in vivo* methods. The study determined whether repaglinide had an inhibitory effect on pioglitazone metabolism. The authors observed a discrepancy in the result between the experiments (Xiao *et al*., 2015) (Fig. 2).

In a different modality of study, a nanoscale formulation was evaluated by Litou *et al*. (2019). In the study design, *in vitro* results were coupled to a PBPK model. The evaluation was with aprepitant (EMEND), which is indicated for nausea and vomiting, especially during chemotherapy. In cases involving nanomeric formulations, it is necessary to apply innovative tools to understand their *in vivo* performance and guide the regulatory process (Fig. 2).

The approach used with perampanel was structured with data from *in vitro* studies and a phase I trial (Patsalos, 2015). The peak plasma concentration of perampanel (C_{max}) and time to C_{max} showed no apparent differences when perampanel was administered alone versus with ketoconazole (Gidal *et al*., 2017).

Monte Carlo simulation

The Monte Carlo simulation or Monte Carlo method, which is a branch of experimental or applied mathematics involving random numbers, has applications in several areas of knowledge, such as mathematics, physics, economics, and even medical sciences (Carvalho, 2017).

The method or model is essentially characterized by the use of software that, with simulation platforms, expands the sample size of a study and provides simulations for the outcome of treatment or, more precisely, for a particular therapeutic target, considering different situations, such as changes in a dose or frequency of drug administration (Federico *et al*., 2017).

In the study by Zhang *et al*. (2011), Monte Carlo simulation was applied to generate hypothetical cohorts with 7,000 patients characterizing the so-called discrete event simulation (DES) (Fig. 3). In the research, we investigated the effectiveness of rivaroxaban in preventing stroke in patients with atrial fibrillation. Hypothetical patient cohorts were generated using data from ROCKET AF (Patel *et al*., 2011) (FDA registration code NCT00403767) and two other observational studies (Amin *et al*., 2017; Laliberté *et al*., 2014) and Xantus (Camm *et al*., 2016). The results confirmed that rivaroxaban was noninferior to warfarin for the prevention of stroke/systematic embolism, with no significant risk of major bleeding in atrial fibrillation in large populations. This was similar to the results of ROCKET AF.

In a process that involved applying data from previously performed clinical trials, Najafzadeh *et al*. (2018) used data from the RE-LY study (2009), as well as cohorts of equal size with covariate distributions identical to the study of Graham *et al*. (2015). Cohort simulations were performed using the Monte Carlo method and compared to a randomized clinical trial. Another study that used Monte Carlo simulations to interpret data from a randomized clinical trial was performed by Cuadros *et al*. (2014); in this study, study simulations involving male circumcision in trials with valaciclovir for the suppression of herpes simplex were performed (Fig. 3).

Opioids are subject to evaluation, due mainly to their application in pain, to evaluate long-acting opioids in patients with nonmalignant chronic pain classified as moderate to severe. Neil *et al*. (2013) developed a Monte Carlo simulation. Long-term opioid efficacy and adverse events were obtained from clinical trials with tapentadol ER versus oxycodone CR; other data were taken from the literature. The use of tapentadol proved to be superior in effectiveness and cost-effectiveness, demonstrating the successful use of Monte Carlo in a pharmacoeconomics study.

Another study on chronic pain was carried out by Murthy *et al*. (2007) with once-daily extended-release tramadol (tramadol ER) approved in the US for moderate to moderately severe chronic pain in adults. Monte Carlo simulation was performed to assess switching in patients who received immediate-release tramadol by ER tramadol. PK analyses showed that switching from a total daily dose of tramadol IR 200 or 300 mg to tramadol ER 200 and 300 mg once daily is equivalent.

STELLA®

STELLA® software is a dynamic systems simulation that helps one understand complex correlations within a system of data relationships. It is used in modeling, providing tools to convert numerical models into formulation evaluation (Naimi *et al*., 2012).

Three studies of Shono were found to use STELLA® software: one from 2011, another from 2010, and a third from 2009. The first study, by Shono *et al*. (2011), developed an *in silico* PBPK for poorly soluble nelfinavir mesylate in water and of weakly basic pH-generating plasma profiles and of coupling dissolution results and precipitation estimates with gastrointestinal parameters.

The second study, by Shono *et al*. (2010), coupled biorelevant dissolution test results with *in silico* simulation technology to predict the *in vivo* oral absorption of aprepitant formulations with micronized and nanosized particles in the preprandial and postprandial states.

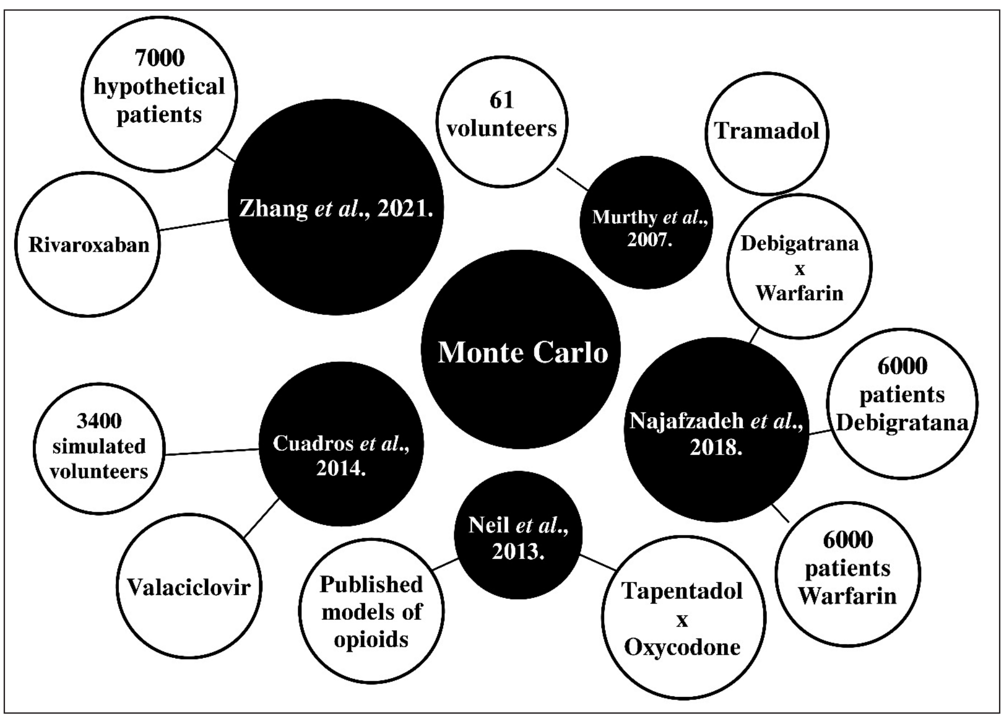

Figure 3. Infographic illustrating the studies mapped to Monte Carlo simulation with key data, drugs, and authors.

The third and oldest study, by Shono *et al*. (2009), determined the rate of intestinal absorption of poorly soluble drugs and dissolution in the gastrointestinal tract. In this study, *in vitro* dissolution tests using biorelevant media coupled with PBPK *in silico* were applied to predict the effects of food on the absorption of a poorly soluble drug, celecoxib, from celecoxib 200 mg capsules.

DISCUSSION

This study described and characterized the types of *in silico* methods for research involving new drugs and the improvement of existing ones. Simulation models have advanced in recent years, and have been shown to be tools increasingly used in drug development and formulation studies. Such development and innovation motivated several researchers to evaluate new software for conducting clinical trials in their work.

The most applied and tested *in silico* studies by the scientific community within the parameters researched pointed to the use of software such as GastroPlus™, NONMEM®, Simcyp™, Monte Carlo, and STELLA®.

Of the tests evaluated, the GastroPlus™ software was continuously employed in human PK and PD assessments of several different drug types and formulations. The *in silico* method was also able to discriminate between bioequivalent and nonbioequivalent batches. With the software, it was also possible to perform *in silico* clinical evaluations of the influence of changes in gastric pH and food intake on the PK of a drug.

In terms of evaluating new compounds, two studies studied new drugs. These were new formulation clinical investigations and, most importantly, highlighted a practical application of PBPK modeling in solving problems involving undesirable food effects on weakly basic compounds based on *in vitro*/*in vivo* data. The various studies retrieved in the proposed search demonstrated that the *in silico* method using GastroPlus™ is efficient in evaluating different drug formulations, changes in the drug's crystalline arrangement, or even the use of known and regularized drugs at different stages of the digestion process.

Other publications pointed out the use of NONMEM® software. The searches retrieved ten scientific articles evaluating several drugs and the application of the software aimed to establish pediatric doses, inhaled drugs, drug interactions, and pharmacometry.

Some studies clearly did dosage reviews or sought to determine new dosages in different audiences.

The development of innovative drugs is not the only application of *in silico* methods but may well lend itself to developing better evaluations of already regulated drugs, which have a variable PK profile, and also the impact that food can have.

The remaining studies found were conducted using the Simcyp™ Simulator software to determine the human dosage of various compounds. They also evaluated the drug–drug interaction and PK of several drugs, as well as the behavior of different formulations.

Of the articles found in the research, three pointed to the use of the Monte Carlo method, which was applied to expand the sample of volunteers and create simulations of responses.

To evaluate the drugs nelfinavir, celecoxib, and aprepitant, studies were found that used the STELLA® software to evaluate the dissolution in the moments before and after the meal.

CONCLUSION

The *in silico* studies observed in this work proved its applicability in the research of new drugs, as well as in the improvement of the evaluated formulations, with the approaches of PK evaluation and drug–drug interaction evaluation.

The evaluated studies have differences in terms of the drug evaluated, the number of simulated patients, the protocol adopted, and the *in silico* technology addressed. For this reason, comparing results is difficult. However, it is possible to observe the application of software and the evaluation of drugs in different simulated approaches.

The application of *in silico* methods to evaluate a drug or medication intensified in the last decade and its use has been expanding. This meets the need for more agile studies with lower costs in the development of new drugs.

ACKNOWLEDGMENTS

The authors would like to acknowledge the staff members of Universidade Federal do Rio de Janeiro, the Faculty of Pharmacy, for their support of this work.

AUTHOR CONTRIBUTIONS

Concept and design, acquisition of data, or analysis and interpretation of data were carried by Colli and Cabral. Drafting the article and revising it critically for important intellectual contente were carried out by Matos, Rodrigues and Sousa.

FINANCIAL SUPPORT

There is no funding to report.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article and in the searchRxiv platform in the link https://doi.org/10.1079/searchRxiv.2022.00006.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

REFERENCES

Albers S, Meibohm B, Mir TS, Laer S. Population pharmacokinetics and dose simulation of carvedilol in pediatric patients with congestive heart failure. Br J Clin Pharmacol, 2008; 65(4):511–22.

Amin A, Keshishian A, Trocio J, Dina O, Le H, Rosenblatt L, Liu X, Mardekian J, Zhang Q, Baser O, Vo L. Risk of stroke/systemic embolism, major bleeding and associated costs in non-valvular atrial fibrillation patients who initiated apixaban, dabigatran or rivaroxaban compared with warfarin in the United States Medicare population. Curr Med Res Opin, 2017; 33(9):1595–604.

ANMAT. Nuevos aranceles para mantenimiento de registros de productos médicos y especialidades medicinales [Online]. Available via https://www.argentina.gob.ar/noticias/nuevos-aranceles-para-mantenimiento-de-registros-de-productos-medicos-y-especialidades (Accessed 13 February 2022).

ANVISA. Protocolo de segurança e eficácia de medicamentos inovadores. 2021 [Online]. Available via https://www.gov.br/anvisa/pt-br/setorregulado/regularizacao/medicamentos/informes/medicamentos-sinteticos/protocolo-de-seguranca-e-eficacia-de-medicamentos-inovadores (Accessed 13 February 2022).

Berndt ER, Nass D, Kleinrock M, Aitken M. Decline in economic returns from new drugs raises questions about sustaining innovations. Health Affairs, 2015; 34(2):245–52.

Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof, Kuhls S, van Eickels M, Turpie AG, XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J, 2016; 37(14):1145–53.

Cardozo L, Khullar V, El-Tahtawy A, Guan Z, Malhotra B, Staskin D. Modeling dose-response relationships of the effects of fesoterodine in patients with overactive bladder. BMC Urol, 2010; 10(1):1–11.

Carvalho ARD. Método Monte Carlos e suas aplicações. 122 f. Dissertação (Mestrado em Matemática), Universidade Federal de Roraima, Boa Vista, Brazil, 2017.

Certara. SIMCYP PBPK Simulator. Versão 21. Phoenix: Certara, 2022 [Online]. Available via https://www.certara.com/software/simcyp-pbpk/ (Accessed 4 April 2022).

Clermont G, Bartels SJ, Kumar R, Constantine G, Vodovotz Y, Chow C. *In silico* design of clinical trials: a method coming of age. Crit Care Med, 2004; 32(10):2061–70.

Cuadros DF, Abu-Raddad LJ, Awad SF, García-Ramos G. Use of agent-based simulations to design and interpret HIV clinical trials. Comput Biol Med, 2014; 50:1–8.

Dimasi JA, Hansen RW, Grabwski HC, Lasagna L. Research and development costs for new drugs by therapeutic category. Pharm Econ, 1995; 7(2):152–69.

EMA. Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation, 2016 [Online]. Available via http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211315.pdf (Accessed 27 May 2022).

EMA. Research and development [Online]. Available via https://www.ema.europa.eu/en/human-regulatory/research-development (Accessed 13 February 2022).

FDA. Guidance for industry: physiologically based pharmacokinetic analyses—format and content, 2016 [Online]. Available via https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf (Accessed 27 May 2022).

FDA. Learn about clinical studies. 2019. [Online]. Available via https://clinicaltrials.gov/ct2/about-studies/learn (Accessed 13 February 2022).

FDA. The drug development process. Step 3: Clinical research. FDA, 2018. [Online]. Available via https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (Accessed 13 February 2022).

Federico MP, Sakata RAP, Pinto PFC, Furtado GHC. Noções sobre parâmetros farmacocinéticos/farmacodinâmicos e sua utilização na prática médica. Rev Soc Brasil Clín Méd, 2017; 15(3):201–5.

Fransson M, Gréen H. Comparison of two types of population pharmacokinetic model structures of paclitaxel. Eur J Pharm Sci, 2008; 33(2):128–37.

Friberg LE, De Greef R, Kerbusch T, Karlsson MO. Modeling and simulation of the time course of asenapine exposure response and dropout patterns in acute schizophrenia. Clin Pharm Ther, 2009; 86(1):84–91.

Gidal BE, Maganti R, Laurenza A, Yang H, Verbel DA, Schuck E, Ferry J. Effect of enzyme inhibition on perampanel pharmacokinetics: why study design matters. Epilepsy Res, 2017; 134:41–8.

Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, ... Kelman JA. Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation, 2015; 131(2):157–64.

ICH. M4 Organisation of the common technical document for the registration of pharmaceuticals for human use guidance for industry. ICH, Geneva, Switzerland, 2004.

Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp® population-based ADME simulator. Expert Opin Drug Metab Toxicol, 2009; 5(2):211–23.

Jensen EJ. Research expenditures and the discovery of new drugs. J Indus Econ, 1987; 36:83–95.

Jereb R, Opara J, Bajc A, Petek B. Evaluating the impact of physiological properties of the gastrointestinal tract on drug *in vivo* performance using physiologically based biopharmaceutics modeling and virtual clinical trials. J Pharm Sci, 2021; 110(8):3069–81.

Ji Z, Yan K, Li W, Hu H, Zhu X. Mathematical and computational modeling in complex biological systems. BioMed Res Int, 2017; 2017:1–16.

Kar S, Leszczynski J. Recent advances of computational modeling for predicting drug metabolism: a perspective. Curr Drug Metab, 2017; 18(12):1106–22.

Kato T, Nakagawa H, Mikkaichi T, Miyano T, Matsumoto Y, Ando S. Establishment of a clinically relevant specification for dissolution testing using physiologically based pharmacokinetic (PBPK) modeling approaches. Eur J Pharm Sci, 2020; 151:45–52.

Kowalski KG, Olson S, Remmers AE, Hutmacher MM. Modeling and simulation to support dose selection and clinical development of SC-75416, a selective COX-2 inhibitor for the treatment of acute and chronic pain. Clin Pharmacol Ther, 2008; 83(6):857–66.

Laliberté F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. Curr Med Res Opin, 2014; 30(7):1317–25.

Li CH, Sherer EA, Lewis LD, Bies RR. Clinical trial simulation to evaluate population pharmacokinetics and food effect: capturing abiraterone and nilotinib exposures. J Clin Pharmacol, 2015; 55(5):556–62.

Litou C, Patel N, Turner DB, Kostewicz E, Kuentz M, Box KJ, Dressman J. Combining biorelevant *in vitro* and *in silico* tools to simulate and better understand the *in vivo* performance of a nano-sized formulation of aprepitant in the fasted and fed states. Eur J Pharm Sci, 2019; 138:105031.

Ma L, Zhao L, Xu Y, Yim S, Doddapaneni S, Sahajwalla CG, Wang Y, Ji P. Clinical end point sensitivity in rheumatoid arthritis: modeling and simulation. J Pharmacokinet Pharmacodyn, 2014; 41(5):537–43.

Mancini T, Mari F, Massini A, Melatti I, Salvo I, Sinisi S, Tronci E, Ehrig R, Röblitz S, Leeners B. Computing personalised treatments through *in silico* clinical trials. A case study on down regulation in assisted reproduction. Intell Artif, 2018; 2271:1–16.

Mollmann H, Wagner M, Krishnaswami S, Dimova H, Tang Y, Falcoz C, Daley-Yates PT, Krieg M, Stöckmann R, Barth J, Lawlor C, Möllmann AC, Derendorf H, Hochhaus G. Single-dose and steady-state pharmacokinetic and pharmacodynamic evaluation of therapeutically clinically equivalent doses of inhaled fluticasone propionate and budesonide, given as Diskus or Turbo haler dry-powder inhalers to healthy subjects. J Clin Pharmacol, 2001; 52(5):487–95.

Murthy BP, Skee DM, Danyluk AP, Brett V, Vorsanger GJ, Moskovitz BL. Pharmacokinetic model and simulations of dose conversion from immediate-to extended-release tramadol. Curr Med Res Opin, 2007; 23(2):275–84.

Nathan RA, Berger W, Yang W, Cheema A, Silvey M, Wu W, Philpot E. Effect of once-daily fluticasone furoate nasal spray on nasal symptoms in adults and adolescents with perennial allergic rhinitis. Ann Allerg Asth Immunol, 2008; 100(5):497–505.

Naimi B, Voinov A. Stella R: a software to translate Stella models into R open-source environment. Environ Modell Software, 2012; 38:117–8.

Najafzadeh M, Schneeweiss S, Choudhry NK, Wang SV, Gagne JJ. Simulation for predicting effectiveness and safety of new cardiovascular drugs in routine care populations. Clin Pharmacol Ther, 2018; 104(5):1008–15.

Neil N, Merchant S, Provenzano D, Ogden K, Mody SH. Clinical simulation model of long-acting opioids for treatment of chronic non-cancer pain in the United States. J Med Econ, 2013; 16(2):307–17.

Page MJ, Moher D. Extensions in development: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Syst Rev, 2018; 6(1):1–14.

Pappalardo F, Russo G, Tshinanu FM, Viceconti M. *In silico* clinical trials: concepts and early adoptions. Brief Bioinform, 2019; 20(5):1699–708.

Parrott NJ, Yu LJ, Takano R, Nakamura M, Morcos PN. Physiologically based absorption modeling to explore the impact of food and gastric pH changes on the pharmacokinetics of alectinib. AAPS J, 2016; 18(6):1464–74.

Patel A, Wilson R, Harrell AW, Taskar KS, Taylor M, Tracey H, Riddell K, Georgiou A, Cahn AP, Marotti M, Hessel EM. Drug interactions for low-dose inhaled nemiralisib: a case study integrating modeling, *in vitro*, and clinical investigations. Drug Metab Dispos, 2020; 48(4):307–16.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer De, Hacke W. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med, 2011; 365(10):883–91.

Patsalos PN. The clinical pharmacology profile of the new antiepileptic drug perampanel: a novel noncompetitive AMPA receptor antagonist. Epilepsia, 2015; 56(1):12–27.

Peters MD, Godfrey C, McInerney P, Khalil H, Larsen P, Marnie C, Pollock D, Tricco AC, Munn Z. Best practice guidance and reporting items for the development of scoping review protocols. JBI Evid Synth, 2022; 20(4), 953–968.

Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: Scoping reviews. In: Aromataris E, Munn Z (Eds.). JBI Manual for evidence synthesis. JBI, 2020. [Online] Available via https://synthesismanual.jbi.global (Accessed 20 February 2022).

PMDA. History [Online]. Available via https://www.pmda.go.jp/english/about-pmda/outline/0002.html (Accessed 13 February 2022).

Rebeka J, Jerneja O, Igor L, Boštjan P, Aleksander B, Simon Ž, Albin K. PBPK absorption modeling of food effect and bioequivalence in Fed State for two formulations with crystalline and amorphous forms of BCS 2 class drug in generic drug development. AAPS PharmSciTech, 2019; 20(2):1–10.

Ryan CJ, Smith MR, Fong L, Rosenberg JE, Kantoff P, Raynaud F, Martins V, Lee G, Kheoh T, Kim J, Molina A, Small EJ. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol, 2010; 28(9):1481.

Samant TS, Dhuria S, Lu Y, Laisney M, Yang S, Grandeury A, Mueller-Zsigmondy M, Umehara K, Huth F, Miller M, Germa C, Elmeliegy M. Ribociclib bioavailability is not affected by gastric ph changes or food intake: *in silico* and clinical evaluations. Clin Pharmacol Ther, 2018; 104(2):374–83.

Shono Y, Jantratid E, Kesisoglou F, Reppas C, Dressaman, JB. Forecasting *in vivo* oral absorption and food effect of micronized and nanosized aprepitant formulations in humans. Eur J Pharm Biopharm, 2010; 76(1):95–104.

Shono Y, Jantraid E, Janssen N, Kesisoglou F, Mao Y, Vertzoni M, Reppas C, Dressman JB. Prediction of food effects on the absorption of celecoxib based on biorelevant dissolution testing coupled with physiologically based pharmacokinetic modeling. Eur J Pharm Biopharm, 2009; 73(1):107–14.

Shono Y, Jantratid E, Dressman JB. Precipitation in the small intestine may play a more important role in the *in vivo* performance of poorly soluble weak bases in the fasted state: case example nelfinavir. Eur J Pharm Biopharm, 2011; 79(2):349–56.

Sinisi S, Alimguzhin V, Mancini T, Tronci E, Leeners B. Complete populations of virtual patients for *in silico* clinical trials. Bioinformatics, 2020; 36(22–3):5465–5472.

Tanaka C, Yin OQ, Sethuraman V. Clinical pharmacokinetics of the BCR-ABL tyrosine kinase inhibitor nilotinib. Clin Pharmacol Ther, 2010; 87(2):197–203.

Van Hest R, Mathot R, Vulto A, Weimar W, Van Gelder T. Predicting the usefulness of therapeutic drug monitoring of mycophenolic acid: a computer simulation. Ther Drug Monit, 2005; 27(2):163–7.

Wang B, Higgs BW, Chang L, Vainshtein I, Liu Z, Streicher K, Liang M, White WI, Yoo S, Richman L, Jallal B, Roskos L, Yao Y. Pharmacogenomics and translational simulations to bridge indications for an anti-interferon-α receptor antibody. Clin Pharmacol Ther, 2013; 93(6):483–92.

Xia B, Heimbach T, Lin TH, Li S, Zhang H, Sheng J, He H. Utility of physiologically based modeling and preclinical *in vitro*/*in vivo* data to mitigate positive food effect in a BCS class 2 compound. AAPS PharmSciTech, 2013; 14(3):1255–66.

Xiao Q, Tang L, Xu R, Qian W, Yang J. Physiologically based pharmacokinetics model predicts the lack of inhibition by repaglinide on the metabolism of pioglitazone. Biopharm Drug Dispos, 2015; 36(9):603–12.

Yu Y, Loi CM, Hoffman J, Wang D. Physiologically based pharmacokinetic modeling of palbociclib. J Clin Pharmacol, 2017; 57(2):173–84.

Zhang C, Wang WW, Pan MM, Gu ZC. Simulation of anticoagulation in atrial fibrillation patients with rivaroxaban—from trial to target population. Rev Cardiovasc Med, 2011; 22(3):1019–27.

Zytiga™. [Bula]. Toronto: Patheon Inc. 2013. [Online]. Available via http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202379lbl.pdf (Accessed: 02 March 2022).

How to cite this article:
Colli LFM, Cabral LM, Matos GC, Rodrigues CR, de Sousa VP. Application of *in silico* methods in clinical research and development of drugs and their formulation: A scoping review. J Appl Pharm Sci, 2023; 13(04):001–010.