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Review Article

QSP For Mechanisms Of Pharmacological Responses

Quantitative Systems Pharmacology: An Overview

Dr. Virendra Kushwaha[1], Dr. Pooja Agrawal[2*], Dr. Vipul Shukla[1] and Dr. Geeta Singh Rana[1]

[1]Department of Pharmacology, GSVM Medical College Kanpur

*Department of Pharmacology, Rani Durgawati Medical College Banda

Abstract: Quantitative systems pharmacology (QSP) attempts to quantitatively resolve the complex mechanisms and interactions between physiology and medications. Systems biology-based mechanistic models describe biological pathways and their regulatory networks at molecular, cellular, tissue, organ, patient, and/or population levels. QSP models are developed at various biological scales to present various multiscale mechanisms of pharmacological responses. PK PD (Pharmacokinetic pharmacodynamic) and QSP modeling differ in technical aspects such as data requirements, model implementation, and model evaluation/qualification methods. Previous evaluations have not examined the technical differences between PKPD and QSP modeling. Data needs, model implementation, and model evaluation/qualification are key distinctions. Our review addresses the gap by comparing PKPD modeling to QSP modeling, revealing QSP's superiority. The final gap left by previous evaluations is a limited examination of the applications of QSP for comprehending combination cancer therapies and systems-level analysis. Not enough has been said about pathway analysis, network modeling, logical modeling, virtual patient simulations, multi-scale systems pharmacology platforms, and identifying non-identifiable models. Our review fills in these voids and offers valuable insights into the significance of these approaches for elucidating the complex behavior of biological systems and their responses to medications. The aim and objective of this review are to clarify QSP's unique contributions and correct earlier assessments' lack of comparability. Secondly, we study QSP modeling computational approaches such as molecular docking, molecular dynamics modeling, machine learning, and similarity analysis. These methods can model drug-target interactions, filling the gap left by earlier studies and improving pharmacological knowledge. Pathway analysis and network modeling are vital to understanding the complicated regulatory processes that develop from biological component interactions. We examine how network and route analysis might enhance cancer combination treatment, transcending previous evaluations' limited scope. This review improves on earlier reviews by analyzing QSP more thoroughly. It illuminates QSP's potential for personalized medicine, treatment optimization, and illness management

Keywords: Quantitative Systems Pharmacology (QSP), Pharmacokinetic-Pharmacodynamic (PKPD) Modeling, Systems Biology, Drug Development, Virtual Patient

***Corresponding Author**

Dr. Pooja Agrawal , Department of Pharmacology, Rani Durgawati Medical College Banda

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1. INTRODUCTION

Since its introduction in 2011 as a method documented in a white paper published by the NIH (National Institutes of Health), quantitative systems pharmacology (QSP) has grown in favor of drug development[1]. While there is no clear definition of QSP at this time, it comprises an attempt to quantitatively resolve the complex mechanisms and interactions between physiology and medications (including investigational drugs) in order to predict reactions in the face of a drug intervention[2]. Systems biology-based mechanistic models describe biological pathways and their regulatory networks at molecular, cellular, tissue, and organ system levels to further the understanding of biological processes[3].

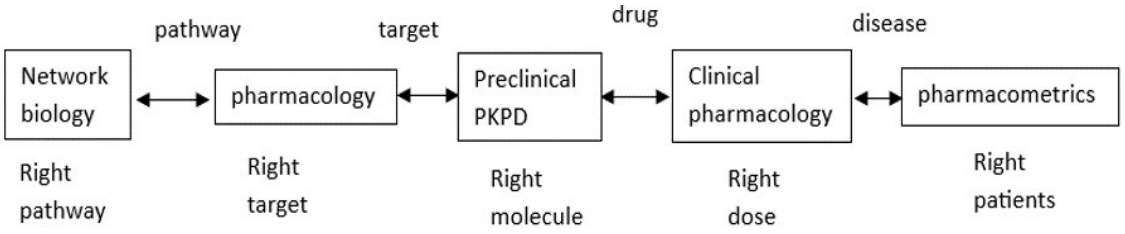

Fig 1: Main areas QSP aims to tackle to reach a wider 'systems-level' perspective.

Impact of combining modeling and measuring methodologies on crucial milestones in the drug development process, ranging from locating the appropriate target to locating the appropriate patients to treat. This figure is a reproduction that was done by the QSP Workshop Group based on the NIH White Paper. Pharmacokinetic-pharmacodynamic (PKPD) modeling aims towards understanding pharmacological responses by quantifying the relationship between observed drug exposure and its observed nonclinical or clinical endpoints, often linking exposure to one endpoint while QSP models are commonly used to capture multiple biomarkers. PK PD (Pharmacokinetic, Pharmacodynamic) modeling is a top-down approach because it is driven by previously observed data, whereas systems biology-based modeling is a bottom-up approach because it begins with fundamental biological knowledge such as molecular or cellular signaling pathways to predict the behavior of biological systems (fig 1). In this context, quantitative systems pharmacology modeling can be viewed as a balanced platform of bottom-up and top-down modeling approaches that allow for the integration of biological knowledge available as presumptive and observed data obtained analytically to aid drug development decisions in a scientifically informed and practical manner. QSP models are developed at various biological scales ranging from cellular, molecular, tissue, organ, patient, and/or population levels, thereby highlighting the use of these models to present various multiscale mechanisms of pharmacological responses[4]. The ultimate goal of QSP is to understand a biological, toxicological, or pathological process mechanistically and quantitatively in response to therapeutic modulation[5]. Formal mathematical models are often developed, which incorporate data at many temporal and spatial scales and include enough biological information to allow extrapolation beyond the data used to generate and/or qualify the model[6]. Furthermore, in order to have the most impact in preclinical drug discovery, QSP models must be fit for purpose to answer specific challenges, be actionable, and be built in a time frame that allows for speedy decision-making[7]. QSP integrates diverse data, including preclinical and clinical information, to analyze dynamic interactions between a drug or drug combination and multi-scale biological systems, with the goal of understanding the behavior of the systems as a whole[8,9]. QSP typically consists of three steps: collecting sufficient information, such as disease-related targets, biomarkers, pathways, drug-target interactions, and phenotypic characteristics; developing a primary model based on the foregoing information; and calibrating and validating the model by comparing its predictions with preclinical and clinical data[10].

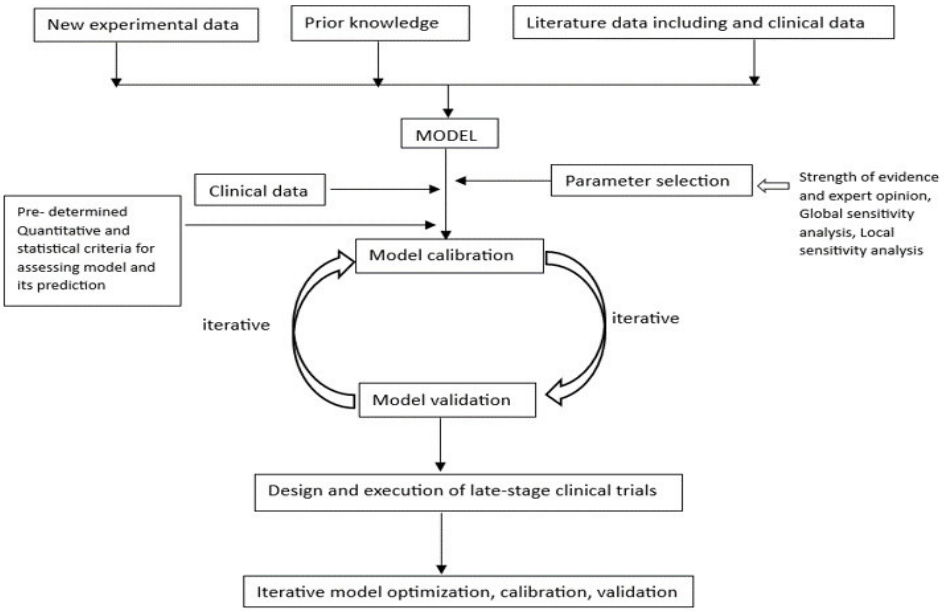

Fig2: Quantitative systems pharmacology workflow.

Collaboration between specialists from many fields, such as pharmacology, biology, mathematics, and engineering, is essential throughout the QSP workflow in order to ensure the integration of a wide range of knowledge and skills from a variety of fields. The iterative nature of the workflow makes it possible for the model to be continuously refined and improved, which ultimately results in more accurate predictions and choices about drug development and personalized medicine that are better informed[11]. QSP is a potential method for quantitatively examining the interactions between drugs and systems, such as targets, pathways, cells, and organs, and gives a thorough understanding of the underlying mechanisms of drug action[12]. QSP is becoming a discipline, and its research requires describing the PK/PD characteristics of drugs, identifying their targets and drug-target interactions, and investigating the factors responsible for differences in the omics data of cells, tissues, and patients[13,14]. Conventional drug development adheres to the maximum "one drug, one target, one disease" and attempts to treat a disease by modifying a single target responsible for the sickness. This straightforward technique encourages the development of selective medicines for specific targets. QSP integrates the understanding of complex networks of diseases and employs quantitative analytical and predictive methodologies, so providing a practical strategy for the development of new multi-target medications and the research of their mechanisms of action. QSP was described in a 2011 white paper by the National Institutes of Health based on workshops and conversations with academic, government, and industry experts[15-18]. This study aims to define QSP's distinctive contributions and corrects the lack of comparability that existed in past assessments. In the second part of our research, we investigate various computational methods for QSP modeling. These methods include molecular docking, molecular dynamics modeling, machine learning, and similarity analysis.

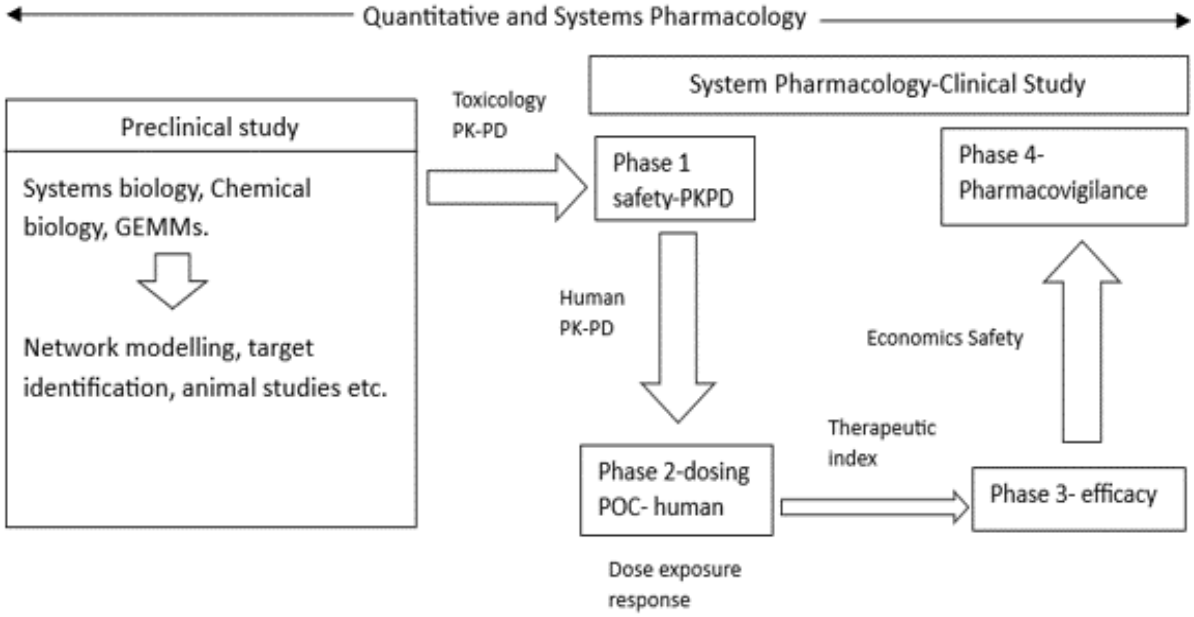

Fig 3: Traditional drug discovery phases in which QSP can have an impact.

QSP seeks to bridge the divide between the preclinical-focused academic disciplines of systems biology, chemical biology, and mouse modeling of human disease, and the pharmaceutical industry's well-established systems pharmacology. QSP attempts to encompass the pharmacokinetic/pharmacodynamic (PK/PD) modeling, prediction of dose-exposure responses, and evaluation of the market potential of such drugs. This figure was reproduced by the QSP Workshop Group from the NIH White Paper.[19] These approaches can mimic drug-target interactions, therefore closing the knowledge gap created by prior investigations and contributing to improvements in pharmacological understanding. Understanding the intricate regulatory mechanisms that arise from the interactions of biological components requires both pathway analysis and network modeling, both of which are very necessary. In this study, we investigate the ways in which network and route analysis could improve cancer combination treatment, going beyond the restricted scope of earlier analyses. This evaluation is an improvement over previous assessments since it does a more in-depth analysis of QSP.[19]

1.1. Comparing PKPD and QSP

PKPD modeling has proven to be quite useful in drug development, explaining the link between the pharmacokinetics (PK) of therapeutic intervention and the resulting pharmacodynamic (PD) effect[20]. This was especially true in the translational space, where estimated PKPD parameters derived from relevant preclinical studies and appropriately adjusted for the clinical scenario allowed prospective simulations to evaluate key drug development questions like clinical dose level and frequency[21,22]. Over time, translational PKPD modeling has progressed beyond empirical models to add more mechanistic components in order to develop mechanism-based PKPD models that enable biologic-driven translations across species and/or patient populations. Although the value of PKPD modeling has been widely recognized, its main focus is to establish a relationship between drug PK and selected elements of the biological system that are perturbed by a particular drug treatment. As a result, PKPD models may have limited ability to extrapolate past data sets. Furthermore, these biosignals may have causal linkages within a network of signaling pathways that cannot be

overlooked or dismissed. Although the degree of mechanistic detail and scientific questions addressed by PKPD and QSP models differ, the two approaches also differ in technical aspects such as data requirements, model implementation e.g., data fitting vs. virtual subject simulations), and model evaluation/qualification methods[23-25.]

1.2. Comparing PBPK (Physiologically based Pharmacokinetic) and QSP

PBPK models are another type of model often debated as to whether it falls within the definition of a QSP model. Like the PKPD evolution to QSP, mechanistic PBPK models demonstrated that highly mechanistic models could provide predictive biological insights and deliver value to the pharmaceutical industry, assigning the groundwork for QSP models. Although PBPK models can have significant mechanistic detail and depend on system and drug-dependent parameters, it is the focus on PD and disease biology/pathophysiology components that separate the two modeling approaches. PBPK models are focused predominantly on absorption, distribution, metabolism, excretion, and PK questions, whereas QSP models are focused on the modulation of a target and the subsequent impact on the underlying biology and/or disease pathology[26]. Although the primary focus of the two modeling approaches may be different, it is important to emphasize that these approaches are not exclusive, and it could be desirable to connect a PBPK model to a QSP model to drive target tissue-specific drug concentrations for example2.

1.3. QSP models are widely used to predict the PK properties of candidates:

Despite their uniqueness in assessing the safety and efficacy profiles of medicinal candidates. Drug research and development employ whole-body physiologically based pharmacokinetic (PBPK) models. Preclinical animal PK data are allometrically scaled to predict human PK. Combining the candidate's expected human PK with PD thresholds like target coverage (e.g., 90% receptor occupancy at the trough in steady state) gives a dosage regimen.[27] This technique cannot predict tissue level PK, requires in vivo data for model calibration, and is unclear across patient subpopulations such as age, illness status, etc. PBPK models account for fundamental processes determining drug disposition at the tissue/organ level, such as permeability across tissue barriers, organ blood flow, population variability, and disease factors, and provide a more detailed understanding and usable prediction of clinical PK. Unlike macroscopic lumped characteristics like the whole-body volume of distribution, PBPK model parameters may be acquired from in vitro tests, minimizing the necessity for in vivo investigations. Next-generation PBPK models demonstrate this system's approach's value. Next-generation PBPK models can predict oral PK based on in vitro solubility and permeability inputs by accounting for complex drug dissolution, gut absorption, and population variability of predicted PK by accounting for enzyme expression differences related to genetic polymorphism.[28]

2. METHODS FOR QSP

2.1. Evaluation and simulation at the molecular level

At the molecular level, QSP focuses on evaluating molecular characteristics and identifying drug-target interactions. Several methods, including ADME/T analysis, chemical space analysis, and drug-likeness evaluation, can provide information regarding the metabolic properties of pharmaceuticals or substances. The commonly used PK/PD models contain the most fundamental information regarding drug absorption, distribution, metabolism, excretion, and toxic properties [29-30]. PK and PD data reveal how medicines alter in vivo over time and the features of their targets in order to clarify the mechanism of drug action [31-32]. For instance, Rostami-Hodjegan accounted for physiology and biology-based pharmacokinetics when predicting the effects of intrinsic and extrinsic pharmacological variables. Many computational methods, such as molecular docking, molecular dynamics modeling, machine learning, and similarity analysis, can mimic drug-target interaction. In addition to machine learning and similarity analysis, drug-target and drug-drug interactions can also be investigated by machine learning and similarity analysis. Machine learning is a technique used to improve the performance of a particular model using data, and it plays a crucial role in systems [pharmacology33-37.] Chiu and Xie merged coarse-grained normal mode analysis with multi-target machine learning in order to accurately predict protein-ligand binding/unbinding kinetics [38].

2.2. Pathway analysis and network modelling

Network modeling incorporates disease-related genes, pathways, targets, and medications into a sophisticated network model and gives frameworks for understanding how regulation develops from the interactions of biological components nodes represent molecular entities (DNA, RNA, proteins, and tiny compounds) and processes, whereas edges reflect the interactions between nodes[38-40]. Using network analysis, significant nodes and edges in the network can be discovered. The network model can provide valuable information, such as major targets in regulatory networks and the interaction mechanism between medications and targets. These network-based approaches are useful for comprehending the basis of cancer combination therapy, discovering treatment regimens with optimal efficacy[41], identifying the origins of drug-induced adverse events[42-44], and demonstrating how drug combinations can mitigate serious adverse effects[45]. Wu, for instance, created an integrated network and cheminformatics tool (SDTNBI) for the systematic prediction of drug-target interactions and drug repositioning[46-47]. Pathway analysis is a method for investigating the therapeutic mechanism by evaluating the links between drug targets and disease-related regulatory networks. It is a universal format that serves as the foundation for numerous QSP variants48. Typically, topological analysis is used to quantify the significance of genes in order to reduce a complex pathway network to an organized collection of related genes. It can effectively lessen the difficulty of modeling and analyzing the disease-causing pathway network. Combining network modeling with molecular docking, we have created a pathway network-based method for assessing the efficacy of drugs. Network connectivity is measured globally by network efficiency (NE) and network flux (NF). The edge values of the pathway network were reset based on the Michaelis-Menten equation, which used the binding constant and drug concentration to calculate the degree of inhibition of the target protein in the pathway. The dose-response curve was sigmoid, and the anticipated effects of chemicals correlated well with experimental findings[49-51.]

2.3. *Systems-level methods: Logical Modeling*

Logical modeling is a form of mathematical technique based on a mechanism that can provide an item with a logical structure. It can provide information on a wide range of topics and phenomics profiles by examining the logical link between phenotype and mechanism[52,53-55].

2.4. *Virtual patient*

Applying the QSP model to transform complex biological processes into a sequence of intuitive equations is a potential method for gaining an understanding of the curative effects of medication discovery and disease therapy. Unfortunately, there are gaps in the preclinical and clinical data necessary to develop models. To lessen the need for data, numerous scientists have reduced the models using alternative parameterization; this technique is also known as "virtual patient"[56-59]. A thorough analysis (virtual population) introduced a mechanistically-based weighting mechanism for matching clinical trial statistics at the population level[26]. Table 1: Computational methods for QSP.QSP's computational models aim to describe the complicated behavior of living systems and predict how they will react to drugs. These models can include many different levels of biological organization, from molecular and cellular processes to the function of organs and groups of patients. By combining trial data with what is known about drug properties, target biology, and how diseases work, computer models can simulate how drugs work, predict how well they will work, find the best way to give them, and look into possible side effects.[60]

Table 1: Computational methods for QSP

Method	Classification	Description
Molecular level	Evaluation of molecular characteristics	Drug molecular properties (ADME/T, PK/PD model, chemical space analysis, and drug-likeness evaluation) are provided.
	Identification of drug-target interaction	Drug/compound-target interaction prediction and assessment (molecular docking, molecular dynamics simulation, machine learning, and similarity analysis)
Network level	Drug-target network analysis	Analysing drug-target interactions
	Protein-protein interaction network analysis	Topological structure analysis of a complex protein-protein interaction network
	Pathway analysis	Investigating the relationships between therapeutic targets and illness regulatory networks, as well as evaluating medication efficacy in the context of a route network
Systems level	Logical modeling	A mathematical method based on mechanisms to give the object logical structure.
	Multiscale systems pharmacology platform	Evaluating the treatment impacts of therapeutic regimens and examining the MoA by integrating preclinical/clinical medication and disease phenotypic data (TCMSP, Virtual Tumour, Cancer HSP, etc).
	Virtual patient	A simplified model for translating complicated biological processes into a sequence of simple equations.

2.5. *Multi-scale systems pharmacology platforms*

QSP investigates the association between drug administration and disease in order to hypothesize about the underlying mechanisms. Personalized medicine is also guided by combining genetic knowledge. Multiscale systems pharmacology focuses on various medicines, targets, pathways, biomarkers, and phenomics in relation to disease. Multiple multi-scale systems pharmacology platforms such as TCMSP (Traditional Chinese Medicine System Pharmacology)[25], Virtual Tumour [61], Cancer HSP [62], C2 Maps [63], VisANT 4.0[64], PDTCM (Psoriasis database of traditional Chinese medicine) [65], CVDHD (cardiovascular disease herbal database) [66], Lipoprotein Metabolism and Kinetics (LMK) Platform [67], Rheumatoid Arthritis Physio Lab platform[63], and others have been developed[68-73]. Musante et al. reported an Immuno Oncology platform to investigate the effects of two types of cancer regimens and to propose potential applications based on clinical data and analysis of mechanism [69]. Kirouac et al. developed a multi-scale systems model of ErbB signaling to support the preclinical investigation of a bispecific antibody targeting HER2 and HER3 in cancer[74]. These platforms, which combine preclinical/clinical data from numerous aspects and disease phenotypes, can evaluate the treatment effects of therapy regimens and study the mechanism of action.

2.6. *Systems approach for analyzing biological networks and understanding pharmacologic mechanisms: Systems Pharmacology*

Drug response is determined by drug-target interactions (DTI), molecular mechanisms, and phenotypic pathways and networks. Small molecule pharmacology involves various pathways and networks, creating cascades of signals and pharmacological activities.[75] Traditional molecular pharmacology cannot describe this complexity. Quantitative Systems Pharmacology (QSP) predicts medication interactions and adverse effects using mathematical models of biological networks, aiding systems biology-pharmacology research. To improve drug design and understand system-level medication activities and illness complexity, the goal is to identify therapeutic drug response targets, pathways, and networks.[51] Network analysis helps find medication targets and optimize efficacy, side effects, and toxicity. Network-based approaches can find drugs that bind to one or more targets, including allosteric interactions, by using chemical and protein structure similarity, protein-protein interactions, signaling pathways, disease-gene associations, and target molecular and metabolic functions. Network-based medication development has treated infections, cancer, metabolic disorders, neurodegenerative illnesses, and aging.[76] Traditional herbal medicine benefits from systems pharmacology. Medicinal herbs are excellent for network-based, multi-target drug

development due to their complex chemical makeup and processes. Systems-based methods can identify active molecules, targets, and pharmacological mechanisms to produce novel plant-based therapies. Network pharmacology's use in cardiovascular disorders and traditional Chinese medicine shows its promise in comprehending complicated pharmacological processes. Ligand similarity, drug molecular signatures, and target deconvolution help understand molecular pathways. These approaches improve medication development by revealing disease-related pathways and processes. Systemic pharmacology facilitates the development of multi-target medications with improved effectiveness and safety compared to single-target treatments.[77]

2.7. Systems approach for interpreting drug action: predicting adverse drug effects

Adverse medication responses allow prevention, dosage modification, or discontinuation. WHO Adverse Reaction Terminology classifies ADR into Dose-related, non-dose-related, dose-time-related, withdrawal, and therapeutic failure. Drug recalls follow 100,000 yearly drug deaths. Systems pharmacology predicts side effects by studying off-target binding. QSP studies pharmacologic and toxicologic pathways using systems biology.[78] Drug activity and off-targets explain pharmacological adverse effects. In vivo, systems analysis shows pathophysiology and intervention-related molecular and cellular processes. Quantitative measurement of intracellular signal activities, extracellular cytokines and chemokines, and immune cell types in mouse model tissue under diverse perturbation conditions, integrated via multivariate computational regression analysis, has helped elucidate complex intestinal inflammation mechanisms and predict kinase inhibitor and antibody effects in vivo. Medicine biomarkers are multimodal.[79] Drug-target connections and SEs are predicted in silico. Chemical and route approaches exist. Drug SEs interact physiologically. These methods address molecular networks, metabolizing enzymes, gene-disease-drug links, drug-drug interactions, clinically discovered SEs, and drug-disease correlations. New pharmacological networks and algorithms predict adverse drug responses for undiscovered drugs-SEs relationships.[80] Campillos et al. examined phenotypic SE similarities to determine if two therapies share a target and uncover potential therapeutic targets from medicines with comparable SEs. Lee et al. suggested a co-occurrence-based multi-level process-drug-SE network to automatically recognize biological processes and SEs. Cheng et al. predicted DTIs from an authorized drug-target protein DTI network using drug SE similarity inference. Yang and Agarwal recommended realistic disease-SE medication repositioning. SE-naïve Bayes predicted disease signs. Scheiber, Xie, Wallach, and Takarabe suggested linking drug SEs to biological pathways. Scheiber et al. contrasted hazardous and non-toxic biological processes. Xie and Wallach predicted SEs by docking medicines into protein-binding pockets like their primary targets and correlating the greatest docking scores to biological processes. Takarabe et al. predicted unknown DTIs using the FDA's adverse event reporting system.[81]

2.8. QSP in addition to Identifying and Non-Identifiable Models

The development of QSP models is primarily motivated by the fact that our understanding of biology and pharmacology has become too complex for spontaneous decisions. Mathematical biologists and computational modelers actively build mathematical models to comprehend the biological and physiological principles behind system behavior. Emergent behavior can arise from either small or large models; however, depicting complex physiology frequently requires building mathematical models of enormous biological systems with a disproportionately high number of unknown model structures and parameters, which can lead to unidentifiable models (due to overparameterization and limited data). Model identifiability, parameter identifiability, and model parameter identifiability are considered identical for the purposes of this article and, to our knowledge, by the QSP modeling and allied groups. Recent publications (including Raue et al. 2009 and Saccomani et al. 2013) have evaluated identifiability analysis approaches, which can be categorized as structural and practical non-identifiability. Structural non-identifiability (Cobelli and DiStefano, 1980) relates to the model's structure and whether or not each model parameter can exert an independent influence on the observed model output.

2.9. Survey studies on the usage of QSP among various phases of drug discovery

QSP helps drug discovery target identification and validation. QSP models can explain complicated illness mechanisms and identify therapy targets, according to surveys. QSP models simulate biochemical networks and predict target modulation using genetic, proteomic, and pathway data. Researchers may prioritize goals and organize validation trials, simplifying lead optimization. QSP models optimize lead compounds by considering drug metabolism, distribution, target engagement, and system-level responses. These models predict dose-response interactions and recommend safe and effective dosages.[82] Surveys show QSP models are used in preclinical and clinical research. QSP models reliably predict drug behavior in complicated biological systems in vitro and in vivo. These models can evaluate different dosing regimens, predict pharmaceutical effects, and optimize trial designs. QSP models let drug developers evaluate therapeutic efficacy and safety using preclinical and clinical biomarker data. Regulatory agencies are also using QSP models to approve medications. These models simulate medication-drug interactions, anticipate adverse events, and assess drug response variability. QSP models assist regulators prevent late-stage failures by improving medication effect comprehension and prediction. Medication repurposing and combination therapies also use QSP models. Surveys show that QSP can imitate illness pathways to find new therapeutics. These algorithms predict pharmaceutical synergy and optimize combination therapy doses.[83] QSP can speed therapeutic application development and enhance treatment results by using combination medications**.**

2.10. Latest Original Qsp Model Categories to Be Published

2.10.1. Immuno-oncology (IO)/malignancies QSP models

According to the World Health Organization, cancer will account for 10 million deaths worldwide in 2020, making it one of the world's leading causes of death. Breast cancer will be the most prevalent cancer in 2020 with 2.26 million cases, but lung cancer will be the worst with 1.8 million deaths and 2.21 million cases. Understanding the tumor microenvironment (TME) and immunosurveillance has led to the development of potential cancer immunotherapy approaches over the past

decade[8]. Many immunotherapies target T cells for their cytotoxic and anticancer properties. Immune checkpoints manage the immune system and are the key targets for cancer immunotherapy in numerous disease types[84,85]. FDA-approved CPIs target CTLA-4(cytotoxic T-lymphocyte-associated antigen 4), PD-1, and PD-L in order to avoid T-cell suppression by cancer cells. Blocking these receptors increases the activation and multiplication of effector cells in response to stimulation and antigen recognition; hence, it is easier to remove cancer cells[86] when these receptors are suppressed. CAR-T is a cell-based therapy that employs genetically modified autologous T cells to enhance tumor antigen recognition and intracellular signaling pathways in T cell activation [66].

2.10.2 Breast Neoplasm

In Breast cancer, Human epidermal growth factor receptor 2 (HER2) is a neoantigen protein that can promote the development of cancer cells in breast cancer neoplasms[87]. Wang et al. provided two separate dynamical models of the Tumor microenvironment to assess the efficacy of existing breast cancer treatments. They focus on triple-negative breast cancer. This type of BC is distinguished by the lack of three receptors (estrogen, progesterone receptors, and low HER2 expression). It is a very invasive illness with few treatment choices and a poor prognosis [88]. The researchers created a virtual patient cohort of atezolizumab (anti-PD-L1) and nab-paclitaxel therapy for this cancer in order to identify immunological biomarkers and the optimal treatment for clinical trials [89]. Using a trastuzumab-resistant HER2-positive BC cell line, the second QSP model examines the individual and combined efficacy of lapatinib (LAP), abemaciclib (ABE), and 5-fluorouracil to combat drug resistance.

2.10.3 Lung Neoplasm

The anti-PD-1 therapy for lung tumors improves the survival rate of patients with advanced non-small-cell lung cancer[40].It includes tumor formation, antigen processing and presentation, T cell activation and trafficking, anti-PD-1, and antibody kinetic responses. The model predicted that the concentration of anti-tumor effector T cells in the blood will correlate with a stronger treatment response than the concentration of pro-tumor regulatory T cells [90].

2.10.4 Prostatic neoplasm

The ODE-based model (ordinary differential equation) examines castration-resistant prostate cancer, for which there are presently no therapies[91]. This research provides a QSP immunotherapy model for prostate cancer that integrates multiple immune cells, tumor compartments, and seven treatments.

2.11 Nutritional and metabolic disorder QSP Model

2.11.1 Diabetes Mellitus, type 2

Type 2 DM is a metabolic disorder translated by the accumulation of glucose in the blood due to defects of insulin function and expression[92].A recently licensed class of anti-diabetic drugs includes gliflozins that target sodium-glucose co-transporter (SGLT), which is responsible for more than 80 percent of glucose reabsorption[93]. Using the human systemic glucose dynamics (HSGD) model, which integrates glucose metabolism, intestinal uptake, and renal reabsorption, Mori-Anai et al. evaluated the inhibitory effect of three different SGLT2 inhibitors following food ingestion in the first model. The model provided a quantitative examination of the effect of drugs on dynamic glucose absorption after a meal[94]. A QSP model examined SGLT1 and SGLT2 activity in renal glucose circuits and calculated the PK/PD of SGLT2 inhibitors using clinical data from healthy and T2DM patients. The QSP model demonstrated that only canagliflozin inhibits renal SGLT1, leading to the development of a crucial treatment strategy for optimizing SGLT2 inhibition[87]. Because glucose accumulation is insulin-dependent, the model examines the short- and long-term glucose-insulin dynamics following the treatment of dapagliflozin. This paradigm suggests that dapagliflozin is more beneficial for patients with inadequate insulin-mediated glucose control [95].

2.12 Neuronal QSP Model

2.12.1 Alzheimer's disease (AD)

Alzheimer's disease is a progressive and irreversible neurological disorder that causes neurocognitive decline. Using three relevant drugs (elenbecestat, verubecestat, and semagacestat) and four anti-Ab monoclonal antibodies, Madrasi et al. created a QSP model of the Ab pathways (aducanumab, crenezumab, solanezumab, bapineuzumab). AD is distinguished by the formation of amyloid plaques as a result of the deposition of insoluble extracellular amyloid-beta (Ab), which promotes inflammation and neurotoxicity [96]. A clinical study utilising aducanumab in conjunction with a number of genotypes associated with cognitive performance (apolipoprotein E, Catechol -O -methyl Transferase, and 5-HT transporter genotypes). This study demonstrated the clinical response heterogeneity between phases II and III, which was mostly influenced by the numerous changes and baseline Ab peptide accumulation [97].

2.12.2 Challenges in QSP

Quantitative Systems Pharmacology (QSP) must overcome a number of obstacles before it can be successfully applied to drug discovery. First, the complexity of QSP models and the scarcity of high-quality data make parameter estimation and model calibration challenging. Integrating disparate, inconsistent, and sometimes heterogeneous data from diverse sources is an additional challenge. Ensure data quality and manage missing or incomplete data with considerable care. Validation and verification of QSP models against experimental data is essential, but difficult due to model complexity and limited availability of comprehensive datasets. Also challenging is the interpretation of complex QSP models and the comprehension of the contribution of individual factors to overall behavior. Transparent and interpretable models are necessary for fostering confidence and facilitating decision-making. As the complexity of QSP models increases, scalability and computational efficiency become concerns, necessitating efficient algorithms, and model reduction techniques. The absence of established frameworks and standardized guidelines for model development, validation, and qualification hinders the regulatory acceptability of QSP models. To overcome these obstacles, interdisciplinary collaborations, advances in computational methodologies, and the implementation of standardized practices are required. By addressing these obstacles, QSP can maximize its revolutionary potential in drug discovery and development.

3. DISCUSSION

Quantitative systems pharmacology (QSP) has gained popularity in drug development since its introduction in 2011. QSP aims to quantitatively resolve complex mechanisms and interactions between physiology and medications to predict reactions in the face of a drug intervention. It is a balanced platform of bottom-up and top-down modeling approaches that integrate biological knowledge available as presumptive and observed data obtained analytically to aid drug development decisions in a scientifically informed and practical manner. QSP models are developed at various biological scales, ranging from cellular, molecular, tissue, organ, patient, and/or population levels. QSP aims to bridge the divide between preclinical-focused academic disciplines of systems biology, chemical biology, and mouse modeling of human disease, and the pharmaceutical industry's well-established systems pharmacology. It aims to encompass pharmacokinetic/pharmacodynamic (PK/PD) modeling, prediction of dose-exposure responses, and evaluation of the market potential of such drugs. However, PKPD models may have a limited ability to extrapolate past data sets and may have causal linkages within a network of signaling pathways. Physiologically based Pharmacokinetic (PBPK) and Quantitative Structural Programming (QSP) models provide predictive biological insights and value to the pharmaceutical industry. Both approaches are widely used to predict the drug properties of candidates, but their primary focus may differ. QSP models are used to analyze biological networks and understand pharmacologic mechanisms, such as drug-target interactions (DTI), molecular mechanisms, and phenotypic pathways and networks. They help improve drug design and understand system-level medication activities and illness complexity. Network analysis helps find medication targets, and optimize efficacy, side effects, and toxicity. QSP models are widely used in preclinical and clinical research to predict drug behavior in complex biological systems, evaluate dosing regimens, predict pharmaceutical effects, and optimize trial designs. They also help drug developers evaluate therapeutic efficacy and safety using preclinical and clinical biomarker data. The latest original QSP models include immuno-oncology (IO)/malignancies, breast cancer, lung neoplasm, diabetes mellitus, and Alzheimer's disease. By addressing these obstacles, QSP can maximize its revolutionary potential in drug discovery and development.

4. CONCLUSION

This study examines QSP's potential to transform drug discovery and development. QSP analyses complicated drug-biological system-disease interactions using quantitative modeling, computational simulations, and experimental data. QSP integrates physiological, biochemical, and pharmacological data to explain treatment response and illness progression. It also allows virtual drug behavior modeling, eliminating costly trial-and-error methods. QSP models can help adapt medicines to maximize efficacy and minimize side effects, improving patient outcomes and lowering healthcare costs. Establishing QSP standards and guidelines requires high-quality data, modeling technique development, and collaboration between scientists, regulators, and pharmaceutical businesses. QSP might revolutionize the pharmaceutical business and enable more accurate, effective, and personalized therapy with future developments and multidisciplinary cooperation.

5. AUTHOR'S CONTRIBUTION STATEMENT

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6. CONFLICT OF INTEREST

Conflict of interest declared none.

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