

Physiologically Based Pharmacokinetic Modelling and Simulation Study to Predict the Plasma Concentration Profile of Chrysin Obtained from the Extract of *Mangifera Indica*

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Abstract

Chrysin is the identified flavonoid compound present in the mango pulp extract, having antioxidant properties. The aim of this study is to develop a physiologically based pharmacokinetic (PBPK) model of chrysin to simulate its plasma concentration profile in rats and humans after oral administration of the extract of *Mangifera indica*. The physiologically based pharmacokinetic model of chrysin is developed and verified by the pharmacokinetic data in rats. Then the PBPK model has been extrapolated to humans with PK-Sim® software. In order to assess the accuracy of the extrapolation, the extrapolated model is compared with the multiple-dose clinical study of chrysin. The predictive performance of the PBPK model is mainly evaluated by visual predictive checks and fold error of C_{max} and AUC_{0-t} of chrysin (the ratio of predicted to observed). Finally, the adult PBPK model is extended to several subpopulations, including liver disease patients. Chrysin undergoes rapid metabolism in rat and human liver microsomes by phase II metabolic enzymes like UGT and SULT. By utilizing literature data, the PBPK model of chrysin is well established in rats and humans. The predicted plasma concentration profiles of chrysin are consistent with the corresponding observed data from previous studies, and the fold error values are within the 2-fold acceptance criterion. No significant pharmacokinetic differences are observed after extrapolation for liver disease patients in PK-Sim software. The established PBPK model of chrysin gives valuable insight into the use of the flavonoid extract of *Mangifera indica* in liver disease patients, in spite of its poor bioavailability.

Keywords: *Chrysin; Physiologically Based Pharmacokinetic (PBPK) Model; PK-Sim® Software*

Introduction

Chrysin is a key flavonoid compound identified in *Mangifera indica* (mango) pulp extract, known for its significant antioxidant properties. This study utilizes Physiologically Based Pharmacokinetic (PBPK) modeling to predict its plasma concentration profile in both rats and humans (Boonpawa, 2017). In the human body system, the flavonoid chrysin undergoes extensive phase II metabolism in the liver, catalyzed by UGT and SULT enzymes to form chrysin-7-O-sulfate and chrysin 7-O-glucuronide conjugates (Panchal *et al.*, 2026). The pharmacokinetic model of chrysin incorporates enterohepatic recycling (Tu *et al.*, 2021; Chou *et al.*, 2025), where conjugates are transported into the intestine, hydrolyzed by microbial β -glucuronidases in the colon, and reabsorbed as free chrysin. This chrysin, when circulated through blood plasma, plasma protein albumin, can act as a carrier molecule. These adsorption, digestion, metabolism, and excretion (ADME) kinetics result in high accumulation of chrysin in the liver periportal tissue, which indicates the important role of chrysin for treating liver disease. The pharmacokinetics of chrysin in the gastrointestinal system is schematically represented in Figure 1.

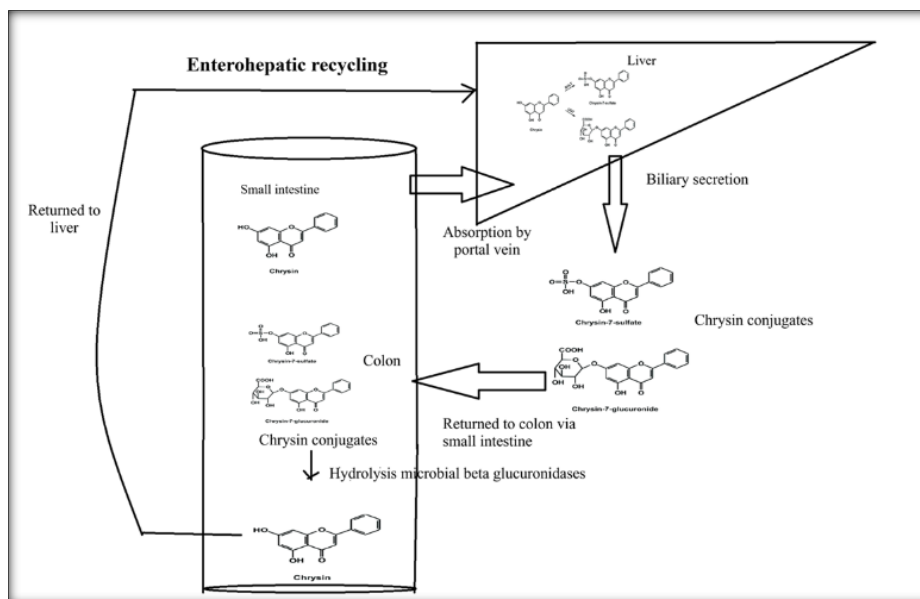


Figure 1: Schematic Representation for Pharmacokinetics of Chrysin

Methodology

Pharmacokinetic parameters of chrysin are calculated by PK-Sim v9.0, which is part of the Open Systems Pharmacology suite (www.open-systems-pharmacology.org) (Lippert *et al.*, 2019; Bharadwaj, 2024). The optimization and sensitivity analysis of model input parameters are carried out by PK-Sim. The steps for a physiologically based pharmacokinetic modeling and simulation study for the nutraceutical chrysin have been depicted in figure 2.

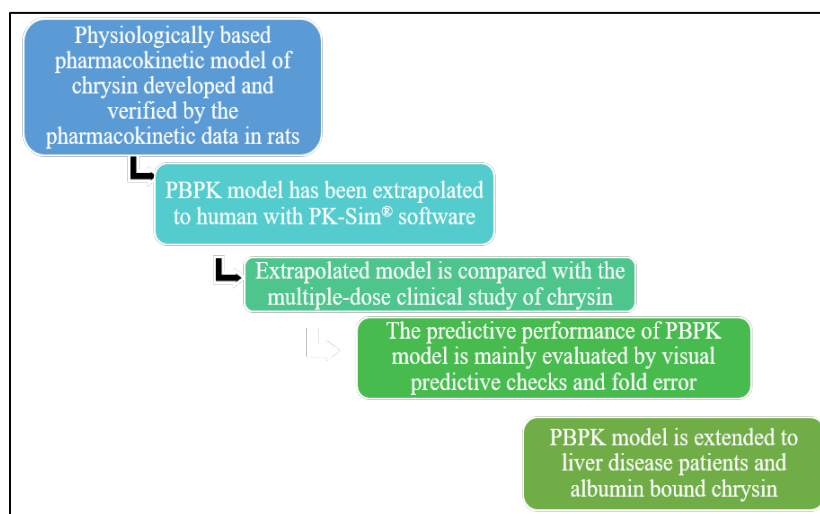


Figure 2: Flowchart for Physiologically Based Pharmacokinetic Modelling and Simulation Study

The most common tool in the area, the Open Systems Pharmacology (OSP) Suite, is an open-source platform for PBPK modeling. PK-Sim (Willmann *et al.*, 2003) functions as a whole-body modeling program within this package, enabling the development, optimization, and simulation of PBPK models. MoBi (Hack *et al.*, 2020; Balhara *et al.*, 2022) serves as a Quantitative Systems Pharmacology (QSP) modeling platform in the OSP Suite when used with PK-Sim. By enabling the use of bespoke models for organs, MoBi expands the suite's PBPK modeling capabilities. A thorough investigation of chrysin molecular behavior at both the

systemic and organ-specific levels is made possible by the ability to simulate these organ-specific models separately or incorporate them into whole-body PBPK models created using PK-Sim.

Results

PKML models encompass chemical species, reactions, and transport processes, which exist in various compartments of the body and serve as containers. Model parameters are depicted with descriptors considering compartments, chemicals, reactions, transports, etc. Every parameter in the model has a value, a dimension, and a distinct route. This route typically connects physical and chemical descriptors to chemicals, reaction rates to specific reactions, transport rates to mechanisms, and dosages to events; it may also link anatomical or physiological data to model compartments. The chrysin molecule in its free form and bound form with serum albumin protein is pharmacokinetically modelled in the gastrointestinal system in Figure 3.

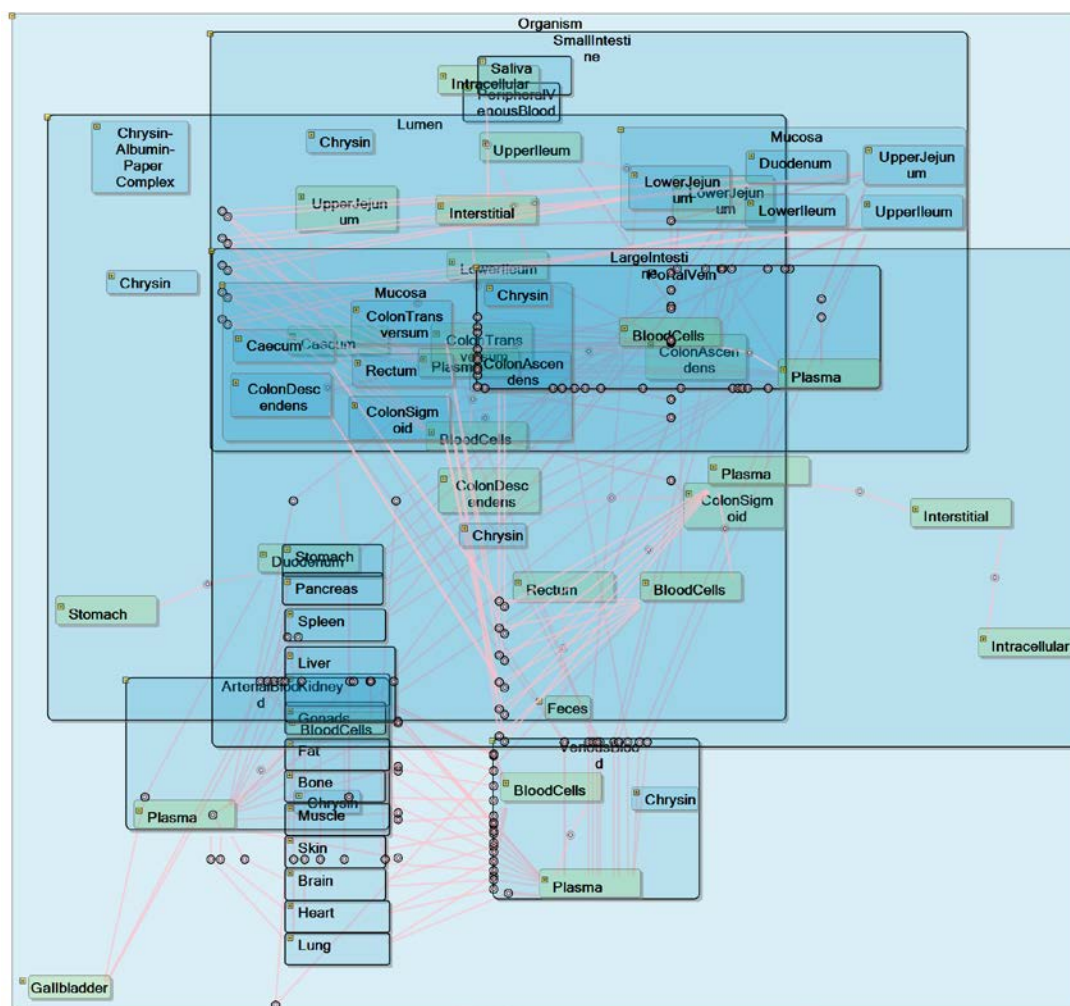


Figure 3: Diagram for Chrysin and Chrysin Bound Albumin in Different Compartments

A PBPK model has been developed in rats, and the plasma concentration profile of chrysin over time in different organs or compartments, such as the liver, kidney, duodenum, ileum, jejunum, large intestine, and arterial and venous blood, is shown in Figure 4a. The similar plasma concentration profile curve for the human body system is also exhibited in Figure 4b.

Physiologically Based Pharmacokinetic Simulation of Chrysin Plasma Profile

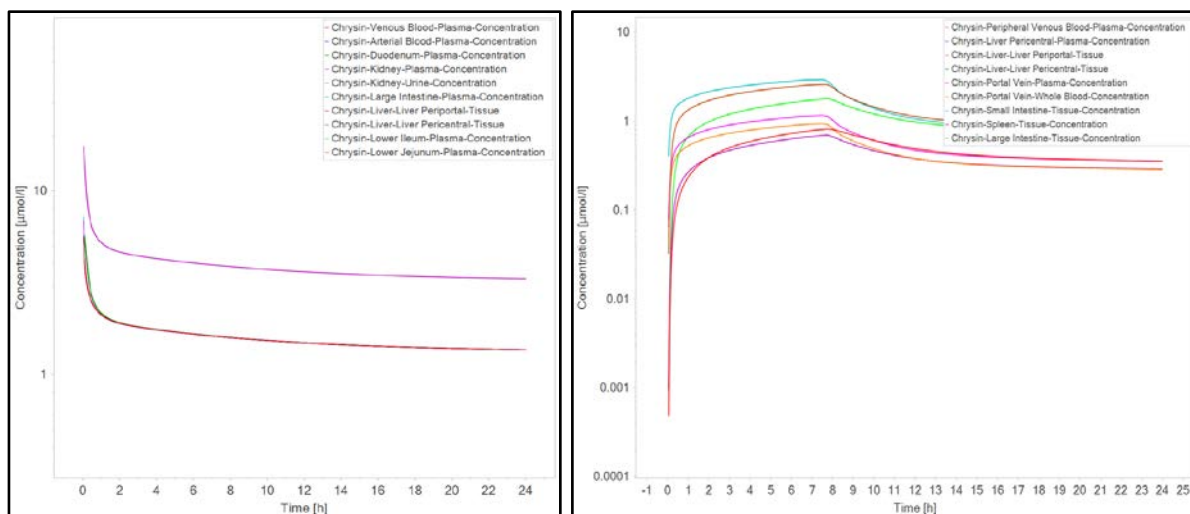


Figure 4: a) Plasma Concentration Profile of Chrysin with Time in Rat, b) Plasma Concentration Profile of Chrysin with Time in Human

A pharmacokinetic sensitivity analysis plot for the rat model is created using a tornado plot and shown in Figure 5.

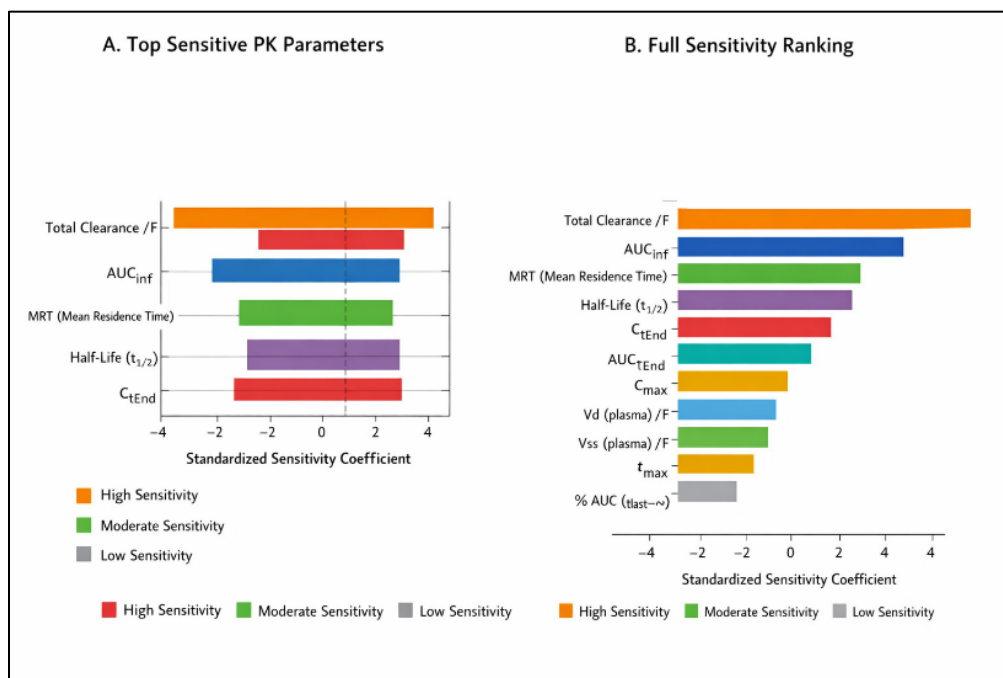


Figure 5: Pharmacokinetic Sensitivity Analysis Using Tornado Plot for Rat Model

The sensitivity analysis shows that the pharmacokinetic variability of chrysin in the rat model is mostly controlled by processes related to clearance. Metrics such as AUC_inf are highly sensitive to the elimination kinetics, whereas the distribution parameters have a secondary effect on this metric. The parameters associated with terminal phase extrapolation have virtually no effect on the total uncertainty of the exposure metric, indicating adequate representation of the elimination phase through modeling.

All of the above demonstrate how critical the role of elimination and clearance processes are in modulating the pharmacokinetics of chrysin, as visualized in Figure 6.

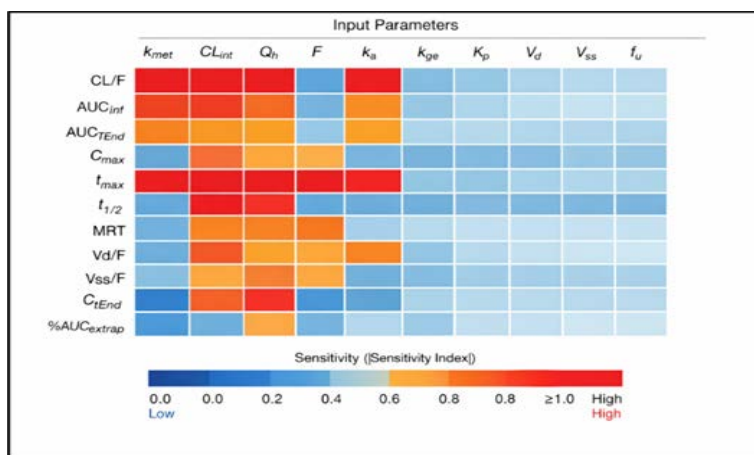


Figure 6: Visualization of Pharmacokinetics Sensitivity Analysis by Heat Map method

The visualization of the parameter-output relationship demonstrates that metabolic clearance is the most important process impacting the overall pharmacokinetics. Additionally, drug absorption influences both peak exposure and the timing of peak levels, whereas distribution parameters only modulate pharmacokinetics without controlling them. All of the above results provide a mechanistic basis for optimization of chrysin pharmacokinetic experiments, based on metabolism.

The chrysin PBPK model is verified by comparison with the available human pharmacokinetic data of chrysin after both intravenous and oral dosing methods (Gao *et al.*, 2021). The simulated profiles of pharmacokinetics are highly comparable with those described in scientific literature, showing fold errors within an acceptable 2-fold error range. The simulations revealed the presence of a large amount of chrysin molecules in the liver periportal tissue.

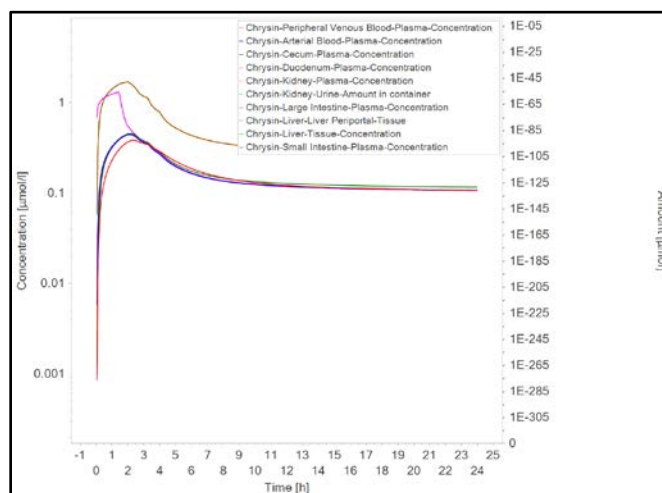


Figure 7: Chrysin Concentration in Blood Plasma with Liver Diseased Condition in Different Organs in Human

Utilizing PK-Sim® software, the PBPK model is used for extrapolation of the distribution of chrysin into humans having liver disease. The time-concentration curve indicates the maximal concentration of chrysin in the periportal tissue of the liver relative to plasma and other organs. These results show that despite physiological changes associated with the development of liver disease, the pharmacokinetic parameters do not change significantly, supporting the potential therapeutic use of *Mangifera indica* extract for the treatment of diseases of the liver.

Physiologically Based Pharmacokinetic Simulation of Chrysin Plasma Profile

Both Table 1 and Figure 8 show a global pharmacokinetic analysis for all rats, healthy humans, and humans with liver disease.

Table 1: The Comparison of Global Pharmacokinetic Parameters for Rats, Healthy Humans, And Humans with Liver Disease

Parameter	Rat	Healthy Human	Diseased Human
Vss (plasma) (mg/kg)	2604.37	3966.43	9141.99
Vd (plasma) (mg/kg)	2628.14	4106.73	9446.55
Total plasma clearance (mg/min/kg)	0.15288	0.51224	0.57291
Bioavailability		0.13504	0.08472
Fraction absorbed		0.17131	0.05497

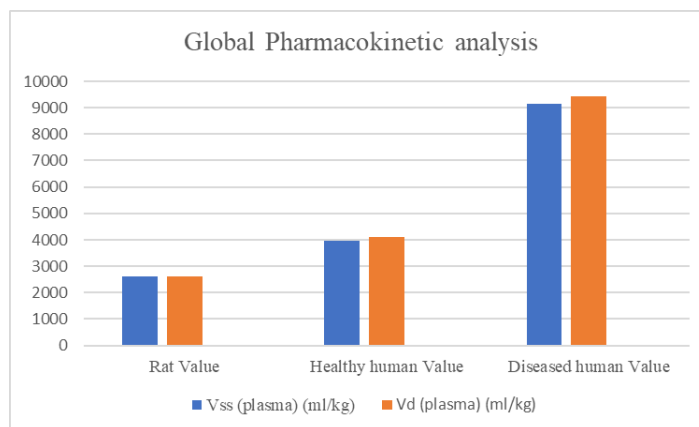


Figure 8: Two Types of Volume of Distributions of Chrysin in Rat and Human Models

The comparative data clearly indicate the presence of distinct pharmacokinetic differences caused by liver diseases. The first parameter, which should be emphasized, is the volume of distribution (Vss), being 9141.99 ml/kg in comparison with healthy individuals at 3966.43 ml/kg. Thus, the accumulation in the tissues takes place much more efficiently in diseased patients. It can also be seen from Figure 8 that both bioavailability and fraction absorbed decrease (0.085 and 0.135, respectively) with the presence of liver disease. This means that despite increased uptake, systemic exposure is affected negatively because of altered absorption.

Table 2: Pharmacokinetic Parameters for Different Tissues in Rat and Human Beings for Both Normal and Diseased Ones

Parameter	Rat Liver Periportal	Human Healthy Small Intestine	Diseased Human Liver
AUC _{inf} [$\mu\text{mol}\cdot\text{min}/\text{l}$]	62251.47656	9217.473633	5811.99
AUC _{inf_norm} [$\mu\text{g}\cdot\text{min}/\text{l}$]	1.58268E+13	6.84289E+11	4.3E+11
AUC _{tEnd} [$\mu\text{mol}\cdot\text{min}/\text{l}$]	5634.948242	2142.894043	693.268
AUC _{tEnd_norm} [$\mu\text{g}\cdot\text{min}/\text{l}$]	1.43263E+12	1.59085E+11	5.1E+10
C _{max} [$\mu\text{mol}/\text{l}$]	17.56756401	2.942610741	1.69445
C _{max_norm} [mg/l]	4466377.258	218454.3014	125793
C _{tEnd} [$\mu\text{mol}/\text{l}$]	3.32366538	0.800254107	0.27841
Total body clearance/F [ml/min/kg]	0.063183907	1.461370382	2.31765
% AUC (tlast- ∞)	0.90948087	0.767518282	0.88072
MRT [h]	281.0208984	133.651766	291.995
t _{max} [h]	0.05	7.5	2
Half-Life [h]	196.7887044	102.1284912	212.395
Vd (plasma)/F [ml/kg]	1076.297641	12919.1227	42610.6
Vss (plasma)/F [ml/kg]	1065.359831	11718.88447	40604.4

Table 2 illustrates the Pharmacokinetic Analysis of the Tissues with the Maximum Level of Chrysin in Rats, Healthy People, and Diseased People.

In this analysis, the primary concern will be the tissues that show maximum chrysin uptake by the subject groups, which include rats, healthy people, and humans with liver diseases. As indicated, the half-life of chrysin in diseased people is much higher than that of healthy individuals, that is, 212.4 hours vs. 102.1 hours. Furthermore, the volume of chrysin distribution (V_{ss}/F) in diseased people is higher than in healthy subjects, implying that chrysin is mainly sequestered in liver tissues when the patient suffers from a hepatic disorder. This means that chrysin stays longer at the target site, despite low levels of it in the plasma.

The effect of albumin binding as a chrysin transporter in the pharmacokinetic modeling of chrysin: Albumin constitutes the main protein present in plasma. Numerous chemicals and drugs can interact with albumin and eventually become released into the plasma. Therefore, chrysin is dynamically equilibrated in between its unbound form (free chrysin) and its bound form (albumin-bound chrysin). Albumin-bound chrysin plays an important role as a chrysin reservoir, and once free chrysin gets depleted, the bound chrysin is released to maintain equilibrium. This interaction between chrysin and albumin produces various impacts on the pharmacodynamics of chrysin, including long circulation time, steady plasma concentration, and minimal toxicity. Figure 9 illustrates the dynamic behavior of both forms of chrysin in the human body system.

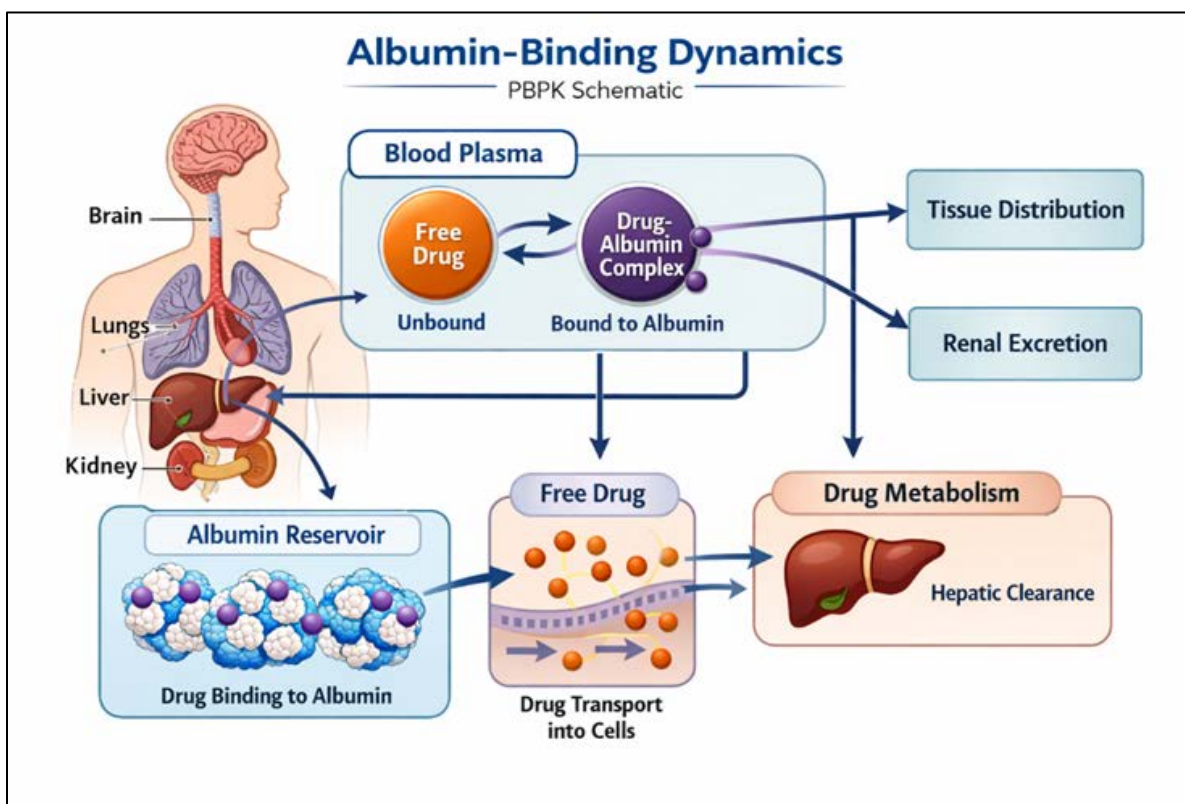


Figure 9: Schematic Diagram for Dynamic Behavior of Both Free form and Bound Form of Chrysin with Albumin

The plasma concentration graph against time for both the bound form with human serum albumin and the unbound form of chrysin is illustrated in Figure 10.

Physiologically Based Pharmacokinetic Simulation of Chrysin Plasma Profile

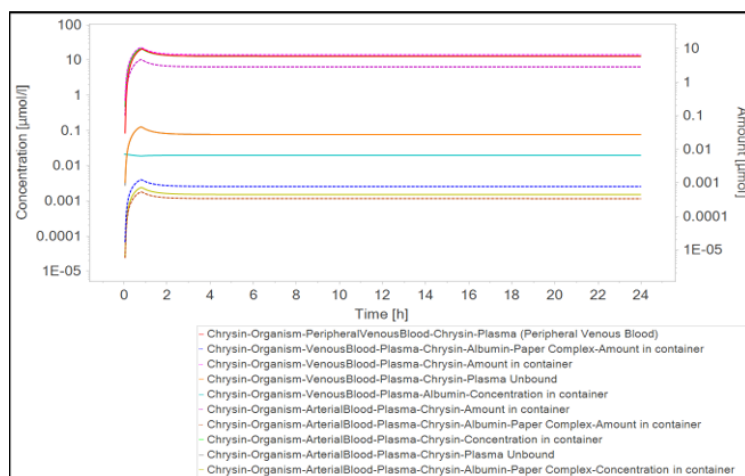


Figure 10: Plasma Concentration Profile of Bound and Unbound Chrysin

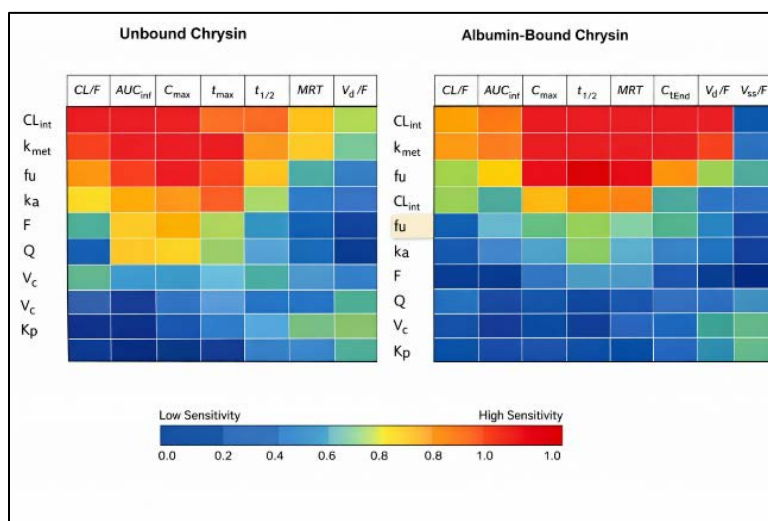


Figure 11: Comparison of Unbound Chrysin with Its Albumin Bound Form Considering Different Pharmacokinetic Parameters

Binding to albumin significantly modulated both the magnitude and variability of pharmacokinetic outputs of the chrysin molecule. Albumin binding with chrysin regulates chrysin clearance, reducing the fraction of chrysin available for hepatic metabolism. This results in lower apparent clearance variability as well as increased systemic stability of the chrysin molecule. Since only free chrysin is cleared from the system, albumin binding increases systemic exposure and ultimately stabilizes parameter AUC (area under plasma concentration time curve) by limiting rapid elimination. Plasma protein albumin binding reduces the free peak concentration of chrysin, which is acting as a reservoir that releases chrysin gradually in the human body system. Albumin-bound chrysin shows prolonged half-life and MRT (mean residence time) values and also shows reduced sensitivity to clearance fluctuations. Moreover, that albumin protein binding maintains prolonged terminal-phase concentrations, which is consistent with the depot-like behavior of the chrysin molecule.

Discussion

The development and validation of the physiologically based pharmacokinetic (PBPK) model according to the 2-fold criterion proves the accuracy of simulating the in vivo processes that reflect the highly complex

disposition pattern of chrysin in rats and humans (Yamazaki & Shimizu, 2025). The global sensitivity analysis reveals that the overall pharmacokinetics of chrysin depends on its metabolic clearance kinetics; it is consistent with conventional sensitivity analyses performed using the platform of the Open Systems Pharmacology Suite (Najjar *et al.*, 2024). Nevertheless, the dynamic equilibrium provided by the binding of the compound to plasma serum albumins plays the role of an essential "distribution-buffering" effect. This process decreases the fraction of the compound available for fast phase II metabolism in the liver (Panchal *et al.*, 2026), and therefore it results in decreased clearance variance, decreased rate of compound elimination, and increased exposure, which is shown by a stable AUC profile along with increased half-life and MRT values. In addition, this continuous exposure is due to a specific recycling process of chrysin within the body, including its enteric recycling (Tu *et al.*, 2021). Notably, upon projection into a human population with a liver condition using PK-Sim® (Lippert *et al.*, 2019; Willmann *et al.*, 2003; Niederalt *et al.*, 2018), the significant physiological changes resulted in an increase in the volume of distribution (V_{ss}/F) and the elimination half-life of chrysin within the liver and peripherally targeted tissue, despite relatively minimal drops in the overall systemic bioavailability and the absorption fraction. The pronounced accumulation of chrysin suggests that there is pooling of chrysin in the relevant target site. Overall, these results establish a sound and strong physiological basis for addressing bioavailability challenges in formulations and maximize its potential (Gao *et al.*, 2021; Kurkiewicz *et al.*, 2025; Stompor-Gorący *et al.*, 2021). These results, therefore, clearly highlight the clinical potential for applying extracts from *Mangifera indica* in the treatment of liver conditions.

Conclusion

By utilizing literature data, the PBPK model of chrysin is successfully established and verified in both rat and human systems. The predicted plasma concentration profiles are consistent with observed clinical data, with fold error values falling strictly within the 2-fold acceptance criterion. Time profile analysis reveals that the very high concentrations of chrysin are specifically in the liver periportal tissue of diseased human individuals. Finally, it results in the effective localization of chrysin at the disease site.

The PBPK model of chrysin is well established in rats and humans. Time profile analysis shows very high concentrations of chrysin in plasma, in the liver periportal tissue of rats, in the small intestine of healthy humans, and in the liver periportal tissue of diseased humans. The established PBPK model of chrysin provides valuable insight into the use of the flavonoid extract of *Mangifera indica* in liver disease patients, in spite of its rapid metabolism and poor water solubility.

Albumin binding with chrysin during the transport of the chrysin molecule through blood plasma can stabilize pharmacokinetic parameters in the human body system. In rat models' metabolic clearance processes are the primary determinants of overall pharmacokinetics performances. In the human model, this clearance sensitivity is attenuated in the bound form of chrysin with albumin. Moreover, that exposure (AUC) increases significantly upon albumin binding. Lastly, half-life and MRT are prolonged due to reduced free fraction. Finally, it can be concluded that albumin protein binding to chrysin fundamentally shifts chrysin's pharmacokinetics from a clearance-dominated to a distribution-buffered system.

Acknowledgment

The authors would like to acknowledge Vellore Institute of Technology, Vellore, India and Gurudas College, India for providing support.

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