Captopril in Focus: Open Pharmacokinetic Dataset and PBPK Modeling

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Background

Our group has developed **PK-DB** [1], an open pharmacokinetics database from clinical and preclinical research. The objective of this study was to expand PK-DB with data on the angiotensin - converting enzyme (ACE) inhibitor **captopril**, develop an open and FAIR [2] **PBPK/PD model**, and improve our understanding of the intraindividual variability in captopril pharmacokinetics.

Methods

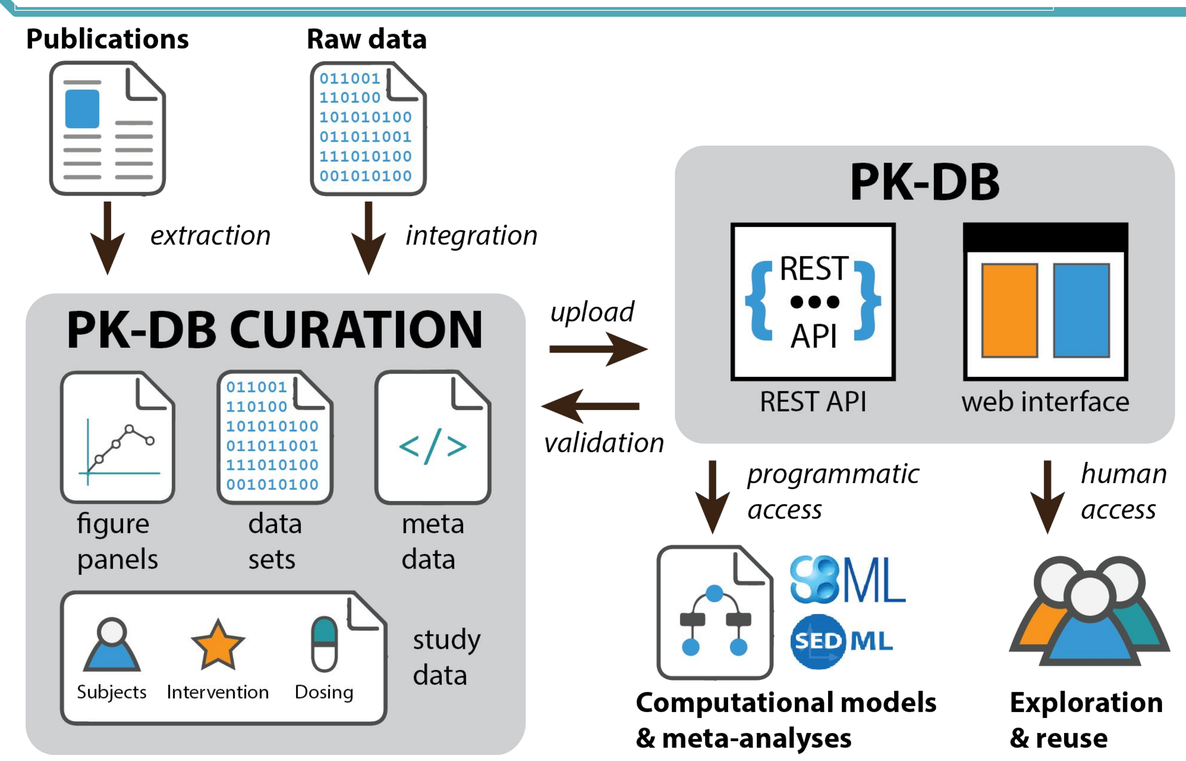

Figure 1. Workflow overview.

Over 600 publications on captopril pharmacokinetics were reviewed through a systematic literature search, with 29 studies curated in PK-DB. The PBPK model was developed using a compartmental approach and encoded in **Systems Biology Markup Language** (SBML) [3] for accessibility and reproducibility based on established workflows [4, 5].

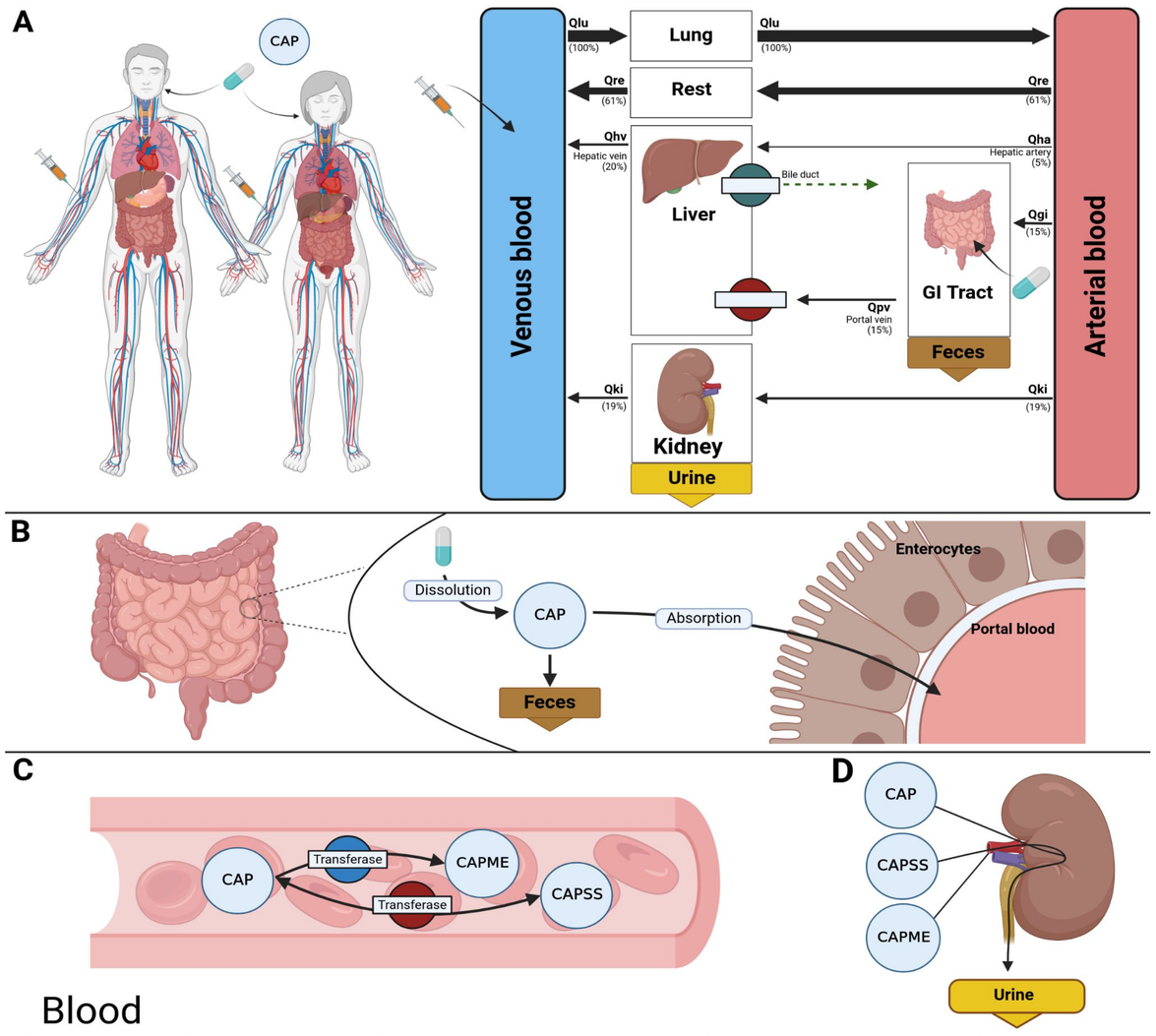

Figure 2. A) Overview of PBPK captopril model. **B)** Intestinal absorption captopril (CAP). **C)** In blood CAP is converted to disulfides (CAPSS) and S-methyl captopril (CAPME). **D)** All captopril metabolites are excreted by kidneys, while disulfides also undergo hepatobiliary circulation.

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Results

Identifier		Data		Metabolites				Health					PK			PD RAAS			PD cardiovascular					
Study	PK-DB	pharmaco-kinetics	pharmaco-dynamics	all captopril	total captopril	captopril disulfide	S-methyl-captopril	healthy	hyper-tension	renal impairment	hepatic impairment	cardiac impairment	plasma	urine	feces	ACE activity	renin	aldosterone	arterial pressure	blood pressure	heart rate	cardiac output	PCWP	SVR
AlFuraih1991	PKDB00810	✓	✓					✓					✓				✓			✓	✓			
Anuta2021	PKDB00811	✓						✓					✓											
Arroyo1997	PKDB00748	✓						✓					✓											
Cody1982	PKDB00812	✓	✓		✓							✓	✓						✓				✓	✓
Cohen1984	PKDB00813	✓			✓	✓	✓	✓					✓											
Creasey1986	PKDB00814	✓			✓		✓	✓					✓	✓										
Creasey1988	PKDB00815	✓		✓				✓					✓											
Drummer1987	PKDB00816	✓	✓		✓				✓	✓			✓							✓				
Duchin1982	PKDB00817	✓		✓				✓					✓	✓	✓									
Duchin1984	PKDB00818	✓		✓						✓			✓	✓	✓									
Foster2009	PKDB00819	✓			✓			✓					✓											
Giudicelli1984	PKDB00820	✓	✓						✓	✓			✓			✓	✓	✓	✓					
Giudicelli1987	PKDB00821	✓	✓		✓				✓				✓			✓	✓			✓	✓			
Jankowski1995	PKDB00822	✓						✓					✓											
Jehanli1996	PKDB00823	✓						✓					✓											
Kok1997	PKDB00824	✓			✓			✓					✓											
Kripalani1980	PKDB00825	✓		✓		✓		✓					✓	✓	✓									
Li1996	PKDB00826	✓						✓					✓											
McElnay1995	PKDB00827	✓	✓					✓					✓											
McElnay1996	PKDB00828	✓	✓									✓	✓				✓			✓	✓			
Ohman1985	PKDB00829	✓	✓		✓				✓				✓	✓			✓		✓					
Onoyama1981	PKDB00830	✓			✓			✓		✓			✓	✓										
Rezende2007	PKDB00831	✓						✓					✓											
Richer1984	PKDB00832	✓	✓						✓				✓			✓	✓			✓	✓			
Salem2005	PKDB00833	✓						✓					✓											
Schaefer1998	PKDB00834	✓	✓					✓					✓							✓				
Shaw1985	PKDB00835	✓	✓									✓	✓				✓		✓		✓	✓		✓
Singhvi1982	PKDB00836	✓		✓				✓					✓	✓	✓									
Vancea2009	PKDB00837	✓						✓					✓											

Figure 3. Studies used in calibration of model parameters.

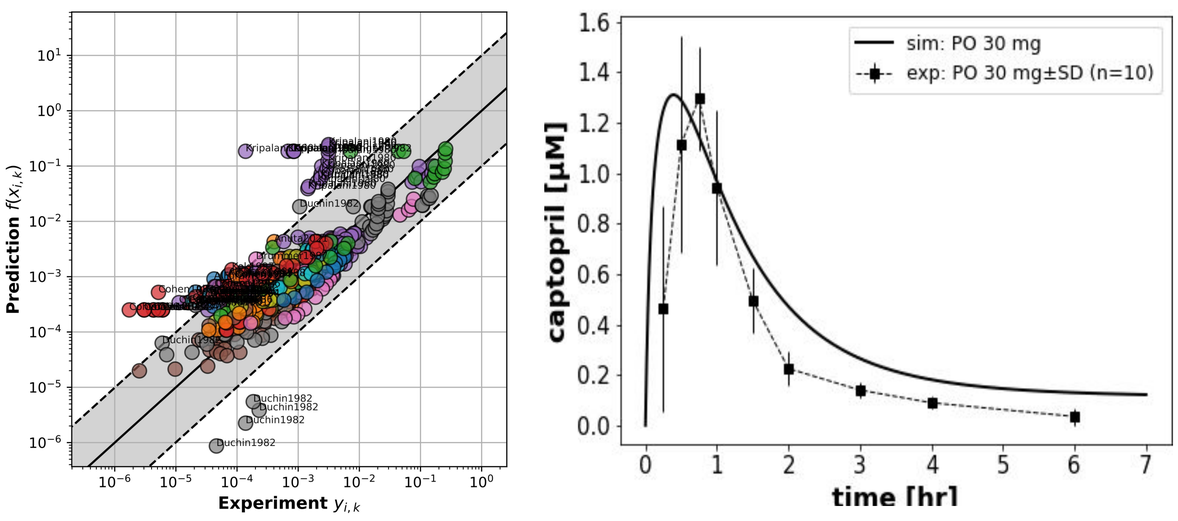

Figure 4. Parameter optimization (goodness of fit) & example prediction.

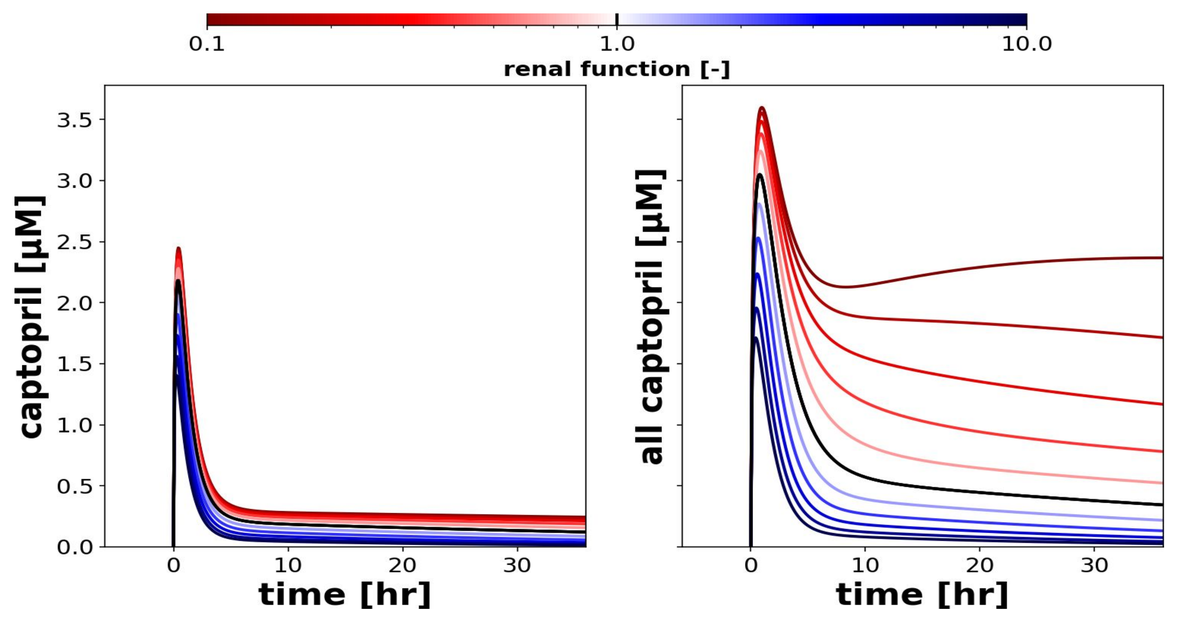

Figure 5. Effect of renal function on captopril pharmacokinetics.

Conclusions

This study successfully establishes **a freely accessible, comprehensive dataset** and an **open PBPK** model of captopril, enhancing our understanding of its pharmacokinetic behavior across different patient groups. Our findings emphasize **the significance of renal function in captopril elimination**.

References

[1] PK-DB: pharmacokinetics database for individualized and stratified computational modeling. Grzegorzewski et al., Nucleic Acids Res. 2021, 10.1093/nar/gkaa990.

[2] The FAIR Guiding Principles for scientific data management and stewardship. Wilkinson et al., Scientific Data 2016, 10.1038/sdata.2016.18.

[3] SBML Level 3: an extensible format for the exchange and reuse of biological models. Keating et al., Mol Syst Biol. 2020, 10.15252/msb.20199110

[4] Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan. Grzegorzewski et al., Front Pharmacol. 2022, 10.3389/fphar.2022.1029073

[5] Pharmacokinetics of caffeine: A systematic analysis of reported data for application in metabolic phenotyping and liver function testing. Grzegorzewski et al., Frontiers in Pharmacology 2022, 10.3389/fphar.2021.752826