

Supplementary Material

***In silico* pharmacogenetics CYP2D6 study focused on the pharmacovigilance of herbal antidepressants**

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TABLE S1 | Overview of literature sources for CYP2D6 inhibition. If literature for a compound on the topic could not be found, this is indicated as “unknown”.

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Natural Product	CYP2D6 inhibition	Ref
(-)-Cytisine	moderate	Qu et al., 2014
4-Hydroxyisoleucine	unknown	-
5-Isopropyl-2-methylphenol	unknown	-
Auraptanol	unknown	-
Chelidonic acid	unknown	-
D-(-)-Synephrine	unknown	-
Honokiol	moderate	Cho et al., 2014
Isorhynchophylline	moderate	Qu et al., 2014
L-Theanine	none	Sadzuka et al., 2006
Magnolol	moderate	Zhang et al., 2019
Naringenin	none	Lu et al., 2011
Orcinol	none	Yamaori et al., 2011
Piperine	weak	Shamsi et al., 2017
Protopine	potent	Li et al., 2011
Psoralidin	none	Shi et al., 2016
Salvigenin	unknown	-
Scopoletin	unknown	-
Trans-Methylisoeugenol	unknown	-
cannabidiol (CBC)	potent	Yamori et al., 2011

TABLE S2 | Overview of literature sources for P450 metabolism. If literature for a compound on the topic could not be found, this is indicated as “unknown”.

Natural Product	P450 metabolism (major isoforms)	Ref
(-)-Cytisine	unknown	-
4-Hydroxyisoleucine	unknown	-
5-Isopropyl-2-methylphenol	CYP2A6	Dong et al., 2012
Auraptanol	unknown	-
Chelidonic acid	unknown	-
D-(-)-Synephrine	unknown	-
Honokiol	CYP1A2, CYP2C8, CYP2C9, CYP2C19	Xu et al., 2008
Isorhynchophylline	CYP2D, CYP1A1, CYP1A2, CYP2C	Wang et al., 2010
L-Theanine	none	Sadzuka et al., 2006
Magnolol	CYP2E1, CYP3A4, CYP1A2	Huang et al., 2019
Naringenin	P450-dependent	Sousa et al., 2013
Orcinol	unknown	-
Piperine	unknown	-
Protopine	CYP2D1, CYP2C11	Paul et al., 2004
Psoralidin	CYP2C19	Shi et al., 2016
Salvigenin	unknown	-
Scopoletin	unknown	-
Trans-Methylisoeugenol	P450-dependent	Cartus et al., 2011
cannabidiol (CBC)	CYP2C19, CYP3A4	Jiang et al., 2011

TABLE S3 | Overview of literature sources for crossing of blood brain barrier (BBB). If literature for a compound on the topic could not be found, this is indicated as “unknown”.

Natural Product	BBB	Ref
(-)-Cytisine	poor	Mineur et al., 2009
4-Hydroxyisoleucine	unknown	-
5-Isopropyl-2-methylphenol	unknown	-
Auraptanol	unknown	-
Chelidonic acid	unknown	-
D-(-)-Synephrine	poor	Stohs et al., 2011
Honokiol	√	Lin et al., 2012
Isorhynchophylline	√	Zhang et al., 2017
L-Theanine	√	Takeshima et al., 2016
Magnolol	√	Tsai et al., 1996
Naringenin	√	Youdim et al., 2004
Orcinol	√	Wang et al., 2015
Piperine	√	Eigenmann et al., 2016
Protopine	√	Metha et al., 2016
Psoralidin	unknown	-
Salvigenin	√	Kavvadias et al., 2004
Scopoletin	√	Basu et al., 2016
Trans-Methylisoeugenol	unknown	-
cannabidiol (CBC)	√	Blanco et al., 2016

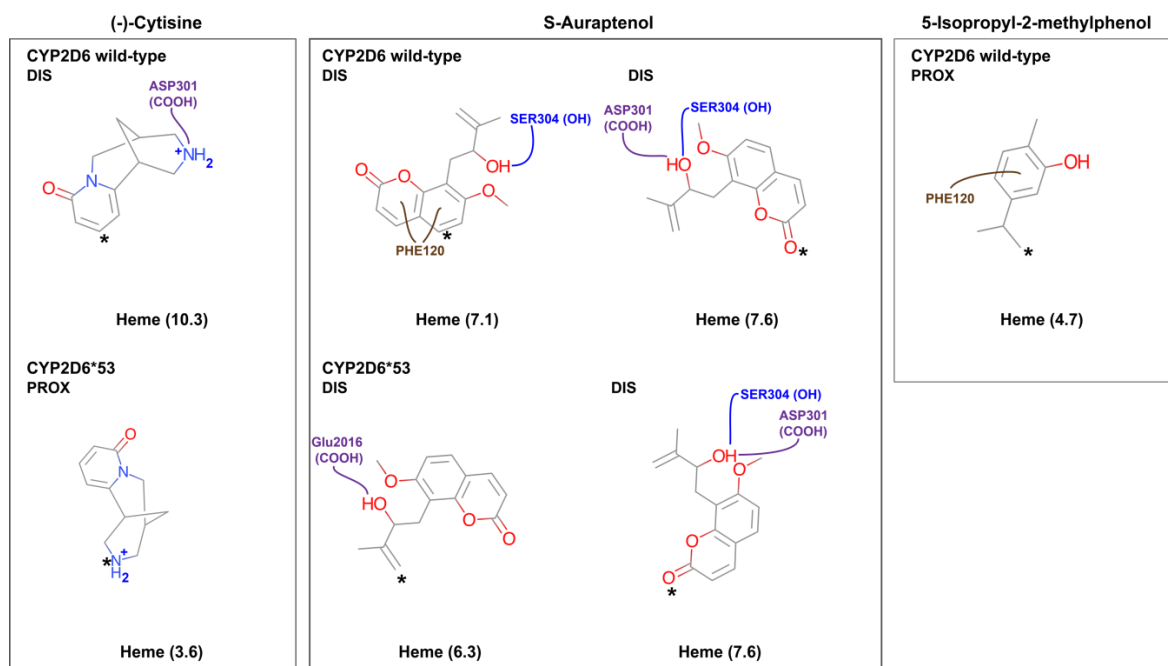


FIGURE S1 | The best scored binding modes (in 2D) for (-)-Cytisine, S-Auraptanol and 5-isopropyl-2-methylphenol are shown in CYP2D6 wild-type and CYP2D6*53. The asterisk indicates the atom closest to the heme-iron. Color code: hydrophobic interactions; brown, electrostatics; purple, and hydrogen bonds; blue. Proximal: distance between heme-Fe and closest atom < 6 Å and distal; > 6 Å.

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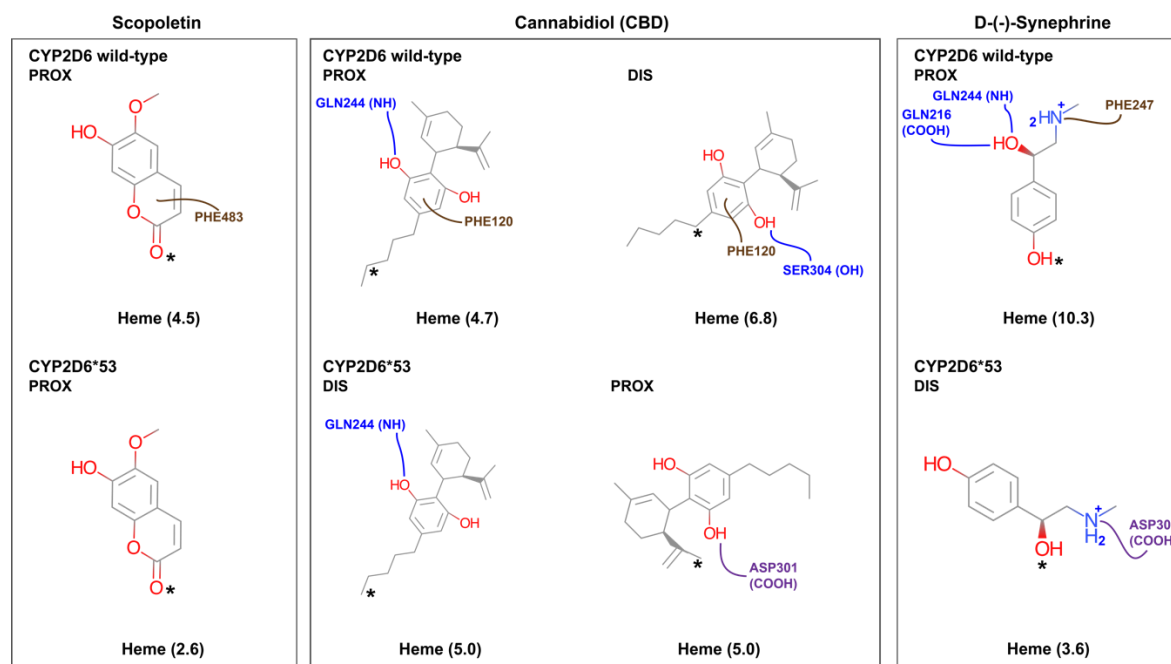


FIGURE S2 | The best scored binding modes (in 2D) for Scopoletin, Cannabidiol (CBD) and D-(-)-Synephrine are shown in CYP2D6 wild-type and CYP2D6*53. The asterisk indicates the atom closest to the heme-iron. Color code: hydrophobic interactions; brown, electrostatics; purple, and hydrogen bonds; blue. Proximal: distance between heme-Fe and closest atom < 6 Å and distal; > 6 Å.

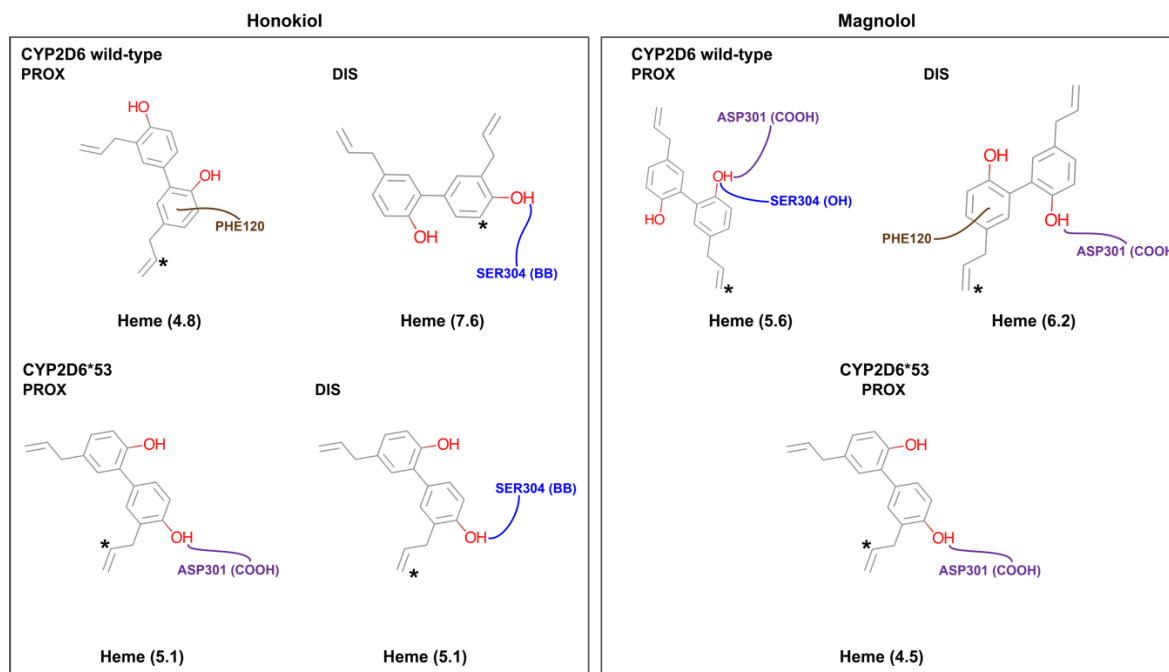


FIGURE S3 | The best scored binding modes (in 2D) for Honokiol and Magnolol are shown in CYP2D6 wild-type and CYP2D6*53. The asterisk indicates the atom closest to the heme-iron. Color code: hydrophobic interactions; brown, electrostatics; purple, and hydrogen bonds; blue. Proximal: distance between heme-Fe and closest atom < 6 Å and distal; > 6 Å.

TABLE S4 | Overview of the various types of interactions found in the best binding modes for CYP2D6 wild-type.

Natural Product	4WNW WT		Distance	Heme	
	AA	Type	(Å)	(Å)	
Thymol	F120	π stacking	~3.8	4.7	
	D301	ionic	2.3	7.6	
s-auraptanol	S304	H-bond	2.4		
	D301	ionic	2.6	6.1	
D-(-)-synephrine	01	F120	π -stacking	~ 4.7	
		E216	ionic	2.3	5.1
	02	Q244	H-bond	2.3	
		F247	π stacking	~ 4.3	
Honokiol	01	F120	π stacking	~ 4.3	4.7
	02	F120	π stacking	~ 3.9	7.6
		S304	H-bond	2.5	
Magnolol	01	D301	ionic	1.9	6.0
		F120	π stacking	~ 4.0	
	02	D301	ionic	2.6	5.4
		S304	H-bond	2.3	
Piperine		F120	π stacking	~3.8	5.4
		F483	π stacking	~ 4.0	
Protopine		Q244	H-bond	2.4	5.9
		F120	π stacking	3.1	
		F120	π stacking	6.5	
		F483	π stacking	3.5	
Scopoletin		S304	H bond	2.4	5.3
		F120	π stacking	~ 3.8	
Cannabidiol	01	Q244	H-bond	2.3	4.7
		F120	π stacking	3.6	
	02	S304	H-bond	2.4	7.8
		F120	π stacking	~ 4.0	

TABLE S5 | Overview of the various types of interactions found in the best binding modes for CYP2D6*53.

Natural Product	4WNW V53		Distance	Heme	
	AA	Type	(Å)	(Å)	
Thymol		F120	π stacking	~3.8	4.7
		D301	ionic	2.3	7.6
s-auraptanol		S304	H-bond	2.4	
		D301	ionic	2.6	6.1
D-(-)-synephrine	01	F120	π -stacking	~ 4.7	
		E216	ionic	2.3	5.1
	02	Q244	H-bond	2.3	
		F247	π stacking	~ 4.3	
Honokiol	01	F120	π stacking	~ 4.3	4.7
	02	F120	π stacking	~ 3.9	7.6
		S304	H-bond	2.5	
Magnolol	01	D301	ionic	1.9	6.0
		F120	π stacking	~ 4.0	
	02	D301	ionic	2.6	5.4
Piperine		S304	H-bond	2.3	
		F120	π stacking	~3.8	5.4
		F483	π stacking	~ 4.0	
Protopine		Q244	H-bond	2.4	5.9
		F120	π stacking	3.1	
		F120	π stacking	6.5	
		F483	π stacking	3.5	
Scopoletin		S304	H bond	2.4	5.3
		F120	π stacking	~ 3.8	
Cannabidiol	01	Q244	H-bond	2.3	4.7
		F120	π stacking	3.6	
	02	S304	H-bond	2.4	7.8
		F120	π stacking	~ 4.0	

TABLE S6 | Overview QikProp descriptors with Schrödinger explanation

Descriptor	Explanation (Schrödinger – QikProp)
log_{HERG}	Predicted IC50 value for blockage of HERG K ⁺ channels
P_{Caco}	Predicted apparent Caco-2 cell permeability in nm/sec. Caco2 cells are a model for the gut-blood barrier. QikProp predictions are for non-active transport.
log_{BB}	Predicted brain/blood partition coefficient. Note: QikProp predictions are for orally delivered drugs so, for example, dopamine and serotonin are CNS negative because they are too polar to cross the blood-brain barrier
P_{MDCK}	Predicted apparent MDCK cell permeability in nm/sec. MDCK cells are considered to be a good mimic for the blood brain barrier (BBB). QikProp predictions are for non-active transport.
HOA (%)	Predicted human oral absorption on 0 to 100% scale. The prediction is based on a quantitative multiple linear regression model.
CNS	Predicted central nervous system activity on a -2 (inactive) to +2 (active) scale.