Supporting information

Table S1. Physiological parameters in human.[1]

Parameters	Symbol	Human
Body weight (kg)	BW	70
Tissue volumes (% body weight)		
Lumen	VLu	1.4
Small intestine	VI	0.9
Liver	VL	2.6
Kidney	VK	0.4
Rapidly perfused tissues	VR	4.0
Slowly perfused tissues	VS	75.7
Blood	VB	7.9
Cardiac output (l/h)	QC	310.4
Blood flow to tissue (% cardiac output)		
Small intestine	QI	18.1
Liver (exclude portal vein)	QL	4.6
Kidney	QK	17.5
Rapidly perfused tissues	QR	29.8
Slowly perfused tissues	QS	30

[1]Physiological parameters were obtained from Brown *et al*. (Brown *et al.*, 1997).

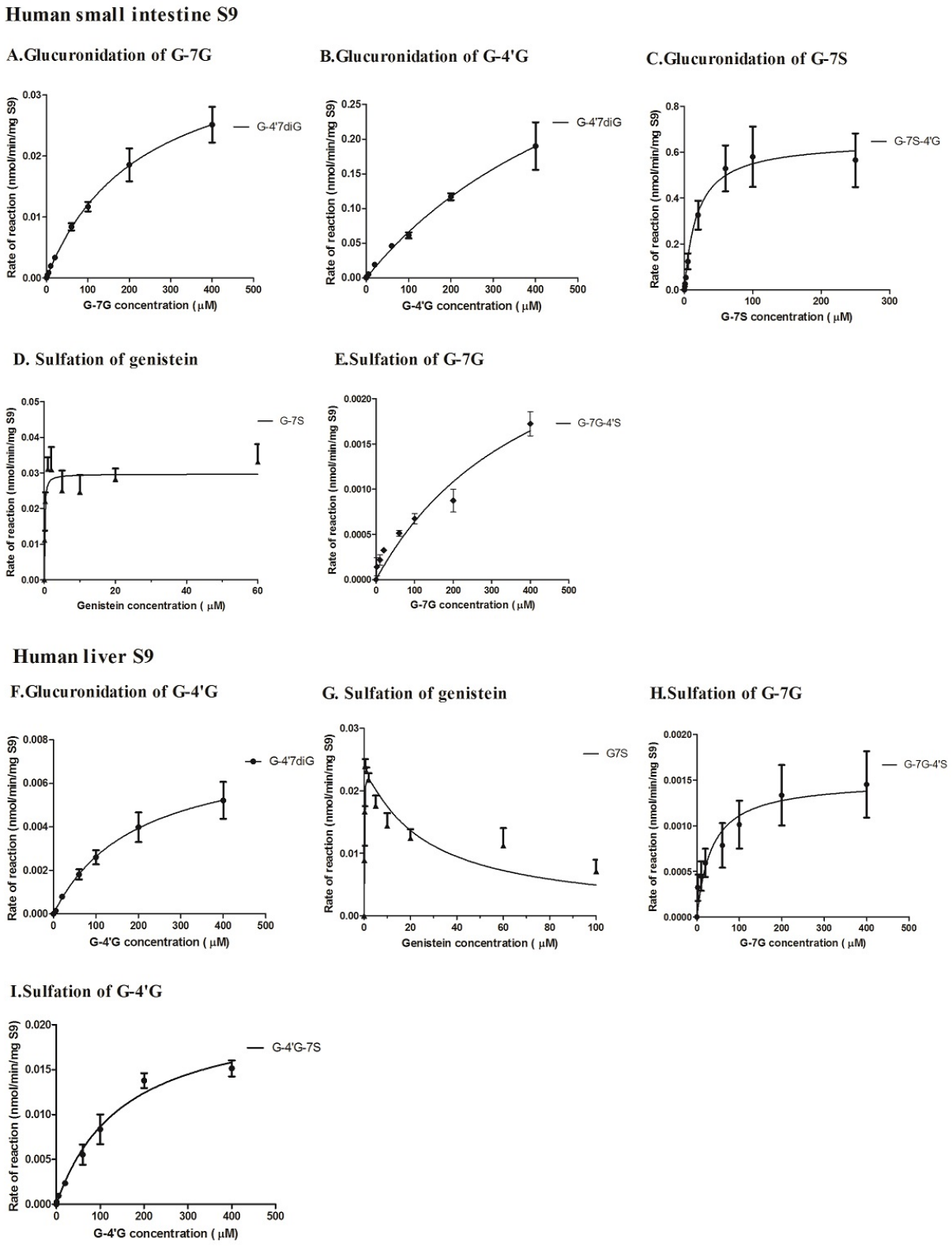


Figure S1. Concentration-dependent formation of genistein mono-conjugates and genistein di-conjugates with pooled mixed-gender human small intestine S9 (A – E) or liver S9 (F – I): genistein-7-O-glucuronide (G-7G), genistein-4´-O-glucuronide (G-4´G), genistein-7-O-sulfate (G-7S), genistein-4´,7-O-diglucuronide (G-4´7diG), genistein-7-O-glucuronide-4´-O-sulfate (G-7G-4´S), and genistein-4´-O-glucuronide-7-O-sulfate (G-4´G-7S).

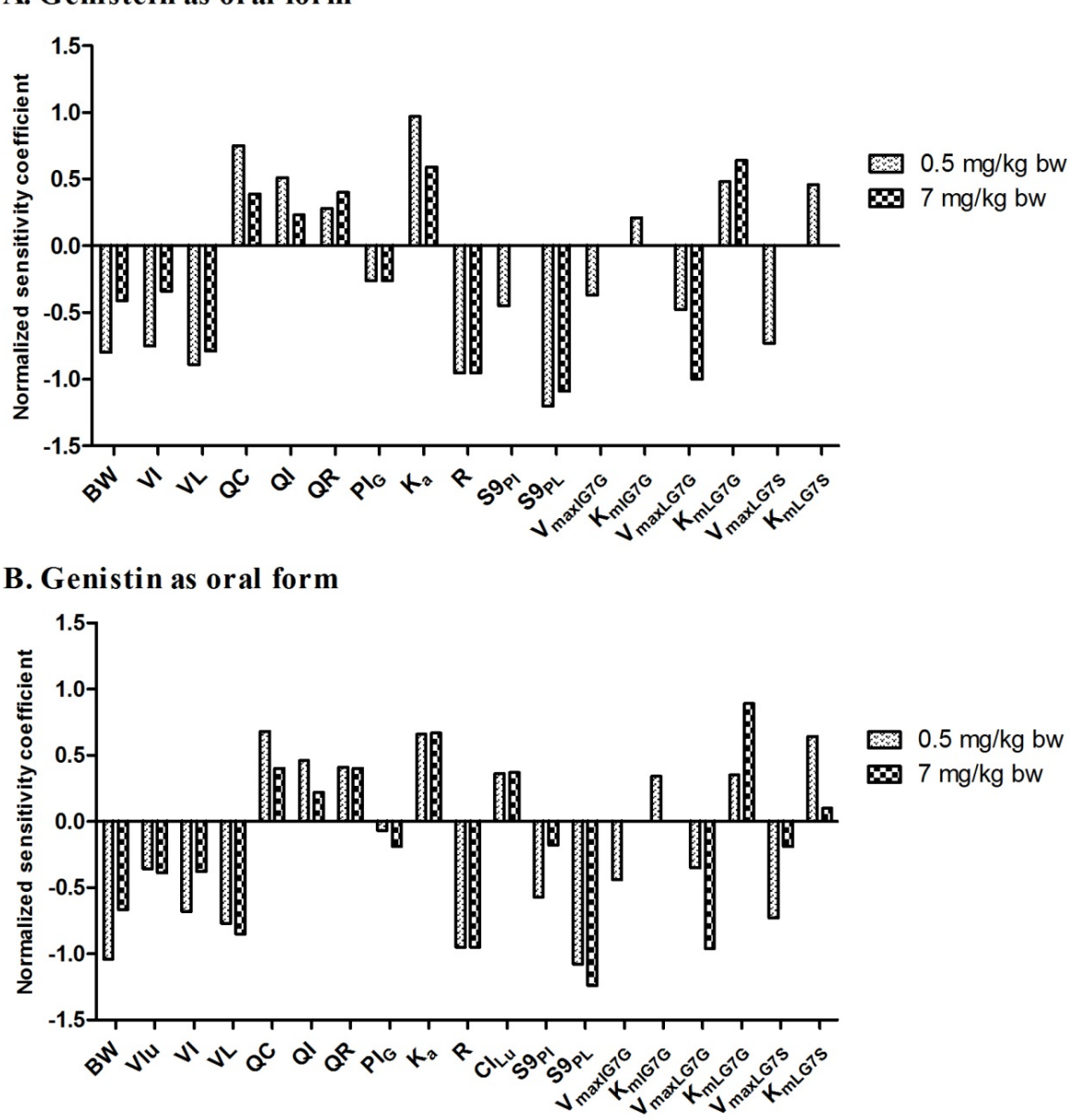
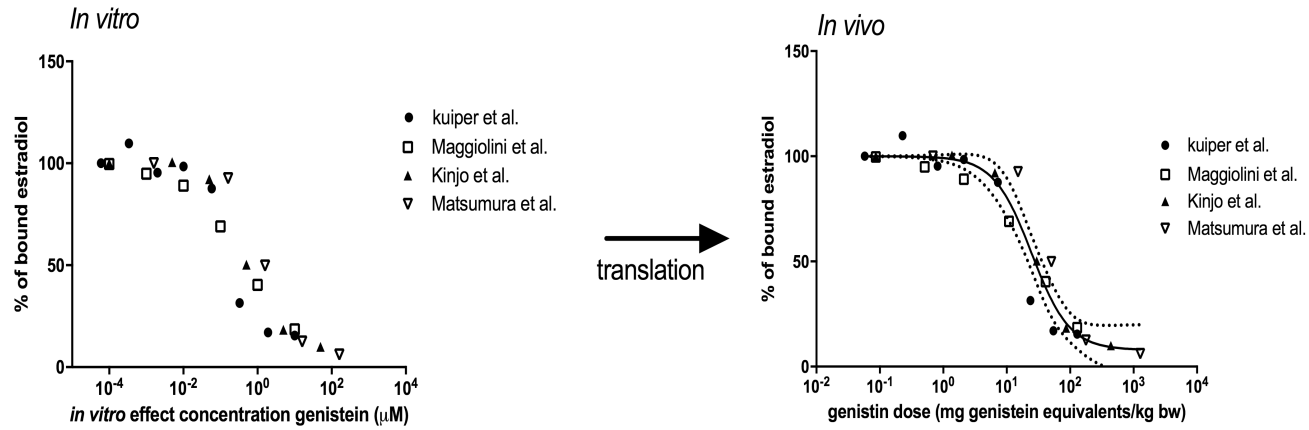
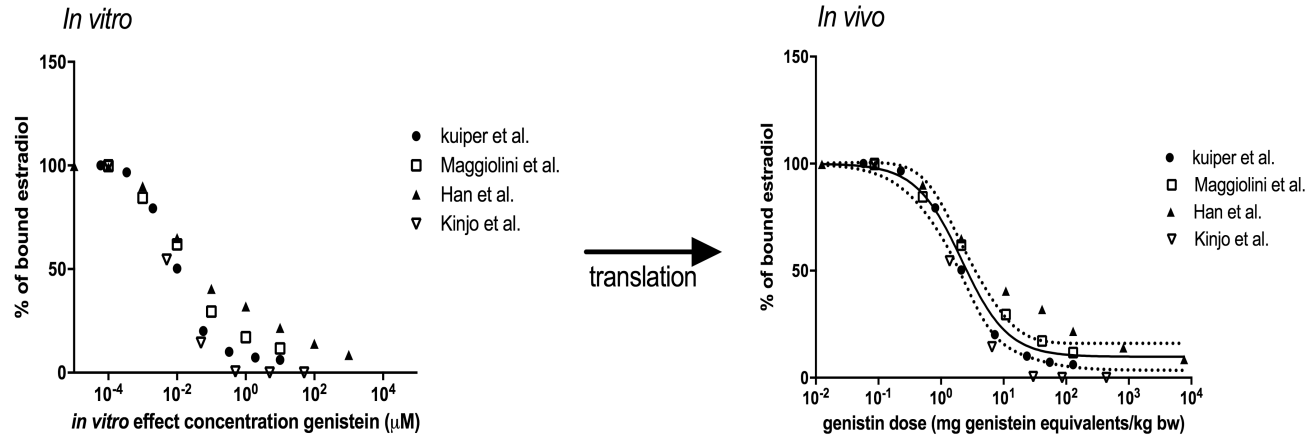


Figure S2. Sensitivity analysis of the predicted plasma C_{max} of genistein aglycone at an oral dose of 0.5 and 7 mg (kg bw)$^{-1}$ (A) genistein and (B) genistin. The parameters stand for: BW = body weight, VTi = tissue volumn (Ti = I (small intestine), L (liver), BR (breast), R (rapidly perfused tissues), and S (slowly perfused tissues), QC = cardiac output, QTi= reginal blood flow through tissue, PTi_G = partition coefficient of genistein in tissue, K_a = uptake rate constant of genistein, R = blood to plasma ratio, $S9_{PI}$ = small intestinal S9 protein content, $S9_{PL}$ = liver S9 protein content, V_{max} and K_m = the maximum rate of formation and the Michaelis-Menten constant for formation of genistein-7-O-glucuronide (G7G) and genistein-7-O-sulfate (G7S).

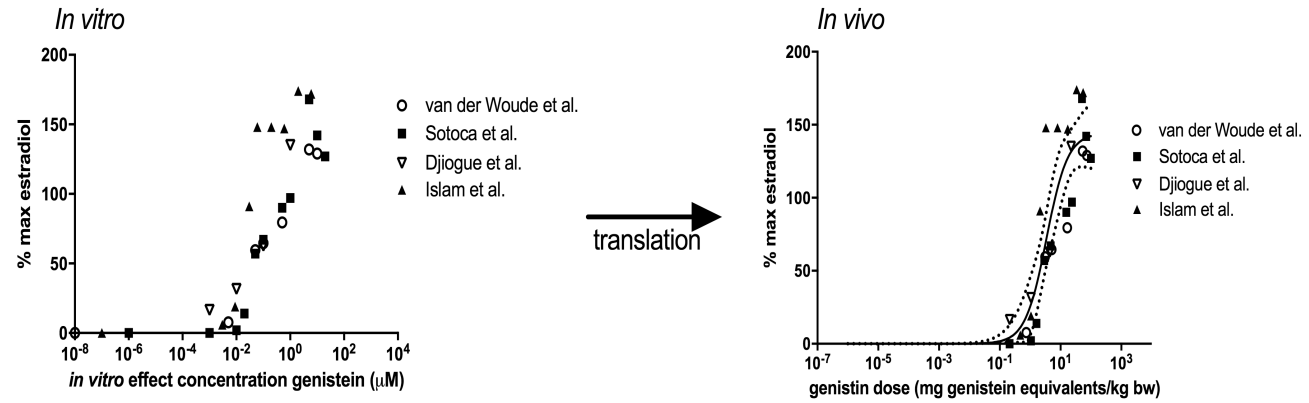
A. ERα binding



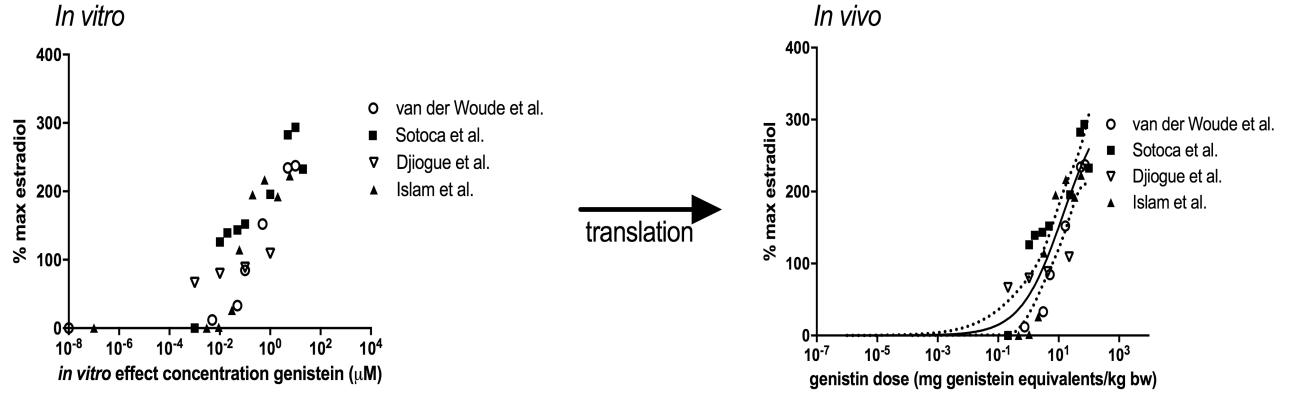
B. ERβ binding



C. ERα transcriptive induction



D. ERβ transcriptive induction



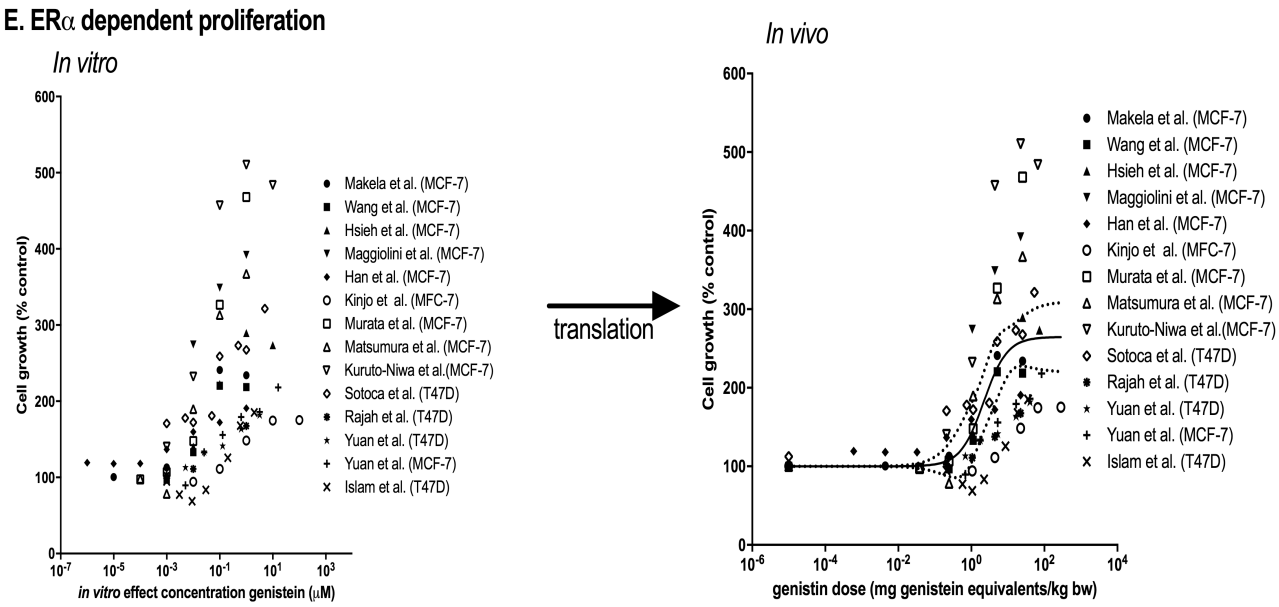


Figure S3. Translation of *in vitro* estrogenic concentration-response curves for genistein dependent (A) binding to ERα (Kuiper *et al.*, 1998; Maggiolini *et al.*, 2001; Kinjo *et al.*, 2004; Matsumura *et al.*, 2005), (B) binding to ERβ (Kuiper *et al.*, 1998; Maggiolini *et al.*, 2001; Han *et al.*, 2002; Kinjo *et al.*, 2004), (C) ERα mediated gene expression in U2OS reporter gene assays (van der Woude *et al.*, 2005; Sotoca *et al.*, 2008; Djiogue *et al.*, 2010; Islam *et al.*, 2015), (D) ERβ mediated gene expression in U2OS reporter gene assays (van der Woude *et al.*, 2005; Sotoca *et al.*, 2008; Djiogue *et al.*, 2010; Islam *et al.*, 2015), and (E) ERα dependent proliferation of MCF-7 and T47D breast cancer cells (Makela *et al.*, 1994; Wang *et al.*, 1996; Hsieh *et al.*, 1998; Maggiolini *et al.*, 2001; Han *et al.*, 2002; Kinjo *et al.*, 2004; Murata *et al.*, 2004; Matsumura *et al.*, 2005; Kuruto-Niwa *et al.*, 2007; Sotoca *et al.*, 2008; Rajah *et al.*, 2009; Yuan *et al.*, 2012; Islam *et al.*, 2015), to *in vivo* human genistin dose-response curves using PBK model based reverse dosimetry based on plasma C_{max} values of genistein aglycone. The solid lines represent the central *in vivo* dose-response curve, whereas the dashed lines represent the 95% lower and upper confidence limits.

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