Supporting Information for

Original Article

Identification of bioactive anti-angiogenic components targeting tumor endothelial cells in Shenmai injection using multidimensional pharmacokinetics

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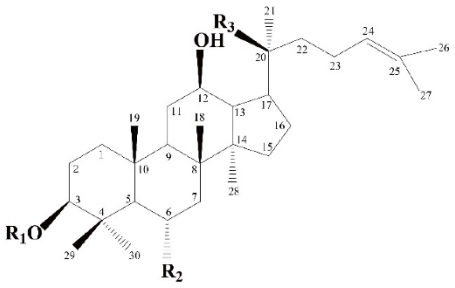
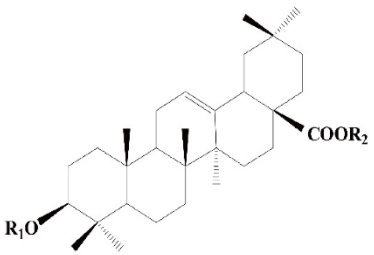


Type	Ginsenoside	R_1	R_2	R_3
PPD	Rb1	Glc^2-Glc	H	*O*-Glc^6-Glc
	Rb2	Glc^2-Glc	H	*O*-Glc^2-arap
	Rb3	Glc^2-Glc	H	*O*-Glc^2-xyl
	Rc	Glc^2-Glc	H	*O*-Glc^6-araf
	Rd	Glc^2-Glc	H	*O*-Glc
	Rg3	Glc^2-Glc	H	OH
PPT	Re	H	*O*-Glc^2-Rha	*O*-Glc
	Rf	H	*O*-Glc	*O*-Glc



Type	Ginsenoside	R_1	R_2
Oleanane	Ro	Glc^2-Glc	Glc

Glc=*β*-D-glucose; arap=*α*-L-arabinose (pyranose); araf=*α*-L-arabinose (fluranose); xyl=*β*-D-xylose; Rha=*α*-D-rhamnose

Figure S1 The structure of ginsenosides detected in plasma after intraperitoneal injection of SMI to xenograft mice.

Pharmacokinetic study design of ginsenosides in plasma and tumor tissues after single or multiple doses of SMI

Table S1 Pharmacokinetic study of ginsenosides in plasma and tumor tissues after single dose of SMI.

Group	Number of mice	Time points for blood sampling	Time points for sacrifice and dissection of tumor tissues
1	5	5 and 20 min	20 min
2	5	10 min and 2 h	2 h
3	5	40 min and 12 h	12 h
4	5	1, 8 and 24 h	24 h
5	5	4, 48 and 96 h	96 h

Table S2 Pharmacokinetic study of ginsenosides in plasma and tumor tissues after multiple doses of SMI.

Group	Number of mice	Time points for blood sampling	Time for sacrifice and dissection of tumor tissues
1	5	20 min	20 min
2	5	10 min and 2 h	2 h
3	5	40 min and 12 h	12 h
4	5	1, 8 and 24 h	24 h
5	5	4, 48 and 96 h	96 h

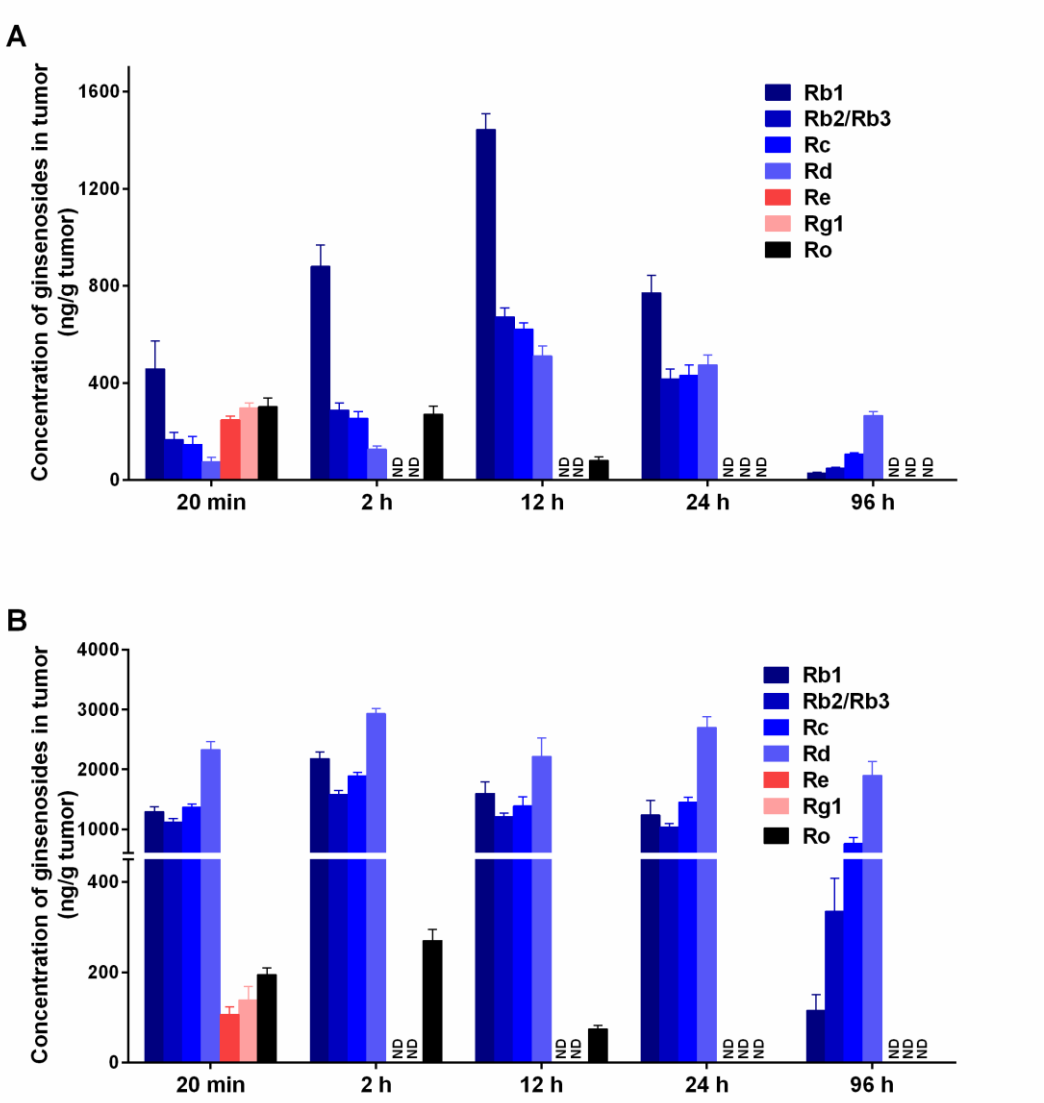


Figure S2 The concentrations of ginsenosides detected in tumors at predesigned time points following treatment of SMI. (A) and (B) The concentrations of ginsenosides detected in tumors at 20 min, 2, 12, 24 and 96 h with single (A) or multiple (B) administration of SMI 10 mL/kg in Balb/c mice harboring LoVo xenografts (n = 5). ND, not detected.

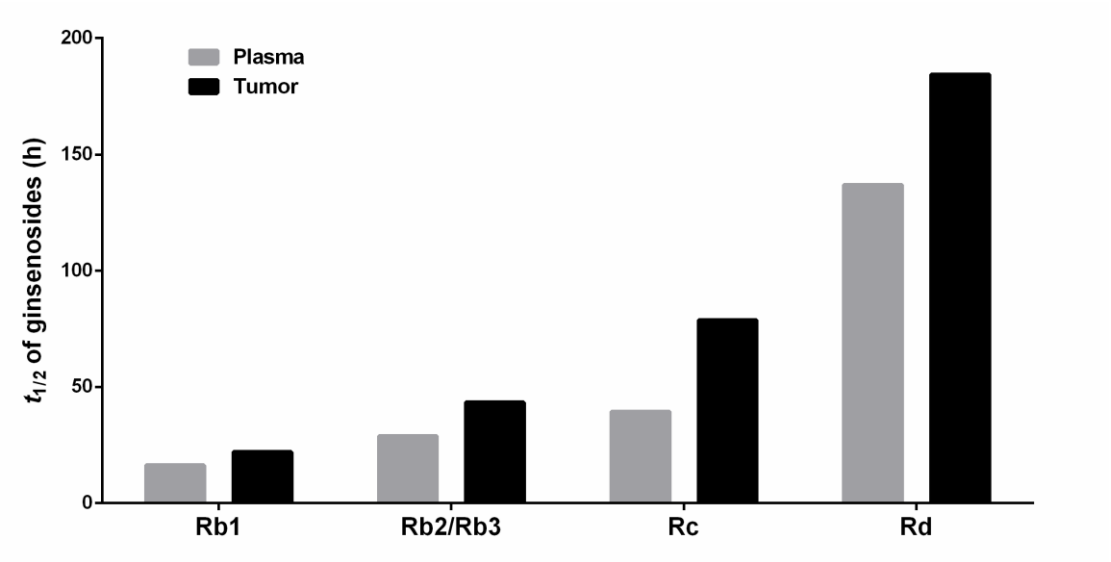


Figure S3 The elimination half-life of Rb1, Rb2/Rb3, Rc and Rd in plasma or tumors after multiple administration of SMI to Balb/c mice harboring LoVo xenografts. The elimination half-life of ginsenosides was calculated based on Figs. 2B and 3B.

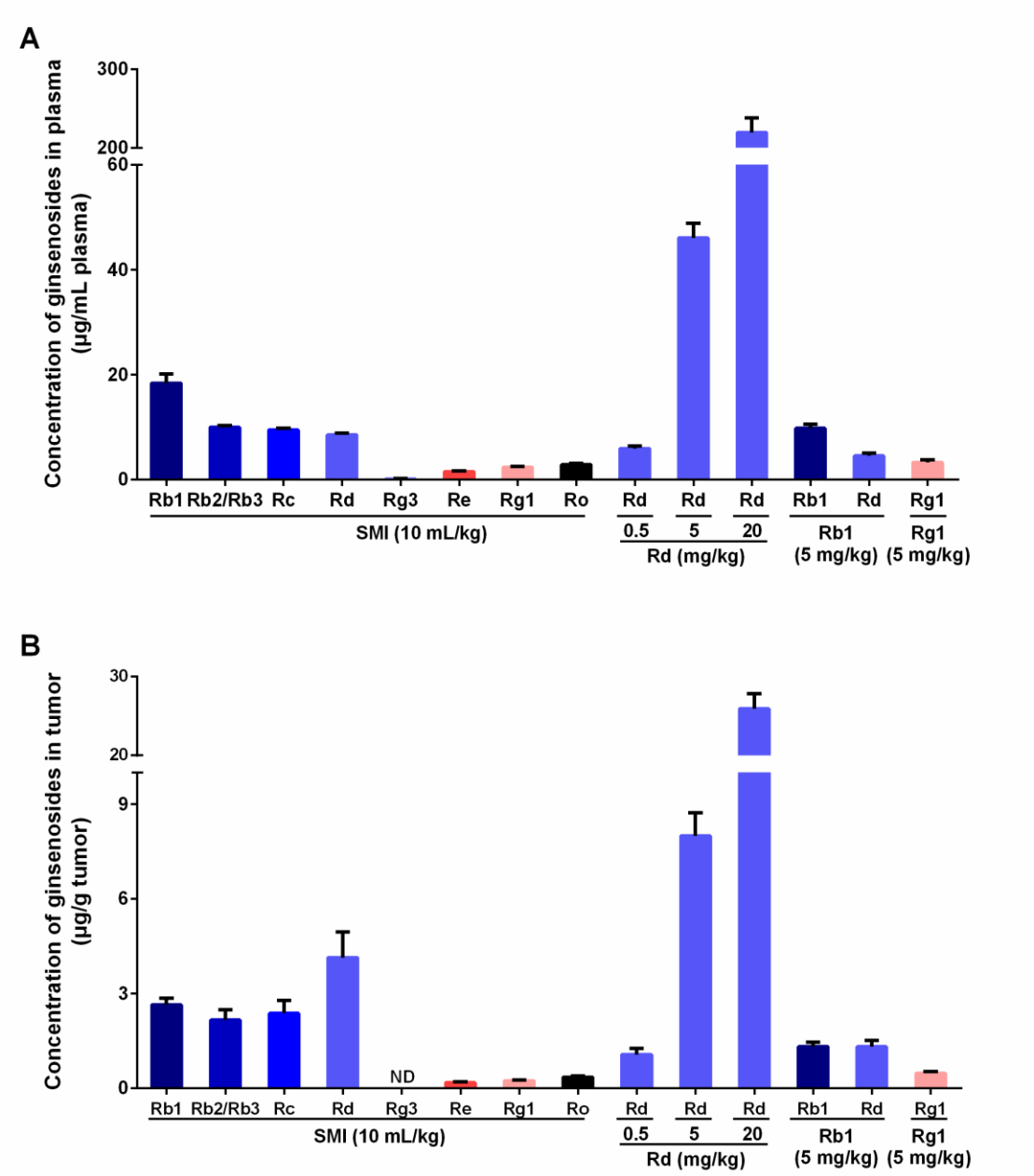


Figure S4 The conversion of Rb1 to Rd in plasma and tumors. The concentrations of ginsenosides in plasma and tumors was detected at 20 min with 15-day treatment of SMI, Rd, Rb1 or Rg1 in Balb/c mice harboring LoVo xenograft (n = 6). ND, not detected.

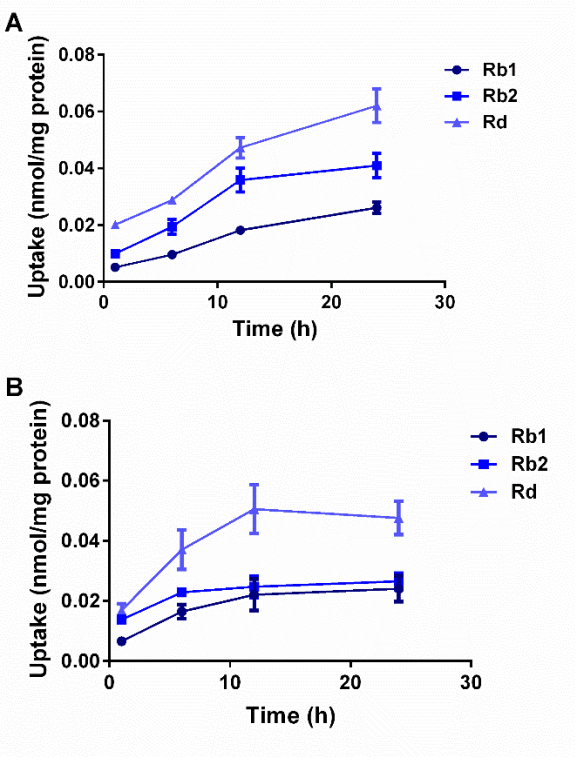


Figure S5 The ingestion ability of HUVEC or LoVo to Rb1, Rb2 and Rd. HUVEC (A) or LoVo (B) was treated with 10 μmol/L Rb1, Rb2 or Rd and the concentrations of ginsenosides in cells were determined at 1, 6, 12 and 24 h (n = 3).

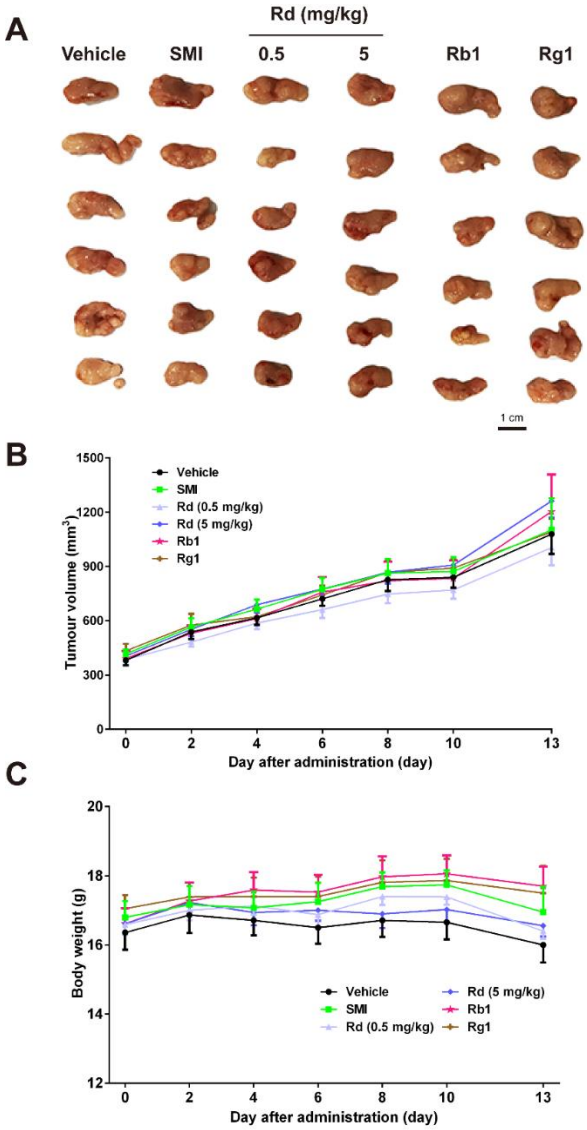


Figure S6 SMI, Rb1, Rg1 or Rd had no significant effect on tumor growth and mice weight. Balb/c mice harboring LoVo xenografts were treated with SMI, Rd, Rb1 or Rg1 once daily for 15 days.(A) Image of tumors with 15-day treatment with SMI, Rd, Rb1 or Rg1 (n = 6; scale bar = 1 cm). (B) Tumor volume during treatment. (C) Mice body weight during treatment. SMI: SMI 10 mL/kg; Rb1: Rb1 5 mg/kg; Rg1: Rg1 5 mg/kg.