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Supplementary Materials:

Structural Elucidation and In Silico-Aided Toxicity Prediction of Forced Degradation Products of Ginsenoside Re Using Ultra-High-Performance Liquid Chromatography Equipped with a Diode Array Detector and Charged Aerosol Detector (UHPLC-DAD-CAD) and Liquid Chromatography Coupled to a High-Resolution Mass Detector (LC-HRMS)

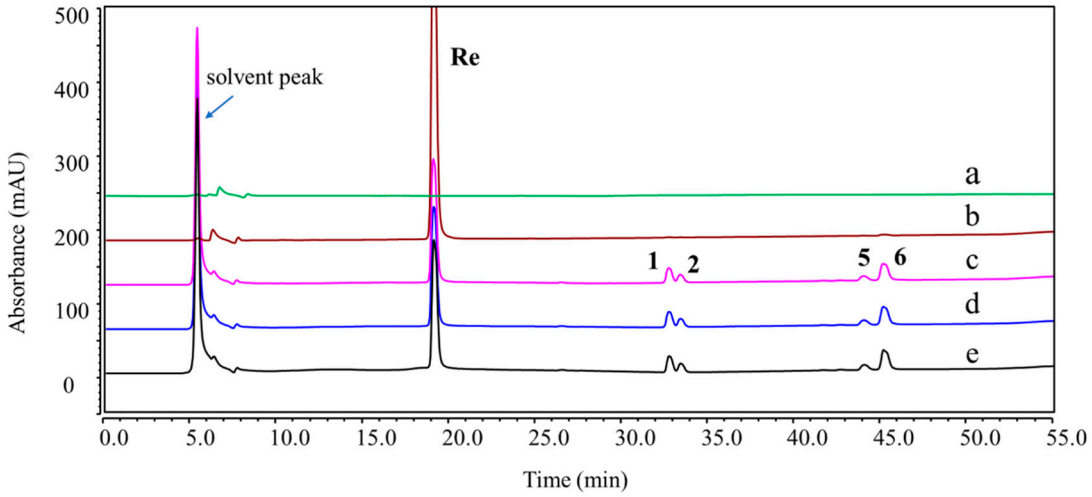


Figure S1. Overlay chromatograms of Re and its DPs under basic hydrolysis using UHPLC-UV (203 nm). **(a)** blank; **(b)** Re; **(c-e)** basic hydrolysis (1.0 M NaOH, 37℃) for 1, 3 and 6 h.

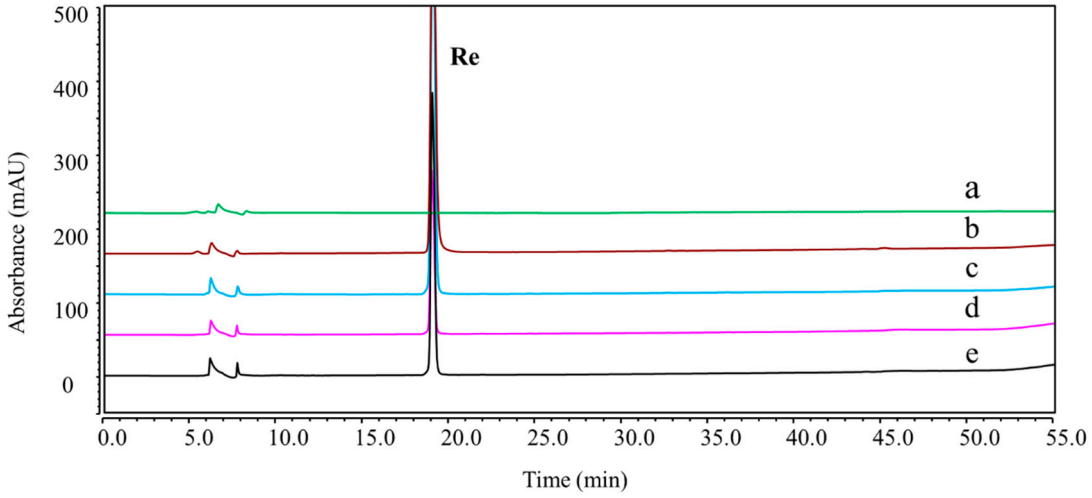


Figure S2. Overlay chromatograms of Re and its DPs under neutral hydrolysis using UHPLC-UV (203 nm). **(a)** blank; **(b)** Re; **(c-e)** neutral hydrolysis at 70℃ for 1, 7 and 10 d.

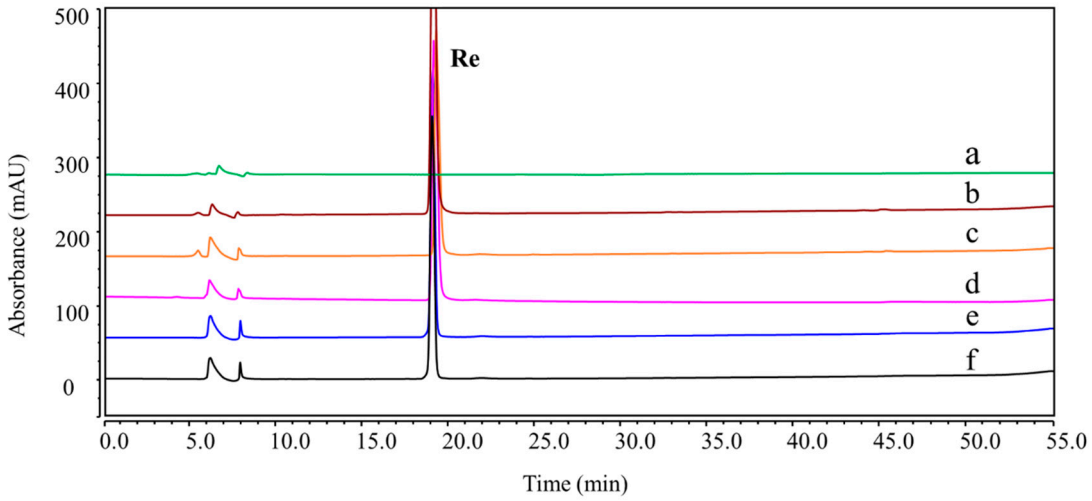


Figure S3. Overlay chromatograms of Re and its DPs exposed to high humidity and high temperature conditions (UHPLC-UV at 203 nm). **(a)** blank; **(b)** Re; **(c)** high humidity for 10 days (90% RH, 25℃, 10 d); **(d-f)** high temperature at 50℃ for 5, 10 and 50 d.

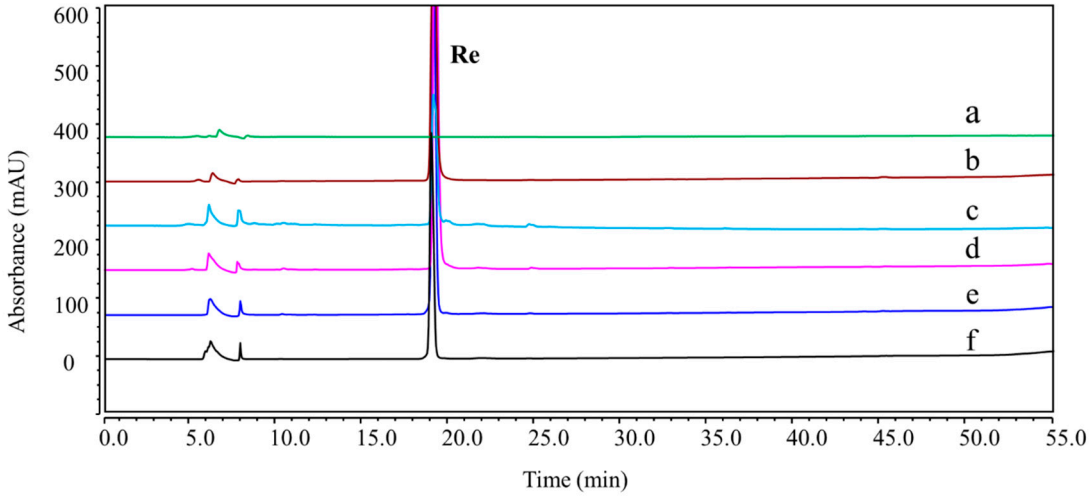


Figure S4. Overlay chromatograms of Re and its DPs exposed to photolysis condition (UHPLC-UV at 203 nm). **(a)** blank; **(b)** Re; **(c)** UV light for 30 d; **(d-f)** visible light for 14, 30 and 55 d.

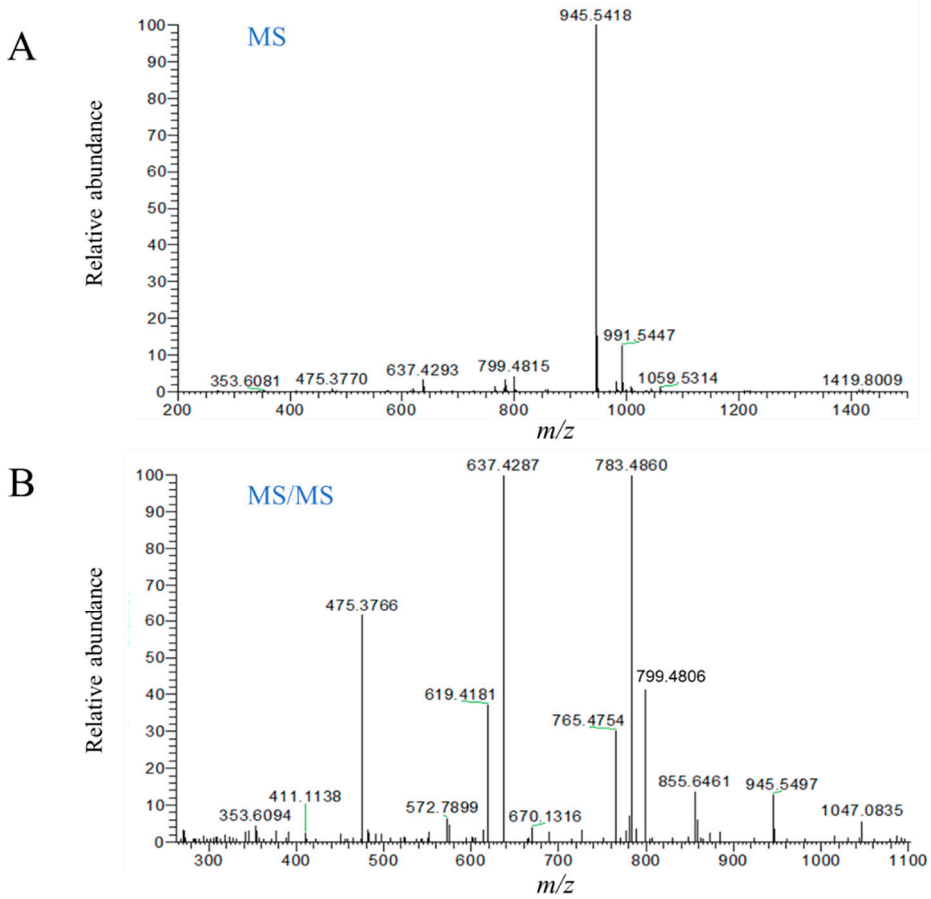


Figure S5. Mass spectrum of Re in ESI negative mode.

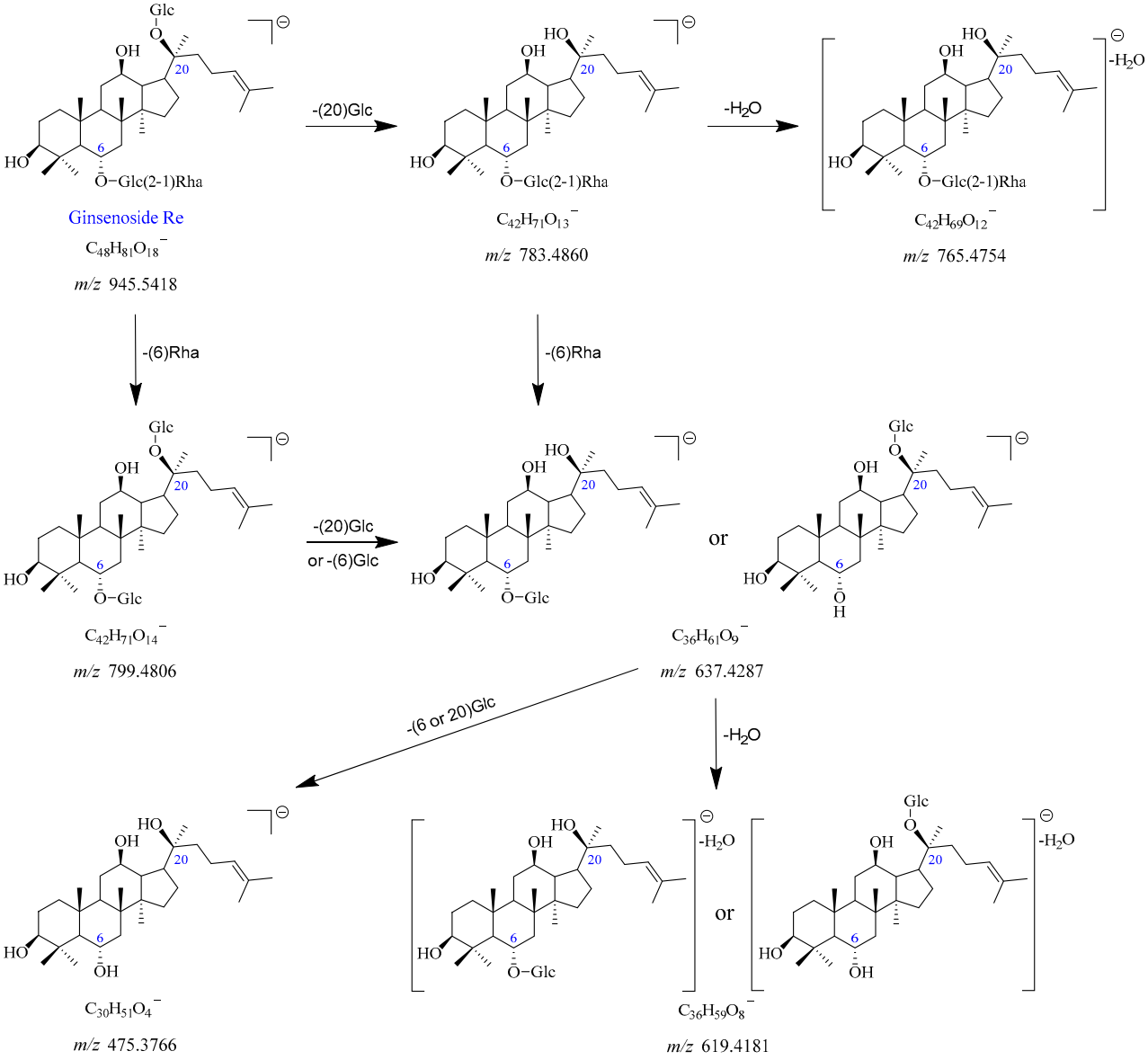


Figure S6. Proposed mass fragmentation pathway of Re.

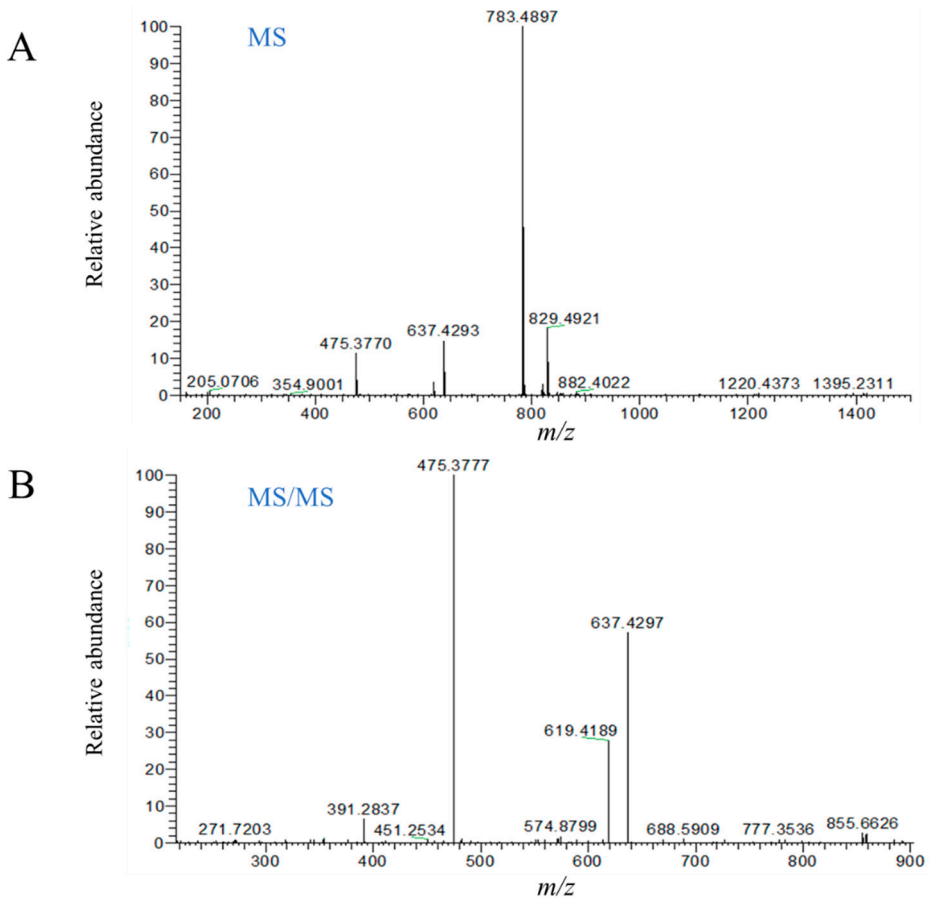


Figure S7. Mass spectrum of DP-1 & DP-2 in ESI negative mode.

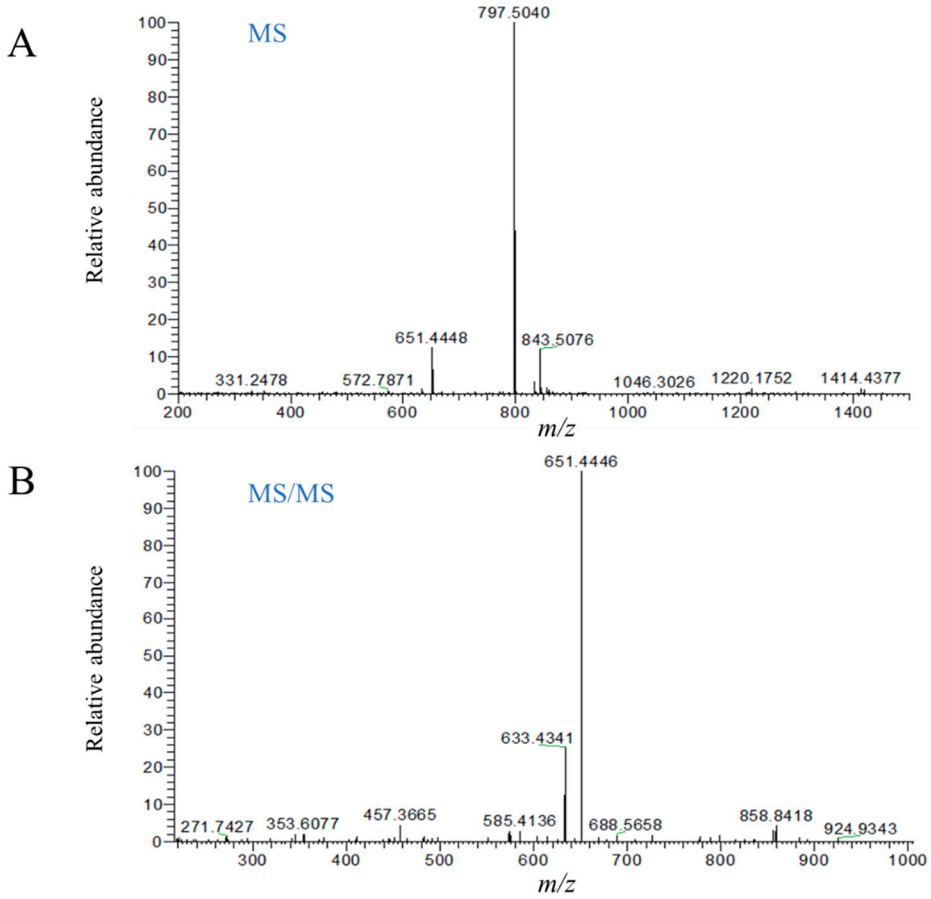


Figure S8. Mass spectrum of DP-3 & DP-4 in ESI negative mode.

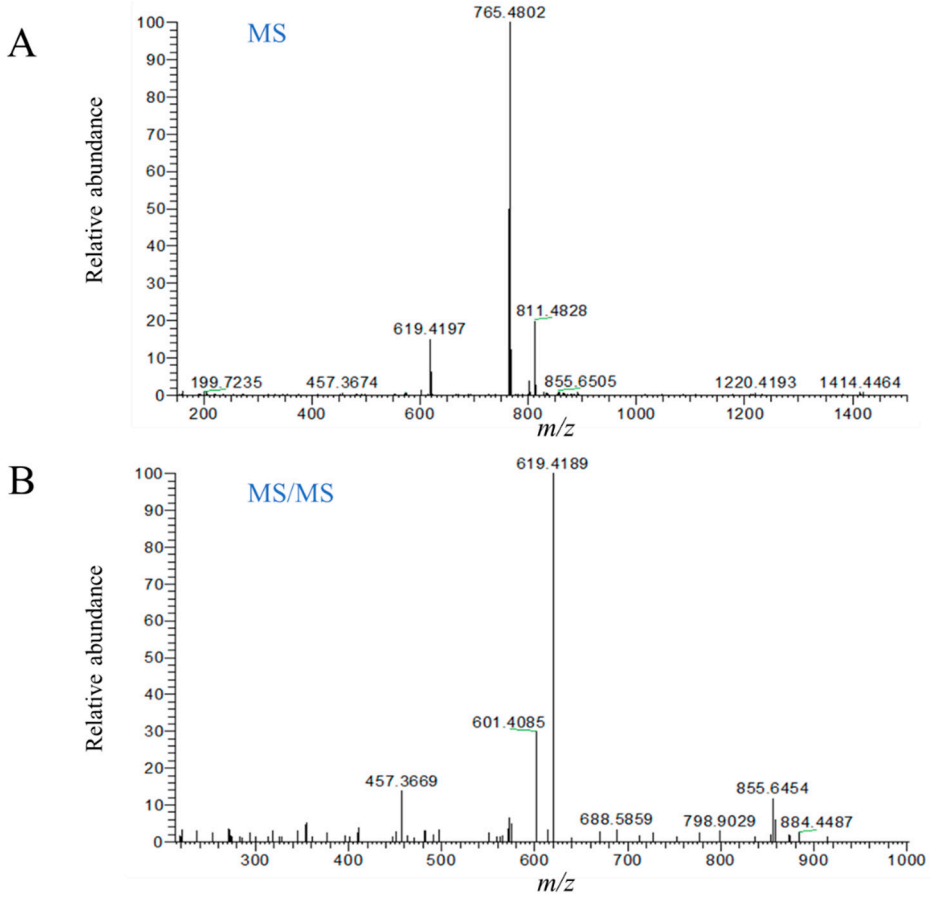


Figure S9. Mass spectrum of DP-5 & DP-6 in ESI negative mode.

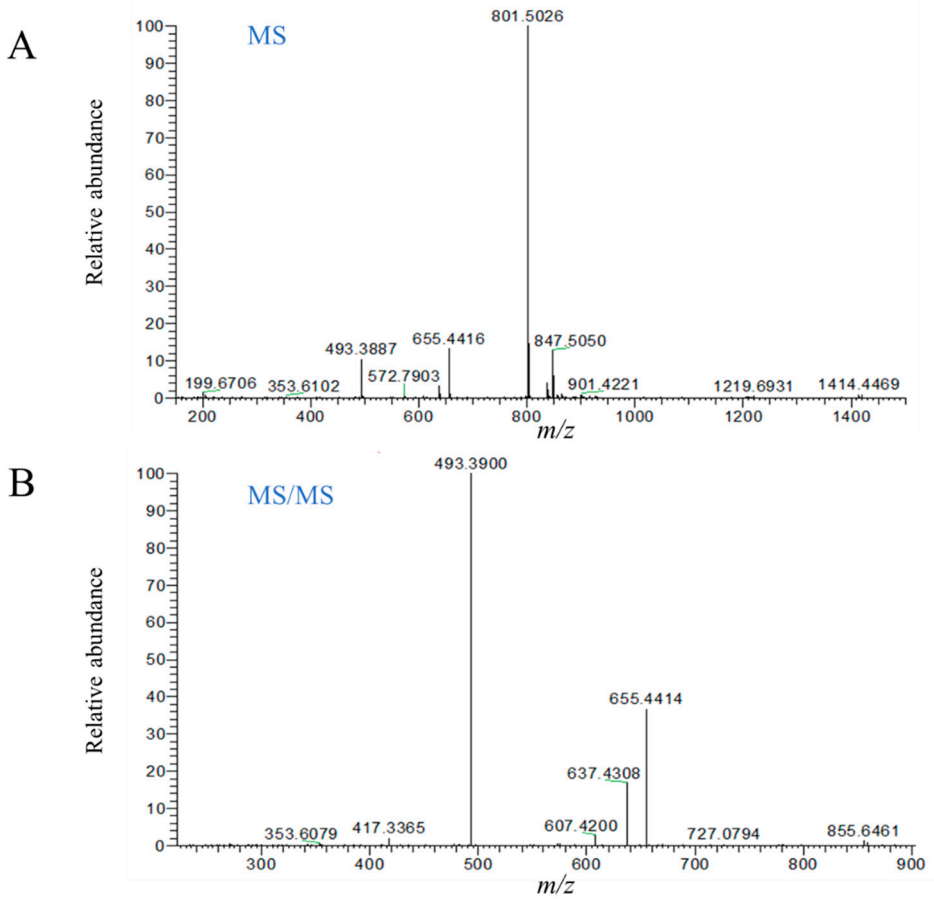


Figure S10. Mass spectrum of DP-7 & DP-8 in ESI negative mode.

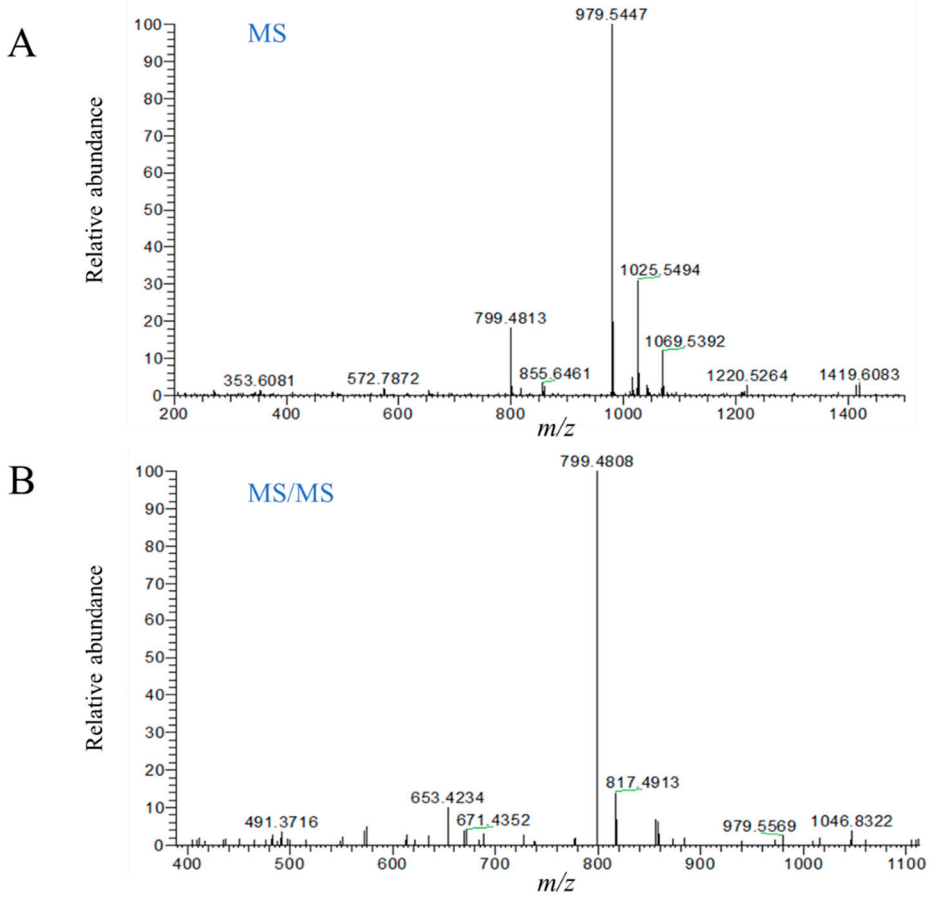


Figure S11. Mass spectrum of DP-9 & DP-10 in ESI negative mode.

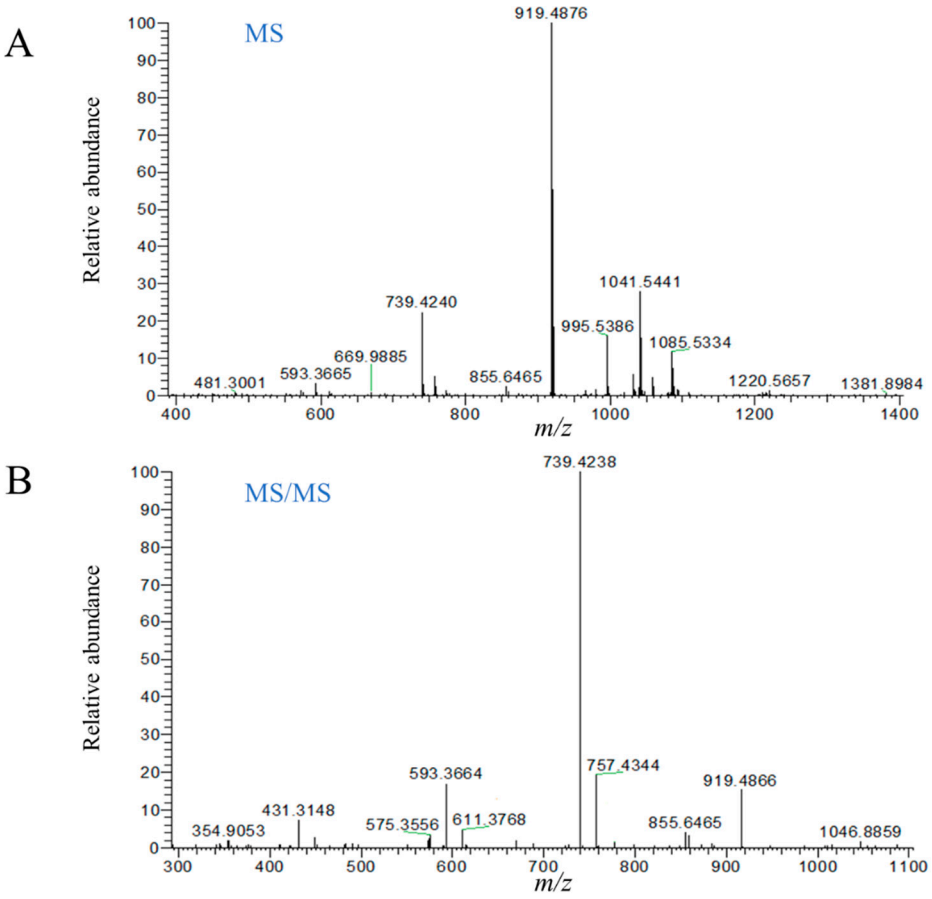


Figure S12. Mass spectrum of DP-11 & DP-12 in ESI negative mode.

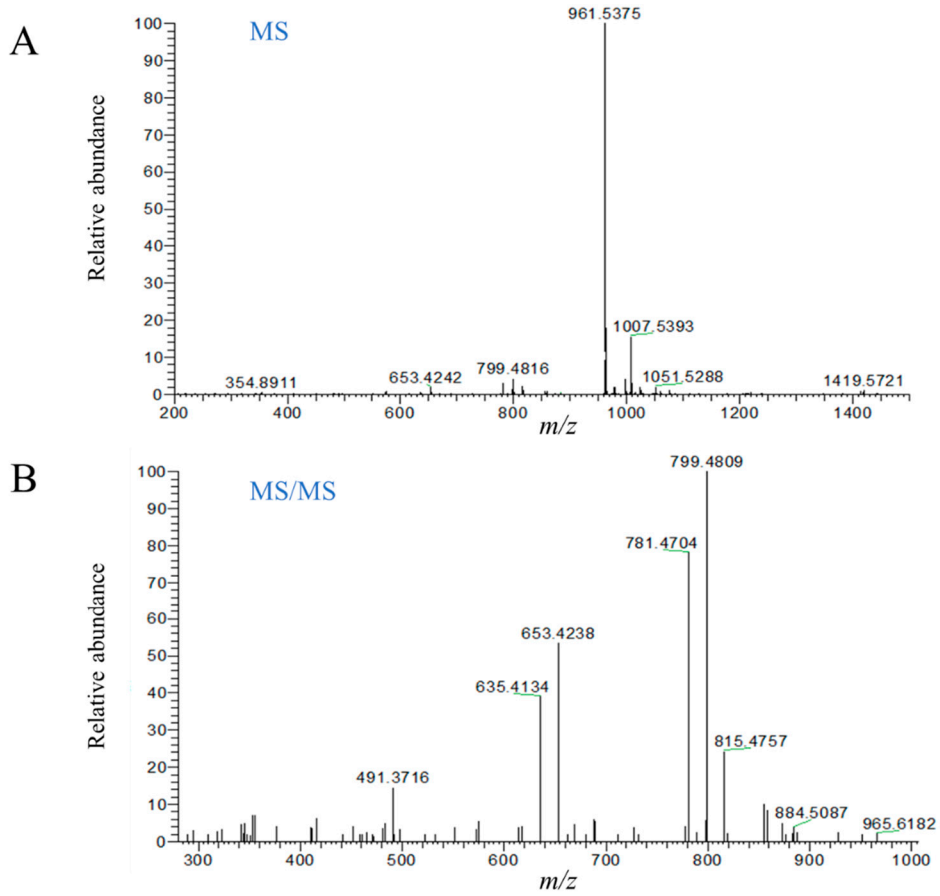


Figure S13. Mass spectrum of DP-13 in ESI negative mode.

Table S1. *In silico* toxicity predictions of Re and its DPs by Derek Nexus software.

Alert structures / Toxicity	Re and its degradation products															
	Re		**DP-1 and DP-2**		**DP-3 and DP-4**		**DP-5 and DP-6**		DP-7 and DP-8		DP-9 and DP-10		DP-11 and DP-12		DP-13	
Carcinogenicity	-	-	-	-	-	-	-	-	-	-	-	-	Carcinogenicity	Oxidising agent	-	-
Genotoxicity	-	-	-	-	-	-	-	-	-	-	-	-	Mutagenicity in vitro	Hydroperoxide	-	-
Irritation	Skin irritation/ corrosion	Terpenoid	Skin irritation/ corrosion	Terpenoid	Skin irritation/ corrosion	Terpenoid	Skin irritation/ corrosion	Terpenoid	-	-	-	-	Skin irritation/ corrosion	Hydroperoxide or peracid	-	-
													Irritation (of the eye)	Alkyl hydroperoxide		
													Irritation (of the respiratory tract)	Alkyl hydroperoxide		
Miscellaneous endpoints	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Neurotoxicity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Organ toxicity	-	-	-	-	-	-	-	-	-	-	-	-	Hepato-toxicity	Organic peroxide	-	-
Reproductive toxicity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory sensitisation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin sensitisation	-	-	-	-	-	-	-	-	-	-	-	-	Skin sensitization HPC	HPC08_1: Class 8: Organic peroxides	-	-

Table S2. *In silico* prediction of drug metabolism properties for Re and its DPs by Meteor Nexus software.

Re and its DPs	Biotransformation Name	Phase	Enzyme
Re	Allylic hydroxylation	I	CYP450 [a]
DP-1 and DP-2	Allylic hydroxylation	I	CYP450
	Epoxidation of 1,1,2-trisubstituted alkenes	I	CYP450
DP-3 and DP-4	Allylic hydroxylation	I	CYP450
	Epoxidation of 1,1,2-trisubstituted alkenes	I	CYP450
	Oxidative *O*-demethylation	I	CYP450
DP-5 and DP-6	Allylic hydroxylation	I	CYP450
	Epoxidation of 1,1,2-trisubstituted alkenes	I	CYP450
	Hydroxylation of methyl carbon adjacent to an aliphatic ring	I	CYP450
DP-7 and DP-8	Hydroxylation of terminal methyl	I	CYP450
	Hydroxylation of methyl carbon adjacent to an aliphatic ring	I	CYP450
	Glucuronidation of primary and secondary aliphatic and benzylic alcohols	II	UGT [b]
DP-9 and DP-10	Hydroxylation of methyl carbon adjacent to an aliphatic ring	I	CYP450
	Glucuronidation of primary and secondary aliphatic and benzylic alcohols	II	UGT
DP-11 and DP-12	Hydroxylation of methyl carbon adjacent to an aliphatic ring	I	CYP450
	Glucuronidation of primary and secondary aliphatic and benzylic alcohols	II	UGT
DP-13	Vicinal diols from epoxides	I	EH [c]

Note: [a] CYP 450, cytochrome P450 enzyme system; [b] UGT, uridine diphosphate glucuronate transferase; [c] EH, epoxide hydrolases.