Experimental supporting information

Rhein peptide synthesis: The peptide derivatives were synthesized by solid phase peptide synthesis (SPPS) using 2-chlorotrityl chloride resin, the corresponding N-Fmoc protected amino acids with side chains properly protected by different group. The first amino acid (Fmoc-Asp(OtBu)-OH or Fmoc-Glu(OtBu)-OH) were loaded on the resin at the C-terminal with the loading efficiency about 1.0 mmol/g. Anhydrous N,N'-dimethyl formamide (DMF) containing 20% piperidine was used to remove Fmoc protected group. To couple the next amino acid to the free amino group, O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) was used as coupling reagent. The growth of the peptide chain was according to the established Fmoc SPPS protocol. At the final step, Rhein was used to couple with the peptide. After the last coupling step, excessive reagents were removed by a single DMF wash for 5 times (about 5 ml per gram of resin), followed by five steps of washing using DCM for 5 times (about 5 ml per gram of resin). The peptide derivative was cleaved using 95% of trifluoroacetic acid with 2.5% of TIS and 2.5% of H2O for 30 minutes. Twenty mL per gram of resin of ice-cold diethylether was then added to cleavage reagent. The resulting precipitate was centrifuged for 10 min at 4 °C at 10 000 rpm. Afterward the supernatant was decanted, and the resulting solid was dissolved in DMSO for HPLC separation using CH_3OH and H_2O containing 0.1% of TFA as eluents.

Characterization of Rh-GFFYERGD: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 – 8.14 (m, 2H), 8.13 – 8.05 (m, 2H), 7.92 – 7.82 (m, 1H), 7.77 (d, J = 6.4 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 34.4 Hz, 9H), 7.04 (d, J = 8.2 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 4.46 (dd, J = 15.1, 5.7 Hz, 3H), 4.30 (d, J = 13.9 Hz, 2H), 3.94 (s, 1H), 3.91 – 3.77 (m, 4H), 3.11 (dd, J = 34.2, 6.1 Hz, 4H), 2.95 (dd, J = 22.9, 9.7 Hz, 3H), 2.85 – 2.65 (m, 3H), 2.55 (s, 2H), 2.29 – 2.24 (m, 1H), 1.99 – 1.89 (m, 1H), 1.79 (d, J = 6.9 Hz, 1H), 1.54 (s, 2H), 1.25 (d, J = 9.0 Hz, 1H). HR-MS: calcd. M^+ = 1255.4458, obsvd.

$(M+H)^+$ = 1256.4531.

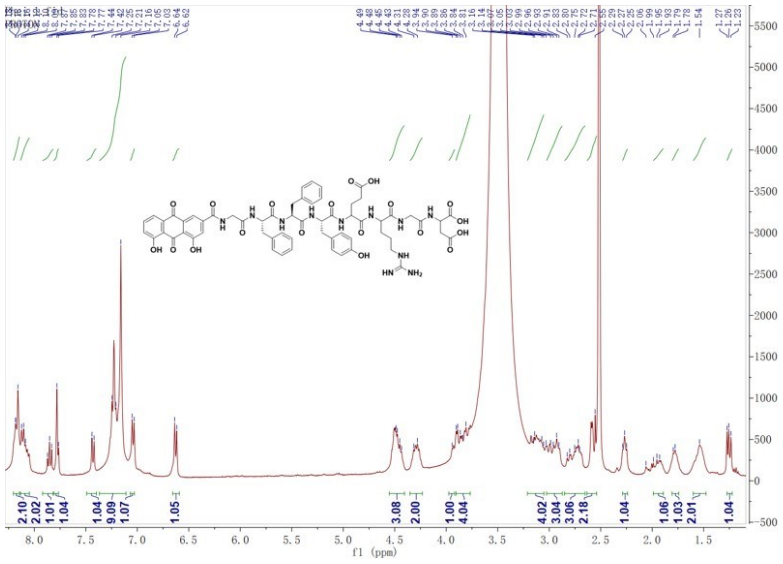

Figure S1. ^{1}H NMR spectrum of Rh-GFFYERGD

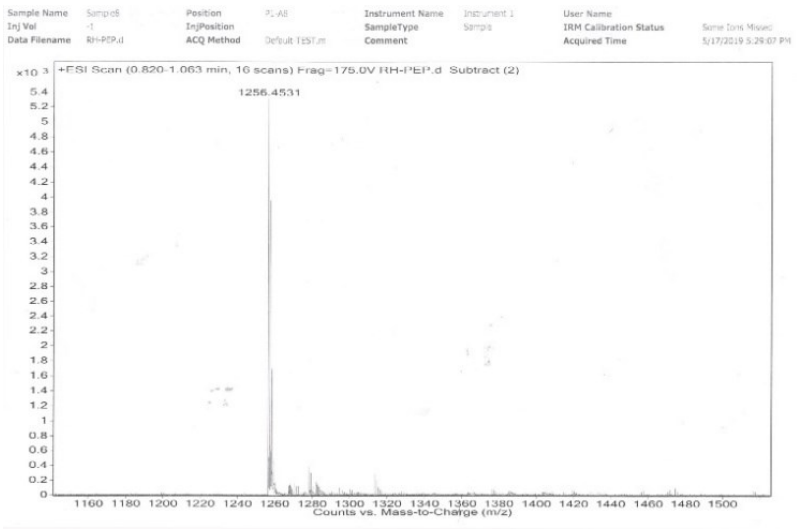

Figure S2. HR-MS spectrum of Rh-GFFYERGD

Characterization of Rh-GFFYERGE: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 – 8.14 (m, 2H), 8.13 – 8.02 (m, 3H), 7.78 (s, 1H), 7.50 – 7.41 (m, 1H), 7.34 – 7.19 (m, 4H), 7.16 (d, J = 5.8 Hz, 5H), 7.03 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 8.4 Hz, 1H), 4.50 (dt, J = 8.5, 4.4 Hz, 2H), 4.33 – 4.21 (m, 2H), 3.96 – 3.76 (m, 2H), 3.75 – 3.45 (m, 4H), 3.21 (d, J = 15.5 Hz, 2H), 3.15 – 3.02 (m, 2H), 2.99 – 2.83 (m, 2H), 2.80 – 2.65 (m, 2H), 2.55 (s, 2H), 2.27 (t, J = 7.1 Hz, 3H), 2.06 – 1.88 (m, 1H), 1.85 – 1.62 (m, 2H), 1.61 –

1.39 (m, 2H). HR-MS: calcd. M^+ = 1269.4615, obsvd. $(M+H)^+$ = 1270.4670.

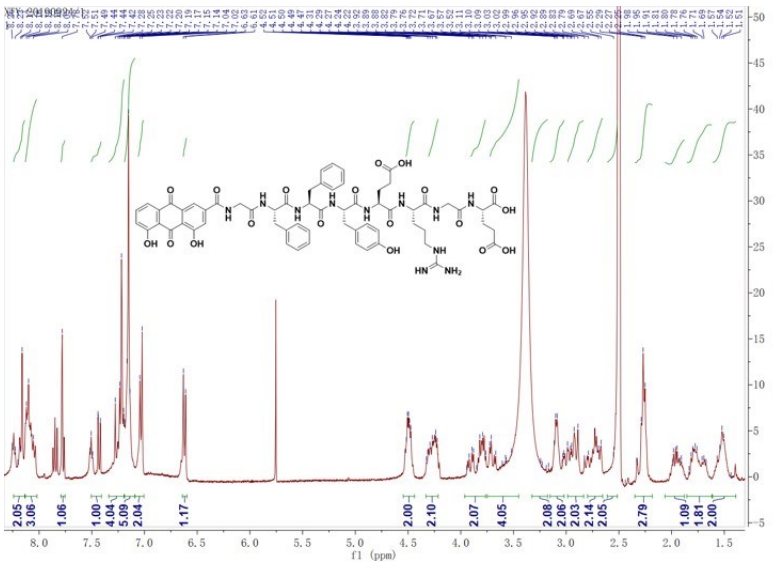

Figure S3. ^{1}H NMR spectrum of Rh-GFFYERGE

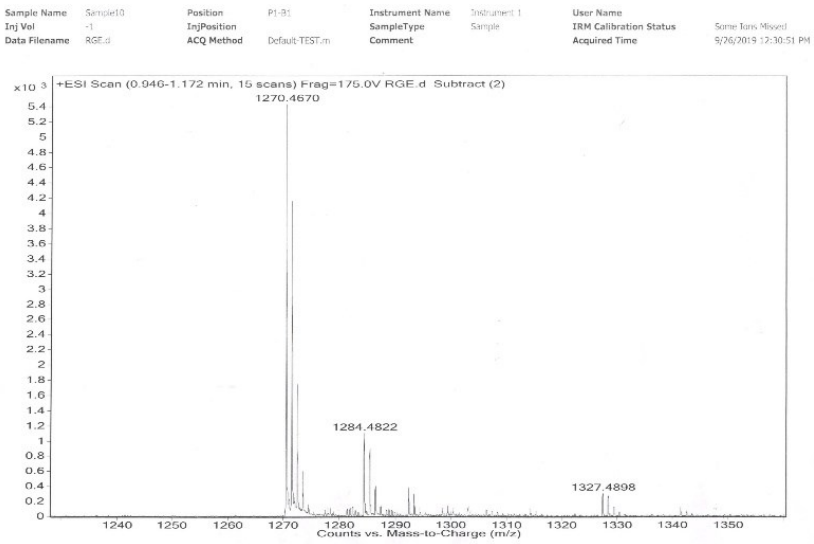

Figure S4. HR-MS spectrum of Rh-GFFYERGE

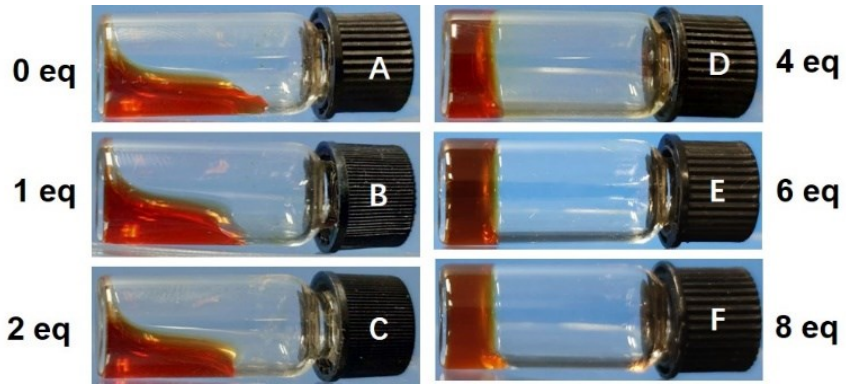

Figure S5. Optical images of gels formed by treating the solution containing 0.4 wt.% of Rh-pep (3.2 mM) with different equiv. of cisplatinum: (A) 0, (B) 1, (C) 2, (D) 4, (E) 6 and (F) 8 equiv. to Rh-pep.

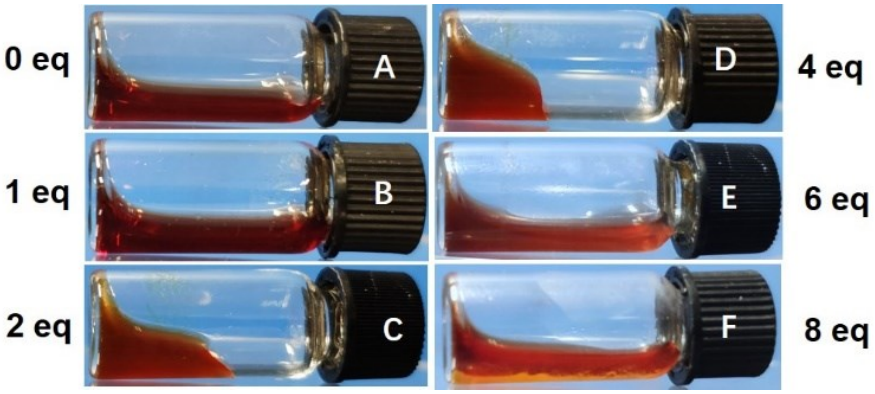

Figure S6. Optical images of gels formed by treating the solution containing 3.2 mM of Rh-GFFYERGE with different equiv. of cisplatinum: (A) 0, (B) 1, (C) 2, (D) 4, (E) 6 and (F) 8 equiv. to Rh-GFFYERGE

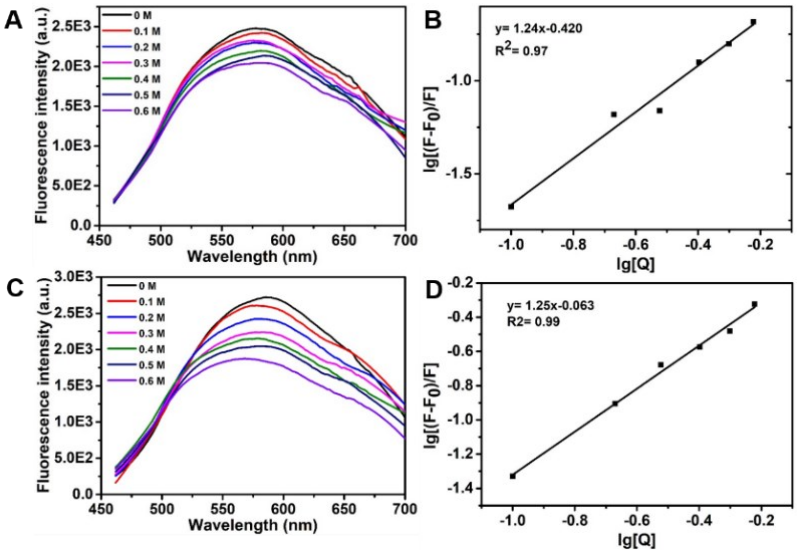

Figure S7. (A)Emission spectra of Rh-pep in the presence of various concentrations of cisplatinum. (B) Plot of lg[(F_0-F) /F] against lg[Q] of Rh-pep quenched by cisplatin. (C) Emission spectra of Rh-GFFYERGE in the presence of various concentrations of cisplatinum. (D) Plot of lg[(F_0-F) /F] against lg[Q] of Rh-GFFYERGE quenched by cisplatinum.

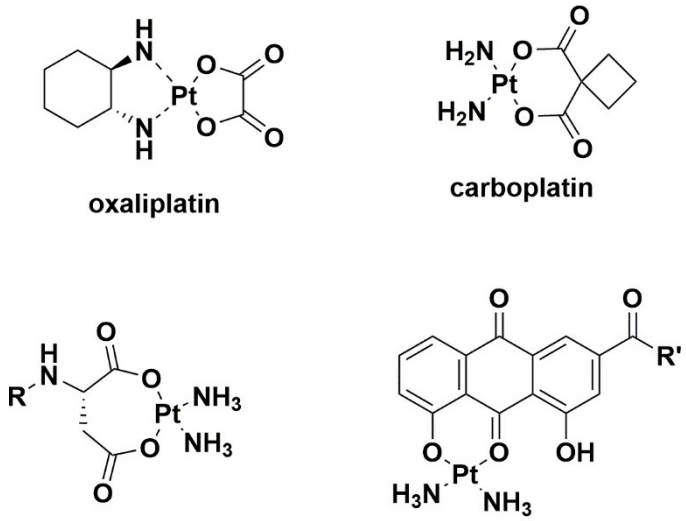

Figure S8. Chemical structures of oxaliplatin and carboplatin and possible chelation modes between Rh-pep and cisplatinum

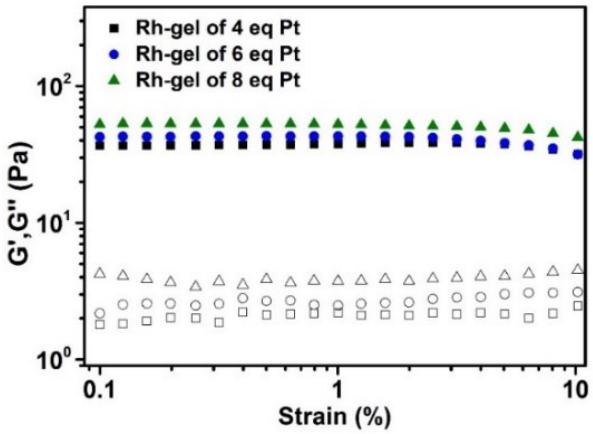

Figure S9. Dynamic strain sweep at the frequency of 1 rad/s of gels containing 0.4 wt.% of the Rh-pep and different amounts of cisplatinum (filled symbols: G' and open symbols: G'').

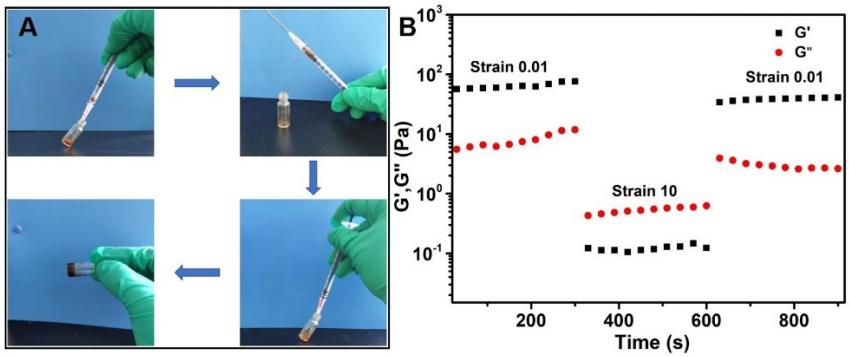

Figure S10. (A) Injectability property of Rh-gel. (B) Step-strain rheological experiments of Rh-gel

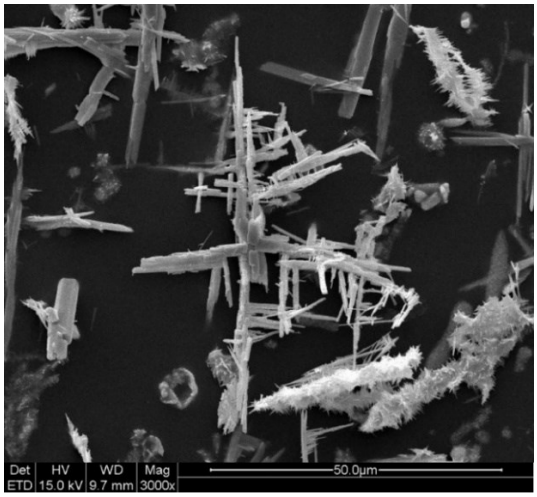

Figure S11. Scanning electron microscopy (SEM) images of the solution of cisplatinum (0.1 wt.%)

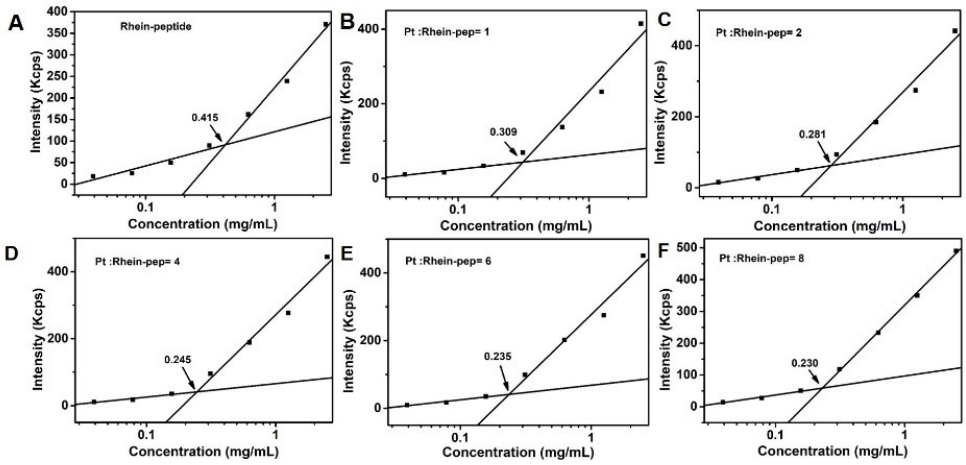

Figure S12. Critical aggregation concentration (CAC) value of A) Rh-pep and Rh-gels with different concentrations of cisplatinum: (B) 1 equiv., (C) 2 equiv., (D) 4 equiv., (E) 6 equiv., (F) 8 equiv. to Rh-pep

Sample	Added Pt gross (mg/mL)	Pt in supernatant (mg/mL)	Loading Pt calculated (mg/mL)	Drug encapsulation efficiency (≈%)
Rhpep+1 eq cisplatin	0.99	0.098	0.892	90.1
Rhpep+2 eq cisplatin	1.98	0.208	1.772	89.49
Rhpep+4 eq cisplatin	3.96	0.413	3.547	89.57
Rhpep+6eq cisplatin	5.94	0.628	5.312	89.42
Rhpep+7eq cisplatin	6.93	0.759	6.171	89.04
Rhpep+8eq cisplatin	7.92	1.41	6.51	82.2
Rhpep+10eq cisplatin	9.90	2.96	6.94	70.1

Table S1. Encapsulation efficiency of cisplatinum in Rh-gels with different equiv. cisplatinum

Accumulative Pt released (%)

Time (h)	Rh-gel of 4 eq Pt	Rh-gel of 6 eq Pt	Rh-gel of 8 eq Pt
2	4.98	3.61	3.17
4	10.73	10.69	7.85
6	16.34	16.09	13.34
8	23.08	21.39	16.52
10	29.93	26.58	19.33
16	34.91	31.15	23.87

Table S2. The accumulative amount of cisplatin released from Rh-gels at different time points

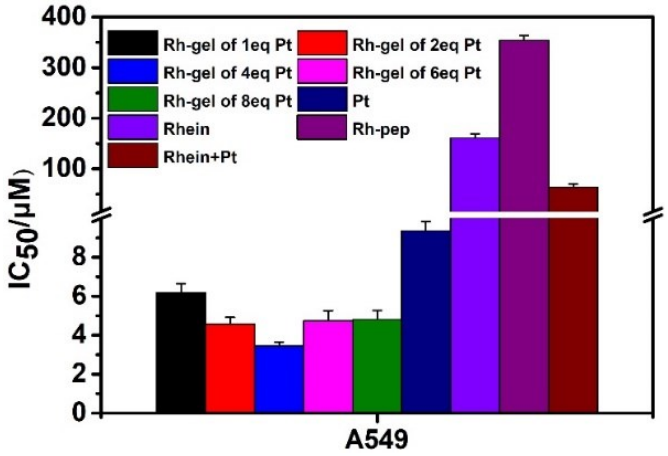

Figure S13. The IC_{50} values of Rh-gels with different amounts of Pt, Pt, Rhein, Rh-pep and Rhein+Pt against A549 cells (mean ±SEM, n = 3).

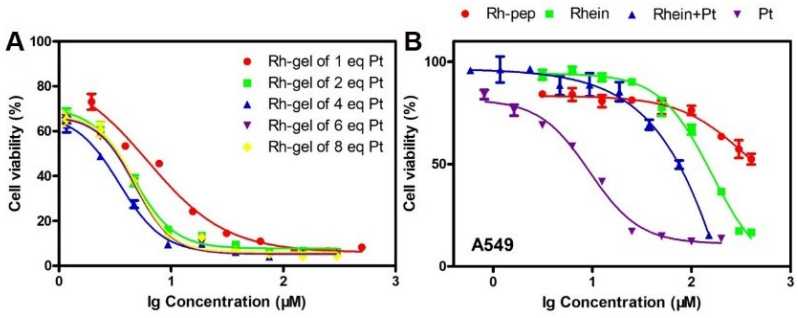

Figure S14. IC_{50} profiles of of A) Rh-gels with different amounts of cisplatinum, B) Pt, Rhein, Rh-pep and Rhein+Pt against A549 cells. each result was obtained by average nine separate cell viability experiments. (mean ±SEM, n = 3).

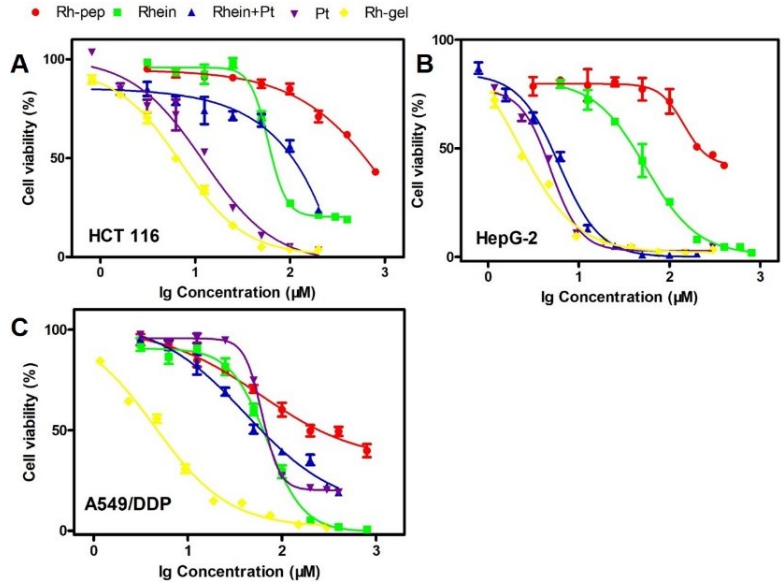

Figure S15. IC_{50} profiles of different drugs against (A) HCT116, (B) HepG-2, (C) A549/DDP cancer cells. each result was obtained by average nine separate cell viability experiments. (mean ±SEM, n = 3).

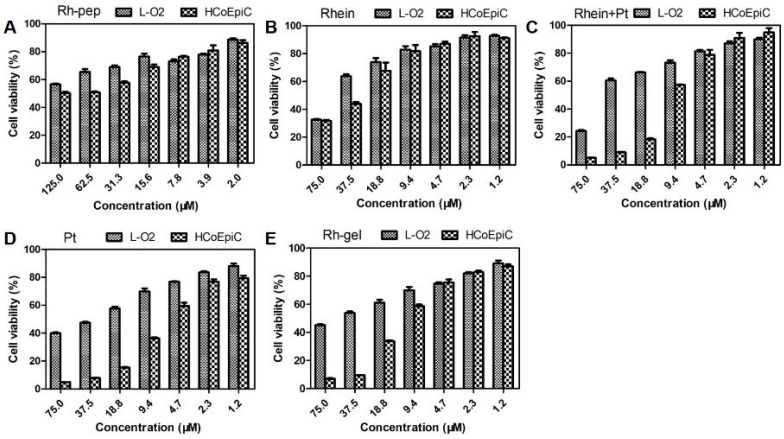

Figure S16. MTT assay study of L-O2 cells and HCoEpiC cells after treatment with (A) Rh-pep, (B) Rhein, (C) Rhein+Pt, (D) Pt, (E) Rh-gel. (mean ±SEM, n = 3).

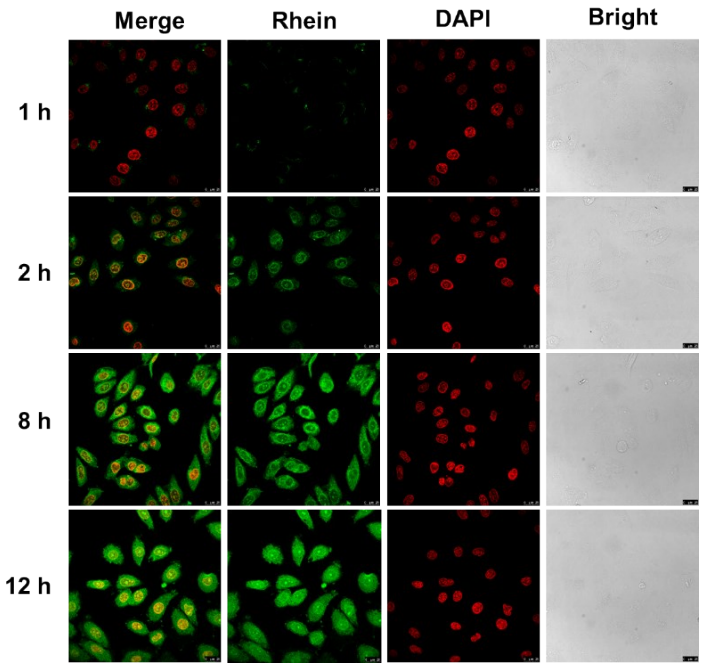

Figure S17. Confocal fluorescence microscopy images of A549 cells treated with Rh-gel at 1, 2, 8 and 12 h time point containing 200 μM Rh-pep, Scale bar: 25 μm.(Rhein excitation wavelength = 488 nm for green channel, DAPI excitation wavelength = 405 nm for red channel).

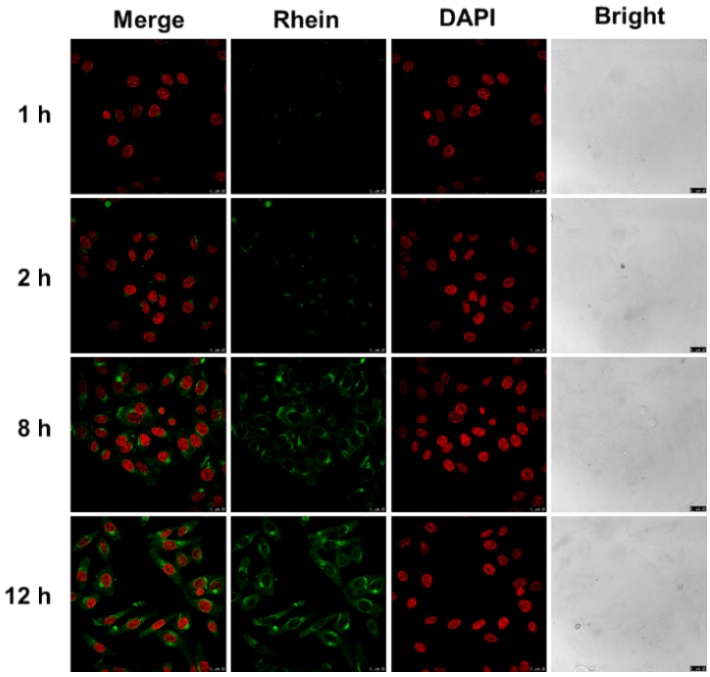

Figure S18. Confocal fluorescence microscopy images of A549 cells treated with Rh-pep (200 μM) at 1, 2, 8 and 12 h time point, Scale bar: 25μm.

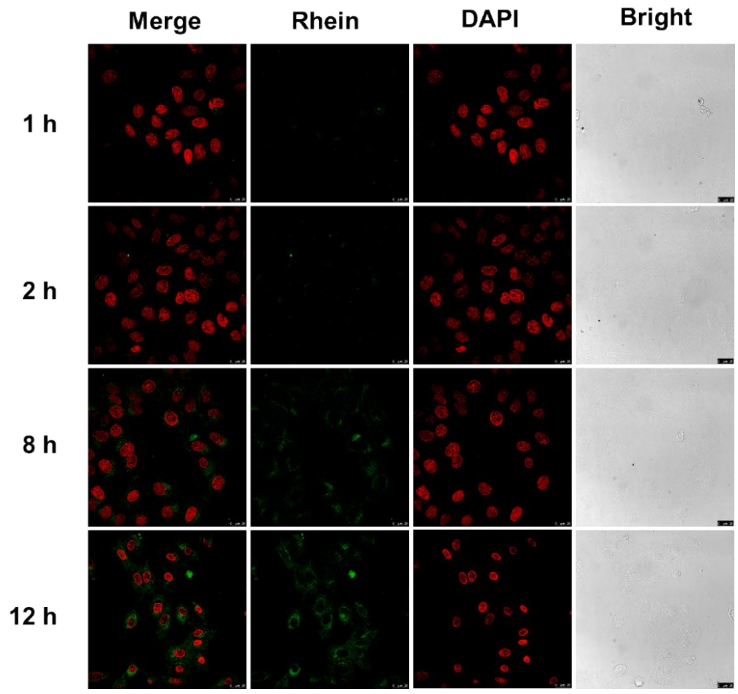

Figure S19. Confocal fluorescence microscopy images of A549 cells treated with Rhein/Pt at 1, 2, 8 and 12 h time point containing 200 μM Rhein, Scale bar: 25μm.

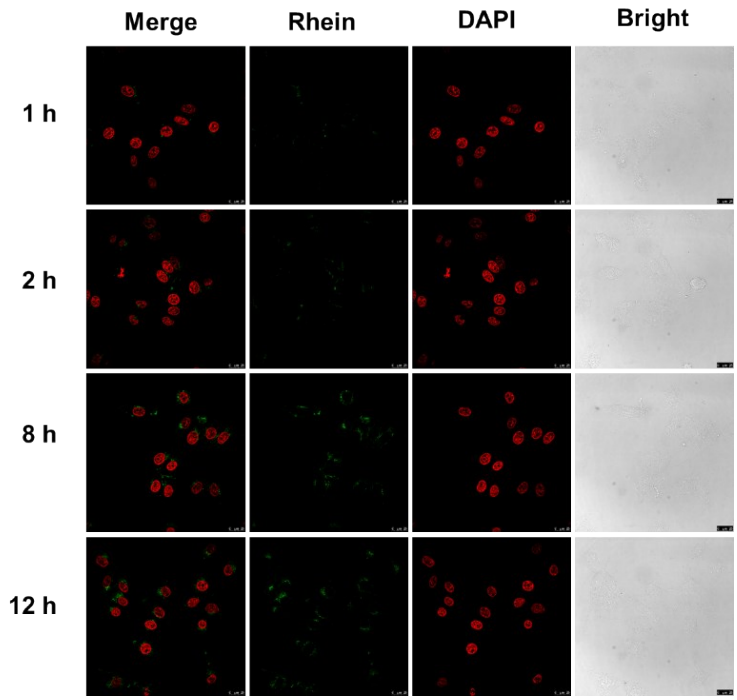

Figure S20. Confocal fluorescence microscopy images of A549 cells treated with Rhein (200 μM) at 1, 2, 8 and 12 h time point, Scale bar: 25μm.

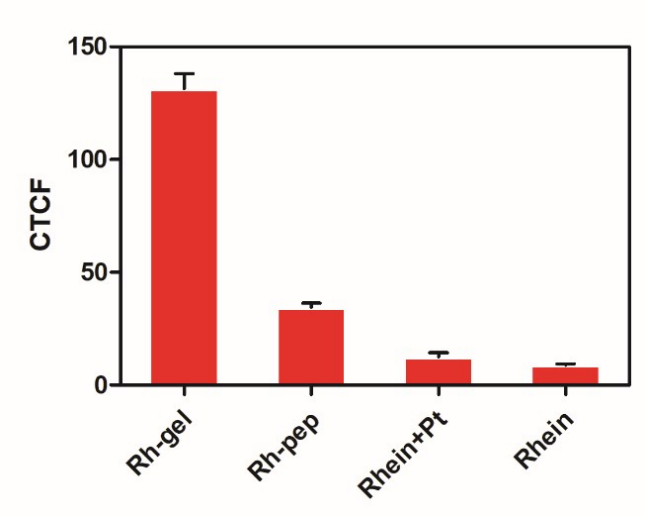

Figure S21. Corrected total cell fluorescence of A549 cells treated with 200 μM of Rh-gel, Rh-pep, Rhein+Pt and Rhein at 8 h time point. (SEM ± mean, n = 3).

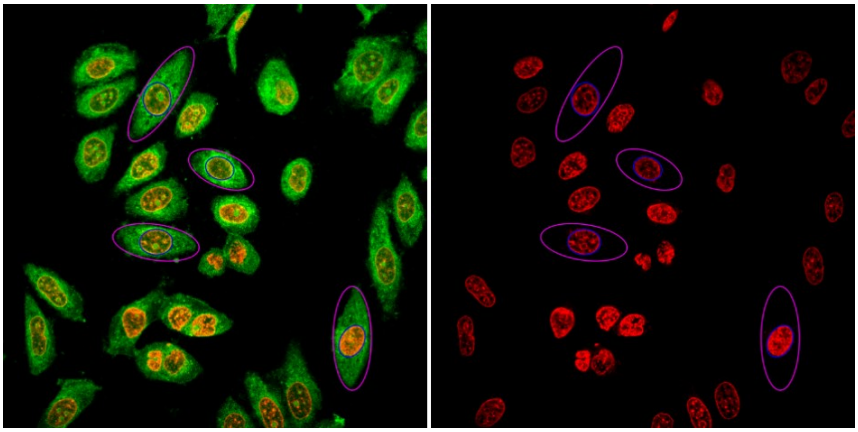

Figure S22. The nuclear import efficiency was calculated by the ratio of the statistical fluorescence intensity in the blue circle to the statistical fluorescence intensity in the pink circle

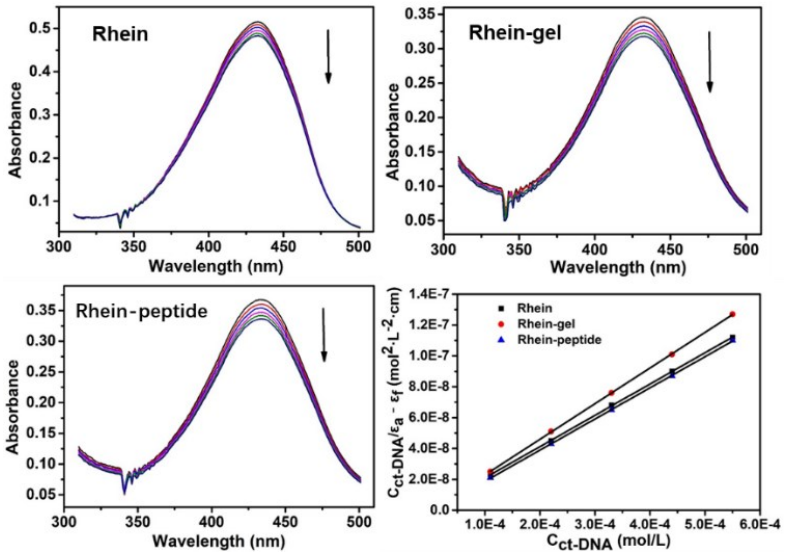

Figure S23. (A) UV spectra of interaction between Rhein with ct-DNA. (B) UV spectra of interaction between Rh-gel with ct-DNA. (C) UV spectra of interaction between Rh-pep with ct-DNA. (D) Plot of $C_{ct\text{-}DNA}$ /(ε_a-ε_f) against $C_{ct\text{-}DNA}$ of three compounds.

Group	Drug	Dose (mg/kg)
Saline	Saline	0.9%
Pt	Cisplatin	1.5 mg/kg
Rhein	Rhein	1.13 mg/kg
Rh-pep	Rh-GFFYERGD	5 mg/kg (content of rhein equal to Rhein group)
Rh-gel	Rh-GFFYERGD/Pt	1.81 mg/kg (content of cisplatin equal to Pt group)

Table S3. Drug formulations and doses for evaluation of tumor inhibition.

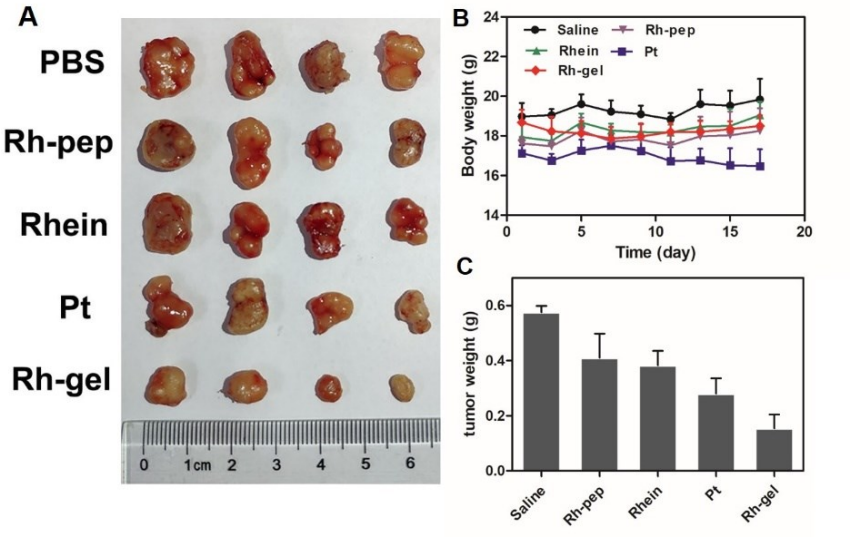

Figure S24. (A) Optical images of tumors after the last treatment, (B) body weight of mice of different groups, (C) weight of tumors after the last treatment (SEM ± mean, n = 4).

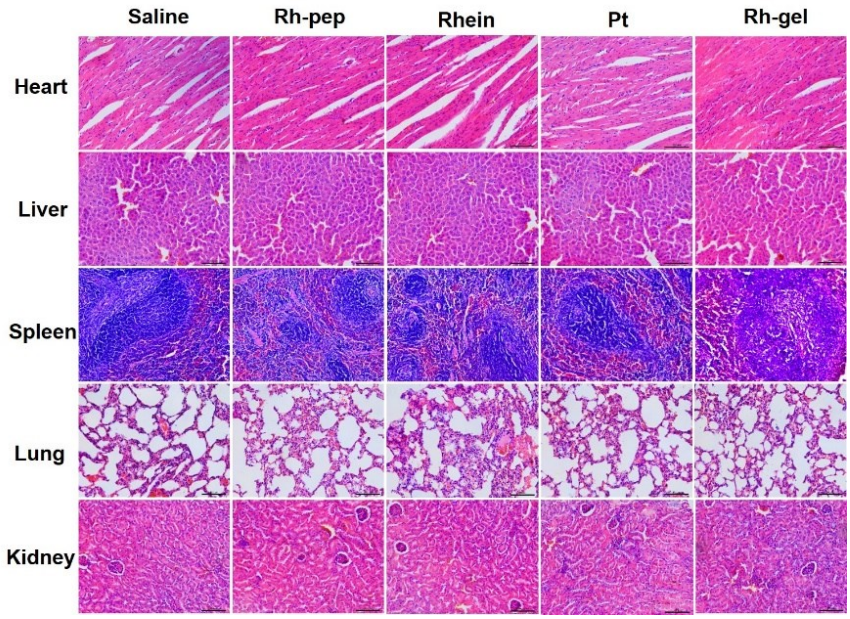

Figure S25. H&E staining of the main organs tissues in different groups. Scale bar: 200 μm.

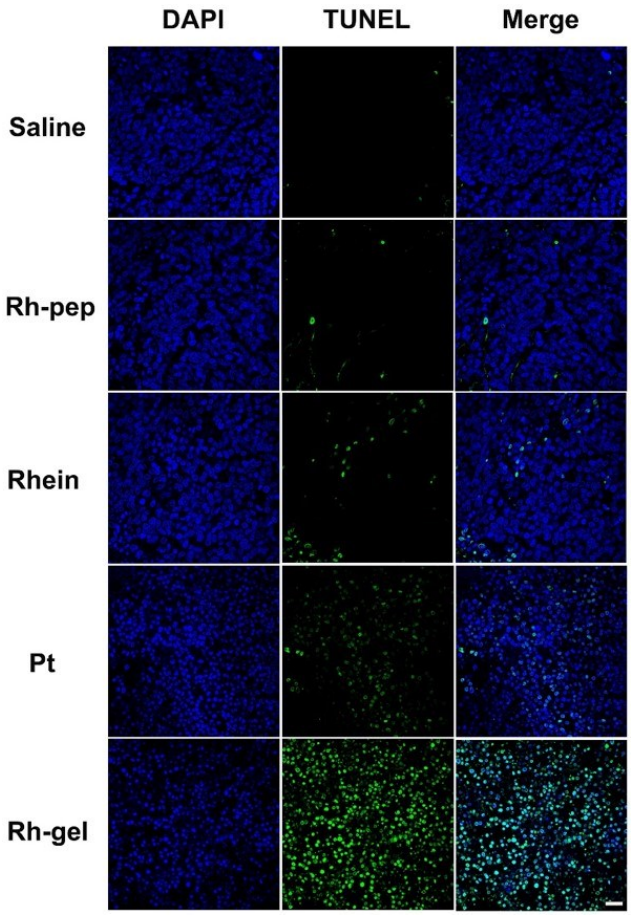

Figure S26. The tunel staining of tumor tissues in different groups, Scale bar: 25μm.