Supplementary materials

1 Patients' inclusion and exclusion criteria

Serum ALT in 6 out of 81 patients showed an obvious increase, and was set as the susceptible group (ALT > 2 ULN, ULN means the upper limit of normal). In order to eliminate the interference of other factors, but also limited by the volume of serum before PM ingestion, among the remaining patients, 15 patients whose serum ALT was within the normal range after consuming PM were matched with the conditions of similar age, dosage, medication time and no underlying disease.

Table S1. The clinical characteristics of excluded other patients

Patient's description	Number of patients
Patients older than 40 years old or younger than 25 years old	4
Patients with underlying diseases	6
Patients with ALT levels more than 1 ULN but less than 2 ULN	4
Patients with insufficient serum samples.	37
Patients lost to follow-up	9

2 TNF-α dosage screening

As shown in Figure S1, compared with normal control group (N), there were no significant changes in plasma aminotransferases ($P > 0.05$) in T10 group with a TNF-α dose of 10 ng/g and T20 group with a TNF-α dose of 20 ng/g; In the T40 group with a TNF-α dose of 40 ng/g, the plasma ALT and AST activities were obviously increased ($P < 0.05$ or $P < 0.01$). The results indicated that TNF-α alone could cause liver damage in mice when administered in large doses. Compared with the N group, there were no obvious differences in plasma transaminase level in the PM group that was given the extract of PM (6.24 g/kg) alone ($P > 0.05$). The results showed that the administration of PM extract at this dose did not cause liver damage in mice. However, no matter compared with the N group, PM group or T group, the

plasma transaminase levels in PM combined with different doses of TNF-α administration groups were markedly increased in a dose-dependent relationship ($P < 0.05$ or $P < 0.01$).

Taken together, these results indicated that high-dose TNF-α (40 ng/g) itself could induce liver damage in mice; while low-dose TNF-α (10 ng/g or 20 ng/g) contributed to increase the susceptibility of PM-DILI. Considering the magnitude of the increase in transaminase levels, the final dose of TNF-α was selected as 20 ng/g.

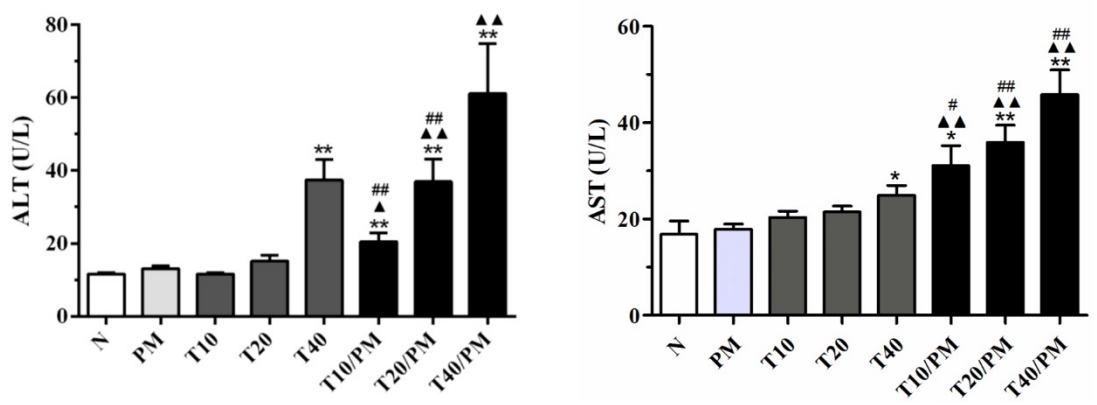

Figure S1 Effects of different doses of TNF-α alone or in combination with PM on plasma transaminase ALT and AST activities in mice (n = 8, per group). $^{*}P < 0.05$, $^{**}P < 0.01$ vs N group; $^{▲}P < 0.05$, $^{▲▲}P < 0.01$ vs PM group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs T group.

3 The expression levels of 33 serum cytokines in the two groups

Table S2 Cytokine profile with statistical significance between the two groups

Cytokine	Tolerant group	Susceptible group	Fold change	P value
TNF-α	0.88 ± 1.45	3.65 ± 2.65	4.16	0.006
EGF	11.90 ± 8.09	42.71 ± 53.73	3.59	0.037
CXCL1	5.81 ± 8.66	16.04 ± 12.59	2.76	0.045
G-CSF	2.61 ± 8.29	14.08 ± 25.56	5.39	0.128
IL-10	0.86 ± 0.11	0.94 ± 0.09	1.09	0.135
IL-2	2.60 ± 3.64	5.10 ± 5.46	1.96	0.232
CCL3	2.81 ± 3.34	1.11 ± 1.56	0.39	0.250
IL-17A	0.60 ± 0.54	0.83 ± 0.28	1.38	0.355
IL-21	49.96 ± 115.49	12.62 ± 8.66	0.25	0.446

IL-4	3.60 ± 3.28	4.66 ± 2.06	1.29	0.476
IL-1β	1.38 ± 0.96	1.78 ± 1.64	1.30	0.481
IL-1α	20.01 ± 59.31	3.70 ± 1.37	0.18	0.515
CXCL10	13.24 ± 11.86	17.94 ± 20.64	1.36	0.516
CX3CL1	15.38 ± 29.96	7.70 ± 3.51	0.50	0.545
GM-CSF	9.29 ± 5.66	10.56 ± 3.67	1.14	0.622
CXCL8	6.33 ± 7.52	8.09 ± 6.98	1.28	0.628
IL-13	1.72 ± 1.02	1.93 ± 0.83	1.12	0.633
IL-22	49.03 ± 82.10	65.98 ± 38.12	1.35	0.637
IL-6	0.60 ± 1.41	0.94 ± 1.53	1.55	0.640
IL-7	0.54 ± 0.32	0.62 ± 0.41	1.14	0.664
IFN-γ	4.85 ± 3.58	5.49 ± 2.52	1.13	0.692
CCL2	9.05 ± 5.74	10.03 ± 3.06	1.11	0.698
IL-3	189.75 ± 390.69	41.00 ± 15.80	0.22	0.730
IL-16	524.66 ± 598.52	455.90 ± 537.72	0.87	0.810
IL-27	18.74 ± 16.16	17.29 ± 17.39	0.92	0.858
IL-18	5.22 ± 3.95	5.53 ± 2.56	1.06	0.862
IL-12p70	2.37 ± 0.18	2.38 ± 0.10	1.01	0.866
IL-37	4.64 ± 3.36	4.88 ± 2.83	1.05	0.881
CCL11	35.77 ± 24.35	37.08 ± 18.86	1.04	0.908
IL-5	1.60 ± 0.85	1.65 ± 0.75	1.03	0.914
IL-9	16.60 ± 9.59	16.89 ± 10.26	1.02	0.951
IL-23	12.20 ± 10.18	11.93 ± 5.58	0.98	0.952
VEGF-A	537.19 ± 1315.52	526.83 ± 194.92	0.98	0.985

Data are presented as mean ± SD.

4 Correlation between cytokines and liver injury markers

Table S3 Correlations between liver injury markers and cytokines.

Injury markers	Cytokines	r	P-value

ALT	TNF-α	0.61	0.003
	EGF	0.49	0.023
	GRO-α	0.46	0.037
	G-CSF	0.45	0.042
AST	TNF-α	0.55	0.011
	EGF	0.46	0.035
TBIL	IL-23	0.47	0.031