

Material S1: Details of animal experimentation

Male Sprague Dawley rats (150-200 g) were purchased from the Small Animal Breeding Station, Agricultural University, Mannuthy, Kerala and were maintained under standardized environmental conditions (22-28°C, 60-70% relative humidity, 12 hr dark/light cycle) and fed with standard rat feed (Lipton India) and water ad libitum. All animal experiments were conducted during the present study got prior permission from Institutional Animal Ethics Committee (IAEC approved) and followed the guidelines of IAEC.

Groups I (normal) and II (control) received no pre-treatment. Group III (standard) received a 15 day long pre-treatment using the standard drug, silymarin at a dosage of 100 mg/kg body weight, orally. Groups IV (AML) and V (AMH) were orally administered with an aqueous suspension of *Annona muricata* fruit pulp at dosages of 1 and 2 g/kg body weight, respectively for 14 days, prior to the induction of hepatotoxicity. The administration volume was adjusted to 2 ml for the above groups. On the 15th day of the study, all groups, except normal were orally induced with paracetamol at a dosage of 2.5 g/kg body weight so as to induce liver damage. After 24 h of hepatotoxicity induction which included a 10 h terminal starvation period, all the animals were sacrificed; and blood and liver tissues were collected for various experiments.

Table S1. Statistical comparison details of table 3

	Mean Difference	95.00% CI of difference	Adjusted P Value
Aspartate transaminase			
Normal vs. APAP	-36.91	-43.13 to -30.69	<0.0001
Normal vs. APAP+ Silymarin	-5.68	-11.9 to 0.5435	0.0916
Normal vs. APAP+ AML	-10.68	-16.9 to -4.456	<0.0001
Normal vs. APAP+ AMH	-13.92	-20.14 to -7.696	<0.0001
APAP vs. APAP+ Silymarin	31.23	25.01 to 37.45	<0.0001
APAP vs. APAP+ AML	26.23	20.01 to 32.45	<0.0001
APAP vs. APAP+ AMH	22.99	16.77 to 29.21	<0.0001
APAP+ Silymarin vs. APAP+ AML	-5	-11.22 to 1.224	0.1786
APAP+ Silymarin vs. APAP+ AMH	-8.24	-14.46 to -2.016	0.0032
APAP+ AML vs. APAP+ AMH	-3.24	-9.464 to 2.984	0.6045
Alanine transaminase			
Normal vs. APAP	-46.08	-52.3 to -39.86	<0.0001
Normal vs. APAP+ Silymarin	-23.68	-29.9 to -17.46	<0.0001
Normal vs. APAP+ AML	-12.82	-19.04 to -6.596	<0.0001
Normal vs. APAP+ AMH	-5.8	-12.02 to 0.4235	0.0806
APAP vs. APAP+ Silymarin	22.4	16.18 to 28.62	<0.0001
APAP vs. APAP+ AML	33.26	27.04 to 39.48	<0.0001
APAP vs. APAP+ AMH	40.28	34.06 to 46.5	<0.0001
APAP+ Silymarin vs. APAP+ AML	10.86	4.636 to 17.08	<0.0001
APAP+ Silymarin vs. APAP+ AMH	17.88	11.66 to 24.1	<0.0001
APAP+ AML vs. APAP+ AMH	7.02	0.7965 to 13.24	0.0185
Alkaline phosphatase			
Normal vs. APAP	-23.22	-29.44 to -17	<0.0001
Normal vs. APAP+ Silymarin	-4.32	-10.54 to 1.904	0.3130
Normal vs. APAP+ AML	-15.23	-21.45 to -9.006	<0.0001
Normal vs. APAP+ AMH	-10.08	-16.3 to -3.856	0.0001
APAP vs. APAP+ Silymarin	18.9	12.68 to 25.12	<0.0001
APAP vs. APAP+ AML	7.99	1.766 to 14.21	0.0047
APAP vs. APAP+ AMH	13.14	6.916 to 19.36	<0.0001
APAP+ Silymarin vs. APAP+ AML	-10.91	-17.13 to -4.686	<0.0001
APAP+ Silymarin vs. APAP+ AMH	-5.76	-11.98 to 0.4635	0.0841
APAP+ AML vs. APAP+ AMH	5.15	-1.074 to 11.37	0.1555
Total Protein			
Normal vs. APAP	1.24	-4.984 to 7.464	0.9818
Normal vs. APAP+ Silymarin	0.1	-6.124 to 6.324	>0.9999
Normal vs. APAP+ AML	0.36	-5.864 to 6.584	0.9999
Normal vs. APAP+ AMH	1.6	-4.624 to 7.824	0.9540
APAP vs. APAP+ Silymarin	-1.14	-7.364 to 5.084	0.9867
APAP vs. APAP+ AML	-0.88	-7.104 to 5.344	0.9950
APAP vs. APAP+ AMH	0.36	-5.864 to 6.584	0.9999
APAP+ Silymarin vs. APAP+ AML	0.26	-5.964 to 6.484	>0.9999
APAP+ Silymarin vs. APAP+ AMH	1.5	-4.724 to 7.724	0.9634

APAP+ AML vs. APAP+ AMH	1.24	-4.984 to 7.464	0.9818
Total bilirubin			
Normal vs. APAP	-1.05	-7.274 to 5.174	0.9902
Normal vs. APAP+ Silymarin	-0.39	-6.614 to 5.834	0.9998
Normal vs. APAP+ AML	-0.48	-6.704 to 5.744	0.9995
Normal vs. APAP+ AMH	-0.42	-6.644 to 5.804	0.9997
APAP vs. APAP+ Silymarin	0.66	-5.564 to 6.884	0.9984
APAP vs. APAP+ AML	0.57	-5.654 to 6.794	0.9991
APAP vs. APAP+ AMH	0.63	-5.594 to 6.854	0.9986
APAP+ Silymarin vs. APAP+ AML	-0.09	-6.314 to 6.134	>0.9999
APAP+ Silymarin vs. APAP+ AMH	-0.03	-6.254 to 6.194	>0.9999
APAP+ AML vs. APAP+ AMH	0.06	-6.164 to 6.284	>0.9999
Albumin			
Normal vs. APAP	4.07	-2.154 to 10.29	0.3741
Normal vs. APAP+ Silymarin	0.05	-6.174 to 6.274	>0.9999
Normal vs. APAP+ AML	0.23	-5.994 to 6.454	>0.9999
Normal vs. APAP+ AMH	0.02	-6.204 to 6.244	>0.9999
APAP vs. APAP+ Silymarin	-4.02	-10.24 to 2.204	0.3870
APAP vs. APAP+ AML	-3.84	-10.06 to 2.384	0.4348
APAP vs. APAP+ AMH	-4.05	-10.27 to 2.174	0.3792
APAP+ Silymarin vs. APAP+ AML	0.18	-6.044 to 6.404	>0.9999
APAP+ Silymarin vs. APAP+ AMH	-0.03	-6.254 to 6.194	>0.9999
APAP+ AML vs. APAP+ AMH	-0.21	-6.434 to 6.014	>0.9999

Table S2. Statistical analysis details of Figure 1 (antioxidant parameters)

	Mean Difference	95.00% CI of difference	Adjusted P Value
GSH			
Normal vs. APAP	1.53	0.921 to 2.139	<0.0001
Normal vs. APAP+ Silymarin	0.11	-0.499 to 0.719	0.9872
Normal vs. APAP+ AML	0.23	-0.379 to 0.839	0.8337
Normal vs. APAP+ AMH	0.21	-0.399 to 0.819	0.8748
APAP vs. APAP+ Silymarin	-1.42	-2.029 to -0.811	<0.0001
APAP vs. APAP+ AML	-1.3	-1.909 to -0.691	<0.0001
APAP vs. APAP+ AMH	-1.32	-1.929 to -0.711	<0.0001
APAP+ Silymarin vs. APAP+ AML	0.12	-0.489 to 0.729	0.9823
APAP+ Silymarin vs. APAP+ AMH	0.1	-0.509 to 0.709	0.9911
APAP+ AML vs. APAP+ AMH	-0.02	-0.629 to 0.589	>0.9999
Superoxide dismutase			
Normal vs. APAP	0.11	-0.499 to 0.719	0.9872
Normal vs. APAP+ Silymarin	0.011	-0.598 to 0.62	>0.9999
Normal vs. APAP+ AML	0.041	-0.568 to 0.65	0.9997
Normal vs. APAP+ AMH	0.009	-0.6 to 0.618	>0.9999
APAP vs. APAP+ Silymarin	-0.099	-0.708 to 0.51	0.9914
APAP vs. APAP+ AML	-0.069	-0.678 to 0.54	0.9979
APAP vs. APAP+ AMH	-0.101	-0.71 to 0.508	0.9908
APAP+ Silymarin vs. APAP+ AML	0.03	-0.579 to 0.639	>0.9999
APAP+ Silymarin vs. APAP+ AMH	-0.002	-0.611 to 0.607	>0.9999
APAP+ AML vs. APAP+ AMH	-0.032	-0.641 to 0.577	0.9999
Glutathione peroxidase			
Normal vs. APAP	2.64	2.031 to 3.249	<0.0001
Normal vs. APAP+ Silymarin	0.79	0.181 to 1.399	0.0042
Normal vs. APAP+ AML	-0.07	-0.679 to 0.539	0.9978
Normal vs. APAP+ AMH	-0.38	-0.989 to 0.229	0.4213
APAP vs. APAP+ Silymarin	-1.85	-2.459 to -1.241	<0.0001
APAP vs. APAP+ AML	-2.71	-3.319 to -2.101	<0.0001
APAP vs. APAP+ AMH	-3.02	-3.629 to -2.411	<0.0001
APAP+ Silymarin vs. APAP+ AML	-0.86	-1.469 to -0.251	0.0014
APAP+ Silymarin vs. APAP+ AMH	-1.17	-1.779 to -0.561	<0.0001
APAP+ AML vs. APAP+ AMH	-0.31	-0.919 to 0.299	0.6231
Catalase			
Normal vs. APAP	4.41	3.801 to 5.019	<0.0001
Normal vs. APAP+ Silymarin	1.03	0.421 to 1.639	<0.0001
Normal vs. APAP+ AML	3.46	2.851 to 4.069	<0.0001
Normal vs. APAP+ AMH	1.47	0.861 to 2.079	<0.0001
APAP vs. APAP+ Silymarin	-3.38	-3.989 to -2.771	<0.0001
APAP vs. APAP+ AML	-0.95	-1.559 to -0.341	0.0003
APAP vs. APAP+ AMH	-2.94	-3.549 to -2.331	<0.0001
APAP+ Silymarin vs. APAP+ AML	2.43	1.821 to 3.039	<0.0001
APAP+ Silymarin vs. APAP+ AMH	0.44	-0.169 to 1.049	0.2722

APAP+ AML vs. APAP+ AMH	-1.99	-2.599 to -1.381	<0.0001
MDA			
Normal vs. APAP	-0.347	-0.956 to 0.262	0.5148
Normal vs. APAP+ Silymarin	-0.047	-0.656 to 0.562	0.9995
Normal vs. APAP+ AML	-0.228	-0.837 to 0.381	0.8381
Normal vs. APAP+ AMH	-0.062	-0.671 to 0.547	0.9986
APAP vs. APAP+ Silymarin	0.3	-0.309 to 0.909	0.6521
APAP vs. APAP+ AML	0.119	-0.49 to 0.728	0.9829
APAP vs. APAP+ AMH	0.285	-0.324 to 0.894	0.6946
APAP+ Silymarin vs. APAP+ AML	-0.181	-0.79 to 0.428	0.9232
APAP+ Silymarin vs. APAP+ AMH	-0.015	-0.624 to 0.594	>0.9999
APAP+ AML vs. APAP+ AMH	0.166	-0.443 to 0.775	0.9429