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SUPPORTING INFORMATION

Supplementary Figures

- **Flow chart for Synthesis of NPs**

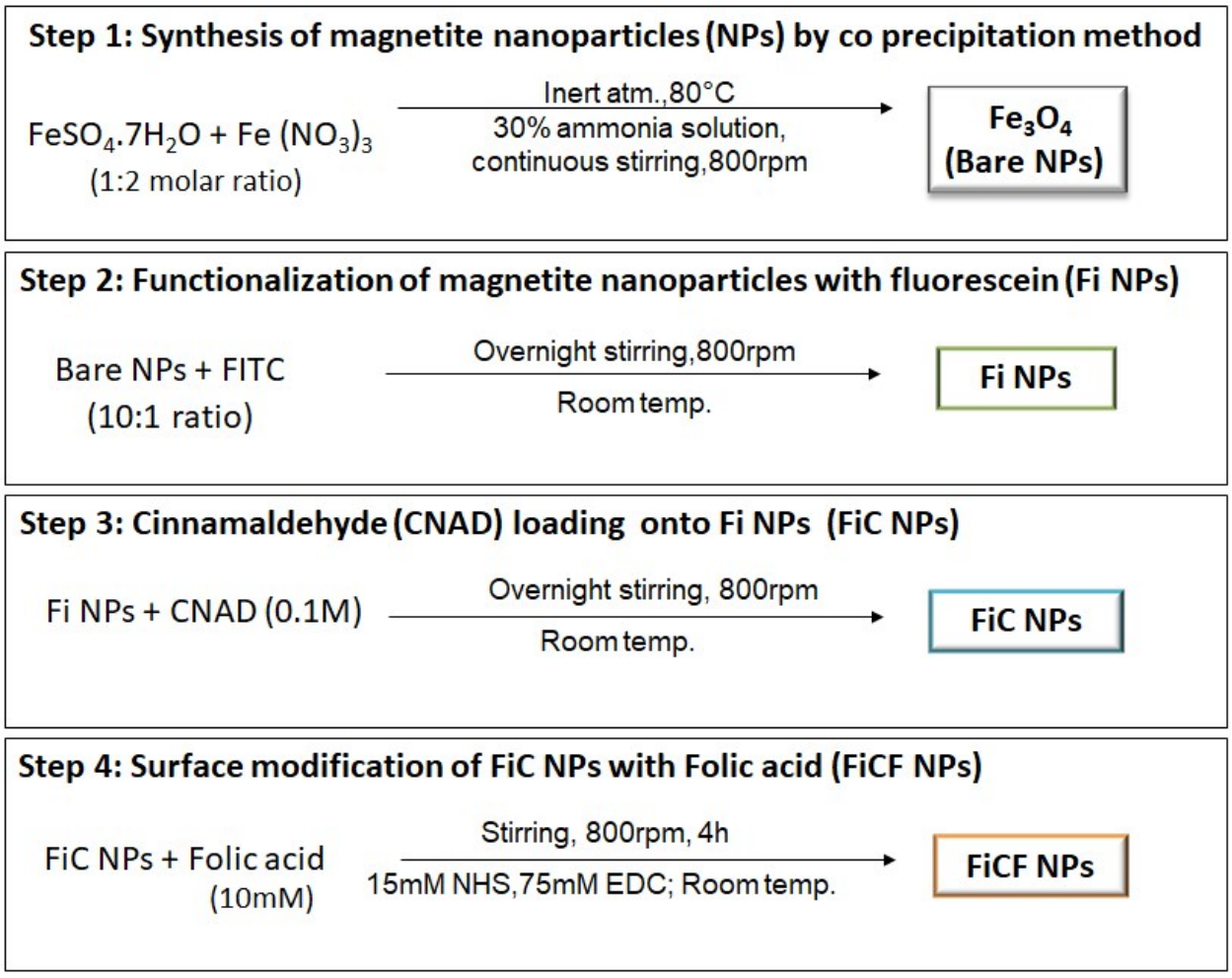

Fig.S1: Flow chart for the synthesis scheme of FiCF NPs

- **FiCF NPs exhibited good stability and biocompatibility**

  The colloidal stability of FiCF NPs **(Supplementary file, Fig. S1)** was studied in different fluids such as DW, PBS, FBS and DMEM (with or without FBS). The NPs were found to be hydrophilic and remained stable in all the fluids up to 150 min and showed higher colloidal stability in DMEM supplemented with FBS.

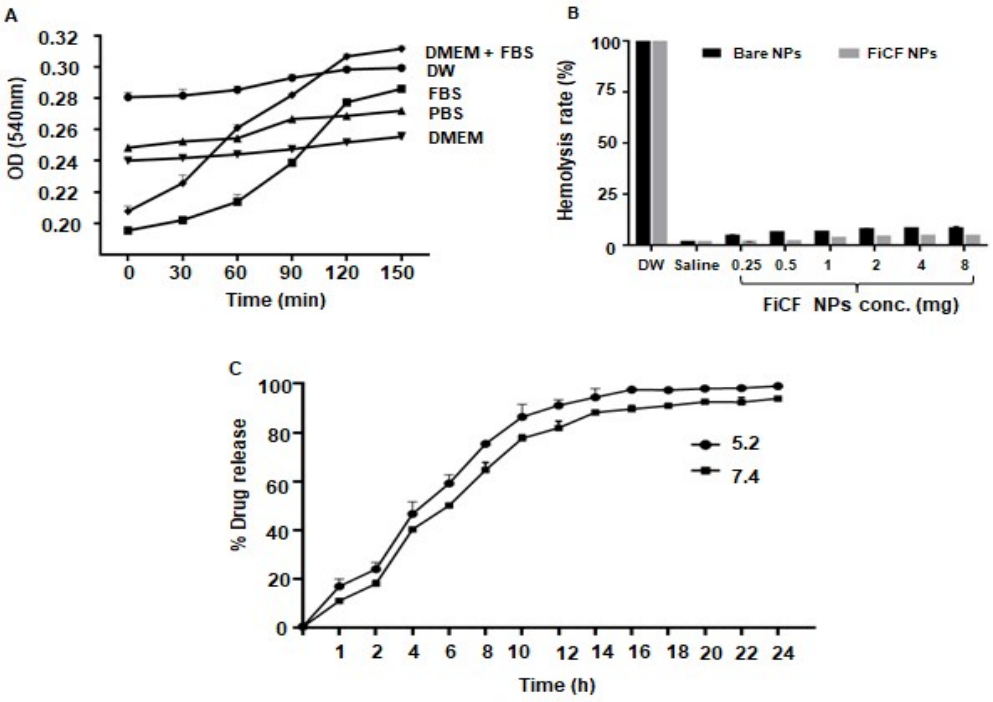

Fig.S2.Stability, biocompatibility, Cinnamaldehyde release profile.(A) Stability of FiCF NPs in different solutions was monitored by UV-VIS spectroscopy**.(B)** Biocompatibility of FiCF NPs performed in freshly collected human blood, DW and saline were used as positive and negative controls, respectively. **(C)** Cinnamaldehyde release profiles from FiCF NPs at different pH values and time points. The data has been presented as mean±SD of three independent experiments at $p<0.001$, indicating statistically significant differences between different solutions.

The safe nature of NPs was tested by checking their hemocompatibility for which the hemolytic rate (HR) was evaluated (supplementary file**,** Fig. S1.B). At 0.25, 0.5, 1, 2, 4 and 8 mg/ml concentrations, HR of bare NPs was found to be 4.51, 6.48, 6.72, 7.71, 8.26, 8.70% and of FiCF NPs was found to be 1.78, 2.02, 3.68, 4.27, 4.63, 4.74 %, respectively, compared to the DW (100%) and saline (1.66%) controls. Negligible hemolytic activity of FiCF NPs (less than 5%) at higher concentrations indicated its high biocompatibility. Hemocompatibility is a measure of the damaging effects resulting from the interaction of biological materials with the blood, including whether they can cause thrombosis, destruction of red blood cells, reduction or activation of platelets, and activation of clotting factors and the complement system.[1, 2] There are reports which have shown that folic acid coating of the iron oxide NPs is responsible for reducing the blood hemolysis. [3,4]

CNAD release from FiCF NPs was determined by exposing NPs to pH 7.4 (physiological pH) and 5.2 (to mimic the slightly acidic tumour microenvironment) at 37°C (supplementary file**,**

Fig. S1.C). NPs showed controlled release of CNAD at both pH values. However, more release was observed in acidic pH, which could be due to higher partitioning of CNAD at pH 5.2. pH-dependent release of drug from the NPs shows their efficiency as controlled drug delivery system. Such NPs could deliver the drugs more efficiently at the tumor site by responding to small changes in pH, without affecting the normal cells. [5, 6]

References:

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2. Nosrati H, Sefidi N, Sharafi A, Danafar H, Manjili HK. Bovine serum albumin (BSA) coated iron oxide magnetic nanoparticles as biocompatible carriers for curcumin-anticancer drug. Bioorganic chemistry. 2018 Feb 1; 76:501-9.
3. Jayalekshmi AC, Victor SP, Sharma CP. Magnetic and degradable polymer/bioactive glass composite nanoparticles for biomedical applications. Colloids and Surfaces B: Biointerfaces. 2013 Jan 1; 101:196-204.
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5. Kato Y, Ozawa S, Miyamoto C, Maehata Y, Suzuki A, Maeda T, Baba Y. Acidic extracellular microenvironment and cancer. Cancer cell international. 2013 Dec; 13(1):89.
6. Galbis E, Iglesias N, Lucas R, Tinajero-Díaz E, de-Paz MV, Muñoz-Guerra S, Galbis JA. Validation of smart nanoparticles as controlled drug delivery systems: loading and pH-dependent release of pilocarpine. ACS omega. 2018 Jan 31; 3(1):375-82.

- **Effect of Cinnamaldehyde on viability of breast cancer cells and non-cancerous cells**

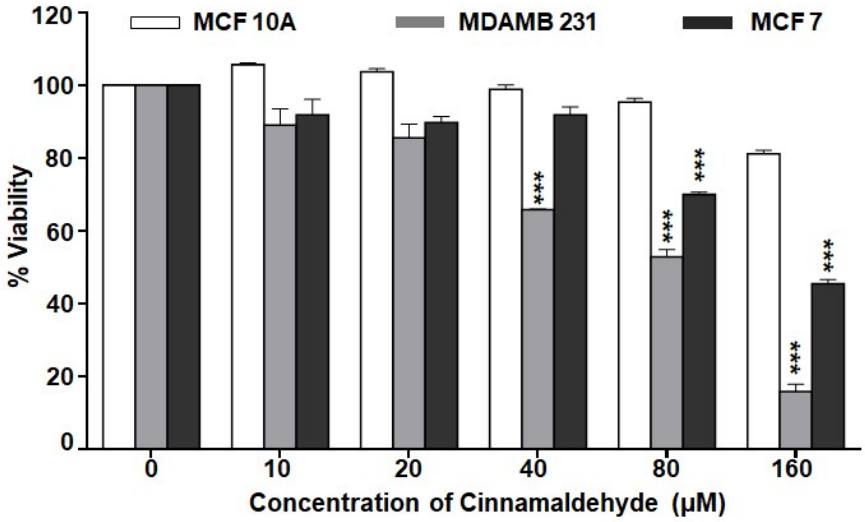

Figure S3: Effect of Cinnamaldehyde on viability of breast cancer (MCF 7 and MDAMB231) **and non-cancerous** (MCF10A) **cells**. All the data are presented as mean±SD of three independent experiments at $p<0.001$, indicating statistically significant differences compared to the control untreated group.

- **Cellular uptake of FiCF NPs**

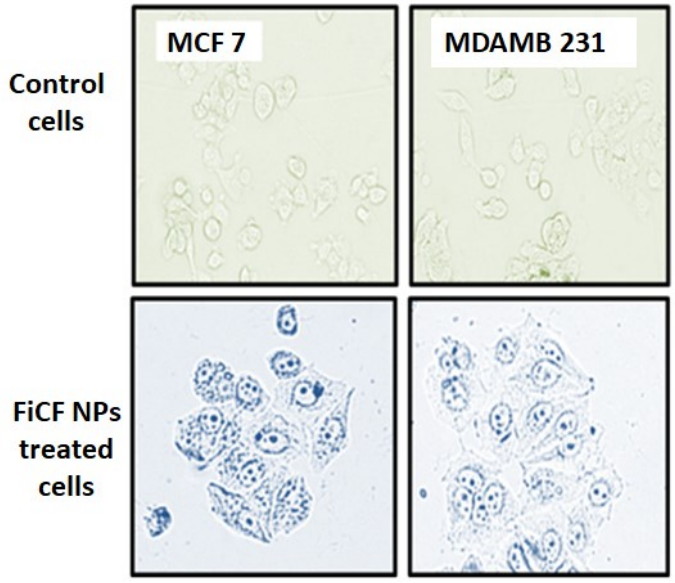

Fig.S4: Cellular uptake of FiCF NPs. Prussian blue staining of MCF 7 and MDAMB231, showing uptake of FiCF NPs in nucleus and cytoplasm of treated cells compared to non-treated control cells. The stained cells were photographed with Sony DSC-S75 cyber-shot camera.

- **Histopathological analysis**

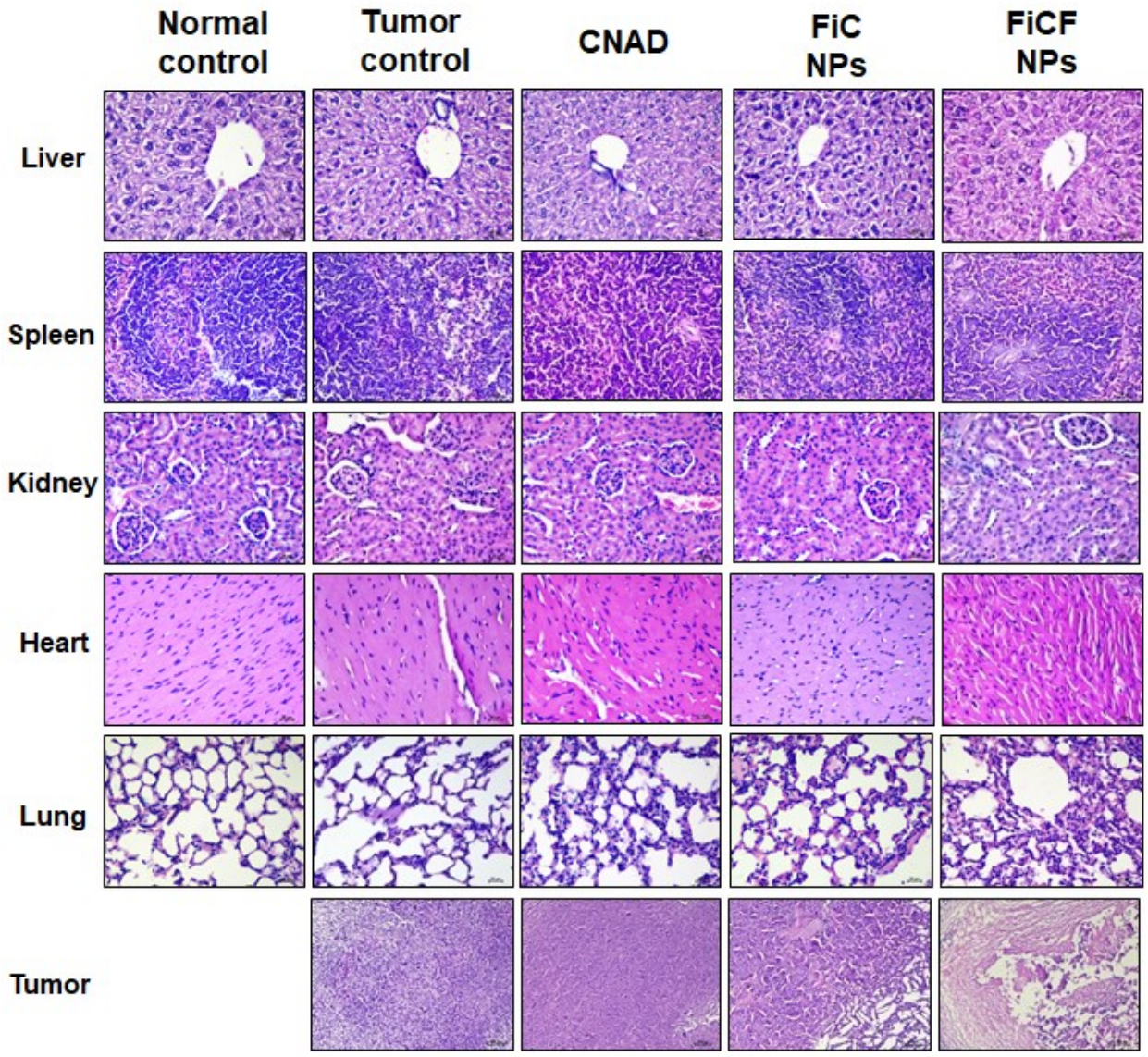

Fig S5: Histopathology of different tissues isolated from treatment and control group. Representative images of histological sections of liver, spleen, kidney, heart and lung from each group **and tumor tissue** from tumor control, FiC NPs and FiCF NPs as seen under the microscope at 40X.

Supplementary Tables:

- **Characterization of FiCF NPs**

  The enhanced particle size of FiCF NPs was in agreement with surface modification of iron oxide NPs. Despite the reduction in the surface charge, FiCF NPs were well dispersed in the aqueous medium, with no significant change in pH and zeta potential and remained dispersed over a period of two months (Supplementary information, Table S1).

Table S1: Zeta potential and stability of FiCF NPs at room temperature

NPs	Appearance	Average particle size (nm) by DLS	PDI	Zeta potential (mV)		pH	
				Day 0	Day 60	Day 0	Day 60
Bare NPs	Black	115.6±3.25	0.439± 0.230	-66.1	-60.6	7.5±0.38	7.7±0.53
FiCF NPs	Brownish black	204.1±13.38	0.425± 0.163	-59.6	-56.9	8.0±0.41	8.1±0.48

- **Effect of Bare NPs, FITC and Folate on viability of breast cancer cells and non-cancerous cells**

  The effect Bare NPs, FITC and Folate on MCF7, MDAMB 231 and MCF 10A was analyzed by using MTT assay (0-20 µg/ml). Bare NPs were non-toxic to both the cell lines, which is in accordance with the previously reported data.[27] Interestingly, MCF 10A showed ≥100% viability post-treatment with bare NPs, FITC and Folate used to coat Fe_3O_4 NPs (**Table S2**). The modification of bare NPs with FITC, CNAD and folic acid showed stepwise decrease in the viability of breast cancer cell lines (**Table S3**).

Table S2: Effect of bare NPs, FITC and Folate on the viability of MCF7, MDAMB 231 and MCF 10A cells.

Conc. (µg/ml)	%Viability								
	Bare NPs			FITC			Folic acid		
	MCF7	MDA MB 231	MCF 10A	MCF7	MDA MB 231	MCF 10A	MCF7	MDA MB 231	MCF 10A
0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
0.312	100.60 ±0.29	100.0 ±0.76	114.55 ±0.48	105.24 ±0.39	109.29 ±0.63	113.08 ±0.44	110.06 ±0.89	105.64 ±1.15	105.50 ±0.20
0.625	100.63 ±0.39	100.39 ±0.49	113.41 ±1.49	104.05 ±0.35	108.74 ±1.79	110.31 ±0.17	107.83 ±0.77	103.07 ±1.09	104.10 ±0.89
1.25	100.44 ±0.31	100.63 ±0.59	112.63 ±1.21	103.91 ±1.60	103.55 ±1.10	109.84 ±0.05	105.94 ±1.27	101.26 ±1.12	110.18 ±0.07
2.5	101.25 ±0.11	101.65 ±0.24	111.46 ±0.21	99.16 ±1.46	100.0 ±0.41	110.94 ±0.27	103.42 ±0.10	100.22 ±0.14	111.40 ±0.94
5	101.09 ±0.22	102.29 ±0.37	111.33 ±1.82	97.69 ±1.31	98.27 ±1.20	113.91 ±0.07	101.19 ±1.69	98.66 ±0.95	112.61 ±0.73
10	100.78 ±0.19	105.12 ±1.40	110.29 ±0.55	94.62 ±0.31	95.27 ±1.17	106.56 ±0.24	98.95 ±1.25	97.24 ±0.48	113.37 ±0.31
20	100.88 ±0.54	105.59 ±0.61	109.64 ±1.25	92.17 ±0.79	93.22 ±0.14	103.63 ±1.53	96.16 ±0.62	94.79 ±0.60	114.29 ±0.98

All the data are presented as mean±SD of three independent experiments at $p<0.001$, indicating statistically significant differences compared to the control untreated cells.

Table S3: Effect of Bare, Fi, FiC and FiCF NPs on the viability of MCF7 and MDAMB 231 cells.

Conc. (µg/ml)	%Viability							
	Bare NPs		Fi NPs		FiC NPs		FiCF NPs	
	MCF 7	MDA MB 231	MCF 7	MDA MB 231	MCF7	MDA MB 231	MCF7	MDA MB 231
0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
0.312	100.60 ±0.29	100.0 ±0.76	113.46 ±1.41	114.12 ±0.54	90.11 ±1.49	98.70 ±1.03	86.68 ±1.41	85.21 ±0.70
0.625	100.63 ±0.39	100.39 ±0.49	101.39 ±0.53	110.18 ±1.23	88.05 ±0.54	95.58 ±0.65	81.76 ±0.97	83.05 ±1.38
1.25	100.44 ±0.31	100.63 ±0.59	99.37 ±1.30	93.71 ±0.68	79.39 ±0.71	75.95 ±0.41	68.34 ±0.82	71.70 ±0.89
2.5	101.25 ±0.11	101.65 ±0.24	92.24 ±0.57	92.41 ±0.76	66.67 ±0.35	74.26 ±0.55	53.46 ±1.32	69.32 ±0.92
5	101.09 ±0.22	102.29 ±0.37	90.56 ±0.59	90.94 ±0.49	45.98 ±0.58	73.74 ±0.86	41.30 ±1.08	60.87 ±0.83
10	100.78 ±0.19	105.12 ±1.40	87.00 ±1.07	86.35 ±0.68	24.81 ±1.53	61.82 ±0.04	17.13 ±0.60	50.99 ±0.58
20	100.88 ±0.54	105.59 ±0.61	86.02 ±1.34	84.83 ±0.39	22.57 ±1.35	59.57 ±0.54	15.88 ±0.85	49.56 ±0.65

All the data are presented as mean±SD of three independent experiments at $p<0.001$, indicating statistically significant differences compared to the control untreated cells.

- **Effect of CNAD, FiC and FiCF NPs on hematological parameters**

Hematological studies showed that there was no statistically significant difference in any of the parameters such as Hb, RBC, HCT, MCV, MCH, MCHC, WBC, L, M, G values between treatment and control groups (**Table S4**). The results suggested that intravenous administration of FiCF NPs in mice did not induce any abnormal changes in hematological parameters.

Table S4: Hematological parameters of the treated and untreated mice in the tumor retardation study

Parameter#	NTC	TC	CNAD	FiC NPs	FiCF NPs	Normal range
WBC ($\times10^3$/µL)	7.4±4.5	10.5.2±1.9	10.5±2.8	9.9±1.5	9.6±4.3	2.0-10.5
RBC ($\times10^3$/µL)	8.9±1.0	10.0±1.1	9.0±0.5	9.2±1.2	9.1±0.9	7.8-10.6
Hb (g/dL)	12.5±1.6	16.5±2.7	15.1±0.1	16.8±2.7	17.4±1.6	10.2-17.6
HCT (%)	45.6±8.1	50.0±7.7	52.2±3.7	50.6±10.8	49.9±3.8	37.5-51.0
MCV (fL)	50.9±3.5	50.7±2.0	51.6±4.5	49.4±4.8	51.2±2.5	45.4-60.3
MCH (pg)	14.2±0.2	15.0±1.2	14.6±0.5	14.7±1.1	14.3±0.6	14.1-19.3
MCHC (g/dL)	27.6±1.6	29.6±1.3	26.4±1.4	27.8±0.5	28.0±1.1	30.2-34.2
PLT ($\times10^3$/µL)	270.0±9.0	290.3±7.5	275.5±9.7	261.7±7.5	258.8±8.5	150-450$\times10^3$
L (%)	76.3±9.9	78.1±3.5	81.7±9.8	71.5±9.1	75.8±1.4	55.0-95.0
M (%)	0.3±0.3	0.4±0.2	0.4±0.2	0.5±0.1	0.4±0.2	1.0-4.0

G (%)	1.7±1.7	2.0±0.1	1.7±1.3	2.0±0.5	1.5±1.1	0.0-2.0

Values are expressed as mean±standard deviation, n=3. FiCF NPs treated groups showednon-significant differences as compared with control mice ($p>0.05$). #WBC: White blood cells; **RBC:** Red blood cells; Hb: Hemoglobin; **HCT**: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Haemoglobin; MCHC: Mean Corpuscular Haemoglobin Concentration; PLT: Platelet counts; L: Lymphocyte count; M: Monocyte count; G: Granulocyte count

- **Effect of CNAD, FiC and FiCF NPs on food consumption, body weights and relative organ weights**

The effect on food consumption (**Table S5)**, body weights (**Table S6)**and relative organ weights (**Table S7)** of NPs treated C57BL/6J mice in the study are given below-

Table S5: Food consumption of C57BL/6J mice

Treatment days	Food consumption in grams of mice in treatment groups				
	NTC	**TC**	**CNAD**	**FiC NPs**	**FiCF NPs**
1	23.2±0.9	20.4±0.4	22.4±1.2	23.1±0.4	25.1±0.4
3	25.2±1.2	19.0±0.5	22.3±0.7	22.6±0.3	24.4±0.3
6	25.9±1.7	23.2±072	23.1±0.3	25.4±0.1	23.8±0.4
9	27.5±1.2	21.5±1.3	24.1±0.7	22.1±0.4	22.4±0.5
12	23.7±0.2	22.8±0.4	23.4±0.4	20.5±0.6	22.2±0.6
14	24.4±0.7	21.2±0.2	23.1±0.6	21.9±0.3	23.1±0.1

All the data are presented as mean±SD

Table S6: Body weights of C57BL/6J mice

Treatment days	Body weight of study animal (in grams)				
	NTC	**TC**	**CNAD**	**FiC NPs**	**FiCF NPs**
1	22.33±1.9	22.35±2.0	22.16±1.9	22.25±1.7	21.67±1.5
3	22.45±1.7	22.0±2.3	21.58±1.9	22.67±1.1	22.5±2.7
6	22.3±2.2	21.35±2.8	22.0±1.6	22.33±1.4	22.25±1.8
9	22.22±2.0	21.00±1.8	21.33±1.37	22.66±2.9	23.67±1.1

12	23.03±0.93	20.33±1.7	21.51±2.1	22.95±1.03	24.05±0.91
14	23.66±1.5	19.77±1.9	20.68±2.0	23.36±1.32	24.41±1.25

All the data are presented as mean±SD

Table S7: Relative organ weights of C57BL/6J mice

Organ weights of study animals (in grams)						
Groups	**Thymus**	**Heart**	**Lung**	**Liver**	**Spleen**	**Kidney**
NTC	0.45±0.12	0.52±0.12	0.97±1.14	5.06±0.99	0.5±0.05	1.02±0.18
TC	0.29±0.07	0.60±0.13	1.05±1.16	5.85±1.2	0.51±0.06	1.27±0.21
CNAD	0.33±0.02	0.60±0.03	1.0±0.08	5.79±0.5	0.61±0.19	1.48±0.04
FiC NPs	0.34±0.14	0.50±0.02	0.91±0.23	5.39±0.61	0.60±0.23	1.17±0.16
FiCF NPs	0.31±0.16	0.49±0.05	0.88±0.14	5.06±0.68	0.56±0.32	1.07±0.19

All the data are presented as mean±SD

- **Acute Toxicity study**

We further tested the safety of NPs in vivo, in Swiss albino mice (acute toxicity study) and the results were compared with vehicle treated control mice. FiCF NPs were found to be safe for the mice treated with a single dose of 100 mg/kg b.w. During the observation period of 14 d, the treated mice did not exhibit mortality, change in the body weight (**Supplementary Table S8**), abnormal physical signs and/or any behavioral changes (no obvious signs of dehydration, locomotor impairment, and weakness, inability to eat or drink) or any toxicity related symptoms as compared to the control group.

Table S8: Body weights of C57BL/6J mice of acute toxicity study

Treatment days	**Body weight of study animal (in grams)**	
	Control (saline)	**FiCF NPs**
1	20.0±1.0	20.3±0.6

3	20.66±1.1	20.3±0.6
6	21.33±0.6	21.3±0.7
9	22.3±0.6	22.3±0.2
12	23.3 ±0.6	23.0±1.0
14	23.66±0.7	23.3±0.6

All the data are presented as mean±SD