

Appendix A: Literature search for specific toxicology studies with novel supplement formulations

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Searches for studies investigating the toxicity of vitamin C, CBD, and curcumin in novel formulations were conducted in PubMed using the search strings listed in table 1.

Table 1. Search strings and number of total and relevant results.

Search string	Results Relevant	
"Vitamin C" AND "toxicity" AND "encapsulated"	7	0
"Vitamin C" AND "toxicity" AND "liposomal"	5	0
"Vitamin C" AND "toxicity" AND "micelles"	6	0
"Vitamin C" AND "toxicity" AND "emulsion"	3	0
"CBD" AND "toxicity" AND "encapsulated"	1	0
"CBD" AND "toxicity" AND "liposomal"	0	0
"CBD" AND "toxicity" AND "micelles"	0	0
"CBD" AND "toxicity" AND "emulsion"	0	0
"Curcumin" AND "toxicity" AND "encapsulated"	121	7
"Curcumin" AND "toxicity" AND "liposomal"	33	5
"Curcumin" AND "toxicity" AND "micelles"	84	8
"Curcumin" AND "toxicity" AND "emulsion"	27	3

PM = PubMed; WoS = Web of Science.

Relevant results were only retrieved for novel formulations of curcumin. A total of 23 studies were identified, 11 of which were *in vitro* studies and 11 of which were *in vivo* studies. Three studies were performed in human subjects and are reviewed in the main paper. A few of the relevant hits were retrieved by more

than one search string and in these cases such results were omitted from the 'relevant' count in the subsequent strings such that all 'relevant' counts are unique. Publications investigating the toxicology of novel curcumin formulations *in vitro* and *in vivo* are briefly summarised table 2 and the full references are listed below table 2.

Table 2. Summary of studies investigating the toxicity of novel curcumin formulations.

Formulation - In Vitro	System	Key findings	Study
Curcumin nano-blisomes	Non-cancer cell line (Wi-38I)	Lower cytotoxicity vs unformulated curcumin	Abbas <i>et al.</i> 2022
	Immortalised fibroblasts		
	Glioblastoma LN229	Reduced cell viability.	
Micellar curcumin	Human endothelial cell line	Reversible genotoxicity (comet assay).	Beltzig <i>et al.</i> 2021
	Primary vascular endothelial cells	Similar efficacy of native vs. micellar curcumin.	
	Primary smooth muscle cells		
	Primary pericytes		
Liposomal curcumin	Human lymphocytes	Empty DMPC liposomes toxic.	Chen <i>et al.</i> 2009
	EBV-transformed B-cells (LCL)	Liposomal curcumin inhibited LCL proliferation.	

Micellar curcumin	Breast tumor cell line	Induced apoptosis in tumour cells and spheroids.	Do <i>et al.</i> 2022
	Human stromal cells	Reduced viability in stromal cells.	
	Zebrafish embryotoxicity assay	Toxicity to zebrafish embryo development. Micellar curcumin more toxic.	
Curcumin chitosan nanoparticles	Cervical tumour cells	Cytotoxicity to tumour cells.	Facchi <i>et al.</i> 2019
	VERO cells	Biocompatible with VERO cells.	
Liposomal curcumin	Human synovial fibroblasts	Liposomal curcumin less toxic to cells.	Kloesch <i>et al.</i> 2016
	Mouse macrophages		
Curcumin microemulsion	HepG2 cells	Cytotoxicity to HepG2 cells, greater with smaller emulsion droplet size.	Lin <i>et al.</i> 2014
Micellar curcumin	HepG2 cells	Cytotoxicity to HepG2 cells.	Phan <i>et al.</i> 2016
Solid lipid curcumin nanoparticles	3T3 fibroblasts	Reduction in cell viability and alteration of lipid profile (dependent upon particle composition).	Rosa <i>et al.</i> 2022

Liposomal curcumin	Red blood cells in vitro	Dose-dependent echinocyte formation and increases in mean cellular volume.	Storka <i>et al.</i> 2013
Liposomal solid curcumin gels	Huh7it cell line	Non-cytotoxic.	Yusuf <i>et al.</i> 2022
Formulation - In Vivo	System	Key findings	Study
Curcumin PLGA nanoparticles	Mice RAW 264.7 cell line	Increased lymphocytes. No changes in hepatotoxic biomarkers. Higher toxicity in RAW 264.7 cells at higher concentrations, but not at lower concentrations.	Busari <i>et al.</i> 2017
Curcumin-loaded hydrogel nanoparticles	" <i>in vivo</i> " [abstract only]	Low toxicity. No genotoxicity observed.	Dandekar <i>et al.</i> 2010
Hydrogenated curcumin	Sprague Dawley rats	No treatment related toxicity.	Gopi <i>et al.</i> 2016
Alginate-curcumin conjugate; micelle forming	Mouse tumour models.	No toxicity observed in blood parameters, histology, comet assay, or cytokine levels.	Karabasz <i>et al.</i> 2019
Nano-micelle curcumin	Male Wistar rats	Testicular toxicity observed; DNA damage.	Moshari <i>et al.</i> 2017

Nano-micelle curcumin	Male Wistar rats	Testicular toxicity observed; suppression of spermatogenesis; DNA damage.	Radmanesh <i>et al.</i> 2021
Nano-liposome curcumin with tetrandrine	Zebrafish	No developmental toxicity.	Song <i>et al.</i> 2022
Chitosan solid lipid nanoparticle curcumin with sulforaphane	BALB/c mice	No toxicity in acute, subacute, or chronic tests.	Thakkar <i>et al.</i> . 2016
Micellar curcumin	Male Wistar rats	No haematopoietic or liver tissue toxicity.	Tzankova <i>et al.</i> 2016

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