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

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

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-38l).	Lower cytotoxicity vs unformulated curcumin.	Abbas *et al*. 2022

Micellar curcumin	Immortalised fibroblasts; Glioblastoma LN229; Human endothelial cell line; Primary vascular endothelial cells; Primary smooth muscle cells; Primary pericytes.	Reduced cell viability; Reversible genotoxicity (comet assay); Similar efficacy of native vs. micellar curcumin.	Beltzig *et al*. 2021
Liposomal curcumin	Human lymphocytes; EBV-transformed B-cells (LCL).	Empty DMPC liposomes toxic; Liposomal curcumin inhibited LCL proliferation.	Chen *et al*. 2009
Micellar curcumin	Breast tumor cell line; Human stromal cells; Zebrafish embryotoxicity assay.	Induced apoptosis in tumour cells and spheroids; Reduced viability in stromal cells; Toxicity to zebrafish embryo development; Micellar curcumin more toxic.	Do *et al*. 2022

Curcumin chitosan nanoparticles	Cervical tumour cells ; VERO cells.	Cytotoxicity to tumour cells; Biocompatible with VERO cells.	Facchi *et al*. 2019
Liposomal curcumin	Human synovial fibroblasts; Mouse macrophages.	Liposomal curcumin less toxic to cells.	Kloesch *et al*. 2016
Curcumin microemulsion	HepG2 cells.	Cytotoxicity to HepG2 cells, greater with smaller emulsion droplet size.	Lin *et al*. 2014
Micellar curcumin	HepG2 cells.	Cytotoxicity to HepG2 cells.	Phan *et al*. 2016
Solid lipid curcumin nanoparticles	3T3 fibroblasts.	Reduction in cell viability and alteration of lipid profile (dependent upon particle composition).	Rosa *et al*. 2022
Liposomal curcumin	Red blood cells in vitro.	Dose-dependent echinocyte formation and increases in mean cellular volume.	Storka *et al*. 2013
Liposomal solid curcumin gels	Huh7it cell line.	Non-cytotoxic.	Yusuf *et al*. 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 *et al*. 2017
Curcumin-loaded hydrogel nanoparticles	"*in vivo*" [abstract only].	Low toxicity; No genotoxicity observed.	Dandekar *et al*. 2010
Hydrogenated curcumin	Sprague Dawley rats.	No treatment related toxicity.	Gopi *et al*. 2016
Alginate-curcumin conjugate; micelle forming	Mouse tumour models.	No toxicity observed in blood parameters, histology, comet assay, or cytokine levels.	Karabasz *et al*. 2019
Nano-micelle curcumin	Male Wistar rats.	Testicular toxicity observed; DNA damage.	Moshari *et al* . 2017
Nano-micelle curcumin	Male Wistar rats.	Testicular toxicity observed; suppression of spermatogenesis; DNA damage.	Radmanesh *et al*. 2021

Nano-liposome curcumin with tetrandrine	Zebrafish.	No developmental toxicity.	Song *et al*. 2022
Chitosan solid lipid nanoparticle curcumin with sulforaphane	BALB/c mice.	No toxicity in acute, subacute, or chronic tests.	Thakkar *et al*. 2016
Micellar curcumin	Male Wistar rats.	No haematopoietic or liver tissue toxicity.	Tzankova *et al*. 2016

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