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Anti-Inflammatory Activity of Curcumin-Loaded Chitosan Nanoparticles in a Carrageenan-Induced Paw Oedema Model

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ABSTRACT

Curcumin, the main pigment of turmeric, has a long record of anti-inflammatory activity in laboratory animals, but it is poorly absorbed and chemically unstable. Encapsulation in chitosan nanoparticles is widely proposed as a remedy, and the carrageenan-induced paw oedema model is the usual first test of whether the approach works. This narrative review asks how far that test can support the claim. It draws on published work on the model, on the pharmacology of curcumin and on chitosan-based carriers, and it reports no new data. The model is good at showing that swelling falls under controlled conditions and poor at explaining why. Much of the reported benefit of nanoformulation is better understood as improved handling, such as dispersion, stability and exposure, than as a new pharmacological action, and the apparent advantage depends heavily on the comparator used. Common weaknesses include comparison only with poorly soluble free curcumin, absent empty-particle controls, single time points, little measurement of tissue exposure and incomplete reporting of randomisation and blinding. The review concludes that a reduction in acute swelling is plausible, that its size and source are not established, and it lists what a decisive study would contain.

Keywords: Curcumin; Chitosan nanoparticles; Carrageenan; Paw oedema; Anti-inflammatory; Drug delivery; Narrative review

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Article Class: Narrative Review

1. Introduction

Inflammation is the body's organised response to injury and infection, and it is useful until it is not (1). The search for gentler alternatives to anti-inflammatory drugs, drawn from food plants, has run for decades. Curcumin, the main yellow

pigment of turmeric, is probably the most studied of these candidates (2, 3). It also shows the usual problem: it looks active in many assays and then performs unevenly once it has to reach tissue in a living animal (4, 5). That background shapes what follows.



Encapsulation in chitosan nanoparticles is one of the more popular answers to that difficulty. Chitosan is a cationic polysaccharide derived from chitin, and it can be formed into small particles under mild, water-based conditions (6, 7). The usual test of whether such a particle helps is the carrageenan-induced paw oedema model in the rat or mouse, a quick, cheap and long-established screen for anti-inflammatory activity (8, 9). A formulation that reduces swelling in that model is often described as having anti-inflammatory activity, and the particle is credited for the improvement.

This article asks whether that chain of reasoning holds. It is a narrative review of the published literature on curcumin, chitosan carriers and the carrageenan model. It does not report experiments, animals or measurements of our own, and no local data from any laboratory are presented. Our aim is to set out what the model can and cannot show, what is known about the compound and the carrier, and what a convincing study would contain.

2. Literature Review

2.1 The Carrageenan Paw Oedema Model

Carrageenan is a sulphated polysaccharide from red seaweed, and a small injection under the skin of the hind paw provokes a local, reproducible swelling (10). The method was introduced as a screen for anti-inflammatory drugs in the early 1960s and has changed little since (8). Its appeal is practical: the readout is a simple change in paw volume or thickness, and untreated controls behave predictably when conditions are held constant (9).

The swelling is not a single process. Studies in rats described an early phase in which amines and kinins matter, followed by a later phase in which prostaglandins

and the recruitment of neutrophils dominate (11). The mouse paw shows a similar two-stage pattern, with nitric oxide and cyclooxygenase-2 contributing at different times and the size of the response depending on the age and weight of the animal (12). Table 1 summarises the phases and what interference at each stage would mean for the interpretation of a drug effect.

Two cautions follow. First, an agent that lowers swelling in the late phase only is acting on a different part of the cascade from one that lowers it throughout, so a single end-point at one time tells the reader less than a time course. Second, the model measures acute oedema and says little about chronic or resolving inflammation (13, 14).

Table 1. Phases of carrageenan paw oedema and what interference implies.

Phase	Main contributors	Reading of an effect
Early	Amines, kinins, early vascular leak (11)	Action on initial mediators or vascular response
Late	Prostaglandins, nitric oxide, neutrophils (11, 12)	Action on cyclooxygenase pathway or cell recruitment
Throughout	Both of the above	Broad action, or a local effect on the irritant
Resolution	Not captured by the model (13)	Needs other models

Note: Qualitative summary of the cited literature; timing differs between species and laboratories.

2.2 What Curcumin Is Known to Do

Curcumin was reported to have anti-inflammatory activity in rodent models, including carrageenan oedema, in the 1970s and early 1980s (15, 16). Later work attributed a long list of molecular actions to it, among them suppression of the transcription factor NF-kappa B and reduced expression of cyclooxygenase-2 (17, 18). Broad reviews describe it as



acting on many targets at once (19, 20).

That breadth is a reason for caution as well as interest. Medicinal chemists have pointed out that curcumin is chemically reactive and unstable under physiological conditions, degrades in buffer within a short time, and tends to appear as an active compound in assays for reasons unrelated to a specific target (5, 21). It belongs to a class of compounds that screening campaigns learned to treat with suspicion (22). None of this means curcumin has no effect in animals, only that a positive result should be read alongside the question of what, chemically, was present in the tissue. Clinical evidence is more modest than the laboratory literature suggests: trial reviews describe small studies and varied preparations (23), and a meta-analysis in joint pain qualified its benefit by the quality of the trials (24).

2.3 The Bioavailability Problem

The reason curcumin is so often reformulated is that, given by mouth, very little of it reaches the circulation in an unchanged form (4). Measurements in rats found low levels of the parent compound after oral dosing (25), and a classic study showed that co-administration of piperine, an inhibitor of drug metabolism, raised the systemic exposure in both rats and human volunteers (26).

A consequence for paw oedema work is easily missed. How much compound reached the paw is rarely answered. If a particle changes absorption, stability or local retention, the improvement may be real, but it will be a pharmacokinetic improvement and not necessarily a new pharmacological activity.

2.4 Chitosan Nanoparticles as Carriers

Chitosan is obtained by deacetylation of chitin, and its properties depend on the degree of deacetylation and on molecular weight (6). It is biodegradable and

generally well tolerated, though behaviour varies with grade (27). Because of its positive charge it can be cross-linked with polyanions to form small particles under gentle conditions, and the chitosan particle literature is large (7, 28, 29).

Several groups have encapsulated curcumin in chitosan-based particles, sometimes blended with other polymers, and described their size, charge, release and effects on cultured cells (30, 31). An aqueous curcumin nanoparticle formulation has also been shown to improve stability and alter pharmacokinetics in animals (32). Reviews of curcumin nanoformulations describe a field with many designs and relatively few direct comparisons between them (33, 34). Table 2 lists the formulation variables that most often differ between reports.

Table 2. Formulation variables that differ between curcumin–chitosan reports.

Variable	Why it matters	What to report
Chitosan grade	Deacetylation and molecular weight alter behaviour (6, 27)	Source, grade, weight
Particle size	Affects distribution and uptake (35, 36)	Size and spread
Loading	Determines the dose actually given	Drug content and efficiency
Release and stability	Curcumin degrades in buffer (21, 32)	Release and storage data
Cross-linker or blend	Changes charge and release (30, 31)	Full composition

Note: Variables are those discussed in the cited reviews; no values are given because they differ between preparations.

Particle size and its spread matter for behaviour in the body (35, 36), as does particle design (37), and even in the better-studied case of tumours only a small share of administered particles has been found to reach the target, which should



temper claims about delivery to an inflamed paw (38).

3. Materials and Methods

3.1 Scope

This is a narrative review. It considers three bodies of published work: the carrageenan paw oedema model, the pharmacology of curcumin, and chitosan-based nanoparticle carriers. It attempts no quantitative synthesis and reports no experiment by the authors.

3.2 Literature Assembly

Sources were gathered by the authors from their own knowledge of the field and by following citations in key papers, reviews and methodological guidance. No formal systematic search was run, no protocol was registered, and no search dates or databases are claimed. The selection therefore reflects judgement and may favour well-known papers over obscure ones.

3.3 Appraisal Framework

Studies and reviews were read against a short set of questions drawn from reporting and risk-of-bias guidance for animal experiments (39, 40, 41). Was the control group appropriate? Was allocation random and was the person measuring blind to treatment? Was the unit of analysis the animal? Was the particle characterised, and was the free compound given in an equivalent form? They are a reading aid, not a scoring instrument.

4. Results

4.1 What the Model Can Establish

Read against the questions above, the carrageenan model is best at one thing: showing whether an agent reduces acute swelling relative to a vehicle under controlled conditions (8, 10). A time course also says something about timing in relation to the two phases (11, 12).

Figure 1 sets out the path from formulation to paw and marks where each step can be checked.

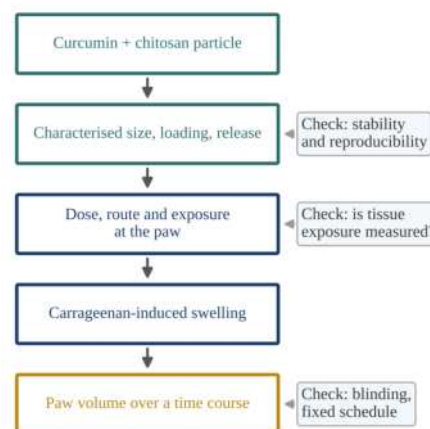


Figure 1. Path from formulation to paw and the checks that apply at each step (schematic, not data).

The model is much less able to say why the swelling fell. A reduction can come from a true anti-inflammatory action, from an effect on carrageenan retention, from local irritation or sedation, or from an uneven injection. A positive control shows that the assay works in a given laboratory, not that the test material acts in the same way (9).

4.2 What the Evidence Says About Nano-Curcumin

Across the curcumin-nanoparticle literature, the most consistent theme is better handling of the compound: improved dispersion in water, protection from degradation, and altered release and exposure (30, 31, 32). The claim that this translates into stronger anti-inflammatory effects in vivo is common, but the support for it depends heavily on the comparator. A particle compared with unformulated curcumin suspended in water is a weak test, because that comparator is itself poorly absorbed (4, 25).

A fair comparison would include the free compound in a solubilised or otherwise optimised form, empty chitosan particles to separate carrier effects from drug effects, and a reference anti-inflammatory



drug. Chitosan is not necessarily inert, and an empty-particle group addresses that (27, 29). Figure 2 sets out how confident a reader can be about different claims, given the usual structure of these studies.

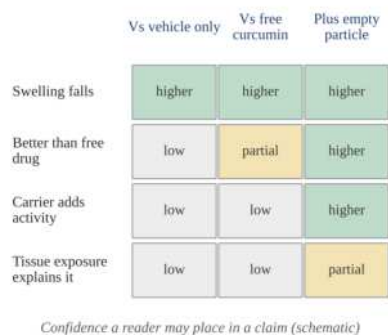


Figure 2. Qualitative confidence in claims, by study design (schematic matrix, not data).

4.3 Reporting and Design Weaknesses

Methodological guidance for animal research has stressed randomisation, blinding, sample-size reasoning and full description of the animals and conditions (39, 40, 42). Editors and funders have also called for more transparent reporting of preclinical work (43). Table 3 lists the items most relevant to paw oedema studies and what is at stake in each.

Table 3. Reporting items for paw oedema studies and the concern behind each.

Item	Concern	Guidance
Randomisation	Allocation bias (41)	Describe the method
Blinding	Observer bias in swelling readings (39)	State who measured
Unit of analysis	Animals sharing a cage (42)	Analyse per animal
Comparators	Free drug and empty carrier needed	Include both
Time course	Single time points hide phase (12)	Fixed schedule
Full reporting	Selective reporting (40, 43)	Follow ARRIVE

Note: Items follow the cited reporting and risk-of-bias guidance and are not attributed to any single study.

Species is a further limit. Work comparing mouse models of inflammatory disease with the human conditions found that gene-level responses can diverge greatly, so conclusions about people should be drawn cautiously (44). For the paw model the practical implication is simple: it is a screen, and positive results are leads to be tested, not verdicts.

5. Discussion

5.1 Interpreting the Evidence

The main finding of this review is a conditional one. Curcumin has a long record of anti-inflammatory activity in rodents, chitosan nanoparticles are a credible way to improve its handling, and the carrageenan model is a sensible first screen. Put together, these make it plausible that curcumin-loaded chitosan particles reduce paw swelling. What the literature does not settle is how much of that effect comes from improved exposure, how much from the carrier itself, and whether it reflects any real change in the underlying biology.

Figure 3 gives a simple way to reason about a reported reduction in swelling. The questions are ordered so that the cheapest checks come first.

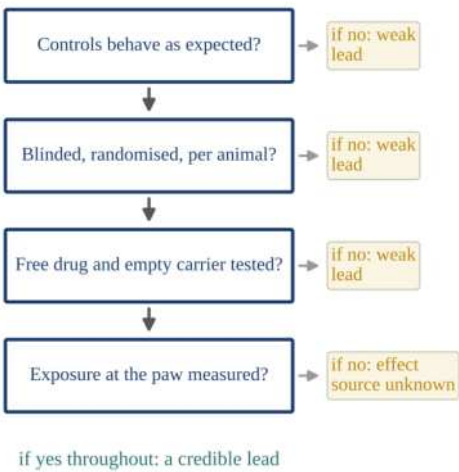


Figure 3. Decision sequence for reading a reported reduction in swelling (schematic, not data).



5.2 Limitations

This review has the limits of its method. The literature was not searched systematically, so the selection may be uneven, and conclusions about the whole field rest on a limited number of papers.

5.3 Future Work

Three kinds of study would move the field. The first is a direct, well-controlled comparison of the particle against optimised free curcumin and against empty particles, with blinded measurement on a fixed schedule and the animal as the unit of analysis. The second is measurement of curcumin in the inflamed tissue itself, so that effect and exposure can be linked. The third is extension to models in which inflammation persists and resolves, where a carrier that prolongs local retention might show benefit a short screen would miss (14, 23). These points apply with equal force to any poorly soluble natural product, not only to curcumin.

6. Conclusion

Curcumin-loaded chitosan nanoparticles are a reasonable idea with a reasonable test, and it is likely that they reduce carrageenan-induced swelling. The published literature does not yet allow a firm statement about how large that benefit is, how it compares with well-prepared free curcumin, or how much it owes to the carrier. What it does show is how a study should be built to answer those questions.

The message for researchers is practical: include the right comparators, characterise the particle, measure on a schedule and report the design in full. Readers should treat reports of anti-inflammatory activity in this model as promising leads, not proof of therapeutic value. That is a modest claim, and it is the one the literature will currently bear.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

I.O. conceived the review and wrote the sections on inflammation models and curcumin pharmacology. B.P. wrote the sections on study design and reporting. J.B. wrote the sections on chitosan carriers and formulation. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No animals were used and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

13. References

1. Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature*, 454(7203), 428–435. DOI: [10.1038/nature07201](https://doi.org/10.1038/nature07201)
2. Aggarwal, B. B., & Harikumar, K. B. (2009). Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *The International Journal of Biochemistry & Cell Biology*, 41(1), 40–59. DOI: [10.1016/j.biocel.2008.06.010](https://doi.org/10.1016/j.biocel.2008.06.010)
3. Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: A review of its effects on human health. *Foods*, 6(10), 92. DOI: [10.3390/foods6100092](https://doi.org/10.3390/foods6100092)
4. Anand, P., Kunnumakkara, A. B., Newman, R. A., & Aggarwal, B. B. (2007). Bioavailability of curcumin: Problems and promises. *Molecular Pharmaceutics*, 4(6), 807–818. DOI: [10.1021/mp700113r](https://doi.org/10.1021/mp700113r)



5. Nelson, K. M., Dahlin, J. L., Bisson, J., Graham, J., Pauli, G. F., & Walters, M. A. (2017). The essential medicinal chemistry of curcumin. *Journal of Medicinal Chemistry*, 60(5), 1620–1637. DOI: [10.1021/acs.jmedchem.6b00975](https://doi.org/10.1021/acs.jmedchem.6b00975)
6. Rinaudo, M. (2006). Chitin and chitosan: Properties and applications. *Progress in Polymer Science*, 31(7), 603–632. DOI: [10.1016/j.progpolymsci.2006.06.001](https://doi.org/10.1016/j.progpolymsci.2006.06.001)
7. Agnihotri, S. A., Mallikarjuna, N. N., & Aminabhavi, T. M. (2004). Recent advances on chitosan-based micro- and nanoparticles in drug delivery. *Journal of Controlled Release*, 100(1), 5–28. DOI: [10.1016/j.jconrel.2004.08.010](https://doi.org/10.1016/j.jconrel.2004.08.010)
8. Winter, C. A., Risley, E. A., & Nuss, G. W. (1962). Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. *Proceedings of the Society for Experimental Biology and Medicine*, 111(3), 544–547. DOI: [10.3181/00379727-111-27849](https://doi.org/10.3181/00379727-111-27849)
9. Morris, C. J. (2003). Carrageenan-induced paw edema in the rat and mouse. *Methods in Molecular Biology*, 225, 115–121. DOI: [10.1385/1-59259-374-7:115](https://doi.org/10.1385/1-59259-374-7:115)
10. Necas, J., & Bartosikova, L. (2013). Carrageenan: A review. *Veterinarni Medicina*, 58(4), 187–205. DOI: [10.17221/6758-VETMED](https://doi.org/10.17221/6758-VETMED)
11. Di Rosa, M., Giroud, J. P., & Willoughby, D. A. (1971). Studies of the mediators of the acute inflammatory response induced in rats in different sites by carrageenan and turpentine. *The Journal of Pathology*, 104(1), 15–29. DOI: [10.1002/path.1711040103](https://doi.org/10.1002/path.1711040103)
12. Posadas, I., Bucci, M., Roviezzo, F., Rossi, A., Parente, L., Sautebin, L., & Cirino, G. (2004). Carrageenan-induced mouse paw oedema is biphasic, age-weight dependent and displays differential nitric oxide cyclooxygenase-2 expression. *British Journal of Pharmacology*, 142(2), 331–338. DOI: [10.1038/sj.bjp.0705650](https://doi.org/10.1038/sj.bjp.0705650)
13. Serhan, C. N., & Savill, J. (2005). Resolution of inflammation: The beginning programs the end. *Nature Immunology*, 6(12), 1191–1197. DOI: [10.1038/ni1276](https://doi.org/10.1038/ni1276)
14. Gilroy, D. W., Lawrence, T., Perretti, M., & Rossi, A. G. (2004). Inflammatory resolution: New opportunities for drug discovery. *Nature Reviews Drug Discovery*, 3(5), 401–416. DOI: [10.1038/nrd1383](https://doi.org/10.1038/nrd1383)
15. Srimal, R. C., & Dhawan, B. N. (1973). Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. *Journal of Pharmacy and Pharmacology*, 25(6), 447–452. DOI: [10.1111/j.2042-7158.1973.tb09131.x](https://doi.org/10.1111/j.2042-7158.1973.tb09131.x)
16. Mukhopadhyay, A., Basu, N., Ghatak, N., & Gujral, P. K. (1982). Anti-inflammatory and irritant activities of curcumin analogues in rats. *Agents and Actions*, 12(4), 508–515. DOI: [10.1007/BF01965935](https://doi.org/10.1007/BF01965935)
17. Singh, S., & Aggarwal, B. B. (1995). Activation of transcription factor NF-kappa B is suppressed by curcumin (diferuloylmethane). *Journal of Biological Chemistry*, 270(42), 24995–25000. DOI: [10.1074/jbc.270.42.24995](https://doi.org/10.1074/jbc.270.42.24995)
18. Goel, A., Boland, C. R., & Chauhan, D. P. (2001). Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. *Cancer Letters*, 172(2), 111–118. DOI: [10.1016/S0304-3835\(01\)00655-3](https://doi.org/10.1016/S0304-3835(01)00655-3)
19. Menon, V. P., & Sudheer, A. R. (2007). Antioxidant and anti-inflammatory properties of curcumin. *Advances in Experimental Medicine and Biology*, 595, 105–125. DOI: [10.1007/978-0-387-46401-5_3](https://doi.org/10.1007/978-0-387-46401-5_3)
20. Shishodia, S. (2013). Molecular mechanisms of curcumin action: Gene expression. *BioFactors*, 39(1), 37–55. DOI: [10.1002/biof.1041](https://doi.org/10.1002/biof.1041)
21. Wang, Y.-J., Pan, M.-H., Cheng, A.-L., Lin, L.-I., Ho, Y.-S., Hsieh, C.-Y., & Lin, J.-K. (1997). Stability of curcumin in buffer solutions and characterization of its degradation products. *Journal of Pharmaceutical and Biomedical Analysis*, 15(12), 1867–1876. DOI: [10.1016/S0731-7085\(96\)02024-9](https://doi.org/10.1016/S0731-7085(96)02024-9)
22. Baell, J., & Walters, M. A. (2014). Chemistry: Chemical con artists foil drug discovery. *Nature*, 513(7519), 481–483. DOI: [10.1038/513481a](https://doi.org/10.1038/513481a)
23. Gupta, S. C., Patchva, S., & Aggarwal, B. B. (2013). Therapeutic roles of curcumin: Lessons learned from clinical trials. *The AAPS Journal*, 15(1), 195–218. DOI: [10.1208/s12248-012-9432-8](https://doi.org/10.1208/s12248-012-9432-8)
24. Daily, J. W., Yang, M., & Park, S. (2016). Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: A systematic review and meta-analysis of randomized clinical trials. *Journal of Medicinal Food*, 19(8), 717–729. DOI: [10.1089/jmf.2016.3705](https://doi.org/10.1089/jmf.2016.3705)
25. Yang, K.-Y., Lin, L.-C., Tseng, T.-Y., Wang, S.-C., & Tsai, T.-H. (2007). Oral bioavailability of curcumin in rat and the herbal analysis from *Curcuma longa* by LC–MS/MS. *Journal of Chromatography B*, 853(1–2), 183–189. DOI: [10.1016/j.jchromb.2007.03.010](https://doi.org/10.1016/j.jchromb.2007.03.010)
26. Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., & Srinivas, P. S. S. R. (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Medica*, 64(4), 353–356. DOI: [10.1055/s-2006-957450](https://doi.org/10.1055/s-2006-957450)
27. Kean, T., & Thanou, M. (2010). Biodegradation, biodistribution and toxicity of chitosan. *Advanced Drug Delivery Reviews*, 62(1), 3–11. DOI: [10.1016/j.addr.2009.09.004](https://doi.org/10.1016/j.addr.2009.09.004)



28. Sinha, V. R., Singla, A. K., Wadhawan, S., Kaushik, R., Kumria, R., Bansal, K., & Dhawan, S. (2004). Chitosan microspheres as a potential carrier for drugs. *International Journal of Pharmaceutics*, 274(1–2), 1–33. DOI: [10.1016/j.ijpharm.2003.12.026](https://doi.org/10.1016/j.ijpharm.2003.12.026)
29. Mohammed, M. A., Syeda, J. T. M., Wasan, K. M., & Wasan, E. K. (2017). An overview of chitosan nanoparticles and its application in non-parenteral drug delivery. *Pharmaceutics*, 9(4), 53. DOI: [10.3390/pharmaceutics9040053](https://doi.org/10.3390/pharmaceutics9040053)
30. Das, R. K., Kasoju, N., & Bora, U. (2010). Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells. *Nanomedicine: Nanotechnology, Biology and Medicine*, 6(1), 153–160. DOI: [10.1016/j.nano.2009.05.009](https://doi.org/10.1016/j.nano.2009.05.009)
31. Anitha, A., Deepagan, V. G., Divya Rani, V. V., Menon, D., Nair, S. V., & Jayakumar, R. (2011). Preparation, characterization, in vitro drug release and biological studies of curcumin loaded dextran sulphate-chitosan nanoparticles. *Carbohydrate Polymers*, 84(3), 1158–1164. DOI: [10.1016/j.carbpol.2011.01.005](https://doi.org/10.1016/j.carbpol.2011.01.005)
32. Mohanty, C., & Sahoo, S. K. (2010). The in vitro stability and in vivo pharmacokinetics of curcumin prepared as an aqueous nanoparticulate formulation. *Biomaterials*, 31(25), 6597–6611. DOI: [10.1016/j.biomaterials.2010.04.062](https://doi.org/10.1016/j.biomaterials.2010.04.062)
33. Yallapu, M. M., Jaggi, M., & Chauhan, S. C. (2012). Curcumin nanoformulations: A future nanomedicine for cancer. *Drug Discovery Today*, 17(1–2), 71–80. DOI: [10.1016/j.drudis.2011.09.009](https://doi.org/10.1016/j.drudis.2011.09.009)
34. Ghalandarlaki, N., Alizadeh, A. M., & Ashkani-Esfahani, S. (2014). Nanotechnology-applied curcumin for different diseases therapy. *BioMed Research International*, 2014, 394264. DOI: [10.1155/2014/394264](https://doi.org/10.1155/2014/394264)
35. Danaei, M., Dehghankhold, M., Ataei, S., Hasanzadeh Davarani, F., Javanmard, R., Dokhani, A., ... Mozafari, M. R. (2018). Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. *Pharmaceutics*, 10(2), 57. DOI: [10.3390/pharmaceutics10020057](https://doi.org/10.3390/pharmaceutics10020057)
36. Hoshyar, N., Gray, S., Han, H., & Bao, G. (2016). The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. *Nanomedicine*, 11(6), 673–692. DOI: [10.2217/nnm.16.5](https://doi.org/10.2217/nnm.16.5)
37. Blanco, E., Shen, H., & Ferrari, M. (2015). Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology*, 33(9), 941–951. DOI: [10.1038/nbt.3330](https://doi.org/10.1038/nbt.3330)
38. Wilhelm, S., Tavares, A. J., Dai, Q., Ohta, S., Audet, J., Dvorak, H. F., & Chan, W. C. W. (2016). Analysis of nanoparticle delivery to tumours. *Nature Reviews Materials*, 1, 16014. DOI: [10.1038/natrevmats.2016.14](https://doi.org/10.1038/natrevmats.2016.14)
39. Kilkenny, C., Browne, W. J., Cuthill, I. C., Emerson, M., & Altman, D. G. (2010). Improving bioscience research reporting: The ARRIVE guidelines for reporting animal research. *PLoS Biology*, 8(6), e1000412. DOI: [10.1371/journal.pbio.1000412](https://doi.org/10.1371/journal.pbio.1000412)
40. Percie du Sert, N., Hurst, V., Ahluwalia, A., Alam, S., Avey, M. T., Baker, M., ... Würbel, H. (2020). The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. *PLoS Biology*, 18(7), e3000410. DOI: [10.1371/journal.pbio.3000410](https://doi.org/10.1371/journal.pbio.3000410)
41. Hooijmans, C. R., Rovers, M. M., de Vries, R. B. M., Leenaars, M., Ritskes-Hoitinga, M., & Langendam, M. W. (2014). SYRCLE's risk of bias tool for animal studies. *BMC Medical Research Methodology*, 14, 43. DOI: [10.1186/1471-2288-14-43](https://doi.org/10.1186/1471-2288-14-43)
42. Festing, M. F. W., & Altman, D. G. (2002). Guidelines for the design and statistical analysis of experiments using laboratory animals. *ILAR Journal*, 43(4), 244–258. DOI: [10.1093/ilar.43.4.244](https://doi.org/10.1093/ilar.43.4.244)
43. Landis, S. C., Amara, S. G., Asadullah, K., Austin, C. P., Blumenstein, R., Bradley, E. W., ... Silberberg, S. D. (2012). A call for transparent reporting to optimize the predictive value of preclinical research. *Nature*, 490(7419), 187–191. DOI: [10.1038/nature11556](https://doi.org/10.1038/nature11556)
44. Seok, J., Warren, H. S., Cuenca, A. G., Mindrinos, M. N., Baker, H. V., Xu, W., ... Tompkins, R. G. (2013). Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proceedings of the National Academy of Sciences*, 110(9), 3507–3512. DOI: [10.1073/pnas.1222878110](https://doi.org/10.1073/pnas.1222878110)