Effects of Zeolite as a Drug Delivery System on Cancer Therapy: A Systematic Review

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Introduction

- Zeolite, an aluminosilicate, has a unique porous structure and pH-sensitivity that allows for the controlled uptake and release of anticancer drugs.
- Conventional anticancer drugs face drawbacks, such as poor specificity and high toxicity, which can lead to systemic toxicity for healthy tissues [1,2].
- Zeolite can mitigate the drugs' drawbacks by selectively releasing them in the acidic tumor microenvironment.
- **We reviewed *in vitro* and *in vivo* studies that evaluated the potential enhancement of various anticancer drugs using zeolites as a drug delivery nanoplatform.**

Methods

- **Databases:** PubMed, Scopus, Embase, Web of Science, and grey literature databases.
- No limits were set on the year or language of the publication.
- **Inclusion Criteria:** Full-text studies that pertained to the therapeutic effect of zeolites as a drug delivery system towards cancers.
- **Exclusion Criteria**: Studies that only reported the effect of pure zeolites on cancers. Exclude case reports, abstracts, notes, short communications, observational studies, and review articles/letters
- The initial search yielded 1279 studies. After exclusion of duplicates and application of inclusion and exclusion criteria, 53 full-text articles were selected.

Results

- Within the 53 selected articles, the most common anticancer drugs loaded were doxorubicin, 5-fluorouracil, curcumin, cisplatin, and miR-34a.
- The articles also employed a variety of both ZIFs and natural/synthetic zeolites. 36 studies utilized ZIFs, 9 utilized faujasite (FAU), 5 utilized Zeolite A/Linde Type A, and 3 utilized clinoptilolite.

Discussion

	What is it?	Problems	How can zeolite help?
Doxorubicin	• An anthracycline antibiotic • intercalates between the base pairs of DNA → inhibits topoisomerase II activity → prevents DNA replication → hinders protein synthesis	• lack of specificity • strong cardiotoxicity & cytotoxicity • multidrug resistance in cancer cells	• ↓ tumor volume; ↑ apoptotic cells • dual stimuli (ie. NIR laser, glutathione) further ↑ specificity • co-delivery with verapamil HCl or photosensitizers → reverse multidrug resistance and induce apoptosis.
5-fluorouracil	• antimetabolite drug • inhibits activity of thymidylate synthase and incorporates its metabolites into RNA and DNA	• lack of specificity • cytotytoxicity	• Can also add metal ions + organic ligands for synergistic therapeutic effect •↓ drug release in circulation, ↑ circulation time, ↑ biocompatibillity
Cisplatin	• crosslinks with DNA's purine bases to cause DNA damage and interfere with its repair mechanisms → apoptosis in cancer cells	• lack of specificity • cytotytoxicity • multidrug resistance in cancer cells	• ↑ specificity through pH- and ATP-responsive nanoplatform • ↑ cellular uptake and ↓ toxicity than cisplatin alone • co-delivery with oleanolic acid → reverse multidrug resistance and induce apoptosis.
Curcumin	• natural phenolic drug from turmeric • contains curcuminoids that block growth enzymes, modulate cellular progressions, and inibit lipid peroxidation and ROS production	• Poorly soluble in aqueous solutions → poor bioavailability → somewhat mitigated by a high dosage in oral formulations	• high drug encapsulation, good chemical stability, and fast drug release in tumor microenvironment • ↑ cytotoxicity to HeLa; ↑ antitumor efficacy in mice
mi-34a	• nucleic acid drugs that plan a vital role in miRNA modulation therapy	• delivery challenges due to *in vivo* stability and low delivery efficiency	•↓ anti-apoptotic Bcl-2 → ↑apoptosis • inhibit oncogenes AEG-1 & SOX-9 • inhibit tumor growth via synergistic gene/chemodynamic therapy

Conclusions

- **In vitro and in vivo tests reveal that loaded zeolites/ZIFs successfully delivers conventional chemotherapy drugs into the tumor microenvironment and enhance cancer cell uptake of the drugs.**
- Innovative surface modifications of zeolites can ↑ effectiveness of drug delivery
- **Future directions**: **1)** More in vivo studies to further support zeolites' tumor-targeting potential. **2)** extend the application of zeolites/ZIFs to other types of cancers, such as oral cancer.

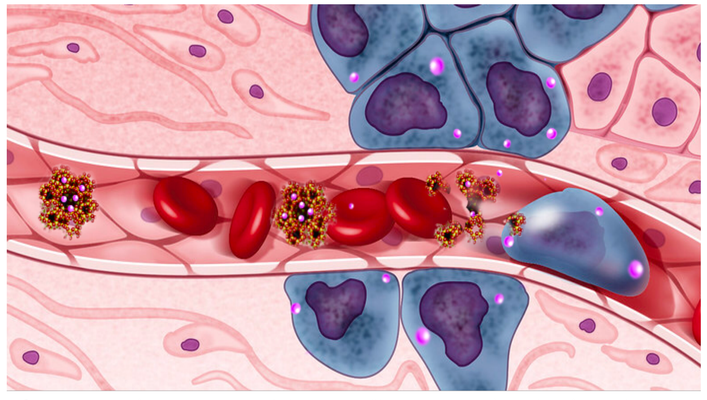

Figure 1: The pH-sensitive zeolite can selectively release anticancer drugs into the acidic tumor microenvironment while minimally impacting normal cells.

Works Cited

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