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REVIEW

Nanoformulated Phytochemicals Against Pancreatic Cancer: Emerging Advances in Therapeutic Strategies

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Background: Pancreatic cancer (PC) is an aggressive malignancy that has become one of the leading causes of cancer-related death worldwide. Remarkably, phytochemical-based nanoformulations have demonstrated great potential in combating cancer progression. Therefore, the objective of this scoping review is to analyze the most recent advances in the application of nanoformulated phytochemicals against PC.

Methods: This scoping review included English-language articles published between 2018 and 2025 that reported advances in the development of phytochemical-based nanoformulations and their therapeutic evaluation in PC biological models. On the contrary, nanoformulation studies focused on cancers other than PC were excluded, as were those based solely on computational analyses or addressing a phytochemical or a nanoplatform without combining both into a nanoformulation. Different types of scientific communication, such as reviews, book chapters, commentaries, and news, were not considered. The literature searches were conducted across 6 databases, including Scopus, Web of Science, and PubMed.

Results: In this work, 26 eligible studies with preclinical data encompassing more than 20 distinct nanotechnological platforms were reviewed. Most of the conclusions from these investigations were drawn from cell proliferation assays, primarily involving the PC cell lines PANC-1, MIA PaCa-2, and HPAF-II. A smaller subset of investigations supplemented these findings with data from xenograft PC models treated with phytochemical-loaded nanoformulations. Among the phytochemicals most frequently incorporated into the nanoformulations were paclitaxel, curcumin, lawsone, and sulforaphane.

Conclusion: Phytochemical-containing nanoformulations hold considerable promise as innovative therapeutic alternatives for PC. However, many available studies present notable limitations, such as the use of preclinical models with limited translatability to humans and a lack of a standardized method for preparing nanoformulations. Therefore, further investigations are required to clarify the therapeutic efficacy, safety profile, pharmacodynamics, pharmacokinetics, and overall clinical potential of these nanotechnology-driven approaches.

Keywords: pancreatic cancer, nanoformulation, phytochemicals, nanomedicine, anticancer therapy

Introduction

Pancreatic cancer (PC) is an aggressive and heterogeneous disease whose global incidence has been rising over the last years. The early stages of PC are usually asymptomatic, and the pancreas's deep anatomical position is one of the leading causes of delayed diagnosis.[1–3] During PC pathogenesis, tumors tend to invade nearby tissues rapidly and show limited responsiveness to both chemotherapy and radiotherapy.[4,5] In 2022, PC accounted for 510,566 new cases and 467,005 deaths worldwide, making it the sixth most common cause of death from cancer.[6] Further, in 2024, 66,440 new cases of PC and 51,750 PC-related deaths were estimated in the United States.[7] Remarkably, by 2050, the incidence of PC is projected to reach 998,663 new cases, representing an estimated 95.4% increase from 2022.[8] Although the clinical presentation of PC can be variable and

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often lacks specificity for a definitive diagnosis, the most commonly reported symptoms include weight loss, pain, depression, and ascites.[9] The poor prognosis and limited treatment success associated with PC also have a profound impact on the patients' quality of life, often leading to marked deterioration, particularly in psychological well-being, cognitive functions, and the ability to cope with the disease.[10]

Accordingly, the development of effective and safe treatments for PC is of utmost relevance for researchers and global authorities. Currently, the most common strategies for PC management include surgery, chemotherapy, and radiotherapy. Surgery (usually pancreaticoduodenectomy/Whipple procedure) is the only potentially curative option and is typically performed in early-stage cases.[11,12] Chemotherapy is frequently used either before (neoadjuvant) or after surgery (adjuvant), or as the primary treatment in advanced stages. Radiation therapy may also be combined with chemotherapy to help shrink tumors or alleviate symptoms.[11,12] However, over the last decade, numerous novel therapeutic candidates against PC have emerged, including non-coding RNA (ncRNA)-based drugs,[13,14] immunotherapeutic approaches,[15] oncolytic viruses,[16] phytochemicals,[17] and nanotechnological platforms.[18] Particularly, nanoparticles (NPs) have arisen as prospective therapeutic agents for cancer treatment due to their unique properties that allow them to function both as anticancer drugs and as delivery vehicles (nanocarriers).[19–23]

NPs are tiny particles (usually ranging from 1–100 nm) with unique properties that make them useful in medicine, especially for targeted drug delivery and combined therapy.[24–28] Some examples of NP systems studied for PC treatment include solid lipid NPs, polymeric NPs, liposomes, mesoporous silica NPs, peptide-based NPs, and engineered exosomes, among others.[29] On the other hand, phytochemicals comprise a diverse group of bioactive molecules produced by plants and are abundant in fruits, vegetables, grains, and other plant species. Most of these substances are not essential for primary physiological functions such as growth or reproduction and are therefore classified as secondary metabolites. Notably, extensive research over recent decades has demonstrated that many of these metabolites possess significant health-promoting properties, including the ability to reduce the risk of chronic conditions such as cancer, metabolic disorders, and inflammatory diseases, as well as to counteract oxidative stress.[30–33] Phytochemicals are gaining attention for their promising role in PC therapy as these compounds can suppress cancer development through a wide range of mechanisms, such as promoting programmed cell death, suppressing antiapoptotic signals, or impeding cell proliferation by interrupting the cell cycle.[17,34] Some of the key signaling pathways that mediate the anticancer activity of phytochemicals are nuclear factor kappa B (NF-κB) signaling, MAPK pathway, PI3K/AKT/mTOR pathway, and JAK-STAT pathway.[35] In addition, the most representative phytochemicals studied for PC therapy include apigenin, curcumin, fisetin, kaempferol, luteolin, paclitaxel, quercetin, and resveratrol.[17,34]

Interestingly, integrating NPs with phytochemicals offers a promising strategy for developing nanoformulations, combining the bioactive potential of plant-derived compounds with the advanced delivery capabilities of nanotechnology. In this regard, nanoformulations are nanotechnology-based systems that enhance the delivery and effectiveness of therapeutic compounds.[36] When used with phytochemicals, nanoformulations improve their stability, absorption, and bioavailability by protecting them and enabling controlled release.[37,38] Indeed, emerging evidence indicates that the application of nanotechnology in combination with phytochemicals can optimize delivery within the tumor microenvironment (TME) and enhance PC treatment efficacy.[39] Other advantages of nanoformulated phytochemicals comprise improved solubility, enhanced half-life of the bioactive compound, targeted delivery to cancer cells, minimized off-target effects, extended circulation time, and the possibility of combining the phytochemical with other anticancer therapies through the design of co-loaded nanoformulations.[40,41] Some of the advantages and potential mechanisms of action of nanoformulated phytochemicals are depicted in Figure 1.

It is worth noting that there are currently some FDA-approved nanoformulated phytochemical drugs that are either licensed or under clinical trials for PC treatment, including Abraxane (a paclitaxel albumin-stabilized NP formulation) in combination with gemcitabine, Genexol-PM (also known as IG-001, cynviloq, or nant-paclitaxel; a paclitaxel-loaded micellar diblock copolymer), as well as Onivyde (an irinotecan hydrochloride liposome).[42–45] Accordingly, these facts indicate that phytochemical-based nanoformulations have great potential to reach the clinical landscape of PC therapeutics in the near future, underscoring the importance of critically examining recent advances in this research arena. Some of the most representative registered clinical trials (https://clinicaltrials.gov/) evaluating nanoformulated phytochemicals against PC are shown in Supplementary Table 1.

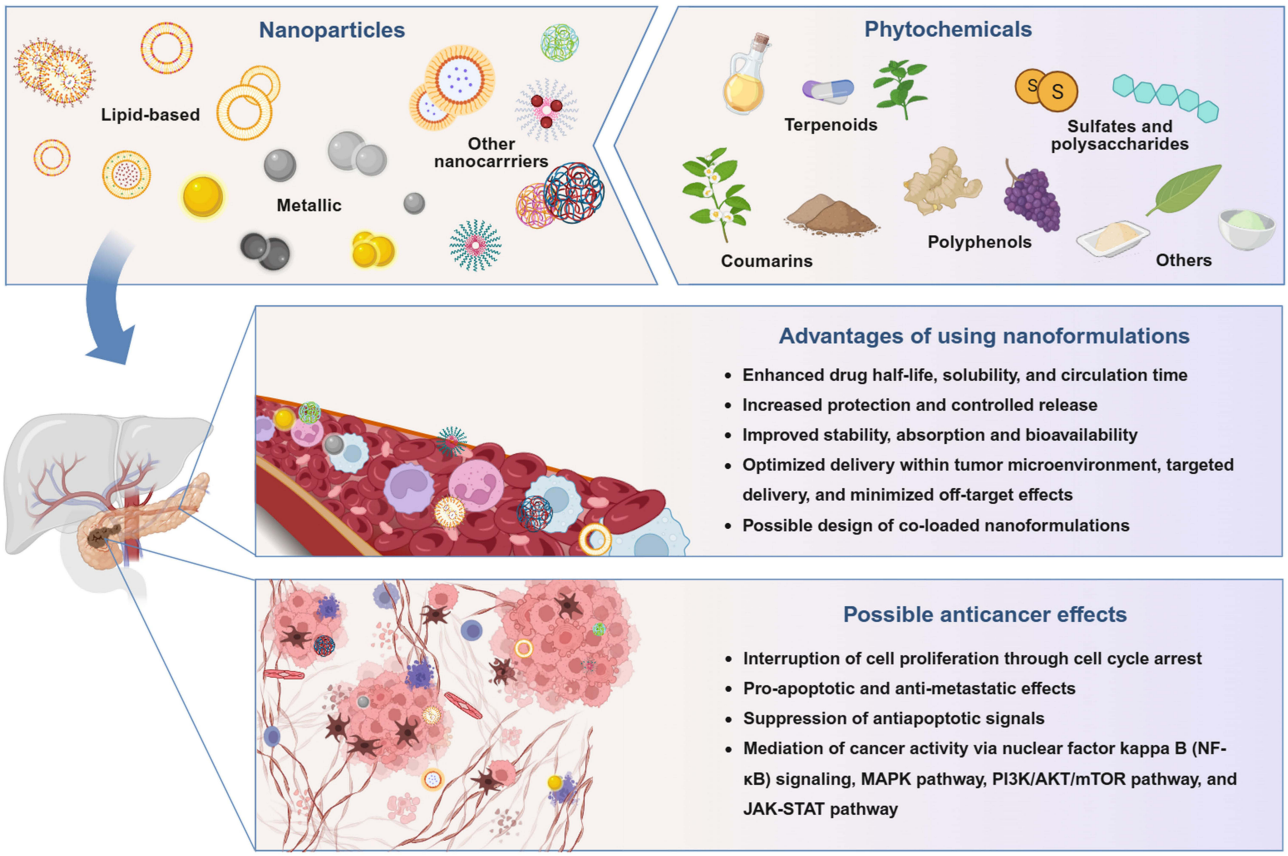

Figure 1 Overview of the components of nanoformulated phytochemicals for PC, the advantages of using nanotechnology-based formulations of phytochemicals, and their potential anticancer effects. Nanocarriers enhance drug half-life, stability, solubility, and targeted delivery while reducing off-target effects. These nanoformulations cause various anticancer responses, including cell-cycle arrest, pro-apoptotic activity, anti-metastatic effects, and the modulation of key signaling pathways like NF-κB, MAPK, PI3K/AKT/mTOR, and JAK-STAT (created with a licensed version of BioRender.com).

Despite the fact that several noteworthy reviews have discussed the therapeutic applications of phytochemical-based nanoformulations against PC,[39,46–48] the availability of reviews in this field that adhere to the strict Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[49,50] is still scarce. In addition, reports based on recent studies in PC biological models can provide a broad overview of data that can be of great benefit to oncologists and policymakers in developing innovative therapies for PC. Therefore, this scoping review aims to comprehensively discuss the novel advances in the exploration of the therapeutic potential of phytochemical nanoformulations for PC. Additionally, this work does not seek to replicate or update earlier reviews. By moving beyond a purely narrative synthesis and undertaking a more rigorous, in-depth examination of the available literature, our work focuses on analyzing recent progress and identifying areas requiring further refinement in the design of nanoformulated phytochemicals for PC therapeutics. Ultimately, drawing on our analysis, we outline a series of recommendations to strengthen the scientific rigor of forthcoming studies and promote greater uniformity in methodological descriptions and the reporting of experimental findings.

Materials and Methods

This scoping review was conducted in accordance with the PRISMA 2020 guidelines[49] and the PRISMA-ScR guidelines.[50] The entire methodological process was carried out without the use of automation tools and independently by four reviewers (LAB-V, APR-G, KAM-A, and GER-G). Any disagreements or ambiguities encountered during the process were discussed and resolved with the other four reviewers (PS, GL-B, AKD, and SP). No other protocol was developed or registered beyond the methods detailed in this article.

Eligibility Criteria

In this scoping review, we included articles published in English between 2018 and 2025. The study selection procedure was based on the PICO framework, determined as follows: biological models of PC (Population), treated with a phytochemical-based nanoformulation (Intervention), and the nanomedicine's anticancer effect evaluated (Outcome). In this case, the Comparison element of the PICO framework was not explicitly considered, as the included studies inherently assessed the impact of the corresponding nanoformulations by contrasting their outcomes between treated biological models and their respective control groups (untreated). Thus, studies exploring the anticancer effects of nanoformulated phytochemicals in biological models of PC were included in this scoping review. Conversely, we did not include reports in which phytochemical nanoformulations were tested against other cancer types. Articles relying solely on bioinformatic approaches, or those focusing exclusively on either a phytochemical or a nanotechnological platform, without addressing the design and application of a nanoformulation, were also excluded. Other scientific materials were also omitted, including review papers, retracted articles, book chapters, commentaries, conference abstracts, and retracted studies, news, among others.

Search Strategy, Information Sources, and Study Selection

The literature searches for this scoping review were performed on February 3, 2025. Seeking to maximize the scope of our searches, we considered six bibliographic databases during the search methodology. Such databases were Scopus, Web of Science, PubMed, Taylor & Francis Journals, Wiley Online Library, and Gale Academic OneFile. General searches on Google Scholar complemented the strategy. Besides, to maintain the relevance and concordance of the collected studies with the focus of our investigation, our searches were limited to abstracts, or title and abstract in the case of PubMed, and restricted to publications from the past six years. The keyword combinations were carefully crafted and tested through preliminary searches to confirm their alignment with the established inclusion and exclusion criteria (no records were retrieved during these primary searches). Detailed information on the database searches, including keywords used, coverage periods, and specific search strings, is provided in Supplementary Table 2.

All the database searches were performed in triplicate using the previously designed search strings and date ranges to ensure reproducibility. Duplicate entries were removed using the Rayyan free web app for systematic reviews.[51] The titles and abstracts of the remaining studies were manually screened in the same web app using the predetermined inclusion and exclusion criteria. Subsequently, the full-text versions of the potentially eligible articles were retrieved. The non-open-access articles were obtained either through institutional access credentials or via interlibrary loan services, both provided by our institution, ie, Tecnológico de Monterrey. Finally, the complete texts were manually screened in the Rayyan app and selected or excluded according to the established eligibility criteria.

Data Extraction and Data Items

The data extraction procedure was conducted through a thorough examination of the full texts of the selected articles. From this analysis, the data items collected from the articles consisted of the first author and year of publication, the type of nanotechnological platform and phytochemical used in the nanoformulation, the encapsulation/loading percentage of the phytochemical in the nanoformulation or any data related to the amount of phytochemical present within the nanoformulation, the PC biological model used for testing the nanoformulation, as well as the effective dose against PC or measurable outcome reported by the authors in the evaluated PC cell line (eg, IC_{50} or cell colony survival fraction).

Data Synthesis and Analysis

To perform data synthesis and analysis, the studies were classified by the type of nanotechnological platform used as the carrier in the nanoformulation. This was due to the wide variability in plant-derived molecules used in the studies, which made it difficult to categorize the research by phytochemical type. In contrast, classifying based on nanotechnological platforms yielded three sections. The content of each selected article was carefully analyzed and summarized in the main body of our review, and the data items were organized in a summary table.

Results

Selection of Sources of Evidence

At the first stage of the search and selection process, 214 records were extracted from the databases, and 94 duplicate entries were removed. Later, the titles and abstracts of the remaining 120 records were screened, and 88 were excluded because they were outside the scope of the review. The complete texts of the remaining 32 studies were sought for retrieval, and 1 of them could not be obtained. As this is a scoping review, aimed at mapping the existing evidence and providing recommendations for future publications in this field rather than conducting a statistical synthesis, the absence of this single study is unlikely to introduce meaningful bias into our overall suggestions and conclusions. Notwithstanding this, any potential impact could only be determined through a formal risk-of-bias assessment in a systematic review. Following full-text screening, 5 articles were excluded based on the predefined inclusion and exclusion criteria outlined in our methodology. Consequently, this scoping review ultimately comprised 26 eligible records. The selection methodology is illustrated in Figure 2.

General Overview of the Included Studies

According to the data analyzed in this review, the nanocarriers used to design different nanoformulations targeting PC include a wide range of platforms. Still, they are not limited to, metallic NPs, solid lipid NPs (SLNs), poly(lactic-co-glycolic acid) (PLGA) NPs, niosomes, liposomes, among others. The most frequently reported phytochemicals in these nanoformulations were paclitaxel (3 studies out of 26), curcumin (3 studies out of 26), lawsone (2 studies out of 26), and sulforaphane (2 studies out

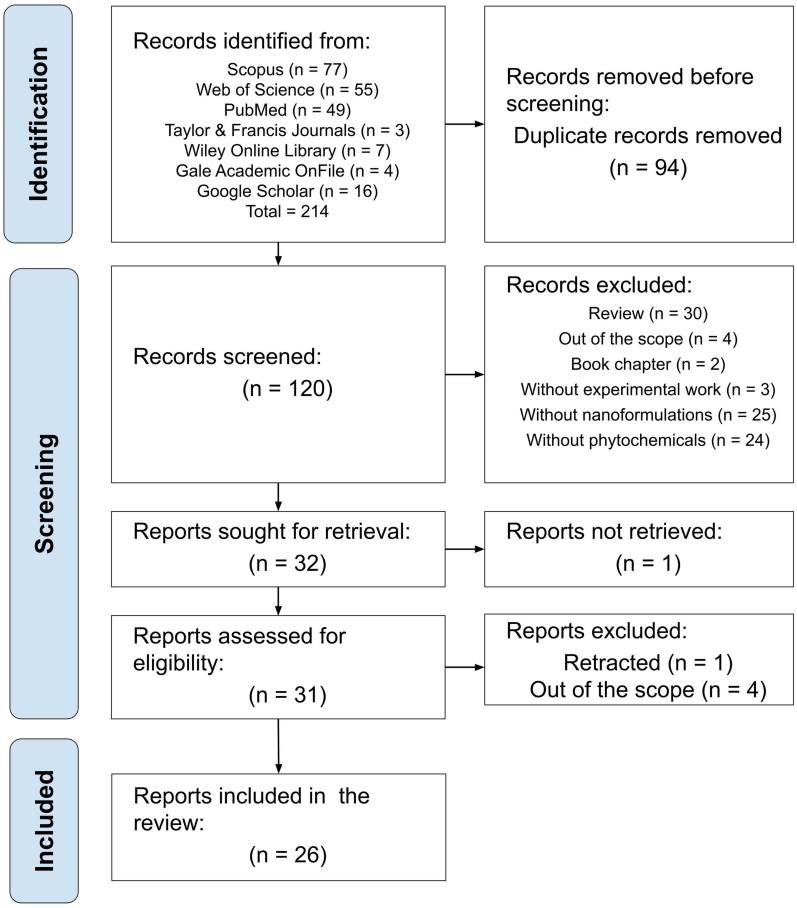

Figure 2 PRISMA flow diagram summarizing the identification and selection process of the studies included in this scoping review. A total of 214 records were identified across the databases (Scopus: 77, Web of Science: 55, PubMed: 49, Taylor & Francis Journals: 3, Wiley Online Library: 7, Gale Academic OnFile: 4, and Google Scholar: 16). After removing 94 duplicates, 120 records were screened, of which 88 were excluded based on their titles and abstracts (review articles, out-of-scope studies, book chapters, lack of experimental work, absence of nanoformulations, or absence of phytochemicals). Full-text retrieval was attempted for 32 articles; however, one could not be obtained despite searching in multiple sources. Of the 31 full texts retrieved, five were excluded (retracted or out of scope), resulting in 26 studies included in the review.

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of 26). On the other hand, some of the less common phytochemicals used in the nanodrugs include camptothecin, nimbolide, herniarin, berbamine, and 4-farnesyloxycoumarin, amongst others. The most commonly used cell lines to test the cytotoxicity of the phytochemical-loaded nanoformulations were PANC-1 (15 out of 26 studies), MIA PaCa-2 (7 studies out of 26), and HPAF-II (3 studies out of 26), while less commonly used cell lines included AsPC-1, BxPC-3, and RIN-5F. However, not all studies extended the evaluation of phytochemical-based nanoformulations to assess their therapeutic efficacy and safety in animal models. In this regard, only 5 of 26 investigations tested the anticancer effect of their corresponding phytochemical nanoformulation in animal models, including Kras* orthotopic murine models of PC, genetically engineered mouse models of PC, xenograft PC mouse models, and xenograft PC zebrafish models. Table 1 enlists the included studies in chronological order and presents the data items extracted from each report, and a graphical summary of some key characteristics detected in the studies is presented in Supplementary Figure 1.

Metallic Nanocarriers

Metallic NPs are gaining attention as powerful tools for cancer drug delivery, thanks to their ability to improve stability, solubility, and targeted release.[78] On the other hand, phytochemicals, with their natural anticancer potential, often face challenges like poor absorption and rapid metabolism, which limit their clinical use.[79] Incorporating phytochemicals into metallic NPs can help overcome these barriers, enhancing efficacy and potentially reducing side effects.[80] In the context of PC, a malignancy characterized by late diagnosis, high resistance to conventional therapies, and poor prognosis, metallic NP-based delivery of phytochemicals offers a promising strategy to potentiate their anticancer potential and expand the therapeutic landscape for this challenging disease, as it has been evidenced in different remarkable reports.

For instance, in a study conducted by Thipe et al,[54] resveratrol was employed both as a reducing and capping agent to synthesize resveratrol-conjugated gold NPs (Res-AuNPs), with gum arabic (GA) incorporated to enhance the colloidal stability of Au NPs and to serve as a supportive matrix for improved trans-resveratrol delivery. These authors systematically varied the thickness of the resveratrol layer coating the Au NP surface to examine its impact on anti-tumor activity against breast (MDA-MB-231), pancreatic (PANC-1), and prostate (PC-3) cancer cell lines. As a result, the nanoformulation with a higher resveratrol coating, ie, 3× Res-AuNPs and 3× Res-GA-AuNPs, demonstrated significantly superior antiproliferative effects, attributed to enhanced cellular uptake and increased resveratrol bioavailability. Lower doses did not achieve effective IC_{50} values; these formulations were the only ones capable of reaching effective IC_{50} values of 79 μg/mL (3× Res-AuNPs) and 72 μg/mL (3× Res-GA-AuNPs) in PANC-1 cells. These findings illustrate a clear correlation between the density of resveratrol coating and therapeutic efficacy, highlighting Res-AuNPs as promising candidates for oncological applications.

Karabatak et al[65] described the development of multifunctional copper oxide (CuO) NPs coated with kappa carrageenan and polyethylene glycol (PEG), forming κCA/PEG-CuO NPs as both a digital colorimetric biosensor for dopamine and an anticancer drug nanocarrier. The NPs were also loaded with the well-established anticancer drug cisplatin (Cis) and, after physicochemical characterization, MTT assays were performed to assess cytotoxic activity of the nanoformulation on PC cells (MIA PaCa-2) as well as in other cell lines (hepatocellular carcinoma cells and human umbilical vein endothelial cells). The resulting IC_{50} value for Cis-loaded κCA/PEG-CuO NPs on MIA PaCa-2 cells (3.5 μg/mL) was significantly lower compared to the IC_{50} value of free Cis (12.5 μg/mL). The cytotoxic effect was attributed to the nanoformulation's capacity to generate ROS, induce apoptosis via the mitochondrial (intrinsic) pathway, activate caspases, trigger the p53-mediated DNA damage response, and activate MAPK signaling. The authors also observed that the undiluted Cis-loaded κCA/PEG-CuO NPs exhibited cytotoxicity in 42% of MIA PaCa-2 cells. In contrast, only 28% cytotoxicity was observed in non-cancerous HUVEC cells, thus demonstrating selective cytotoxicity toward cancer cells and reinforcing its potential as a therapeutic agent against PC.

In research conducted by Abdelhameed et al,[72] bimetallic ZnO-CuO NPs were loaded with the phytochemicals rhein or emodin via a green synthesis method using the plant extract as a natural reducing and stabilizing agent, to assess their anticancer efficacy against PC and ovarian cancer cell lines. Regarding the therapeutic effect of these nanoformulated phytochemicals against PC, MTT assays in the PANC-1 cell line showed IC50 values of 11.1 μg/mL for rhein and 6.7 μg/mL for emodin. Conversely, those values decreased significantly once the phytochemicals were incorporated into the bimetallic NPs, to 1.4 μg/mL for rhein and 0.64 μg/mL for emodin. The induction of apoptosis, which underlies these results, was confirmed through annexin V/PI staining. It was found that the delivery system induced an overall apoptotic cell death rate of 34.9% in PC cells,

Table 1 Information Derived from Studies Addressing the Therapeutic Applications of Nanoformulated Phytochemicals Against PC

First Author and Publication Year	Nanotechnological Platform	Phytochemical	Name of the Nanoformulation	Data Regarding Loading/Encapsulation	Biological Model	In vitro Potency	In vivo Administration Regimen (If Evaluated)
Zhao et al (2018)[52]	Polymeric micelles	Paclitaxel (co-delivered with cyclopamine)	M-CPA/PTX	100.5 ± 3.5% for paclitaxel at day 90 (relative loading of paclitaxel)	Kras* orthotopic murine model of PC, which has a mutation in the oncogene $Kras^{G12D}$	NA	5 mg/kg/drug for 3 days administered intravenously
					Genetically engineered mouse model of PC (KPC-Luc mice that were bred from LSL-$Kras^{G12D/+}$, LSL-$p53^{T172H/+}$, Pdx1-Cre mice)	NA	5 mg/kg/drug/dose over 2 weeks (6 doses in total) administered intravenously
Desai et al (2019)[53]	Self-microemulsifying drug delivery system	Sulforaphane (codelivered with loratadine)	LOR SMEDDS-SFN	Not reported for sulforaphane	MIA PaCa-2 cell line	IC_{50}: 0.64 μM	NA
					PANC-1 cell line	IC_{50}: 0.82 μM	NA
Thipe et al (2019)[54]	Gold NPs	Resveratrol	Res-AuNPs and Res-GA-AuNPs (gum arabic was used to stabilize the AuNPs in one nanoformulation)	Res-AuNPs: 423 ng/mL (resveratrol found in the AuNPs)	PANC-1 cell line	Res-AuNPs (IC_{50}): Not reported	NA
				3× Res-AuNPs: 16,181 ng/mL (resveratrol found in the AuNPs)		3× Res-AuNPs (IC_{50}): 79 μg/mL	NA
				Res-GA-AuNPs: 914 ng/mL (resveratrol found in the AuNPs)		Res-GA-AuNPs (IC_{50}): 200.4 μg/mL	NA
				3× Res-GA-AuNPs: 18,350 ng/mL (resveratrol found in the AuNPs)		3× Res-GA-AuNPs (IC_{50}): 72 μg/mL	NA
Massey et al (2019)[55]	Multi-layered Pluronic F127 and polyvinyl alcohol stabilized, and poly-L-lysine coated poly(lactic-co-glycolic acid) NP formulation	Paclitaxel	PPNPs	72-86% (encapsulation efficiency)	MIA PaCa-2 cell line	IC_{50}: ~5 nM	NA
					PANC-1 cell line	IC_{50}: ~5 nM	NA
					HPAF-II cell line	IC_{50}: 20 nM	NA
					Orthotopic xenograft PC model of athymic nude mice (generated with HPAF-II-luciferase cells)	NA	An initial dosage of 1 mg/kg twice weekly for two weeks, followed by 10 mg/kg twice weekly for three weeks

(*Continued*)

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Table 1 (Continued).

First Author and Publication Year	Nanotechnological Platform	Phytochemical	Name of the Nanoformulation	Data Regarding Loading/Encapsulation	Biological Model	In vitro Potency	In vivo Administration Regimen (If Evaluated)
Desai et al (2020)[56]	Self-microemulsifying drug delivery system	Sulforaphane (codelivered with loratadine)	LOR SMEDDS-SFN	Not reported	MIA PaCa-2 cell line	Survival fraction of 0.20 in a colony formation assay	NA
					PANC-1 cell line	Survival fraction of 0.35 in a colony formation assay	NA
Chauhan et al (2020)[57]	Nanocomplexes of modified pectin and tannic acid	Tannic acid (used due to its anticancer properties and for its ability to interact with other drugs and make them soluble)	MPT-NCs	> 92–95% (loading efficiency)	PANC-1 cell line	Gemcitabine-loaded MPT-NCs (IC_{50}): 71.92 nM 5-fluorouracil-loaded MPT-NCs (IC_{50}): 44.9 µM Irinotecan-loaded MPT-NCs (IC_{50}): 35 µM	NA
					HPAF-II cell line	Gemcitabine-loaded MPT-NCs (IC_{50}): 70.74 nM 5-fluorouracil-loaded MPT-NCs (IC_{50}): 88.8 µM Irinotecan-loaded MPT-NCs (IC_{50}): 50.41 µM	NA
Shetty et al (2020)[58]	Poly(lactic-co-glycolic acid) NPs	Paclitaxel (co-delivered with gemcitabine in some nanoformulations)	PPNPs	Not reported	PANC-1 and HPAF-II cell lines	Not reported, but the article mentions that the nanoformulation PPNPs (10 nM)/GEM (100 nM) significantly inhibited the proliferation of PC cells when compared to the other treatments	NA
Greene et al (2020)[59]	Antibody-targeted NPs created using cetuximab F (ab)	Camptothecin	CPT-loaded nanoformulations	Native CTX F(ab) CPT NP with the polymer PLGA-PEG-NHS: 3.4 ± 1.8 µg/mg (camptothecin entrapped)	MIA PaCa-2 cell line	Not reported, but a clonogenic assay indicated a significant reduction in colony formation mediated by the modified CTX F (ab) CPT NP [disulfide] nanoformulation	NA
				Modified CTX F(ab) CPT NP [disulfide] with the polymer PLGA-PEG-azide: 3.9 ± 1.4 µg/mg (camptothecin entrapped)			NA
Maniam et al (2021)[60]	Niosomes	Tocotrienols (Span 60, cholesterol and D-α-tocopheryl polyethylene glycol 1000 succinate, codelivered with gemcitabine)	GEM + TRF niosome	34.52 ± 0.10% (encapsulation efficiency of tocotrienols)	Panc 10.05 cell line	IC_{50}: Reported graphically	NA
					SW 1990 cell line	IC_{50}: Reported graphically	NA
					AsPC-1 cell line	IC_{50}: Reported graphically	NA
					BxPC-3 cell line	IC_{50}: Reported graphically	NA

Markowski et al (2021)[61]	Poly(lactic-co-glycolic acid) NPs	Ursolic acid	UA-PLGA	47.4 ± 10.5% (encapsulation efficiency)	AsPC-1 cell line	IC_{50}: 10.1 ± 1 μM	NA
					BxPC-3 cell line	IC_{50}: 12.6 ± 4.5 μM	NA
Elbialy et al (2022)[62]	Casein NPs coated with alginate and chitosan, and decorated with folic acid	Curcumin	fCs-Alg@CCasNPs	75% (encapsulation efficiency)	PANC-1 cell line	IC_{50}: 17.5 mg/mL	NA
					Xenograft PC model of BALB/c mice (generated with Ehrlich ascites tumor)	NA	40 μL intratumorally (2 doses/week) or 100 μL intraperitoneally (2 doses/week)
Singh et al (2022)[63]	Poly(lactic-co-glycolic acid) NPs	Nimbolide	Nim NPs	~90% (encapsulation efficiency)	MIA PaCa-2 cell line (induced to form pancreatospheres)	IC_{50} at 48 h: 4.8 μM IC_{50} at 72 h: 0.59 μM	NA
Karole et al (2022)[64]	Effervescent-based self-assembled nano-gas carrier (NG)	Luteolin	LUT-NG	Not reported	PANC-1 cell line	IC_{50}: 24.98 μM	NA
Karabatak et al (2022)[65]	Kappa carrageenan/ polyethylene glycol-CuO NPs	Kappa carrageenan (used to entrap cisplatin)	κCA/PEG-CuO NPs	Not reported	MIA PaCa-2 cell line	Cisplatin-loaded κCA/PEG-CuO NPs (IC_{50}): 3.5 μg/mL	NA
Tang et al (2022)[66]	Dopamine polymerization-polylactide-TPGS NPs	Berbamine	BBM-NPs	Not reported	PANC-1 cell line	At 0.5 μg/mL, both PANC-1 and AsPC-1 cells showed a marked reduction in activity compared to controls	NA
					AsPC-1 cell line		BA
					Xenograft PC model of BALB/c nude mice (generated with PANC-1 cells)	NA	40 mg/kg of body weight of BBM-NPs on days 1, 3, and 5
Arya et al (2022)[67]	Poly(lactic-co-glycolic acid)-chitosan core-shell NPs	Embelin (co-delivered with RPI-1)	PaCTNDS	76.3% (encapsulation efficiency of embelin)	PANC-1 cell line	IC_{50}: Not assessed for the nanoformulation	NA
					Xenograft PC model of zebra fish (generated with PANC-1 cells)	NA	50 nL of 5 mg/mL of PaCTNDS administered intraperitoneally
Ilbeigi et al (2023)[68]	Selenium-polyethylene glycol-curcumin NPs	Curcumin	Se-PEG-Cur NPs	Not reported	ASPC1 cell line	Se-PEG-Cur NPs (IC_{50}): 8 μg/mL Cell proliferation was notably inhibited with a combination of ultrasound radiation, Se-PEG-Cur NPs (at IC_{50}), and gemcitabine (at IC_{50}: 62 μg/mL)	NA
Ghafaripour et al (2023)[69]	Poly(lactic-co-glycolic acid) NPs modified with folic acid and chitosan	Lawsone	LWS-PLGA-FA-CS NPs	81% (encapsulation efficiency)	PANC-1 cell line	IC_{50}: 118.4 (the article does not clearly define the units as μL or μg/mL)	NA
Delkhah et al (2023)[70]	Solid lipid NPs	Herniarin	Her-SLN-NPs	91.199% (encapsulation efficiency)	PANC-1 cell line	IC_{50}: 83.744 μL	NA

(*Continued*)

Table 1 (Continued).

First Author and Publication Year	Nanotechnological Platform	Phytochemical	Name of the Nanoformulation	Data Regarding Loading/Encapsulation	Biological Model	In vitro Potency	In vivo Administration Regimen (If Evaluated)
Firouzi Amandi et al (2024)[71]	Magnetic niosomal NPs	Resveratrol	RSV-MNIONPs	90.38 ± 0.1% (encapsulation efficiency)	Capan-1 cell line	IC_{50} at 24 h: 25 μg/mL	NA
						IC_{50} at 48 h: 18 μg/mL	NA
						IC_{50} at 72 h: 12 μg/mL	NA
Abdelhameed et al (2024)[72]	Bimetallic ZnO-CuO NPs	Rhein and emodin	Rhein-conjugated ZnO-CuO NPs	Not reported	PANC-1	Rhein-conjugated ZnO-CuO NPs (IC_{50}): 1.4 μg/mL	NA
			Emodin-conjugated ZnO-CuO NPs			Emodin-conjugated ZnO-CuO NPs (IC_{50}): 0.64 μg/mL	NA
Naeeni et al (2024)[73]	Liposomal NPs coated with chitosan-folate	Lawsone	L-LNPs-CF	83.8% (encapsulation efficiency)	PANC (specific cell line not specified)	IC_{50}: 171.94 μg/mL	NA
Pour et al (2024)[74]	Solid lipid NPs	Naringenin	Nar-SLN	Not reported	RIN-5F cell line	IC_{50}: 478.1611 μg/mL	NA
Al-Baidhani et al (2025)[75]	Liposomal NPs	4-farnesyloxycoumarin	4-FLC-LNPs	82.4% (encapsulation efficiency)	PANC (specific cell line not specified)	IC_{50}: > 500 μg/mL	NA
Demirci et al (2025)[76]	Emulsome NPs	Curcumin	CurEm	4.4% (encapsulation efficiency)	PANC-1	IC_{50} at 24 h: 132.58 μM	NA
						IC_{50} at 48 h: 37.76 μM	NA
						IC_{50} at 72 h: 32.43 μM	NA
Al Rashid et al (2025)[77]	Glyceryl monooleate NPs	Berberine	BER-GNPs	95 ± 2.55% (encapsulation efficiency)	MIA PaCa-2 cell line	IC_{50}: 37.16 ± 1.44 μg/mL	NA
					PANC-1 cell line	IC_{50}: 32.04 ± 2.03 μg/mL	NA

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compared to 4.19% in untreated controls, and caused cell cycle arrest in the S-phase of PANC-1 cell proliferation, as shown by a cell cycle analysis. Finally, an RT-PCR-based gene expression analysis revealed that the treatment with emodin-loaded NPs upregulated the pro-apoptotic genes *p53, BAX* and *caspases 3, 8*, and *9*, while downregulating the anti-apoptotic gene *BCL2*, thus indicating the activation of both mitochondrial and death receptor apoptotic pathways. The enhanced stability, solubility, and controlled release provided by the nanoformulations underlie their superior efficacy, highlighting their potential as promising therapeutic candidates against PC.

Lipid-Based Nanocarriers

Lipid-based nanocarriers are nanoscale drug-delivery systems composed primarily of lipids, designed to encapsulate and deliver therapeutic agents. They have emerged as versatile platforms for cancer therapy, offering biocompatibility, controlled drug release, and improved bioavailability of therapeutic compounds.[81] Encapsulation in lipid-based systems helps overcome the drawbacks inherent to phytochemicals, facilitating their delivery and enhancing their therapeutic impact.[82] Remarkably, lipid-based nanocarriers represent a promising strategy to maximize the benefits of phytochemicals in PC therapy.

Co-encapsulation of gemcitabine (GEM) and a tocotrienol-rich fraction (TRF) in niosomes was explored by Maniam et al[60] as a dual-drug delivery strategy for PC. The nanoformulation was prepared via the film hydration method at a 1:1 drug ratio, and the entrapment efficiencies were 20.07 ± 0.22% for GEM and 34.52 ± 0.10% for TRF, demonstrating stability over several months. In vitro assays using multiple PC cell lines (ie, Panc 10.05, SW 1990, AsPC-1, and BxPC-3) revealed that the antiproliferative effect of GEM was markedly enhanced in combination with TRF, with up to a 2.78-fold increase in Panc 10.05 cells. In addition, niosome-mediated delivery further enhanced this effect, yielding a 9-fold increase in cytotoxicity. Although IC_{50} values for the nanoformulation were not explicitly reported, but only presented graphically, the data clearly support enhanced efficacy. Importantly, modulation of the TRF: GEM ratio within the niosomes significantly enhanced GEM uptake in Panc 10.05 cells. These findings provide a proof-of-concept for niosomal-mediated dual-drug delivery in PC, underscoring its potential to improve therapeutic outcomes.

Tang et al[66] crafted berbamine-loaded dopamine polymerization-polylactide-d-α-tocopheryl PEG 1000 succinate (TPGS) NPs (BBM-NPs). The nanoformulation was first characterized and then evaluated in vitro using the PANC-1 and AsPC-1 cell lines and in vivo in PC xenograft models in BALB/c nude mice. It was found that the nanosystem remained stable, with an average particle size of 134 nm, and exhibited a slow, sustained drug-release profile compared to free BBM. Indeed, the release pattern proved pH-dependent, being slower at alkaline pH. In vitro analyses showed that the BBM-NPs suppressed migration and invasion and exerted a more substantial inhibitory effect on cancer cell viability and proliferation than free BBM in the two cell lines. The nanoformulation was more cytotoxic; however, no IC_{50} value was reported. Mechanistically, BBM-NPs promoted apoptosis, induced reactive oxygen species production, and increased the expression of BAX, Cleaved caspase-3, and γ-H2AX, while decreasing the protein expression of MMP2, MMP9, and BCL2 in PANC-1 and AsPC-1 cells.[66]

On the other hand, a xenograft tumor model of PC was generated by subcutaneously injecting 4-week-old male BALB/c nude mice with 1×10^6 PANC-1 cells. Subsequently, mice were administered with 40 mg/kg body weight of free BBM and BBM-NPs on the first, third and fifth days, and tumor growth was monitored for 30 days until the mice were sacrificed. Results of this in vivo study showed that, although there were no significant changes in the mice´s body weight, both free BBM and BBM-NPs exhibited a strong inhibitory effect on the growth of xenograft tumors, as demonstrated by tumor weight measurements. Interestingly, BBM-NPs had the greatest impact on tumor weight, showing the plausibility of this nanoformulation against PC.[66]

Delkhah et al[70] evaluated the cytotoxic and anti-metastatic properties of herniarin (7-methoxycoumarin) encapsulated in SLNs against various human cell lines, including the PANC-1 PC line, which showed the highest sensitivity with an IC_{50} of approximately 83.7 µM. Viability assays (MTT), flow cytometry, fluorescent staining (DAPI), and qPCR demonstrated that herniarin-SLNs induce apoptosis via both intrinsic and extrinsic pathways by increasing the expression of *CASP9, CASP8*, and *CASP3*, while reducing BCL2 expression. In addition, significant downregulation of the metastasis-related genes *MMP2* and *MMP9* was observed, which may be mediated by PI3K/Akt pathway inhibition, as suggested by previous studies. The authors propose that herniarin-SLNs represent a promising nanotherapeutic

strategy for the treatment of PC, as they induce apoptosis and reduce tumor metastatic potential by significantly decreasing MMP2 gene expression, as evaluated by RT-PCR.

Later, Firouzi Amandi et al[71] developed resveratrol-loaded magnetic niosomal NPs (RSV-MNIONPs) as an advanced delivery system for PC therapy. The formulation achieved a high encapsulation efficiency (85%) and exhibited sustained release, favoring stability and controlled drug availability. In Capan-1 cells, RSV-MNIONPs markedly enhanced cytotoxicity, particularly under an external magnetic field, and induced a more pronounced cell cycle arrest at the G0/G1 checkpoint than free resveratrol. Moreover, the minimum IC_{50} for RSV-MNIONPs in this study was 12 μg/mL at 72 hours. These effects were closely associated with significant modulation of key regulatory genes, including the upregulation of pro-apoptotic markers (*BAX, P53, FAS*) and the downregulation of anti-apoptotic and proliferative genes (*Bcl-2, Cyclin D, hTERT*). Such transcriptional reprogramming provided a mechanistic explanation for the nanoformulation's improved anticancer efficacy, supporting its potential as a robust therapeutic platform for PC.

Naeeni et al[73] synthesized and characterized lawsone-loaded liposomal NPs coated with chitosan-folate (L-LNPs-CF). The formulation displayed high encapsulation efficiency (83.8%) and demonstrated strong antioxidant capacity, as evidenced by significant free radical scavenging in DPPH and ABTS assays. Biological evaluation further demonstrated that L-LNPs-CF markedly inhibited PC cell proliferation (IC_{50} = 171.94 μg/mL) and promoted apoptosis by upregulating caspase-3, caspase-9, and Bax. Additionally, the L-LNPs-CF nanoformulation did not exert cytotoxicity on normal cells (represented by the HFF cell line) at any of the concentrations tested. Collectively, these findings indicate that L-LNPs-CF has an enhanced effect against PC cells, potentially driven by the incorporation of chitosan, which may facilitate cellular uptake of the nanodrug, and represents a promising therapeutic strategy against PC.

In another report by Pour et al.[74] SLNs loaded with naringenin (Nar-SLNs) were developed. The cytotoxic effect of Nar-SLNs was evaluated in vitro, using Rat Pancreatic RIN-5F cells through the MTT assay, and the concentrations tested varied in a range from 4–1024 g/mL. The resulting IC_{50} values were 478.1611 g/mL and 442.093 g/mL for Nar-SLNs and free Nar, respectively. Although Nar-SLNs demonstrated greater cytotoxic efficacy than Nar at the specific concentrations of 64 and 128 μg/mL, an analysis of the expression of autophagy-related factors was also conducted, and the results suggested that both treatments, ie, Nar-SLNs and Nar, promoted the expression of autophagy markers (*AKT, LC3, Beclin1*, and *ATG5*) and decreased miR-21 levels in PC cells. Nevertheless, the Nar-SLNs formulation markedly enhanced the inhibition of cell proliferation and modulation of autophagy pathways. This superior efficacy is attributed to the improved solubility, stability, and sustained release of naringenin achieved through encapsulation within SLNs. The lipid matrix and surfactant composition in the NPs increased the drug's aqueous dispersibility by reducing particle size and preventing crystallization, thereby enhancing solubility. Simultaneously, the lipid core protects naringenin from premature degradation and oxidation, thereby enhancing its stability. Finally, the NP matrix facilitated a controlled and sustained release profile, ensuring prolonged drug delivery over time.[74] Accordingly, Nar-SLNs deserve further investigation so that they can advance into preclinical and clinical trials.

Al-Baidhani et al[75] loaded 4-farnesyloxycoumarin (4-FLC) into nanoliposomes composed of lecithin-cholesterol-PEG (4-FLC-LNPs) to evaluate the anticancer and anti-metastatic effects of the nanoformulation. As a result, an encapsulation efficiency of 82.4% was obtained. Subsequently, cytotoxicity was measured against different cancer cell lines. In the PANC cell line, the IC_{50} was greater than 500 μg/mL, and no toxic effects were observed at concentrations below 62 μg/mL. Immunostaining and flow cytometry were used to analyze the expression of apoptosis- and metastasis-related genes in the presence of 4-FLC-LNPs. The nanoformulation induced BAX expression and decreased *BCL-2, MMP2*, and *MMP9 expression*. The antioxidant capacity of 4-FLC-LNPs was also assessed using ABTS and DPPH. It was also noticed that the average IC_{50} value for ABTS radicals was 31 μg/mL, and the highest inhibition reached was about 74%. Meanwhile, DPPH showed concentration-independent inhibition, ranging from 57% to 68%. Although the antioxidant activity of 4-FLC-LNPs was promising, its high IC_{50} value against the PANC cell line underscores the need to improve this nanoformulation, particularly for PC therapeutics.

Demirci et al[76] evaluated the anticancer effects of curcumin-loaded emulsome NPs (CurEm) on the PANC-1 PC cell line. CurEm significantly reduced cell viability in a dose- and time-dependent manner, with an IC_{50} of 32.43 μM at 72 hours, demonstrating greater efficacy than free curcumin. Additionally, CurEm induced cell cycle arrest at the G2/M phase and induced morphological changes consistent with apoptosis, including spheroidal cell formation. Moreover,

through colony formation and scratch assays, a notable inhibition of cell migration and colony formation was observed. At the molecular level, the expression of *p53, p21, BAX*, and *CASP-3* was upregulated, along with downregulation of *BCL-2*, suggesting apoptosis activation via the p53 signaling pathway. These findings support the use of CurEm as a promising nanocarrier system that facilitates sustained release and improves the stability and bioavailability of curcumin for potential PC therapy.

Other Nanocarriers

In this section, we examine a set of studies that highlight therapeutic approaches using diverse nanocarriers, including PLGA NPs, nanocomplexes, self-microemulsifying systems, polymeric micelles, and antibody-functionalized NPs, among others. Exploring such a variety of delivery platforms for phytochemicals is crucial, as it enables the identification of the most effective and clinically translatable strategies for PC therapy. In fact, by systematically evaluating different carriers for stability, cellular uptake, therapeutic efficacy, and safety, researchers can better predict which methods are most likely to succeed in clinical trials, thereby laying the groundwork for the rational design of next-generation phytochemical-based therapeutics.

In this context, Zhao et al[52] investigated a strategy to overcome primary resistance to immunotherapy in PC by modulating the tumor stroma using a polymeric micelle nanoformulation loaded with cyclopamine, a hedgehog pathway inhibitor that disrupts the stromal fibrosis characteristic of PC, and paclitaxel. The formulation was designed to modify the dense, desmoplastic TME, which acts as a physical and immunosuppressive barrier, hindering immune cell infiltration and the delivery of pharmacological agents. This approach was evaluated in Kras* orthotopic murine PC models and genetically engineered mice that closely mimic human PC progression. The outcomes of this investigation revealed that the nanoformulation combined with PD-1 blockers (immune checkpoint inhibitors that restore T-cell activation and enhance the immune system's ability to attack cancer cells) significantly improved survival and anti-tumor efficiency. These effects were attributed to increased intratumoral vasculature density, which promoted the infiltration of cytotoxic CD8+ T cells into the tumor without depleting tumor-restraining fibroblasts or disrupting the collagen matrix. This restoration of equilibrium subsequently reversed immunosuppression and stimulated IFN-mediated immune response, thereby enhancing therapeutic efficacy.

In a subsequent investigation, Desai et al[53] developed a synergistic chemoprevention strategy for PC using a combination of loratadine (LOR) and sulforaphane (SFN) formulated in a self-microemulsifying drug delivery system (SMEDDS). A series of in vitro MTT assays was conducted as part of the analysis using the PC cell lines MIA PaCa-2 and PANC-1. Among the most notable results, the IC_{50} values of the free LOR-SFN combination were 4.6 μM and 9.51 μM for MIA PaCa-2 and PANC-1, respectively. On the other hand, the incorporation of LOR and SFN into the SMEDDS formulation reduced the IC_{50} values to 0.64 μM and 0.82 μM, respectively, for MIA PaCa-2 and PANC-1. These improvements are attributed to the increased solubility and bioavailability of LOR and SFN provided by the SMEDDS platform, along with SFN's enhanced antioxidant activity, which activates the Nrf2 pathway, augmenting cellular antioxidant defenses and modulating key signaling pathways controlling cell cycle arrest and apoptosis. Accordingly, this nanoformulation showed enhanced anticancer efficacy at lower doses, underscoring its potential as a promising therapeutic strategy against PC.

Desai et al[56] further evaluated the LOR SMEDDS-SFN nanoformulation. An in vitro colony-forming assay was performed on two distinct PC cell lines, PANC-1 and MIA PaCa-2. The survival fractions observed for the LOR SMEDDS-SFN system were 0.35 and 0.20 for PANC-1 and MIA PaCa-2 cells, respectively. These results demonstrate the enhanced solubility of the phytochemicals and indicate that the SMEDDS formulation facilitates greater interaction with cancer cells, thereby promoting increased cellular uptake and permeation, ultimately leading to increased cell death. Regarding in vivo studies, a pharmacokinetic assay was performed in male Sprague-Dawley rats following oral administration of a single 200 μL dose containing 4 mg/kg LOR and 0.16 mg/kg SFN (LOR SMEDDS-SFN). Blood plasma samples were collected at predetermined time points and analyzed to determine the drug concentration over time. The resulting bioavailability value of 20,274.8 ± 3711 ng·h/mL and maximum plasma concentration of 503.2 ng/mL demonstrated a significant enhancement compared to conventional formulations. These pharmacokinetic parameters confirm the improved absorption and systemic exposure afforded by the nanoformulated system, thereby supporting the potential of LOR SMEDDS-SFN as a promising chemopreventive strategy for PC.

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Massey et al[55] developed a paclitaxel NP formulation (PPNPs), consisting of a PLGA core stabilized with Pluronic F127 and polyvinyl alcohol (PVA), and coated with poly-L-lysine. PC cell lines PANC-1, HPAF-II, and AsPC-1 were used for cytotoxic assays. The formulation exhibited cytotoxicity with IC_{50} values of approximately 5 nM for MIA PaCa-2 and PANC-1, and 20 nM for HPAF-II, as evidenced by MTT assays and colony formation assays. At the molecular level, PPNPs induced apoptosis, G2/M phase cell cycle arrest, and reduced cell migration and invasion. In an orthotopic xenograft model in mice generated with HPAF-II-luciferase cells, PPNPs at 10 mg/kg significantly reduced tumor volume and tumor weight, as confirmed by bioluminescence imaging. Likewise, a significant reduction in pancreatic bioluminescence intensity and the presence of necrotic areas were observed in the histopathological analysis of the excised tumors. It should be noted that although all control mice had foci in lymph nodes, liver, and lungs, minimal foci were detected in the lungs of mice treated with PPNPs, even while maintaining high efficiency in mice pretreated with PTX, indicating the ability to overcome drug resistance. In addition, a decrease in nuclear expression of Ki-67 (a cell proliferation marker) and of proteins associated with epithelial-mesenchymal transition, such as vimentin and Slug, was observed, supporting a reduction in tumor invasive capacity.[55] Collectively, these findings highlight PPNPs as a safe and promising therapeutic platform for the treatment of PC, offering distinct advantages over conventional anticancer drugs.

Chauhan et al[57] developed modified pectin-tannic acid nanocomplexes (MPT-NCs) to encapsulate GEM, 5-fluorouracil (5-FU), or irinotecan (IRI) via tannic acid binding. Tannic acid is an anticarcinogenic phytochemical known to enhance bioavailability, improve drug entrapment efficiency, and increase water solubility of drug molecules by promoting hydrogen bond formation. Characterization of the nanoformulation revealed a loading efficiency of over 91%. The cytotoxicity of the loaded NPs was assessed in vitro using two PC cell lines. In PANC-1 cells, the IC_{50} values of GEM, 5-FU, and IRI nanopreparations were 71.92 nM, 44.9 μM, and 35 μM, respectively. Likewise, the IC_{50} values of GEM, 5-FU, and IRI in HPAF-II cells were 70.74 nM, 88.8 μM, and 50.41 μM. Furthermore, the analysis of cellular uptake and colony formation in both PANC-1 and HPAF-II cell lines showed that the nanoformulation increased drug uptake per cell and inhibited the formation of cancer cell colonies.

Shetty et al[58] evaluated a PLGA-based paclitaxel NP formulation (PPNPs) in combination with GEM for the treatment of PC. Paclitaxel was encapsulated in PLGA-F127-PVA NPs coated with poly-L-lysine. Afterwards, human PC cell lines PANC-1 and HPAF-II were treated with the nanoformulation, showing dose-dependent cytotoxicity. Mechanistically, this nanodrug exerted its effects by inducing apoptosis, disrupting lipid membrane integrity, neutralizing cell-surface charge, and causing G2/M cell cycle arrest. Zeta potential and Rh123 exclusion assays demonstrated that the PPNPs enhance GEM uptake by inhibiting P-glycoprotein efflux activity. Additionally, a significant downregulation of proteins crucially involved in *de novo* lipid synthesis (ie, FASN, ACC, Lipin, and Cox-2) was observed, which are essential for tumor survival, progression, and chemoresistance because *de novo* lipid synthesis activates drug resistance, allowing membranes, energy, and signals that favor survival against drugs to be maintained. Consistently, these observations suggest that PPNPs potentiate GEM efficacy by inhibiting lipid metabolism, inducing apoptosis, and promoting membrane remodeling, proposing this combination as an innovative therapeutic strategy against PC.

Greene et al[59] optimized antibody-targeted delivery of camptothecin-loaded NPs using F(ab) fragments derived from the epidermal growth factor receptor (EGFR) antibody cetuximab to develop an efficient treatment against PC. Polymeric NPs were first functionalized with anti-EGFR antibodies to enhance their affinity to EGFR-expressing PC cells. The cellular models used in this study were BxPC-3, MIA PaCa-2, and PANC-1 cells due to their ability to express the antigen targeted by the functionalized NPs. The binding affinity of these optimized NPs to the cell lines was assessed by flow cytometry; the results confirmed the enhanced specificity of the modified NPs for surface-expressed EGFR. A clonogenic assay was also performed in MIA PaCa-2 cells to evaluate the impact on cell survival and colony formation when the optimized antibody-targeted NPs were administered. At the same time, uptake of the free phytochemical was insufficient to affect cell survival significantly; treatment with antibody-conjugated NPs carrying the phytochemical notably reduced colony formation. The effective targeting provided by the antibodies paired with high internalization efficiency mediated by the NPs facilitated the delivery of camptothecin to PC cells; these factors enhanced cytotoxicity, supporting the nanoformulation's potential for selective and improved PC therapy.

In another investigation, Markowski et al[61] assessed the cytotoxic activity of ursolic acid (UA) encapsulated in PLGA or PEGylated PLGA NPs against two PC cell lines, ie, AsPC-1 and BxPC-3. The IC_{50} values for UA-PLGA were reported to be

10.1 ± 1 μM (AsPC-1) and 12.6 ± 4.5 μM (BxPC-3). However, the authors indicate that the UA-loaded NPs showed highly similar values across all formulations and samples studied, ranging from 10.1 μM to 14.2 μM, with no significant differences, suggesting comparable potency to free UA. Confocal microscopy confirmed that cytotoxicity did not result from premature PLGA degradation and UA release into the extracellular medium, but rather from NP internalization via endocytosis, leading to intracellular UA release. While free UA and encapsulated UA showed similar effects in AsPC-1 cells, a statistically significant increase in cytotoxicity was observed in BxPC-3 at 20 μM with the nanoformulation. Finally, the authors noticed that PLGA-based nanoformulations, including PEGylated versions, retain UA cytotoxicity and may improve circulation and tumor targeting, supporting their potential for further evaluation in PC models.

Elbialy et al[62] developed a curcumin nanocarrier system based on NPs that was created with a casein matrix coated with alginate and chitosan layers, and functionalized with folic acid. This nanoformulation was denominated fCs-Alg@CCasNPs. The system was characterized using various assays, and its effectiveness was evaluated in vitro and in vivo. The in vitro release study of the fCs-Alg@CCasNPs showed enhanced curcumin release in the TME (pH 5.5) up to 53%, demonstrating that protein surface modification prevents contact between the release media and curcumin, thus controlling the drug release rate and improving curcumin bioavailability. Afterward, cytotoxicity was assessed in PANC-1 cells through the SRB assay, and it was observed that curcumin induced higher cytotoxicity when paired with fCs-Alg@CCasNPs (IC_{50} of 17.5 g/mL), as compared with free curcumin (IC_{50} of 76 g/mL). These results were attributed to the greater adhesion capacity between cancer cells and NPs, which increased cellular penetration and folate ligand binding. I*n vivo* studies used BALB/c mice as animal models. Mice were intraperitoneally inoculated with Ehrlich ascites tumor cells to establish the tumor mo afterwards, the nanocarrier system was delivered via intratumoral injection and intraperitoneally, with 2 doses of 40 μL of fCs-Alg@CCasNPs per week for 3 weeks. Regarding pharmacokinetics, the maximum plasma curcumin concentration for the fCs-Alg@CCasNPs was 27.5 ng/mL, much lower than the free curcumin concentration (117 ng/mL), evidencing improved curcumin bioavailability with prolonged circulation time.[62] The efficient drug delivery achieved through this nanoformulation resulted in a pronounced antitumor effect, evidenced by an inhibitory rate of 71% for fCs-Alg@CCasNPs. Comet and histopathology assays revealed that fCs-Alg@CCasNPs demonstrated superior therapeutic efficacy compared to free curcumin by significantly increasing DNA damage in cancer cells while sparing vital organs, indicating high specificity and safety.[62]

Besides, Singh[63] et al assessed the effect of nimbolide (Nim), a phytochemical with anticancer properties, encapsulated in PLGA NPs, on PC stem cells (CSCs). MIA PaCa-2 cells were cultured under pancreatosphere-forming conditions, a strategy that enriches the CSC population. Although the IC_{50} value was not reported, MTT viability assays, apoptosis assays, and pancreatosphere formation assays demonstrated that Nim NPs more effectively reduced cell viability, induced apoptosis, and decreased self-renewal capacity compared to free Nim. At the molecular level, Nim and Nim NPs showed high-affinity binding to AKT and mTOR, inhibiting both proteins, as confirmed by molecular docking, molecular dynamics simulations, and Western blot analysis. This dual inhibition triggered mesenchymal-to-epithelial transition, which was evidenced by increased levels of E-cadherin and decreased expression of vimentin, N-cadherin, fibronectin, and ABCG2 (a drug-resistance marker). The authors suggest that Nim-loaded NPs could overcome chemoresistance and reduce tumor initiation capacity, as CSCs are associated with intrinsic drug resistance and the ability to regenerate tumors. Overall, Nim NPs can induce MET, apoptosis, and loss of the CSC phenotype, offering a promising strategy to overcome chemoresistance and tumor initiation in PC.

Karole et al[64] demonstrated another nanocarrier system for the phytochemical luteolin (LUT), which was formulated as enteric-coated effervescent granules (LUT-NG). This nanoformulation was projected to enhance the intestinal epithelial absorption of LUT and facilitate its effective transport to the pancreas via the oral route by protecting the formulation from the harsh gastric environment. After the physicochemical characterization of the nanodrug, an in vitro drug release assay was executed, the results showed a minor quantity of LUT being released at first (pH 1.2) but once the pH was raised to intestinal pH (7.4) the concentration of the released drug increased, showcasing the protection effect of the coating and confirming the delivery potential of the drug through the oral route with the nanocarrier. Further, MTT and Live/Dead assays performed in PANC-1 cells to assess the anticancer effects of the delivery system revealed an IC_{50} of 24.98 μM for LUT-NG, which was significantly lower than that of free LUT (50.56 μM). These findings validate the improved solubility of the nanoformulation, which, in turn, translates into greater cytotoxicity against PC cells. Results

from other tests, including Hoechst 33258 staining, caspase-3 activation detection, and G2/M cell cycle arrest analysis, collectively reinforced the enhanced anticancer effects of LUT-NG. These effects were mediated by inducing apoptosis through the regulation of cell cycle-related molecules, inhibiting tumor angiogenesis and metastasis, and directly suppressing tumor cell proliferation.

Arya et al[67] introduced a personalized nanodelivery approach called the PC-targeted PLGA-chitosan core-shell NP delivery system (PaCTNDS), designed for PC therapy by harnessing the synergistic effects of embelin (Emb) and RPI-1. Embelin is a natural benzoquinone that inhibits the X-linked inhibitor of apoptosis protein via the NF-kB pathway. At the same time, RPI-1 is an indolinone derivative that targets c-MET, a key biomarker in PC. The optimized synergistic ratio of Emb to RPI-1 (1:4.7) demonstrated enhanced cytotoxicity against PC cells (PANC-1) while minimizing toxicity to normal cells (WI-38). In vitro studies revealed significant anticancer effects, including apoptosis induction, mitochondrial membrane depolarization, cell cycle arrest at G2/M and S phases, and anti-metastatic properties such as reduced migration, invasion, and colony formation. Meanwhile, in vivo experiments using zebrafish xenograft models showed favorable biodistribution, marked tumor volume reduction, and improved survival rates with 50 nL of 5 mg/mL administered intraperitoneally. Metabolomic analysis via SERS and LC-MS identified alterations in purine, pyrimidine, and carbohydrate metabolism, further elucidating the apoptotic mechanisms triggered by Emb and RPI-1. These findings underscore the potential of PaCTNDS as a targeted and effective therapeutic strategy for PC, warranting further preclinical and clinical evaluations.

As a novel sonosensitizer for sonodynamic therapy (SDT) of PC cells, Selenium-PEG-curcumin NPs (Se-PEG-Cur NPs) were synthesized by Ilbeigi et al.[68] The nanoformulation demonstrated substantial anticancer effects, primarily through enhanced reactive oxygen species production and apoptosis induction. Se-PEG-Cur NPs exhibited dose-dependent cytotoxicity with an IC_{50} value of 8 μg/mL, while GEM showed an IC_{50} of 62 μg/mL. The combination of Se-PEG-Cur NPs and GEM, with ultrasound (US) radiation, significantly reduced ASPC1 cell viability to 10%, demonstrating a synergistic therapeutic effect (combination index of 1.6). The mechanism of action of this nanoformulation involved ROS generation, mitochondrial membrane disruption, and DNA damage, facilitated by the cavitation effects of US and the sonosensitizing properties of Se-PEG-Cur NPs. The nanoformulation's stability, biocompatibility, and ability to enhance drug delivery to tumor sites underscore its potential as an efficient and targeted treatment for PC.

Ghafaripour et al[69] successfully developed lawsone-encapsulated PLGA NPs modified with chitosan and folic acid (LWS-PLGA-FA-CS NPs) to evaluate their anticancer potential against the PANC-1 cell line. The nanoformulation had an encapsulation efficiency of 81%, which is favorable for drug delivery systems. Besides, LWS-PLGA-FA-CS NPs significantly inhibited PANC-1 cell growth in a dose-dependent manner, with an IC_{50} of 118.4 μL, and showed no cytotoxicity in normal HFF cells. Mechanistically, the loaded NPs induced apoptosis by upregulating the pro-apoptotic *BAX* gene and downregulating the anti-apoptotic *BCL2* gene, suggesting activation of the intrinsic apoptotic pathway. Additionally, flow cytometry revealed an increased proportion of cells in the sub-G1 phase, confirming the induction of apoptosis. The nanoformulation also exhibited potent antioxidant activity, with IC_{50} values of 250 μg/mL (DPPH assay) and 62.5 μg/mL (ABTS assay), and antibacterial activity against Gram-negative bacteria, including *E. coli* and *P. aeruginosa*. These findings highlight the potential of LWS-PLGA-FA-CS NPs as a promising candidate for PC treatment, leveraging their multifunctional therapeutic properties.

More recently, Al Rashid et al[77] created berberine-loaded glyceryl monooleate NPs (BER-GNPs) as a putative therapeutic approach against PC. Characterization revealed that this nanoformulation had high stability and successfully encapsulated berberine, enhancing its bioavailability and sustained release. I*n vitro* experiments also demonstrated that BER-GNPs significantly enhanced cellular uptake and cytotoxicity in MIA PaCa2 (IC_{50} of 37.16 ± 1.44 μg/mL) and PANC-1 cells (IC_{50} of 32.04 ± 2.03 μg/mL), with the loaded NPs showing superior antiproliferative effects compared to native berberine. Mechanistically, BER-GNPs predominantly inhibited the AKT signaling pathway by suppressing AKT phosphorylation, leading to increased pro-apoptotic Bax and decreased anti-apoptotic Bcl-2, thereby activating intrinsic apoptotic pathways. Eventually, in silico docking studies supported these findings, showing favorable binding interactions of berberine with AKT. Overall, these observations indicate that the BER-GNP nanocomposite enhances berberine's stability and efficacy, induces apoptosis by suppressing AKT-mediated survival signaling, and represents a promising

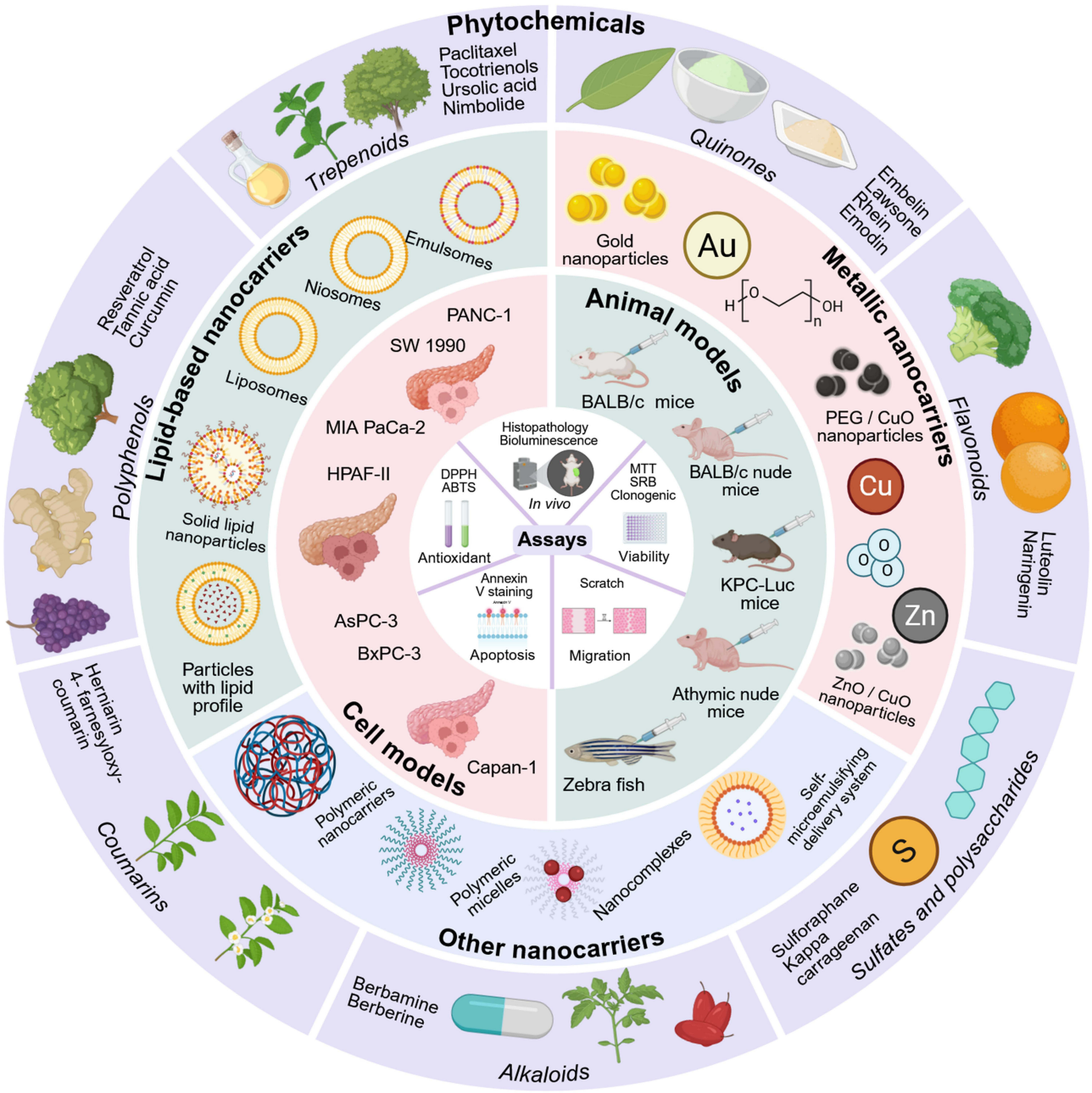

Figure 3 Overview of the main research strategies involving nanoformulated phytochemicals for PC therapy. The figure depicts representative classes of phytochemicals (terpenoids, quinones, flavonoids, polyphenols, coumarins, and alkaloids), the principal nanocarriers used (lipid-based systems, polymeric NPs and micelles, metallic NPs, nanocomplexes, and polysaccharide- or sulfate-based carriers), and common in vitro and in vivo models (PC cell lines such as MIA PaCa-2, HPAF-II, SW1990, AsPC-3, BxPC-3, Capan-1; and mouse models including BALB/c mice, KPC-Luc, and zebrafish). Central icons summarize the main assays used to evaluate these nanoformulations, ie, assessments of cell viability, apoptosis, cell migration/invasion, oxidative stress, and in vivo tumor development (created with a licensed version of BioRender.com).

nanotechnological strategy for PC therapy. An overview of the key phytochemicals, nanocarriers, biological models, and assays performed to evaluate the efficacy of the nanoformulations discussed herein is illustrated in Figure 3.

Discussion

The insights from this scoping review indicate that nanoformulated phytochemicals have remarkable potential to be developed as innovative drugs for the treatment of PC, as evidenced by a handful of studies that tested their effectiveness. Notwithstanding this, several concerns and hurdles must be addressed in future research to enable these nanoformulations

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for cancer treatment to reach the clinical landscape, as exemplified by the case of the nanodrug Abraxane (NP-albumin-bound paclitaxel).[83] Indeed, the emergence of newly approved nanoformulated phytochemicals could be a turning point in this field, as the number of such nanomedicines targeting PC that are in clinical trials or already licensed remains very limited, as noted earlier in the Introduction. In this context, concerted efforts from scientists, policymakers, and the pharmaceutical industry are essential to achieve this objective, and the insights provided in this review may serve as a valuable resource toward that goal.

One of the main limitations identified during the analysis of the evidence sources is that most conclusions were based solely on cell viability or proliferation assays (21 out of 26 studies). Although cell cultures provide a cheap and general approach to understanding the inhibitory effects of phytochemical-centered nanoformulations in cancer cell lines and their cytotoxicity in healthy cells, they poorly reflect the complexity and heterogeneity of patient tumors, as tumor behavior is strongly influenced by interactions with the extracellular matrix and surrounding host cells, which are factors that are absent in standard tissue culture systems.[84,85] In this regard, scaffold-based 3D cell cultures may provide tumor models that simulate in vivo conditions, enabling better study of cancer progression, drug responses, and microenvironment interactions. Moreover, patient-derived scaffolds can be applied to generate personalized medicine, potentially increasing the accuracy of therapeutic predictions during anticancer drug testing.[86] On the other hand, patient-derived cancer organoids, along with animal models including genetically engineered mice, patient-derived xenografts, rabbits, and non-human primates, could provide a broader perspective on the effects of novel anticancer drugs,[87,88] such as nanoformulated phytochemicals for PC. Nevertheless, there is currently no biological model that fully mirrors the complexity of patients' reality; instead, the clinical development and assessment of anticancer drugs should rely on integrated data derived from multiple models.[89]

Hence, most of the phytochemical nanoformulations discussed herein warrant further in-depth investigation, particularly through future evaluations across diverse biological models, to comprehensively assess their efficacy and safety before entering human trials. This clinical chronology is depicted by Zhao et al,[52] Massey et al,[55] Elbialy et al,[62] Tang et al,[66] and Arya et al,[67] as these researchers evaluated the anticarcinogenic effects of their phytochemical-loaded nanoformulations in animal models of PC. Additionally, conducting comprehensive analyses on pharmacokinetics, pharmacodynamics, and safety profiles, including the evaluation of potential adverse effects, is essential to ensure the clinical viability of phytochemical-based nanoformulations for PC, as previously stated for these nanotechnological approaches.[90] Such evaluations will help to confirm the absence of toxicities or off-target effects, thereby supporting the development of these nanoplatforms as reliable and safe therapeutic strategies. Particularly, only 3 out of the 26 revised articles evaluated the safety of the nanoformulated phytochemicals through histopathological examination,[55,56,62] while only Desai et al[56] and Elbialy et al[62] performed pharmacokinetic studies.

Safety concerns related to the different nanocarriers reviewed may arise mainly from their physicochemical properties and their interactions within more complex biological systems. For instance, metallic NPs generate reactive oxygen species that can lead to oxidative stress and inflammation, and their leaching can induce cytotoxic effects and accumulate in organs, specifically the liver and spleen, causing long-term toxicity issues. However, surface modification of these nanocarriers, such as coating with biocompatible materials, can mitigate these effects.[91] Other types of nanoplatforms, such as polymeric or lipid NPs, offer effective alternatives if the chosen components are non-toxic and fully characterized for immunotoxicity; otherwise, it might risk activation of the immune system, causing adverse reactions, and could also affect pharmacokinetic parameters like circulation time and clearance, which are essential for dosing and efficacy considerations.[92,93] Additional nanomaterials, including dendrimers and carbon-based NPs, may pose risks, including hemolysis, cytotoxicity, and interference with normal cellular functions. For dendrimers, reported toxicity is often linked to their positive surface charge, which can be mitigated by replacing cationic groups with neutral or anionic groups via glycolation, PEGylation, or conjugation with peptides and carbohydrates. As for carbon-based NPs, they exhibit reduced toxicity when functionalized with groups that enhance solubility and biocompatibility, such as carboxyl or polyamidoamine (PAMAM) dendrimer coatings, thereby improving cellular uptake and reducing inflammation.[94,95]

Regarding the profiles a nanoformulation should entail leading to an Investigational New Drug (IND) application, the appropriate in vitro and in vivo studies must be performed; they should include a complete physicochemical characterization of the nanosystem (size, charge, morphology, drug loading, stability, and release kinetics) as well as pharmacokinetic studies including adsorption, distribution, metabolism excretion (ADME) assessments, plasma concentration-time

profiles, bioavailability, and organ-specific biodistribution in appropriate animal models. Pharmacodynamic assays should verify that the target is engaged correctly, demonstrate the mechanism of action, establish dose-response relationships, and identify therapeutic windows.[96,97] Safety evaluations should encompass acute and chronic toxicity studies, histological examination of major organs to detect off-target effects, immunogenicity assays to monitor hypersensitivity or immune activation, genotoxicity and inflammation biomarkers; especially regarding polymeric and metallic NPs, immunotoxicological assays are crucial. Finally, complementary reproductive and developmental toxicity testing should be considered as well.[96,97] All these evaluations must be conducted in strict compliance with the relevant regulatory guidelines, ensuring thorough standardization and robust data to support the safety and efficacy profile required for clinical trial authorization. However, there remains a lack of well-established, standardized protocols specifically designed to ensure the safety of NPs during early developmental stages. Despite this, there is consensus among researchers and regulatory organizations that the parameters mentioned earlier should be thoroughly studied before NPs are considered "safe".[98–100]

Working with animal models in drug-testing studies presents several substantial challenges, including financial costs, the need for strict ethical oversight, the requirement for specialized and properly equipped facilities, and the continuous care and maintenance of animals, demands that significantly increase as the biological requirements of the animal model increase.[101,102] These constraints help to explain why a considerable proportion of studies in this field have not yet advanced to in vivo experimentation. To reduce the need for animal testing, remarkably, to follow the recommendations of the FDA Modernization Act 2.0/3.0,[103] researchers can integrate alternative approaches such as organ-on-chip systems, advanced computational modeling, and refined experimental designs.[104,105] Given that the studies that advanced to in vivo evaluation demonstrated that nanoformulated phytochemicals can effectively suppress PC tumor growth, providing valuable insights into their potential clinical translatability, animal experimentation continues to play an essential role in this area of research. Nevertheless, to reduce the number of animals used in experiments, instead of conducting a single study with a whole cohort, the initial group size can be partitioned into multiple smaller cohorts, each treated at different time points, so that reproducibility is preserved without requiring huge test groups. In this regard, a design initially requiring nine animals could instead be implemented as three separate mini-studies, each involving three biological replicates.[106]

Another critical issue that should be considered in forthcoming studies is the encapsulation or loading efficiency of a phytochemical into a nanocarrier, which was reported in only 14 of 26 studies, with 95 ± 2.55% as the maximum reported encapsulation efficiency. This parameter depends on factors such as the physicochemical compatibility between the drug and the carrier, the NP's surface properties, and the formulation method.[107,108] Given that this efficiency will be related to the actual amount of phytochemicals delivered to a given biological system (effective dose), it can be improved by incorporating ligands that specifically bind the phytochemical to the NP,[109] or by using stabilizers, such as chitosan, casein, saponins, PEG, among others, which can enhance stability mainly through electrostatic interactions and outer layer formation,[110] these strategies have been considered in several articles included in this review. Additionally, nanotechnological platforms can enable precise control over phytochemical release, enabling prolonged, site-specific delivery. This can be accomplished by integrating smart, stimuli-responsive components into the delivery platform that respond to defined signals to trigger the release of therapeutics at the desired site. These stimuli include, but are not limited to, changes in pH, temperature shifts, or specific enzymatic activities.[111] However, as observed in our analysis, these techniques have been applied sparingly in the design of phytochemical-based nanoformulations for PC and should therefore be explored in depth in future studies.

A notable limitation across nearly all the investigations discussed herein is the absence of a systematic optimization process for preparing phytochemical-loaded nanoformulations. In this matter, one of the most crucial aspects in nanoformulation development is the optimization of its physicochemical and functional characteristics. This process can be effectively guided by the Quality by Design (QbD) methodology. QbD employs statistical experimental designs to optimize key parameters, including particle size, zeta potential, polydispersity index, surface morphology, entrapment efficiency, and drug release profiles, thereby enhancing the quality and reliability of the final product and simplifying the formulation process.[112,113] Since emerging research on nanoformulations containing phytochemicals for cancer therapy is incorporating the QbD approach in their methods,[114–116] nanotechnologists are encouraged to consider adopting this strategy in future studies to advance the standardization of the production methods for phytochemical-based

nanoformulations targeting PC, as it was exemplified by Desai et al,[53] who applied QbD in their protocol to develop LOR SMEDDS-SFN for treating PC.

Unfortunately, most phytochemicals exhibit poor aqueous solubility, which represents a major obstacle to the development of effective therapies for PC. For example, potent anticarcinogenic phytochemicals such as curcumin, quercetin, and resveratrol are poorly soluble in water,[117,118] limiting their dispersibility, bioavailability, and therapeutic efficacy. In this context, specific nanocarriers (eg, SLNs, dendrimers, and polymeric micelles) offer a promising strategy to overcome these limitations by enabling the effective dispersion of hydrophobic compounds within an aqueous phase, thereby enhancing solubility and bioavailability, and also allowing the codelivery of phytochemicals with existing anticancer medicines.[119] Although the successful use of various nanocarriers has been demonstrated in the articles reviewed here, other nanoplatforms remain to be explored in the field of phytochemical-based nanoformulations for PC management. In this context, nanozymes and nanoemulsions can be combined with phytochemicals to develop stable, multifunctional nanoformulations. Predominantly, nanozymes are nanomaterials with intrinsic enzyme-like catalytic activities that can enhance anticancer efficacy by promoting oxidative stress and/or modulating the conditions of the TME.[120] Although the combination of phytochemical-nanozymes has been barely examined in cancer therapy, it has been reported that iron-based nanozymes containing capsaicin were able to mitigate sepsis-associated acute lung injury, mainly through modulation of the NF-κB signaling pathway.[121] This premise suggests that the therapeutic effects of nanozymes functionalized or loaded with phytochemicals could be extrapolated to anticancer drugs in the near future.

Furthermore, nanoemulsions are oil-water dispersions stabilized by surfactants that can improve the solubility, stability, and bioavailability of poorly water-soluble molecules, like phytochemicals, ensuring homogeneous drug distribution during treatment.[122] Since nanoemulsions containing naringenin[123] and epigallocatechin-3-gallate[124] have shown substantial anticancer effects in lung cancer cells, these types of approaches should begin to be tested in PC therapy. In fact, Grzeszczak et al[125] developed a nanoemulsion containing the phytochemical phenethyl isothiocyanate, which displayed significant cytotoxic effects on the PC cell lines AsPC-1 and BxPc-3, thus evidencing the potential of phytochemical-containing nanoemulsions for PC treatment. Remarkably, nanoemulsions also broaden the horizon for the delivery of multiple therapeutic agents targeting cancerous cells. For example, Bahadori et al[126] found that a pH-responsive nanoemulsion containing cyclodextrin, zein, and TiO_2 NPs, loaded with quercetin, not only minimized side effects on healthy tissues but also showed cytotoxicity in the A549 lung cancer cell line.

The term "nano-phytochemical" typically refers to phytochemicals encapsulated or loaded onto a nanocarrier.[127–130] However, it is worth noting that phytochemicals can also serve as NPs on their own, as some can be converted via physicochemical methods (eg, wet milling) into nano-sized particles that usually require lower dosages to exert their therapeutic effects.[122,131] For instance, Kumar et al[132] and Zamanidehyaghoubi et al[133] reported the production of nanocurcumin from curcumin, which was successfully utilized in anticancer and antibacterial strategies, respectively. Other examples of phytochemicals that can be transformed into nanocompounds include naringenin,[134] apigenin,[135] quercetin,[136] and resveratrol.[137] Since a few of the articles evaluated in this scoping review considered the use of nano-sized phytochemicals, we endorse exploring the anticancer potential of these compounds in forthcoming research focused on PC. Likewise, investigations should also focus on other phytochemicals with demonstrated activity against PC, thereby expanding the current therapeutic repertoire and fostering the development of novel nanoformulations. Among phytochemicals with proven therapeutic effects against PC that could be considered for future nanoformulations are baicalein,[138] Corynoxine,[139] celastrol,[140] shikonin,[141] and piperlongumine.[142]

Even though the molecular mechanisms of action of many phytochemicals have been widely described,[143] it remains crucial to determine whether these mechanisms are preserved when delivered via nanocarriers, since the NPs themselves may also exert therapeutic effects.[144] To address this, transcriptomic, proteomic, and metabolomic profiling analyses would be highly valuable, as they can help explain the underlying mechanisms of action of phytochemical-based medicines.[145,146] Notably, among the reviewed investigations, only a few incorporated this type of analysis, highlighting a significant gap that warrants further investigation. Anyhow, the current body of research in this field indicates that, even though the precise mechanisms of action of several phytochemical-laden nanoformulations designed to treat PC are unknown, these types of nanotechnological platforms offer a viable way to overcome several of the challenges that are

intrinsic to the nature of phytochemicals, which include low permeability through the cell membrane, rapid metabolism and body clearance, poor solubility, and low bioavailability.[90]

Overcoming these biological obstacles can enhance anticancer effects mediated by various factors. For instance, the use of soluble nanosystems or the functionalization of NPs with hydrophilic components increases the solubility of the cargo, therefore facilitating its delivery to cancer cells.[147] Due to their nanometric dimensions, these nanoformulations exhibit enhanced capacity to interact with cell membranes and can be efficiently taken up by cells via multiple internalization pathways, such as endocytosis.[148] As well, the nanoencapsulation of phytochemicals embeds them within a protective matrix that safeguards these compounds from destabilization by physiological and environmental factors, including enzymatic breakdown in the gastrointestinal tract and degradation caused by light or oxygen exposure, thereby prolonging their time in the body and mediating a prolonged therapeutic effect.[149] Finally, the use of both passive and active targeting strategies could help to overcome the significant barrier of selectivity in drug delivery and promote the anticancer activity of nanoformulated phytochemicals. In particular, functionalizing the surfaces of the nanoplatforms with molecules, such as ligands or antibodies, enables selective recognition of cancer cells and can help minimize off-target effects in healthy tissues.[150]

Importantly, incorporating TME remodeling strategies into next-generation nanoformulated phytochemical-based therapies, rather than focusing solely on the cytotoxic effects of these nanosystems, is essential, as the TME's conditions profoundly influence drug penetration, therapeutic responsiveness, and overall treatment efficacy. Some examples of these strategies include the incorporation of coatings containing DSPE-PEG2000-galactose, which can help regulate lactate production and counteract immune suppression in the TME.[151] As well, the inhibition of glycolysis and induction of cuproptosis are mechanisms that have been demonstrated to remodel the TME when phloretin-loaded calcium carbonate NPs are coated with luteolin-copper networks.[152] The incorporation of agents capable of triggering tumor vessel dilatation (thereby diminishing hypoxia), such as hydralazine,[153] is another approach that should be considered in future designs of phytochemical-loaded nanoformulations. Furthermore, combining Arg_9 to enhance cellular penetration with the encapsulation of the nanoplatform within M1 macrophage-derived membrane vesicles to promote the reactivation of immunosuppressed M2 macrophages constitutes a dual strategy that has proven effective in remodeling the TME in NP-based systems.[154] Last but not least, targeting the genetic factors associated with TME development by adding tailored gene therapies (eg, CRISPR, RNA interference, and ncRNAs) to the nanoformulation is another approach that should not be overlooked.[155–157]

Additionally, it is imperative that future research evaluate the potential for resistance to nanoformulated phytochemicals against PC, as previous evidence indicates that certain cancer cell types can acquire resistance to phytochemical-based treatments. Regarding this, it has been observed that hepatocellular carcinoma cells can develop resistance to resveratrol[158] and bladder cancer cells to paclitaxel,[159] while Bonham et al[160] noticed that tumors in LuCaP 35 prostate cancer xenograft models acquired resistance to baicalein and resumed growth, reaching volumes of approximately 1000 mm^3. It is highly likely that simpler nanoformulation designs, ie, those consisting solely of a nanocarrier and a phytochemical, may be the most vulnerable to PC resistance mechanisms, including drug efflux pumps and the persistence of cancer stem cells.[161] Consequently, beyond the incorporation of multiple therapeutic modalities within a single nanosystem, the nanoformulation should also strategically integrate features that hinder resistance mechanisms by targeting cancer stem cells,[162,163] inhibiting efflux pump activity,[164,165] and promoting stromal reprogramming.[166,167]

This scoping review presents notable strengths, including the use of a systematic and transparent methodology supported by an extensive multi-database search. Moreover, our search strategy underwent several refinements before its final application on article identification and extraction, ensuring extensiveness and reliability. Another strength lies in our strict adherence to PRISMA principles, which helped minimize potential biases arising from human error during the review process. However, one potential limitation is the exclusion of studies published before 2018. Nevertheless, considering the availability of prior reviews on this subject, as highlighted in the introduction, our scoping review was intentionally directed toward more recent contributions to this research arena, restricting the analysis to studies published between 2018 and 2025. Another limitation is that all the data included in this review were derived from preclinical studies, which displayed considerable heterogeneity in aspects such as experimental design, PC cell lines, cell proliferation assays, type of nanocarrier, phytochemical employed, methodology followed to prepare the nanoformulation,

effective concentrations, and even the units reported for each effective concentration (eg, μg/mL, μM, or μL). Although efforts were made to address this heterogeneity by organizing studies by nanocarrier type, the findings should be interpreted cautiously, as these differences may influence overall conclusions about the true therapeutic potential of phytochemical-based approaches against PC.

In this regard, given the variability in study designs, experimental conditions, and reporting formats across the available literature, conducting a systematic review with meta-analysis at this moment is not entirely viable to estimate the overall therapeutic efficacy of phytochemical-loaded nanoformulations against PC. Nevertheless, the guidance offered in this scoping review is intended to help establish a foundation for future research on nanoformulated phytochemicals for PC, encouraging greater consistency in methodological reporting and data presentation. Such standardization will eventually support the feasibility of a comprehensive systematic review and meta-analysis once a more harmonized body of evidence becomes available. In parallel, to better account for this variability and refine the assessment of the anticancer efficacy of nanoformulated phytochemicals for PC, additional evidence from both preclinical evaluations and future clinical trials will be essential, ideally enabling reviews with robust statistical assessments through meta-analysis, as exemplified by Al-Samydai et al[168] and Boroughani et al.[169] Lastly, the restriction to English-language publications may have excluded relevant studies in other languages. However, the small number of such records suggests that their inclusion would not significantly alter our conclusions.

The available findings from preclinical studies on phytochemical-based nanoformulations for PC suggest a promising therapeutic potential. A recent meta-analysis of nano-phytosomes found that flavonoid-loaded NPs exhibited higher IC_{50} values against cancer than terpenoid-based counterparts.[168] Moreover, a multivariate analysis of covariance performed in the same study highlighted that the phytochemical exerted a significant effect on therapeutic outcomes, even when accounting for cancer cell type and phospholipid composition as covariates.[168] These data imply that phytochemical-containing nanoformulations for PC might follow a similar trend. Nonetheless, as previously discussed, the current body of information is mainly based on observations from cell line studies and, therefore, further validation in clinically relevant models is required to confirm whether these nanoformulations can consistently achieve high efficacy against PC. Once clinical trial data on nanoformulated phytochemicals for PC become available, it will be essential to conduct systematic reviews that compare the therapeutic efficacy of different nanoplatforms. Accordingly, the present scoping review should be considered as a preliminary step toward future systematic reviews with meta-analyses, which would allow for the construction of statistically robust conclusions on the relative effectiveness of these emerging nanotechnological therapies.

Overall, upcoming investigations on nanoformulations containing phytochemicals for PC treatment should adopt a structured, multilayered research pipeline that begins with comprehensive in vitro testing across a diverse panel of PC cell lines to capture phenotypic and genotypic variability. Promising candidates should then be evaluated in biologically relevant in vivo PC models (considering ethically and statistically reliable practices) to define better therapeutic efficacy, biodistribution, and safety within an integrated physiological context. On the other hand, to enable meaningful comparisons across studies, researchers must consistently report key physicochemical parameters of the nanoformulations, including particle size, polydispersity index, zeta potential, encapsulation efficiency, and drug-release behavior under simulated physiological conditions. Notably, cytotoxicity metrics, such as IC_{50} values, should be reported in standardized units, as this practice can facilitate comparisons across nanoformulations. We recommend adopting μg/mL (μg of nanoformulation per mL of solution) as the standardized unit for reporting nanoformulation potency. Since these nanosystems comprise multiple components (including nanocarriers, phytochemicals, ligands, and other auxiliary materials), determining an accurate molar concentration (μM) for the complete formulation is highly impractical. In contrast, reporting IC_{50} values in μg/mL might help to integrate the nanoformulation into a unified therapeutic entity.

Furthermore, the characterization of the mechanisms of action of the nanosystems should be strengthened through transcriptomic, proteomic, and/or metabolomic analyses to elucidate the molecular pathways that are modulated by these treatments. Additional considerations (that can be reported in a complementary article) include assessing long-term toxicity, safety, pharmacokinetics, and pharmacodynamics; incorporating 3D culture or organoid models as intermediate validation systems; and evaluating the possibility that PC models may develop resistance to treatment with the nanoformulation. Collectively, with these recommendations, we aim to propose a guideline to enhance methodological

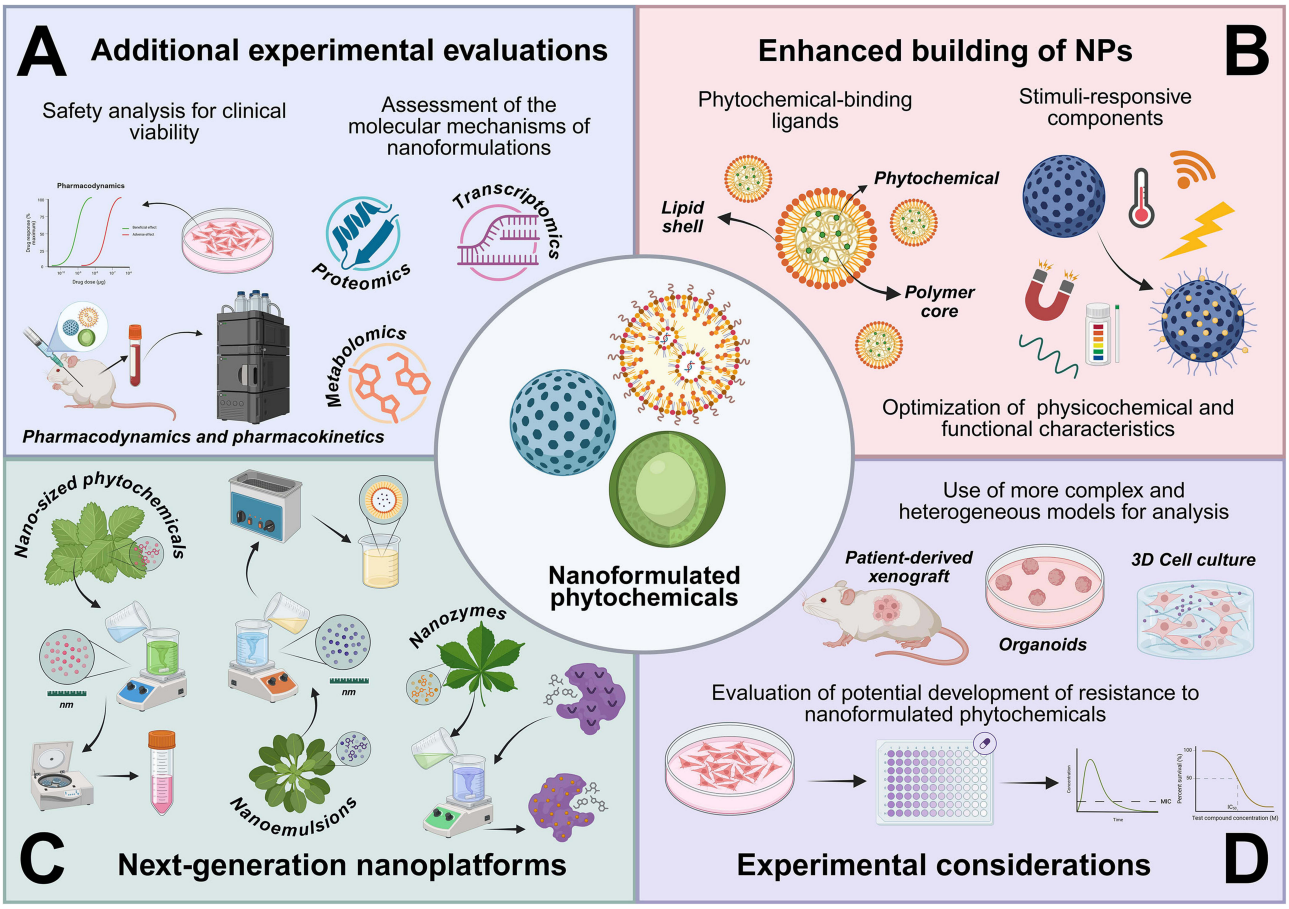

Figure 4 Future perspectives for nanoformulated phytochemicals. (**A**) Additional experimental assessments, including pharmacokinetic and pharmacodynamic assays, comprehension of the molecular mechanisms induced by the phytochemical-based nanoformulations, as well as evaluations of safety and clinical viability. (**B**) Enhanced NP design based on the incorporation of phytochemical-binding ligands, stimuli-responsive components, and optimization of physicochemical and functional properties. (**C**) Development of next-generation nanoplatforms such as nano-sized phytochemicals, nanoemulsions, and nanozymes with improved functions. (**D**) Experimental considerations involving more complex biological models, including patient-derived xenografts, organoids, 3D cell culture, and assessment of resistance emergence to phytochemical-loaded nanoformulations (created with a licensed version of BioRender.com).

rigor, reproducibility, and translational relevance in the emerging field of phytochemical-based nanotherapeutics for PC. The key future directions that we recommend pursuing in this research field are shown in Figure 4.

Conclusion

Phytochemical-based nanoformulations hold considerable promise as innovative therapeutic strategies for PC; however, significant challenges remain before they can be translated into clinical practice. Some of these key challenges include the need for extensive validation in advanced models such as xenograft animal models of PC and 3D cell cultures, alongside comprehensive analyses of their pharmacodynamics, pharmacokinetics, mechanisms of action, and potential toxicities. Furthermore, future research should expand beyond the most frequently studied compounds to explore other overlooked phytochemicals and alternative approaches, such as nano-sized phytochemicals, which may further enhance the potential of these nano-based therapies. As a closing call to action, we emphasize the urgent need to standardize experimental procedures and reporting practices in studies evaluating phytochemical-based nanoformulations against PC. Such harmonization is essential to enable meaningful comparison across platforms and to accelerate the clinical translation of these nanodrugs. Importantly, nanoformulated phytochemicals should not be regarded as standalone alternatives but rather as versatile platforms that can be strengthened through complementary strategies, such as gene therapy, as well as agents that can help remodel the TME and overcome PC drug resistance. The central challenge then becomes identifying combinations of these agents that are mutually compatible and optimizing their relative proportions

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so that they function synergistically within a single nanoscale delivery system, achieving therapeutic efficacy at a safe, clinically feasible dose. In light of this, this scoping review provides valuable insights to guide nanotechnologists in the rational design of future phytochemical-based nanoformulations aimed at treating PC.

Data Sharing Statement

No data was used for this manuscript, as it is a review article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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