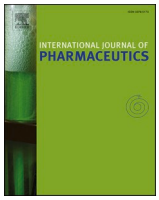
International Journal of Pharmaceutics 667 (2024) 124919

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm



Review

Transforming cancer treatment: The potential of nanonutraceuticals

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ARTICLE INFO

Keywords:
Nutraceuticals
Cancer
Nanonutraceuticals
Ligands
Nanocarrier

List of chemical compounds:
Curcumin
Quercetin
Silymarin
Epigallocatechin gallate
Coenzyme Q
Ellagic acid
Beta-carotene

ABSTRACT

Chemotherapy in the management of cancer is constrained by limitations like off-target effects, poor bioavailability, and dose-dependent toxicity. Nutraceuticals have been explored as an innovative strategy to overcome chemotherapy drawbacks. However, the clinical utility of nutraceuticals is restricted due to their complex structures, less water solubility, reduced stability, decreased bioavailability and more obstacles in the gastrointestinal tract. Nanonutraceuticals are nanosized nutraceutical particles having enhanced solubility, improved bioavailability, stability, and targeted delivery to specific cells. Nutraceuticals can be co-delivered with other chemotherapeutic drugs in nanocarriers to elicit synergistic effects. The targeting of nutraceuticals against cancer cells can be enabled by coupling ligands with the nanocarriers, which direct to the overexpressed receptors found at the surface of the cancer cells. Transitioning a nanonutraceutical from pre-clinical research to clinical trials is a pivotal step. This focus on advancing their application holds great potential for impacting clinical research and improving the treatment landscape for cancer patients. This review focuses on the role of nutraceuticals for cancer treatment, various nanocarriers for the efficient delivery of nutraceuticals along with co-administration of nutraceuticals with chemotherapeutic drugs using nanocarriers. Also, emphasize the targeting of ligands coupled nanocarriers to the cancer cells along with patents and clinical trials for nanonutraceuticals.

1. Introduction

Cancer remains one of the world's leading causes of mortality. It is a general designation for the uncontrolled proliferation of aberrant cells, and is also known as malignant tumors and neoplasms (Hassanpour and Dehghani, 2017; Majérus, 2022). There were approximately 20 million new cancer cases in 2022, with 9.7 million deaths due to cancer, according to the International Agency for Research on Cancer. About one from every five persons has cancer while one in twelve women and one in 9 men die from the cancer (Bray et al., 2024). There are various risk factors for cancer such as family history, race, ethnicity, gender, age, comorbid conditions, lifestyle, etc. Various drugs are used for the treatment of cancer; however, they have limitations, which include toxicity, non-specific targeting resulting in resistance and diminishing cancer activity (de Castro et al., 2023; Mthimkhulu et al., 2022). These limitations can be overcome by using phytochemicals of natural origin i.e., nutraceuticals (Jose et al., 2022).

The term "nutraceutical" evolved from two terms: "nutrition" and

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https://doi.org/10.1016/j.ijpharm.2024.124919
Received 6 June 2024; Received in revised form 28 October 2024; Accepted 5 November 2024
Available online 7 November 2024

"pharmaceutical" and refers to a dietary ingredient, or portion of an ingredient, that provides health benefits, either preventative or curative, and can be taken as pills, capsules, powder, or in any other form (Andlauer and Fürst, 2002; Paolino et al., 2021; Shende and Mallick, 2020). Hippocrates is credited with coining the classic phrase "Let food be thy medicine and medicine be thy food," which captures the essence of a nutritious diet and the ways in which various foods' components might have healing properties (Witkamp and van Norren, 2018). Along similar lines, there were several ancient civilizations including the Greeks, Romans, and Egyptians, emphasized the importance of natural compounds in treating diseases (Ruchi et al., 2017). Plants have been used for their healing properties such as ginseng, thyme, cumin, turmeric, honey, garlic, etc. in many instances. These findings imply that for decades there has been a lot of curiosity regarding the beneficial effects of active compounds in food or natural products and all this sparked an upsurge of research in the field of nutraceuticals (Helal et al., 2019; Castro et al., 2017). Nutraceutical products are nothing more than a drug-food blend. Nutraceuticals can range from diet plans, extracted nutrients, and dietary supplements to genetically amended "designer" foods, bioactive products, and processed foods including soups, cereals, and drinks. Many of these compounds undoubtedly have relevant physiological functions and significant biological activities (Andlauer and Fürst, 2002). Despite the positive impact of nutraceuticals on human health, their clinical translation is lacking due to various hurdles such as low aqueous solubility, inappropriate physical and chemical stability, and hepatic metabolism, fast metabolism resulting in poor bioavailability, high doses, and targeting incompetence (Muthukrishnan, 2022; Shende and Mallick, 2020).

The application of nanotechnology has opened up new avenues to address the hurdles associated with nutraceuticals resulting in enhanced beneficial characteristics and efficacy (Andrade et al., 2015). Several research organizations have paid close attention in the past few years to the integration of nutraceuticals with nanotechnology. Therefore, nanotechnology may open the door to the creation of ground-breaking supplemental nutritional products with more health benefits and fewer adverse effects (Chopra et al., 2022).

Nanonutraceuticals raised the interest of various researchers, owing to their potential for therapy in have had a significant influence on cancer conquering and reducing the risk of cancer cell formation, CNS disorders, cardiovascular illnesses, diabetes, orthopedic diseases and immunological diseases. The growing number of federally licensed nanonutraceuticals, as well as many more in clinical trials, demonstrates the importance of these technologies. Nanonutraceuticals provide distinct advantages over generally available solutions, such as increased bioavailability and efficacy, customized release, faster commencement of action, and site-specific targeting (Bhavin and Gajjar, 2021). Many nutraceuticals that have been transferred into nanoparticles and are helpful in "nano-chemotherapy" and "nano chemoprevention" include coenzyme Q, quercetin, curcumin, silymarin, Epigallocatechin gallate and thymoquinone (Nair et al., 2010).

2. Conventional treatment approach for cancer along with challenges

The major management strategy for cancer includes surgery, chemotherapy, radiation therapy, and immunotherapy (Nair et al., 2021). Radiation therapy and surgical excision are generally considered to be highly effective methods for removing the original tumor, but a common worry is the possibility of returning disease because of metastases or leftover malignant cells. Chemotherapy is therefore frequently used to address these issues (de Santana et al., 2018). But the chemotherapy also faces various obstacles in efficient treatment of cancer which mainly include severe adverse effects and chemoresistance (Grover et al., 2021).

Short-term adverse effects of chemotherapy include hair loss, fatigue, bleeding and easy bruising, frequent infections, nausea, vomiting, anemia, appetite changes, stomatitis, constipation, myelosuppression, and thromboembolism. Weight gain, infertility, heart dysfunction, lower lung capacity, early menopause, renal disease, bone disorders, and secondary leukemia are long-term adverse effects (Partridge et al., 2001). Various chemotherapeutic agents approved by FDA for the treatment of cancer are summarized in Table 1.

Table 1
A summarized list of chemotherapeutic drugs approved by FDA for the treatment of cancer.

Drug category	Chemotherapeutic drug	Adverse effects
Alkylating agents	Nitrogen mustard Chlorambucil Cyclophosphamide Melphalan Nitrosoureas Chloroethylnitrosoureas	Immunosuppression, myelosuppression, alopecia, nausea, and vomiting
Platinum agents	Carboplatin CisplatinOxaliplatin	Myelosuppression, nephrotoxicity, neurotoxicity, ototoxicity,
Antimetabolites	Pyrimidine analogues Methotrexate 5-fluorouracil Cytidine derivatives Gemcitabine Cytosine arabinoside Purine derivatives6-merceptopurine	Myelosuppression, mucositis, thrombocytopenia, leukopenia, pulmonary embolism, neutropenia, and diarrhea
Topoisomerase inhibitors	Topoisomerase I inhibitors Camptothecin Irinotecan Topotecan Topoisomerase II inhibitors Daunorubicin Doxorubicin Mitoxantrone Etoposide	Myelosuppression, mucositis, cardiotoxicity, GI toxicity, alopecia, and secondary leukemia
Antimitotic agents	Vinca alkaloids Vincristine Vinblastine Taxanes Docetaxel PaclitaxelCabazetaxel	Myelosuppression, neurotoxicity, and febrile neutropenia
Hormonal drugs	Selective estrogen receptor modifier RaloxifeneTamoxifen	Vaginal dryness, hot flashes, depression, and sleep disturbances
Molecular targeted agents	Antibodies Bevacizumab Trastuzumab Small molecules Imatinib BortezomibGefitinib	Thrombocytopenia, mucositis, skin rashes, nausea, and vomiting

Adapted from (G. Kumar et al., 2023; Patel, 2011).

Secondly, chemoresistance causes obstacles in the treatment of cancer, which is occupied by almost 90 % of chemotherapeutic agents. Tumors might be innately resistant to a specific medicine or develop resistance during therapy. The treatment for acquired resistance requires more attention, since tumors develop resistance to existing treatments and new drugs. Drug resistance can be greatly impacted by various factors such as mutations or changes in drug target expression levels or faulty apoptotic mechanisms. As the primary mechanism by which drugs have their cytotoxic impact, any flaw in programmed cell death will reduce therapeutic efficiency and finally trigger resistance. The majority of chemoresistance cases result from the activation of multidrug resistance genes and survival signals by drugs. In general, the complexity and multifaceted nature of molecular drug resistance makes it a perennial problem. The processes that limit drug absorption and its interaction with the tumor microenvironment are also important variables in drug sensitivity. As a result, any method that may overcome drug resistance could have an enormous effect on cancer cure and thus

Table 2
Summarized list of nutraceuticals for cancer treatment under clinical trials.

Natural compound	Source	Biological activity	Phase in the clinical trial	Clinical trial identifier
Artemisinin	*Artemisia annua*	Anticancer	Phase 1Phase 2	NCT00764036NCT03093129
Caffeic acid	Eucalyptus, coffee	Antioxidant, anticancer, and anti-inflammatory	Phase 3	NCT04648917
Camptothecin	*Camptotheca acuminate*	Anticancer	Phase 1	NCT02769962
Curcumin	*Curcuma longa*	Tumor cell proliferation inhibition	Phase 3	NCT03769766
Combretastatin	*Combretum caffrum*	Anticancer	Phase 2	NCT00113438
Epigallocatechin gallate (EGCG)	Green, black and white tea	Chemopreventive	Early Phase 1	NCT02891538
Genistein	Plants (soyabean, lupins)	Anticancer	Phase 3	NCT00584532
Resveratrol	Blueberries grapes, mulberries	Anticarcinogenic, cardio-protective	Phase 1	NCT00256334
Lycopene	Tomato	Anticancer	Phase 2Phase 3	NCT00068731NCT01105338
Quercetin	Fruits, red onions, kale	Anticancer, anti-inflammatory	Phase 2	NCT03476330
Silibinin	Coffee Milk, thistle	Anticancer, hepatoprotection	Phase 2	NCT00487721
Thymoquinone	Herbs, spices	Anticancer, hepatoprotective	Phase 2	NCT03208790
Ellagic acid	Pomegranate	Colorectal cancer	Phase 2	NCT01916239
Allicin	Garlic	Lymphoma	Phase 2	NCT00455416
Berberine	European barberry, goldenseal, goldthread, Oregon grape	Colorectal cancer	Phase 2	NCT03281096
Colchicine	Colchicum autumnale	Hepatocellular carcinoma	Phase 2	NCT03281096
Fisetin	Strawberry, apple, persimmon, grape, onion, and cucumber	Breast cancer	Phase 2	NCT05595499

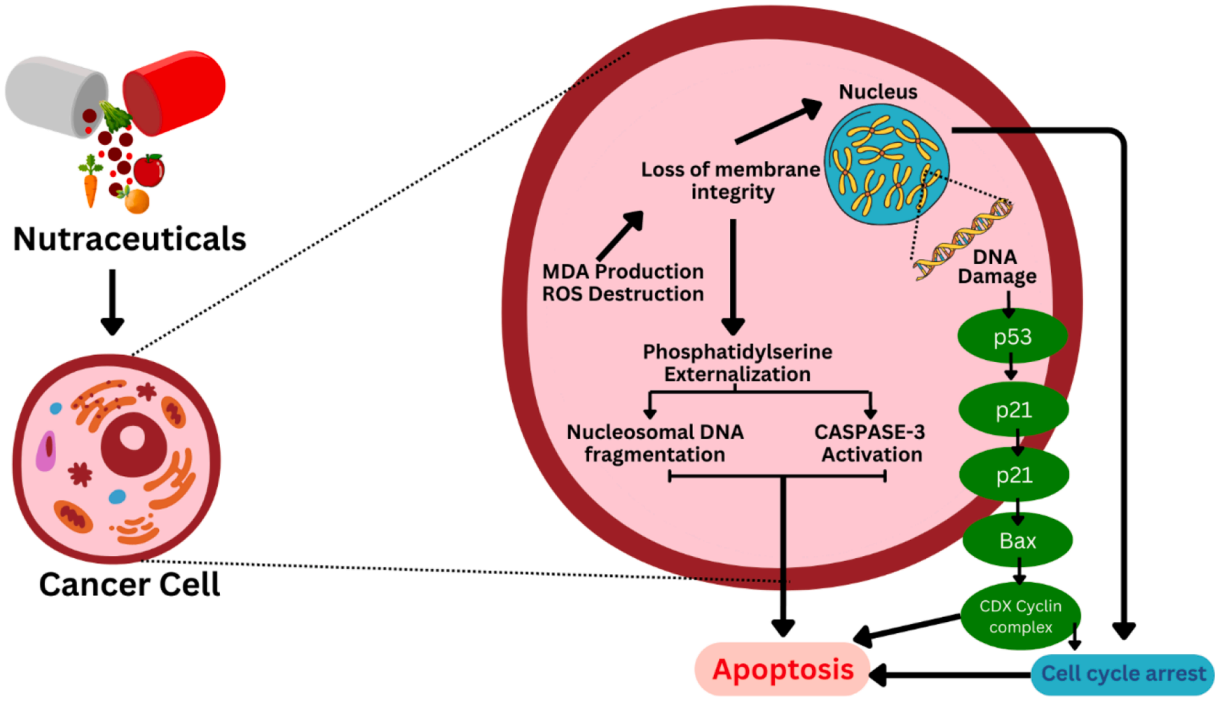

Fig. 1. Molecular mechanism of targeting cancer cells by nutraceuticals.

boost survival rates (Longley and Johnston, 2005; Nair et al., 2021).

3. Role of nutraceuticals in cancer

As is evident, the conventional approaches for the treatment of cancer have serious side effects and there is the probability of chemo-resistance. This is the significance of searching nature for novel lead molecules that are completely non-toxic to normal cells and can improve the therapeutic efficacy of currently available drugs. Numerous nutraceuticals, especially phytochemicals, have been shown through bio-prospecting and molecular pharmacology studies to modify the survival pathways that are activated by carcinogens, chemotherapeutics, and cancer cells. Since the dawn of time, Indian and Chinese medicine have utilized numerous plant-derived agents having anticancer potential due to their abundance of benefits such as fewer side effects, activity through different pathways, and affordability (Bahuguna et al., 2023). Many nutraceuticals with anticancer potential are under clinical trials, out of which some have got approval as summarized in Table 2. Additionally, nutraceuticals can be integrated with chemotherapy to decrease its adverse effects (Sreedhar et al., 2018).

Nutraceuticals can control DNA transcription and the processes in tumor cells that damage DNA. The pleiotropic nature of natural components has been shown to be advantageous in re-sensitizing drug-resistant tumors by altering many signaling pathways, including the NF-kB signaling route, EGF-mediated signaling pathways, and AMPK signaling pathways. With the help of their molecular targets, nutraceuticals can target cancer cells at different stages and induce apoptosis or cell cycle arrest by reducing the proliferation of cancer cells and

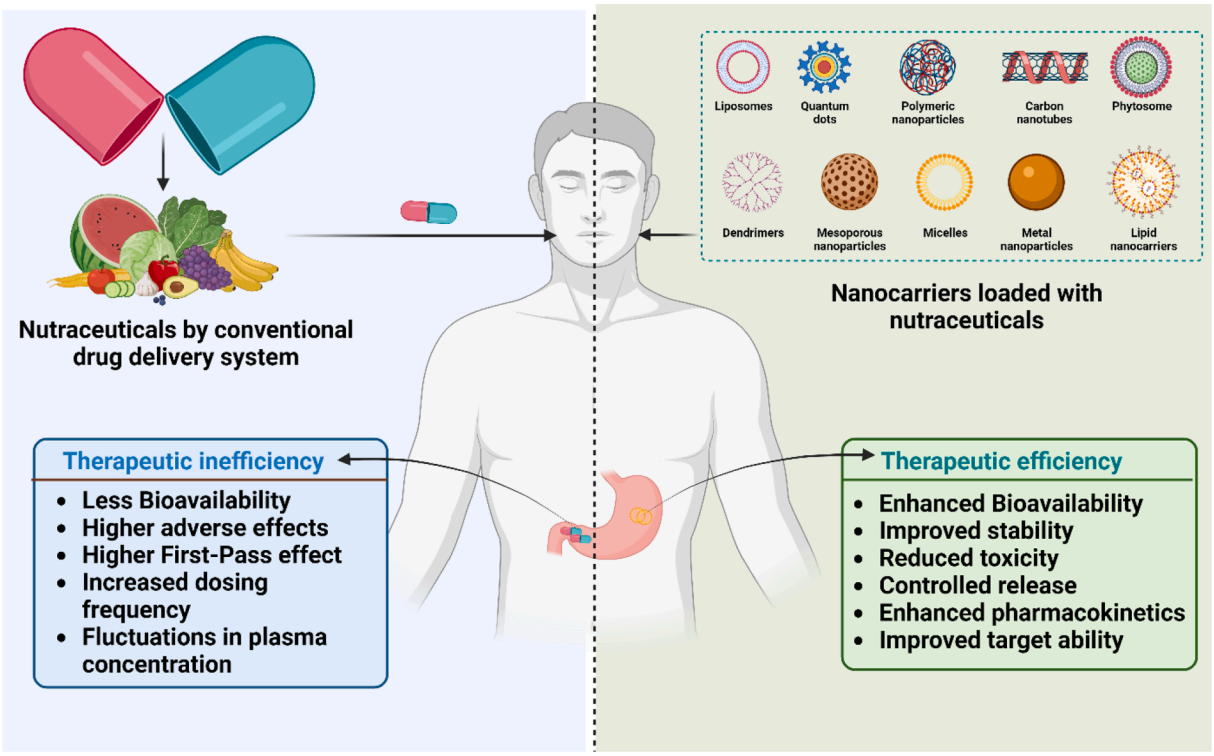

Fig. 2. Representation of advantageous characteristics of nanonutraceuticals over nutraceuticals.

preventing invasion, metastasis, or angiogenesis depicted in Fig. 1 (Ahmad et al., 2015). For instance, oleuropein primarily inhibits cell proliferation by upregulating cyclin-dependent kinase (CDK) inhibitors, which in turn inhibits the cell cycle. Additionally, oleuropein modifies the genic expression accountable for inducing intrinsic and extrinsic apoptosis passageways by upregulating p53 and p21. Moreover, oleuropein may modify the activity of important molecules implicated in the development and advancement of cancer, including fatty acid synthase (FASN) enzyme, MAPKs, and the proto-oncogene c-Met (Ahmad et al., 2015). The downregulation of signal transduction pathways necessary for cancer, such as Akt, PI3K, NFkB, mTOR, and others, is brought about by a number of nutraceutical products, such as curcumin, soy isoflavones, resveratrol, lycopene indole-3-carbinol, epigallocatechin-3-gallate, and green tea polyphenols (Sarkar et al., 2010). Despite their potential as an anticancer agent, nutraceuticals have not been successful in human therapy, in part because of poor absorption, low bioavailability, hepatic metabolism, poor stability, and restricted permeability across various physiological barriers (Meenambal and Srinivas Bharath, 2020). The possession of poor pharmacokinetic profile responsible for inefficiency of phytochemicals can be clarified by research in which Joseph et al. investigated the pharmacokinetic profile of pure quercetin and compared to novel formulation of quercetin, hybrid-hydrogel in human volunteers. It was found that pure quercetin had $AUC_{0\text{-}24}$ and C_{max} of 27.44 ± 7.49 ng.h/mL and 14.48 ± 6.65 ng/mL, respectively. On the other hand, the novel formulation of quercetin possessed $AUC_{0\text{-}24}$ and C_{max} of 1703.50 ± 348.67 ng.h/mL and 314.66 ± 135.46 ng/mL, respectively. The results displayed poor pharmacokinetic properties of pure quercetin than novel formulation. Therefore, it is essential to create plans to increase the nutraceuticals' bioavailability and delivery at the target site using appropriate approaches.

4. Nanocarrier for nutraceuticals delivery

Nanotechnology provides a special platform to overcome the above-mentioned limitations associated with nutraceuticals by encapsulating them within nanocarriers. This strategy improves the cellular uptake of nutraceuticals while simultaneously increasing their solubility and stability, enabling the regulated and precise delivery of nutraceuticals to tumor locations (Singla et al., 2023). In addition, nanotechnology-based drug delivery systems offer various benefits of the inability of drug targeting to a specific site, biocompatibility, biodegradability, prolonged dosing intervals, nano-size, fewer side effects, lower doses, enhanced stability, and incapacity to transport both hydrophilic and lipophilic agents (Pushpalatha et al., 2017; Amol and Pratibha, 2014).

Nanocarriers can pass through a variety of physiological barriers and allow the drug to be accumulated in the targeted malignant cell in sufficient amount, to improve drug bioavailability and prevents side effects (Edis et al., 2021). It is possible to give a nutraceutical agent with desired pharmacokinetic and pharmacodynamic properties by altering the size and form of the nanocarrier resulting in improved therapeutic efficacy and lowering the adverse effects (Pushpalatha et al., 2017). Various nanocarriers employed for the delivery of nutraceuticals include phytosomes, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions (NEs), dendrimers, nano-micelles, metallic nanoparticles, nanofibers, carbon nanotubes (CNTs), metallic nanoparticles which have all been thoroughly covered in detail in a further section. Their advantages in delivering nanonutraceuticals are depicted in Fig. 2 (Amol and Pratibha, 2014; Asghar et al., 2018).

The encapsulation of nutraceuticals into nanocarriers is a growing field in food science and biotechnology due to the challenges posed by poor solubility, stability, and low absorption of many bioactive compounds. Major types of nutraceuticals commonly encapsulated in nanocarriers include polyphenols (Curcumin, Resveratrol, Quercetin, EGCG), vitamins (Vitamin A, D, E, K and C), fatty acids (Omega-3 and Omega-6), carotenoids (β-Carotene, Lycopene, Astaxanthin, Lutein), flavonoids (Quercetin, Rutin, Naringenin, Catechins), phytosterols (β-Sitosterol, Campesterol), coenzyme Q10, essential oils (Peppermint oil, Lemon oil, Eucalyptus oil), minerals (Calcium, Iron, Zinc, Magnesium), and proteins and peptides (Whey protein, Casein, Collagen peptides) (Awuchi et al., 2022). The encapsulation of these nutraceuticals in nanocarriers not only improves their solubility and stability but also facilitates their targeted delivery and sustained release enhancing their

therapeutic potential.

The interactions between nutraceuticals and nanocarriers are crucial for optimizing the encapsulation, protection, bioavailability, and controlled release of nutraceuticals (Sawant et al., 2024). These interaction mechanisms include hydrophobic interactions, hydrogen bonding, electrostatic interactions, covalent bonding, van der Waals forces, etc (Alharbi et al., 2021). Numerous nutraceuticals, including fat-soluble vitamins, carotenoids, and polyphenols, are hydrophobic. These compounds can be encapsulated by hydrophobic interactions with the hydrophobic core of nanocarriers, especially lipid-based ones (such as liposomes, SLNs, and NLCs). Hydrophobic interactions increase nutraceutical solubility, increasing their bioavailability and shielding them from degradation in the GIT (Jacob et al., 2024). Nutraceuticals having charged functional groups like proteins, peptides, and vitamin C form electrostatic interaction with nanocarriers like chitosan nanoparticles having opposite charges, resulting in enhanced encapsulation efficiency and controlled release in response to various environmental alterations such as pH and ionic strength of the GIT (Baek et al., 2021). Compounds like quercetin, and catechins having polar functional groups (amine, carbonyl, and hydroxyl) form hydrogen bonds with the polar groups on the surface of nanocarriers like chitosan nanoparticles, cyclodextrins, and polysaccharides-based nanoparticles causing improved stability and successive release of encapsulated nutraceuticals (Roy and Rhim, 2021). Nutraceuticals and nanocarriers may potentially be associated with weak, non-specific interactions like van der Waals forces. These are crucial for stabilizing nutraceuticals in lipid-based nanocarriers and polymeric matrices, because they are caused by transient dipoles in molecules. For example, resveratrol may be associated with SLNs via van der Waals forces to provide stabilization and safeguard from atmospheric degradation (Tang, 2021). Covalent bonding is another important interaction mechanism through which nutraceuticals are chemically conjugated to nanocarriers, such as functionalized polymeric nanoparticles, dendrimers, and conjugated liposomes. This interaction is very helpful for targeted delivery systems, in which the nutraceutical is attached to a nanocarrier that releases it at a specified location, like in gastrointestinal targeting or cancer treatment. For example, folic acid covalently conjugated to nanocarrier surface targets the cancer cells without harm to non-cancer cells (Ebrahimnejad et al., 2022). Covalent bonding can protect nutraceuticals from premature degradation and guarantee their delivery to a specific place in the body by enabling continuous and targeted release. These interactions between nutraceuticals and nanocarriers are essential to overcome the problems of low bioavailability, poor solubility, and instability of many nutraceuticals, confirming they reach their desired targets and delivering maximum therapeutic benefits.

4.1. Liposomes

Liposomes are spherical vesicles made up of bilayers of cholesterol and phospholipids, which provide two microenvironments to deliver hydrophilic and hydrophobic drugs (Saraf et al., 2020). In food and nutraceutical production, liposomes are ideal for encapsulating sensitive agents, enhancing product solubility and bioavailability, and precisely targeting encapsulated agents. Liposomes enhance oral bioavailability and guard against GI tract degradation by boosting nutraceuticals retention and cellular contact (Akram et al., 2023). Liposomes are coated with polyethylene glycol (PEG), which inhibits liposome breakdown by macrophages in the reticulo-endothelial system (RES) and increase nutraceutical retention (Vandchali et al., 2021). They benefit on the increased permeability and retention effect (EPR) and binding with overexpressed receptors on cancer cell surface by using targeting strategies. Liposomes reduce nutraceutical exposure in healthy tissues, while raising its concentration in malignant cells (Wang et al., 2023a).

The rationale of liposomes to deliver curcumin in the treatment of lung cancer was studied by Wang L et al. The findings demonstrated reduced tumor volume in LL/2 cancer model treated with curcumin loaded liposomes than control group (Wang et al., 2012). In another example, liposomes were fabricated to deliver the epigallocatechin gallate (EGCG) in the treatment of cancer. The results displayed that injecting liposomes loaded with EGCG into basal cell carcinoma (BCCs) with a slight modification efficiently increased EGCG deposition (Minnelli et al., 2018).

4.2. Phytosomes

Phytosomes are a complex of phospholipids and naturally active phytochemicals bound in their structures, formed by the reaction between phosphatidylcholine (or other hydrophilic polar head groups) and phytoconstituents like polyphenols in an aprotic solvent (Barani et al., 2021). They are structurally like liposomes but are more efficacious to deliver certain nutraceuticals at cancer sites due to their unique structural composition. The phospholipid bilayer of the phytosomes aids contact-facilitated drug transport, in which there is a lipid-lipid interaction between the cell membrane and carrier, allowing the diffusion of nutraceuticals into the cancer cell. Phytosomes can also improve the efficacy of lipophilic nutraceuticals diffusion across the small intestinal brush barrier. Typically, these agents agglomerate, and hydrolytic digestion impedes the controlled and sustained release of nutraceuticals into the systemic circulation. The phosphatidylcholine in phytosomes produces a monolayer in the GIT to prevent drug agglomeration (Singh et al., 2024).Thus, phytosomes boost the bioavailability of nutraceuticals, improving their efficacy and enabling non-invasive delivery (Toma et al., 2024).

The potential of phytosomes to deliver quercetin in the treatment of breast cancer was evaluated by Alhakamy et al. Quercetin-loaded phytosomes showed reduced IC50 value than free quercetin. Moreover, quercetin loaded phytosomes greatly elevated the Bcl-2, Bax, p53, and mRNA expression of caspase-9 and dramatically reduced the NF-B and TNF- activity in terms of the inflammatory markers (Alhakamy et al., 2021a). In another study, Marczylo et al. revealed the improved bioavailability of curcumin loaded phytosomes over unloaded curcumin in male Wistar rats. Moreover, the levels of curcumin in the liver were increased for phytosomal formulation when compared to unloaded curcumin. The concentration of curcumin from phytosomal formulation was reduced in GIT compared to unloaded curcumin, displaying that systemic levels of curcumin were increased from phytosomal formulation as compared to unloaded curcumin (Marczylo et al., 2007).

4.3. Solid lipid nanoparticles (SLNs)

SLNs consist of solid lipid components coupled with surfactants used for drugs encapsulation. Their particle size varies from 50 to 500 nm (Akanda et al., 2023). SLNs contain a solid lipid core that protects nutraceuticals from chemical degradation and allows for sustained release due to the zero-order breakdown kinetics of the solid lipid matrix (Vimala and Kannan, 2021).SLNs enhance higher gastrointestinal absorption through surfactant-induced permeability alterations, as well as longer residence periods in the stomach and upper small intestine due to their lipidic composition and attachment to the intestinal underlying epithelium (Fathi et al., 2012). By enhancing intracellular uptake by M cells from Peyer's patches, SLNs have been shown to increase oral bioavailability of nutraceuticals. Indeed, the impact of highly lipophilic surfactants has been observed to cause brief opening of tight junctions (gaps between two neighbouring intestinal epithelial cells), enhancing paracellular absorption (Elmowafy and Al-Sanea, 2021).

The rationale of SLNs to deliver nutraceuticals in the treatment of cancer can be explained on the basis of various *in vitro* and *in vivo* studies. For instance, β-carotene (BC) loaded SLNs demonstrated increased antitumor potential against breast cancer cell lines than plain BC. BC loaded SLNs exhibited reduced IC50 value than plain BC along with increased retention which could occur due to increased accumulation of SLNs within the cells (Dutta et al., 2024). Quercetin (QT)

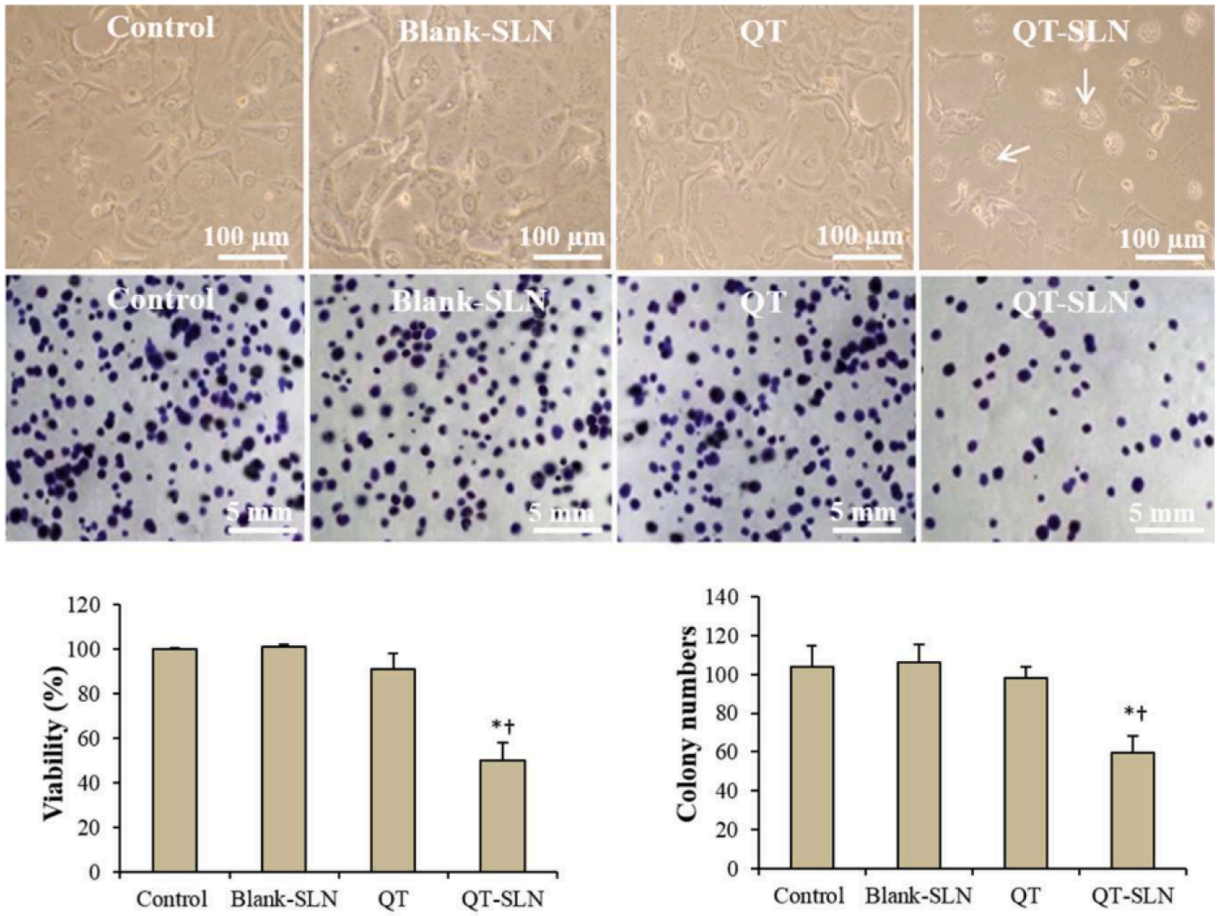

Fig. 3. Morphological representation of MCF-7 cancer cell lines in above images and colony formation in below images on treatment with control, blank SLNs, quercetin (QT), and quercetin SLNs (QT-SLNs). The values for percentage cell viability and colony formation were also expressed as mean ± SD. Reprinted with permission from (Niazvand et al., 2019).

loaded SLNs demonstrated enhanced inhibtion of MCF-7 cancer cell lines (human breast cancer) than unloaded QT as shown by reduced IC_{50} values. In addition, percentage cell viability and colony numbers were significantly decreased in QT loaded SLNs treated MCF-7 cell lines than plain QT treated MCF-7 cell lines (Niazvand et al., 2019) as depicted in the Fig. 3.

While SLNs offer various advantages in the management of cancer, there are significant disadvantages as well. These include an increased frequency of polymorphic transitions, drug ejection, unanticipated clumping, and low drug loading capacity. All of these need to be taken into consideration (J et al., 2023).

4.4. *Nanostructured lipid carriers (NLCs)*

To address the aforementioned limitatons of SLNs, NLCs have shown their ability as sophisticated carrier (Nguyen et al., 2022). These are composed of both liquid and solid lipids, which leads to lipid matrix imperfections. The presence of imperfections in the lipid matrix of NLCs causes a greater gap between fatty acid chains enabling the incorporation of larger amounts of nutraceuticals, as well as a reduction in expulsion during polymorphic transitions (Babazadeh et al., 2017; Ahalwat et al., 2023). NLCs make it possible for nutraceuticals to be targeted through the lymphatic system, which has numerous benefits comprising avoiding hepatic metabolism, reducing hepatotoxicity, and improving bioavailability (Salvi and Pawar, 2019). Morover, all beneficial characterstics of SLNs are also available with NLCs.

Recently, various *in vitro* and *in vivo* studies have demonstrated the efficacy of NLCs to deliver nutraceuticals in the treatment of cancer. For example, a previous work evaluated the improved efficacy of apigenin (APG) in the treatment of lung cancer when encapsulated in the form of NLCs than free APG. APG loaded NLCs displayed greater potential to prevent the propagation of NCI-H1299 cells than free APG. Morphological changes were higher on treatment with apigenin-loaded NLCs than plain apigenin which demonstrates the improved cytotoxic effect of apigenin-loaded NLCs (Wang et al., 2023b). It can also be explained by a study in which the anti-oral cancer potential of silymarin (SME) was improved by formulating it as NLC mucoadhesive in-situ gel. The NLC mucoadhesive in-situ gel of SME demonstrated remarkable reduction in IC_{50} value than simple mucoadhesive in-situ gel of SME and free SME. It also provided greater inhibition of human KB oral cancer cells due to increased permeation (Shete et al., 2023).

4.5. *Nanoemulsions (NEs)*

NEs are optically isotropic and thermodynamically unstable non-homogeneous, transparent colloidal dispersions with size range of 20–200 nm (Kumar et al., 2022b). Because of their nano size, they permeate in tissues deeply, allow prolonged circulation, and engage in special bio-nano interactions (Wilson et al., 2022). NEs are effective ways for encapsulating, transporting, and delivering nutraceuticals because of their capacity to contain them within food matrices, protect their beneficial properties during storage, and allow for their regulated release through the gastrointestinal tract (Kumar et al., 2022a). NEs dramatically reduced the risk of nutraceuticals degrading during the digestive process, by providing a greater surface area for better interaction at the target biological locations leading to improved bio-

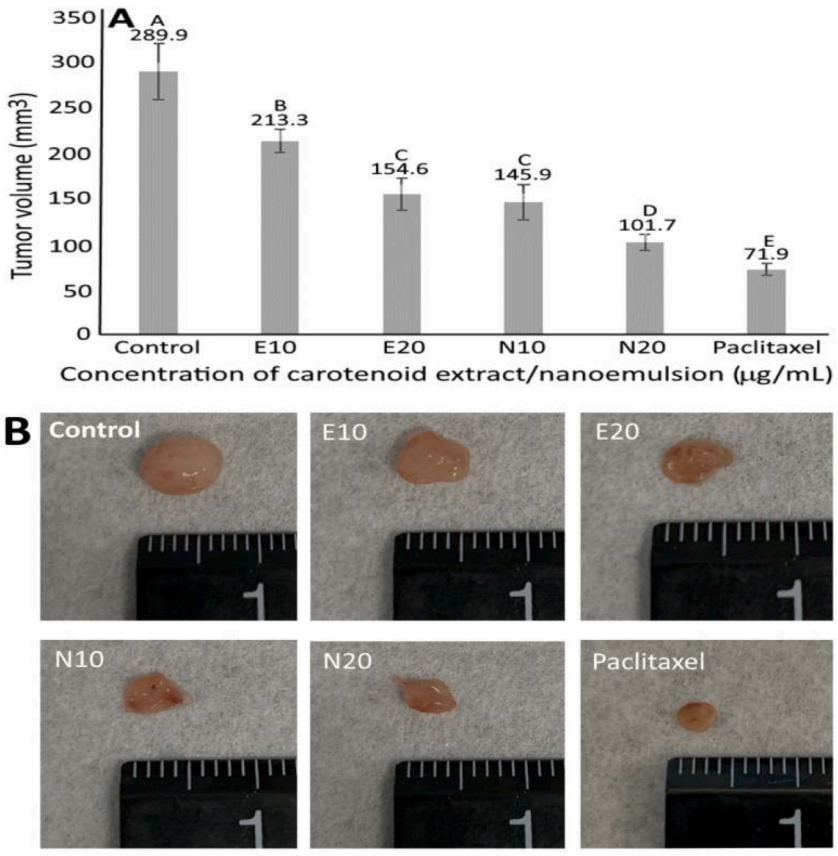

Fig. 4. Effect of carotenoid NE, carotenoid extract, and paclitaxel drug on tumor volume (A) and tumor size (B). E10 and E20 represent carotenoid extract 10 µg/mL and 20 µg/mL. N10 and N20 represent carotenoid NE 10 µg/mL and 20 µg/mL. Reprinted with permission from (Hsu and Chen, 2022).

absorption (Tarhan and Spotti, 2021). These are of two types namely water-in-oil (W/O) and oil-in-water (O/W) due to which they can encapsulate both hydrophilic and lipophilic nutraceuticals, increasing their *in vitro* activity and bioavailability (Choi and McClements, 2020). Various nutraceuticals like lycopene, carotenoids, polyunsaturated fatty acids-rich oil, curcumin, astaxanthin, quercetin, and thymoquinone have been successfully delivered employing NEs as nanocarriers.

NEs can be functionalized by conjugating with various compounds like antibodies to target certain locations, which can be exemplified by a study in which antibody conjugation of nutraceuticals resulted in drug integration into cancer cells (Sánchez-López et al., 2019).

The benefits of NEs to deliver nutraceuticals in the treatment of cancer can be assessed by a study in which NEs were developed to deliver carotenoid in the treatment of breast cancer. As compared to control, paclitaxel (standard) reduced maximum tumor volume followed by NE of carotenoid at 10 µg/mL, 5 µg/mL, carotenoid extract at 10 µg/mL, and 5 µg/mL. The same findings were found for the tumor weight and tumor size as illustrated in Fig. 4 (Hsu and Chen, 2022). It can also be assessed in another study in which NEs encapsulated with lycopene and gold particles demonstrated high efficiency in the treatment of cancer. NEs encapsulated with lycopene and gold nanoparticles exhibited 15 folds improved apoptosis of HT-29 cancer cells (Huang et al., 2015a).

4.6. Polymeric nanoparticles (PNPs)

PNPs are solid colloidal particles with a size range of 10–1000 nm and are made of biodegradable and biocompatible polymers, in which the therapeutic agents can be encapsulated, physically adsorbed on the surface of the carrier, or chemically bonded to the surface (Sharma et al., 2022a; Fonte et al., 2016). These provide improved safety of encapsulated nutraceuticals and effective delivery at the target sites. In addition, PNPs consist of various advantageous characteristics such as nano-size (less than 200 nm), higher surface volume ratio, biodegradability, biocompatibility, and prone to surface modification (Kumar et al., 2023; Begines et al., 2020). The size of less than 200 nm providesenhanced permeability and retention (EPR) effect,which leads to increased penetration and prolonged retention of nanoparticles in the tumor environment (Arora and Jaglan, 2016). Due to the existence of several functional groups on their surface, anticancer agents can be targeted to specific tumor locations (Virmani et al., 2023). PNPs can be tailored to resist being engulfed by phagocytes, whiich improves cellular absorption and extends the circulation duration, which leads to greater efficiency.

Several biodegradable polymers such as poly(D, L-lactic-co-glycolic acid) (PLGA), poly (Ɛ-caprolactone) (PCL), poly(ethylene glycol) (PEG), poly (D, L-lactic acid) (PLA), tocopheryl polyethylene glycol succinate (TPGS), and have been shown their potential for efficacious delivery of nutraceuticals in various kinds of ailments (Salari et al., 2022; Oliveira et al., 2018).Various polysaccharides polymers like alginate, pectin, and chitosan also have been employed for the preparation of PNPs encapsulating nutraceuticals (Colone et al., 2020).

To prolong the duration of nutraceuticals in systemic circulation and reduce interactions of nutraceuticals with blood proteins, PNPs can be coated for PEG. Additionally, PEGylation makes drug molecules more hydrophilic and makes it possible for PNPs to encapsulate both hydrophilic and lipophilic pharmaceuticals, allowing for regulated drug release (Truong et al., 2015). It's interesting to note that PNPs can be modified to increase their selectivity for malignant cells by combining them with different compounds, like folic acid and antibodies.

The rationale of adopting the PNPs to deliver nutraceuticals in the treatment of cancer can be shown by a study in which QT loaded PLGA

NPs displayed noteworthy reduction in cell viability of breast cancer and cervical cancer cell lines. QT loaded PLGA PNPs decreased the average number of tumors and delayed the tumor latency period (Yadav et al., 2022). In another example, PLGA NPs were developed to deliver piperine (PPN) for effective treatment of the cancer. PPN-laden PLGA NPs displayed a higher cytotoxic effect towards A549, HeLa, PC-3, HT1080, and MCF-7 cell lines while poor cytotoxicity towards HEK-293 cell lines. The findings suggested that encapsulating PPN in PNPs would be a more effective way to demonstrate its superior effectiveness in cancer treatment (Kaur et al., 2021).

4.7. Polymeric prodrugs

Polymeric prodrugs have garnered a lot of interest in the field of anticancer drug delivery by combining the benefits of both prodrugs and nanoparticles (Wang et al., 2022). A polymeric prodrug is the coupling of anticancer moiety with polymer chains through particular linkages. These linkages are stable in a physiological environment and can be broken down to release the drug in tumor microenvironment (Chu et al., 2023). Polymeric prodrugs offer several benefits, such as extended drug action, regulated drug release, site specific action, and immune-suppression during cancer treatment (Abdelghafour et al., 2022). It can be well studied by a research in which withaferin A (WA) was modified at C27-OH using chain transfer agent (CTA) for reversible addition-fragmentation chain transfer (RAFT) polymerization to develop polymeric prodrug. N,N-dimethylacrylamid (DMA) was employed as hydrophilic polymer which yielded highly water soluble conjugate of WA than non-functionalized WA. However, the findings of cytotoxicity studies displayed significantly reduced cytotoxicity for polymer prodrug of WA then unloaded WA which could be attributed to inadequate ester bond Cleavage between the polymer and WA (Van Herck et al., 2019).

4.8. Nano-micelles (NMs)

These nano-sized colloidal dispersions, which contain a hydrophobic core, and a hydrophilic exterior have demonstrated a promising capacity to deliver nutraceuticals. These have the unique characteristic of the formation of regular nano micelles having an inward hydrophobic core and outward hydrophilic portion in an aqueous medium whereas the formation of reverse nano micelles in a non-polar medium (Li et al., 2022a; Andrade et al., 2016). Due to this property, nano micelles can deliver hydrophilic as well as hydrophobic nutraceuticals simultaneously. Additionally, the hydrophilic outer layer protects the drug within the encapsulation from the external environment and inhibits its interaction with plasma components, which leads to long circulation properties in humans. A regulated release of the entrapped nutraceuticals is possible because of the lipophilic core, which also makes poorly water-soluble nutraceuticals more soluble (Tawfik et al., 2021). These could enable the protection of entrapped nutraceuticals from biodegradation resulting in the deposition of a greater number of nutraceuticals at the targeted tumor site. In addition, the nano size of nano micelles (20–200 nm) increases the amount of time they spend in blood circulation, avoiding glomerular clearance and hepatic and splenic filtration. It also facilitates cellular absorption and the capacity to cross epithelial barriers period of nutraceuticals (Qiu et al., 2017).

Casein micelles are one type of micelle used for loading nutraceuticals in the treatment of cancer (Bahadori et al., 2017). These are spherical colloidal carriers having particle sizes of 50–500 nm comprising α_{s1}-casein, α_{s2}-casein, β-casein, and κ-casein (Lisitsyn et al., 2021). Various nutraceuticals such as curcumin, quercetin, β-carotene, and vitamin D have been delivered using casein nano micelles.

The stability of these nanocarriers can be improved using surface modification with polyethylene glycol (PEG). PEG modified nanocarriers become hydrophilic and achieve near zero zeta potential, preventing or reducing the attachment of opsonins (serum proteins), which increases the likelihood of phagocytosis. Therefore, PEGylated nanocarriers can bypass the mononuclear phagocyte system. PEG chains with high hydration levels could further increase the hydrodynamic size of PEG-modified nanocarriers to protect them from renal clearance, as well as preventing the access of proteolytic enzymes and antibodies. As a result, PEGylation can provide nanocarriers, a much longer circulation lifetime than unmodified nanocarriers, extending these features to any encapsulated pharmaceuticals in PEG based delivery systems (Hoang Thi et al., 2020).

Polyvinylpyrrolidone (PVP) is another hydrophilic polymer that has grown in prominence as an element in nutraceutical delivery systems due to its capacity to build a stable amorphous matrix with the entrapped nutraceutical. This can prevent the nutraceutical from crystallizing, allowing it to remain more soluble and amorphous. Amorphous drugs are often more soluble than crystalline drugs, which might contribute to better dissolution and absorption in the gastrointestinal system (Rusdin et al., 2024). In addition, PVP is used as a surface stabilizer to control the nucleation rate of nanoparticles and restrict their aggregation via repulsive forces from contacts of their hydrophobic carbon chains in solvent (Loo et al., 2023). Owing to these characteristics, various particulate nutraceutical delivery technologies, including microspheres, liposomes, nanoparticles, and diblock polymer micelles, have utilized polyvinylpyrrolidone in a variety of formulations.

The potential of NMs to deliver the nutraceuticals in the treatment of cancer can be assessed by a study in which QT loaded NMs were developed to treat lung cancer. QT entrapped NMs exhibited enhanced anticancer activity than control group and group treated with QT suspension in A549 cancer cell lines and the murine xenograft model. NMs formulation was better tolerated in animals with cancer along with no noteworthy alteration in body weight after 10 weeks of study duration (Tan et al., 2012). In another study, polymeric NMs and mixed NMs were fabricated to improve the oral absorption of silymarin. NMs of silymarin exhibited 6 folds improved solubility than unloaded silymarin. NMs formulation provided improved intestinal permeation supported by the parallel artificial membrane permeability assay. The permeation through Caco-2 cell lines demonstrated that mixed NMs have greater potential for permeation than polymeric NMs (Piazzini et al., 2019).

4.9. Dendrimers

Dendrimers are multibranched, star-shaped polymeric vesicles that resemble a tree. The structure is made up of internal branches, a central core, and external functional groups (Pérez-Ferreiro et al., 2023). The rationale for employing dendrimers to deliver nutraceuticals is because the core is favorable for entrapping the nutraceuticals, since the existence of multiple surface groups lead to an increase loading percentage of nutraceuticals, and the potential conjugation of surface groups with target ligands. The central core has cavities which create cages and channels to form the branching units and to house the nutraceuticals (Yousefi et al., 2020). In addition to being able to be modified, dendrimers' surfaces can be complex with a wide variety of nutraceuticals (Yousefi et al., 2020). In contrast to other nanocarriers, dendrimers can selectively absorb a wide range of nutraceuticals thanks to their mutable branches.

The widely used polymers for the fabrication of dendrimers are polyamidoamine (PAMAM), polyethyleneimine, polypropyleneimine, and poly-(N-isopropylacrylamide) (Munavalli et al., 2019). PAMAM dendrimers are broadly used to treat cancer due to its hydrophilicity, non-immunogenicity, and biocompatibility (Fana et al., 2020). But the safety of dendrimers is seriously questioned due to their cytotoxic and hemolytic properties (Sanyakamdhorn et al., 2016). These toxic effects can be mitigated by surface functionalization of dendrimers by PEG (Kesharwani and Iyer, 2015).Various nutraceuticals such as curcumin, carotenoids, ursolic acid, resveratrol, fullerenol, folate, anthocyanins etc. have been encapsulated and delivered employing dendrimers (Yousefi et al., 2020).

The potential of dendrimers to deliver nutraceuticals in the treatment of cancer can be seen in research conducted by Gallien et al., in which surface-modified PAMAM dendrimers (G4 90/10-Cys) encapsulating curcumin exhibited improved anticancer potential against Glioblastoma cell lines namelyhuman-U87, mouse-GL261, and rat-F98. Curcumin encapsulating G4 90/10-Cys provided enhanced reduction in viability of all these cell lines than unloaded curcumin (Gallien et al., 2021). In another work, Telodendrimers encapsulating gambogic acid (GA) exhibited better antitumor activity towards HT-29 cancer cell lines than the GA-Cremophor EL formulation at the same dose. The formulation was found to have reduced toxic effects along with increased therapeutic potential demonstrating the potential of dendrimers for effective delivery of nutraceuticals (Huang et al., 2015b).

4.10. Albumin nanoparticles

Albumin nanoparticles are advantageous as drug carriers due to various properties including biocompatibility, biodegradability with minimal cytotoxicity and immunogenicity. They are extensively employed in cancer treatment due to its ability to be delivered under controlled conditions, target delivery either passively or actively, and circumvent drug resistance mechanisms (Chilom et al., 2024). Albumin nanoparticles loaded with nutraceuticals like curcumin have a high drug loading capacity along with few harmful effects. Additionally, because of the various drug-binding sites found in the albumin molecule, a significant amount of therapeutic molecules can be integrated into the particle matrix of albumin nanoparticles (Karami et al., 2020). The presence of carboxylic and amino group in albumin facilitate decoration of albumin nanoparticles with various targeting moieties to elicit site specific action (Hassanin and Elzoghby, 2020). Abraxane®, a paclitaxel albumin nanoparticle formulation has been approved for the treatment of breast cancer which shows the potential of albumin nanoparticles to deliver the therapeutic molecules in the treatment of cancer (Yuan et al., 2020).

The potential of albumin nanoparticles to deliver the nutraceuticals in cancer can be well explained by a study in which folate conjugated albumin nanoparticles of baicalin (FA-BSANPs/BA) were developed to target breast cancer. The findings demonstrated that FA-BSANPs/BA can significantly suppress tumor growth in comparison to BA and can specifically target tumors in MCF-7 xenograft tumors-carrying naked mice. FA-BSANPs/BA had a substantially higher absorption efficiency than BSANPs/BA, which increases the likelihood of apoptosis (Meng et al., 2021). In another work, PDL-1 binding peptide conjugated albumin nanoparticles of curcumin were fabricated to target breast cancer. The results of cellular uptake study displayed greater internalization for PDL-1 conjugated albumin nanoparticles. The assessment of cell viability and apoptosis revealed that albumin nanoparticles of curcumin were more lethal to breast cancer cells than unloaded curcumin (Hasanpoor et al., 2020).

4.11. Carbon nanotubes (CNTs)

CNTs are made of tubular graphene sheets that have been “rolled” up. There are mainly two types: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs), depending on the presence of several sheets of graphene (Rathinavel et al., 2021). Drug molecules of varying sizes can be loaded on different sites of CNTs like tips, within, and sides depending on the intention of application. Many different biomolecules can be functionalized on CNTs, enabling the delivery of entrapped molecules precisely at desired sites. Given their ease of penetration into cells and capacity to transport drugs directly to the cytoplasm or nucleus, CNTs have significant benefits over other drug delivery technologies.

The application of CNTs to deliver nutraceuticals in cancer can be well observed in a study in which Alimohammadi et. al. formulated chitosan-coated QT loaded SWCNTs to target cervical cancer. Chitosan coated QT loaded SWCNTs provided a 56 % reduction in viability of HeLa cells after 72 h at 100 μg/mL which was 43 % for pure QT. This can be attributed to the strong interaction between HeLa cells and QT partially released from chitosan coated SWCNTs (Dolatabadi et al., 2011). In another study, curcumin loaded SWCNTs were fabricated to treat prostate cancer. The formulation displayed better inhibition of PC-3 cells than plain curcumin which demonstrates the potential of CNTs as nanocarriers for cancer (Li et al., 2014).

4.12. Inorganic nanocarriers

Inorganic nanocarriers have a core made up of inorganic material like silver, gold, silica, iron oxide etc., and a shell comprised of organic materials like polymers. The shell serves as a location of attachment for biomolecules or receptors and shields the confined molecules from external physiological changes (Unnikrishnan et al., 2023). Because of their characteristics, including photosensitivity, conductivity, magnetic attraction, and thermal adeptness, these nanocarriers can be used as therapeutic agents and drug carriers. The therapeutic potential of inorganic nanocarriers provides synergistic effect on encapsulation of anticancer molecules (Narayana et al., 2024). INPs can be produced from metals, metal oxides, and non-metallic materials (carbon and silica). As drug carriers, they have several benefits, such as increased drug-loading capacity, as well as the capacity to engage in photothermal therapy (PTT) and photodynamic therapy (PDT) (Arora and Jaglan, 2016). These have the potential as effective carriers for nutraceuticals due to innumerable features like unique physiochemical properties (size, shape), augmented surface area, chemical composition, and proficiency to functionalization for better targeting at the tumor site (Zhao et al., 2015).

Gold nanoparticles (AuNPs) have been touted as having improved targeting, gene silencing, drug delivery capabilities, and especially when equipped with ligands that permit controlled deposition into cancer cells (Sharma et al., 2018). These can be easily taken by the cells, which is an advantageous feature in the treatment of cancer. The rationale of AuNPs to deliver nutraceuticals was assessed by Sharifiaghdam et al. Apigenin coated AuNPs were developed to alleviate the doxorubicin-induced cardiotoxicity via the process of apoptosis. Apigenin coated AuNPs reduced more Bax-positive cells than doxorubicin whilst Bcl-2 positive cells were increased in animals treated with doxorubicin + apigenin coated AuNPs than animals treated only with doxorubicin. The injury markers were decreased in animals treated with apigenin coated AuNPs (Sharifiaghdam et al., 2023). In another study, AuNPs improved the anticancer potential of epigallocatechin-3-gallate (EGCG). EGCG loaded AuNPs provided superior anticancer activity than plain EGCG which was indicated by smaller tumor volume and weight as well as increased body weight of mice in case of EGCG loaded AuNPs treatment (Safwat et al., 2020).

The efficient delivery of nutraceuticals has also piqued the interest of magnetic nanoparticles (MNPs) because of a number of advantageous characteristics, including enhanced therapeutic index, which results in increased therapeutic efficacy and decreased toxicity, drug targeting due to magnetic properties, improved stability, increased solubility, longer circulation times for entrapped agents in the body, higher concentrations of agents in diseased organs, controlled drug release, and the capacity to co-deliver therapeutic agents (Koksharov et al., 2022). The presence of magnetic properties enables the stimuli-based release of the entrapped agents and drug targeting to specific cancer sites (Liu et al., 2019). MNPs based on iron oxides, such as maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4) are well suited for the delivery of nutraceuticals because nanophase iron oxide is low in toxicity, abundant in biological systems, and amenable to cellular metabolism (Geppert and Himly, 2021). In a study, MNPs were prepared by Yallapu et. al. to advance the therapeutic potential of curcumin in breast cancer. The results of the concentration-dependent uptake of internalized MNPs of curcumin in MDA-MB-231 cells revealed that the particles are internalized through

Table 3
Various nanoformulations loaded with nutraceuticals showing anti-cancer activity.

Nanocarrier	Loaded nutraceutical	Type of cancer	Cell line	Result findings	Ref.
Liposomes	Quercetin	Colorectal cancer	SW48	Displayed more than 80 % reduction in cell viability of SW48 cells at 50 μg/mL which was 66 % for plain quercetin. The rate of apoptosis was 54.8 % for liposomes of quercetin whilst it was only 27.6 % for plain quercetin. Conversely, Epidermal growth factor receptor (EGFR) gene expression was much lower in cells treated with liposomes loaded with quercetin than in cells treated with quercetin alone.	(Keshavarz et al., 2023)
	Beta-carotene	Breast cancer	MCF-7	The IC50 value for liposomes of B-carotene was 121 μg/ml whilst it was 21.15 μg/ml for plain B-carotene demonstrating the potential of B-carotene loaded liposomes.	(Mahrous et al., 2022)
	Curcumin	Lung cancer	A549	Observed highest cytotoxic activity (IC50: 11.7 ± 0.24 μg/ml) against A549 cell lines after 72 h of exposure, and provided dose-dependent inhibition of human umbilical vein endothelial cell (HUVEC) proliferation with an IC50 of 2.64 ± 0.21 μg/ml.	(Ibrahim et al., 2018)
	Curcumin	Pancreatic cancer	MIA PaCa-2 cell line	Provided that curcumin-loaded liposomal formulation caused improved inhibition of tumor growth than untreated groups.	(Ranjan et al., 2013)
	Curcumin	Breast cancer	MCF-7	Provided noteworthy potential as an anticancer agent against MCF-7 cell lines and KHOS cell lines.	(Dhule et al., 2012)
	Luteolin	Colorectal cancer	Colon tumor 26 (CT26)	Luteolin-loaded liposomal formulation exhibited superior anticancer activity than free luteolin which was supported by a greater reduction in tumor weights than other groups.	(Wu et al., 2018)
	Thymoquinone	Breast cancer	MCF-7, T47D	Demonstrated that thymoquinone-loaded liposomes exhibit a low degree of toxicity towards normal periodontal ligament fibroblasts while effectively inhibiting the proliferation of breast cancer cell lines MCF-7 and T47D.	(Odeh et al., 2012)
	Baicalein	Pancreatic cancer	AsPC-1 and Biopsy xenograft of Pancreatic Carcinoma line-3 (BxPC-3 PDAC)	Exhibited improved IC50 values indicating potent anticancer potential towards BxPC-3 PDAC and AsPC-cell lines along with negligible toxicity and no hemolytic activity.	(Markowski et al., 2023)
	Hesperetin	Breast cancer, lung cancer	H441 and MDA-MB-231	Hesperetin loaded liposomal formulation exhibits a greater decline in cell sustainability than hesperetin loaded in Dimethyl sulfoxide (DMSO) and had the same anticancer potential in the presence of MDR-1 proteins.	(Wolfram et al., 2016)
	Epirubicin	Breast cancer	MDA-MB-435, MDA-MB 435/ADR	Demonstrated effective restriction of both MDA-MB 435/ADR and MDA-MB-435 cells by liposomal formulation of epirubicin, exhibited high permeability on both the membrane of the cell nucleus and the tumor cell, and proved that anticancer effect of the formulation is not due to P-gp efflux pump which indicates that liposomal formulation would not interfere with regular physiological functions of the membrane proteins.	(Zhao et al., 2013)
	Omega-3 fatty acids	Myeloid leukemia	T27A	Omega-3 fatty acids possess anticancer potential but incorporation into liposomal formulation provided improved anticancer potential than plain Omega-3 fatty acids.	(Jenski et al., 1995)
Phytosomes	Curcumin	Prostatic cancer	Prostate cancer 3 (PC3)	Demonstrated adequate cytotoxicity and reduced half maximal inhibitory concentration (IC_{50}) value than curcumin and Phospholipon®-scorpion venom separately, Cell cycle apprehension was observed at the pre-G1 and G2-M phases, and higher necrosis of PC3 cells was observed.	(Al-Rabia et al., 2022)
	Quercetin	Breast cancer	Michigan Cancer Foundation-7 (MCF-7)	Provided more sensitivity of MCF-7 cells towards phytosomal formulation than plain quercetin, cell cycle apprehension at the S phase, enhanced levels of B-cell lymphoma 2 (Bcl-2), caspase-9, and p53mRNA expression than plain quercetin, and noteworthy reduction in inflammatory markers like nuclear factor kappa B (NF-kB) and Tumor Necrosis Factor alpha (TNF-α) than plain quercetin.	(Alhakamy et al., 2021b)
	Thymoquinone	Lung cancer	Adenocarcinomic human alveolar basal epithelial cells (A549)	Exhibited a considerable drop in the IC50 value against the A549 cell line representing a dose-dependent cytotoxicity increase, enhanced apoptotic induction and cell necrosis of phytosomal formulation by caspase-3 activation.	(Alhakamy et al., 2020)
	Luteolin	Breast cancer	MDA-MB 231	Luteolin-loaded Phytosomes decreased nuclear factor erythroid 2-related factor 2 (Nrf2) gene	(Sabzichi et al., 2014)

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Table 3 (*continued*)

Nanocarrier	Loaded nutraceutical	Type of cancer	Cell line	Result findings	Ref.
				expression at the mRNA level in cells than luteolin alone. In a similar vein, there was a significant decrease in the expression of downstream Nrf2 genes, such as Heme oxygenase 1 (Ho1) and multidrug resistance protein 1 (MDR1), and a significant increase in cancer cell mortality was seen with inhibition of Nrf-2 expression.	
	Aloe vera extract	Breast cancer	MCF-7	Demonstrated noteworthy cytotoxic potential towards MCF-7 cell lines along with better biocompatibility.	(Murugesan et al., 2021)
	Genistein	Hepatocellular carcinoma	hepatoblastoma cell line (HepG2)	Displayed that Phytosomes of genistein prepared from Lipoid® S100 and Phosal®75 SA stored genistein in hepatic cells. In HepG2 cells, they markedly elevated the intracellular accumulation of genistein in its complex form and they had a greater anticancer potential as compared to genistein suspension.	(Komeil et al., 2021)
SLNs	Silymarin	Breast cancer	MCF-7	Demonstrated the significant reduction in the growth of MCF-7 cancer cell lines by silymarin-loaded SLNs as compared to plain silymarin.	(Rahman, 2022)
	Ellagic acid	Prostate cancer	PC3	Provided that ellagic acid-loaded SLNs inhibited the development of prostate cancer cell lines at a little IC50 value in contrast to plain ellagic acid and showed that ellagic acid-loaded SLNs enhanced the up-regulation of Bax.	(Hajipour et al., 2018)
	Quercetin	Triple-negative breast cancer	MCF-7, MDA-MB 231	It was shown that quercetin-loaded SLNs have a large increase in apoptosis through the control of Bcl-2 and Bax at both gene and protein levels and a significant decrease in colony formation, angiogenesis, and cell survival when compared to plain quercetin.	(Hatami et al., 2023)
	Quercetin	Bladder cancer	T-24	The cytotoxicity profile showed concentration-dependent toxicity with an IC50 for quercetin ranging from 1.6 to 8.9 μg/mL, compared to SLN dispersions, SLNs loaded gels showed much-improved retention on bladder tissues, and the coated SLNs showed superior penetrating abilities when compared to the uncoated ones.	(Shawky et al., 2022)
	Curcumin	Breast cancer	SKBR3 cells	Curcumin-loaded SLNs exhibited increased cytotoxicity against SKBR3 cells, revealing an increased uptake efficiency for the curcumin on *in vitro* evaluation. Additionally, SKBR3 cells treated with curcumin-loaded SLNs underwent a higher rate of apoptosis than cells treated with free curcumin.	(Wang et al., 2018)
	Curcumin	Not specific	HeLa, A549, CT-26	Curcumin-loaded SLNs provided improved cytotoxicity in CT-26, HeLa, and A549 cells than pure curcumin. Moreover, the anticancer potential of the formulation was dependent on the type as well as the size of cell lines.	(Yeo et al., 2022)
	Naringenin	Lung cancer	A549	The relative bioavailability of naringenin-loaded SLNs was 2.53 folds greater than plain naringenin and cellular uptake of SLNs in A549 cell lines was found to be highly time-dependent throughout 3 h.	(Ji et al., 2016)
	Beta carotene	Breast cancer	MCF-7	Demonstrated enhanced anticancer activity by beta carotene loaded SLNs than free beta carotene and showed 1.92 folds improved Area under the curve (AUC) as compared to free beta carotene depicting the increase in bioavailability also.	(Jain et al., 2019)
		Brain cancer	Rattus norvegicusrats	Biodistribution of rutin after 54 h of injecting of SLN formulation was found 15.23 ± 0.32 % in brain, 8.68 ± 0.63 % in heart, 4.78 ± 0.28 % in kidney, 0.37 % in liver, and 0.92 ± 0.04 % in the lungs and molecular docking studies discovered the grater binding energy of − 150.973 kJ/mol of rutin with targeted protein namely epidermal growth factor receptor.	(Pandian et al., 2021)
	Epigallocatechin gallate (EGCG)	Breast cancer, prostate cancer	MDA-MB 231, DU-145	EGCG-loaded SLNs were shown to have cytotoxicity that was 8.1 times higher than that of pure EGCG towards MDA-MB 231 cancer cells and 3.8 times higher than DU-145 cancer cells.	(Radhakrishnan et al., 2016)
	Sclareol	Lung cancer	A549	Demonstrated sclareol-loaded SLNs exhibited improved inhibition of A549 cancer cell lines than plain sclareol.	(Hamishehkar et al., 2018)
NLCs	Curcumin	Brain cancer	U373MG	Curcumin-loaded NLCs exhibited a % relative bioavailability of 439 ± 9.86 and provided	(Madane and Mahajan, 2016)

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Table 3 (*continued*)

Nanocarrier	Loaded nutraceutical	Type of cancer	Cell line	Result findings	Ref.
				increased inhibition of U373MG cell lines than plain curcumin.	
	Tetrahydrocurcumin	Breast cancer	MDA-MBA-231	As compared to unencapsulated tetrahydrocurcumin, the chitosan-coated NLCs of tetrahydrocurcumin showed markedly improved *in vitro* skin penetration, cytotoxicity, and cell uptake to MD-MBA-231 cancer cells.	(Truong et al., 2022)
NEs	Silymarin	Hepatic cancer	HepG2	Optimized formulation of silymarin loaded NE provided greater AUC, Maximum drug concentration (C_{max}), and maximum time (T_{max}) than free silymarin and its suspension. In addition, silymarin-loaded NE provided a higher reduction in the viability of HepG2 cell lines than free silymarin and its suspension.	(U. Ahmad et al., 2017)
	Rutin	Prostate cancer	PC3	Rutin-loaded NE exhibited a decline in PC3 cell sustainability in dose dependent fashion and significant reactive oxygen species (ROS) induction caused the apoptosis process.	(M. Ahmad et al., 2017)
	EGCG	Lung cancer	H-1299, A549, BEAS2B	Both EGCG and EGCG loaded NE provided suppression of proliferation of H1299 cell lines having half-maximal inhibitory doses of 36.03 and 4.71 Mm, respectively.	(Chen et al., 2020a)
	Apigenin	Skin cancer	HaCaT, A431	Apigenin-loaded NE formulation displayed improved penetrability of apigenin through the skin of the goat. In addition, it exhibited toxicity in A431 cells but low toxicity in HaCaT cells.	(Jangdey et al., 2017)
	Piperine	Lung cancer	A549	Piperine encapsulated NE exhibited cell viability of 85 %, 43 %, 22 %, and 16 % at concentrations of 0.02, 0.03, 0.04, and 0.05 Mm whilst pure piperine exhibited cell viability of 97 %, 54 %, 33 % and 20 % at same concentration demonstrating the better anticancer efficacy of piperine in NE formulation.	(Alshehri et al., 2023)
	Quercetin	Not specific	HeLa, A549, MIA PaCa-2	NE formulation of quercetin provided cytotoxic effects in all human cancer cell lines established on the IC_{50} values.	(Das et al., 2022)
	d-α-tocopherol	Colon cancer	Caco-2	All NEs provided cell viability greater than 90 % using Caco-2 cell lines depicting the safety profile of the formulation.	(Teixeira et al., 2017)
PNPs	Ellagic acid	Colon cancer	HCT-116	Ellagic acid-loaded PNPs demonstrated 3.6 times greater AUC and comparatively lower viability of HCT-116 cells than plain ellagic acid.	(Mady and Shaker, 2017)
	Curcumin	Colon cancer	HCT-116, HT 29	Curcumin-encapsulated PNPs exhibited superior anti-colorectal potential towards HT 29 and HCT-116 cell lines than plain curcumin due to easy uptake by cells and quick induction of apoptosis.	(Udompornmongkol and Chiang, 2015)
	Lycopene	Prostate cancer	PC-3	Lycopene-entrapped PNPs displayed noteworthy improvement in the release of lycopene along with greater anti-prostate cancer potential based on morphological studies and *in vitro* cytotoxicity studies.	(Goswami et al., 2022)
	EGCG	Lung cancer	Patient-derived xenograft model	EGCG-loaded PNPs provided increased efficacy in the prevention of activation and decreasing the expression of genes organized by NF-κB as compared to free EGCG and displayed superior anticancer potential in the Patient-derived xenograft model.	(L. Zhang et al., 2020a)
NMs	Quercetin	Prostate cancer	PC-3	Quercetin-entrapped NMs exhibited lower IC_{50} values of 20.2 Mm than free quercetin (>200 nm). In addition, NE formulation of quercetin provided superiority in the suppression of proliferation and activation of death of PC3 cell lines than free quercetin.	(Zhao et al., 2016)
	Curcumin	Oral cancer	Cis-KB	The NE formulation of curcumin demonstrated much more cytotoxicity and cellular absorption in parental oral cancer cells and cisplatin drug-resistant oral cancer cell lines than free curcumin.	(Kumbar et al., 2022)
	Piperine	Not specific	A549 and $HepG_2$	NMs of piperine provided 1.56 times improved AUC and 1.2-fold higher mean residence time than plain piperine. Moreover, the NM formulation of piperine provided anticancer potential increased than plain piperine against A549 and $HepG_2$ cancer cell lines.	(Ding et al., 2018)
Dendrimers	Curcumin	Glioblastoma	Mouse-GL261, rat-F98, and human-U87	Surface-modified PAMAM dendrimers provided a reduction in viability of all cell lines than non-cancer control cells. Moreover, unencapsulated curcumin was not able to kill the cancer cells whilst	(Gallien et al., 2021)

(*continued on next page*)

Table 3 (*continued*)

Nanocarrier	Loaded nutraceutical	Type of cancer	Cell line	Result findings	Ref.
				unmodified dendrimers provided noteworthy reduction of both cancer as well as non-cancer cells.	
	GA	Colon cancer	HT-29	The optimized formulation of GA demonstrated a higher level of antitumor activity at equivalent doses in human colon cancer models than the GA-Cremophor EL formulation.	(Huang et al., 2015a)
SWCNTs	Curcumin	Prostate cancer	PC3	Curcumin-loaded SWCNTs provided 6-fold greater uptake of curcumin by PC3 cells as compared to plain curcumin demonstrating the potential of SWCNTs as nanocarrier for delivery of nutraceuticals in cancer.	(Li et al., 2019)
MWCNTs	Silibinin	Not specific	HepG2 and A549	Silibinin-encapsulated MWCNTs demonstrated superior anticancer potential as compared to free silibinin.	(Tan et al., 2014)
AuNPs	Silibinin	Lung cancer	A549	Silibinin-conjugated AuNPs exhibited 4–5 times greater killing of cancer cells as compared to free silibinin.	(Ravi et al., 2022)
MNPs	Curcumin	Colon cancer, breast cancer	HCT-116, MCF-7	As compared to free curcumin, AuNPs of curcumin provided increased apoptotic and antiproliferative efficiency against HCT-116 and MCF-7 cancer cell lines.	(Elbialy et al., 2019)
	Quercetin	Breast cancer	MCF-7 and MDA-MB-231	AuNPs of quercetin inhibited the migration and invasion of MDA-MB-231 and MCF-7 cells in comparison to free quercetin. The AuNPs-Qu-5-treated HUVECs showed reduced cell viability and the formation of tubes that resembled capillaries.	(Balakrishnan et al., 2016)
	EGCG	Not specific		EGCG-loaded AuNPs had far greater anticancer activity than pristine EGCG evident by low tumor volume and tumor weight.	(Safwat et al., 2020)
	Curcumin	Breast cancer	MDA-MB-231	Comparing MNPs of curcumin to free curcumin, powerful anticancer effects were seen. When compared to free curcumin, MNPs of curcumin also increased the production of reactive oxygen species and loss of potential integrity after treatment.	(Mm et al., 2012)
PLGA-PEG-Iron oxide MNPs	Silibinin	Lung cancer	A549	Silibinin-loaded iron oxide MNPs exhibited dose and time-dependent cytotoxic behavior and IC50 values demonstrated the higher potential of MNPs as cytotoxic agents than free silibinin.	(Amirsaadat et al., 2017)
Quantum dots	Curcumin	Colon cancer, breast cancer	HCT-116, MCF-7	Optimized formulation caused greater inhibition of colon cancer cells and breast cancer cells as compared to other formulations. In addition, there was no inhibition of normal cells (HEK-293) after treatment with the formulation.	(Khan et al., 2020)

SLNs: Solid lipid nanoparticles; NLCs: Nanostructured lipid carriers; NEs: Nanoemulsions; PNPs: Polymeric nanoparticles; NMs: Nano-micelles; SWCNTs: Single-walled carbon nanotubes; MWCNTs: Multi-walled carbon nanotubes; AuNPs: Gold nanoparticles; MNPs: Magnetic nanoparticles.

endocytosis rather than being adhered to the cell surface. In comparison to free curcumin, MNPs of curcumin demonstrated potent anticancer activities (Mm et al., 2012).

The remarkable promise of quantum dots for the delivery of nutraceuticals can be attributed to their facile synthesis, tunable optoelectronic properties, low toxicity, high biocompatibility, superior photo stability, and exceptional water solubility. Moreover, the higher drug loading capability, ability to target the entrapped agents at specific sites and higher stability increase their efficacy as nanocarriers for the delivery of nutraceuticals (Yadav et al., 2023b; Hu et al., 2023). Quantum dots loaded with curcumin were prepared by Khan et al. to impede the promotion of breast cancer, colon cancer, and microbial infection. Curcumin quantum dots entrapped in Eudragit RS 100 nanoparticles provided only 10.32 % and 10.64 % cell viability of MCF-7 (breast cancer) and HCT-116 (colon cancer) cell lines respectively whilst HEK-293 cell lines (normal cells) were not affected by formulation (Khan et al., 2020). Various nanocarriers loaded with nutraceuticals for cancer treatment have been summed up in Table 3.

5. Co-administration of nutraceuticals with chemotherapeutic drugs using nanocarriers

As mentioned above, nutraceuticals are attracting the attention of researchers in the treatment of cancer due to many advantages like removal of adverse effects, focus on metastasis, and tumor induction (Cheon and Ko, 2022). Since cancer is a complex illness, relying solely on one strategy with a stand-alone drug may not be sufficient to guarantee effectiveness. Combining various nutraceuticals with traditional chemotherapeutic agents in a multi-pronged manner may improve efficacy at a lower dosage, lessen nonspecific cytotoxicity, lessen unfavorable side effects, and prevent the emergence of chemoresistance (Sundaram et al., 2019). Additionally, nutraceuticals make cancerous cells more susceptible to apoptosis and DNA damage brought on by chemotherapeutic medicines while also decreasing the augmentation and metastasis of diseased cells (Jiang and Huang, 2020). When nutraceuticals are codelivered with chemotherapeutic agents, the development of chemoresistance is inhibited. This is because drug uptake by cancer cells is reduced, DNA repair mechanisms are activated, drug-resistant proteins are expressed unchecked, and carriers that increase drug outflow are overexpressed (Gao et al., 2022). The elicitation of anticancer activity in monotherapy requires higher dosages of chemotherapeutic drugs, which can have severe side effects, including hepatotoxicity, nephrotoxicity, cardiotoxicity, and ototoxicity (Aktaş et al., 2020; Liu et al., 2018). Hence co-administration of nutraceuticals having antioxidants with chemotherapeutic drugs may lead to significant reductions in toxicity, enabling a greater number of patients to finish their prescribed regimens and increasing the chances of success concerning survival and tumor response (Glasauer and Chandel, 2014).

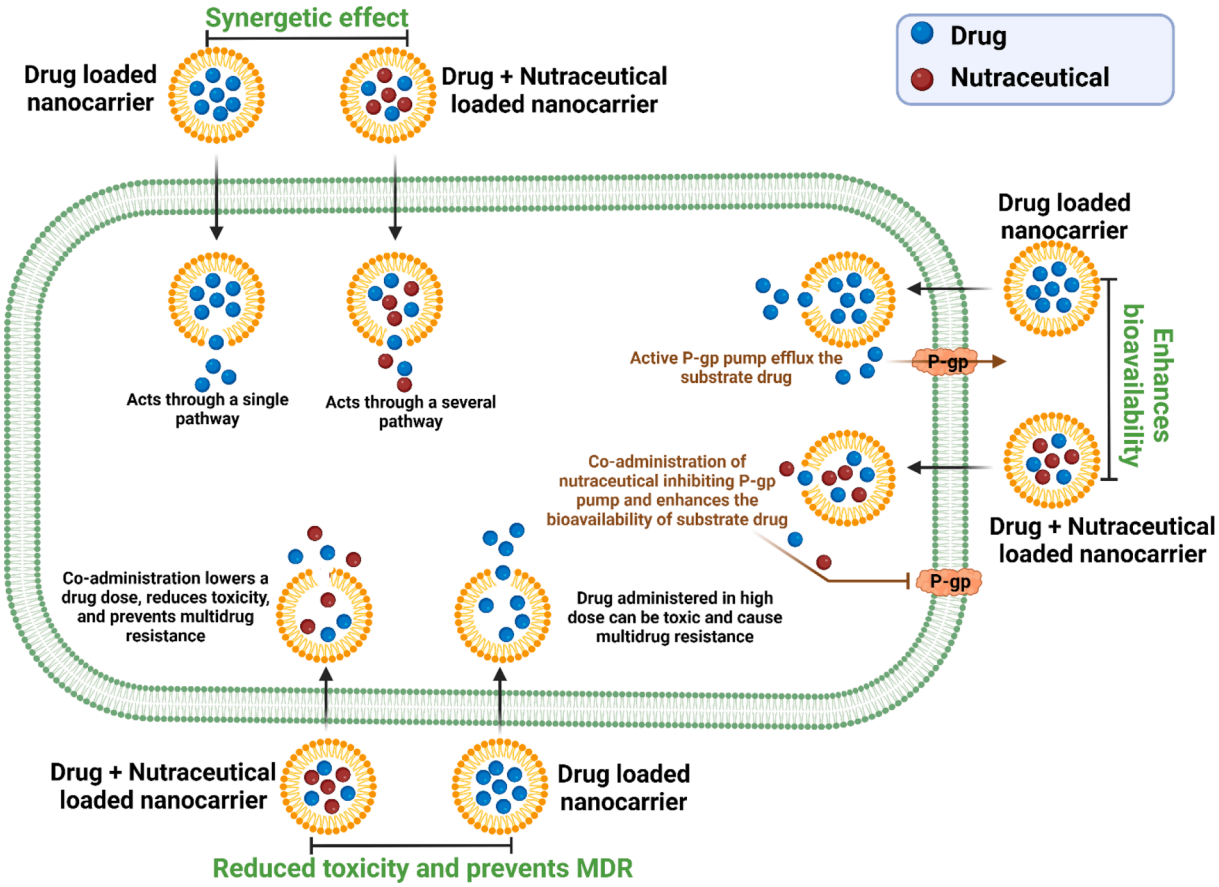

Fig. 5. Representation of benefits of co-administration of nutraceuticals with chemotherapeutic drugs in the form of nanoformulations.

Given this, the delivery of nutraceuticals in combination with chemotherapeutic agents not only can combat cancer and reverse chemoresistance but also lessen the negative effects associated with these drugs. Various research reports strongly indicate that combining conventional chemotherapeutic drugs with nutraceuticals such as resveratrol, curcumin, lycopene, quercetin, silymarin, piperine, apigenin, ellagic acid, and epigallocatechin-3-gallate (EGCG), among others, may be able to lessen the resistance of cancer treatments to these drugs and have chemoprotective effects (Jakobušić Brala et al., 2023). Despite the fact that combination therapy is superior to monotherapy, its low bioavailability, duration at the target site, and poor water solubility lead to subpar clinical outcomes (Mohapatra et al., 2022). Because of these benefits including higher bioavailability, lower side effects, and synergistic effects, co-administration of nutraceuticals and chemotherapeutic medicines within a single nanocarrier has attracted a lot of attention recently as illustrated in Fig. 5 (Arora and Jaglan, 2016).

Recently, SLNs of a combination of curcumin and paclitaxel were fabricated by Pi et al. to enhance the therapeutic efficiency for lung cancer. The findings demonstrated that SLNs of a combination of paclitaxel and curcumin significantly reduced the dose of paclitaxel while maintaining the same therapeutic impact on four cancer cell lines as compared to paclitaxel and the combination of curcumin and paclitaxel. The AUC of paclitaxel and curcumin was 2.88-fold and 1.40-fold greater in SLNs of combination of paclitaxel and curcumin. The treatment of lung cancer with SLNs of the combination of curcumin and paclitaxel in a nude mouse xenograft tumor model provided a tumor suppression rate of 78.42 % which was 51.56 % and 40.53 % for a combination of curcumin and paclitaxel and paclitaxel respectively demonstrating increased therapeutic efficacy in cancer (Pi et al., 2022). In another research, Far et al. formulated nanoparticles of a combination of thymoquinone and doxorubicin to alleviate the cardiotoxicity induced by doxorubicin for breast cancer and colorectal cancer. The findings displayed those nanoparticles of a combination of thymoquinone, and doxorubicin ominously decreased the size of the tumor as well as caused a reduction in the doxorubicin-induced cardiotoxicity. Moreover, nanoparticles of combination provided an increase in Bax levels in HCT116 (colorectal cancer cell lines) and a decrease in Bcl2 levels in MDA-MB-231-Luc (Breast cancer cell lines) (El-Far et al., 2021). Numerous combinations of nutraceuticals and chemotherapeutic drugs in nanocarriers have been tabulated in Table 4.

6. Tumor targeting by ligands coupled nanoformulations of nutraceuticals

The clinical applicability of nanoformulations of nutraceuticals in the treatment of cancer is constrained due to difficulty in targeting the cancer cells by crossing the biological barriers, off-target effects, and biodistribution issues (Hristova-Panusheva et al., 2024). Hence, designing selective nanocarriers that can target specific tumor cells is required. Selective nanocarriers target the overexpressed receptors (integrin receptor, transferrin receptor, folate receptor (FR), CD44 receptor, human epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), luteinizing hormone-releasing hormone receptor (LHRH), and Integrin αvβ3 receptor) present on the surface of the cancer cells by conjugating with various ligands (proteins, antibodies, aptamers, protein/peptides, nucleic acids, and carbohydrates)having specificity to these receptors (Chen and Cong, 2023; Junyaprasert and Thummarati, 2023).

The overexpression of these unique receptors increases the specific recognition between the normal cells and cancer cells by ligands conjugated nanocarriers (Raj et al., 2021). The ligands are specific to

Table 4
A list of nanocarrier-based co-administration of nutraceuticals with anticancer drugs for the alleviation of cancer.

Type of nanocarrier	Chemotherapeutic drug	Nutraceutical	Category of cancer	Cell lines	Findings	Ref.
Nanoliposomes	5-Fluorouracil	Curcumin	Colon cancer	HT-29, HCT-116, and HGC-27	Nanoliposomes loaded with 5-fluorouracil and curcumin provided the greatest cytotoxic effect as compared to the single drug as well as a physical mixture of a combination of both drugs.	(Liu et al., 2023)
Liposomes	Cisplatin	Curcumin	Breast cancer		Liposomal formulation of a combination of cisplatin and curcumin significantly decreased the viability of breast cancer cells (82.5 %) as compared to free and liposomal cisplatin.	(Mahmoudi et al., 2021)
Liposomes	Doxorubicin	Lycopene	Skin cancer	B16	Liposomes of a combination of lycopene and doxorubicin exhibited noteworthy enhancement in cytotoxicity along with a reduction in cardiotoxicity.	(Zhu et al., 2019a)
Liposomes	Doxorubicin	Pachymic acid and dehydrotumulosic acid	Breast cancer	MCF 7	As compared to single-drug treatments, the anticancer impact of doxorubicin in tumor-bearing animals significantly enhanced liposome-mediated codelivery.	(Li et al., 2020)
Liposomes	Irinotecan	Berberine	Pancreatic cancer	BXPC-3	Liposomes encapsulated with irinotecan and berberine enhanced the distribution of both agents in tumors while maintaining their synergistic ratio in the body along with significant suppression of tumor growth.	(Wang et al., 2021a)
Liposomes	Doxorubicin	Berberine	Breast cancer	4 T1	Liposomes loaded with doxorubicin and berberine dramatically reduced tumor growth in the 4 T1 mouse mammary cancer model along with a total reversion of the toxicity of Doxil-induced cardiac rupture in mice.	(Zhang et al., 2020b)
NLCs	Raloxifene	Naringenin	Breast cancer		NLCs loaded with a combination of raloxifene and naringenin exhibited superior antioxidant properties than conventional suspension of a combination of raloxifene and naringenin.	(Alhalmi et al., 2022)
NLCs	Tamoxifen	Sulforaphane	Breast cancer		The oral bioavailability of tamoxifen and sulforaphane was increased by 5.2 and 4.8 times respectively in NLCs along with a reduction in toxicity of tamoxifen.	(Mangla et al., 2020)
NLCs	Morin	Quercetin	Breast cancer	MCF 7	NLCs loaded with a combination of morin, and quercetin exhibited greater cytotoxicity than individual components and their physical mixture.	(Palei et al., 2023)
NLCs	Doxorubicin, docosahexaenoic acid	α-tocopherol succinate	Breast cancer	4 T1	Doxorubicin, docosahexaenoic acid loaded NLCs with α-tocopherol succinate demonstrated superior anticancer activity evident by reduction in growth of 4 T1 cancer cell lines along with decreased toxicity associated with doxorubicin.	(Lages et al., 2020)
PNPs	Paclitaxel	Curcumin	Breast cancer	4 T1, MDA-MB-231, RAW	Nanoparticles loaded with a combination of curcumin and paclitaxel displayed improved suppression of cancer and therapeutic outcomes.	(Lin et al., 2023)
PNPs	Paclitaxel	Curcumin	Ovarian cancer	SKOV3, SKOV3-TR30	Nanoparticles co-loaded with paclitaxel and curcumin exhibit synergistic anti-ovarian cancer effects in nude mice bearing ovarian tumors. Moreover, nanoparticles reduced the resistance of paclitaxel to improve the anticancer effect.	(Zhao et al., 2019)
PNPs	Doxorubicin	Naringenin	Breast cancer	MDA-MB-231, MCF-7, T47D, and HBL-100	Doxorubicin and naringenin-loaded PNPs were efficiently absorbed by cells inhibiting tumor growth and reducing the tumor volume with the mice's steady bodyweight.	(Khan et al., 2021)
PNPs	Methotrexate	Curcumin	Breast cancer	SK-Br-3	Nanoparticles of a combination of curcumin and methotrexate provided improved cytotoxicity than nanoparticles of curcumin and methotrexate individually and IC50 value for nanoparticles of combination was 1.7 times lower than nanoparticles of individual drugs after 48 h.	(Vakilinezhad et al., 2019)
PNPs	5-Fluorouracil	Chrysin	Colon cancer	HT29	PNPs loaded with a combination of 5-Fluoro-uracil and chrysin were found to have much stronger growth inhibitory effects towards HT29 cell lines than PNPs of individual drugs.	(Khaledi et al., 2020)
PNPs	Paclitaxel	Silybin	Lung cancer	A549	Exhibited effective drug accumulation in the tumor site, reduction of tumor development, and silybin's sensitization effect on paclitaxel cytotoxic treatment.	(Huo et al., 2020)
NEs	Cisplatin	Quercetin	Breast cancer	MDA-MB-231	Encapsulation of both cisplatin and quercetin simultaneously in NEs displayed synergistic efficacy against MDA-MB-231 cell lines in the	(Ceramella et al., 2021)

(*continued on next page*)

Table 4 (*continued*)

Type of nanocarrier	Chemotherapeutic drug	Nutraceutical	Category of cancer	Cell lines	Findings	Ref.
					treatment of breast cancer. Moreover, the cytotoxic effect of cisplatin was reduced on HEK-293 normal cell lines.	
NEs	Cisplatin	Caffeic acid, tocotrienols	Lung cancer	A549, HEP G2, HEK 293	NEs loaded with a combination of caffeic acid, and tocotrienols with cisplatin provided increased cytotoxicity towards A549 and HEP G2 cancer cell lines along with enhanced cell viability of more than 95 % against HEK 293 cell lines which was only 33 % for cisplatin.	(Raviadaran et al., 2021)
NEs	Paclitaxel	Baicalein	Breast cancer	4 T1	In comparison to other treatments, NEs loaded with a combination of paclitaxel and baicalein markedly increased cellular ROS, cell cycle arrest, and depression of mitochondrial membrane potential in the 4 T1 breast cancer cell line along with improved bioavailability and greater accumulation of paclitaxel at the tumor site.	(Yadav et al., 2023a)
Gelatin nanoparticles	Cisplatin	EGCG	Lung cancer	A549	When compared to cisplatin alone, a comparatively lower concentration of nanoparticles of a combination of cisplatin and EGCG demonstrated notable cytotoxicity. The nanoparticles loaded with a combination of cisplatin and EGCG were taken easily by the cancer cells resulting in enhancement of concentration of drugs inside the cancer cells.	(Chen et al., 2020b)
AuNPs	Doxorubicin	EGCG	Prostate cancer	PC-3	Both an enzyme-responsive intracellular release of doxorubicin and a suppression of PC-3 tumor cell growth were displayed by the AuNPs of a combination of doxorubicin and EGCG.	(Tsai et al., 2016)
MWCNTs	Tamoxifen	Quercetin	Breast cancer	MDA-MB-231	Provided lower IC_{50} values and improved cellular uptake in drug-resistant MDA-MB-231 cells which was followed by increased drug availability in mice' systemic circulation as compared to plain drug.	(Kumar et al., 2018)
MWCNTs	Docetaxel	Piperine	Breast cancer	MCF 7	Exhibited better cytotoxic potential than the plain drug in MCF 7 cancer cell lines.	(Raza et al., 2016)
NMs	Paclitaxel	Curcumin	Breast cancer, ovarian cancer	MDA-MB-231, SKOV-3	NMs loaded with a combination of paclitaxel and curcumin displayed superior anticancer activity as compared to marketed nanoformulation in both breast and ovarian cancer cell lines.	(Riedel et al., 2021)

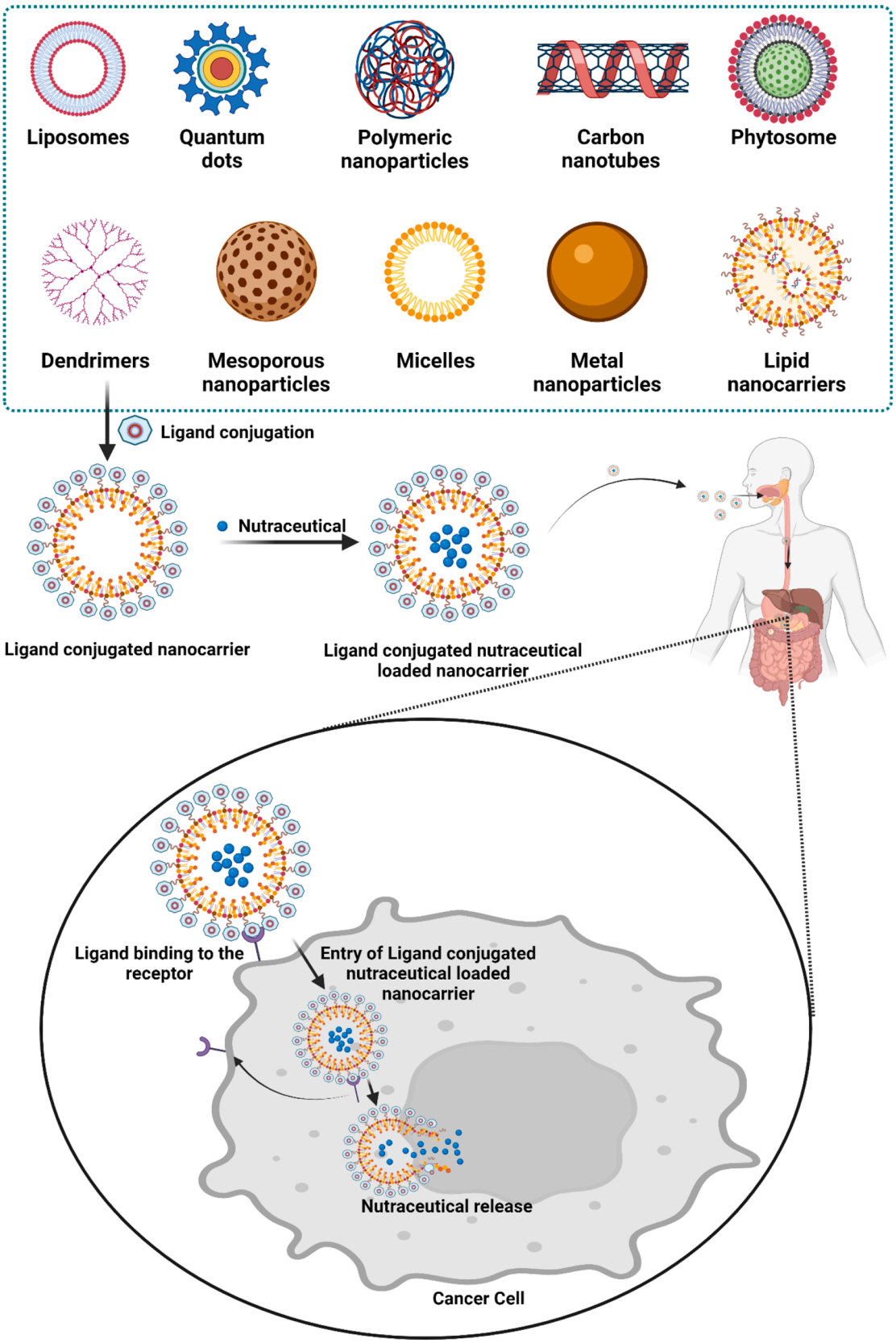

Fig. 6. Representation of targeting of ligands conjugated nanocarriers to overexpressed receptors present at the surface of cancer cell resulting in higher accumulation of loaded nutraceuticals in cancer cell.

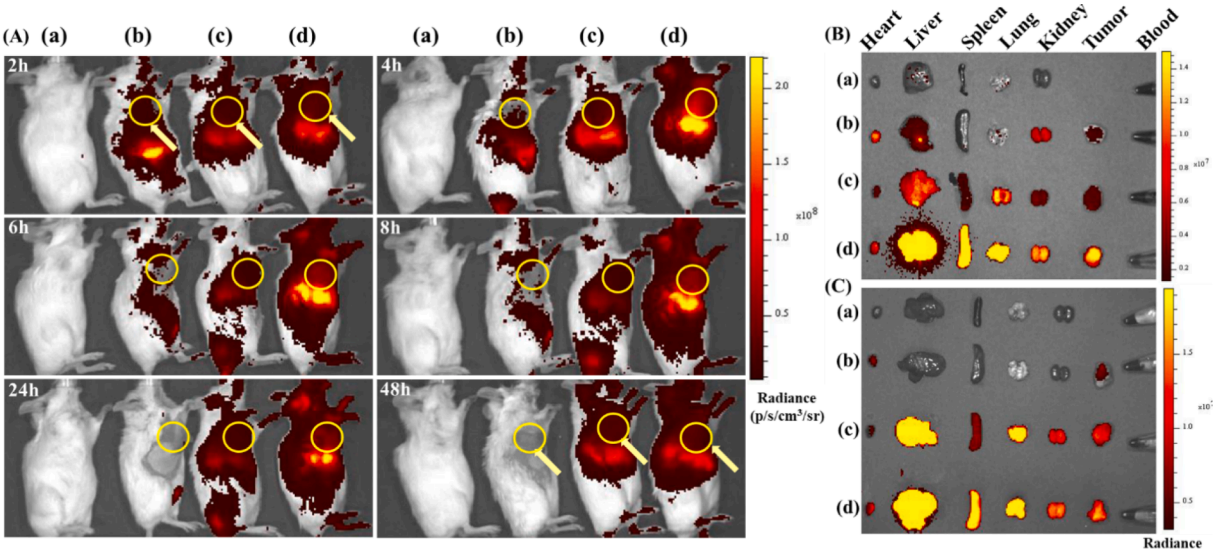

Fig. 7. Representation of distribution of plain Cyanine5, Cyanine5-labeled Lut/Oxi-αCD NPs, and Cyanine5-labeled Lut/FA-Oxi-αCD NPs in 4 T1 tumor bearing animal. **(A)***In vivo* fluorescence intensity Images of Cyanine5, Cyanine5-labeled Lut/Oxi-αCD NPs, and Cyanine5-labeled Lut/FA-Oxi-αCD NPs at various time points, (a) Control (b) Free cyanine5 (c) Cyanine5-labeled Lut/Oxi-αCD NPs (d) Cyanine5-labeled Lut/FA-Oxi-αCD NPs. **(B)***Ex vivo* fluorescence intensity images of excised tumor and main tissues at 24 h. **(C)***Ex vivo* fluorescence intensity images of excised tumor and main tissues at 48 h. *Reprinted with permission from* (Y. Wang et al., 2021).

different types of overexpressed receptors present on the surface of cancer cells. For example, folic acid (FA) interacts with folate receptors, trastuzumab or cetuximab interacts with EGFR and transferrin binds with transferrin receptor. These ligands use physical adsorption or chemical conjugation to decorate the surface of nanocarriers. Cancer targeting using ligand conjugated nanoformulations of nutraceuticals anchorages specific ligand-receptor interactions to internalization of nutraceuticals at cancer site, enhancing availability and effectiveness of nutraceuticals at desired site along with reducing off-target effects as depicted in Fig. 6 (Zhu et al., 2018). This innovative technique enhances therapeutic outcomes by boosting selective absorption by tumor tissues, overcoming drug resistance, and delivering controlled and sustained release of nutraceuticals, ultimately changing cancer therapy into a more targeted, efficient, and patient-friendly manner.

Several research works have demonstrated the rationale of ligands conjugated nanonutraceuticals in the treatment of cancer both *in vitro* and *in vivo*. For example, FA conjugated liposomes of curcumin showed enhanced antitumor activity than PEGylated liposomes against cervical cancer along with absence of acute toxicity (Wang et al., 2019). In another work, FA functionalized PNPs of apigenin demonstrated stronger anticancer activity against HePG-2 cells than pure apigenin. Moreover, FA functionalized PNPs of apigenin provided increased p53 gene expression, cell cycle arrest, increased caspase-9 levels, and decreased expression of the MMP9 gene and Bcl-2 protein (Mabrouk Zayed et al., 2022). Y. Wang et al. demonstrated the targetability of FA conjugated ROS stimuli nanoparticles of luteolin (Lut/FA-Oxi-αCD NPs) in breast cancer. The findings of *in vitro* cellular studies displayed improved internalization by 4 T1 cells resulting in increased release of luteolin which would significantly reduce the tumor effectively. The results of fluorescence intensity showed higher fluorescence intensity for cyanine-5 labeled Lut/FA-Oxi-αCD NPs than free cyanine-5 and cyanine-5 labeled unconjugated NPs of luteolin in tumor area after 2, 4, 6, 8, 24, and 48 h administration as illustrated in Fig. 7**(A).** These results showed improved retention time of luteolin in tumor site in the form of NPs. Furthermore, a substantial fluorescence intensity in liver, lung, and spleen tissues was obtained on *ex vivo* imaging of these tissues at 24 h and 48 has represented in Fig. 7 **(B, C),** indicating that NPs might be retained by macrophages of these tissues. Although these NPs unavoidably collected in the liver and spleen, the accumulation of NPs in tumor tissues was amplified (Wang et al., 2021b). Table 5 summarizes ligands conjugated nanonutraceuticals for targeting the various types of cancer which demonstrate the rationale of conjugating the ligands with nanonutraceuticals to increase their potential in the treatment of cancer.

7. Patents associated with nanoformulations of nutraceuticals

The patents for nanoformulations containing nutraceuticals demonstrate the growing interest in harnessing the therapeutic potential of nutraceuticals. These patents showcase the creativity and innovation of the scientists, researchers, and industries that are committed to developing unique formulations, delivery systems, and dosage forms for nutraceuticals. They cover various aspects, including the composition, preparation methods, specific therapeutic applications, and potential synergies with other compounds or drugs (Sharma et al., 2022b). The analysis of these patents clearly indicates that the main rationale for the application of nanoformulations in the administration of nutraceuticals for the treatment of cancer is their substantial capacity to improve water solubility, bioavailability, and stability. This development is essential to optimizing nutraceuticals' therapeutic efficacy and, eventually, altering their promise in oncology. A comprehensive search for patents on nutraceuticals encapsulated nanoformulations was conducted using Google Patents, the USPTO Patent Search, Patent Lens, and the WIPO IP Portal. Several patents were discovered that focused on nutraceuticals entrapped in nanoformulations for various therapeutic applications, including cancer treatment. Most of the patents were related to improving solubility, bioavailability, stability, and targeting cancer cells. Various patents related to nanoformulations of nutraceuticals for cancer treatment have been summarized in Table 6.

8. Clinical translation of nanonutraceuticals for the treatment of cancer

It is well established that nanonutraceuticals have great potential as treatment modalities for various kinds of ailments and the advanced pharmacological tools have enabled the development of many nanonutraceuticals based therapeutic moieties that are now in clinical use (Sharma et al., 2022c). Numerous published research has shown the potential of nanonutraceuticals in the treatment of cancer but there was

Table 5
A list of ligands coupled with nanoformulations encapsulating nutraceuticals for targeting cancer.

Type of nanocarrier	Ligand	Receptor	Nutraceuticals/ Chemotherapeutic drugs/ Both	Type of cancer	Findings	Ref.
PNPs	FA	Folate	EGG	Breast cancer	FA-coupled PLGA nanoparticles showed noticeably more cellular internalization in MDA-MB-231 cells together with promising cytotoxic potential than uncoupled PLGA nanoparticles.	(Kazi et al., 2020)
PNPs	FA	Folate	EGCG	Prostate cancer	The antiproliferative effect of EGCG against PCa cell lines was markedly improved by the FA-conjugated PNPs.	(Alserihi et al., 2022)
LNPs	FA	Folate	EGCG	Breast cancer	FA functionalized nanoparticles of EGCG exhibited improved anticancer potential against MCF-7, MDA-MB-231 cancer cell lines whilst not affecting normal cell lines (MCF10A) than non-functionalized nanoparticles of EGCG.	(Farabegoli et al., 2022)
PNPs	FA	Folate	Luteolin	Breast cancer	Greater accumulation of luteolin at tumor sites was observed using FA functionalized PNPs of luteolin along with 3 times higher suppression of tumor growth than plain luteolin.	(Wang et al., 2021a)
Albumin nanoparticles	FA	Folate	Baicalin	Breast cancer	FA-coupled albumin nanoparticles of baicalin reduced MCF-7 cell viability in comparison to the control and free baicalin groups and increased the number of S phase cells, apoptotic bodies, pro-apoptotic proteins, autophagy markers, and autophagosomes.	(Liu et al., 2022)
Albumin nanoparticles	FA	Folate	Chrysin		FA-conjugated albumin nanoparticles of chrysin provided increased cytotoxicity as compared to non-conjugated albumin nanoparticles and plain chrysin.	(Nosrati et al., 2018)
NMs	FA	Folate	Silibinin	Liver cancer	Cell viability of liver cancer cells (HepG2) was decreased on treatment with FA functionalized NMs than non-functionalized NMs or free silibinin.	(Ghalehkhondabi et al., 2021)
NMs	FA	Folate	Curcumin difluorinated analog	Cervical and ovarian cancer	Folate receptor-targeted NMs exhibited high anticancer activity in ovarian and cervical cancer-causing significant cell population to undergo apoptosis due to the upregulation of tumor suppressor phosphatase and tensin homolog (PTEN) and inhibition of nuclear factor kappa-B (NFκB).	(Luong et al., 2017)
Ethoniosomes	FA	Folate	Pterostilbene	Lung cancer	FA-conjugated ethoniosomes of pterostilbene exhibited improved noteworthy uptake at the cellular level due to the presence of FA as a targeting moiety for folate receptor than non-conjugated ethoniosomes.	(Hanafy et al., 2023)
NMs	HA	CD 44	Curcumin	Breast cancer	The cytotoxic potential of HA-coated NMs of curcumin against MDA-MB-231 cancer cell lines was greater than non-coated NMs and free curcumin. The IC50 values of free curcumin, curcumin-loaded NMs, and curcumin-loaded HA-coated NMs were 4.11, 3.20, and 2.83 μg/mL, respectively.	(Soleymani et al., 2021)
Pluronic F127 micelles	FA	Folate	Fisetin	Breast cancer	As compared to free fisetin, the bioavailability of fisetin from FA-conjugated fisetin-loaded micelles increased six-fold along with exhibition of active targeting effect on folate-overexpressed human breast cancer MCF-7 cells.	{Citation}
LNPs	HA	CD 44	Apigenin	Lung cancer	HA functionalized LNPs of apigenin exhibited superior cytotoxicity in combination with docetaxel.	(Mahmoudi et al., 2019)
AuNRs	RGD peptide	Integrin	Curcumin + paclitaxel	Lung cancer	RGD peptide conjugated AuNRs of a combination of paclitaxel and curcumin demonstrated significantly increased apoptosis and S phase arrest *in vitro*, as well as improved drug accumulation in tumor sites and tumor growth inhibition *in vivo* as compared to single drug or unconjugated AuNRs.	(Zhu et al., 2019b)
SLNs	Transferrin	Transferrin	Curcumin	Brain cancer	Transferrin-conjugated SLNs of curcumin exhibited 1.5-fold greater permeability through blood blood–brain barrier.	(Neves et al., 2021)
PNPs	Transferrin	Transferrin	Gefitinib + thymoquinone	Non-small cell Lung cancer	Transferrin-conjugated PLGA nanoparticles having thymoquinone along with gefitinib exhibited superior anticancer potential in the treatment of non-small cell lung cancer.	(Upadhyay et al., 2021)
Carbon dots	EGFR	EGF	Sulforaphane		Sulforaphane-conjugated carbon dots provided improved cytotoxicity properties as compared to non-conjugated carbon dots and free sulforaphane.	(Lu et al., 2019)

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Table 5 (*continued*)

Type of nanocarrier	Ligand	Receptor	Nutraceuticals/ Chemotherapeutic drugs/ Both	Type of cancer	Findings	Ref.
Hybrid nanoparticles	EGFR	EGF	Sulforaphane + 5-fluorouracil	Colon cancer	EGF-conjugated hybrid nanoparticles of a combination of sulforaphane and 5-fluorouracil exhibited greater cytotoxic potential than plain hybrid nanoparticles and conventional suspension of both drugs.	(Li et al., 2022b)
Chitosan nanoparticles	EGFR	EGF	Curcumin	Gastric cancer	EGF functionalized nanoparticles demonstrated a greater photodynamic effect in the gastric cancer cells along with about 4 times reduced IC50 value.	(Tsai et al., 2018)
Magnetic mesoporous silica nanoparticles	FA	Folate	Quercetin	Colorectal cancer	Provided marked suppression of tumor and activated mitochondrial-dependent apoptosis via a redox-regulated cellular signaling system.	(Mishra et al., 2020)
Liposomes	EGFR	EGF	Curcumin	Pancreatic cancer	When EGFR overexpressed human pancreatic cancer cells were exposed to the targeted formulation, their cytotoxicity significantly increased in comparison to the non-targeted one.	(Le et al., 2018)
SWCNTs	Integrin	RGD tetrapeptide	Curcumin	Not specific	RGD peptide conjugated SWCNTs provided increased delivery of curcumin in B16F10 cancer cell lines than NIH3T3 cells.	(Das et al., 2017)

Table 6
List of patents related to nutraceuticals entrapped nanoformulations for cancer.

Patent Number	Depiction	Nutraceutical	Purpose	Therapeutic use	Year
IN202241000705	Lung cancer treatment using astragalus, cisplatin and vinorelbine	Astragalus, cisplatin and vinorelbine	The novel formulation of astragalus, cisplatin and vinorelbine provided enhanced anticancer potential	Lung cancer	2022
IN202021048696	Cytotoxic herbal silver nanoparticles as a remedy for mammary carcinoma	Brassica oleracea L.	Demonstrated enhanced anticancer effect in mammary cancer cells	Mammary cancer, hepatocarcinoma	2020
WO2018098247A1	Broccoli-derived nanoparticles	Broccoli	Improvement in the anticancer property to treat colon cancer	Colon cancer	2018
US20180064821A1	The polymer-curcumin combination was encased in nano- or microparticle-sized particles.	Curcuminoid components (curcumin, bisdemethoxycurcumin, demethoxycurcumin and others)	Increase in solubility, stability, and bioavailability of curcumin to improve the antagonism of activation of TLR4.	Inflammation, neurodegeneration, and cancer.	2018
EP3144006	Use of a combination of a curcuminoid and a chemotherapeutic agent for use in treatment of glioblastoma	Curcumin	Liposomes of curcumin eliminate QT prolongation to glioblastoma.	Glioblastoma	2017
IN202141046188	Enhanced anticancer activity of quercetin-loaded TPGS nanosuspension for drug impervious mcf-7 human breast cancer cells	Quercetin	Enhancement in anticancer properties due to increase in the dissolution and oral bioavailability	Breast cancer	2021
US20170224636	Curcumin-sophorolipid complex	Curcumin	Enhancement in water solubility, stability, and oral bioavailability of curcumin to elicit improved anticancer activity.	Breast cancer	2017
US20170189343	Drug carrier for tumor-specific targeted drug delivery and use thereof	Various herbals	Providing targeting ability to the entrapped molecules	Hematological cancer	2017
WO2017137957A1	Colloidally stable resveratrol nanoparticles with improved bioavailability and half-life and synthesis thereof	Resveratrol	Improved threshold bioavailability and half-life of the entrapped resveratrol	Anti-cancer, cardiovascular disorders	2017
US10182997B2	Curcumin was loaded into nanoparticles.	Curcumin	Improvement in aqueous solubility and bioavailability of curcumin to provide enhanced therapeutic effect	Anti-cancer	2018

no concrete proof of nanonutraceuticals' ability to prevent cancer through carefully monitored clinical trials. However, recent clinical investigations have begun to bridge the gap between laboratory research and real clinical practice (Gordan, 2017). Now researchers are currently attempting to investigate nanonutraceuticals clinically, where some nanonutraceuticals have qualified for different stages of clinical trials, in light of their ability to prevent and treat cancer in preclinical settings (Mundekkad and Cho, 2022). Various clinical trial studies related to nanonutraceuticals in the treatment of cancer have been given in Table 6. The status of clinical trial studies in Table 7 depicts that some nanoformulations of nutraceuticals have been completed whilst some are under clinical trials. The clinical trial studies of the phytosomal formulation of silybin (NCT00487721) and nanoparticle formulation of camptothecin (NCT01380769) have been completed.

9. Conclusion

Numerous studies in recent decades have demonstrated the remarkable versatility of nutraceuticals and their potential as anticancer agents, with multiple targets that make them a promising group of

Table 7
List of clinical trial studies for nanonutraceuticals in cancer.

Nutraceutical	Type of cancer	Phase	Recruitment status	Clinical trial number
Quercetin	Oral cancer	Phase 2	Not yet recruiting	NCT05456022
Silybin	Prostate cancer	Phase 2	Completed	NCT00487721
Curcumin	Prostate cancer	Phase 2	Unknown	NCT02724618
Leucoselect	Lung cancer	Phase 2	Recruiting	NCT04515004
Camptothecin	Lung cancer	Phase 1	Recruiting	NCT02769962
Camptothecin	Non-small cell lung cancer	Phase 2	Completed	NCT01380769
Luteolin	Oral cancer	Early Phase 1	Unknown	NCT03288298

compounds. However, various clinical and preclinical studies have demonstrated that nutraceuticals possess anticancer and other potential health benefits, but the clinical applicability of the nutraceuticals is restricted. The concept of nanonutraceuticals has arisen as a significant preventive approach against cancer by hindering various limitations of poor aqueous solubility, low bioavailability, and higher toxic effects associated with plain nutraceuticals as well as conventional chemotherapeutic agents. In addition, the therapeutic efficiency of nutraceuticals as well as chemotherapeutic drugs can be further improved by utilizing the delivery of a combination of both in form of the nanoformulations due to synergistic effect, improved bioavailability, and reduction in multi-drug resistance of the drugs. Various combinations of nutraceuticals along with chemotherapeutic drugs for cancer treatment are under the pipeline out of which some have got the patent. Yet the clinical applicability of nanocarriers-based delivery of nutraceuticals and nutraceuticals in conjugation chemotherapeutic agents is limited because of the manifestation of various biological barriers and biodistribution issues. These issues associated with nanoformulations of medicines for alleviation of cancer can be overcome via coupling ligands with nanocarriers which target the overexpressed receptors at the exterior of cancer cells providing the accumulation of therapeutic agents in cancer cells leading to reduced adverse effects in normal cells. It is observed that the application of nanotechnology to nutraceutical administration accurately represents the prospect of advancing these compounds from pre-clinical to clinical trial stages. The lack of understanding about the potential health risks associated with nanoformulations advises for more toxicological studies to determine the safety and regulatory aspects. The creation of innovative nanoformulations, which require FDA and other federal agency approval to be adopted for safety and efficacy, was the primary benefit of nutraceuticals. In the end, this may need conducting additional clinical trials for nutraceutical-loaded nanoformulations, which we do not currently have enough of. It is expected that continuous research in nanoformulations for nutraceuticals will result in the commercialization of a new treatment regimen that will act as a highly effective cancer-killing agent without harming normal cells. However, some aspects like the toxicity of nanomaterials and higher cost need to be worked out for the commercialization of nanonutraceuticals and to reach the common consumer.

CRediT authorship contribution statement

Girish Kumar: Writing – original draft, Data curation. **Tarun Virmani:** Supervision, Investigation. **Vaishnavi Chhabra:** Formal analysis, Conceptualization. **Reshu Virmani:** Visualization, Validation. **Kamla Pathak:** Validation, Supervision. **Md Sayeed Akhtar:** Funding acquisition, Data curation. **Mulazim Hussain Asim:** Writing – review & editing. **Shumaila Arshad:** Writing – review & editing, Software, Formal analysis. **Farzana Siddique:** Writing – review & editing, Visualization. **Pedro Fonte:** Writing – review & editing, Validation, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors acknowledge Fundação para a Ciência e a Tecnologia (FCT), Portugal in the scope of the projects UIDB/04326/2020 (DOI:10.54499/UIDB/04326/2020), UIDP/04326/2020 (DOI:10.54499/UIDP/04326/2020), and LA/P/0101/2020 (DOI:10.54499/LA/P/0101/2020) of the Research Unit Center for Marine Sciences—CCMAR, and UIDB/04565/2020 (DOI:10.54499/UIDB/04565/2020) and UIDP/04565/2020 (DOI:10.54499/UIDP/04565/2020) of the Research Unit Institute for Bioengineering and Biosciences—iBB, and LA/P/0140/2020 (DOI:10.54499/LA/P/0140/2020)of the Associate Laboratory Institute for Health and Bioeconomy—i4HB. 2. The authors extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through Large Research Project under grant number RGP2/317/45.

Data availability

No data was used for the research described in the article.

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