www.directivepublications.org

The Journal of Clinical Oncology

ISSN 3064-7002

Research Article

Breathing New Life into Conventional Chemotherapy drugs: Enhancing Efficacy via Nanoparticle Codelivery along with Phytochemicals.

Dr. Sharadendu Bali, MBBS, MS, PhD

Professor, General Surgery, TMC& RC, TMU, Moradabad

Abstract

Cancer continues to be one of the leading causes of death worldwide, with 10 million fatalities and 19.3 million new cases reported in 2020. Multidrug resistance (MDR), a formidable issue in chemotherapy, is characterized by the ability of cancer cells to evade cytotoxic drugs through mechanisms such as altered drug targets, disrupted DNA repair, and overexpression of ATP-binding cassette (ABC) transporters like P-glycoprotein (P-gp, responsible for drug efflux). While older oral chemotherapeutics, including 5-fluorouracil (5-FU) and methotrexate, have been effective in certain cancers, their clinical applications are frequently limited by poor bioavailability, dose-limiting toxicities, and drug efflux associated with MDR. Recent evidence supports that incorporating old chemotherapeutic agents into nanocarrier systems such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and mesoporous silica nanoparticles can help overcome key barriers like low solubility, rapid metabolism, and P-gp–mediated efflux. Importantly, the co-delivery of these anti-mitotic drugs alongwith phytochemicals such as curcumin, resveratrol, and astragaloside IV can downregulate drug-efflux transporters, reverse both intrinsic and acquired resistance and increase the efficacy of the chemotherapeutic agents.

Among the nanocarrier systems, Lipid-based nanocarriers have demonstrated especial potential in overcoming MDR, including through co-delivery. SLNs, for example, have been found to protect drugs from gastrointestinal degradation, facilitate controlled release, and improve oral absorption through lymphatic transport. NLCs, with their “imperfect” lipid matrix, permit higher drug loading and offer superior stability. These platforms have been successfully utilized to boost the bioavailability of agents such as doxorubicin, paclitaxel, and zerumbone. Polymeric micelles, liposomes, and dendrimers have been utilized to co-encapsulate both hydrophilic and hydrophobic compounds, providing additional versatility. This strategy of co-delivery using nanocarriers can be effective not just in disrupting efflux mechanisms and prolonging circulation time, but can also facilitate selective targeting of cancer cells by surface modification using ligands. This integrative approach holds significant potential to rejuvenate conventional drugs, and can make cancer treatment more convenient, potent, and patient-friendly.

Keywords : Oral chemotherapy, Multidrug resistance (MDR), Phytochemicals, Nanoparticle co-delivery, potentiating older drugs.

INTRODUCTION

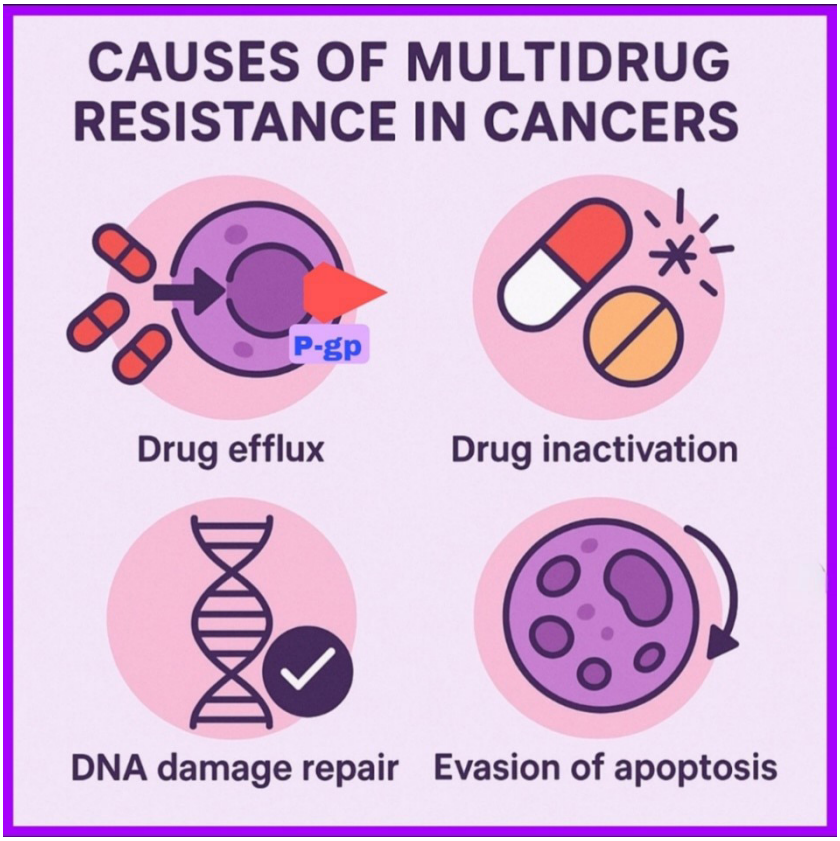
Cancer causes around 10 million deaths a year globally, maintaining its position as a major world-wide cause of mortality [1]. According to projections by GLOBOCAN 2020, “the global cancer burden may rise by 47%, totaling around 28.4 million cases by the year 2040” [1]. National expenditures for cancer care in the United States alone amounted to $150.8 billion in 2018, and this figure is assumed to rise further as newer, more expensive treatments become standard practice. Moreover, low- and middle-income countries account for approximately 70% of global cancer fatalities.

Multidrug resistance (MDR) remains a significant barrier to effective cancer treatment, as it enables cancer cells to evade the cytotoxic effects of chemotherapy [2]. Both intrinsic and acquired forms of MDR occur, with several mechanisms contributing to its development. For example, alterations in drug targets such as DNA topoisomerases [3], mutations in microtubule-associated proteins and tubulin [4, 5, 6], mitotic arrest [5], and disruptions in DNA repair mechanisms [7], all contribute to resistance [**Figure 1**]. Additionally, mutations in tumor suppressor genes like p53 [8] and defects in apoptotic pathways [9, 10], further facilitate drug resistance. A particularly important mechanism involves the overexpression of ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp/ABCB1), multidrug resistance protein 1 (MRP1/ABCC1), and breast cancer resistance

***Corresponding Author:** **Dr. Sharadendu Bali, MBBS, MS, PhD**, Professor, General Surgery, TMC& RC, TMU, Moradabad, India.
Email: drsharadbali@yahoo.com.
Received: 19-November-2025, Manuscript No. TJOCO-5260 **; Editor Assigned:** 20-November-2025 **; Reviewed:** 05-December-2025, QC No. TJOCO-5260 **;**
Published: 11-December-2025, DOI: 10.52338/tjoco.2025.5260.
Citation: Dr. Sharadendu Bali, MBBS, MS, PhD. Breathing New Life into Conventional Chemotherapy drugs: Enhancing Efficacy via Nanoparticle Co-Delivery along with Phytochemicals. The Journal of Clinical Oncology. 2025 December; 14(1). doi: 10.52338/tjoco.2025.5260.

protein (BCRP/ABCG2), whose normal function in healthy tissues is detoxification, But this process gets upregulated during chemotherapy, reducing intracellular drug concentrations [11, 12, 13, 14]. Specifically, P-gp expels various chemotherapeutics like paclitaxel, doxorubicin, and vinblastine, thereby increasing the likelihood of treatment failure [13, 15]. Similarly, MRP1 and BCRP actively transport drug conjugates and contribute to resistance, with BCRP notably affecting the efficacy of drugs such as mitoxantrone and doxorubicin in breast cancer [13, 16, 17]. Despite progress in understanding these mechanisms, developing effective MDR modulators remains a considerable challenge. Early inhibitors like verapamil and cyclosporine A were abandoned due to high toxicity and limited efficacy [18], while second-generation agents, although safer, faced issues with drug-drug interactions and metabolic enzyme inhibition [19, 20]. Third-generation inhibitors such as tariquidar and zosuquidar, despite offering higher potency and reduced toxicity, have not yet achieved clinical success [21, 22].

Figure 1. Most conventional anticancer drugs have lost much of their effectiveness due to the emergence of multidrug resistance (MDR).



OLD WARRIORS IN THE BATTLE AGAINST CANCER

Among older chemotherapy agents, oral administration is more commonly the norm with 5-Fluorouracil (5-FU) and methotrexate, while intravenous routes have traditionally been used for drugs like cisplatin and docetaxel because of poor oral bioaccesibility and bioavailability [23]. Thymidylate synthase inhibition and incorporation of faulty metabolites into RNA and DNA are known mechanisms by which 5-FU operates, resulting in disrupted essential processes in cancer cells [24]. However, enzymes such as dihydropyrimidine dehydrogenase quickly degrade 5-FU in the gut and liver, leading to near-total inactivation upon oral administration. (25). To overcome this limitation, researchers introduced capecitabine, an orally administered prodrug converted specifically into active 5-FU within tumor tissues. Nevertheless, the presence of efflux pumps like P-glycoprotein still reduces intracellular concentrations of 5-FU, contributing significantly to multidrug resistance. Methotrexate (MTX), an antimetabolite that targets dihydrofolate reductase, is another drug that has been used orally for decades. However, its effectiveness has been constrained by variable absorption, dose-dependent side effects, and resistance mechanisms like enhanced drug efflux or target enzyme alterations [26].

Although DNA crosslinking activity makes cisplatin highly potent, attempts to administer this drug orally have faced considerable obstacles due to poor gastrointestinal absorption and significant nephrotoxicity and gastrointestinal side

effects. Docetaxel, which stabilizes microtubules and triggers mitotic arrest, faces similar challenges, including extensive first-pass metabolism, limited solubility, and P-glycoprotein–mediated drug efflux [27]. The efflux of the drug occurs in the absorptive intestinal epithelium itself, by efflux transporters distributed at the apical side of the intestinal epithelial cells, which actively transport the drug from the enterocytes to the intestinal lumen, which leads to extremely poor absorption of drugs by oral administration [28).

Thus, primary barriers, such as rapid metabolism, low solubility, and efflux-pump activity have restricted the widespread adoption of oral chemotherapy [23]. Innovative formulation strategies, such as polymeric nanoparticles, lipid-based delivery systems, microemulsions, and the concurrent administration of phytochemicals, have shown promising solutions. By protecting active drugs in the upper GIT (stomach and duodenum), enabling tumor-targeted delivery, and simultaneously overcoming drug-resistance mechanisms, nanoparticle-based technologies could potentially transform older chemotherapy agents into convenient, effective oral therapies.

PHYTOCHEMICALS AS NATURAL WARRIORS AGAINST MDR IN CANCER

Phytochemicals restoring 5-FU Sensitivity in Resistant Cancers

Several phytochemicals have demonstrated significant potential in overcoming MDR in cancer cells by targeting various molecular pathways. For example, Das et al. (2023) showed that combining **resveratrol** with BCNU (Carmustine) not only sensitizes 5-FU–resistant colon cancer cells but also downregulates key DNA repair proteins (POL-β, POLH, FEN1, and DDB2) while upregulating the tumor suppressor APC gene (which helps prevent cells from growing and dividing uncontrollably) [29]. This **dual mechanism** markedly reduces the effective doses of resveratrol and Carmustine in combination, required to induce apoptosis, underscoring the potential of resveratrol as an adjunct therapy in resistant cancers. Toden et al. (2015) investigated curcumin's capacity to counteract 5-FU resistance in colorectal cancer by modulating epithelial–mesenchymal transition (EMT) [30]. Their study revealed that curcumin upregulates EMT-suppressive microRNAs, which in turn downregulate critical EMT-promoting genes such as BMI1, SUZ12, and EZH2. This molecular reprogramming resulted in significant tumor growth inhibition in xenograft models, supporting the use of **curcumin** as a complementary agent to enhance chemotherapeutic efficacy. Furthermore, He et al. (2019) demonstrated that curcumin reverses MDR in 5-FU–resistant colon cancer cells by significantly lowering the IC_{50} of 5-FU and inducing G0/G1 cell cycle arrest and apoptosis [31]. Notably, the comprehensive analyses, including flow cytometry, RT-PCR, and Western blotting, confirmed that the combination treatment suppresses the expression of pivotal MDR markers like P-glycoprotein (P-gp) and HSP-27, thereby enhancing drug retention within the cells.

Wang et al. (2017) explored the effects of **astragaloside IV** (ASIV), a natural saponin from Astragalus membranaceus (the resinous exudate is known as *gond katira* in Hindi) on reversing MDR in 5-FU–resistant hepatic cancer cells [32]. Focusing on the JNK/c-Jun/AP-1 signaling pathway, they found that ASIV, similar to the JNK inhibitor SP600125, significantly reduces the levels of phosphorylated JNK and c-Jun, resulting in the downregulation of MDR 1 and P-gp expression. This leads to improved intracellular drug accumulation. Additionally, Hu et al. (2016) examined Ginkgo biloba exocarp extracts (GBEE) for their ability to reverse MDR in S180 tumor cells [33]. Their study outcomes demonstrated that the extracts significantly enhanced intracellular drug accumulation and suppressed resistance markers such as MDR1 and MRP1. In vivo, GBEE combined with cisplatin not only suppressed tumor growth but also prolonged survival in mouse models, partly by enhancing immune cytokine production (IL-3, IL-18, IFN-γ).

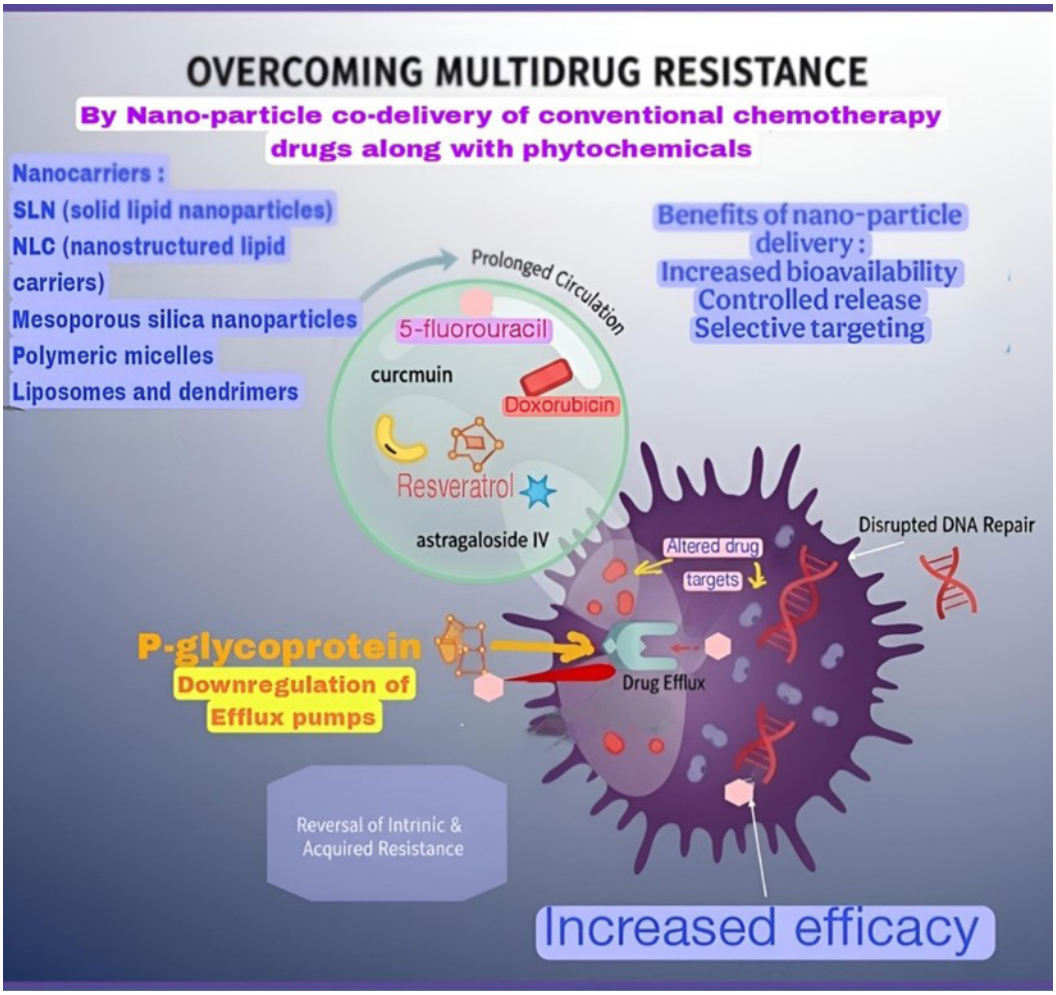
Further, Tang et al. (2017) assessed the efficacy of **epigallocatechin gallate** (EGCG), the predominant polyphenol in green tea, for reversing 5-FU resistance in gastric cancer [34]. They established 5-FU–resistant cell lines (SGC7901/FU and MGC803/FU) that exhibited decreased proliferation and increased levels of MDR markers such as MDR1 and P-gp. EGCG treatment significantly inhibited cell proliferation and tumor growth in these resistant cells both in vitro and in xenograft models. Mechanistically, EGCG downregulated MDR1 and P-gp expression at the mRNA and protein levels and suppressed VEGF by inhibiting its upstream regulator, TFAP2A. The authors concluded that EGCG combats 5-FU resistance through dual mechanisms, reducing drug efflux and suppressing pro-angiogenic signaling, thereby serving as a promising adjunct to conventional chemotherapy.

Role of nano-formulations in increasing bioavailability in co-delivery of 5-FU

Novel nano-formulations play an important role in enhancing the bioavailability of conventional anti-cancer drugs. Sethy and Kundu et al. (2021) provided a comprehensive review on 5-fluorouracil (5-FU) resistance in breast and colorectal cancers [35]. They showed how metabolic alterations, enhanced DNA repair, and the overexpression of efflux transporters contribute to chemoresistance. They suggested that combining phytochemicals such as curcumin and resveratrol with conventional chemotherapy and delivering these combinations via targeted nanoparticle systems

could suppress critical oncogenic pathways and MDR transporters, thereby restoring 5-FU sensitivity [**Figure 2**]. In a related study, Ahmad et al. (2022) developed a novel **multiple nanoemulsion** for oral 5-FU delivery [36]. The developed formulation improved drug solubility, enhanced gastrointestinal absorption, and significantly increased bioavailability in preclinical models. Meanwhile, Blondy et al. (2020) detailed the multifactorial mechanisms behind 5-FU resistance, emphasizing the roles of altered metabolism, EMT, and the tumor microenvironment [37]. Notably, the review further supports the rationale for integrating phytochemicals to modulate these resistance pathways.

Figure 2. Co-delivery of conventional anti-cancer drugs along with phytochemicals by loading these into nano-particles, can help overcome drug resistance.



Phytochemicals Reversing Multidrug Resistance to other conventional chemotherapeutic agents

Tu et al. (2016) investigated the potential of **theaflavin**-3,3'-digallate (TF3), a black tea polyphenol, to overcome **cisplatin** resistance in ovarian cancer using the A2780/CP70 cell line [38]. TF3 exhibited potent antiproliferative effects with an IC_{50} of 23.81 μM in cisplatin resistant cells, while normal ovarian epithelial cells were less sensitive. Flow cytometry confirmed that TF3 induced apoptosis and caused G2 phase arrest by regulating cyclin B1. Central to its action was the upregulation of p53, likely via modulation of the Akt/MDM2 pathway, suggesting that TF3 selectively targets cisplatin-resistant ovarian cancer cells.

In another study, Sun et al. (2015) examined the synergistic anticancer effects of combining **cucurbitacin B with curcumin** to overcome MDR in human hepatoma cells (BEL7402/5-Fu) and in tumor-bearing mouse models [39]. The results revealed that curcumin significantly enhanced cucurbitacin B–induced apoptosis, leading to cell cycle arrest and apoptotic ultrastructural changes. Additionally, **curcumin** reversed MDR by downregulating P-glycoprotein and inducing mitochondrial dysfunction. In vivo, the combination reduced tumor volume, stabilized body weight, activated caspase-3, and lowered ATP levels, supporting its enhanced tumor suppression activity. Weir et al. (2007) investigated curcumin's anticancer effects in cisplatin-resistant human ovarian cancer cells [40]. They found that curcumin effectively inhibited cell proliferation in both resistant and sensitive cells by inducing intracellular superoxide generation and oxidative stress. In resistant cells, curcumin triggered G2/M phase cell cycle arrest, increased phosphorylation of p53, and activated apoptotic pathways, as evidenced by caspase-3 activation

and PARP degradation. Moreover, curcumin modulated key signaling pathways by suppressing Akt phosphorylation and enhancing p38 MAPK activation, thereby promoting cell death.

Cho et al. (2021) evaluated the efficacy of several phytochemicals in overcoming MDR in urinary bladder cancer when combined with **gemcitabine**, using gemcitabine-resistant T24-GCB cells [41]. They found that **capsaicin** exhibited the strongest synergistic effect with gemcitabine, while quercetin, curcumin, and resveratrol produced additive effects. Western blot analyses revealed that capsaicin and quercetin effectively downregulated the membrane transporter ABCC2 and reduced cytoplasmic enzyme levels (DCK, TK1, TK2), whereas resveratrol and curcumin had more complex effects. In vivo, the **capsaicin-gemcitabine** combination significantly inhibited tumor growth, suggesting that capsaicin may serve as a potent adjunct to enhance gemcitabine efficacy in resistant bladder cancer.

Furthermore, Zhang et al. (2018) investigated how **ursolic acid**, a natural triterpenoid, enhances **oxaliplatin** efficacy in colorectal cancer [42]. Using HCT8 and SW480 cell lines, they demonstrated that the combination therapy markedly inhibited cell proliferation, increased apoptosis, and elevated ROS generation compared to either agent alone. Importantly, the combined treatment downregulated key drug resistance genes, suggesting that ursolic acid overcomes chemoresistance via ROS-mediated suppression of resistance pathways. Additionally, Cao et al. (2015) evaluated CIP-36, a novel synthetic derivative of podophyllotoxin, for its ability to overcome MDR in human leukemia cells [43]. Their study, conducted on both K562 and **adriamycin**-resistant K562/A02 cell lines, demonstrated that CIP-36 induced significant growth inhibition, apoptosis, and cell cycle arrest. Mechanistically, CIP-36 inhibited topoisomerase IIα activity, disrupting DNA topology critical for cancer cell survival, especially in MDR phenotypes.

These studies highlight the potential role of various phytochemicals as adjuncts for overcoming MDR in cancer by targeting key resistance mechanisms, thereby enhancing the efficacy of conventional chemotherapy.

NANOCARRIER SYSTEMS FOR DRUG DELIVERY

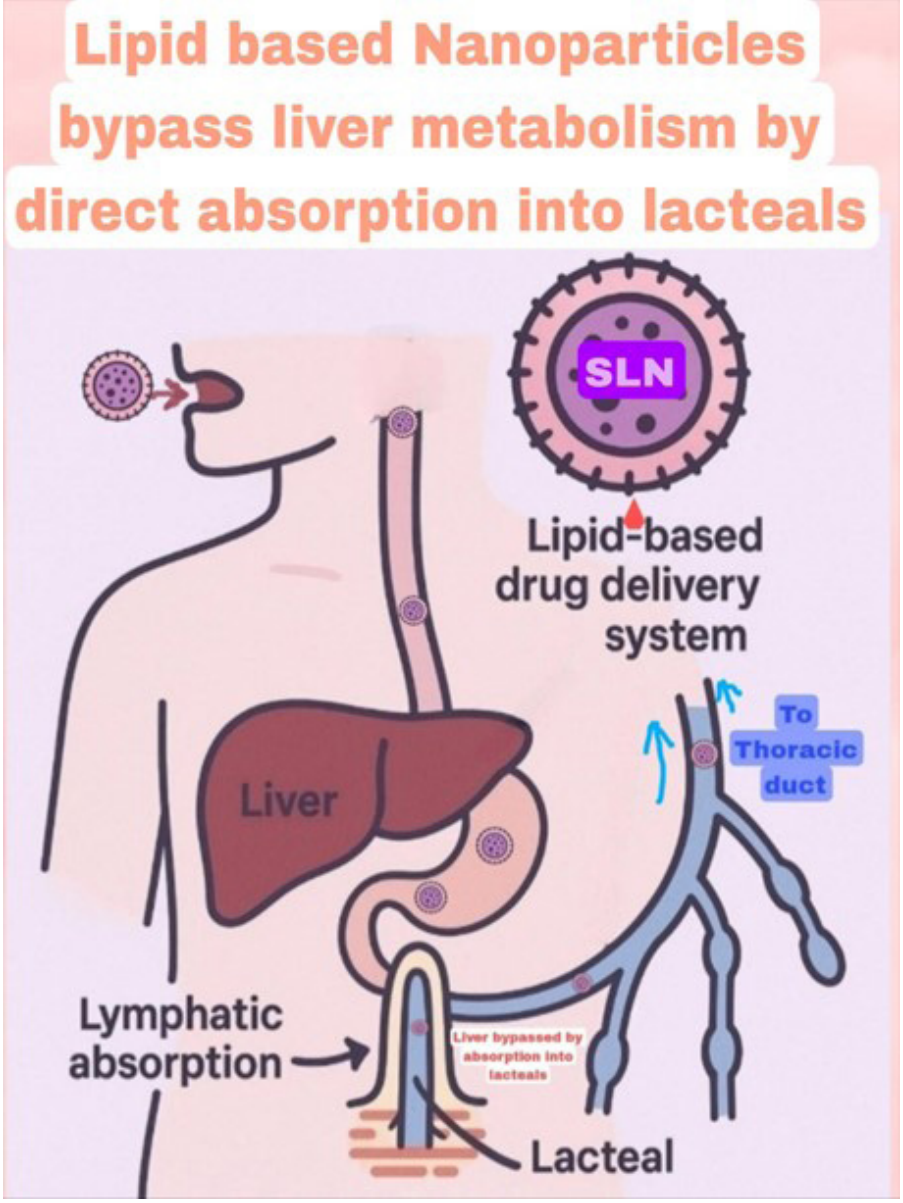
Numerous nanoscale drug delivery systems have been devised and studied in detail, each offering unique advantages and challenges in regard to efficiency of drug encapsulation, release kinetics, and biological performance. Some of these efficient nanocarrier systems can be utilized for the co-delivery of conventional chemotherapy drugs alongwith phytochemicals, and offer a key strategy to overcome MDR, as these systems improve drug bio- accessibility and bioavailability, in addition to enabling targeted delivery to cancer cells and even to Cancer Stem Cells (CSC).

One highly effective nano formulation, introduced in the early 1990s, is **Solid lipid nanoparticles** (SLNs), which are lipid-based colloidal carriers that enhance the pharmacokinetics and stability of the loaded therapeutic agents [44]. Created from biocompatible lipids such as glycerides, fatty acids, and fatty alcohols, and stabilized by surfactants, the solid lipid matrix of SLNs is particularly suitable for encapsulating hydrophobic drugs. SLNs provide improved physical stability compared to liquid systems like emulsions or liposomes, by preventing leakage of drug and fusion of particles. In a study on SLNs, Patro et al. (2013) developed doxorubicin-loaded solid lipid nanoparticles (DOX-SLNs) using a modified **double-emulsification technique** [45]. Pharmacokinetic studies in Sprague–Dawley rats revealed that intravenously injected DOX-SLNs markedly enhanced the bioavailability of doxorubicin, as evidenced by a higher peak plasma concentration, a significantly greater area under the curve, lower plasma clearance, and a reduced volume of distribution. These studies indicate the significant potential of nanocarrier systems such as SLNs for the co-delivery and enhanced bioavailability of chemotherapeutic agents in cancer therapy. Further, the strong lipid matrix of SLNs protects encapsulated drugs from chemical and enzymatic degradation, a critical benefit during gastrointestinal transit [46,47]. In addition, SLNs offer sustained release profiles and significantly enhance oral bioavailability by promoting lymphatic uptake and bypassing first-pass hepatic metabolism, which is especially valuable for drugs such as paclitaxel and doxorubicin [47]. This liver bypass is possible because the lipidic nanoparticles are taken up into lacteals, which are lymphatics present inside intestinal villi (**Figure 3**). The lymph from the lacteals drains into the Thoracic duct, and thus the particles do not enter the liver through the portal circulation. Furthermore, by utilizing SLN encapsulation, even parenterally used drugs can be administered orally, with increased bioaccessibility and greatly enhanced bioavailability (48,49). Moreover, SLNs can be adapted for co-delivery; by encapsulating both chemotherapeutic agents and phytochemicals, they may inhibit drug-efflux pumps or sensitize resistant cells, leading to synergistic anticancer effects [50].

Mesoporous silica nanoparticles (MSNs) represent another promising platform for co-delivery of traditional anti-mitotic drugs along with phyto-compounds [51]. Silica nanoparticles are characterized by their highly ordered porous structures, with tunable pore sizes ranging from 2 to 50 nm, and a large surface area that facilitates the simultaneous loading of multiple drugs. MSNs can further be functionalized with various groups, including PEG coatings or “targeting” ligands

such as hyaluronic acid, to enhance tumor specificity. Their ability to independently accommodate both hydrophilic and hydrophobic drugs makes them ideal for combination therapies where different solubility profiles are involved [51,52]. The significant stability of MSNs in biological fluids ensures efficient drug retention until the nanoparticles reach tumor sites.

Figure 3. Lacteal absorption allows lipid-based nanoparticles to bypass hepatic metabolism and breakdown.



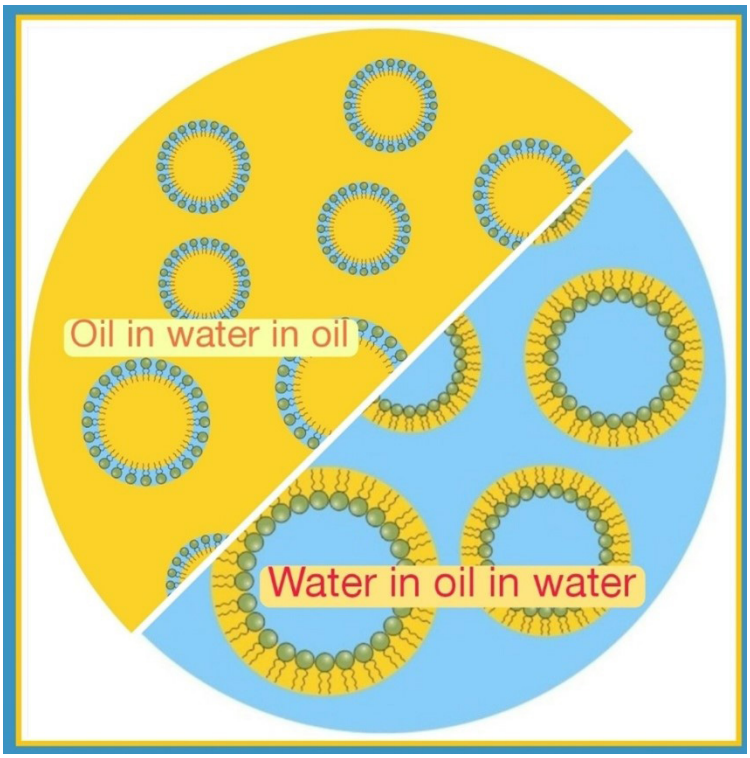
Microemulsions (MEs) are thermodynamically stable systems consisting of oil, water, surfactants, and co-surfactants [53]. They combine the advantages of emulsions with those of nanocarriers, offering significant solubility benefits for lipophilic chemotherapeutic agents and phytochemicals. MEs enhance gastrointestinal absorption through lymphatic transport, similar to SLNs. Co-delivery of both hydrophilic and hydrophobic molecules is achievable in double microemulsions, using specialized formulations (e.g., water-in-oil-in-water -w/o/w, or oil-in-water-in-oil -o/w/o multiple emulsions), which create separate compartments for different classes of agents [53,54]. However, maintaining the stability of microemulsions can be challenging due to their sensitivity to temperature and ionic conditions **(Figure 4)**.

Optimized surfactant and co-surfactant combinations are essential to stabilize particle size and prevent phase separation. **Nanoemulsions** also offer delivery advantages, as shown by Ganta et al, in 2009, who found that Flaxseed oil nanoemulsions co-delivering paclitaxel and curcumin yielded improved therapeutic outcomes in ovarian cancer cells [55].

Several other advanced, but expensive, nanocarrier systems have also been developed, that demonstrate efficacy in multi-agent delivery. For example, Wu et al. developed **polymeric micelles** decorated with phenylboronic acid (which works by targeting sialic acid, a molecule overexpressed on the surface of many cancer cells), that achieved extremely high loading

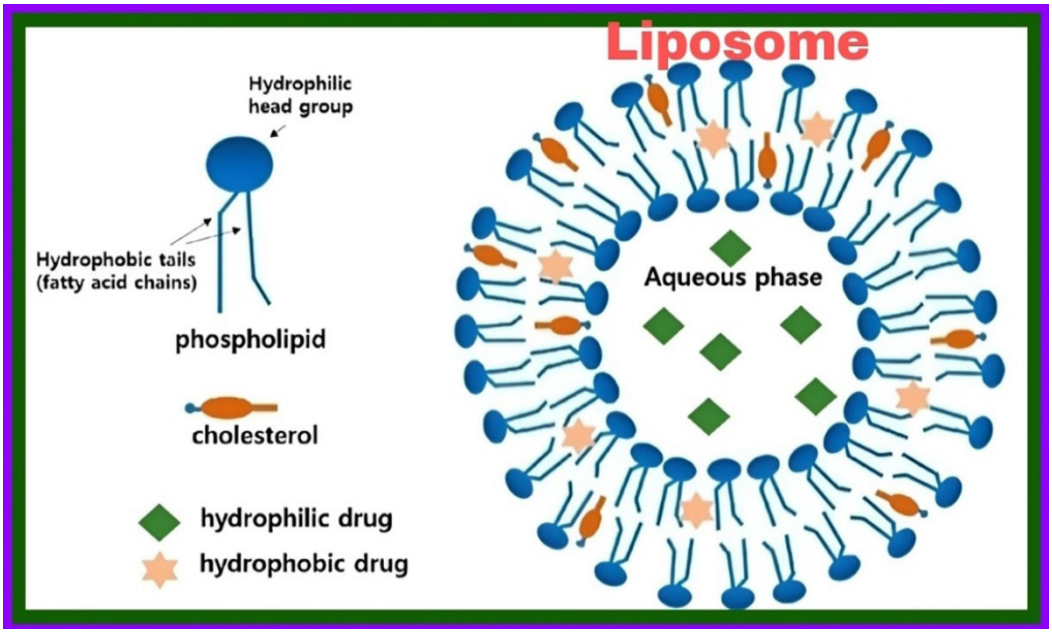
efficiencies (>95%) for doxorubicin and irinotecan [56]. These micelles featured reactive oxygen species (ROS)-triggered drug release mechanisms, enabling selective payload release within the tumor microenvironment. Also, Torres-Perez et al. reported on glycosylated PAMAM **dendrimers** that effectively targeted triple-negative breast cancer cells using methotrexate [57]. These costly Dendrimers can incorporate additional phytochemicals such as resveratrol on their surface, supporting simultaneous dual-drug release at tumor sites.

Figure 4. Double emulsions can be used to load and deliver both hydrophilic and hydrophobic compounds.



Liposomes have long been utilized for co-delivery, since they can effectively encapsulate both hydrophilic and hydrophobic drugs. Transferrin-targeted liposomes co-loaded with tetrandrine and vincristine have been shown to reverse MDR, target glioma cells, and traverse the blood-brain barrier [58]. Incorporating phytochemical efflux inhibitors such as curcumin into these liposomes could further enhance their therapeutic efficacy **(Figure 5)**.

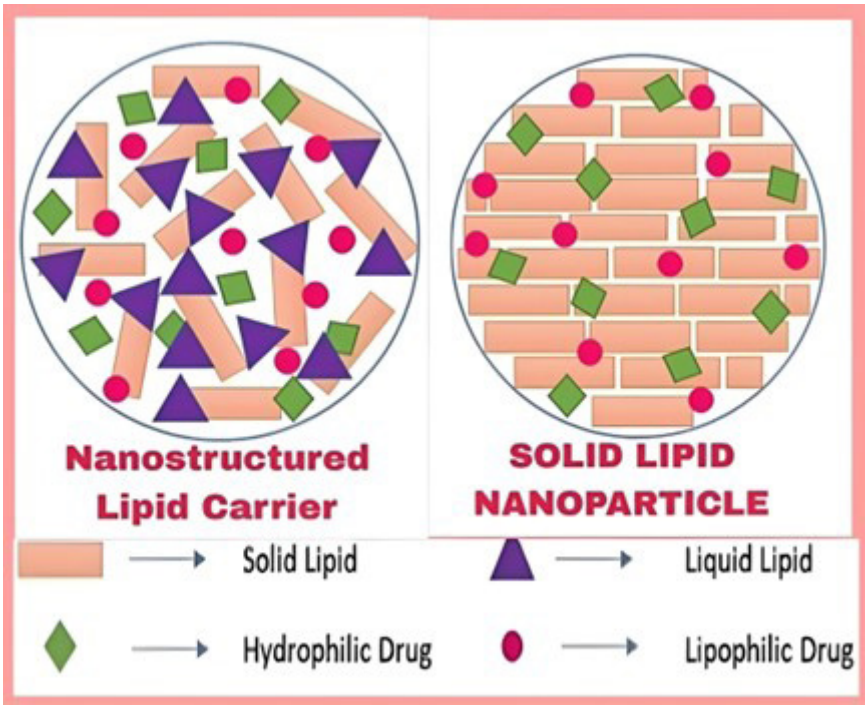
Figure 5. Structurally, liposomes contain both lipid and aqueous phases, hence they can be loaded with both lipophilic and hydrophilic compounds.



Besides, functionalized carbon nanotubes and graphene oxide derivatives can carry multiple drugs via π–π stacking and acid-labile linkers, offering multimodal therapeutic delivery that includes photothermal or photodynamic effects alongside chemotherapy [59,60]. These nanocarrier systems for the co-delivery of anticancer drugs and phytochemicals present a multifaceted approach to overcoming MDR. By protecting the therapeutic cargo, enhancing bioavailability, and enabling targeted delivery, these systems can modulate key resistance mechanisms while minimizing systemic toxicity.
The selection of an appropriate nanocarrier depends on factors such as drug properties, the intended route of administration, and the tumor microenvironment, with lipid-based platforms like SLNs frequently emerging as superior choices for oral co-delivery applications. Cost of production is also an important factor in developing countries, and SLNs can be produced relatively cost-effectively compared to other drug delivery systems like liposomes. Patra et al. (2024) demonstrated that GAHBA-modified solid lipid nanoparticles (SLNs) could effectively deliver **chlorambucil** across the blood-brain barrier, offering improved encapsulation and sustained release, which is critical for treating brain tumors [44]. Complementing this approach, Ahmed et al. (2023) developed chlorambucil nanoformulations using ultrasonication techniques to enhance anticancer efficacy and reduce systemic toxicity in colon cancer models [36].

Nanostructured lipid carriers (NLCs) are structurally a little different from SLNs, by virtue of containing some lipid in liquid form **(Figure 6)**. NLCs have also been effectively used to enhance the oral delivery of anticancer drugs. In a study, auraptene-loaded NLCs (ART-NLCs) were formulated to manage testosterone-induced benign prostatic hyperplasia, showing that ART-NLC treatment at 5–10 mg/kg significantly inhibited glandular growth and reduced inflammation [61]. Similarly, citral-loaded NLCs (CT-NLCs) in a 4T1 breast cancer mouse model notably suppressed local inflammation and prevented metastasis, while raloxifene-loaded NLCs enhanced cytotoxicity against MCF-7 cells and achieved approximately a five-fold increase in bioavailability compared to conventional suspensions [62,63]. These examples show the versatility of NLCs in improving the therapeutic outcomes of oral anticancer therapies.

Figure 6. SLNs and NLCs are both suitable lipoid nano-particles for co-delivery of legacy anti-cancer drugs along with phytochemicals.



DISCUSSION

Several chemotherapy drugs have been used for decades, both orally and by intravenous route. Many of these, such as 5- FU are given for palliation, when the cancer has metastasized to organs such as the liver and lungs. These drugs are now proving to be only minimally effective, and are associated with severe side effects, raising questions on the utility of administering these. On the other hand, research conducted in the past few years on the anti-mitotic actions of several phytochemicals has yielded

astonishing results, and using these in combination with legacy chemotherapy drugs such as 5-FU, has the potential to vastly improve the cytotoxic effects of the latter. The phytochemicals exert their cytotoxic actions on cancer cells using several mechanisms, including down- regulation of key DNA repair proteins, upregulating the tumor suppressor APC gene, inhibiting the growth of blood vessels that supply the growing cancer cell mass, and enhancing intracellular drug accumulation of cytotoxic agent by inhibition of drug-efflux transporters. Thus, co-delivery of traditional cytotoxic drugs alongwith anti-mitotic phytochemicals results in synergistic effects on the destruction of cancer cells.

Since most phytochemicals have low bioavailability, the latter is a key barrier to the above approach. The solution lies in developing an appropriate delivery mechanism, that can increase bioavailability, and also target the cancer cells, whilst causing minimal side effects. These criteria can be achieved by delivering the compounds using nano-structured drug carriers of various types, as described in section 6. The most appropriate carrier system may be LBDDS (Lipid based drug delivery systems), such as micro emulsions, SLNs, liposomes and NLCs (nano-structured lipid carriers), since the cell membranes of intestinal mucosa, like all cell membranes in the body, are composed mainly of lipids and are able to absorb lipidic (hydrophobic) substances avidly. This increases bioavailability considerably, and the cancerous cells also readily take up the LBDDS particles. Nanoparticle delivery also protects the drugs from acid and enzymatic degradation in the stomach and upper GIT. Surface modifications using specific ligands can help target cancerous cells, and also cancer stem cells. Thus, nanoparticle-based technologies have the potential to revolutionize older chemotherapy agents by safeguarding active drugs in the upper gastrointestinal tract (stomach and duodenum), facilitating targeted delivery to tumors, and overcoming drug resistance mechanisms, thereby enabling more convenient and effective oral therapies.

CONCLUSION

Long-used oral chemotherapy drugs like 5-FU and methotrexate, as well as intravenous agents such as Cisplatin and docetaxel, may all be administered with more effective results, by delivering them within nanoparticle formulations. Further, by co-delivering these drugs along with specific phytochemicals, such nano-formulations have the potential ability to overcome drawbacks such as low oral bioavailability, toxicity, and multidrug resistance (MDR). Phytochemicals have proved to be powerful agents that can block drug efflux, reverse key survival pathways, and boost the cytotoxicity of these drugs. Advanced nanocarrier systems such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and mesoporous silica nanoparticles (MSNs) which significantly improve drug encapsulation, protect drugs from metabolic degradation, and enable targeted delivery, can be simultaneously loaded with both the cytotoxic drugs and phytochemicals, enabling co-delivery. This synergy of phytochemical and conventional anti-mitotic drugs by co-delivering these using nanoparticle formulations, offers potential in restoring the effectiveness of traditional chemotherapy while reducing systemic toxicity. Moving forward, optimizing the choice of nanocarrier, phytochemical combination, and release mechanism for each drug and tumor type will be essential, potentially transforming established treatments into safer, more convenient, and more effective oral therapies that improve patient outcomes and quality of life.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. doi:10.3322/caac.21660

2. Wang X, Zhang H, Chen X. Drug resistance and combating drug resistance in cancer. Cancer Drug Resist. 2019;2:141–60. doi:10.20517/cdr.2019.10

3. Brown GA, McPherson JP, Gu L, Hedley DW, Toso R, Deuchars KL, et al. Relationship of DNA topoisomerase IIα and β expression to cytotoxicity of antineoplastic agents in human acute lymphoblastic leukemia cell lines. Cancer Res. 1995;55:78–82.

4. Zhang CC, Yang JM, White E, Murphy M, Levine A, Hait WN. The role of MAP4 expression in the sensitivity to paclitaxel and resistance to vinca alkaloids in p53 mutant cells. Oncogene. 1998;16:1617–24. doi:10.1038/sj.onc.1201658

5. Kamath K, Wilson L, Cabral F, Jordan MA. βIII-tubulin induces paclitaxel resistance in association with reduced effects on microtubule dynamic instability. J Biol Chem. 2005;280:12902–7. doi:10.1074/jbc.M414477200

6. Wang Y, Cabral F. Paclitaxel resistance in cells with reduced β-tubulin. Biochim Biophys Acta Mol Cell Res. 2005;1744:245–55. doi:10.1016/j.bbamcr.2004.12.003

7. Bernstein C, Bernstein H, Payne CM, Garewal H. DNA repair/pro-apoptotic dual-role proteins in five major DNA repair pathways: fail-safe protection against carcinogenesis. Mutat Res Rev Mutat. 2002;511:145–78. doi:10.1016/S1383-5742(02)00009-1

8. O'Connor PM, Jackman J, Bae I, Myers TG, Fan S, Mutoh M, et al. Characterization of the p53 tumor suppressor pathway in cell lines of the National Cancer Institute anticancer drug screen and correlations with the growth-inhibitory potency of 123 anticancer agents. Cancer Res. 1997;57:4285–300.

9. Tanaka K, Iwamoto S, Gon G, Nohara T, Iwamoto M, Tanigawa N. Expression of survivin and its relationship to loss of apoptosis in breast carcinomas. Clin Cancer Res. 2000;6:127–34.

10. Simstein R, Burow M, Parker A, Weldon C, Beckman B. Apoptosis, chemoresistance, and breast cancer: insights from the MCF-7 cell model system. Exp Biol Med. 2003;228:995–1003. doi:10.1177/153537020322800903

11. Borst P, Evers R, Kool M, Wijnholds J. A family of drug transporters: the multidrug resistance-associated proteins. J Natl Cancer Inst. 2000;92:1295–302. doi:10.1093/jnci/92.16.1295

12. Durmus S, Hendrikx JJ, Schinkel AH. Apical ABC transporters and cancer chemotherapeutic drug disposition. Adv Cancer Res. 2015;125:1–41. doi:10.1016/bs.acr.2014.10.005

13. Chen Z, Shi T, Zhang L, Zhu P, Deng M, Huang C, et al. Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: a review of the past decade. Cancer Lett. 2016;370:153–64. doi:10.1016/j.canlet.2015.10.010

14. Wink M. Molecular modes of action of cytotoxic alkaloids: from DNA intercalation, spindle poisoning, topoisomerase inhibition to apoptosis and multiple drug resistance. Alkaloids Chem Biol. 2007;64:1–47. doi:10.1016/S1099-4831(06)64001-2

15. Trock BJ, Leonessa F, Clarke R. Multidrug resistance in breast cancer: a meta-analysis of MDR1/gp170 expression and its possible functional significance. J Natl Cancer Inst. 1997;89:917–31. doi:10.1093/jnci/89.13.917

16. Doyle LA, Yang W, Abruzzo LV, Krogmann T, Gao Y, Rishi AK, et al. A multidrug resistance transporter from human MCF-7 breast cancer cells. Proc Natl Acad Sci U S A. 1998;95:15665–70. doi:10.1073/pnas.95.26.15665

17. Coley HM. Mechanisms and strategies to overcome chemotherapy resistance in metastatic breast cancer. Cancer Treat Rev. 2008;34:378–90. doi:10.1016/j.ctrv.2008.01.007

18. Daenen S, van der Holt B, Verhoef GE, Löwenberg B, Wijermans PW, Huijgens PC, et al. Addition of cyclosporin A to mitoxantrone and etoposide in refractory acute myeloid leukaemia: a phase II HOVON trial. Leuk Res. 2004;28:1057–67. doi:10.1016/j.leukres.2004.03.001

19. Wandel C, Kim RB, Kajiji S, Guengerich FP, Wilkinson GR, Wood AJ. P-glycoprotein and cytochrome P-450 3A inhibition: dissociation of inhibitory potencies. Cancer Res. 1999;59:3944–8.

20. Syed SB, Coumar MS. P-glycoprotein mediated multidrug resistance reversal by phytochemicals: a review of SAR & future perspective for drug design. Curr Top Med Chem. 2016;16:2484–508. doi:10.2174/1568026616666160212123814

21. Cripe LD, Uno H, Paietta EM, Litzow MR, Ketterling RP, Bennett JM, et al. Zosuquidar, a modulator of P-glycoprotein, in acute myeloid leukemia: a randomized trial (ECOG 3999). Blood. 2010;116:4077–85. doi:10.1182/blood-2010-04-277269

22. Kelly RJ, Draper D, Chen CC, Robey RW, Figg WD, Piekarz RL, et al. Pharmacodynamic study of docetaxel with P-glycoprotein antagonist tariquidar (XR9576). Clin Cancer Res. 2011;17:569–80. doi:10.1158/1078-0432.CCR-10-1725

23. Lonardi S, Bortolami A, Stefani M, et al. Oral anticancer drugs in the elderly. Drugs Aging. 2007;24(5):395–410. doi:10.2165/00002512-200724050-00004

24. Lind MJ. Principles of systemic anticancer therapy. Medicine. 2016;44(1):20–4. doi:10.1016/j.mpmed.2015.10.009

25. Milano G, McLeod HL. Can dihydropyrimidine dehydrogenase impact 5-fluorouracil-based treatment? Eur J Cancer. 2000;36(1):37–42. doi:10.1016/S0959-8049(99)00211-7

26. Jing N, Huang L, Shen Y, Pan H, Wang S, Zhao H, et al. Methotrexate resistance and its regulatory mechanisms in pediatric tumors and beyond. Drug Resist Updat. 2025;81:101225. doi:10.1016/j.drup.2025.101225

27. Sohail MF, Rehman M, Sarwar HS, Naveed S, Salman O, Bukhari NI, et al. Advancements in the oral delivery of docetaxel: challenges, current state-of-the-art and future trends. Int J Nanomedicine. 2018;13:3145–61. doi:10.2147/IJN.S164518

28. Lu R, Zhou Y, Ma J, Wang Y, Miao X. Strategies and mechanism in reversing intestinal drug efflux in oral drug delivery. Pharmaceutics. 2022;14(6):1131. doi:10.3390/pharmaceutics14061131

29. Das D, Preet R, Mohapatra P, Satapathy SR, Kundu CN. 1,3-Bis(2-chloroethyl)-1-nitrosourea enhances the inhibitory effect of resveratrol on 5-fluorouracil sensitive/resistant colon cancer cells. World J Gastroenterol. 2013;19(42):7374–88. doi:10.3748/wjg.v19.i42.7374

30. Toden S, Okugawa Y, Jascur T, Wodarz D, Komarova NL, Buhrmann C, et al. Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of EMT in colorectal cancer. Carcinogenesis. 2015;36(3):355–67.

31. He WT, Zhu YH, Zhang T, et al. Curcumin reverses 5-fluorouracil resistance by promoting apoptosis and down-regulating HSP27 and P-glycoprotein. Chin J Integr Med. 2019;25:416–24. doi:10.1007/s11655-018-2997-z

32. Wang PP, Luan JJ, Xu WK, Wang L, Xu DJ, Yang CY, et al. Astragaloside IV downregulates MDR1 in hepatic cancer cells via JNK/c-Jun/AP-1 inhibition. Mol Med Rep. 2017;16(3):2761–6.

33. Hu BY, Gu YH, Cao CJ, Wang J, Han DD, Tang YC, et al. Reversal effect and mechanism of Ginkgo biloba exocarp extracts in multidrug resistance of mice S180 tumor cells. Exp Ther Med. 2016;12(4):2053–62.

34. Tang H, Zeng L, Wang J, Zhang X, Ruan Q, Wang J, et al. Reversal of 5-fluorouracil resistance by EGCG via inactivation of TFAP2A/VEGF signaling in gastric cancer. Oncotarget. 2017;8(47):82842–53. doi:10.18632/oncotarget.20666

35. Sethy C, Kundu CN. 5-Fluorouracil resistance and new strategies to enhance sensitivity: DNA repair inhibition. Biomed Pharmacother. 2021;137:111285. doi:10.1016/j.biopha.2021.111285

36. Ahmad N, Albassam AA, Khan MF, Ullah Z, Buheazah TM, AlHomoud HS, et al. 5-Fluorouracil multiple-nanoemulsion enhances oral bioavailability for colorectal cancer treatment. Saudi J Biol Sci. 2022;29(5):3704–16.

37. Blondy S, David V, Verdier M, Mathonnet M, Perraud A, Christou N. 5-Fluorouracil resistance mechanisms in colorectal cancer: from classical pathways to promising processes. Cancer Sci. 2020;111(9):3142–54. doi:10.1111/cas.14532

38. Tu Y, Kim E, Gao Y, Rankin GO, Li B, Chen YC. Theaflavin-3,3'-digallate induces apoptosis and G2 arrest via Akt/MDM2/p53 pathway in cisplatin-resistant ovarian cancer cells. Int J Oncol. 2016;48(6):2657–65. doi:10.3892/ijo.2016.3472

39. Sun Y, Zhang J, Zhou J, Huang Z, Hu H, Qiao M, et al. Synergistic effect of cucurbitacin B with curcumin via apoptosis and multidrug resistance reversal in hepatoma cells. Eur J Pharmacol. 2015;768:28–40.

40. Weir NM, Selvendiran K, Kutala VK, et al. Curcumin induces G2/M arrest and apoptosis in cisplatin-resistant human ovarian cancer cells by modulating Akt and p38 MAPK. Cancer Biol Ther. 2007;6(2):178–84. doi:10.4161/cbt.6.2.3577 — PubMed

41. Cho CJ, Yu CP, Wu CL, Ho JY, Yang CW, Yu DS. Decreased drug resistance of bladder cancer using phytochemicals treatment. Kaohsiung J Med Sci. 2021;37(2):128–35. https://doi.org/10.1002/kjm2.12306

42. Zhang Y, Huang L, Shi H, Chen H, Tao J, Shen R, Wang T. Ursolic acid enhances the therapeutic effects of oxaliplatin in colorectal cancer by inhibition of drug resistance. Cancer Sci. 2018;109(1):94–102. https://doi.org/10.1111/cas.13425

43. Cao B, Chen H, Gao Y, Niu C, Zhang Y, Li L. CIP-36, a novel topoisomerase II-targeting agent, induces apoptosis of multidrug-resistant cancer cells in vitro. Int J Mol Med. 2015;35(3):771–6. https://doi.org/10.3892/ijmm.2015.2068

44. Patra S, Dey J, Kar S, Chakraborty A. Delivery of chlorambucil to the brain using surface modified solid lipid nanoparticles. ACS Appl Bio Mater. 2024;7(5):3403–13. https://doi.org/10.1021/acsabm.4c00326

45. Patro NM, Devi K, Pai RS, Suresh S. Evaluation of bioavailability, efficacy, and safety profile of doxorubicin-loaded solid lipid nanoparticles. J Nanopart Res. 2013;15(2124):1–18. https://doi.org/10.1007/s11051-013-2124-1

46. Ahmed S, Nadeem M, Hussain I, Fatima S, Rizvi MMA, Tabish M. Preparation, characterization and biochemical studies of nanoformulations of chlorambucil to enhance anticancer efficacy. New J Chem. 2023;47(44):20476–89. https://doi.org/10.1039/d3nj03760f

47. Akanda M, Mithu MSH, Douroumis D. Solid lipid nanoparticles: An effective lipid-based technology for cancer treatment. J Drug Deliv Sci Technol. 2023;86:104709. https://doi.org/10.1016/j.jddst.2023.104709

48. Dastidar DG, Das A, Datta S, Ghosh S, Pal M, Thakur NS, Banerjee UC, Chakrabarti G. Paclitaxel-encapsulated core–shell nanoparticle of cetyl alcohol for active targeted delivery through oral route. Nanomedicine. 2019;14(16):2121–50. https://doi.org/10.2217/nnm-2018-0419

49. Baek JS, So JW, Shin SC, Cho CW. Solid lipid nanoparticles of paclitaxel strengthened by hydroxypropyl-β-cyclodextrin as an oral delivery system. Int J Mol Med. 2012;30(4):953–9. https://doi.org/10.3892/ijmm.2012.1086

50. Pi C, Zhao W, Zeng M, Yuan J, Shen H, Li K, Zhao L. Anti-lung cancer effect of paclitaxel solid lipid nanoparticles delivery system with curcumin as co-loading partner in vitro and in vivo. Drug Deliv. 2022;29(1):1878–91. https://doi.org/10.1080/10717544.2022.2086938

51. Moreira AF, Dias DR, Correia IJ. Stimuli-responsive mesoporous silica nanoparticles for cancer therapy: A review. Microporous Mesoporous Mater. 2016;236:141–57. https://doi.org/10.1016/j.micromeso.2016.08.006

52. Pasqua L, Leggio A, Sisci D, Andò S, Morelli C. Mesoporous silica nanoparticles in cancer therapy: Relevance of the targeting function. Mini Rev Med Chem. 2016;16(9):743–53. https://doi.org/10.2174/1389557516666160225150559

53. Flores SE, Rial-Hermida MI, Ramirez JC, Pazos A, Concheiro A, Alvarez-Lorenzo C, Peralta RD. Microemulsions for colorectal cancer treatments: General considerations and formulation of methotrexate. Mini Rev Med Chem. 2016;16(6):498–508. https://doi.org/10.2174/1389557516666160125111031

54. Qu D, Wang L, Liu M, Shen S, Li T, Liu Y, Huang M, Liu C, Chen Y, Mo R. Oral nanomedicine based on multicomponent microemulsions for drug-resistant breast cancer treatment. Biomacromolecules. 2017;18(4):1268–80. https://doi.org/10.1021/acs.biomac.7b00011

55. Ganta S, Amiji M. Coadministration of paclitaxel and curcumin in nanoemulsion formulations to overcome multidrug resistance in tumor cells. Mol Pharm. 2009;6(3):928–39. https://doi.org/10.1021/mp800240j

56. Wu Y, Lv S, Li Y, He H, Ji Y, Zheng M, Liu Y, Yin L. Co-delivery of dual chemo-drugs with precisely controlled, high drug loading polymeric micelles for synergistic anti-cancer therapy. Biomater Sci. 2020;8(3):949–59. https://doi.org/10.1039/c9bm01662g

57. Torres-Perez SA, Ramos-Godínez MP, Ramon-Gallegos E. Glycosylated one-step PAMAM dendrimers loaded with methotrexate for target therapy in breast cancer cells MDA-MB-231. J Drug Deliv Sci Technol. 2020;58:101769. https://doi.org/10.1016/j.jddst.2020.101769

58. Song XL, Liu S, Jiang Y, Gu LY, Xiao Y, Wang X, et al. Targeting vincristine plus tetrandrine liposomes modified with DSPE-PEG2000-transferrin in treatment of brain glioma. Eur J Pharm Sci. 2017;96:129–40. Available from: https://www.sciencedirect.com/science/article/pii/S092809871630389X

59. Wu B, Li M, Wang L, Iqbal Z, Zhu K, Yang Y, et al. Size-transformable nanohybrids with pH/redox/enzymatic sensitivity for anticancer therapy. J Mater Chem B. 2021;9(21):4319–28. Available from: https://pubs.rsc.org/en/content/articlehtml/2021/xx/d1tb00396h

60. Tang L, Xiao Q, Mei Y, He S, Zhang Z, Wang R, et al. Insights on functionalized carbon nanotubes for cancer theranostics. J Nanobiotechnol. 2021;19:28. Available from: https://link.springer.com/article/10.1186/s12951-021-01174-y

61. Almukadi H, Eid BG, Shaik RA, Abdel-Naim AB, Esmat A. Auraptene nanoparticles ameliorate testosterone-induced benign prostatic hyperplasia in rats: Emphasis on antioxidant, anti-inflammatory, proapoptotic and PPARs activation effects. Biomed Pharmacother. 2021;143:112199. Available from: https://www.sciencedirect.com/science/article/pii/S0753332221009835

62. Nordin N, Yeap SK, Rahman HS, Zamberi NR, Mohamad NE, Abu N, et al. Antitumor and anti-metastatic effects of citral-loaded nanostructured lipid carrier in 4T1-induced breast cancer mouse model. Molecules. 2020;25(11):2670. Available from: https://www.mdpi.com/1420-3049/25/11/2670

63. Soni NK, Sonali LJ, Singh A, Mangla B, Neupane YR, Kohli K. Nanostructured lipid carrier potentiated oral delivery of raloxifene for breast cancer treatment. Nanotechnology. 2020;31(47):475101. Available from: https://iopscience.iop.org/article/10.1088/1361-6528/abaf81/meta