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Nanocarrier based Strategies to Deliver Plant-Derived Bioactive Phytoconstituents for Cancer Treatment: A Comprehensive Review

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Abstract: This comprehensive review highlights the recent advances in nanocarrier-mediated delivery of plant-derived phytoconstituents for cancer treatment. Various nanocarriers such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, nanoemulsions, and metallic nanoparticles are discussed in terms of their design, functionalization, and role in improving pharmacokinetics, stability, tumor targeting, and controlled release of phytoconstituents. The synergistic potential of co-delivery systems, surface modification strategies (e.g., PEGylation, ligand conjugation), and stimuli-responsive nanocarriers are also elaborated. Furthermore, the review explores in vitro and in vivo studies demonstrating enhanced anticancer efficacy, reduced systemic toxicity, and improved therapeutic index of phytoconstituents via nano delivery. Key challenges in clinical translation such as large-scale manufacturing, regulatory approval, and safety profiling are addressed along with future directions. Overall, nanocarrier-based strategies represent a promising frontier for integrating phytomedicine into mainstream oncology, enabling targeted, safe, and effective cancer therapy. This review aims to provide researchers, formulators, and clinicians with a foundational understanding of the nanotechnological advancements driving the next generation of plant-based anticancer therapeutics.

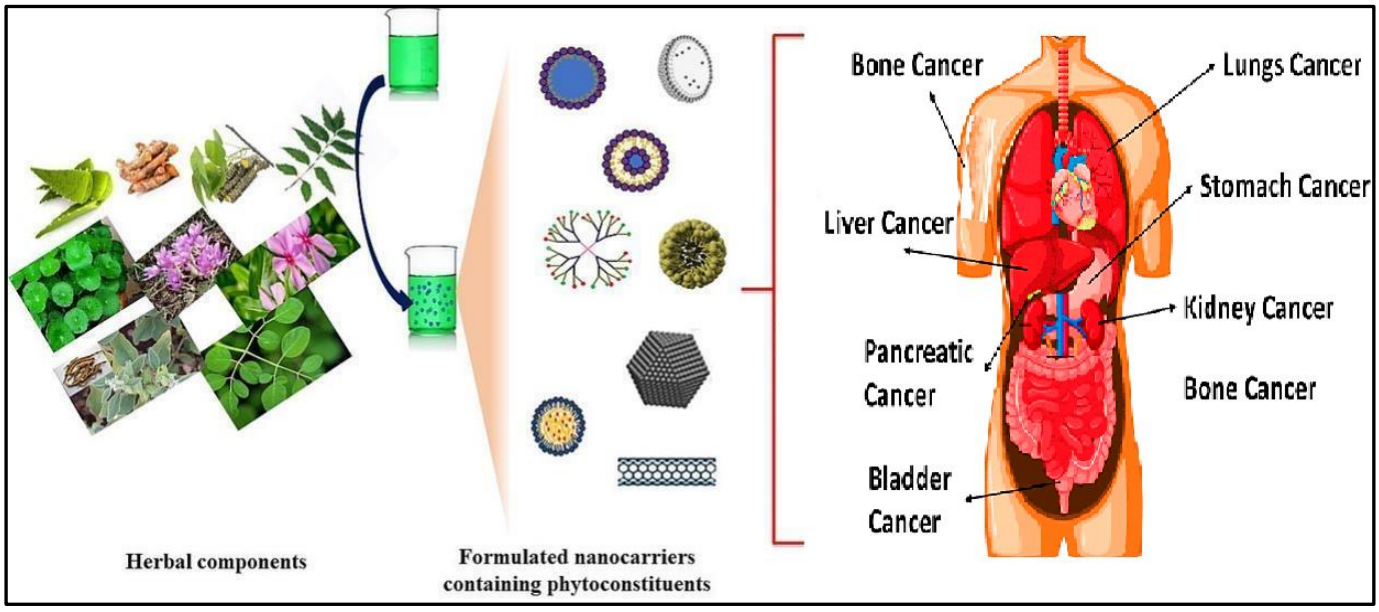

Fig 1 Graphical Abstract

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I. INTRODUCTION

Therapeutic materials have been administered through drug delivery systems (DDS) in preclinical and clinical route in order to treat diseases. Oral ingestion or injection are the two administration methods for conventional DDS. Despite the various benefits features the traditional DDS, including its widespread patient acceptance and ease of administration, but it also has some significant drawbacks and restrictions:(Mehta et al. 2010) Limited efficiency, When taken orally, many medications have varied rates of absorption. Additionally, the low pH of the stomach and the presence of digestive enzymes can break down some medications before they reach the bloodstream. Due to its poor biodistribution, oral medication administration is not optimal for treatments that need to target specific organs. Drug intake may be highly concentrated in detoxifying organs like the liver or kidney, which may lead to toxicity in those tissues.

Due to the development of nanotechnology, nanoparticles are now an appropriate choice for controlled medication delivery systems. Particles with a diameter of between 10–1000 nm are commonly referred to as nanoparticles. When employed as a DDS, nanoparticles can extend the half-life of the medication, make some hydrophobic drugs more soluble, and release the medication in a controlled or prolonged manner, all of which can increase the medication's effectiveness. Moreover, stimuli responsive nanoparticles can aid in reducing toxicity and managing the biodistribution of medications. In the 1960s, liposomes—the first nanoparticles to be discovered—were employed as protein and drug carriers. Ever since, an increasing number of components have been created into nanoparticles and utilized as DDSs. The FDA has approved 51 nanoparticles, and 77 items are undergoing clinical testing, according to a 2016 analysis by Bobo et al. Polymeric and liposomal materials make up a significant share of all the components authorized for use in nanoparticles. Nevertheless, scientists think that more sophisticated materials, including as protein-based, metallic, and micelle materials, can also be employed as DDSs for nanoparticles.(Liu et al. 2014)

This review will concentrate on the Strategies employing biomacromolecule-based nanocarriers to provide bioactive components obtained from plants for the cure of cancer. investigating the idea of several nano-formulations containing herbal medicine components to prevent cancer.

➢ *Overview of Cancer Treatment Challenges:*

Cancer remains one of the most formidable health challenges globally, with its incidence steadily rising. Despite significant advancements in cancer research and treatment modalities, including surgery, chemotherapy, radiation therapy, and targeted therapies, many cancer types still pose substantial challenges to effective management. These challenges encompass diverse factors such as tumor heterogeneity, metastasis, acquired drug resistance, and adverse effects associated with conventional treatments. Additionally, the high cost of cancer care and limited accessibility to advanced therapies further exacerbate the burden on patients and healthcare systems worldwide. Thus, there is an urgent need for innovative and more efficacious treatment approaches to address these complex challenges and improve patient outcomes.(Freag, Saleh, and Abdallah 2018)

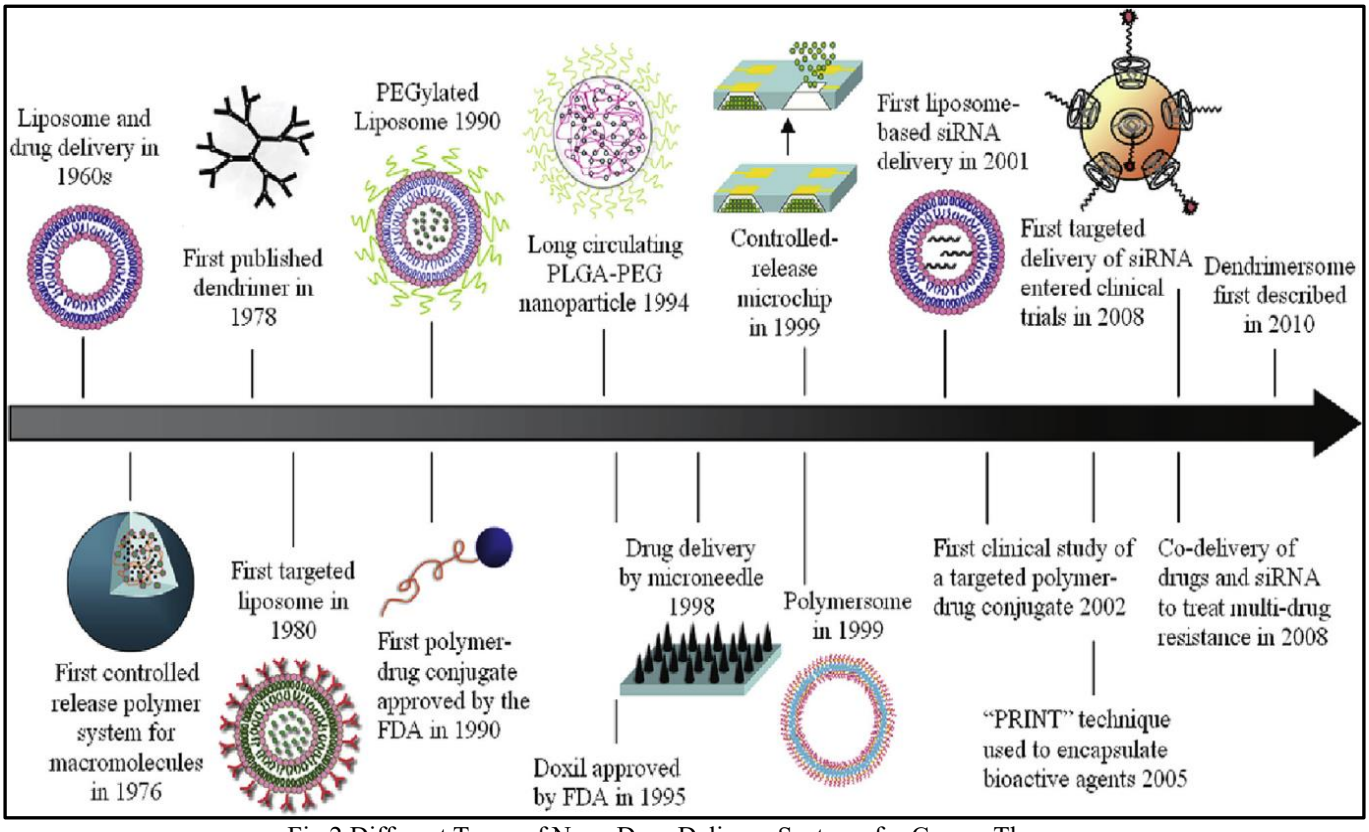

Fig 2 Different Types of Nano Drug Delivery Systems for Cancer Therapy

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➢ *Importance of Plant-Derived Bioactive Components:*

Plant-derived bioactive components have garnered significant interest in cancer research due to their diverse pharmacological properties and relatively low toxicity compared to synthetic drugs. These natural compounds, often found in fruits, vegetables, herbs, and traditional medicinal plants, exhibit various anti-cancer activities, including inhibition of tumor cell proliferation, induction of apoptosis, suppression of angiogenesis, and modulation of immune responses. Importantly, many plant-derived compounds possess pleiotropic effects, targeting multiple signaling pathways implicated in cancer pathogenesis, which may enhance their therapeutic potential. Furthermore, these compounds often exhibit synergistic interactions with conventional cancer treatments, thereby offering opportunities for combination therapies to overcome drug resistance and improve treatment outcomes. Given their abundance in nature and the long history of human consumption, plant-derived bioactive components represent a valuable and sustainable source of anti-cancer agents that warrant further investigation and development.(Salaria et al. 2022)

➢ *Rationale for Combination Strategies:*

While monotherapy has traditionally been the cornerstone of cancer treatment, emerging evidence suggests that combination therapies hold promise for achieving synergistic effects, enhancing efficacy, and reducing toxicity. The rationale for employing combination strategies in cancer treatment is multifaceted. Firstly, cancer is a complex and heterogeneous disease driven by multiple genetic and molecular alterations, making it unlikely that a single agent will effectively eradicate all cancer cells. By targeting complementary pathways or mechanisms of resistance, combination therapies can more comprehensively suppress tumor growth and improve treatment response rates. Moreover, combining agents with distinct mechanisms of action may overcome compensatory signalling pathways activated in response to single-agent therapy, thereby circumventing drug resistance and extending the duration of response. Additionally, combination therapies offer the potential to lower individual drug doses, reducing the risk of adverse effects while maintaining therapeutic efficacy. Overall, the rationale for combination strategies in cancer treatment stems from the recognition of the multifactorial nature of cancer biology and the need for more effective therapeutic approaches to improve patient outcomes.(Ferreira et al. 2017)

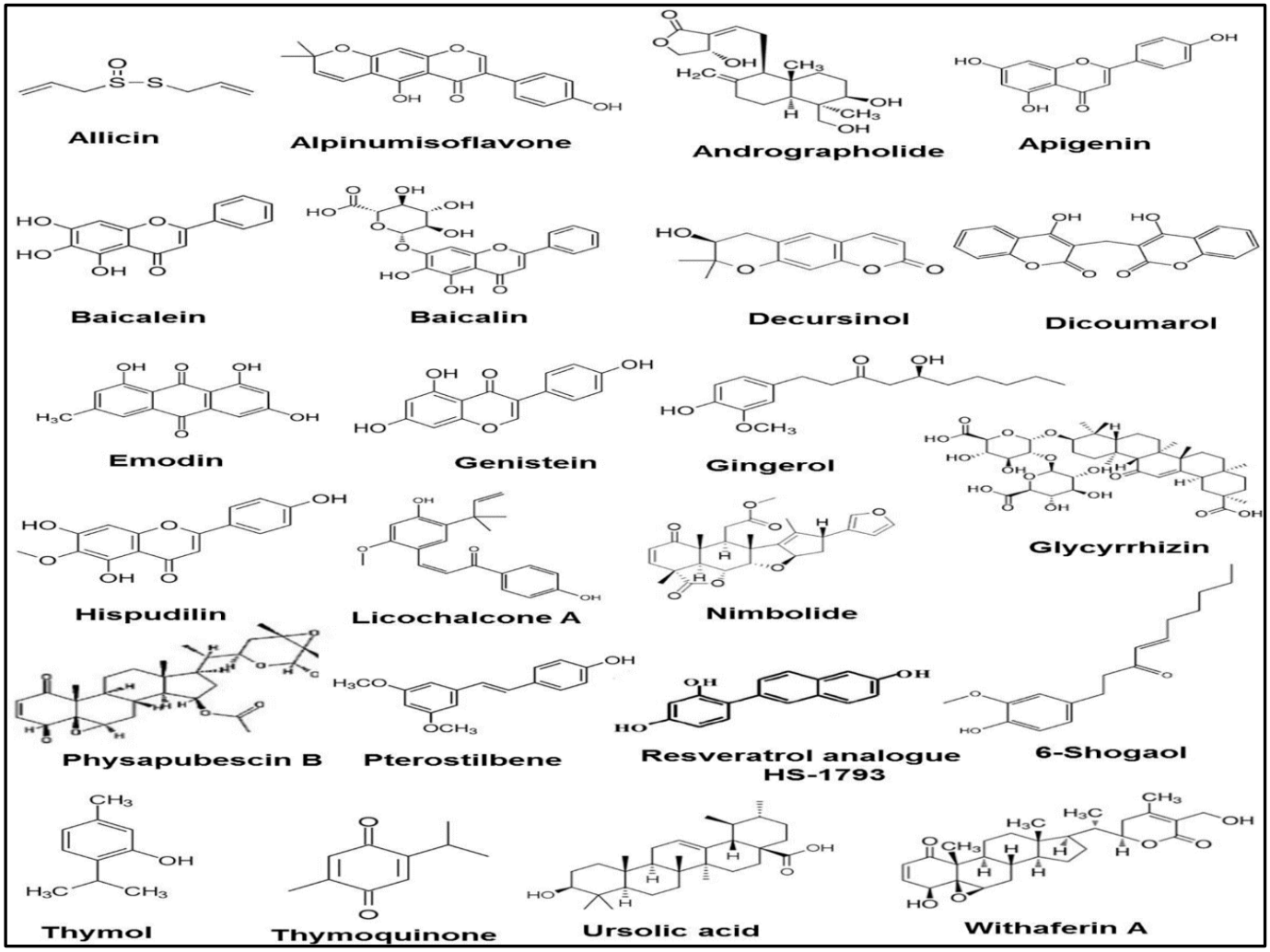

Fig 3 Different Types of Phytoconstituents for Cancer Therapy

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➢ *Objectives of the Review:*

The primary objective of this review is to provide a comprehensive overview of the current landscape of combination strategies involving plant-derived bioactive components for cancer treatment. Specifically, the review aims to:

Summarize the challenges associated with conventional cancer treatments and the potential of plant-derived compounds as alternative therapeutic agents. Discuss the rationale for employing combination strategies in cancer therapy, highlighting the advantages and mechanisms underlying synergistic interactions between different agents. Explore the various delivery systems and formulations used to enhance the bioavailability and efficacy of plant-derived bioactive components in combination therapies. Review preclinical and clinical studies investigating the safety and efficacy of combination therapies involving plant-derived compounds, with a focus on their mechanistic insights and translational potential. Discuss the regulatory considerations, intellectual property issues, and commercialization prospects associated with developing combination therapies for cancer treatment using plant-derived bioactive components. By addressing these objectives, this review aims to contribute to the growing body of literature on combination cancer therapies and provide insights into the future directions of research and clinical practice in this field.

II. PLANT-DERIVED BIOACTIVE COMPONENTS

Plant-derived bioactive components offer promising avenues for cancer therapy due to their diverse pharmacological properties and relatively low toxicity profiles compared to synthetic drugs. These natural compounds, found abundantly in fruits, vegetables, herbs, and traditional medicinal plants, have demonstrated various anti-cancer activities, including inhibition of tumor cell proliferation, induction of apoptosis, suppression of angiogenesis, and modulation of immune responses.

The applications of plant-derived bioactive components in cancer therapy are multifaceted. Firstly, these compounds serve as valuable sources of lead compounds for drug discovery and development, with many undergoing preclinical and clinical evaluation as potential anti-cancer agents. Additionally, plant-derived compounds can be incorporated into combination therapies to enhance efficacy and overcome drug resistance mechanisms. Their pleiotropic effects allow them to target multiple signalling pathways implicated in cancer pathogenesis, offering synergistic interactions with conventional cancer treatments.

Moreover, the relatively low cost and widespread availability of plant-derived compounds make them attractive candidates for cancer therapy, particularly in resource-limited settings. Furthermore, the growing interest in complementary and alternative medicine has spurred research into the use of plant-derived bioactive components as adjuvant therapies to improve the quality of life and outcomes for cancer patients. Overall, the applications of plant-derived bioactive components in cancer therapy hold immense potential for advancing the field and improving patient care.(Garcia-Oliveira et al. 2021)

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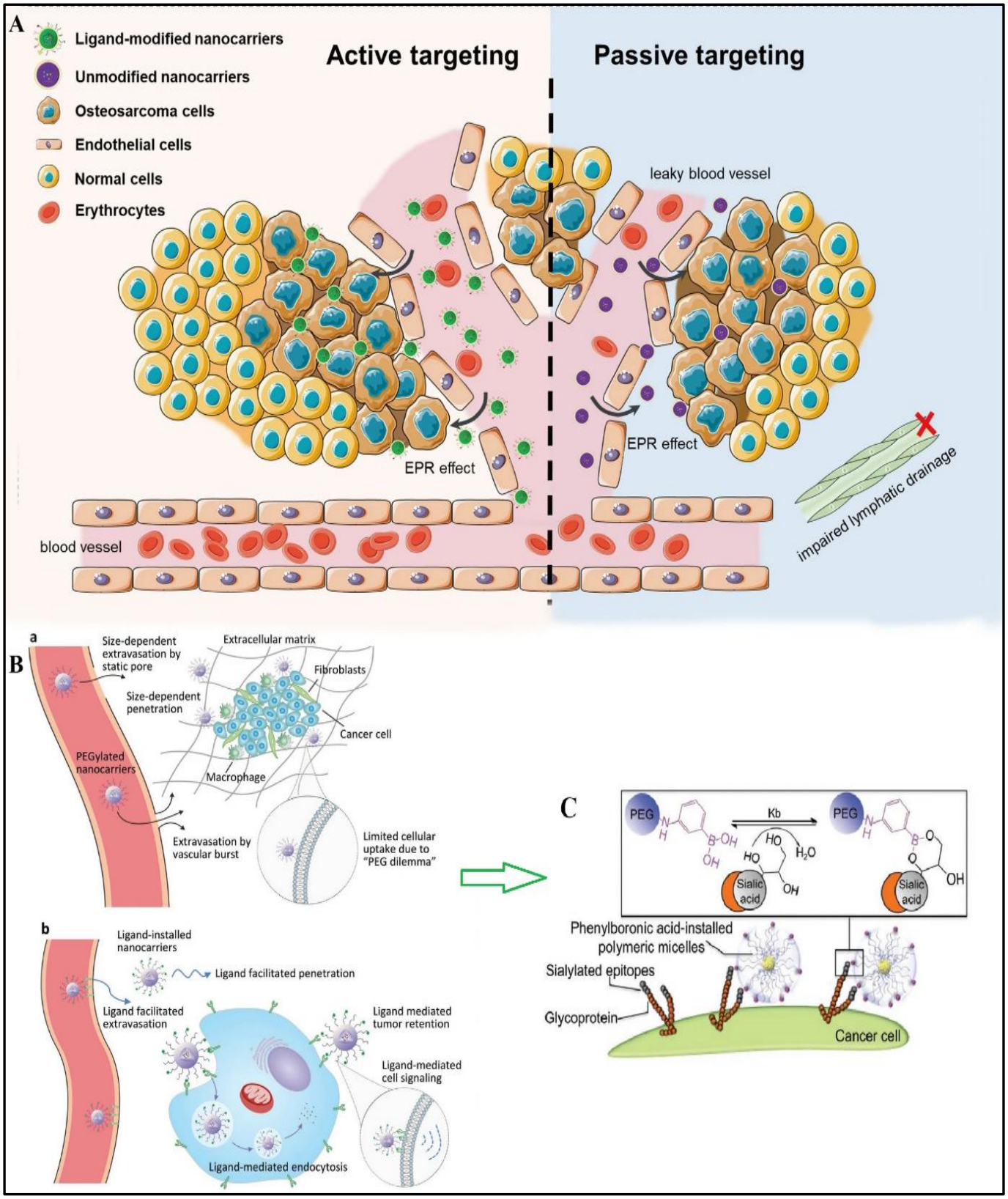

Fig 4 Different Types of Targeting Strategies for Cancer Therapy

➢ *Classification of Plant-Derived Bioactive Components:*

Plant-derived bioactive components encompass a diverse array of chemical compounds with therapeutic potential against cancer. These compounds can be classified based on their chemical structure, source, or mode of action. Common classes of plant-derived bioactive components include:

- Polyphenols: Phenolic compounds found in fruits, vegetables, and herbs, such as flavonoids, phenolic acids, and lignans.

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- Alkaloids: Nitrogen-containing compounds found in plants, including vinca alkaloids (e.g., vincristine, vinblastine) and alkaloids from the Papaveraceae family (e.g., morphine, codeine).
- Terpenoids: Compounds derived from isoprene units, including monoterpenes (e.g., limonene), diterpenes (e.g., taxanes), and sesquiterpenes (e.g., artemisinin).
- Saponins: Glycosides with soap-like properties found in various plant species, such as ginsenosides from ginseng and triterpenoid saponins from liquorice.
- Lectins: Proteins or glycoproteins capable of binding to specific carbohydrate moieties, often found in legumes and seeds.
- Carotenoids: Pigmented compounds responsible for the yellow, orange, and red color of fruits and vegetables, including beta-carotene, lycopene, and lutein.
- Essential oils: Aromatic compounds extracted from plant materials, such as thymol from thyme and eugenol from cloves. This classification provides a framework for understanding the structural diversity and biological activities of plant-derived bioactive components, facilitating their investigation and development as cancer therapeutics.(Gothai et al. 2016)

➢ *Mechanisms of Action in Cancer Treatment:*

Plant-derived bioactive components exert their anti-cancer effects through various mechanisms, which can be broadly categorized into:

- *Antioxidant Activity:*

Many plant compounds possess antioxidant properties, scavenging reactive oxygen species (ROS) and reducing oxidative stress, which contributes to cancer development and progression.

- *Anti-Inflammatory Activity:*

Chronic inflammation is a hallmark of cancer, and several plant-derived compounds exhibit anti-inflammatory effects by inhibiting pro-inflammatory mediators and signaling pathways.

- *Apoptosis Induction:*

Numerous plant compounds induce programmed cell death (apoptosis) in cancer cells by activating intrinsic or extrinsic apoptotic pathways, disrupting mitochondrial function, or modulating apoptotic regulators.

- *Cell Cycle Arrest:*

Plant-derived compounds can arrest the cell cycle at various checkpoints, preventing uncontrolled cell proliferation and promoting cancer cell death.

- *Anti-Angiogenic Activity:*

Angiogenesis, the formation of new blood vessels, is crucial for tumor growth and metastasis. Certain plant compounds inhibit angiogenesis by targeting pro-angiogenic factors or endothelial cell functions.

- *Immunomodulatory Effects:*

Some plant-derived compounds enhance anti-tumor immune responses by activating immune cells, suppressing immune evasion mechanisms, or modulating cytokine production.

- *Anti-Metastatic Effects:*

Metastasis is a major cause of cancer-related mortality, and plant-derived compounds can inhibit various steps of the metastatic cascade, including cell migration, invasion, and epithelial-mesenchymal transition (EMT). Understanding these diverse mechanisms of action is essential for elucidating the anti-cancer potential of plant-derived bioactive components and optimizing their therapeutic use in combination strategies.(Nakonieczna, Grabarska, and Kukula-koch 2020)

➢ *Examples of Promising Plant-Derived Compounds:*

Numerous plant-derived compounds have shown promise as anti-cancer agents in preclinical and clinical studies. Some notable examples include:

- *Curcumin:*

A polyphenolic compound found in turmeric (Curcuma longa), curcumin exhibits anti-inflammatory, antioxidant, and anti-cancer properties through multiple mechanisms, including modulation of NF-κB signaling, induction of apoptosis, and inhibition of angiogenesis.

- *Resveratrol:*

A polyphenol abundant in grapes, berries, and red wine, resveratrol possesses antioxidant, anti-inflammatory, and anti-cancer activities, targeting various signaling pathways involved in cell proliferation, apoptosis, and metastasis.

- *Epigallocatechin gallate (EGCG):*

A catechin found in green tea (Camellia sinensis), EGCG exhibits potent antioxidant and anti-inflammatory effects, inhibiting tumor growth, angiogenesis, and metastasis in various cancer models.

- *Paclitaxel:*

A diterpenoid compound derived from the Pacific yew tree (Taxus brevifolia), paclitaxel is a clinically approved chemotherapeutic agent that stabilizes microtubules, leading to cell cycle arrest and apoptosis in cancer cells.

- *Artemisinin:*

A sesquiterpene lactone extracted from Artemisia annua (sweet wormwood), artemisinin and its derivatives exhibit anti-cancer activities through induction of ROS-mediated apoptosis, inhibition of angiogenesis, and disruption of tumor cell metabolism. These examples highlight the diverse chemical structures and mechanisms of action of plant-derived compounds with potential applications in cancer therapy. Further research is warranted to elucidate their efficacy, safety, and optimal delivery strategies in combination therapies for cancer treatment.(Alghamdi et al. 2024)

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Table1 FDA Approved Plant Derived Drugs for Cancer Therapy

FDA Approved Drug/Year	Initial Discovery	Plant Source	Cancer Type	Mechanism of Action
Paclitaxel/1992	1960s	*Taxus brevifolia* Nutt. (bark)	Breast, ovarian, lung, pancreatic	Stabilizes microtubule
Homoharringtonine/2012	1970s	*Cephalotaxus harringtonii* (Knight ex J.Forbes) K.Koch (bark)	Chronic myeloid leukaemia	Disables the elongation of peptide chain inhibiting protein synthesis
Camptothecin/1996	1960s	*Camptotheca acuminata* Decne (bark and stem)	Gastrointestinal, ovarian, small-cell lung	Inhibits deoxyribonucleic acid (DNA) re-ligation through interaction with topoisomerase-type I DNA complex causing DNA damage
Vincristine sulphate/1963	1950s	*Catharanthus roseus* (Linnaeus) G.Don (leaf)	Leukemia	Inhibits the formation of microtubules and interferes with nucleic acid and protein synthesis by blocking glutamic acid utilization
Vinblastine sulphate/1965	1950s	*Catharanthus roseus* (leaf)	Lymphoma, choriocarcinoma, breast	Inhibits microtubule formation resulting in cell cycle arrest
Teniposide (semisynthetic analogues of podophyllotoxin)/1990	1960s	*Podophyllum peltatum* Linnaeus (rhizome)	Leukaemia	Inhibits type II DNA topoisomerase complex
Etoposide (semisynthetic analogues of podophyllotoxin)/1983	1960s	*Podophyllum peltatum* Linnaeus (rhizome)	Testes, lung	Inhibits type II DNA topoisomerase complex

III. FORMULATION OF PLANT DERIVED PHYTOCONSTITUENTS

Derived bioactive components for cancer therapy poses several challenges, primarily related to their poor solubility, low bioavailability, rapid metabolism, and potential toxicity. These challenges significantly limit their efficacy and clinical translation. Here are the key challenges in delivering plant-derived bioactive components

Many plant-derived bioactive compounds exhibit poor aqueous solubility, which hampers their absorption and bioavailability upon oral administration. Limited solubility can lead to low systemic exposure and suboptimal therapeutic effects. Overcoming this challenge requires the development of suitable formulation strategies to enhance the solubility and dissolution rate of these compounds.(Psimadas et al. 2012) Even when plant-derived bioactive components are administered, their absorption and systemic availability can be limited due to factors such as poor permeability across biological membranes and extensive first-pass metabolism in the liver. This results in low plasma concentrations and reduced therapeutic efficacy. Strategies to improve bioavailability may include formulation approaches such as nanoencapsulation, lipid-based delivery systems, and prodrug strategies.(Akanda, Mithu, and Douroumis 2023)

Plant-derived bioactive compounds are often metabolized quickly in the body, leading to short half-lives and rapid clearance from circulation. Metabolism by phase I and II enzymes can result in the formation of inactive or less potent metabolites, diminishing their therapeutic effects. Designing delivery systems that can protect these compounds from enzymatic degradation and prolong their systemic exposure is crucial to enhancing their efficacy.(Porter, Trevaskis, and Charman 2007) While plant-derived bioactive components are generally perceived as safe due to their natural origins, some compounds may exhibit dose-dependent toxicity or adverse effects. For example, high doses of certain alkaloids or terpenoids can cause cytotoxicity or organ damage. Therefore, ensuring the safety of these compounds through rigorous toxicity assessments and dose optimization is essential for their clinical application.(Zhang et al. 2022)

- *Bioavailability Issues:*

Bioavailability, referring to the proportion of a drug or compound that enters systemic circulation after administration and becomes available at the site of action, is a critical factor influencing the efficacy of plant-derived bioactive components in cancer therapy. Several factors contribute to bioavailability issues, including poor aqueous solubility, low permeability across biological membranes, and extensive first-pass metabolism. To address these challenges, various formulation strategies can be employed to improve the bioavailability of plant-derived compounds. These strategies include following (Gilani et al. 2019)

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Nanoencapsulation: Formulating plant-derived compounds into nanoparticles can enhance their solubility, stability, and systemic absorption, thereby improving bioavailability.

Lipid-based delivery systems: Lipid-based formulations, such as liposomes, micelles, and lipid nanoparticles, can enhance the solubilization and bioavailability of hydrophobic plant-derived compounds.(Chehelgerdi et al. 2023)

Prodrug approaches: Chemical modification of plant-derived compounds to produce prodrugs with improved physicochemical properties, such as enhanced solubility or membrane permeability, can enhance their bioavailability.

Co-administration with absorption enhancers: Co-administering plant-derived compounds with absorption enhancers, such as surfactants or bile salts, can improve their intestinal absorption and bioavailability.(Lin et al. 2018)

Use of permeation enhancers: Formulating plant-derived compounds with permeation enhancers, such as penetration enhancer peptides or cell-penetrating peptides, can enhance their transport across biological barriers. By employing these formulation strategies, the bioavailability of plant-derived bioactive components can be improved, leading to enhanced therapeutic efficacy in cancer treatment.(Bhalani et al. 2022)

- *Metabolism and Elimination:*

Metabolism and elimination processes play crucial roles in determining the systemic exposure and duration of action of plant-derived bioactive components. These compounds are often metabolized by phase I and II enzymes in the liver and other tissues, leading to the formation of metabolites that may exhibit altered pharmacological activity or toxicity.

Co-administration of plant-derived compounds with metabolic inhibitors, such as cytochrome P450 inhibitors or glucuronidation inhibitors, can reduce their metabolism and prolong their systemic exposure. Designing prodrugs of plant-derived compounds that undergo metabolic activation to release the active moiety can enhance their stability and bioavailability. Formulation with metabolic modulators: Formulating plant-derived compounds with metabolic modulators, such as enzyme inducers or inhibitors, can alter the metabolic fate of these compounds and enhance their pharmacokinetic profile. Renal excretion enhancement: Co-administration of plant-derived compounds with compounds that enhance renal excretion, such as diuretics or organic anion transport inhibitors, can increase their elimination rate and reduce systemic exposure. By employing these strategies, the metabolism and elimination of plant-derived bioactive components can be modulated to optimize their pharmacokinetic properties and improve their therapeutic efficacy in cancer treatment.(Gulia et al. 2022)

- *Toxicity Concerns:*

While plant-derived bioactive components are generally perceived as safe due to their natural origins, some compounds may exhibit dose-dependent toxicity or adverse effects that limit their clinical utility. Toxicity concerns may arise due to the inherent chemical properties of these compounds, such as their chemical structure, concentration, or route of administration. To address toxicity concerns associated with plant-derived bioactive components, several strategies can be employed. Determining the maximum tolerated dose and therapeutic window of plant-derived compounds through dose-ranging studies can minimize the risk of toxicity while maintaining therapeutic efficacy. Modifying the formulation of plant-derived compounds to control their release kinetics, reduce systemic exposure, or enhance their targeting to tumor tissues can mitigate off-target toxicity. Combining plant-derived compounds with other anti-cancer agents that exhibit complementary mechanisms of action can reduce the required dose of each compound, minimizing toxicity while maximizing therapeutic efficacy. Developing targeted delivery systems that selectively deliver plant-derived compounds to tumor tissues while sparing healthy tissues can minimize off-target toxicity and enhance therapeutic index.(Arora, Rajwade, and Paknikar 2012)

- *Strategies to Overcome Delivery Challenges*

Overcoming delivery challenges is crucial for maximizing the therapeutic efficacy of plant-derived bioactive components in cancer therapy. Several strategies can be employed to enhance the delivery of these compounds to tumor tissues while minimizing off-target effects: Formulating plant-derived compounds into nanoparticles can improve their solubility, stability, and systemic circulation time, facilitating their accumulation in tumor tissues via the enhanced permeability and retention (EPR) effect. Functionalizing nanoparticles with targeting ligands, such as antibodies or peptides, can enhance their specificity for cancer cells, enabling selective delivery of plant-derived compounds to tumor tissues. Designing nanoparticles that respond to tumor-specific stimuli, such as low pH or elevated enzyme levels, can trigger controlled release of plant-derived compounds within the tumor microenvironment, enhancing their therapeutic efficacy. Combining plant-derived compounds with other anti-cancer agents, such as chemotherapy drugs or targeted therapies, can synergistically enhance their therapeutic effects and overcome drug resistance mechanisms. Administering plant-derived compounds directly to tumor tissues via local injection or implantation can bypass systemic delivery barriers and achieve high local concentrations, minimizing systemic toxicity.(Yang et al. 2018)

Achieving targeted delivery of plant-derived bioactive components to tumor sites while minimizing off-target effects on healthy tissues remains a significant challenge. Selective accumulation within tumors can be challenging due to the complex tumor microenvironment, including barriers such as the enhanced permeability and retention (EPR) effect, heterogeneous blood supply, and interstitial fluid pressure. Developing delivery systems that can actively target cancer cells or exploit tumor-specific characteristics is critical for improving therapeutic outcomes and reducing systemic toxicity.(Chen et al. 2018)

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IV. COMBINATION STRATEGIES IN CANCER THERAPY

Combination strategies in cancer therapy involve the simultaneous or sequential use of multiple treatment modalities to target different aspects of cancer biology, ultimately enhancing therapeutic efficacy and overcoming treatment resistance. Recent developments in this field have focused on innovative approaches to optimize combination therapies, exploit synergistic interactions between treatment modalities, and personalize treatment regimens based on individual patient characteristics.(Wu et al. 2017)

One recent development is the integration of immunotherapy with other treatment modalities, such as chemotherapy, targeted therapy, or radiation therapy. Immunotherapy, particularly immune checkpoint inhibitors, has revolutionized cancer treatment by harnessing the body's immune system to recognize and eliminate cancer cells. Combining immunotherapy with other modalities can enhance anti-tumor immune responses, overcome immune evasion mechanisms, and improve treatment outcomes. For example, the combination of immune checkpoint inhibitors with chemotherapy has shown promising results in various cancer types, including lung cancer and melanoma.(Wang et al. 2016)

Another recent advancement is the development of molecularly targeted combination therapies based on the genomic profiling of tumors. Advances in cancer genomics have enabled the identification of specific molecular alterations driving cancer growth and survival, allowing for the rational design of combination therapies targeting multiple pathways simultaneously. For instance, combination therapies targeting different oncogenic pathways, such as the PI3K/AKT/mTOR and MAPK pathways, have shown synergistic effects in preclinical and clinical studies, particularly in patients with genetically defined subtypes of cancer.

Furthermore, recent developments in drug delivery technologies have facilitated the development of novel combination therapy formulations with improved pharmacokinetic profiles and enhanced tumor targeting. Nanoparticle-based drug delivery systems, liposomal formulations, and polymer-drug conjugates offer opportunities to co-deliver multiple therapeutic agents with distinct mechanisms of action, optimize drug release kinetics, and minimize off-target effects. These advanced delivery systems can also overcome biological barriers, such as the blood-brain barrier or the stromal barrier in solid tumors, thereby improving the penetration and distribution of therapeutic agents within the tumor microenvironment.

Additionally, the emergence of combination immunotherapy approaches, such as chimeric antigen receptor (CAR) T cell therapy combined with immune checkpoint inhibitors or cytokine therapy, holds promise for achieving durable responses and long-term remissions in certain cancer types, including haematological malignancies and solid tumors.

Recent developments in combination strategies in cancer therapy encompass the integration of immunotherapy with other treatment modalities, the rational design of molecularly targeted combination therapies, advancements in drug delivery technologies, and the exploration of novel combination immunotherapy approaches. These developments hold great potential for improving treatment outcomes and addressing the challenges of treatment resistance in cancer patients.(Huang, Lu, and Ding 2021; Wu et al. 2017)

- *Rational Design of Combination Therapies:*

Rational design of combination therapies involves strategically selecting and combining different treatment modalities based on a deep understanding of the underlying molecular mechanisms driving cancer progression. This approach aims to exploit synergistic interactions between treatments while minimizing overlapping toxicities. Key principles in the rational design of combination therapies include:

- Targeting Multiple Pathways: Identifying and targeting multiple signalling pathways implicated in cancer development and progression to achieve additive or synergistic effects.
- Overcoming Resistance Mechanisms: Combining treatments with distinct mechanisms of action to overcome inherent or acquired resistance to single-agent therapy.
- Personalized Medicine: Tailoring combination therapy regimens based on individual patient characteristics, including tumor molecular profiles, genetic mutations, and immune status.
- Optimizing Drug release: Determining the optimal sequence, timing, and dosing of combination treatments to maximize therapeutic efficacy and minimize toxicity.
- Preclinical Validation: Conducting preclinical studies to assess the synergistic effects and safety of combination therapies using relevant cancer models.

Rational design of combination therapies holds promise for improving treatment outcomes and addressing the complexity and heterogeneity of cancer biology.(Gao et al. 2022)

- *Synergistic Effects of Plant-Derived Compounds:*

Plant-derived compounds often exhibit pleiotropic effects, targeting multiple signalling pathways involved in cancer pathogenesis. When used in combination, these compounds can exert synergistic effects, leading to enhanced anti-cancer activity compared to monotherapy. Synergistic interactions between plant-derived compounds can occur through various mechanisms. Plant-derived compounds may target different molecular pathways or cellular processes involved in cancer progression, resulting in additive or synergistic effects. Modulation of Drug Metabolism: Some plant-derived compounds can alter the metabolism and pharmacokinetics of co-administered drugs, enhancing their bioavailability and efficacy. Enhanced Cellular Uptake: Plant-derived compounds may facilitate the cellular uptake and intracellular accumulation of co-administered drugs,

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potentiating their anti-cancer effects. Immunomodulatory Effects: Certain plant-derived compounds can modulate the immune response, enhancing the anti-tumor activity of immune-based therapies or increasing tumor sensitivity to immunotherapy. Understanding the synergistic effects of plant-derived compounds is essential for optimizing their use in combination therapies and maximizing their therapeutic potential in cancer treatment.(Vaou et al. 2022)

- *Overcoming Drug Resistance:*

Drug resistance remains a significant challenge in cancer therapy, limiting the efficacy of many treatment modalities. Combination therapies offer a promising approach to overcome drug resistance by targeting multiple pathways or mechanisms simultaneously. Strategies to overcome drug resistance in combination therapies include. Combining treatments that target different signaling pathways or cellular processes implicated in drug resistance to prevent or delay the emergence of resistance. Using compounds that can reverse or modulate drug resistance phenotypes, such as P-glycoprotein inhibitors or multi-drug resistance modulators. Identifying synthetic lethal interactions between drug-resistant mutations and specific targeted therapies to selectively kill drug-resistant cancer cells. Immunomodulation: Harnessing the immune system to overcome drug resistance by combining targeted therapies with immunotherapeutic agents or immune checkpoint inhibitors. Combination therapies offer a multifaceted approach to overcoming drug resistance and improving treatment outcomes in cancer patients.(Noreen et al. 2023)

- *Minimizing Side Effects:*

Minimizing side effects is a crucial consideration in the design of combination therapies to ensure patient safety and tolerability. Selective Targeting: Designing combination therapies that selectively target cancer cells or tumor-specific pathways while sparing normal tissues to minimize off-target effects. Adjusting the doses and schedules of combination treatments to achieve therapeutic efficacy while minimizing toxicity and adverse events. Utilizing targeted drug delivery systems, such as nanoparticles or liposomes, to selectively deliver therapeutic agents to tumor tissues while reducing systemic exposure and off-target effects. Considering the pharmacokinetic interactions between co-administered drugs to minimize drug-drug interactions and potential toxicities. Patient Monitoring: Implementing regular monitoring of patients' clinical status, biomarkers, and adverse events during combination therapy to promptly identify and manage side effects.(Gothai et al. 2016) By incorporating these strategies into the design and implementation of combination therapies, it is possible to minimize side effects and enhance the safety and tolerability of cancer treatment regimens.(Yuan et al. 2022)

V. DELIVERY SYSTEMS FOR PLANT-DERIVED BIOACTIVE COMPONENTS

Delivery systems for plant-derived bioactive components play a crucial role in overcoming the challenges of poor solubility, low bioavailability, rapid metabolism, and potential toxicity, thereby enhancing their therapeutic efficacy in cancer treatment. Several advanced delivery systems have been developed to improve the pharmacokinetic profile and tumor-targeting capabilities of plant-derived compounds:(Gulia et al. 2022)

- *Nanoparticle-Based Delivery Systems:*

Nanoparticle-based delivery systems utilize nanoscale carriers, such as liposomes, polymeric nanoparticles, and lipid nanoparticles, to encapsulate and deliver plant-derived bioactive components. These systems offer several advantages, including improved solubility, stability, and bioavailability of hydrophobic compounds, enhanced tumor targeting, and controlled release of therapeutic agents. Nanoparticle-based delivery systems can be tailored to specific cancer types and can facilitate the delivery of plant-derived compounds across biological barriers, such as the blood-brain barrier or the stromal barrier in solid tumors. By optimizing nanoparticle formulations and surface modifications, researchers can enhance the therapeutic efficacy and minimize the toxicity of plant-derived bioactive components in cancer treatment.(Imperiale, Acosta, and Sosnik 2018)

- *Lipid-Based Formulations:*

Lipid-based formulations, including nano emulsions, lipid micelles, and solid lipid nanoparticles, are effective carriers for delivering plant-derived bioactive components. These formulations utilize lipids as carriers to improve the solubility, stability, and oral bioavailability of hydrophobic compounds. Lipid-based formulations can protect bioactive components from enzymatic degradation, facilitate cellular uptake, and enhance the lymphatic transport of drugs, leading to improved therapeutic outcomes. Additionally, lipid-based formulations can be easily modified to incorporate targeting ligands or stimuli-responsive components, enabling targeted delivery and controlled release of plant-derived compounds in cancer therapy.(Akanda, Mithu, and Douroumis 2023)

- *Polymer-Based Carriers:*

Polymer-based carriers, such as polymer-drug conjugates, dendrimers, and hydrogels, offer versatile platforms for delivering plant-derived bioactive components. These carriers can be tailored to control drug release kinetics, enhance drug stability, and improve tumor targeting. Polymer-based carriers can protect bioactive compounds from degradation, prolong systemic circulation, and enable sustained release of therapeutic agents at the tumor site. Additionally, polymer-based carriers can be engineered to respond to tumor-specific stimuli, such as pH, temperature, or enzymatic activity, allowing for controlled drug release and enhanced therapeutic efficacy in cancer treatment.(Imperiale, Acosta, and Sosnik 2018)

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➢ *Micellar Systems:*

Micellar systems utilize amphiphilic molecules to self-assemble into nanoscale micelles in aqueous solutions, offering efficient carriers for delivering hydrophobic plant-derived bioactive components. Micellar systems can solubilize hydrophobic compounds, improve their stability, and enhance their cellular uptake and bioavailability. Additionally, micellar systems can be modified to incorporate targeting ligands or imaging agents, enabling targeted delivery and real-time monitoring of drug distribution in cancer tissues. By optimizing micellar formulations and surface properties, researchers can tailor these systems for specific cancer types and improve the therapeutic efficacy of plant-derived compounds in cancer treatment.(Sutton et al. 2007)

➢ *Targeted Delivery Approaches:*

Targeted delivery approaches utilize ligands, such as antibodies, peptides, or aptamers, to selectively deliver plant-derived bioactive components to tumor cells or specific cellular receptors overexpressed in cancer tissues. These approaches enable precise targeting of cancer cells while minimizing off-target effects on healthy tissues. Targeted delivery systems can enhance the accumulation and retention of drugs in tumor tissues, improve therapeutic efficacy, and reduce systemic toxicity. Additionally, targeted delivery approaches can be combined with other delivery systems, such as nanoparticles or liposomes, to further enhance tumor targeting and drug delivery in cancer therapy. By incorporating targeted delivery approaches, researchers can maximize the therapeutic potential of plant-derived bioactive components and develop more effective and personalized treatments for cancer patients.(Rosenblum et al. 2018)

➢ *Protein-Based Nanoparticles Containing Phytoconstituents in The Treatment of Cancer*

Recent trends indicate that protein-based carriers are experiencing significant growth due to their non-toxic, biocompatible, and safe drug delivery properties. The delivery systems encapsulate the drug through interactions within a three-dimensional structure, ensuring protection and facilitating sustained release. Nanoparticles were fabricated using various methods involving plant and animal proteins. The research studies also examined comprehensive cancer treatment options.

➢ *Nanocrystals as an Effective Carrier for Phytoconstituents in The Treatment of Cancer*

The stability, high drug loading, and ease of scaling up of nanocrystals make them an attractive drug delivery technology for medicines that are poorly water-soluble. Nanocrystals can be physically stabilized using polymers and/or surfactants. The fabrication methods for nanocrystals are categorized into top-down and bottom-up techniques. Top-down techniques encompass high-pressure homogenization (HPH) methods such as Nanopure®, DissoCubes®, and IDD-P®. In contrast, bottom-up techniques involve media milling with NanoCrystals® and processes related to nucleation and supercritical fluid technology.

➢ *Nanoemulsion Approach in The Improvement of the Anticancer Potential of Phytoconstituents*

Nanoemulsions represent a colloidal dispersion consisting of two immiscible liquid phases. They can be categorized as either oil-in-water emulsions or water-in-oil emulsions based on their specific classification. The emulsifying agent functions to stabilize the system by decreasing the surface tension between two immiscible phases. An ideal emulsifying agent is one that can effectively reduce interfacial tension by quickly adsorbing at the interface and minimizing steric hindrance. This nanoemulsion platform presents a compelling option for researchers and users alike due to its nanometric size, which offers a large surface area and optical clarity. It features an appealing dosage form, notable thermodynamic stability, a straightforward preparation method, biodegradability, and a modified release profile. The formulations demonstrate enhanced efficacy relative to traditional delivery methods and can be administered through various routes.

➢ *Micelles Containing Phytoconstituents in The Successful Treatment of Cancer*

When compared to alternative formulations, micelles, a spherical nanostructure, have been targeted at first-line technology to deliver hydrophobic ingredients because of their well-defined molecular architectures, which made manufacturing them simpler. Micelles are formed by water-soluble surfactants that possess a hydrophilic head and a hydrophobic tail. The amphiphilic characteristics of these colloids lead to aggregation and self-assembly at higher concentrations, resulting in micelle formation. Micelles consist of a hydrophobic core and a hydrophilic surface, typically composed of 50 to 200 monomers.

➢ *Solid Lipid Nanoparticles Assisting the Delivery of Phytoconstituents in Cancer*

Solid lipid nanoparticles (SLNs) are colloidal carriers developed in 1991 to enhance drug delivery methods and targeting within the human body. Solid lipid nanoparticles (SLNs) are synthesized utilizing a lipid matrix, surfactants, and, in some cases, co-surfactants. The lipid matrix exists in a solid state at physiological temperature, leading to the designation of the nanoparticles as solid lipid nanoparticles (SLNs). The choice of appropriate lipids for the solid core is a critical factor in the formulation of solid lipid nanoparticles (SLNs). Following the production of solid lipid nanoparticles (SLNs), polymorphic transitions may occur in the lipid structure during the recrystallization process. The alteration in the crystal structure of lipids may lead to drug expulsion, reduce drug entrapment efficiency, and influence the size or shape of the particles. Consequently, the second generation of solid lipid nanoparticles, known as nanostructured lipid carriers (NLCs), was developed to address the issue of drug expulsion and enhance the drug-loading capacity of nanoparticles. Compared to inorganic or polymeric nanoparticles, solid lipid nanoparticles (SLNs) exhibit superior biocompatibility and biodegradability. Therefore, the likelihood of SLNs inducing toxicity in the human body is reduced.

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➢ *Liposome-Delivery Tools for Improved Targeting of Phytoconstituents*

Dr. A.D. Bangham made the initial discovery of the liposome in 1965. It is a closed spherical structure made of phospholipid bilayers in an aqueous medium. The application of liposomes was subsequently examined in detail due to their capability to encapsulate both hydrophilic and hydrophobic pharmaceuticals. Liposome acts as a protective barrier for the lead compound, preventing degradation and minimizing drug-related toxicity; therefore, it is a widely favored option in drug delivery systems. Furthermore, it serves as an excellent drug carrier due to its biodegradable, biocompatible, and stable properties in colloidal solution. A liposome is a spherical vesicle composed of one or more phospholipid bilayers derived from either plant or animal sources. Liposomes are categorized into uni-lamellar vesicles and multi-lamellar vesicles (MLV). Unilamellar vesicles are characterized by a single phospholipid bilayer sphere, while multilamellar vesicles are composed of multiple phospholipid bilayers.

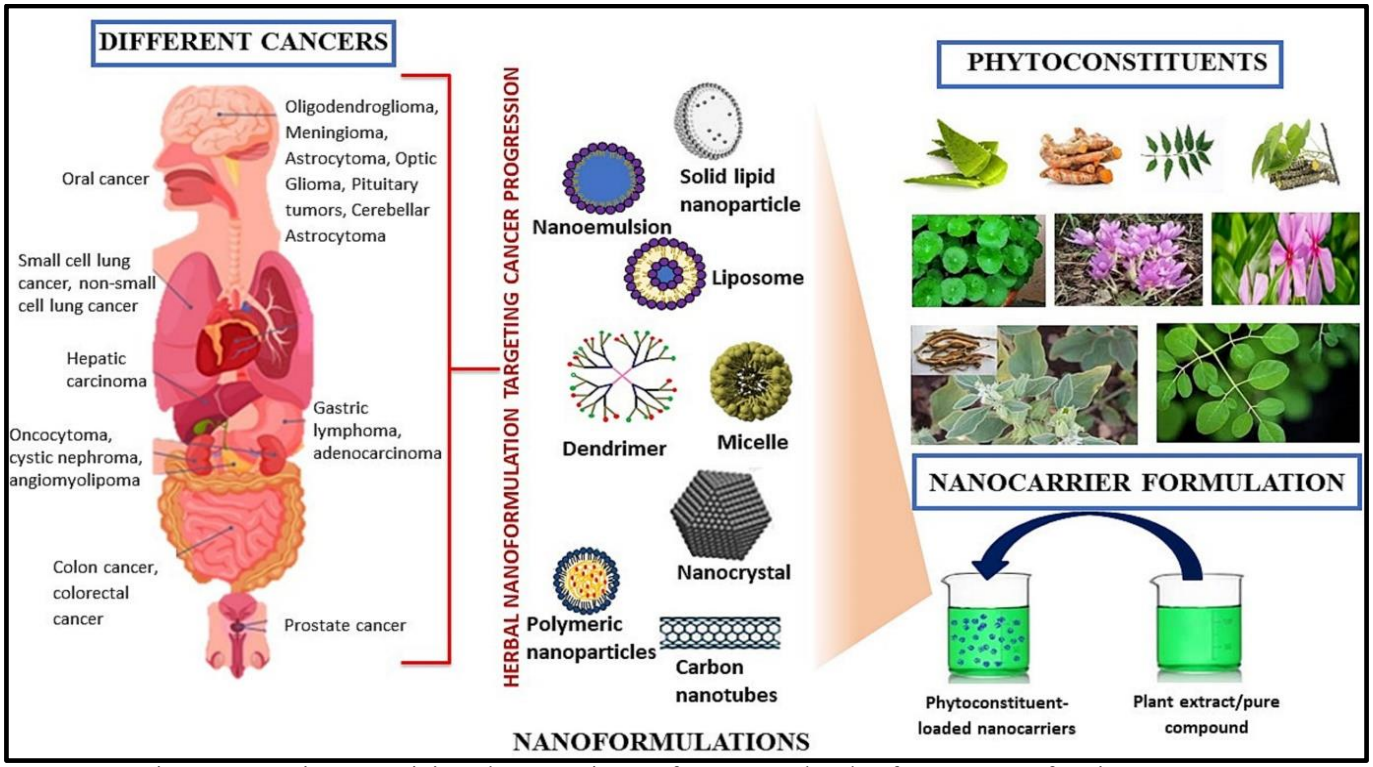

Fig 5 Nanocarriers Containing Phytoconstituents for Improved and Safe Treatment of Various Cancers

VI. PRECLINICAL STUDIES ON COMBINATION THERAPIES

➢ *In vitro Studies:*

Preclinical studies on combination therapies often begin with in vitro investigations to assess the synergistic interactions between different treatment modalities and their effects on cancer cells. In vitro studies involve culturing cancer cells in laboratory settings and exposing them to various combinations of therapeutic agents. Key objectives of in vitro studies on combination therapies include:(Tahir et al. 2017)

Assessing Cell Viability: Using cell viability assays, such as MTT assay or cell counting assays, to evaluate the cytotoxic effects of combination treatments on cancer cells compared to monotherapy. Examining Mechanisms of Action: Investigating the molecular mechanisms underlying the synergistic effects of combination therapies, such as induction of apoptosis, cell cycle arrest, inhibition of proliferation, or modulation of signaling pathways. Evaluating Drug Interactions: Employing mathematical models, such as the Chou-Talalay method, to quantitatively assess drug interactions and determine whether the combination is synergistic, additive, or antagonistic. In vitro studies provide valuable insights into the potential efficacy and mechanisms of action of combination therapies, guiding the selection of promising combinations for further evaluation in preclinical and clinical studies.

➢ *In vivo Efficacy Studies:*

Following promising results from in vitro studies, preclinical evaluation of combination therapies progresses to in vivo efficacy studies using animal models of cancer. In vivo studies involve administering combination treatments to tumor-bearing animals and assessing their effects on tumor growth, metastasis, and overall survival. Key aspects of in vivo efficacy studies on combination therapies include:(Almeida, Sarmento, and Rodrigues 2017)

Monitoring tumor volume or bioluminescence imaging to assess the inhibitory effects of combination treatments on tumor growth compared to control or monotherapy groups. Evaluating the metastatic spread of cancer cells to distant organs, such as the lungs or liver, and assessing the ability of combination therapies to prevent or reduce metastatic colonization. Survival Analysis: Analyzing overall survival rates and median survival times to determine the therapeutic

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efficacy of combination treatments in prolonging survival compared to control groups. In vivo efficacy studies provide critical evidence of the anti-tumor activity of combination therapies in a physiological context, guiding further development and clinical translation.

➢ *Pharmacokinetic Assessments:*

Pharmacokinetic assessments in preclinical studies aim to characterize the absorption, distribution, metabolism, and excretion (ADME) properties of combination therapies in animal models. Key pharmacokinetic parameters assessed in preclinical studies include:(Handa et al. 2021)

Determining the plasma concentration-time profiles of individual drugs and their combinations following administration via different routes, such as oral gavage, intravenous injection, or subcutaneous implantation. Bioavailability: Estimating the systemic exposure and bioavailability of combination therapies relative to monotherapy to assess potential drug-drug interactions and pharmacokinetic changes. Tissue Distribution: Analyzing the distribution of drugs and their metabolites in tumor tissues and healthy organs to assess tumor-targeting capabilities and off-target effects. Pharmacokinetic assessments provide essential data on the pharmacokinetic behaviour of combination therapies, informing dose selection, treatment scheduling, and formulation optimization for further preclinical and clinical studies.

➢ *Toxicity and Safety Evaluations:*

Assessing the toxicity and safety of combination therapies is crucial to ensuring their tolerability and minimizing adverse effects in preclinical studies. Toxicity evaluations involve monitoring systemic toxicity, organ toxicity, and haematological parameters following treatment administration. Key aspects of toxicity and safety evaluations in preclinical studies is important to evaluate.

Assessing acute adverse effects, such as lethargy, weight loss, or changes in behaviour, following a single or short-term exposure to combination therapies. Evaluating subacute adverse effects, such as organ toxicity or haematological abnormalities, following repeated or prolonged exposure to combination therapies over several weeks or months. Performing histopathological examination of major organs, such as the liver, kidneys, lungs, and heart, to identify histological changes indicative of drug-induced toxicity or organ damage. Monitoring haematological parameters, including complete blood count (CBC) and blood chemistry, to assess potential hepatotoxicity or alterations in liver and kidney function. Toxicity and safety evaluations provide critical information on the potential adverse effects of combination therapies, guiding dose selection, treatment regimens, and safety monitoring in subsequent preclinical and clinical studies.(Baby et al. 2021)

VII. CLINICAL TRIALS AND TRANSLATIONAL RESEARCH

➢ *Overview of Clinical Trials:*

Clinical trials are systematic investigations conducted in human subjects to evaluate the safety, efficacy, and optimal use of medical interventions, including drugs, devices, procedures, and behavioral interventions. Clinical trials are essential for advancing medical knowledge, improving patient care, and informing regulatory decision-making. Key phases of clinical trials include:(Gao et al. 2022)

- Phase I:

Assessing the safety, tolerability, and pharmacokinetics of a new intervention in a small group of healthy volunteers or patients.

- Phase II:

Evaluating the efficacy and optimal dosing of the intervention in a larger group of patients with the target disease or condition.

- Phase III:

Confirming the efficacy and safety of the intervention in a large, diverse population of patients to support regulatory approval and clinical use.

- Phase IV:

Monitoring the long-term safety and effectiveness of the intervention in real-world settings after regulatory approval.

Clinical trials follow rigorous protocols and ethical guidelines to protect the rights and well-being of participants and generate reliable evidence for medical decision-making.

➢ *Clinical Progress in Nanocarrier-Based Herbal Therapy*

The use of herbal medicine in cancer treatment, prevention, and management is gaining popularity as they are considered safe compared to current chemotherapeutics. However, the clinical translational of these phytoconstituents is a major setback due to a lack of consistency in absorption, distribution, low bioavailability, and target specificity. Additionally, high doses are required to exert clinical responses. Despite these limitations, a number of clinical studies are performed on herbal medicine either alone or in combination with current treatment to investigate its potential to improve the quality of life of cancer patients and enhance survival rate and immune modulation. However, a hand-count clinical trial has been done on nanoparticulate herbal medicine for cancer treatment. So, this section focuses on the clinical trial to investigate the effectiveness of herbal nanocarriers in cancer treatment.

As discussed above, herbal medications are used in combination with current treatment, but not much is explored as only API for cancer treatment. However, abundant data is available on the safety and efficacy of herbal medicine in the preclinical trial but not in clinical research. Literature showed a lack of evidence regarding proper guidance on the route of administration and target-specific treatment. Furthermore, a specific interaction database is not established with other

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prescribed medications. Clinical translation of phytoconstituent for potential API is required.

➢ *Case Studies of Combination Therapies in Clinical Trials:*

Several case studies demonstrate the potential of combination therapies in improving clinical outcomes and addressing treatment resistance in cancer patients:

CheckMate 067 Trial: This phase III trial evaluated the combination of nivolumab (an immune checkpoint inhibitor) and ipilimumab (a CTLA-4 inhibitor) in patients with advanced melanoma, demonstrating superior overall survival and response rates compared to monotherapy or chemotherapy. FLAURA Trial: This phase III trial investigated the combination of osimertinib (a third-generation EGFR inhibitor) and bevacizumab (an anti-VEGF antibody) as first-line treatment for patients with EGFR-mutant non-small cell lung cancer, showing improved progression-free survival and response rates compared to osimertinib alone. KEYNOTE-189 Trial: This phase III trial evaluated the combination of pembrolizumab (an immune checkpoint inhibitor) with chemotherapy in patients with metastatic non-squamous non-small cell lung cancer, demonstrating improved overall survival and response rates compared to chemotherapy alone. These case studies highlight the potential synergistic effects of combination therapies in clinical settings, paving the way for novel treatment strategies and improved outcomes in cancer patients.(Zafar et al. 2021)

➢ *Future Directions in Clinical Research:*

Future directions in clinical research focus on harnessing innovative technologies, advancing personalized medicine, and addressing unmet medical needs in cancer treatment. Key areas of focus include:

- *Precision Oncology:*

Tailoring cancer treatment strategies based on individual patient characteristics, including tumor molecular profiles, genetic mutations, and immune status, to optimize therapeutic efficacy and minimize toxicity.(Niesen et al. 2019)

- *Immunotherapy Combinations:*

Investigating novel combinations of immune checkpoint inhibitors, adoptive cell therapies, cancer vaccines, and other immunotherapeutic agents to enhance anti-tumor immune responses and overcome resistance mechanisms.(Darvishi et al. 2023)

- *Targeted Therapy Combinations:*

Exploring rational combinations of targeted therapies, including small-molecule inhibitors, monoclonal antibodies, and antibody-drug conjugates, to synergistically target multiple oncogenic pathways and improve treatment outcomes.

- *Biomarker-Driven Trials:*

Designing clinical trials based on predictive biomarkers to identify patient subpopulations most likely to benefit from specific treatments, enabling more efficient patient selection and personalized treatment approaches.(Rapoport and Anderson 2019)

- *Innovative Trial Designs:*

Implementing adaptive trial designs, basket trials, umbrella trials, and other innovative methodologies to accelerate drug development, optimize treatment regimens, and address the challenges of patient heterogeneity and treatment resistance.

VIII. REGULATORY CONSIDERATIONS AND COMMERCIALIZATION

➢ *Regulatory Pathways for Combination Therapies:*

Regulatory approval for combination therapies involves navigating complex pathways governed by regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The regulatory pathway for combination therapies typically depends on the specific agents involved, their intended use, and the therapeutic indication. Key considerations in regulatory pathways for combination therapies include:(Beg, Rahman, and Kohli 2019)

Determining whether the combination therapy constitutes a drug-device combination, a drug-drug combination, or a biologic-drug combination, as each may be subject to different regulatory requirements. Integrated Development Plans: Developing integrated development plans that outline the preclinical, clinical, and regulatory strategies for evaluating the safety, efficacy, and quality of the combination therapy.

Regulatory Submissions: Preparing regulatory submissions, including investigational new drug (IND) applications, new drug applications (NDAs), or biologics license applications (BLAs), that provide comprehensive data on the safety, efficacy, and manufacturing of the combination therapy.

Exploring expedited regulatory pathways, such as accelerated approval, breakthrough therapy designation, or priority review, for combination therapies targeting serious or life-threatening conditions with unmet medical needs. Navigating regulatory pathways for combination therapies requires close collaboration between sponsors, regulatory agencies, and clinical investigators to ensure compliance with regulatory requirements and expedite the development and approval process.

➢ *Intellectual Property and Commercialization Strategies:*

Intellectual property (IP) protection and commercialization strategies play critical roles in the successful development and commercialization of combination therapies. Key considerations in IP and commercialization strategies for combination therapies include:(Beg, Rahman, and Kohli 2019)

Building a robust patent portfolio covering the composition of matter, methods of use, formulations, and delivery systems of the combination therapy to protect against competitors and secure market exclusivity.

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Seeking strategic partnerships and licensing agreements with pharmaceutical companies, biotechnology firms, or academic institutions to leverage complementary expertise, resources, and distribution networks for the commercialization of combination therapies.

Exploiting regulatory exclusivity provisions, such as orphan drug designation, data exclusivity, or patent term extension, to extend market exclusivity and maximize the commercial value of the combination therapy.(Leenes et al. 2017)

Developing pricing and reimbursement strategies that reflect the clinical value, competitive landscape, and market demand for the combination therapy while ensuring patient access and affordability. Effective IP and commercialization strategies are essential for securing investment, generating revenue, and realizing the full commercial potential of combination therapies in the marketplace.

- *Market Potential and Industry Trends:*

The market potential for combination therapies is driven by factors such as the prevalence of target diseases, unmet medical needs, therapeutic innovation, and healthcare market dynamics. Oncology remains a dominant therapeutic area for combination therapies, driven by the high prevalence of cancer, evolving treatment paradigms, and the potential for synergistic interactions between different treatment modalities. The expansion of immuno-oncology therapies, including immune checkpoint inhibitors, CAR-T cell therapies, and cancer vaccines, has created opportunities for combination therapies that enhance anti-tumor immune responses and overcome resistance mechanisms. The adoption of personalized medicine approaches, including biomarker-driven therapy selection and targeted treatment regimens, is driving the development of tailored combination therapies that address specific patient subpopulations and molecular signatures. Evolving regulatory frameworks, such as expedited approval pathways, adaptive trial designs, and real-world evidence generation, are shaping the development and regulatory approval of combination therapies, enabling faster market access and broader patient populations.(Sistare et al. 2011) Increasing collaboration among pharmaceutical companies, academic institutions, and government agencies through consortia, partnerships, and collaborative research initiatives is accelerating the discovery, development, and commercialization of combination therapies. Overall, the market potential for combination therapies is significant, driven by therapeutic innovation, personalized medicine approaches, and strategic partnerships, offering opportunities for growth and differentiation in the competitive landscape of the pharmaceutical and biotechnology industries.(Wiecek and Mikhail 2006)

IX. CONCLUSION AND FUTURE PERSPECTIVES

Combination strategies involving plant-derived bioactive components offer promising avenues for improving cancer treatment outcomes. This review has highlighted several key findings like Plant-derived bioactive components exhibit diverse mechanisms of action, including anti-proliferative, pro-apoptotic, anti-angiogenic, and immunomodulatory effects, making them attractive candidates for combination therapies. Combination strategies involving plant-derived compounds can enhance therapeutic efficacy, overcome drug resistance, and minimize side effects through synergistic interactions and complementary mechanisms of action. Advanced delivery systems, such as nanoparticle-based formulations, lipid-based carriers, and targeted delivery approaches, play a critical role in improving the bioavailability, tumor-targeting capabilities, and safety profiles of plant-derived bioactive components in cancer therapy. Preclinical studies have provided valuable insights into the mechanisms of action, pharmacokinetics, and safety profiles of combination therapies, laying the groundwork for translation into clinical trials. Clinical trials investigating combination therapies have shown promising results in improving patient outcomes, with several combinations demonstrating superior efficacy compared to monotherapy or standard-of-care treatments.

Drug-drug interactions, off-target effects, and potential toxicity pose challenges in the development and clinical translation of combination therapies, requiring careful evaluation and management.(kazemi et al. 2023) Navigating regulatory pathways and obtaining approval for combination therapies involves complex processes, requiring comprehensive preclinical and clinical data to demonstrate safety, efficacy, and quality. Market access and reimbursement considerations, including pricing, reimbursement policies, and payer acceptance, can impact the commercialization and adoption of combination therapies in clinical practice.(Cordaillat-Simmons, Rouanet, and Pot 2020) Advancing the development of targeted delivery systems with enhanced tumor specificity, controlled drug release, and minimal off-target effects to optimize the efficacy and safety of combination therapies.(Mir et al. 2020) Exploring novel combinations of plant-derived compounds with immune checkpoint inhibitors, adoptive cell therapies, and cancer vaccines to enhance anti-tumor immune responses and overcome immunotherapy resistance.(Shrihastini et al. 2021) Implementing innovative trial designs, adaptive strategies, and real-world evidence generation approaches to accelerate the evaluation and regulatory approval of combination therapies in diverse patient populations. Conducting health economics and outcomes research to evaluate the cost-effectiveness, patient-reported outcomes, and long-term benefits of combination therapies in real-world clinical settings.(Legido-Quigley et al. 2012)

In a nutshell, it can be portrayed that the advancement of nanotechnology has progressed well in terms of achieving improved therapeutic outcomes of the phytoconstituents by delivering it more specifically, which in return is able to mitigate complications of multidrug resistance with reduced

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toxicity. As the development of multifunctional nanocarriers is progressing, drugs loaded in nanocarriers can be specifically targeted to the diseased site *via* active and passive targeting. However, despite several efforts towards the development of a vast variety of nanocarriers in recent years that had already been marketed, the intrinsic complexity of biological environments significantly impacts the functionality of nanomaterial incorporated and this often complicates their effective use for therapeutic purposes. This, in return, makes choosing the best nanocarrier not obvious and almost impossible. Thus, the engineering and development of nanomedicine should place more attention on the specific combinations of nanocarriers and target molecules, just like the strategies employed by chemotherapy combinations. This is to improve personalized treatment against cancer which will simultaneously reduce costs together with enhancing the utilization of clinically effective nanocarriers for the targeting of anticancer drugs in the near future. These combinations will also reflect a crucial modality for the diagnosis and treatment of cancer.

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