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HARNESSING NANOTECHNOLOGY TO DELIVER DIETARY BIOACTIVES FOR CANCER PREVENTION AND HEALTH PROMOTION

Areej Iqbal Awan[1], Ananduraj Remesan[2], Khadija Urooj[3], Abira Nadir[4], Muhammad Ahmad Shakir[5], Sawira Malik[6], Abdul Rauf[7], Faiqa Durrani[8], Muhammad Nawaz[9], Maria Aziz[10], Muhammad Taha Bin Husnain[*11]

[1]*School of Nursing and Healthcare, BPP University, London.*
[2]*China Three Gorges University, China.*
[3]*Department of Biochemistry and Molecular Biology, School of Basic Medical Sciences, Southern Medical University, China.*
[4,5,9]*Department of Pathobiology and Biomedical Sciences, Muhammad Nawaz Shareef University of Agriculture, Multan, Pakistan.*
[6]*Department of Biological and Environmental Sciences, Emerson University, Multan, Pakistan.*
[7]*Department of Biotechnology, Virtual University of Pakistan.*
[8]*Department of Zoology, Bahauddin Zakariya University, Multan, Pakistan.*
[10]*Department of Chemistry, Government College University, Lahore, Pakistan.*
[*11]*Department of Biochemistry and Biotechnology, Muhammad Nawaz Shareef University of Agriculture, Multan, Pakistan.*

[*7]tahabinhusnain1@gmail.com

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Corresponding Author: *
Muhammad Taha Bin Husnain

Abstract

As the global cancer burden is overwhelming, there is an urgent need to shift the paradigm and shift towards proactive cancer prevention in which dietary bioactives such as curcumin, resveratrol and EGCG have a large potential. These natural compounds have been shown to possess strong chemopreventive effects such as antioxidant, anti-inflammatory, and anti-proliferative effects. Nonetheless, they have severe clinical translational constraints due to severe biopharmaceutical limitations, which include low aqueous solubility, inadequate chemical stability in the gastrointestinal tract, and extensive pre-systemic metabolism. All these obstacles lead to zero systemic bioavailability and sub-therapeutic efficacy. Nanotechnology has become a revolution, and man has utilized the use of engineered delivery systems, such as lipid-based nanoparticles, polymeric carriers, and nanoemulsions to deal with these challenges. These novel systems are able to ensure that bioactive payloads are not degraded, greatly increase the absorption by the intestines and provide ways of delivering cargo to tissues precisely. This review critically analyzes the fact that nanoformulations significantly enhance cellular uptake and intracellular trafficking, which enhances the modulation of important oncogenic signaling pathways and induces apoptosis. Also, it compiles strong evidence of preclinical evidence of superior anticancer activity and addresses the essential safety, toxicological, and regulatory requirements in clinical translation. The future perspective implies the evolution of intelligent and stimuli-reactive solutions and the fusion of these platforms with personal nutrition. To conclude, the practical application of nanotechnology is a breakthrough moment because it

has changed the food ingredients of bioactives into a highly absorbed substance into a purposeful, effective, and active ingredient to prevent cancer and reduce health-related issues.

INTRODUCTION

History of cancer epidemiology in the international front has shown that there has been a multi-layered canvas of rising cancer rates, which have been interlaced with the shocking finding of different scientific discoveries in explaining the process of carcinogenesis (Horgan et al., 2022). The global health exercise agencies have demonstrated rather alarming statistics regarding the rate of cancer diagnosis with a significant concern on the malignancies attributed to the dietary as well as metabolic health (Clinton et al., 2020). This epidemiological state of affairs has prompted scientific paradigm shift of the exclusively therapeutic interventions to amalgamating prevention interventions which denote the begetting impact of nutritional elements in the homeostasis and carcinogenesis of cells (Srivastava et al., 2022). It is scientific investigation of the traditional diets and the one which has less incidences of cancer in the past, particularly that of the Mediterranean people and the Asian people, which has identified some groups of phytochemical agents with which the capacity of controlling cellular environment against the occurrence of cancer is truly amazing (Goosby et al., 2025). These food ingredients are complex molecules, and some millions of years of evolutionary optimization of the defenses employed by plants, which occur by chance to provide protective effect in the human biological system, occur (Stiller et al., 2021). They do not act as single-target agents but rather as general regulators of cellular signaling pathways, whose byproduct effect is an impact on inflammatory cascades, oxidative balance, detoxification pathways, and epigenetic changes (Wang et al., 2025). However, a fundamental biopharmaceutical quandary to the therapeutic translation of these dietary compounds lies in their highly complex chemical structures which are ideal in molecular recognition and biological activity and that are coupled with significant concerns about gastrointestinal stability, mucosal permeability and systemic distribution (Prajapati et al., 2024). In order to overcome such a bioavailability paradox wherein the most effective compounds tend to exhibit the least absorption behavior, new forms of approaches have been necessitated to promote the correlation between dietary intake and biologic activity (Stielow et al., 2023). The emerging research in the field of nutrigenomics is simply useful in highlighting the reciprocity between food and gene expression that bioactive nutrients may in fact communicate oncogenic pathways in transcriptional and post-transcriptional regulating mechanisms (Bhattacharya et al., 2021). The progress in systems biology has assisted scientist to map the multi-layered interactions between dietary phenols, metabolic enzymes and cell stress responses, revealing to be highly coordinated mechanisms of action and not discrete biochemical actions (Martinset al., 2020). As knowledge has increased, computational modeling and experimental oncology combined has improved at a faster rate in discovering dietary compounds that can increase synergistically when used alongside conventional therapies (Chunarkar-Patil et al., 2024). New developments in the technologies of formulation like nanoencapsulations, biopolymer coating and lipid-based delivery systems are altering the pharmacokinetic profile of the compounds and rendering them far easier to absorb in the intestine and long-lived in the systemic circulation (Alkilani et al., 2022). In addition, there is an increasing body of clinical evidence of dietary phytochemicals as adjuvant agents, and there is a suggestion that the latter agents sensitize chemotherapy and as well as reduce the toxicity of therapy (Sahin et al., 2023). Clinical trials are now being done to provide mechanistic explanations on how to optimize dose, situationism of diet and prolonged physiological effects (Özdemir et al., 2021). Specifically, the new global tendency toward preparing food more specifically emphasizes the need to tailor dietary treatment in line with genetic background, microbiome and metabolic phenotype (Lagoumintzis

et al., 2023). The communication between the phytochemicals and the intestinal microbiota is now seen as a determinant of therapeutic potential due to the fact that the activity or inactivity of the major molecular components can be induced or inhibited by the activity of the microbial metabolism (Santhiravel et al., 2022). Eventually, the molecular nutrition, pharmacology, oncology, and bioengineering technologies would be forced to converge in order to bridge the gap between epidemiological capability and clinical practice (Elazzazy et al., 2025). As the scientific society approaches the actualization of the full therapeutic potential of natural dietary compounds, it can be assumed that the future of cancer prevention and treatment will be a hybrid between ancient nutrition knowledge and the current biomedical science and technology (Goyal et al., 2024).

2. Molecular Structure and Mechanistic Complexity of Dietary Bioactives

The chemical ingenuity of dietary bioactives is a virtual universe of structural diversity with different classes having specialized molecular structures that are optimized to interact with certain biological processes (Kussmann et al., 2023). An estimated 8,000 compounds are known to belong to the polyphenol superfamily; the simplest polyphenols are phenolic acids such as gallic acid, whereas the more complex polyphenols are the flavonoids of anthocyanidins and proanthocyanidins, with distinct hydroxylation patterns on their rings, glycosyl groups and stereochemical structures, which determine their biological functions and metabolic pathways (Maniglia et al., 2021). Carotenoids exhibit large conjugated systems of double bonds that do not only establish their ability to absorb the light and give a bright coloration, but also establish electron-rich areas that can quench the singlet oxygen and intercept free radicals by delocalizing electrons (Polyakov et al., 2023). The sub cellular level of interaction of these compounds involves complex molecular conversations with cell components (Su et al., 2024). The antioxidant activities of them are tripartite, i.e., (1) direct radical scavenging by hydrogen atom transfer or sequential electron proton transfer (2) metal ion chelation that inhibits Fenton chemistry and catalytic production of hydroxyl radicals (3) transcriptional activation of phase II antioxidant enzymes by modulation of the Keap1-Nrf2-ARE pathway (Sundaram Sanjay et al., 2021). The anti-inflammatory effects occur in the form of allosteric inhibition of IKK complex activity, inhibition of MAP kinase phosphorylation cascades and the assembly of inflammasomes (Vervaeke et al., 2025). Most notably, most bioactive compounds have been shown to show context-dependent biphasic responses in that they provoke Nrf2-mediated cytoprotective signalling at nutritional doses and cause ROS-mediated apoptosis in transformed cells at high doses-a form of selective pressure which is the ultimate evolutionary sophistication (Ahmad et al., 2023). The mechanistic interactions between major dietary bioactive classes and intracellular cancer-related signaling pathways are illustrated in Figure 1

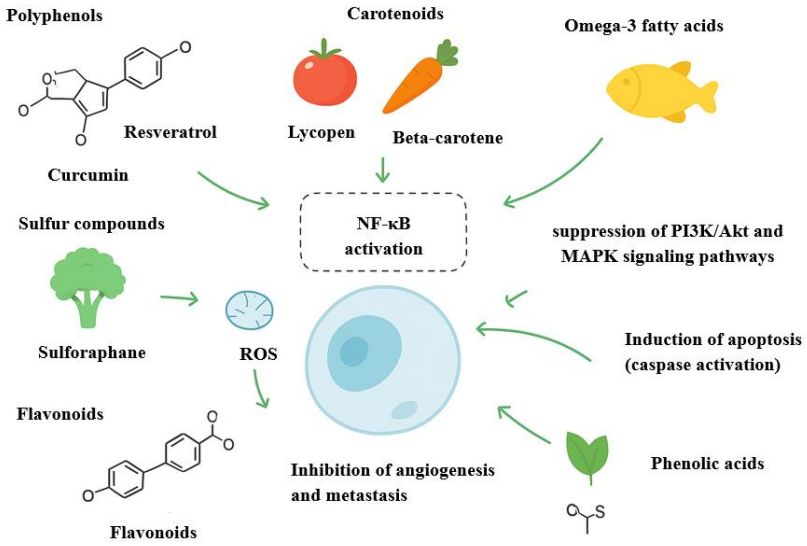

Figure 1. Bioactive dietary compounds targeting key intracellular pathways involved in cancer development.

3. Complex Biopharmaceutical Resistance

The dietary bioactives being absorbed into the body via the mouth to the systemic circulation is a daunting process of biological challenges that jointly reduce its therapeutic efficacy (Liu et al., 2024). It is these barriers that need to be understood in order to come up with the effective delivery strategies that can overcome the number of challenges these compounds undergo before they reach their target tissues (Manzari et al., 2021).

3.1. Difficulties in Dissolution of the Gastrointestinal tract.

Crystalline Structure and Limitations of Solubility:

The first and possibly the most important obstacle is first introduced at the gastrointestinal lumen where the high crystallinity of most bioactive compounds poses a major challenge to dissolution (Tomar et al., 2022). Such compounds as curcumin and resveratrol have firm crystal lattices that are stabilized by strong intermolecular forces such as hydrogen bonding, π- π stacking, and Van der Waals forces (Elangovan et al., 2025). These structural features cause a high melting point and very low aqueous solubility leading to a high energy barrier to solvation (Xiao et al., 2023). Noyes-Whitney equation predicts that the rate at which the particle dissolves is proportional to the dissolution surface area and the concentration gradient between the saturated layer at the particle surface and the bulk solution (Wimalasiri et al., 2021). In such highly crystalline products, the low solubility and limited surface area form an ideal storm of undesirable dissolution properties, grossly limiting their bioavailability (Bhalani et al., 2022). The gastrointestinal tract is a dynamic pH environment, which further poses another challenge to chemical stability (Dima et al., 2020). The extremely acidic environment (pH 1.5-3.5) of the stomach has the capacity to protonate phenolic hydroxyl groups and the sudden change to the neutral-alkaline condition of the small intestine (pH 6.0-7.5) inflicts deprotonation stress on the acid-exposed structure, initiating a series of degradation pathways (Tang et al., 2025). Anthocyanins also form spectacularly plastic structures over the span of this pH, which can be found as flavylium cation in acidic pH and then convert to quinoidal bases in neutral pH, and degenerate further to chalcone structures in alkaline condition (Cruz et al., 2021). Although some of such changes are reversible, the overall effect is important chemical stress that is capable of reducing bioactivity (Khan et al., 2024). In more sensitive compounds such as ECG, the alkalinity of the intestines triggers some irreversible chemical reactions (Zhang et al., 2022). The B-ring catechol structure is subjected to auto-oxidation to produce

reactive quinone intermediates which then polymerize to produce theaflavins and thearubigins (Renzetti et al., 2020). The oxidation process does not only decrease the antioxidant ability of EGCG but forms larger species with a smaller absorption possibility (Dai et al., 2020). The galloyl ester group then is also hydrolyzed under alkali conditions to form fragments of ecgallic acid and epicatechin with different biological activities (Peng et al., 2023).

3.2. Barriers of Intestinal Absorption.

Physical and Structural Obstacles:

The small intestine features a multi-layered barrier system, which is aimed at the selective regulation of the absorption of compounds (Kroon et al., 2025). The first hindrance is the layer of unstirred water, which is a rather immobile layer of aqueous boundary with a thickness of about 30-100 μm producing a steep diffusion gradient (Lopez and Kian Paige, 2025). The compounds have to enter this layer by passing through diffusion that is passive and the diffusion rate is regulated by the Fick Law of Diffusion, which is strongly affected by the size of the molecule, its hydrophobicity and ionization state (Arya et al., 2021). Beyond this aqueous barrier is the glycocalyx complex mesh of glycosaminoglycans and membrane-bound proteins which can sieve selectively compounds based on their size and charge properties (Walter et al., 2021). The final cellular barrier is the apical enterocyte membrane, and its selective permeability is regulated by structure of phospholipid bilayer and transport proteins (Slifer et al., 2020). The fluid mosaic model of membrane structure is the reason why highly lipophilic compounds can diffuse passively through the lipid bilayer, whereas hydrophilic compounds must be transported by special mechanisms (Nicolson et al., 2021). Nonetheless, a significant number of bioactive compounds would be intermediate in hydrophobicity and therefore restrict the passive diffusion process, along with the active transport, which forms a major bottleneck to absorption (Reis et al., 2021).

Medical Metabolism Transformation Systems:

The enterocytes themselves have a large metabolic apparatus that is designed to manipulate compounds that are absorbed (Van Ness et al., 2022). Phase I metabolism is catalyzed by the cytochrome P450 enzyme system, which includes the CYP3A4 and CYP2C9 isoforms, which catalyze hydroxylation and demethylation reactions to add polar groups and conjugate the compounds (Surendradoss et al., 2023). Such oxidative reactions may either activate prodrug compounds, or, as occurs more frequently with dietary bioactives, give rise to metabolites with decreased biological activity (Luca et al., 2020). The conjugation system in phase II is even more of a serious metabolic barrier (Järvinen et al., 2022). UDP-glucuronosyltransferases (UGTs) perform the transfer of glucuronic acid to the phenolic hydroxyl group and sulfotransferases (SULTs) add sulfate acid groups to form highly water-soluble conjugates (Juvonen et al., 2025). The conjugation reactions drastically raise the hydrophilicity and molecular weight of the molecule and inhibit reabsorption and promote biliary excretion via ATP-binding cassettes transporters such as MRP2 (Durník et al., 2022). These conjugation systems are quite efficient, and thus most dietary bioactives often experience a lot of first-pass metabolism, prior to even entering the systemic circulation (Song et al., 2025).

3.3. Hepatic Processing and Systemic Availability.

First-Pass Metabolism and Enterohepatic Recycling:

Of the part of bioactive compounds that are effective in passing through intestinal absorption, hepatic portal system transfers them to the liver, where they face further metabolic pressure (Oracz et l., 2020). Phase I and phase II enzymes are still even more concentrated in hepatocytes than in enterocytes, such that any substance that gets out of intestinal metabolism is subject to additional metabolism (Dutta et al., 2021). The strategic position of the liver in the circulation pathway implies that the compounds have to pass through this metabolic liver bath before being torn to systemic circulation (Andrijevic et al., 2022). Enterohepatic recycling is an added complication to the biliary system (Lemoine et al., 2020). The compounds and their metabolites that are excreted through the bile are recirculated back to the intestinal lumen where they are broken down by bacterial enzymes such as β-glucuronidases recycled into the original compound (Walsh et al., 2020). Although theoretically, this process can be used to increase bioavailability

through the introduction of the second opportunity of absorption, it also creates large variability and slows the attainment of peak plasma concentrations (Stielow et al., 2023). The constant intestinal-liver cycling produces intricate pharmacokinetic profiles that make it more complicated to plan dosing and predict the therapeutic success (Yuan et al., 2024).

Transport Protein-Mediated Elimination:
Canalicular membrane of hepatocytes has ATP-binding cassette transporter (ABC transporter) that actively pumps conjugated metabolites into the bile and paralleled transporters in the renal tubules pump conjugated metabolites into the urine (Veiga-Matos et al., 2020). These efflux systems provide good bioactive removal of bioactives as well as their metabolites, but also decrease systemic availability (Zai et al., 2025). These sequential barriers, which are dissolution barriers, absorption barriers, metabolic barriers, and active elimination barriers, combine to determine why there are significant numbers of potent bioactives in diet that despite their encouraging in vitro actions the bioavailability is so poor (Shahidi et al., 2022). This knowledge of these complex biopharmaceutical barriers gives the necessary basis of creating rational delivery approach that can defend bioactive compounds during their pathing of consumption to circulation, which in the end can give full therapy potential of bioactive compounds in preventing cancer and health promotion (López-Estévez et al., 2024). The major biopharmaceutical barriers limiting the bioavailability of dietary bioactives are summarized in Table 2.

Table 2. Summary of biopharmaceutical barriers limiting the bioavailability of dietary bioactive compounds

Category	Key Barriers / Mechanisms	Details	References
Overall Challenge	Multiple biological barriers reduce therapeutic efficacy of dietary bioactives.	Oral-to-systemic delivery faces dissolution, absorption, metabolism, and elimination challenges.	Liu et al., 2024; Manzari et al., 2021
Dissolution Barriers in GI Tract	Crystalline structure limits solubility	Many bioactives (e.g., curcumin, resveratrol) have strong crystalline lattices stabilized by hydrogen bonding, π–π stacking, and Van der Waals forces, leading to low solubility.	Tomar et al., 2022; Elangovan et al., 2025
	High energy barrier to solvation	High melting point and low aqueous solubility hinder dissolution.	Xiao et al., 2023
	Dissolution governed by Noyes–Whitney equation	Limited surface area and solubility slow dissolution rate.	Wimalasiri et al., 2021; Bhalani et al., 2022
	pH-dependent instability	GI pH changes induce protonation/deprotonation, causing degradation of phenolics.	Dima et al., 2020; Tang et al., 2025
	Structural transformations of anthocyanins	Convert from flavylium cation to quinoidal base to chalcone across pH range.	Cruz et al., 2021; Khan et al., 2024
	Alkaline-triggered degradation of EGCG	Auto-oxidation to quinones → polymerization to theaflavins/thearubigins; hydrolysis of galloyl group.	Zhang et al., 2022; Renzetti et al., 2020; Dai et al., 2020; Peng et al., 2023

Intestinal Absorption Barriers	Physical barriers	Unstirred water layer produces steep diffusion gradient; governed by Fick's law.	Kroon et al., 2025; Lopez & Kian Paige, 2025; Arya et al., 2021
	Chemical/structural barriers	Glycocalyx mesh filters molecules by charge and size.	Walter et al., 2021
	Cellular membrane limitations	Lipid bilayer favors lipophilic diffusion; hydrophilic compounds require transporters.	Slifer et al., 2020; Nicolson et al., 2021
	Limited passive/active transport	Intermediate hydrophobicity restricts diffusion and transport efficiency.	Reis et al., 2021
Enterocytic Metabolism	Phase I CYP metabolism	CYP3A4, CYP2C9 add polar groups via hydroxylation/demethylation, often lowering activity.	Van Ness et al., 2022; Surendradoss et al., 2023; Luca et al., 2020
	Phase II conjugation	UGTs and SULTs add glucuronic acid or sulfate, greatly increasing hydrophilicity and promoting excretion through MRP2.	Järvinen et al., 2022; Juvonen et al., 2025; Durník et al., 2022
	First-pass intestinal metabolism	Extensive conjugation before systemic entry reduces active compound levels.	Song et al., 2025
Hepatic Processing and Systemic Availability	Hepatic first-pass metabolism	Liver performs additional phase I and II metabolism, further reducing active compound levels.	Oracz et al., 2020; Dutta et al., 2021; Andrijevic et al., 2022
	Enterohepatic recycling	Biliary-excreted conjugates deconjugated by gut β-glucuronidase → reabsorption; increases variability and delays peak levels.	Lemoine et al., 2020; Walsh et al., 2020; Stielow et al., 2023
	Complex PK profiles	Intestinal–hepatic cycling complicates dose prediction.	Yuan et al., 2024
Transporter-Mediated Elimination	ABC transporter efflux	Biliary and renal ABC transporters remove conjugated metabolites, lowering systemic exposure.	Veiga-Matos et al., 2020; Zai et al., 2025
Overall Impact	Combined multi-level barriers	Dissolution, absorption, metabolism, and efflux explain low bioavailability despite strong in vitro efficacy.	Shahidi et al., 2022
Implication for Delivery Design	Need for protective delivery systems	Understanding barriers enables rational design of delivery platforms to preserve bioactivity and improve chemopreventive potential.	López-Estévez et al., 2024

4. Advanced Material Science in Delivery System Design

The cross over of pharmaceutical technology and materials engineering, and colloidal science is the development of delivery vehicles of dietary bioactives (Guo et al., 2025). The lipid-based nanocarriers have undergone a successive generation of development beginning with the simple oil-in-water emulsions, through solid lipid nanoparticles with highly ordered crystal structures and eventually nanostructured lipid carriers, involving use of liquid lipids to incorporate

crystal imperfections in order to increase payload capacity (Garg et al., 2022). The latest category of hybrid lipid-polymer nanoparticles consists of the merging of the biocompatibility of lipids along with mechanical stability as well as controlled release of polymers, producing core shell structures which produce step wise release results (Sivadasan et al., 2021). Polymeric nanoparticle-based systems have also been developed, synthetically bio-degradable polymers like PLGA and PCL have allowed easy

control of degradation by varying the ratio of copolymer, and natural polymers like chitosan and alginate have provided the systems with mucoadhesive properties increasing gastrointestinal residence time through ionic interaction between them and mucosal glycoproteins (Orasugh et al., 2024). The liposomal technologies have not only surpassed the traditional phospholipid bi-layers, but also to stimuli-sensitive systems, which contain lipids that are sensitive to pH and, which can switch to a new phase in an acid environment, and ligand-targeted vesicles decorated with folate, transferrin or RGD peptides that bind on over-expressed receptor on a particular type of cell (Alrbyawi et al., 2022). New technologies include mesoporous silica nanoparticles that contain programmable pore structures, carbon quantum dots that achieve surface and exosome-inspired nanovesicles which exploit physiological uptake routes (Sunkara et al., 2024). A comparison of conventional delivery limitations, major nanocarrier platforms, and the resulting therapeutic enhancements is presented in Figure 2.

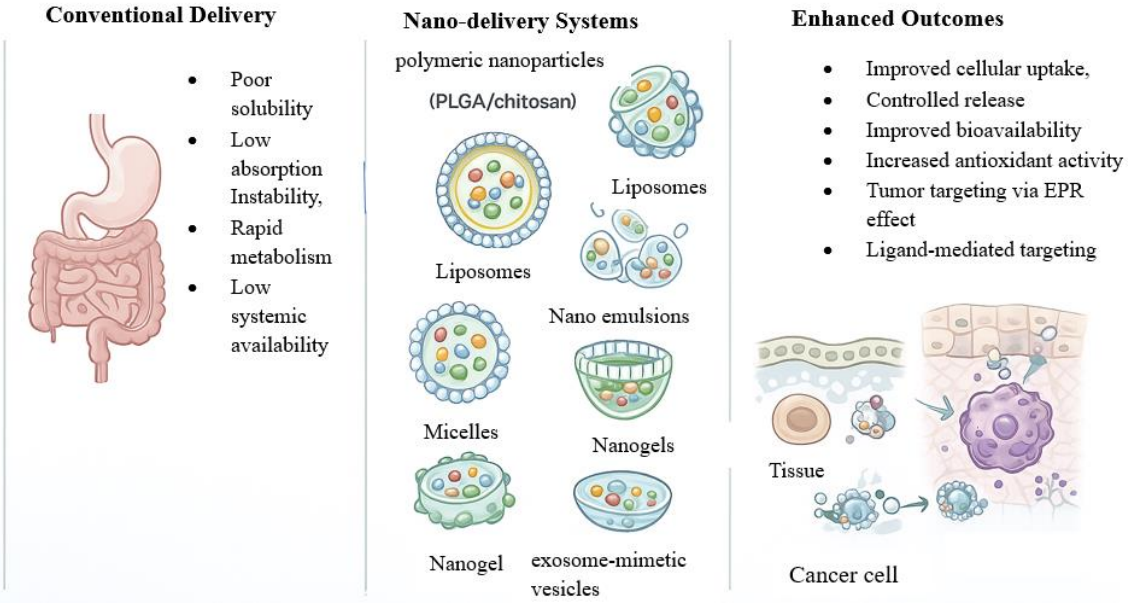

Figure 2. Nanotechnology-based delivery systems for dietary bioactives and their functional advantages in cancer prevention.

5. Optimization of specific Bioactive Compounds on the Molecular Level.

The intricate production of superior regimens of dietary bioactives requires an in-depth understanding of their peculiar molecular folds, peculia
r patterns of breakdown and precise therapeutic goals (Mittal et al., 2024). The chemical sensitivity and metabolic problem of every bioactive compound is individual and thus needs a different nano-encapsulation plan (Rashwan et al., 2022). The section will provide an analytical report of the molecular optimization techniques used on the key dietary bioactives, the chemistry, the formulation technology and the biologic advantages (Shakoor et al., 2023).

5.1. Curcumin

The curcumin molecule is known to possess many weak points limiting its application in the medical sector (Hussain et al., 2022). The 2-diketone frame can readily be broken down in the alkalinity of the intestines and the phenol hydroxyl groups are very susceptible to be glucuronidated and sulfactated by the enterocytes and the hepatocytes (Tanaka et al., 2022). Furthermore, the heptadienone bond in the

between the phenol rings is also susceptible to decomposition by light and the entire molecule exhibits a very low solubility in aqueous solutions (roughly 11 ng/mL) due to the fact that it is very crystalline with strong intermolecular hydrogen bonds (Abdi et al., 2025). The systems utilize a complicated multi-layered framework where the curcumin is dissolved in lipid core of medium-chain triglycerides and then encircled by a protective shell of polymer normally in poly(ε-caprolactone) or Eudragit polymers (Kumar et al., 2024). The polymerization mechanism between interfaces creates a cross-linked structure which becomes the molecular sieve and permits selective diffusion excluding the metabolizing enzymes (Chen et al., 2020). This architecture demonstrates outstanding alkaline hydrolysis and in studies, the stable curcumin in the architecture was at about 85 percent after 4 hours in the simulated intestinal fluid compared to 100 percent degradation in the free curcumin (Zheng et al., 2020).

The hydroxypropyl-b-cyclodextrin and sulfobutylether-b-cyclodextrin can formulate host-guest complex with curcumin and inhibit the conjugative metabolism of the phenolic hydroxyl groups, which is probably the reason why curcumin is thought to produce positive therapeutic outcomes (Houben et al., 2021). The preparation of the curcumin is done through the hydrophobic connection during the aromatic rings of the curcumin molecules with the cyclodextrin cavity but avoids the steric placement of the hydroxyl groups in order to avoid the action of UDP-glucuronosyltransferase (Tagde et al., 2021). The technique leads to over 10,000-fold increase of aqueous solubility and reduction of first-pass metabolism of curcumin; pharmacokinetic studies have revealed 20-30 folds greater plasma AUC of curcumin using the technique compared to native curcumin (Uchiyama et al., 2023). The hydrogen bonded phytosome complexes between the phenolic hydroxyl groups of curcumin and the phosphate groups of the phospholipids yield amphiphilic complexes that interface well into the cellular membranes (Hashemzadeh et al., 2023). This contact permits membrane enhancement of permeability and evades efflux transporters like P-glycoprotein (Husain et al., 2022). The complexation process involves molecular scales of reactions that convert crystalline curcumin to amorphous form, which significantly increases the dissolution rates and the rapid absorption by lymphatic system and to some degree, it avoids the first-pass hepatic metabolism (Kumari et al., 2023).

5.2. Resveratrol

The two isomer forms of resveratrol of which the biologically active trans-resveratrol is actually quickly photoisomerized into less active cis-resveratrol on light exposure (Yoshinaga et al., 2024). The pH-reactive phenolic sites of the molecule are eliminated in alkaline conditions and the large conjugation framework exposes the molecule to oxidative polymerization (Michalicha et al., 2024). On the metabolic level, resveratrol is rapidly conjugated via sulfotransferase SULT1A1 and glucuronidated by UGT1A1 and its half-life is less than 30 minutes in humans (Riccio et al., 2020). The physical constraints of trans-to-cis photoisomerization in resveratrol are fixed in the very high order crystalline structure of the solid lipid nanoparticles (SLNs) of glycerides like Compritol 888 ATO or Precirol ATO5, which is capable of physically preventing rotation of the molecule around the ethylene bridge (Chopra et al., 2022). The crystalline surrounding also develops diffusion impediments that minimize diffusion of oxygen that decreases oxidation corrosion (Doležal et al., 2025). Experiments with differential scanning calorimetry reveal that the molecules of resveratrol are scattered on the lipid matrix on the molecular level with X-ray diffraction demonstrating that the crystalline structure, which provides physical restraint, is kept (Catenacci et al., 2020). The resveratrol nanocrystals of particle size of 200-500 nm via the top-down processes through media milling or high-pressure homogenization

produce massive surface area increase that leads to a sharp increase in the dissolution velocity according to the Noyes-Whitney equation (Ding et al., 2024). The nanocrystals maintain crystalline structure of resveratrol with defects on the surface to create high-energy sites to solubilize quickly (Purohit et al., 2023). This process has demonstrated to be 3-5-fold more saturation solubility and in addition, it has enhanced the dissolution rate 10-15-fold as compared to the traditional powder formulations (Kumar et al., 2022). Oil-in-water nanoemulsions containing mct result in droplet sizes of below 100 nm and are directly absorbed through M-cell absorption in Peyer patches (Izadiyan et al., 2025). The MCT elements are broken down into mixed micelles that dissolve resveratrol and help it to get incorporated into chylomicrons by bypassing the hepatic portal system and first-pass metabolism (Abou Assi et al., 2021). The process has shown remarkable increases in bioavailability wherein reports have shown 5-8 folds increases in plasma AUC and a mammoth increase in elimination half-life to approximately 4-6 hours (Gharat et al., 2024).

5.3. EGCG

Epigallocatechin-3-gallate belongs to the category of the most chemically vulnerable bioactive compounds, which has many weak points like auto-oxidation of B-ring catechol structure, epimerization of the C2 position in neutral and alkaline conditions and hydrolysis of the galloyl ester bond (Mehmood et al., 2022). This molecule reacts highly because there are eight hydroxyl groups in the structure that are involved in hydrogen bonding and oxidation reactions and the planar structure which enables the molecule to stack in order to assist in precipitation (Jena et al., 2022). The multiple binding forces make EGCG entrap itself in the food proteins including casein and zein molecules to form protective nanocomplexes (Chen et al., 2022). The casein micelles have the potential to form a spherical complex where EGCG reacts with the section of the hydrophobes and phosphorylated serine residues which create a protecting environment that avoids the nucleophilic attack on the galloyl group (Sahadevan et al., 2023). Zein is very glutaminated and consequently, the glutaminated molecule is involved into the hydrogen bonding activity with the hydroxyl groups of EGCG and forms hydrophobic-cavities that protect the aromatic rings (Vale et al., 2024). Such protein complexes have been exceptionally stabilized where it has been established that 85-90 percent of the EGCG survives after 4 hours of simulated intestine conditions with 100 percent of free EGCG being destroyed (Goncalves et al., 2021). The ionic gelation of cationic chitosan and anionic tripolyphosphate develops a cross-linked network that entraps EGCG by hydrogen bonding and due to electrostatic interactions (Huang et al., 2025). Cationic property of chitosan provides stabilizing property which prevents auto-oxidation and the cross-linked matrix also provides diffusion barrier which prevents chemical degradation (Owczarek et al., 2023). The system shows the pH-sensitive nature of release, where minimal release is done at gastric environment and controlled release is done at an intestine environment thereby maximizing the delivery to the absorption sites and minimized degradation (Maurya et al., 2024). The introduction of EGCG to starch based or pectin based fabricated aerogels creates huge porous structures with enormous surface areas (200-600 m 2/g) that physically separate the individual EGCG molecules (Abdullah et al., 2023). Supercritical CO2 drying process maintains the mesoporous structure that provides diffusion path restrictions to oxygen and active species (Guastaferro et al., 2021). Hydroxyl-rich environment that surrounds polysaccharide aerogels creates numerous hydrogen bonding with EGCG that in turn fixes the molecule aside preserving its antioxidant potential (Siddiqui et al., 2023). The systems have demonstrated high thermal degradation resistance of 15 percent of EGCG is resistant even after 30 days in temperature of 40 C compared to total degradation of unprotected EGCG (Villamil Watson et al., 2020). All these molecular optimization plans are a higher level of addressing the specific chemical and metabolic issues of specific bioactive molecules, and enables them to be turned into active chemopreventive agents with significantly increased stability, bioavailability, and therapeutic effect (Swetha et al., 2022).

6. Enhanced Biological Performance by way of enhanced delivery

The enhanced bioactivity of encapsulated bioactives via a cascade of levels of enhanced biological activity whereby primordial advancements in the cellular uptake kinetics and intracellular membrane shipping can be observed (Petrovic et al., 2023). Nanoparticle systems can redirect the cellular internalization pathway of a passively diffusive process limited by gradient concentration and membrane permeability, to active endocytic processes, like: clathrin-mediated endocytosis, caveolae-dependent uptake and macropinocytosis that bypasses efflux transporter, and permits much larger intracellular loads (Sun et al., 2023). This enhanced cellular penetration is particularly critical to nurturing nuclear receptor binding compounds and transcription factor which has been reported to substantially enhancement nuclear receptor activation of PPAR7 and FXR by nanoencapsulated bioactive agents (Rahman et al., 2021). At the subcellular level, there is interesting organelle-specific targeting of complex delivery systems (He et al., 2021). Selective accumulation to the mitochondria of the cationic lipid nanoparticles due to its electrostatic interactions with negatively charged mitochondrial membrane increases the activity of compounds that control the mitochondrial permeability transition pores by a large margin (Vasileva et al., 2023). It relies on the help of nuclear localization signal peptide-conjugated systems to deliver the compounds that interact with chromatin-modifying enzyme and transcription factor complexes into the nucleus (Nguyen et al., 2025). The sustained release properties of most encapsulated systems are what enable persistent effects on epigenetic programming and cell differentiation by maintaining therapeutic levels of intracellular concentrations across several cell divisions (Marikar et al., 2022). In addition, co-delivery regimes to accomplish two or more bioactive compounds in a fixed ratio permit severe synergies that occur with Nrf2 stabilization of sulforaphane by flavonoids, which compete with Keap1 binding (Leena et al., 2020). The key mechanisms through which nanoencapsulation enhances the biological performance of dietary bioactive compounds are summarized in Table 3.

Table 3. Mechanisms by which nanoencapsulation enhances the biological performance of dietary bioactives.

Category	Mechanism	Key Details	References
Enhanced Cellular Uptake	Shift from passive diffusion to active endocytosis	Nanoparticles redirect uptake from concentration-dependent passive diffusion to clathrin-mediated endocytosis, caveolae-dependent uptake, and macropinocytosis, bypassing efflux transporters and increasing intracellular cargo.	Petrovic et al., 2023; Sun et al., 2023
Improved Nuclear Receptor Activation	Enhanced delivery of bioactives to nucleus	Nanoencapsulation increases activation of nuclear receptors such as PPARγ and FXR due to higher intracellular and nuclear accumulation.	Rahman et al., 2021
Organelle-Specific Targeting	Mitochondrial targeting	Cationic lipid nanoparticles accumulate in mitochondria via electrostatic interactions with the negatively charged membrane, enhancing activity of bioactives acting on mitochondrial permeability transition pores.	He et al., 2021; Vasileva et al., 2023
	Nuclear targeting	Nuclear localization signal (NLS) peptide-conjugated systems direct compounds to the nucleus for interaction with chromatin-modifying enzymes and transcription factor complexes.	Nguyen et al., 2025
Sustained Intracellular	Prolonged therapeutic levels	Controlled-release nanoformulations maintain intracellular bioactive levels across multiple cell cycles,	Marikar et al., 2022

Release		supporting long-term effects on epigenetic programming and cell differentiation.	
Synergistic Co-Delivery	Delivery of multiple bioactives at fixed ratios	Combined delivery enhances synergistic effects, such as flavonoids stabilizing Nrf2 and increasing sulforaphane activity by competing with Keap1 binding.	Leena et al., 2020

7. Comprehensive Toxicological Profiling and Regulatory Advancement

The safety of nano-encapsulated bioactives is a multi-layered and complex question that should be tackled by both material-specific toxicity and novel biological interactions due to the nanoscale factors (Baghi et al., 2022). Extensive toxicological testing involves high-content screening of cell viability, cell membrane integrity, mitochondrial activity and generation of oxidative stress in the presence of human cell lines representing gastrointestinal mucosal, hepatic tissue and immune system components (Tirumala et al., 2021). Genotoxic potential testing involves using comet assay to determine the presence of DNA strand breaks, gamma H2X immunofluorescence to determine double strand breaks and the formation of micronucleus in co-cultures (Hadi et al., 2025). Biodistribution The applications of synchrotron radiation X-ray fluorescence microscopy to analyze inorganic carrier components and biodistribution Biodistribution studies using the latest techniques such as MALDI imaging mass spectrometry will be used to give spatial mapping of carrier and payload distribution (Sawicki et al., 2025). Laws governing such high-tech delivery systems are rapidly evolving and there are international organizations that are currently coming up with guidance on engineered nanomaterials in food and supplements (Tawiah et al., 2024). Recent standards require rigorous physicochemical characterization such as particle size distribution by dynamic light scattering, surface charge by measuring zeta potential, morphology by electron microscopy and crystalline structure by X-ray diffraction (Joudeh et al., 2022). In the case of lipid-based systems, other characterization involves the content of solid fats, stability of polymorphic forms and lipid crystallization properties (Bertoni et al., 2021). There is an increasing demand to conduct long-term chronic toxicity studies on the impact of continuous exposure especially on systems which show high accumulation of the compound into tissues or where a new synthetic material is involved (Ahmad et al., 2022). The regulatory route also needs the assurance of the lack of immunogenic response, assurance of biodegradation into known safe metabolites, and assurance of consistency and scalability of the manufacturing process (Slijkerman et al., 2025).

8. Futures and Integrative Implementation

There are a number of paradigms shifts in bioactive delivery research that have been forward moving that ensure to redefine the nutritional intervention approaches (Cassotta et al., 2024). Smart delivery systems are stimuli-responsive, and involve designs where the payload is delivered on a quantum basis in response to certain physiological responses such as pH gradient, enzyme presence, redox potential changes, or temperature changes (Shishir et al., 2021). These intelligent systems have the capability of giving spatial and temporal control of release of the compound with maximum effect on therapeutic effects and minimum off-target actions (Manzari et al., 2021). The diagnostics-therapeutic fusion to produce superior theranostic systems facilitates the delivery of bioactive molecules and the monitoring of biological reactions in the body to integrated imaging agents such as quantum dots or magnetic nanoparticles (Sonar et al., 2025). The most promising direction in the future could be seen in the convergence of the technology of delivery and the personalized nutrition (Agrawal et al., 2025). New developments in nutrigenomics and metabolomics are revealing certain genetic versions and metabolic profiles, which determine how different people respond to dietary bioactives (Lagoumintzis et al., 2023). This information will allow developing a unique delivery system that is

based on the individual metabolic capacity, the microbiome composition, and the particular health risk (Shukla et al., 2024). The multi-delivery technologies like encapsulation of nanoemulsions in responsive hydrogels results in multi-stage systems capable of delivering sequential release profiles to bioactive combinations which are complementary (Sakellari et al., 2021). Delivery systems of a complexity previously unknown can be created with new architecture and functional sophistication through the emerging technology of nanofabrication through 3D printing and microfluidic technologies (Fabozzi et al., 2023).

9. Conclusion

The introduction of advanced delivery technologies of nutritional bioactives is a revolution in the field of nutritional science and prevention medicine. We are realizing the full potential of these compounds as potent focused agents to prevent disease and maintain health since we are systematically overcoming the basic biopharmaceutical constraints that have historically limited the efficacy of these compounds. The combination of ancient dietary knowledge with the most modern material science opens up the most extraordinary opportunities to change the way we use the chemical wealth of nature to optimize the use of resources to human health. The further development of this area also requires indeed interdisciplinary cooperation of various fields, food science and pharmaceutical technology as well as molecular biology and clinical medicine. The more we learn of the biological targets of dietary bioactives and the advanced technology of delivery system, the closer we come to the dream of really effective, evidence-based nutritional treatment of cancer prevention. The judicious approach to these technologies, including a great consideration of safety, ease, and compatibility with healthy eating habits, promises to place specific chemoprevention in the practical aspect of the population health. This is not just a technological breakthrough but a complete rethinking of the way we look into health maintenance by using nutritional value as a form of survival.

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