INNOVATIVE NANOPARTICLE DELIVERY OF TEA POLYPHENOLS FOR ENHANCED COLORECTAL CANCER THERAPY

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Abstract

Tea polyphenols have demonstrated potential in the prevention and treatment of colorectal cancer. However, its use in clinical settings has been hampered by drawbacks in terms of stability and bioavailability. This review aims to explore and evaluate the potential of nanoparticles as efficient delivery vehicles for tea polyphenols in the context of colorectal cancer therapy. In this review, we summarise studies on the efficacy of tea polyphenols on colorectal cancer and their limitations for colorectal cancer therapy. Moreover, we also discuss the mechanistic signalling pathway of tea polyphenols and how nanotechnology improves the limitations. Additionally, the mechanisms performed using nanoparticles in drug delivery and the significance of nanoparticles for targeted drug delivery were covered in this review. The future of colorectal cancer therapy may be significantly influenced by the integration of nanotechnology to deliver tea polyphenols. Nanoparticle-based delivery systems promise to overcome inherent challenges associated with the bioavailability and targeted delivery of tea polyphenols. By enhancing solubility, stability, and controlled release, nanotechnology can optimise the therapeutic efficacy of these bioactive compounds.

Keywords: Colorectal Cancer, Drug Delivery, Nanotechnology, Targeted Delivery, Tea Polyphenols

Introduction

Colorectal cancer (CRC) stands as a formidable global health challenge, ranking fourth in incidence and fifth in mortality among various cancers worldwide, according to the GLOBOCAN 2020 reports (1). As we gaze into the future, ominous projections estimate a surge in CRC cases, with an anticipated 3.2 million new diagnoses and 1.6 million deaths by 2040 (2). Traditional cancer treatments, encompassing surgery, chemotherapy, and radiation therapy, while effective, often bring forth adverse side effects, invasiveness, and off-target repercussions (3). Hence, it is of great importance to develop new chemopreventive and chemotherapeutic approaches that are cost-effective, non-invasive, and feasible to reduce the incidence and mortality of colon cancer.

Among the array of potential solutions, attention is shifting towards phytochemicals and nutraceuticals, where tea polyphenols (TPs) are emerging as noteworthy candidates. Tea, derived from *Camellia sinensis*, extends beyond being a beloved global beverage; it harbours nutritional and functional components, notably tea polyphenols, recognised for their capacity in CRC prevention and treatment (4–6). Nevertheless, despite compelling evidence from *in vitro* and *in vivo* models of colon carcinogenesis showcasing the anticancer effects of tea polyphenols (7), their practical applications remain hindered by several challenges. Issues like low aqueous solubility, poor stability, low bioavailability, and inadequate target specificity necessitate unrealistically high therapeutic doses, limiting their feasibility as functional foods and medicines (8).

In recent years, green synthesis of nanoparticles (green nanotechnology) has been an emerging research area in the field of nanobiotechnology (7). Scholars in the field exhibit a strong interest in employing green synthesis techniques for the production of metal, metal chloride, metal oxide, and metal sulphide nanoparticles (8–10). Green nanotechnology incorporates the principles of green chemistry and green engineering to minimise material use and maximise the utilisation of renewable resources, hence mitigating energy consumption. In addition, the progress of environmentally friendly approaches is necessary to obtain secure and efficient therapeutic interventions that surpass traditional therapy methods (11). The diverse applications of green nanotechnology include the medical, nanobiotechnology, nanofabrication, bioengineering, optical engineering, and cosmetics fields (11).

In the context of cancer, nanotherapeutics hold the potential to bring about transformative changes by leveraging processes at the nanoscale level (12). As the global scientific community embraces nanotechnology as a breakthrough in cancer treatment, the synergy between tea polyphenols and nanotechnology emerges as a compelling frontier. This review aims to explore and evaluate the potential of nanoparticles as efficient delivery vehicles for tea polyphenols in the context of CRC therapy. Despite the promising attributes of tea polyphenols, their direct application faces inherent challenges. This article intends to review the challenges associated with the direct application of tea polyphenols; highlight the existing preclinical and clinical studies that utilised nanoparticle-mediated delivery of tea polyphenols for CRC treatment; focus on the benefits of such nanoformulations in terms of retention time, bioactive molecule release duration and overall therapeutic efficacy; and emphasise on the future research directions and potential implications for clinical translation. Therefore, this article presents information that could be used as a foundation for the development of tea polyphenol nanoparticle-mediated delivery for the creation of valuable nutraceutical products, specifically in the treatment of CRC.

Materials and Methods

Literature search

The process of gathering articles on the chosen topic involved utilising various scientific databases, such as Google Scholar, PubMed, Elsevier, ScienceDirect, Springer, and Scopus. After a thorough screening process, a selected group of articles spanning the years 2020–2024 was chosen for summarisation, guided by relevance and necessity criteria. The keywords used include but are not limited to "tea polyphenols", "nanoparticles", "colorectal cancer", "cancer prevention", "encapsulation", "stability", "bioavailability", and "drug delivery". The inclusion criteria are as follows: (i) full-text publications and book chapters written in English; (ii) studies involving tea polyphenol nanoparticles; and (iii) articles regarding *in vitro*, *in vivo*, epidemiological, and clinical studies. The exclusion criteria are as follows: (i) articles not in the English language and (ii) non-peer-reviewed articles on pre-print servers.

Tea polyphenols (TPs)

Tea, scientifically known as *Camellia sinensis* and belonging to the Theaceae family, is widely recognised as the most extensively used beverage globally, second only to water. The composition of tea is influenced by a range of elements, including climatic conditions, horticulture practices, and leaf variety and maturity (13). There are three principal categories of tea: green tea (non-fermented), oolong tea (partially fermented), and black tea (fermented), which are distinguished based on their respective production methods and chemical compositions (14). The leaves undergo heat treatment, such as steaming, boiling, microwaving, or electrical heating, to produce green tea. This heat treatment serves to deactivate oxidative enzymes, specifically polyphenol oxidase while preserving the characteristic polyphenol profile of green tea. Black tea is made by fermenting the leaves under moist and warm conditions (15).

Generally, tea consists of polyphenol compounds, such as catechins, theaflavins (TFs), thearubigins, alkaloids (caffeine, theophylline, and theobromine), carbohydrates, minerals, and other trace elements (fluoride and aluminium) (16). More oligomeric polyphenols are present in green tea, including (–)-epigallocatechin (EGC), (–)-epigallocatechin-3-gallate (EGCG), (–)-epicatechin (EC), and (–)-epicatechin-3-gallate (ECG), which is the most abundant polyphenols in green tea (5). Meanwhile, the main polyphenols of black tea, such as theaflavin (TF1), theaflavin-3-gallate (TF2a), theaflavin-3'-gallate (TF2b), theaflavin-3,3'-digallate (TF3 or TFdiG) and thearubigin, are oxidising products of polyphenols (5).

While black tea production and consumption are higher than green tea (approximately 78%) (13), scientific evidence supporting the chemopreventive effect of tea on CRC is more extensive in green tea than in black tea (16–18). Green tea polyphenol, EGCG, has drawn attention because (i) it is the most prevalent catechin (making about 65% of the total catechin in green tea), (ii) it has the highest biological activity compared to other catechins found in tea, and (iii) interacts differently with cells than other catechins (19). The absorption and metabolism of polyphenols found in green tea and black tea have been thoroughly reviewed by Yang et al. (13). The low bioavailability of black tea may be attributed to the substantial molecular weight of black tea polyphenols, specifically theaflavins (564–868 Da) compared to the smaller molecules found in green tea polyphenols, such as EGCG (458 Da), EGC (306 Da), and EC (290 Da) (13).

Efficacy of tea polyphenols on colorectal cancer (CRC)

Tea polyphenols (primarily EGCG and theaflavins) inhibit carcinogenesis and malignant activity in numerous cancer diseases. Moreover, tea polyphenols can influence the

carcinogenesis process via distinct pathways of tumour initiation, promotion, and progression (20). Li et al. (21) reviewed the multiple pathways involved in the anticancer mechanism of EGCG. Numerous *in vitro*, *in vivo*, and epidemiological investigations have demonstrated that tea polyphenols inhibit the development and progression of CRC (22).

In vitro studies

Several pathways have been proposed based on investigations of tea polyphenols in cell lines. Tea polyphenols may be useful in the treatment of most cancers by causing G0/G1 cell cycle arrest and inhibiting angiogenesis (5). In addition, the anticancer properties of tea polyphenols have been observed in their ability to impede the proliferation of cancer cells by influencing various signalling pathways. These pathways include the (i) mitogen-activated protein kinase (MAPK) pathway, (ii) the phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) pathway, (iii) the Wnt/β-catenin pathway, (iv) the Janus kinase/signal transducer, and (v) transcription activator (JAK/STAT) pathway (5) EGCG, for instance, can function as both an antioxidant and a pro-oxidant. This is achieved through its binding to certain molecules and subsequent activation of signalling cascades or metabolic pathways, ultimately resulting in the suppression of carcinogenesis (13).

Recently, Luo et al. (23) revealed that treatment of EGC led to significant suppression of cell proliferation and apoptosis in three CRC cells, i.e., SW480, SW620 and LS411N cell lines. The IC_{50} of EGC in SW480, SW620, and LS411N cell lines were 75 µg/mL, 83.03 µg/mL, and 103.41 µg/mL, respectively (23). In the study, Western blot analysis revealed that EGC activated caspase-3 and poly ADP-ribose polymerase (PARP), indicative of its induction of apoptosis. Additionally, EGC demonstrated down-regulation of phosphorylated STAT3 and decreased expression of Bcl-2. The luciferase-reporter-activity assay further supported these findings by demonstrating that EGC suppressed the promoter activity of STAT3 (23). Collectively, these results suggest that EGC exerts its effects through the modulation of apoptotic markers and the STAT3 signalling pathway. Furthermore, the same author also found that EGCG significantly downregulated both STAT3 and phosphorylated STAT3 (p-STAT3) in SW480, SW620, and LS411N cell lines (24). EGCG treatment also led to a notable decrease in Bcl-2, MCL-1, and vimentin expression, coupled with an increase in E-cadherin levels. These findings suggest that EGCG possesses anti-migratory and pro-apoptotic properties in CRC cells, potentially mediated through the regulation of STAT3 signalling.

Besides, EGCG was found to induce endoplasmic reticulum (ER) stress (25) and iron chelation properties (26) in a human colorectal adenocarcinoma cell line (HT-29). At a concentration between 25 and 250 µM, EGCG inhibited HT-29 cell growth in a dose-dependent and time-dependent manner (25). Also, EGCG induced ER stress by upregulating the immunoglobulin-binding (BiP), PKR-like endoplasmic reticulum kinase (PERK), phosphorylation of eukaryotic initiation factor 2α subunit (eIF2α), activating transcription 4 (ATF4), and inositol-requiring kinase 1α (IRE1α) (25). The upregulation of transferrin receptor (TfR) protein and downregulation of Ferritin-H (FtH) protein indicates the iron chelation activity of EGCG in HT-29 cells, causing depletion of iron inside the cells and eventually leading to apoptosis (26).

The findings of the study indicated that EGCG, at concentrations ranging from 10 to 60 µM, exhibited inhibitory effects on the ability of CRC cells (DLD-1 and SW480) to form spheroids. Additionally, EGCG was found to suppress the expression of cell markers associated with CRC stem cells, including CD133, CD44, ALDHA1, Nanog, and Oct4. These effects were accompanied by a suppression in cell proliferation and an increase in apoptosis, which were mediated through the Wnt/β-catenin pathway (27). Another study revealed that black tea polyphenol theaflavin-2 (TF2), at concentrations of 50–100 µM, significantly inhibited the expression of the cyclooxygenase-2 (COX-2) gene in Caco-2 cells when compared to EGCG. Meanwhile, it appeared that TF1 and TF3 did not significantly affect COX-2 gene expression at a concentration of 100 µM (28). *In vitro* investigations often employ tea polyphenol concentrations that surpass those attainable *in vivo* as a result of their limited bioavailability (5). Figure 1 depicts a mechanistic diagram of tea polyphenols inhibiting cancer cell proliferation via various pathways.

In vivo studies

The inhibitory effect and mechanism of tea polyphenols on CRC can be identified through the establishment of related animal models. Two main animal models were used in the *in vivo* tumour development of CRC, i.e., the (i) xenograft tumour model and (ii) the carcinogen-induced tumour model (29). The xenograft tumour model was utilised for the development of tumours *in vivo* through the subcutaneous injection of human tumour cells into mice or rats. This process typically advanced over time, contingent upon the concentration of cells injected. Meanwhile, the carcinogen-induced model is produced through intraperitoneal injection, subcutaneous injection, or oral administration of carcinogens. These carcinogens can be administered through drinking water, diet, or oral gavage (29).

Common carcinogens used to induce CRC are dimethylhydrazine (DMH) and azoxymethane (AOM). Wang et al. (30) demonstrated the effect of EGCG on DMH-induced CRC in Wistar rats. DMH (40 mg/kg) was induced subcutaneously twice weekly for two weeks. Treatment with EGCG (50, 100, or 200 mg/kg) was administered once a day for eight weeks via oral gavage. The results indicated that treatment with 200 mg/kg of EGCG significantly reduced the rate of tumour development, the total number of tumours (including cancerous and non-cancerous tumours), the volume of tumours, the formation of ascites, and the number of aberrant crypt

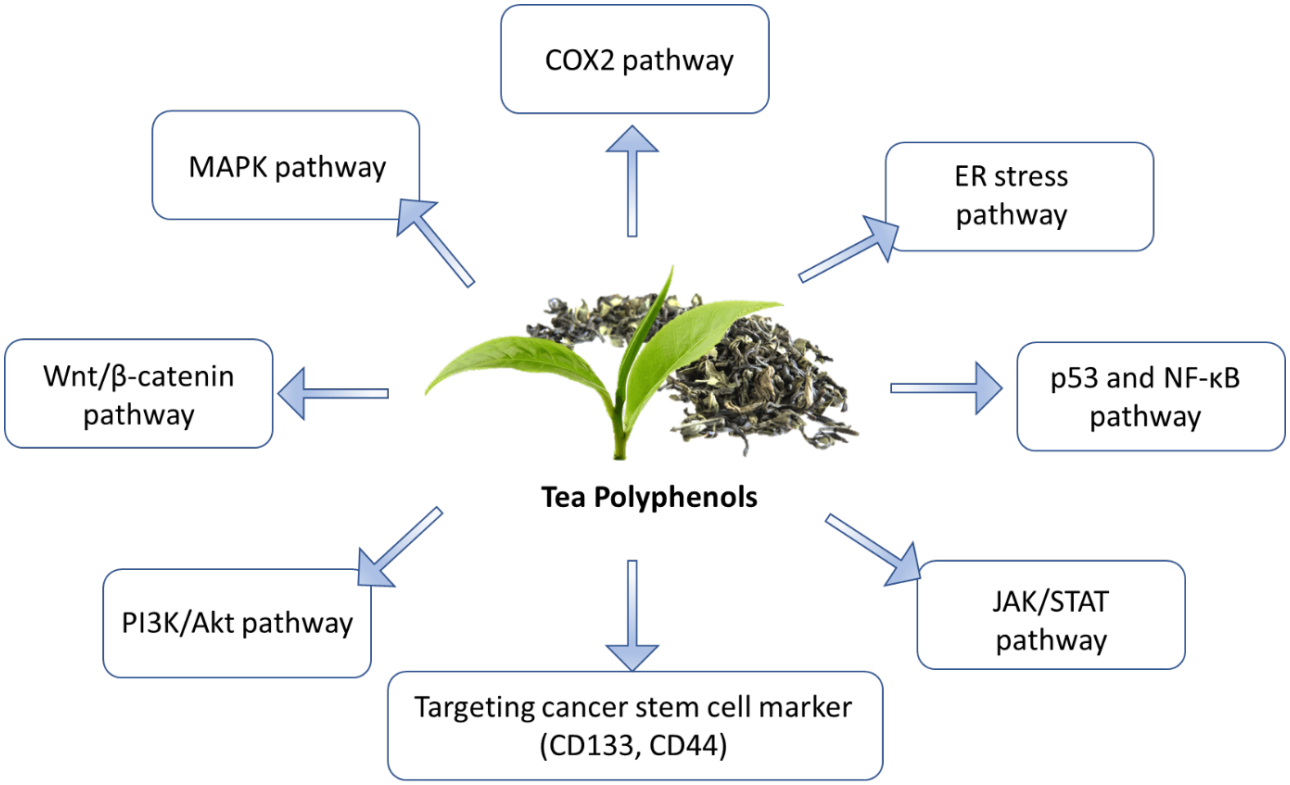

Figure 1: Role of tea polyphenols in inhibiting cancer cell proliferation through different pathways (5, 27)

foci after the completion of the rat treatment at week 12. In addition, it was discovered that EGCG can regulate the signalling pathways of CRC, p53, and PI3K-Akt through the analysis of Kyoto Encyclopaedia of Genes and Genomes (KEGG). Meanwhile, I-kappaB kinase/NF-kappaB signal pathways, apoptosis signal pathways, and MAPK cascades were regulated by EGCG through Gene Ontology (GO) analysis (30).

Hao et al. (31) reported the effect of polyphenon E (PPE), a standardised green tea polyphenol mixture (containing approximately 65% EGCG and other catechins) in F344 rats. Azoxymethane (15 mg/kg) was induced subcutaneously for two weeks. Treatment with dietary PPE (0.24% PPE in a 20% high-fat diet) for 34 weeks greatly increased plasma and colonic levels of tea polyphenols and decreased tumour multiplicity ($p < 0.01$) and size ($p < 0.05$). Additional results included (i) a marked reduction in plasma levels of pro-inflammatory eicosanoids, such as prostaglandin E2 and leukotriene B4; (ii) a reduction in nuclear expression of beta-catenin and the induction of apoptosis; and (iii) an increase in nuclear expression of RXRα, β, and ϒ. Nonetheless, the plasma levels of EC and EGC were higher than those of EGCG because EGCG had lower systemic bioavailability, as it was discovered to be higher in the colonic mucosa (31).

Epidemiological studies

The anticancer effects of tea polyphenols have been observed in various pre-clinical cell cultures and animal model systems. Nonetheless, the utilisation of this compound in clinical settings for human subjects is impeded by a range of factors, such as its stability and bioavailability. Prior epidemiological investigations, including meta-analyses, case-control studies, and prospective cohort studies, have yielded inconsistent findings regarding the association between tea consumption and the occurrence of CRC (32–36). Table 1 presents a compilation of epidemiological studies investigating the effect of tea consumption on the occurrence of CRC.

In summary, evidence of the chemopreventive effect of tea on CRC from population studies is not conclusive and shows mixed findings. This may be caused by the tea drinking habits, tea consumption types and preparation, and tea consumption measurement (37). Other limitations of epidemiological studies include the heterogeneity of the study, bias in the quality and quantity of cases in the included reports, lack of detailed calculation methods or raw data, and statistical bias, which should be considered with caution (38).

Clinical studies

Tea polyphenols have demonstrated significant therapeutic and preventive effects in various molecular, epidemiological, and clinical trials (39). A study by Sinicrope et al. (40) involved a randomised, double-blinded, and placebo-controlled trial to investigate the effectiveness of green tea polyphenols (Poly E, 780 mg EGCG daily for 6 months) in adult individuals (N = 39) with a medical background of current or previous advanced colorectal adenomas or cancer (40). The majority of CRC chemoprevention studies

Table 1: Epidemiological studies on the effect of tea consumption on colorectal cancer

Study type	Study population	Study period	Total participants (N)	Type of tea	Findings	Reference
Meta-analysis (prospective cohort)	Europe, North America, Asia	Up to June 2019	N = 2,068,137 participants	Tea (unclear), black tea, green tea	(i) No significant association between tea consumption and colorectal cancer risk in males (CI = 0.90–1.04) (ii) Marginal significant inverse impact between tea consumption and colorectal cancer risk in females (CI = 0.86–1.00)	(32)
Meta-analysis (cohort and case-control studies)	Asia, Europe, America, Australia	Up to June 2016	N = 1,642,007 participants (46,467 in case-control studies and 1,595,540 in cohort studies)	Green tea	(i) Green tea had a protective effect among female and rectal cancer patients (ii) There was a substantial inverse correlation between an increase of 1 cup/day of tea intake and colorectal cancer risk in the green tea drinking (CI = 0.96–1.01) and female (CI = 0.56-0.81) subgroups	(38)
Case-control	Korea	2010-2014	N = 2,742 participants (922 cases and 1820 controls)	Green tea	(i) Participants with the highest green tea intake showed a 40% reduced risk of CRC. (ii) A high intake of green tea, with or without considering lifestyle variables, was associated with a reduced risk of CRC.	(33)
Case-control	Western Australia	2005-2007	N = 1,802 participants (854 incident cases and 948 controls) aged 49-70 years	Black tea (with and without milk), green tea	Consumption of black tea (with or without milk) and green tea was not significantly associated with the risk of colorectal cancer.	(36)
Prospective cohort	Japan	1992-2008	N = 14,331 participants (13,937 men and 16 374 women) aged ≥35 years	Green tea	(i) No significant association between green tea consumption and colorectal cancer risk in men and women (ii) A weak trend was observed towards a higher intake of green tea with a reduced risk of colon cancer in men.	(34)
Prospective cohort	China	2004-2008	N = 455,981 participants aged 30–79 years	Tea	Tea consumption (> 4.0 g/day) was not associated with colorectal cancer (CI = 0.81–1.45)	(35)

have used adenoma recurrence as the primary endpoint; nevertheless, this study used aberrant crypt foci (ACF) regression as a primary surrogate endpoint biomarker of cancer preventive efficacy. The adenoma recurrence rate was used as a secondary endpoint, as well as evaluation of baseline demographic and clinical information, and an examination of treatment tolerability and adverse events. The findings of the study indicated that the Poly E was well-tolerated and did not exhibit notable toxicity at the specific dosage investigated. However, it did not yield a statistically significant reduction in the quantity of ACF.

Stingl et al. (39) published a protocol outlining a comprehensive study design for a prospective trial. This trial aims to investigate the impact of EGCG diet supplementation, specifically a dosage of 150 mg of EGCG taken twice daily, on a population of elderly individuals in Germany. The participants in this study have a medical history of confirmed colorectal adenomas and have undergone polypectomy (39). Following the study protocol, Seufferlein et al. (41) reported the result of the placebo-controlled clinical trial. The main objective of the study was to determine the occurrence of adenoma/CRC during the subsequent colonoscopy conducted three years after the participants were randomly assigned (N = 632). This study used actual clinical outcomes as the endpoints, where the primary endpoint was the percentage of participants who had at least one colorectal adenoma identified during the follow-up colonoscopy within the 3-year observation period, and the secondary endpoint was the number of carcinomas, serrated adenomas, and advanced lesions (41). The findings indicated that the supplementation of green tea extract (GTE) was well received by participants. However, no statistically significant disparity in adenoma rate was observed between the groups receiving GTE and those receiving a placebo within the entirety of the study population (41). Nonetheless, a notable disparity in the rate of adenoma recurrence was observed, favouring the utilisation of GTE solely among the male participants in the study. This finding, identified through a predetermined subgroup analysis, suggests the existence of a potential gender-specific variation in the effectiveness of chemoprevention, warranting additional research and exploration (41).

The preventive effect of GTE supplements on metachronous colorectal adenoma and cancer in the Korean population was reported by Shin et al. in 2018 (42). The study conducted a randomised clinical trial to investigate the effects of GTE at a dosage of 0.9 g per day over one year. The participants were individuals who had previously undergone endoscopic removal of colorectal adenomas and had no prior history of colorectal surgery (N = 143). This study also used actual clinical outcomes as the endpoints, where the incidence of metachronous adenomas was recorded at the endpoint of colonoscopy. The results of the trial indicated a favourable outcome (42). GTE supplementation reduced metachronous adenomatous polyps and significantly reduced the number of new adenomatous polyps (42).

Shimizu et al. (43) performed a randomised trial (pilot study) to assess the preventive efficacy of GTE supplements (administered at a dosage of 1.5 g GTE per day for 12 months) in a cohort of Japanese patients with a previous medical history of colorectal adenomas (N = 125). In this study, the incidence of metachronous adenomas was the endpoint measured. The findings demonstrated a statistically significant decrease of 50% in the occurrence of metachronous adenomas among participants in the supplementation group compared to those in the control group over one year. Furthermore, it was observed that the relapsed adenomas exhibited a smaller size in the group receiving supplementation compared to the control group (43).

In conclusion, there are still limited clinical trials that report on the effect of tea polyphenols on CRC. Several limitations could potentially hinder the implementation of the clinical trial. These limitations include the difficulty in choosing a suitable surrogate biomarker, limited funds, a small number of participants, a short trial period, and the difficulty in estimating the amount of tea consumed per day (43).

Limitations of tea polyphenols for the treatment of CRC

While there are potential health benefits associated with tea polyphenols, their direct application for human consumption also comes with inherent challenges, such as low bioavailability, low solubility, and poor stability (44, 45). In addition, there are several limitations and challenges when comparing tea polyphenols with standard chemotherapy agents.

Low bioavailability

The effectiveness of tea polyphenols *in vivo* is determined by their systemic delivery and bioavailability (46). Nevertheless, there exists a discrepancy in the outcomes observed *in vitro* and *in vivo* experiments, as well as between laboratory-based assessments and epidemiological investigations. The limited bioavailability of tea polyphenols, which is generally acknowledged to be low (less than 2%–5%), played a significant role in the emergence of these inconsistencies (47). In addition, the therapeutic capacity of these substances is constrained by inadequate systemic absorption after oral administration. This is attributed to factors such as diminished absorption, suboptimal pharmacokinetics and bioavailability, inadequate biodistribution, initial metabolic processing, limited tissue penetration, insufficient accumulation, and reduced efficacy in targeting specific body tissues (48).

Numerous studies have been conducted to examine the kinetics and extent of polyphenol absorption following the consumption of tea polyphenols, utilising measurements of plasma concentrations or urinary excretion. According to the report, upon consumption of two cups of green tea, the average plasma concentration of EGCG in the human body was found to be merely 0.17 μM (49). The plasma

predominantly contained EGCG in its unbound state, and between 0 and 8 hours, more than 90% of the total urinary EGC and EC were excreted, with nearly all of them being in conjugated forms (49). The previous study on green tea catechins incubated in CRC cells (HT-29) showed an IC_{50} value of 88 µM after 72 hours (25). This value, considered a high concentration of the pure compound, indicates its potential as an anti-proliferative agent. The high concentration may be attributed to the low bioavailability of tea polyphenols. Furthermore, the effectiveness of EGCG has been further reduced throughout its metabolism due to processes such as methylation, glucuronidation, sulfurylation, and oxidative degradation (21).

Comparing the bioavailability of tea polyphenols to standard chemotherapy agents is intricate, given their distinct classifications, mechanisms of action, and intended purposes. Tea polyphenols may exhibit limited bioavailability due to factors like poor solubility, metabolism, and rapid elimination (50). These factors could impede their ability to attain therapeutic concentrations in the bloodstream and target tissues. In contrast, chemotherapy drugs are often specifically formulated for optimal bioavailability, ensuring effective concentrations in the intended target tissues. However, it is noteworthy that even chemotherapy drugs, such as 5-fluorouracil, encounter challenges in oral therapeutic effectiveness due to restricted bioavailability. This limitation is primarily linked to obstacles related to poor membrane permeability and absorption in the gastrointestinal tract (51).

Low solubility

The bioavailability of tea polyphenols is significantly influenced by their physicochemical property of solubility (52). Despite the numerous health benefits associated with tea polyphenols, their bioavailability is hindered by a low absorption rate (47). For instance, it has been observed that EGCG exhibits instability when exposed to physiological fluid and water (53). According to a review by Mojzer et al. (54), polyphenols are not readily absorbed by the colon, resulting in a prolonged absorption time of up to 9 hours. In addition, the efficiency of colon-absorbed polyphenols is only 15%–20% of the total polyphenol content absorbed in the intestine.

Unlike some chemotherapy agents that are optimised for enhanced bioavailability, tea polyphenols may require specialised delivery mechanisms to improve their solubility and subsequent absorption, enhancing their therapeutic potential in CRC (55). Standard chemotherapy agents, with their established solubility profiles, have a more straightforward path in terms of formulation, regulatory approval, and clinical adoption, whereas the development of tea polyphenol-based formulations may require additional considerations and refinement.

Poor stability

In general, it has been observed that tea polyphenols exhibit stability when exposed to an acidic gastric environment. However, their degradation has been observed in the neutral and mild alkaline environment of the small intestine (52). For example, it was observed that EGCG exhibited stability under acidic pH conditions but underwent fast degradation when exposed to bodily fluid with a pH of 7.4 (47). In particular, at alkaline or neutral pH (19), EGCG's vicinal trihydroxy structure makes it more vulnerable to air oxidation. A study by Dube et al. (56) showed that the non-encapsulated EGCG, with an initial concentration of 5 µg/mL, exhibited a degradation rate of 50% within 10 minutes when exposed to a potassium hydrogen phosphate buffer at a temperature of 37°C and a pH of 7.4. In contrast, the encapsulating EGCG within chitosan-tripolyphosphate nanoparticles had a protective effect on the compounds. This was evident as the degradation of EGCG by 50% of its starting level at alkaline pH required 40 minutes. EGCG undergoes fast degradation or enzymatic metabolism in the liver and other tissues (53).

Previous research indicated that green tea becomes unstable after passing through the phases of digestion, including the salivary, gastric, and upper small intestinal phases (57). Tea polyphenols are also known to be degraded when subjected to heat, light, or oxidants (46). Hence, encapsulating tea polyphenols in nanoparticles presents an alternative method to stabilise tea polyphenols for *in vivo* oral delivery. The determination of the stability of tea polyphenol nanoparticles can be achieved by measuring the value of zeta potential. The high positive zeta potential improves the stability of nanoparticles, prevents aggregation, and enhances their bioadhesive properties (56).

Tea polyphenols face distinct challenges, primarily centred around their poor stability when compared to meticulously engineered standard chemotherapy agents (58). The latter are specifically designed for enhanced stability in physiological environments, equipped to withstand the complexities introduced by the body's biological processes. The compromised stability of tea polyphenols adds intricacies to their journey in clinical translation. It becomes imperative to ensure unwavering stability throughout the entire drug development process, spanning from formulation to administration, as a critical factor for obtaining regulatory approval and ensuring the successful adoption of these compounds in clinical practice (50).

Nanotechnology improves the limitations of tea polyphenols

Nanotechnology pertains to the scientific investigation of particles that fall within the size range of 100 nm, leveraging the inherent benefits associated with the substantial surface area to volume ratio exhibited by atoms or molecules. The aforementioned attribute enhances surface activity and alters the physical and biological properties of nanomaterials (59). Extensive research in nanotechnology has revealed significant advantages associated with nanoparticle-based delivery methods compared to conventional therapeutic approaches (60).

The implementation of an appropriate nanoencapsulation technique for tea polyphenols has the potential to mitigate the degradation of these compounds while also enabling a controlled and sustained release of tea polyphenols over an extended period. This controlled release profile may contribute to a prolonged therapeutic effect, potentially reducing the frequency of administration compared to conventional drug delivery methods (61).

Another advantage of nanoparticles as a carrier for the delivery of tea polyphenols in cancer therapy is that their size, surface, materials, and shape can be easily manufactured to ensure that they can reach the specific target of cancer cells (62). Surface modifications and functionalisation of nanoparticles can enhance their specificity to cancer tissues, minimising exposure to healthy cells and reducing side effects (63). Besides, targeted delivery and controlled release provided by nanoparticle formulations can potentially reduce the systemic toxicity associated with free-form tea polyphenols. This is achieved by minimising exposure to healthy tissues while maximising the concentration at the tumour site (64). Recent studies have shown that it is possible to substantially increase the bioavailability and stability of tea polyphenols encapsulated in nanoparticles (21). This can lead to better absorption in the gastrointestinal tract, addressing the challenge of low bioavailability associated with free-form polyphenols (50, 65).

Different types of tea polyphenol nanoparticles

Several types of tea polyphenol nanoparticles have been developed to enhance its delivery, such as protein-based, polymer-based, metallic-based, lipid-based, and carbohydrate-based nanoparticles (Table 2, Figure 2). The choice of nanoformulation is important for the objective of the study, as different nanoformulations will result in different properties such as size, surface charge, encapsulation efficiency, and release efficiency. Size plays an important role in determining the bioactive compounds that can reach the target site. The stability, mucoadhesive properties, and impact on permeation enhancement of nanoparticles are determined by their surface charge, which is characterised by the value of zeta potential (66).

Table 2: Different types of tea polyphenol nanoparticles

Type of nanoformulation	Compound used	Average size	Zeta potential	Encapsulation efficiency	Release efficiency	Reference
Protein-based						
Casein nanoparticles	Green tea polyphenols	97 nm	-24.2 mV	76.9%	72% in 48h	(61)
β-lactoglobulin nanoparticles	EGCG	31.3 nm	-35.9 mV	N/A	65% in 48h	(101)
Polymer-based						
Chitosan nanoparticles	Green tea polyphenols	407 nm	+26.1 mV	8-16%	60-70% in 48h	(67)
Chitosan-citrate nanogel	Green tea extract	135.43 nm	+40.40 mV	68.37%	N/A	(102)
Chitosan-caseinophosphopeptides (CS-CPP) nanocomplexes	EGCG	150 nm	+32.2 mV	N/A	N/A	(103)
Chitosan-tripolyphosphate nanoparticles	EGCG	440 nm	+25 mV	N/A	N/A	(104)
Poly(lactide-co-glycolide) (PLGA) nanoparticles	Theaflavins (TF), EGCG	215 nm (TF), 239 nm (EGCG)	-20.2 mV (TF), -24.5 mv (EGCG)	26% (TF), 18% (EGCG)	23% in 3h (TF), 32% in 6h (EGCG)	(105)

Table 2: Different types of tea polyphenol nanoparticles (continued)

Type of nanoformulation	Compound used	Average size	Zeta potential	Encapsulation efficiency	Release efficiency	Reference
Metallic-based						
Zinc complex loaded β-chitosan nanoparticles	Tea polyphenols	84.55 nm	+29.23 mV	97.33%	80% in 5.5h	(68)
Iron oxide nanoparticles	Green tea polyphenols	10 nm	N/A	N/A	N/A	(106)
Gold nanoparticles	EGCG	25 nm	-72.57 mV	N/A	41.9% in 48h	(71)
Gold nanoparticles	EGCG	50 nm	-23.4 mV	N/A	N/A	(107)
Lipid-based						
Liposome nanoparticles	Green tea polyphenols	250 nm	-24.2 mV	77.7%	60% in 48h	(72)

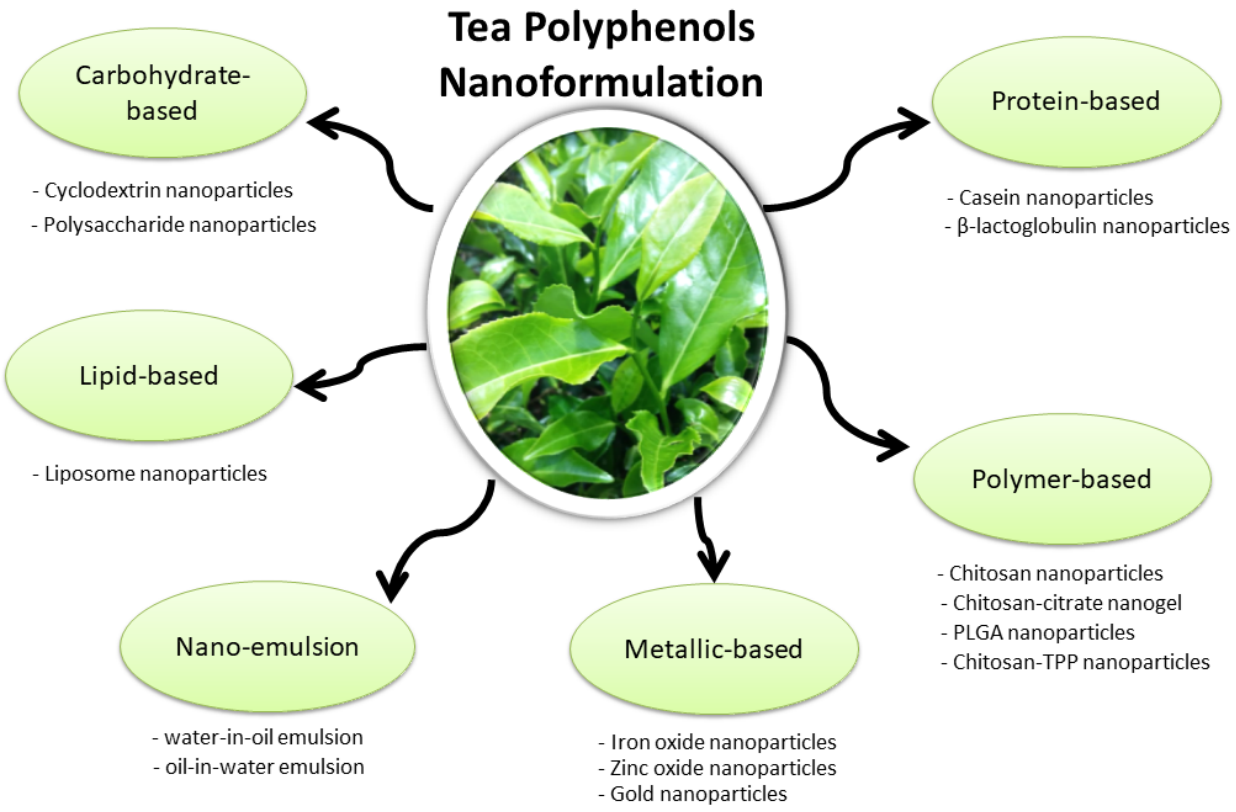

Figure 2: Nanotechnology approach of tea polyphenols

Protein nanoparticles, such as casein, are considered good candidates for drug delivery systems (61). Upputuri and Mandal (61) conducted an evaluation of the release kinetics properties of green tea polyphenols from casein nanoparticles. The results demonstrated that casein-green tea polyphenol exhibited effectiveness at a concentration of 5 mg/mL. Additionally, it demonstrated approximately 88% of free radical scavenging activity within four hours (61). Polymer-based nanoparticles, such as chitosan and poly(lactide-co-glycolide) (PLGA), exhibit characteristics of biodegradability, biocompatibility, and low toxicity. The US Food and Drug Administration (US FDA) has approved PLGA nanoparticles as a secure drug delivery system (59). Chitosan is the most commonly used polysaccharide in nanoparticle systems for oral delivery (52). The positive surface charge (zeta potential) of chitosan-encapsulated tea polyphenols reflects the stable condition of nanoparticle systems with mucoadhesive potential and absorption enhancement properties (67). In their study, Khan et al. (12) demonstrated the slow release of EGCG in acidic pH, specifically in simulated gastric juice. Additionally, they observed a faster release of EGCG in simulated intestinal fluid, which has a neutral pH. This release pattern was observed in chitosan-based nanoformulated green tea EGCG.

Metallic nanoparticles, including zinc oxide, iron oxide, gold, and silver, have been utilised for numerous purposes. Tea polyphenols have often been used to prepare metal complexes due to the presence of active aromatic hydroxyl groups (68). Iron oxide nanoparticles (IONP), which are the most commonly used magnetic nanoparticles, are promising candidates for drug delivery and the treatment of various disorders. They possess specific properties, including superparamagnetic, a high surface-to-volume ratio, a greater surface area, and ease of separation. In addition, IONP has been employed in biomedical contexts, particularly as contrast agents for magnetic resonance imaging (MRI), with the approval of the Food and Drug Administration (FDA) (69, 70). Gold nanoparticles are highly effective in carrying drugs and safeguarding the conjugated bioactive compounds against enzymatic metabolisation (71). Additionally, these materials possess distinctive properties characterised by robust biocompatibility and surface functionalisation flexibility, including surface plasmon resonance (70).

Liposomes are composed of natural or synthetic phospholipids, encapsulating an aqueous core. They can deliver both hydrophobic and hydrophilic drugs (72). Upputuri and Mandal (72) evaluated the sustained release of green tea polyphenols from liposomal nanoparticles that were prepared using phosphatidylcholine and cholesterol. Their findings demonstrated that 60% of the green tea polyphenols were released after 48 hours at a pH of 7.4. In addition to pH, temperature is one of the significant variables that affect the release of tea polyphenols from liposome nanoparticles. The binding between liposomes and green tea polyphenols can be affected by high temperatures, resulting in the release of a higher percentage of compounds (72).

Applications of tea polyphenol nanoparticles for CRC therapy

Nanoparticles have been highlighted for several years as possible drug carrier structures for cancer treatment (73). Moreover, the impact of the nanoformulation technique of tea polyphenols for CRC therapy has gathered vast attention due to the improvement of bioactive stability and bioavailability of tea polyphenols (14), and also for targeted therapy (74). The idea of nano-chemoprevention using tea polyphenols was introduced by Siddiqui et al. (75), where they encapsulated EGCG in polylactic acid-polyethylene glycol (PLA-PEG) nanoparticles. The findings showed that encapsulated EGCG maintains its biological potency by exerting its pro-apoptotic and angiogenesis inhibitory effects with a 10-fold dose advantage (75).

The advantages of nanoparticles as carriers for the delivery of tea polyphenols in cancer therapy are that their size, surface, materials and shape can be easily fabricated to ensure they can reach the cancer cell-specific target of cancer cells (62). In addition, the solubility and bioavailability of tea polyphenol nanoparticles can be increased through surface functionalisation. This process helps protect them from premature degradation, prolongs their circulation time, and induces higher levels of target specificity (76). Multiple articles on the efficacy of tea polyphenol nanoparticles in treating various cancers have been published (Table 3). Nevertheless, the effect of nanoparticles of tea polyphenols on CRC remains limited.

Abdolahad et al. (77) focused on investigating the impact of a formulated combination of green tea-reduced graphene oxide (GT-rGO) on the efficacy of near-infrared (NIR) photothermal therapy for HT29 (grade 1 colon cancer) and SW48 (grade 4 colon cancer) cells. Green tea was used for the reduction of graphene oxide. Exposure of 3 mg/L GT-rGO-included cell solutions to laser ablation for 20 min caused a significant colon cancer cell death (66% and 82% of the HT29 and SW48 cancer cells were destroyed). The green tea polyphenols attached to the graphene oxide act as binding agents to cancer cell surfaces (77).

Alotaibi et al. (78) investigated the effect of EGCG and theaflavins on cellular DNA damage in human lymphocytes from colon cancer patients and healthy people, whether supplied in bulk or nano-encapsulated form. PLGA nanoparticles were used to contain EGCG and theaflavins. The bulk form was found to reduce DNA damage in lymphocytes in a concentration-dependent manner. In contrast, the formation of nanoparticles increased DNA damage in lymphocytes in a concentration-dependent manner (78).

In conclusion, the incorporation of tea polyphenols into nanoparticles can further enhance their bioavailability and efficacy. According to findings from various studies (79), it was also discovered that the nanoformulation of

Table 3: Tea polyphenols nanoparticles and their applications in cancer

Types of nanoparticles	Size and shape	Surface charge	Study Design / Application	Findings	Reference
Chitosan-E-pigallocate-chin-3-O-gallate nanoparticles	60 nm (TEM)	N/A	Breast cancer *In vitro*	*In vitro:* Inhibitory effect up to 21.91% on the growth of MCF-7 breast cancer cells.	(73)
Honokiol nanoparticles based on EGCG functionalized chitin (CE-HK NPs)	80 nm (TEM), spherical (TEM)	+33.8 mV	Liver cancer *In vitro and in vivo*	(i) *In vitro*: CE-HK NPs inhibited HepG2 cell viability via inhibition of the G2/M phase and reduced mitochondrial membrane potential. (ii) *In vivo*: CE-HK NPs (40 mg/kg) inhibited tumour growth by 83.55% in HepG2 tumour-bearing mice; better tumour selectivity.	(108)
Platinum nanoparticles using tea polyphenol (TPP@Pt)	30-60 nm (TEM), flower-shaped (TEM)	N/A	Cervical cancer *In vitro*	(i) *In vitro*: TPP@Pt reduced SiHa cell viability at concentrations from 12.5 to 200 µg/ mL (at 24 and 48 h). (ii) *In vitro*: TPP@Pt treatment substantially increased the cell percentage in the G2/M phase.	(109)
Epigallocatechin gallate/layered double hydroxide (EGCG-loaded LDH) nanohybrids	10 nm (TEM), Hexagonal form (TEM)	+30.6 mV	Prostate cancer *In vitro*	*In vitro*: Incorporation of EGCG into LDH can enhance EGCG's apoptotic activity and improve its anti-tumor activity against PC3 cells over a 5-fold dose.	(110)
Tea polyphenol–coated magnetite nanoparticles	10 nm (TEM), spherical	N/A	Toxicity evaluation *In vitro*	(i) Tea polyphenol coating enhances the saturation magnetization of iron oxide nanoparticles. (ii) *In vitro*: Using MTT assay, the polyphenol-coated sample was found to increase the viability of the L929 mouse fibroblast cell line.	(111)

tea polyphenols accelerated apoptosis in CRC cells. This was achieved by upregulating caspases and Bax levels, which in turn inhibited CRC cell proliferation. Additionally, the nanoformulation downregulated Bcl-2 and ERK1/2 expression.

Mechanistic signalling pathway of tea polyphenols against CRC

The mechanistic signalling pathways affected by tea polyphenols involve intricate interactions at the cellular and molecular levels. Tea polyphenols are known for their strong antioxidant properties. They can neutralise reactive oxygen species (ROS) and reduce oxidative stress in cells. Tea polyphenols may help protect cells from DNA damage and mutations by scavenging free radicals, which are factors contributing to cancer development (80). Truong and Jeong discussed the antioxidant mechanisms of tea polyphenols with relevant evidence in detail (81). Besides, tea polyphenols have been shown to inhibit angiogenesis, the process by which new blood vessels form (82). Inhibiting angiogenesis is a potential strategy for limiting the growth and spread of tumours, including CRC. Rashidi et al. (82) have highlighted the ability of green tea polyphenols to suppress the pathological formation of new blood vessels by inhibiting members of the VEGF family.

In addition, tea polyphenols may also exert their effects on CRC cells through epigenetic modifications, such as DNA methylation and histone acetylation (83). These modifications can influence gene expression patterns and contribute to the regulation of cellular processes.

Li et al. (84) described in detail the role of EGCG as epigenetic regulators, including the expression of miRNA (84). Numerous studies indicate that tea polyphenols can modulate signalling pathways in cancer cells, such as the MAPK pathway, PI3K/Akt pathway, Wnt/β-catenin pathway, and 67 kDa laminin receptor pathway. These modulations contribute to the inhibition of cell proliferation and the promotion of apoptosis (5). Overall, it is important to note that these mechanisms are interconnected, and the overall effect of tea polyphenols against CRC involves a complex interplay of these pathways.

Mechanisms performed using nanoparticles in drug delivery

The utilisation of nanoparticles in drug delivery can be envisioned as a carrier or "vehicle" that is capable of loading medicines. These vehicles can be altered to function as navigators, directing the cargo to the specific site of the disease. This technology is essential because it allows compounds to bypass biological barriers that would otherwise degrade or hinder their accumulation at the target site. By reducing side effects and toxicity, optimal targeted efficacy can still be achieved at lower dosages and dose frequencies. Nanoparticles can be developed into a smart system by manipulating parameters such as size, surface characteristics, and the material used (85). The importance of these parameters lies in their role as the initial step towards achieving a successful drug delivery system before embarking on the development of target-specific drug delivery (85).

Several authors have described the mechanisms performed using nanoparticles in drug delivery. Some of the mechanisms of the nanoparticle drug delivery system consist of passive and self-delivery. Other mechanisms that can represent drug release in nanoparticles include diffusion, solvent, chemical reaction, and stimuli-controlled release (70). Gavas et al. (86) described the mechanisms of cellular targeting using nanoparticles for cancer therapy, which are classified into two approaches, i.e., passive targeting and active targeting.

Passive targeting is a strategy wherein nanoparticle delivery systems are intentionally accumulated at the desired location as a result of pharmacological or physiochemical factors (87, 88). This approach primarily relies on the distinct characteristics of the tumour biology, such as vascularity and leakiness, as well as the properties of the carrier, including size and circulation time (86). The approach that is frequently employed is to deliver drugs to angiogenic tissues, such as tumours (87). The nanoparticles will be transported into the tumour interstitium and cells through permeable tumour capillary fenestrations by passive diffusion or convection (89).

Active targeting, also known as ligand-mediated targeting, is dependent on specific ligands or molecules, such as transferrin and folate, that bind to molecules or receptors that are specifically expressed or over-expressed on the target cells (86). The delivery of pharmaceuticals, genes, and theranostics to the desired site while avoiding normal tissues requires active targeting. The use of this method enhances the efficacy of therapy, diminishes adverse effects, and notably augments the amount of medication transported to the intended location in comparison to unbound drug or passive targeting mechanisms (88). The process of attaching ligand-functionalised nanoparticles to the over-expressed receptors on cancer cells facilitates cell-specific identification and binding (87). The use of this particular approach is expected to boost the nanoparticles' affinities towards the cancer cell surface, resulting in improved drug penetration (88).

While nanoparticles hold great promise for drug delivery, it is important to acknowledge and address several challenges and potential issues associated with their use. First, the heterogeneity of nanoparticle formulation. Nanoparticle formulations often exhibit variations in size, shape, and surface charge. This heterogeneity can affect their behaviour *in vivo* and may lead to inconsistent therapeutic outcomes (90). The lack of uniformity can impact drug release kinetics, biodistribution, and cellular uptake, making it challenging to predict and control the nanoparticle's behaviour (90). Second, the stability of nanoparticles in a biological environment. Nanoparticles may change their physicochemical properties in biological fluids, such as aggregation, degradation, or changes in surface chemistry (91). These alterations can impact the ability of nanoparticles to reach the target site, affecting drug release and therapeutic efficacy. Stability concerns may also lead to premature drug release or inadequate release at the target site (64). Third, the biocompatibility and toxicity of nanoparticles. The potential for unexpected toxicity arises from factors like nanoparticle composition, size, and surface modifications (92). Toxicity can result in adverse reactions, inflammation, or damage to organs and tissues. The immune system may recognise nanoparticles as foreign bodies, triggering an immune response that can compromise the therapeutic benefits (93).

While the use of nanoparticles for drug delivery holds immense potential, it is crucial to confront and overcome the challenges associated with their application. Overcoming these challenges will not only advance the field of nanomedicine but also pave the way for safer and more effective drug delivery strategies, ultimately benefiting patients and improving healthcare outcomes. Most importantly, it is crucial to develop a nanoparticle drug delivery system that possesses an exceptional capacity to bind to the cancer cells being targeted and to minimise or prevent any harm caused by the drugs to the nearby healthy cells.

Significance of nanoparticles for targeted drug delivery

Traditional cancer therapies, including surgical intervention, radiation therapy, and chemotherapy, possess the capacity to inflict damage upon normal tissues while achieving only partial eradication of the tumour. Nanotechnology has the potential to enhance chemotherapy treatment via

its ability to selectively and directly target malignant cells and neoplasms, facilitate the surgical removal of tumours, and improve the therapeutic efficacy of radiation-based and other established treatment modalities (94). The use of nanotechnology in conventional cancer treatment has historically been applied to enhance the pharmacokinetics and mitigate the systemic toxicity of chemotherapies. This is achieved by the selective targeting and delivery of anticancer medicines to tumour tissues (94). Numerous studies have been conducted on nanoparticles as carriers for the targeted delivery of nutraceuticals into the colon (95–97). As previously mentioned, a range of nanoparticles may be engineered with tailored properties to fulfil certain applications. Gold nanoparticles have been discovered to provide advantages such as precise medication administration, focused heating, and radiation amplification (98).

The advantages of colon-targeted nanoparticle delivery systems for colon-specific diseases stem from the fact that nanoparticles can accumulate in diseased areas, boosting therapeutic efficacies and allowing for localised treatments, which in turn reduces systemic toxicity (99). Furthermore, the utilisation of nanoparticles for targeted delivery has the potential to enhance the overall therapeutic index of the administered medication. This approach can augment the permeability and retention effect, as well as regulate the timing and location of drug release by manipulating parameters such as ultrasound, pH, heat, or the chemistry of the material (94). Naeem et al. (99) discussed a few challenges and solutions for the colon-targeted nano-drug delivery system. Nanoparticles have demonstrated significant potential in surmounting anatomical and physiological obstacles within the gastrointestinal (GI) system. They exhibit the ability to differentiate between diseased regions and healthy tissues, selectively target specific cells, and deliver therapeutic drugs in a controlled manner upon request (99). In conclusion, the utilisation of nanoparticles for targeted drug delivery offers several advantages. These include a substantial drug-loading capacity, which mitigates the potential for chemical interactions or toxicity. Additionally, nanoparticles possess a high surface area-to-volume ratio, facilitating the administration of drugs through parenteral routes. Furthermore, nanoparticles enable the implementation of both active and passive drug-targeting strategies. Lastly, nanoparticles provide sustained and continuous dosing options (100).

Conclusion

In moving forward with the application of nanoparticles for tea polyphenol delivery, it is essential to acknowledge and address the potential challenges and limitations inherent in this approach. Despite the advantages discussed earlier, certain issues may arise, such as the potential of nanoparticle aggregation, alterations in physicochemical properties, or unexpected toxicity associated with the nanoparticles themselves. Moreover, the complex interplay between the nanoparticles and biological environments may pose challenges, influencing the stability of the nanoformulations and affecting their overall performance. Additionally, questions regarding the long-term safety and potential systemic effects of sustained nanoparticle exposure warrant careful consideration. The potential for unintended immune responses or off-target effects should be thoroughly explored to ensure the safety and efficacy of tea polyphenol-loaded nanoparticles. Furthermore, challenges in scaling up production processes and ensuring the reproducibility of nanoparticle formulations may impact their practical application. Addressing these challenges will be crucial for the successful translation of tea polyphenol nanoparticles from promising preclinical studies to clinically viable therapeutic options. In conclusion, while the nanoformulation of tea polyphenols offers exciting possibilities, researchers must remain vigilant in addressing and mitigating potential challenges. This proactive approach will contribute to the development of safe, effective, and scalable nanoparticle delivery systems for tea polyphenols, paving the way for their successful integration into clinical practice.

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Competing interests

The authors declare that they have no competing interests.

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