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Review Article

# Recent Updates on Unravelling the Therapeutic Potential of Ginger Bioactive Compounds in Cancer Management

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**ABSTRACT**

This review provides an extensive summary of the most current expansions on the therapeutic potential of ginger bioactive compounds in the context of cancer management. We delve into the individual components of ginger and their distinct anti-cancer properties, highlighting their diverse mechanisms of action, including the modulation of signalling pathways and cellular processes. Additionally, we explore the synergistic effects that ginger bioactive compounds exhibit when combined with conventional cancer treatments. Despite their promising potential, the review also addresses challenges and considerations in the practical application of these compounds in cancer therapy. This paper aims to synthesize current knowledge, offering insights into the multifaceted roles of ginger components in cancer treatment and paving the way for future research and therapeutic development. The findings underscore the promising role of ginger bioactive compounds as potential chemotherapeutic agents against cancer, offering insights into novel avenues for cancer treatment and therapeutic development.

**Keywords:** Anticancer property, Gingerol, Signaling pathways, Cellular processes, Angiogenesis, Apoptosis, Chemotherapy.

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## INTRODUCTION

Cancer is a complicated collection of disorders defined by uncontrolled cell growth and proliferation that constitute a considerable worldwide health risk. With numerous types and subtypes, cancer manifests in various organs, each presenting unique challenges in diagnosis and treatment. Conventional cancer treatments, such as chemotherapy and radiation, often come with side effects, necessitating the exploration of alternative therapeutic approaches. Natural products have garnered attention for their potential role as therapeutic agents in cancer treatment.[1-3] Derived from plants, microbes and marine organisms, these natural compounds exhibit diverse bioactive properties. Many studies highlight their anti-cancer effects, including the capability to make apoptosis (programmed cell death), prevent cell proliferation and interfere with tumor angiogenesis and metastasis.[4] Prominent examples include compounds from plants like curcumin (found in turmeric), resveratrol (found in grapes) and epigallocatechin gallate (found in green tea). These natural products often act through multiple signaling pathways, offering a holistic approach to cancer treatment.[5] Their potential to enhance the efficacy of conventional treatments while mitigating side effects has sparked interest in their integration into cancer therapeutic strategies.

Ginger (*Zingiber officinale*) is a flowering plant renowned for both its culinary and medicinal uses. Originating from Southeast Asia, it has a rich history of being employed in various traditional medicinal practices.[6] The underground rhizome of the ginger plant is the part commonly used for its aromatic and flavorful properties, as well as its potential health benefits. Ginger has a centuries-old history of medicinal use in ancient civilizations such as China and India. Ginger displays a range of effects, including antioxidant, anti-inflammatory, antiemetic, anticancer and antimutagenic belongings. Ginger has a significant presence in old-style chinese medicine, where it is considered to have warming properties that can dispel cold and dampness.[7] It has been historically used to address a variety of ailments, including gastrointestinal issues and joint pain. It was highly valued for its digestive properties and as a remedy for nausea. In Ayurveda, the traditional system of medicine in India, ginger is considered a warming herb with properties believed to balance bodily functions. It has been used to address digestive disorders,[8] arthritis,[9] respiratory conditions[10] and inflammatory diseases.[11] Throughout history, ginger has maintained its status as a versatile and valued herb, appreciated not only for its distinguishing taste but also for its potential health-benefiting properties. In contemporary times, scientific research has provided insights into

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the bioactive compounds within ginger, supporting its continued use in both traditional and modern medicinal contexts.

Ginger contains a diverse assortment of bioactive compounds that contribute to its therapeutic properties specifically in cancer research and treatment (Table 1).[12] Several studies have shown that ginger extract acts as potent anti-cancer agent against various types of cancer (Figure 1).[13-16] Three prominent components found in ginger, each with distinct biological activities, are gingerol, paradol and shogaol.[17,18] Gingerol is the primary bioactive compound accountable for the pungent and spicy flavor of fresh ginger.[19] As the major phenolic compound, it possesses potent antioxidant and anti-inflammatory properties. Research indicates that gingerol exhibits various health benefits, including anti-cancer, anti-diabetic and cardiovascular protective effects.[20] Gingerol, intricately related to capsaicin from chili peppers and piperine found in black pepper, exhibits robust natural antioxidant properties, positioning it as a potent agent in the prevention and treatment of numerous ailments. Its potential by way of a therapeutic intervention for hyperglycemia and associated morbidities, including cardiomyopathy, nephropathy, retinopathy, cataract, bone and joint disorders and periodontitis, is noteworthy. This efficacy is attributed to its modulation of inflammation, oxidative stress and metabolic irregularities. Additionally, gingerol has demonstrated the inhibition of oral bacteria associated with chronic peritonitis, showcasing its multifaceted impact on health. Paradol is another bioactive compound found in ginger, particularly in its dried and processed form. It is formed by the dehydration of gingerol during the drying or cooking process. Paradol was investigated for its anti-inflammatory, anti-cancer and anti-oxidative effects.[21] Shogaol is a dehydrated form of gingerol and is generated when ginger is cooked. It is known for its potent antioxidant and anti-inflammatory effects.[22]

The purpose of this study is to thoroughly investigate and explain the role of ginger components in cancer research and treatment. With ginger being a reservoir of bioactive compounds such as gingerol, paradol and shogaol, each possessing distinctive medicinal properties, this research aims to unravel the underlying mechanisms through which these components exert their effects on cancer cells. Through a systematic investigation, we seek to understand the potential of ginger components in inhibiting cancer cell proliferation, modulating signalling pathways and

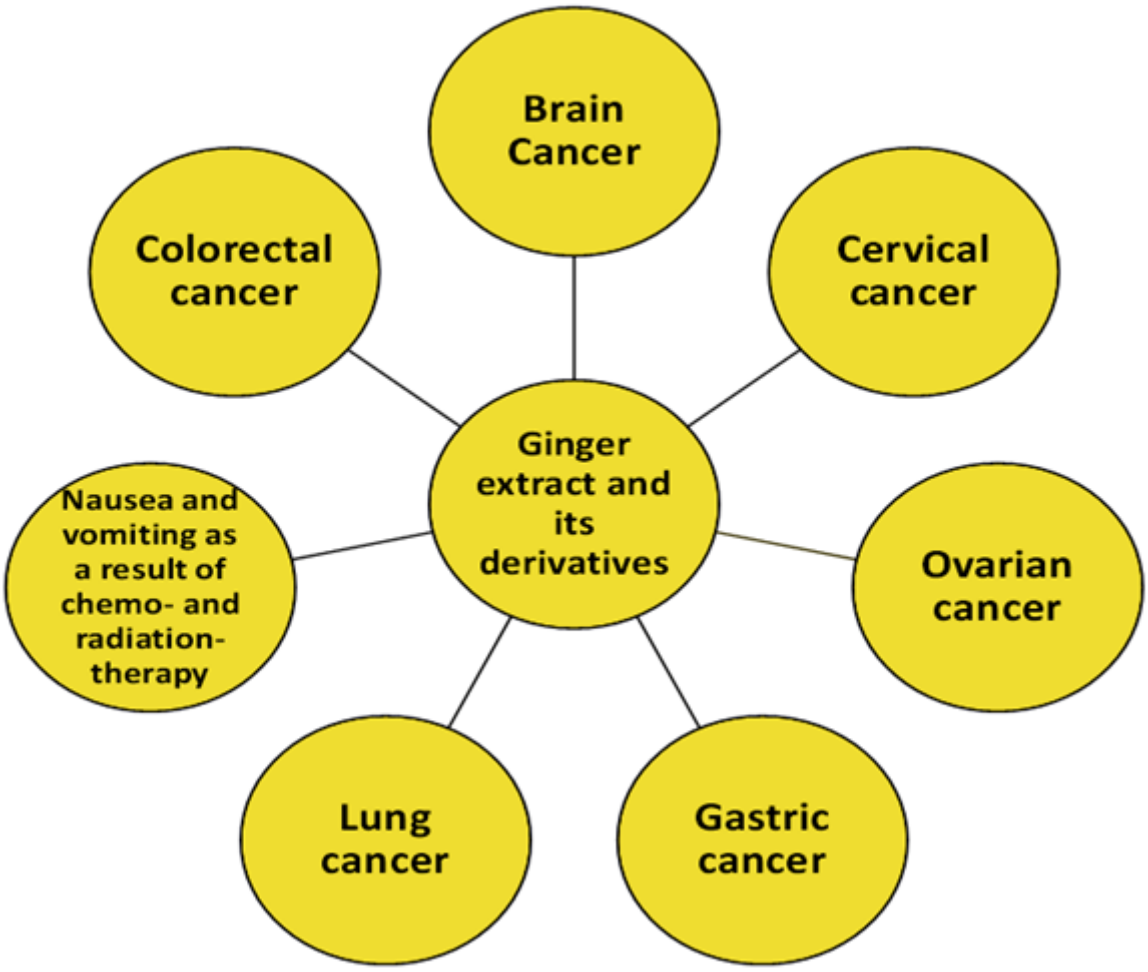
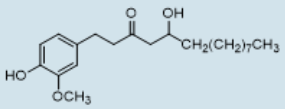
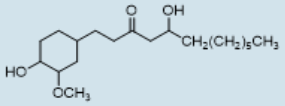
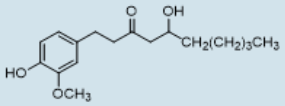
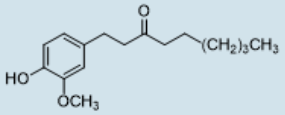
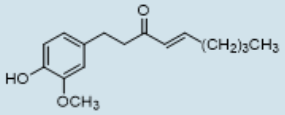
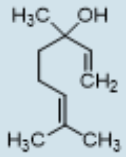
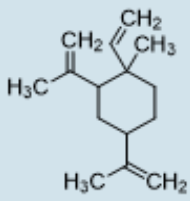
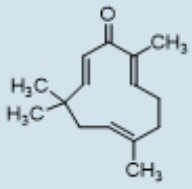
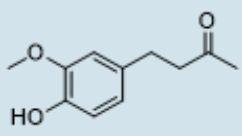



**Figure 1:** Ginger's therapeutic action against various types of cancer and anticancer therapy.

**Table 1: Ginger constituents and their mechanism of anticancer activity.**

| Sl. No. | Ginger constituent | Structure | Mechanism of action | References |
|---|---|---|---|---|
| 1 | Gingerol |  10-gingerol  8-gingerol  6-gingerol | Cell cycle arrest, apoptosis induction, angiogenesis inhibition, induction of growth suppression, signaling pathway modulation. | 23 |
| 2 | Paradol |  | PINK1/ Parkin-associated mitophagy, mediating cell apoptosis. | 24, 25 |
| 3 | Shogaol |  | Cell cycle arrest, apoptosis induction, decrease volume and burden of tumor, restore wild type p53 function, autophagy induction. | 26 |
| 4 | Linalool |  | G0/G1 cell cycle arrest, induction of apoptosis. | 27, 28 |
| 5 | Beta-elemene |  | Induction of apoptosis, autophagy. | 29, 30 |
| 6 | Zerumbone |  | Reduce cell proliferation, apoptosis induction. | 31 |
| 7 | Zingerone |  | Inhibition of transition, migration and invasion. | 32 |

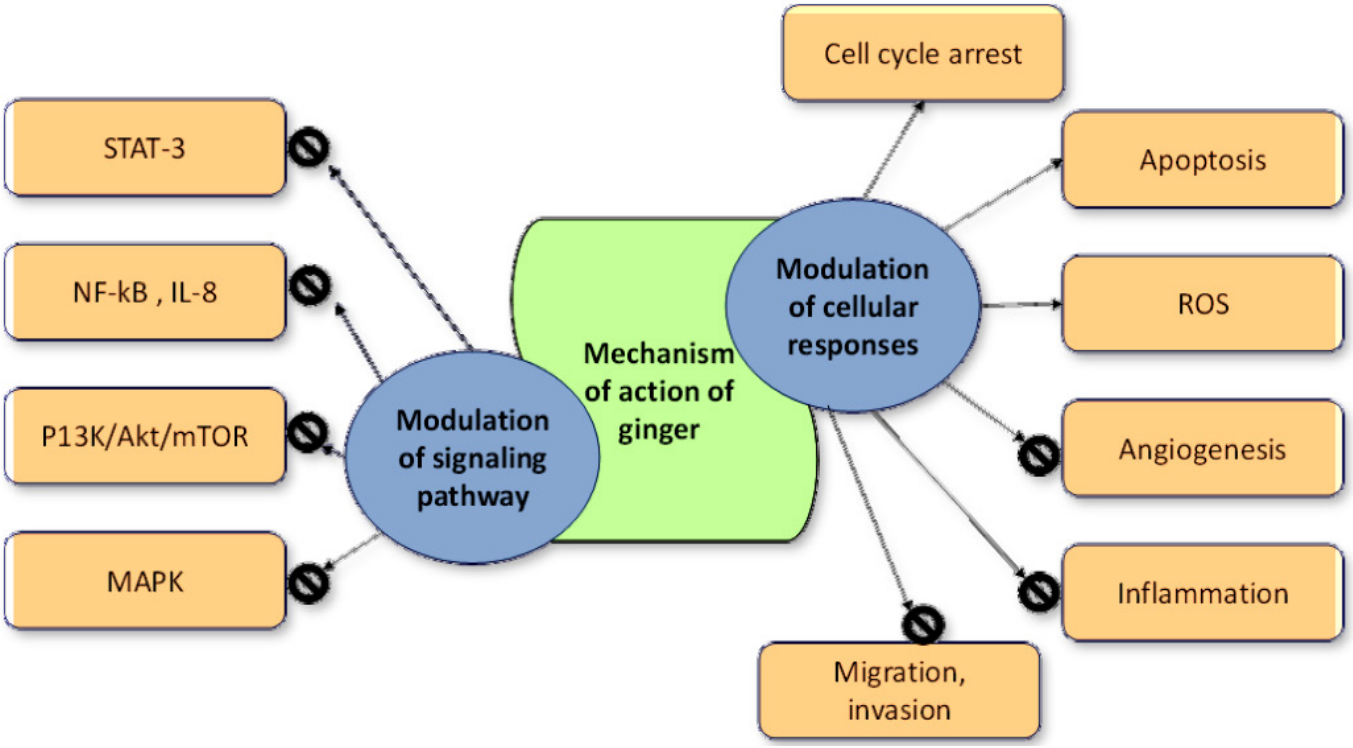



**Figure 2:** Simplified diagram of mechanism of actions of ginger in anticancer management.

influencing key factors involved in tumorigenesis. By delving into the intricate interplay of these bioactive compounds, we aspire to uncover novel insights that may pave the way for innovative therapeutic strategies in cancer treatment. This study is motivated by the prospect of harnessing the inherent properties of ginger components to contribute significantly to the ongoing advancements in cancer research, ultimately translating these findings into effective and targeted treatment modalities for the benefit of cancer patients.

## Bioavailability and drug delivery of ginger

Natural drugs often encounter challenges due to their inadequate physicochemical properties, leading to suboptimal pharmacokinetics and reduced bioavailability in the human body, thus compromising their therapeutic efficacy.[33] Implementing innovative drug delivery systems emerges as a crucial strategy to address the bioavailability issues associated with plant-derived molecules. Self-microemulsion formulations are recognized for enhancing oral bioavailability and serving as effective carriers for hydrophobic drugs. SMEDDS is an isotropic mix of drugs, oil phase and surfactants. It spontaneously emulsifies in the stomach and upper intestine, thus forming stable particles ranging from 1-100 nm. The lesser particle size increases the interface area, facilitating improved drug release and absorption. SMF offers advantages such as increased bioavailability, drug loading efficiency, dispersion rate, stability and ease of preparation. Notably, its unique ability to stimulate lipoprotein and chylomicron production, promote lymphatic transport and bypass the hepatic portal vein's first-pass effect contributes to enhanced drug bioavailability. Additionally, SMF can inhibit intestinal efflux, promoting drug absorption, especially when undergoing lipolysis during digestion. A team of researchers formulated zingerone self-microemulsion drug delivery system (Z-SMEDDS), conducted *in vitro* release studies and investigated pharmacokinetics.[34] All assessments, including TEM, particle size, zeta potential and encapsulation rate of Z-SMEDDS, indicated satisfactory results. The *in vitro* release profile demonstrated a significant improvement in zingerone release and *in vivo* studies revealed substantial enhancement in the oral bioavailability of Z-SMEDDS. Additionally, Z-SMEDDS displayed notable anti-tumor effects. Similarly, a study investigated the krill oil-based Self-Emulsifying Drug Delivery System (SEDDS) to enhance the neutraceutical properties of Ginger Extract (GE).[35] The results demonstrated that GE/KO inhibited the degradation of active ingredients in GE, which could be attributable to KO's antioxidant components. Following oral administration of GE samples in rats, the relative bio availabilities of GE's active components (6-gingerol and 8-gingerol) were roughly 8 times higher in the GE/KO-treated group than in the GE-treated group. Recurrent oral intake of GE/KO (100 mg-GE/kg/day) for four days demonstrated a protective effect on the kidneys in a rat model of acute kidney injury induced by cisplatin, an anticancer drug. For effective and targeted drug delivery, liposome has been used a one of the significant biocarriers. In one study, 6-shogaol and TPGS-coated 6-shogaol liposomes were efficiently created to boost the oral bioavailability of the 6-shogaol.[36] TPGS is

D-a-tocopheryl polyethylene-glycol succinate (a soluble derivative of vitamin-E), widely used to enhance the half-life of the drug in plasma and improve its uptake in cells.[37] The cumulative release rate of TPGS-coated 6-shogaol liposomes exhibited a substantial improvement compared to pure 6-shogaol. These liposomes exhibited an extended duration in the bloodstream and markedly increased oral bioavailability after drug intake.

## Ginger components and their anti-cancer properties

Scientific research has provided compelling evidence regarding the pivotal role of ginger and it has active components in impeding the proliferation of cancer cells.[38] Numerous studies have consistently demonstrated the potent anti-cancer properties of ginger, highlighting its ability to hinder the uncontrolled growth and division of cancerous cells.[39-41] The mechanisms underlying this inhibitory effect are coordinated by significant mediators, influencing essential cellular processes like arresting the cell cycle, inducing cancer cell apoptosis, disrupting redox homeostasis, restraining cell proliferation and impeding cancer cell activities such as angiogenesis, migration and dissemination[42] (Figure 2). For instance, ginger extract exhibits a potent cytotoxic impact on the proliferation of breast and pancreatic cancer cells, showing dose- and time-dependent characteristics. Concurrently, it elevates the expression of p53 protein. Notably, this effect is observed without much affecting the viability of normal cells.[43] Gingerol's impact extends across different types of cancer, reinforcing its potential as a promising natural compound in the development of novel anti-cancer therapies.[44] The scientific consensus on gingerol's efficacy in curtailing cancer cell proliferation underscores its significance as a subject of ongoing exploration in the realm of cancer research and treatment. 6-gingerol not only enhances cervical cancer management through inhibiting cell proliferation and promoting cell apoptosis in the presence of Human Papillomavirus (HPV), also by reactivating p53 without blocking the HPV oncoprotein.[45] It also slows the growth of cervical cancer by inhibiting the proteasome and reactivating p53. In malignant cells, 6-gingerol generated DNA damage by creating ROS, which delayed cancer progression by reactivating p53 in response to DNA damage. While the majority of research has centered on 6-gingerol, the predominant ginger component, which exhibits promising outcomes in hyperglycemia management, further exploration through clinical trials is imperative to validate the medicinal effectiveness of gingerol.[46]

10-gingerol inhibits cervical cancer through apoptosis and altering cell morphology and also via stopping the cell cycle in $G_0$/$G_1$ stage.[47] It is also found to inhibit the proliferation of cancer cells through inhibiting the PI3K/Akt pathway. Furthermore, study has shown that 10-gingerol inhibits human and mouse mammary carcinoma cell growth. It causes Triple-Negative Breast Cancer (TNBC) cells to arrest in S phase by inducing apoptosis which is caspase- and reactive oxygen species-independent.[48]10-gingerol further exhibited ability to inhibit cell migration, adhesion and invasion and induced apoptosis compared to non-tumor cells.[49] These findings suggest that these mechanisms contribute to the antitumor and antimetastatic effects of 10-gingerol observed in both 3D culture and *in vivo* settings.

Notably, paradol's ability to modulate signaling pathways involved in inflammation and cell survival has garnered attention in the context of cancer research. Its distinct molecular structure contributes to its unique biological activities within the ginger plant. In a recent study, researchers evaluated eight ginger compounds, including 6-, 8-, 10-gingerol; 6-, 8-, 10-shogaol; and 6-, 8-paradol and discovered that 8-paradol had the most pronounced inhibitory effect on cell growth in AGS (adenocarcinoma gastric cell line) cells.[25] Using proteomic analysis, the data indicate that the activation of excessive mitophagy may be the primary component contributing to apoptosis in AGS cells following 8-paradol therapy. This suggests that targeting mitophagy may be a promising treatment strategy for 8-paradol, establishing it as a potential drug against gastric cancer.

Furthermore, safety studies showed that 8-paradol can improve liver and kidney damage caused by AGS xenografts. ADME property study reveals the pharmacokinetic features, confirmed the drugability of 8-paradol, providing a solid foundation for further clinical research. Shogaol has demonstrated promising anti-cancer properties, showing potential in inhibiting tumor growth, inducing apoptosis (programmed cell death) and suppressing inflammatory pathways. It also exhibited the antioxidant and antimicrobial activity.[50] The unique characteristics of shogaol make it a key player in the therapeutic potential of ginger. 6-shogaol hinders the advancement of cervical cancer through inducing apoptosis and halting the cell cycle at the G2/M stage via mitochondrial pathways and endoplasmic reticulum stress. Zerumbone exhibits considerable anticancer efficacy by engaging in diverse mechanisms, including inducing cell cycle arrest, promoting apoptosis, modulating multiple molecular targets and inhibiting tumor angiogenesis.[51,52] Additionally, zingerone has been also investigated and found to have anti-tumor activity. A study investigated zingerone effect on a breast cancer cell line (MCF-7) and it was shown that zingerone significantly killed these cancer cells through its free radical scavenging effect proving its antioxidant property.[53]

## Mechanisms of Action

A comprehensive examination of the molecular mechanisms underlying the anti-cancer effects of ginger components involves delving into intricate cellular processes and signaling pathways. As we seen earlier, these mechanisms often include the modulation of key signaling pathways, interference with cell cycle progression, induction of apoptosis (programmed cell death) and regulation of inflammatory responses. Ginger derivatives inhibit cancer cell proliferation and progression by causing cell cycle

arrest in either the G0/G1 or G2/M phases. This action is followed via a significant downregulation of cyclin D1 gene expression, an increase in p21 expression and inhibition of the PI3K/AKT/mTOR and STAT3 signaling pathways.[42] For instance, ginger components have been observed to inhibit the NF-κB pathway, suppress the PI3K/Akt pathway and interfere with the MAPK pathway, all of which are crucial in regulating cell survival, growth and inflammation. Additionally, ginger has been implicated in promoting apoptosis through various pathways, contributing to the prevention and treatment of cancer.

## Modulation of signaling pathway

Cellular signalling pathways play a critical role in cancer, controlling multiple processes such as cell proliferation, differentiation and survival. Cancer cells can develop resistance to standard treatments and that's why understanding signalling pathways can help in developing strategies to overcome drug resistance and improve treatment outcomes. Research has found that 6-shogaol in ginger inhibited ovarian cell growth by inhibiting STAT-3 translocation there by means of inhibiting the over expression of Proliferating Cell Nuclear Antigen (PCNA), cyclin-D1, Bcl-2 and decreased expression of Bax, caspase-9 and 3 in A2780 cancel lines.[54] NF-kB is a transcription factor elaborates in regulating immune responses, inflammation and cell survival. It is involved in cancer development and progression by modulating growth signaling and apoptosis pathways.[55] It also induces angiogenesis and aids in distant metastasis.[56] NF-κB, along with IL-8, holds significance in the process of tumorigenesis due to its capacity to regulate the expression and activities of various genes associated with cell proliferation, continuous angiogenesis and evasion of apoptosis. Numerous tumor varieties, including ovarian cancer, have been observed to exhibit elevated constitutive NF-κB action. Research has demonstrated that the application of 6-gingerol to cultured ovarian cancer cells resulted in substantial growth inhibition. This effect was achieved by suppressing NF-kB activation and reducing the secretion of VEGF and IL-8.[42,57] A recent study revealed that ginger extract produces a substantial protective effect against liver carcinogenesis and can protect the liver from cancer by synergistic multitargeted effects including antioxidants and anti-inflammatory by lowering the expression of NF-kB p65.[58] Gingerol was also found to inhibit COX-2 expression by blocking the activation of NF-kB, thus, inhibiting skin cancer in mouse model.[59] The PI3K/Akt path shows a crucial role in cell survival, growth, proliferation and autophagy of tumor cells. Gingerol downregulated the protein expression levels of p-P13K and p-AKT in a dose dependent manner.[42]

Similarly, shogaol can cause suppression of cell proliferation and migration, cell cycle arrest in G2/M phase in cancerous cells and suppression of the tumor development in cervical carcinoma via P13K/Akt/mTOR pathway.[60] In a study investigating the therapeutic potential of 8-gingerol against colorectal cancer, it was found that 8-gingerol inhibited the Epidermal Growth Factor Receptor (EGFR) signalling.[61] It inhibited cololrectal cancer cell proliferation and migration through cell cycle arrest and increased apoptosis through targeting the EGFR signal transducer and activator of and activator of transcription/extracellular signalregulated kinase pathway. Gingerol also targets lipid rafts associated P13/Akt signaling and induce apoptosis in radio-resistant TNBC cells.[62] suppressing migration, invasion and proliferation of the tumor cells. Besides the gingerol and shogaol, various peptides and polysaccharides have been derived from ginger which act as chemotherapeutic agents against cancer. For instance, a group of researchers has identified a Peptide (P2) from ginger which induced apoptosis via the modulation of p53 which is a key regulator of apoptosis.[63] The study found that treating leukemic cells with P2 increased the expression of p53 and Bcl-2-associated X protein. It also downregulated B-cell lymphoma 2, implying that P2 might be developed as an alternate medication for leukemia treatment by modulating signaling pathways. Zerumbone inhibited cell migration, invasion and metastasis in Glioblastoma Multiforme (GBM) by downregulating mRNA expression levels of IL-1β and MCP-1.[64] It applied an inhibitory outcome on the expression of Akt and total p44/42 MAPK (Erk1/Erk2) against GBM cells. These scientific findings collectively highlight the specific actions of ginger components on critical signaling pathways, providing a molecular basis for their anti-cancer effects. It's important to note that while these studies contribute to our understanding, ongoing research continues to deepen our knowledge of ginger's intricate mechanisms in cancer prevention and treatment.

## Modulation of cellular processes

Apoptosis is a programmed cell death mechanism crucial for eliminating damaged or abnormal cells. Study has found that 6-shogaol induce a dose-dependent loss of mitochondrial membrane potentials through inducing apoptosis by generating Reactive Oxygen Species (ROS).[60] It may also trigger autophagy to alleviate cellular stress. Ginger Extract (GE) has the ability to maintain redox equilibrium, either by lowering the number of ROS-induced tumor-promoting events or by increasing oxidative stress and causing cell death.[65,66] GE instigates cellular changes characterized by cytoplasmic vacuolation via the induction of Endoplasmic Reticulum (ER) stress and dilation.[67] This transformative process is accompanied by a significant decline in mitochondrial membrane potential and ATP production, coupled with the heightened generation of ROS, resulting in pronounced mitochondrial dysfunction. These intricate disruptions ultimately lead to the translocation of apoptosis-inducing factor to the nucleus, triggering the fragmentation of DNA. Thus, ginger extract orchestrates a series of interconnected molecular events, unravelling the cellular landscape and culminating in apoptotic responses. In a recent investigation, researchers focused on a purified ginger polysaccharide known as UGP1, examining its anti-tumor properties specifically on colon cancer.[68] The study

revealed that UGP1 demonstrated the ability to hinder the growth of human colon cancer through inducing apoptosis. This effect was attributed to the modulation of key factors in the apoptosis pathway, including p53, caspase-3 and the Bax/Bcl-2 ratio. Another recent study found that ginger-derived chemical displayed dose-responsive antiproliferation for TNBC cells, providing an effective anticancer medication with preferential antiproliferation, oxidative stress, apoptosis and DNA damage effects.[69] 6-shogaol also caused cytotoxicity, ROS generation and apoptosis in ovarian cancer cell lines.[54]

Angiogenesis, the intricate process of creating new blood vessels from present endothelial tissue, is governed by complex cellular activities including the degradation of extracellular matrix, proliferation, migration of endothelial cells and their morphological differentiation into tube-like structures. This tightly regulated phenomenon involves positive factors like Vascular Endothelial Growth Factor (VEGF) and negative regulators such as endostatin and thrombospondin. While neovascularization is essential in physiological processes like embryonic development, it becomes a critical factor in tumor progression and metastasis. Many cancer therapies target the vasculature associated with tumors. In this context, 6-shogaol emerges as a potential inhibitor of inflammation and angiogenesis in vascular endothelial cells.[70] In another study, 6-gingerol as found to coordinate the structural arrangement of the microvascular network, leading to a reduction in microvessel density through the p-VEGFR2/VE-cadherin/β-catenin/actin complex, ultimately impeding tumor progression.[71] Additionally, 6G facilitates the normalization of tumor vessels, enhances the tumor microenvironment and diminishes microvessel structural entropy. This normalization process aids in improving the delivery of chemotherapeutic agents to the tumor core, resulting in reduced tumor growth and metastasis.

Chronic inflammation is often linked to cancer development and ginger components, particularly gingerol, have been shown to possess anti-inflammatory properties. *In vivo*, 6-shogaol demonstrated a notable reduction in inflammatory hallmarks, including diminished leukocyte infiltration, edema formation and displayed neuroprotective belongings.[72] Concurrently, *in vitro* anti-inflammatory actions were observed, showcasing 6-shogaol's barrier-protective effects in a colonic epithelial cell line. Remarkably, irrespective of the specific inflammatory mechanism, the application of 6-shogaol across diverse cell types or in *in vivo* models consistently resulted in the effective inhibition of well-established markers and signalling pathways associated with inflammation. 6-shogaol inhibited pro-inflammatory factors and mediators, such as NFκB or COX-2, mitigated iNOS levels leading to reduce NO levels and suppressed the release of pro-inflammatory cytokines, including interferon, TNF, interleukins and chemokines. These additional cellular processes complement the previously mentioned signaling pathways, collectively portraying the multifaceted impact of ginger components on various aspects of cancer biology. While research continues to unveil the complexities of ginger's effects, these findings highlight its potential as a holistic approach in cancer prevention and treatment.

## Synergistic Effects with Conventional Cancer Treatments

Ginger constituents target multiple signalling paths to impede the growth of cancer cells, combining ginger with other chemotherapeutic agents may lead to a synergistic enhancement of their anticancer effects, surpassing the efficacy of chemotherapy alone. This synergy could potentially allow for a reduction in the recommended treatment dose, thereby minimizing associated side effects. Synergistic effects of ginger-drug interactions have been main focus as a significant anticancer strategy as it is a cost effective therapy with the advantage of less toxicity and more antitumor efficacy.[73] Usually, there are four common types of synergistic mechanisms- synergistic multi-target effects, pharmacokinetic or physicochemical effect modulation, interference with resistance mechanisms and elimination or neutralization potential.[74,75] Studies have showed that ginger compounds exhibit chemoprotective effects when administered alongside conventional chemotherapeutic agents. One such study demonstrated that combined treatment of ginger with MTX (methotrexate, a chemotherapy agent) increased the cytotoxic effect of MTX to the malignant cancer cells of pediatric acute lymphoblastic leukemia by 1.54 folds while having a negligible cytotoxic activity to the normal mononuclear cells.[76] Another study revealed that mixture of ginger extract and licorice extract was able to suppress cancer cell growth, increase apoptosis and improve colorectal cancer infiltrating to the tumor site In a synergistic manner *in vivo* and *in vitro*.[77] Cisplatin, a widely employed chemotherapeutic agent for various cancers, presents challenges due to its adverse effects on the kidneys and other organs.[78] Consequently, combining ginger with cisplatin has garnered attention as a potential therapeutic strategy. One investigation revealed that testicular changes induced by cisplatin were significantly alleviated by fresh ginger juice.[79] This effect was attributed to the attenuation of oxidative stress and the activation of an anti-inflammatory mechanism. These findings provide substantiation for the antioxidant and anti-inflammatory properties of ginger juice in mitigating cisplatin-induced testicular damage. Combination of 6-gingerol and cisplatin has shown to increase the levels of ROS production in cervical cancer cells.[80] This combination therapy also damaged the DNA stopping the cell cycle in most cells at the G2/M stage, thus suppressing the uncontrolled cell cycle progression which is a hallmark of cancer. One study revealed that zingerone, a ginger derivative, conferred safeguarding of the jejunum of Wistar rats from oxidative damage induced by cisplatin.[8] Moreover, the co-administration of ginger and sodium salicylate nanoemulsion demonstrated

a hepatoprotective effect, ameliorating cisplatin-induced hepatotoxicity in an animal model.[82] Further research has shown that 10-gingerol can be used in combined therapy with anticancer drug doxorubicin to improve its anticancer activity minimizing its toxicity against TNBC cells.[83] A recent study has revealed that treatment with Ginger and Luteolin significantly improved liver enzymes and histopathological examination. Furthermore, the combined therapy demonstrated enhanced antiproliferative activity against ehrlich ascites carcinoma bearing mice compared to individual treatments.[84] The combined effect involved apoptosis initiation through the regulation of Caspase-3 and Bcl-2, as well as inhibition of proliferation and cell cycle arrest via Ki-67 inhibition.

The synergistic effects of ginger components with conventional cancer therapies have garnered substantial scientific attention, as evidenced by a growing body of research.[85] The dual benefit arises from ginger's potential to prevent and treat cancer development by addressing oxidative stress and inflammation-two significant contributors to tumor initiation and promotion-while concurrently mitigating common chemotherapy side effects like vomiting and diarrhea, which often lead to treatment discontinuation.[73,86-88] One such study evaluated the effects of ginger on Chemotherapy-Induced Nausea and Vomiting (CINV) in patients with cervical cancer undergoing treatment with cisplatin and radiotherapy.[89] The results demonstrated that ginger helped minimize chemotherapy-induced nausea and vomiting. Similarly, in a quasi-experimental research design with two groups (control and intervention groups, each with 50 participants), results suggested that ginger tea reduce the experience, development and distress of nausea, vomiting and retching in patients with gynecological cancers receiving cisplatin-based regimens.[90] Recently, a similar study explored the effect of standardized ginger root powder regimen, indicating that ginger supplementation was a safe adjuvant to antiemetics for CINV.[91] Lemon and ginger, both known for their bioactive compounds and potential health benefits, may offer a multifaceted approach to cancer treatment. The unique combination could bring together diverse phytochemicals with antioxidant, anti-inflammatory and anticancer properties.[92] Further investigations into the molecular mechanisms, bioavailability and potential synergies of lemon and ginger compounds could pave the way for novel therapeutic interventions in the field of cancer treatment.

## Nanotechnology role in ginger-mediated anticancer research

Nanotechnology plays a crucial role in the creation of nanoformulations using phytochemicals, employing strategies like nano-liposomes, functionalized Nanoparticles (NPs), polymer nano-conjugates and Self Nano Emulsifying Drug Delivery System (SNEDDS).[93,94] These innovative approaches present solutions to diverse challenges associated with cancer treatment. Nanoparticle formulations of ginger compounds can address issues related to poor solubility and bioavailability.[38] Nanotechnology enables the creation of drug delivery systems that enhance the absorption of ginger's bioactive compounds, ensuring they reach the bloodstream in a more effective manner. For instance, one study assessed the acute toxicity of zerumbone and zerumbone-loaded nanocarriers in BALB/c mice over 14 days through oral administration.[95] Evaluation included clinical, behavioral and toxicological parameters, revealing normal findings in treated mice and various tissues. Zerumbone and its nanocarrier formulation at 100 and 200 mg/kg exhibited no signs of toxicity or mortality, indicating their potential safety for oral administration in BALB/c mice. In one investigation, to improve the water solubility and the oral bioavailability of 6-gingerol, 6-gingerol loaded nanostructured lipid carriers were synthesized.[96] In another study, ginger extract was loaded into chitosan nanoparticles which enhanced the cytotoxicity and reduced cardiotoxicity of doxorubicin in hepatocellular carcinoma in mice model.[97]

Functionalized nanoparticles meticulously engineered with specific ligands or functional groups, showcase a remarkable ability to selectively target cancer cells.[98] This targeted approach stems from the tailored surface modifications that enable precise interactions with overexpressed receptors or unique features present on the cancer cell membrane. Numerous studies have demonstrated the efficacy of functionalized nanoparticles in delivering therapeutic payloads directly to cancerous tissues while sparing healthy cells.[99,100] The surface functionalization not only enhances the nanoparticles' affinity for cancer cells but also enables controlled drug release, optimizing treatment outcomes. This targeted drug delivery minimizes exposure to healthy tissues, reducing side effects and improving the therapeutic index of ginger compounds.[101] For example, Mesoporous Silica Nanoparticles (MSNPs) offer a possible solution for improved cancer treatment through enhanced drug delivery. With beneficial belongings such as high perviousness, a large surface area and versatile pore sizes, MSNPs have demonstrated promise in preclinical studies, particularly when loaded through chemotherapeutic agents like paclitaxel, doxorubicin and docetaxel. These drugs can be either surface-loaded or encapsulated within MSNP pores, allowing for controlled release profiles that accommodate diverse drug properties. To enhance specificity towards cancer cells, targeting ligands such as folic acid, HER2/neu antibodies and aptamers can be attached to MSNPs.[102] This targeted approach has proven effective in improving drug uptake and release, resulting in enhanced anticancer activity. Furthermore, MSNP-based drug delivery has demonstrated improvements in pharmacodynamic and pharmacokinetic properties, ultimately leading to better therapeutic results.

Existing literature suggests that lipid-derived nanoparticles carrying chemical drugs offer notable advantages in cancer therapy. Specifically, delivering doxorubicin through ginger

lipid-derived NPs demonstrated higher efficiency compared to free doxorubicin.[103] Further, natural lipid nanoparticles are viewed as excellent carriers for siRNA delivery. Incorporating CD98-siRNA into lipid nanoparticles allows specific targeting to gut tissues through oral administration, resulting in reduced CD98 expression and exhibiting potential for immunoregulation.[104]

Controlled release nanosystems can prolong the presence of ginger compounds in the body, offering sustained therapeutic effects. This can lead to a more convenient dosing schedule and improved patient compliance. PEGylated nanoniosomes loaded with 6-gingerol have demonstrated increased stability and a slower release of the compound.[105] Additionally, these PEGylated nanoniosomes exhibit stability during storage and possess a notable capacity for drug loading. Nanoparticles can overcome biological barriers such as the blood-brain barrier, facilitating the treatment of cancers in challenging anatomical locations.[106] This expands the potential applications of ginger compounds in treating various types of cancer. Several studies has shown the ginger-based nanoparticles' potential to overcome the blood brain barrier facilitating the treatment and control of glioblastoma multiforme.[107,108]

In nutshell, the integration of nanotechnology with ginger bioactive compounds represents a multifaceted approach to cancer therapy. It not only addresses existing limitations but also opens avenues for innovative and personalized cancer treatments with the potential to significantly improve patient outcomes.

### Challenges and Future Directions

In the world of cancer research, we're facing some tough hurdles that make finding better treatments a real challenge. Multidrug resistance, in which some cancer cells become resistant to the drugs, is a major challenge. Tumors also vary a lot, making each one unique and tricky to treat. The way cancer spreads, called metastasis, is another tough problem. Current treatments can have pretty serious side effects, making it tough for patients. Detecting cancer early is also a puzzle we're trying to solve. Sometimes, the body's defenses get weakened by cancer, making it even harder to fight. Financial constraints related to the high costs of advanced treatments further exacerbate the issue. Moreover, certain cancers lack viable treatment options, necessitating continual research endeavors. Addressing these challenges demands interdisciplinary collaboration, innovative methodologies and an in-depth comprehension of the multifaceted nature of cancer biology. Consideration of factors such as bioavailability, dosage and standardization are the other challenges in translating ginger research into clinical practice.

Toxicity related to nanoparticles poses a significant threat to the long-term treatment. The use of biodegradable nanomaterials ensures that the nanoparticles are metabolized and eliminated from the body without leaving toxic residues. This is crucial for long-term safety and minimizes concerns about potential adverse effects. While nanotechnology offers exciting possibilities, addressing challenges related to clinical translation is crucial. Factors such as scalability, reproducibility, cost-effectiveness and regulatory approval need careful consideration to move ginger-based nanotherapies from the laboratory to clinical practice.

Additional analysis into the detailed molecular mechanisms underlying the anti-cancer effects of specific ginger compounds is required to elucidate their interactions with key signaling pathways and cellular processes. Exploration of specific biomarkers associated with ginger's anti-cancer effects is necessary for the development of personalized treatment strategies. Furthermore, role of gut microbiota in mediating the effects of ginger on cancer can be examined to explore how the interplay between ginger compounds and the microbiome influences anti-cancer responses and treatment outcomes. Comprehensive studies need to be conducted to assess the long-term safety profile of ginger compounds, including potential adverse effects, to establish a thorough understanding of their safety in extended treatment scenarios. Further research can focus on optimizing the formulations of ginger-derived products, considering factors such as bioavailability, dosage forms and delivery methods to enhance their therapeutic potential and clinical applicability.

## CONCLUSION

In conclusion, the therapeutic potential of ginger bioactive compounds in cancer management represents a promising avenue for exploration and advancement in oncology. A mass of evidence has also shown that ginger has anti-tumor effects on digestive tract cancers through a variety of pathways. Our review has provided a comprehensive insight into the individual components of ginger and their unique anti-cancer properties, emphasizing their diverse mechanisms of action, including the modulation of signaling pathways and cellular processes. The synergistic effects observed when combining ginger bioactive compounds with conventional cancer treatments further underscore their potential as adjunct therapies. However, the translation of these promising findings into clinical applications faces challenges and requires careful consideration. Despite these challenges, the accumulating evidence supports the notion that ginger bioactive compounds hold considerable promise in contributing to the evolving landscape of cancer therapeutics. Future research efforts should focus on addressing challenges, refining methodologies and elucidating the intricate interactions between ginger components and cancer pathways, ultimately paving the way for enhanced cancer treatment strategies.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**SEDDS:** Self-Emulsifying Drug Delivery System; **GE:** Ginger Extract; **TNBC:** Triple-Negative Breast Cancer; **VEGF:** Vascular Endothelial Growth Factor; **CINV:** Chemotherapy-Induced Nausea and Vomiting; **GBM:** Glioblastoma Multiforme.

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