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RECENT UPDATE OF ZERUMBONE AS ANTI-COLON CANCER AGENT: A REVIEW

Pembaruan Terbaru Zerumbone sebagai Agen Anti-kanker Usus Besar: Sebuah Tinjauan

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ABSTRACT

Colorectal cancer (CRC) remains a leading cause of cancer-related deaths worldwide, with limited effective therapies due to drug resistance and adverse effects. Zerumbone, a sesquiterpene isolated from Zingiber zerumbet Smith, has emerged as a promising natural anticancer agent. This review examines zerumbone's anti-colorectal cancer properties, including induction of apoptosis and cell cycle arrest, inhibition of invasion and metastasis, anti-angiogenic activity, and anti-inflammatory effects. Additionally, zerumbone demonstrates antioxidant properties, modulates gut microbiota composition, and targets multiple signaling pathways involved in CRC pathogenesis. Structure-activity relationship studies reveal the critical role of the α,β-unsaturated carbonyl group in its bioactivity. Despite promising preclinical evidence, clinical validation remains necessary to establish zerumbone's therapeutic potential for colorectal cancer management.

Keywords: *Apoptosis, Chemoresistance, Colon cancer, Inflammation, Zerumbone*

ABSTRAK

Kanker kolorektal (CRC) tetap menjadi salah satu penyebab utama kematian terkait kanker di seluruh dunia, dengan terapi yang masih terbatas efektivitasnya akibat resistensi obat dan efek samping. Zerumbone, sebuah seskuiterpena yang diisolasi dari Zingiber zerumbet Smith, telah muncul sebagai agen antikanker alami yang menjanjikan. Ulasan ini membahas sifat antikanker kolorektal dari zerumbone, termasuk induksi apoptosis dan penghentian siklus sel, penghambatan invasi dan metastasis, aktivitas antiangiogenik, serta efek antiinflamasi. Selain itu, zerumbone menunjukkan sifat antioksidan, memodulasi komposisi mikrobiota usus, dan menargetkan berbagai jalur pensinyalan yang terlibat dalam patogenesis CRC. Studi hubungan struktur–aktivitas mengungkap peran penting gugus karbonil α,β-takjenuh dalam bioaktivitasnya. Terlepas dari bukti praklinis yang menjanjikan, validasi klinis tetap diperlukan untuk memastikan potensi terapeutik zerumbone dalam penatalaksanaan kanker kolorektal.

Kata Kunci: *Apoptosis, Resistensi kemoterapi, Kanker usus besar, Peradangan, Zerumbone*

INTRODUCTION

Colorectal cancer (CRC) represents a major public health challenge, ranking among the leading causes of cancer-related deaths worldwide. In Indonesia, CRC ranks fifth in mortality with 19,255 deaths and fourth in incidence with 35,677 new cases

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diagnosed annually (GCO, 2022). These statistics position CRC as a significant health concern requiring innovative therapeutic approaches.

CRC develops through a complex, multistep process characterized by genetic alterations, inflammatory processes, and environmental factors. The progression from normal epithelium to adenoma and ultimately to carcinoma typically spans approximately ten years, offering a critical window for intervention through screening, lifestyle modifications, or chemo preventive agents (Li et al., 2021; Malki et al., 2020). Recent research has highlighted the crucial role of the gut microbiome in CRC pathogenesis, with certain bacterial and fungal species contributing to oncogenic transformations through chronic inflammation and genotoxic effects (Dohlman et al., 2022; Okuda et al., 2021).

Current treatment options for CRC include surgery, radiotherapy, and chemotherapy, with 5-Fluorouracil (5-FU) as a commonly used chemotherapeutic agent. However, a major challenge involves the development of drug resistance, particularly when mismatch repair genes are disrupted, enabling tumor cells to evade treatment effects and leading to therapeutic failure (Bukowski et al., 2020; Sethy & Kundu, 2021). This underscores the urgent need for novel therapeutic agents capable of overcoming resistance mechanisms while offering improved safety profiles.

Natural compounds from traditional medicine offer promising alternatives for cancer therapy. The Zingiberaceae family has attracted particular attention due to its rich array of bioactive compounds with demonstrated anticancer properties (Al-Zubairi, 2018). Among these, zerumbone—a sesquiterpene isolated from the rhizome of *Zingiber zerumbet* Smith—has emerged as a compound of exceptional interest. The rhizome of *Z. zerumbet*, commonly known as "lempuyang" throughout Southeast Asian countries, has been traditionally used as an herbal remedy for generations (Girisa et al., 2019).

This review comprehensively analyzes the anti-inflammatory and anti-colorectal cancer properties of zerumbone, discussing its natural origin, chemical structure, molecular mechanisms of action, effects on the gut microbiome, and preclinical evidence supporting its therapeutic potential. By consolidating current knowledge on zerumbone's therapeutic properties, we aim to provide insights that will guide further research and potentially facilitate clinical applications in colorectal cancer management.

COLORECTAL CANCER: PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

Genetic and Molecular Basis of Colorectal Cancer

Colorectal cancer typically originates from polyps that progressively transform into malignant tumors through the adenoma-carcinoma sequence, characterized by stepwise accumulation of genetic and epigenetic alterations. The earliest mutation often occurs in the *APC* gene, resulting in benign adenomas. Within approximately ten years, about 15% of adenomas progress to carcinomas through acquisition of additional mutations (Mármol et al., 2017).

The genetic landscape involves activation of proto-oncogenes such as *KRAS* (occurring in ~40% of CRCs) and inactivation of tumor suppressor genes including *TP53*, *DCC*, and mismatch repair genes (*hMSH2*, *hMLH1*). *TP53* mutations are particularly significant, occurring in approximately 60% of CRC cases. Loss of p53 function disrupts cell cycle control, DNA repair, and apoptosis, leading to enhanced tumor growth (Michel et al., 2021).

Beyond genetic mutations, epigenetic alterations including DNA methylation and histone modifications contribute substantially to CRC development. These modifications can silence tumor suppressor genes without altering DNA sequence, affecting genes involved in DNA repair, cell cycle regulation, and other tumor suppressive functions (Tomicic et al., 2021). Current evidence supports an integrated perspective recognizing that CRC develops through sustained proliferative signalling, evasion of growth suppressors, resistance to cell death, angiogenesis induction, and activation of invasion and metastasis.

The Gut Microbiome and Colorectal Cancer Development

The human gastrointestinal tract harbours a diverse community of microorganisms that play fundamental roles in metabolism, immune function, and tissue homeostasis. In recent years, the gut microbiome has emerged as a crucial factor in colorectal carcinogenesis, with dysbiosis contributing significantly to CRC development and progression through multiple mechanisms including chronic inflammation and genotoxic effects.

Enterotoxigenic *Bacteroides fragilis* (ETBF) represents a key pro-carcinogenic bacterium that has been extensively studied in the context of CRC. ETBF secretes Bacteroides fragilis toxin (BFT), which induces cleavage of E-cadherin in colonic epithelial cells, triggering activation of the NF-κB signalling pathway that promotes inflammation and cell proliferation (Hwang et al., 2019). Studies using animal models have demonstrated that ETBF colonization can initiate and promote colorectal tumor formation, particularly in the context of chronic inflammation.

Microbial metabolites, particularly short-chain fatty acids (SCFAs) produced through bacterial fermentation of dietary fiber, play crucial roles in maintaining intestinal barrier function, regulating inflammation, and influencing oxidative stress and cellular metabolism. Butyrate, a prominent SCFA, serves as the primary energy source for colonocytes and has been shown to inhibit histone deacetylases, thereby affecting gene expression patterns in ways that may suppress tumor development (Liu et al., 2021).

The therapeutic implications of the microbiome-CRC connection are significant. Modulation of the gut microbiota through dietary interventions, probiotics, or natural compounds represents a promising approach for CRC prevention and treatment. Zerumbone has shown potential in restoring gut microbiota composition in animal models of colitis-associated colorectal cancer, as will be discussed in detail in a later section of this review.

CHEMISTRY AND PHARMACOLOGICAL PROPERTIES OF ZERUMBONE

Chemical Structure and Natural Occurence

Zerumbone is a cyclic sesquiterpene representing the predominant bioactive constituent of *Zingiber zerumbet* Smith essential oil, comprising 35.5-84.8% of content depending on geographical location, cultivation conditions, and extraction methods (Tan et al., 2018). First isolated in 1956, zerumbone ($C_{15}H_{22}O$) features an 11-membered monocyclic skeleton with three double bonds, including a critical α,β-unsaturated carbonyl group at positions C-2 and C-10.

This α,β-unsaturated carbonyl group serves as a Michael acceptor, enabling covalent interactions with nucleophilic sites in proteins, particularly cysteine residues—a mechanism underlying many of zerumbone's biological effects (Murakami et al., 2002). While *Z. zerumbet* represents the primary source, zerumbone has also been identified in other Zingiberaceae species including *Zingiber aromaticum*, *Zingiber ottensii*, and *Alpinia mutica*, albeit in lower concentrations.

Pharmacological Activities and Bioavailability

Zerumbone exhibits broad pharmacological activities including antibacterial, anti-inflammatory, and antioxidant effects. Its antibacterial action disrupts bacterial cell membranes through depolarization, showing efficacy against MRSA and *Candida albicans*, while also inhibiting biofilm formation (Albaayit et al., 2022; Shin & Eom, 2019). The anti-inflammatory effects occur through inhibition of COX-2, prostaglandins, and various interleukins, mediated through modulation of the NF-κB pathway.

However, clinical application faces challenges due to poor water solubility and low oral bioavailability. Advanced delivery systems including cyclodextrin complexes, nanosuspensions, and nanostructured lipid carriers are being developed to enhance solubility, stability, and absorption, potentially improving therapeutic potential (Ibáñez et al., 2022).

ANTICANCER MECHANISMS OF ZERUMBONE IN COLORECTAL CANCER

Induction Cell-cycle arrest

The cell cycle represents a highly regulated sequence of events through which cells grow, replicate their DNA, and divide to produce daughter cells. This process is controlled by multiple checkpoints that ensure proper completion of each phase before progression to the next stage. Cancer cells characteristically exhibit dysregulated cell cycle control, allowing them to proliferate uncontrollably. One important mechanism by which anticancer agents can inhibit tumor growth is through induction of cell cycle arrest at specific checkpoints.

Zerumbone has demonstrated significant ability to induce cell cycle arrest in colorectal cancer cells, particularly at the G2/M phase checkpoint. This checkpoint normally serves as a quality control mechanism that ensures DNA has been properly replicated and that any DNA damage has been repaired before the cell proceeds into mitosis. By halting cancer cells at this checkpoint, zerumbone prevents their progression into the mitotic phase where cell division would occur, effectively inhibiting tumor cell proliferation.

In studies examining HT-29 colorectal cancer cells, zerumbone treatment resulted in dose-dependent growth inhibition accompanied by accumulation of cells in the G2/M phase of the cell cycle. This cell cycle arrest was not merely a temporary delay but represented a sustained block that prevented cancer cells from completing their division cycle (Memari et al., 2022). Similar effects have been observed in SW480 colorectal cancer cells, where zerumbone caused accumulation of cells at the G2/M phase with percentages increasing from 17.2% at 50 μM to 26.66% at 100 μM concentration (Sithara et al., 2018).

Induction of Apoptosis Through Multiple Pathways

Apoptosis is a controlled process that can be activated through extrinsic and intrinsic pathways. The extrinsic pathway is triggered through the interaction of Fas ligand with its receptor or the TNF-/TRAIL receptor-ligand system. In contrast, the intrinsic pathway is stimulated by releasing cytochrome c from mitochondria and producing of apoptosomes. Both pathways converge in their final stages with the activation of caspases, enzymes that degrade cellular components, including the actin cytoskeleton and nuclear lamins, ultimately resulting in cell death. Additionally, endonucleolytic DNA is cleaved by caspase-activated DNase (CAD) (Obeng, 2021).

Cancer cells have developed various strategies to evade apoptosis, including mutations in the CD95/Fas gene, promoter methylation, increased the anti-apoptotic proteins expression, and decreased the pro-apoptotic proteins expression (Lopez et al., 2022). Zerumbone has been shown to overcome these resistance mechanisms by inducing apoptosis. Specifically, in the colon cancer cell line (HT-29), zerumbone exhibits antitumor effects by inhibiting cell migration with a dose-dependent manner. It also arrests the G2/M phase. The treatment also affected the upregulation expression of *Bax* (pro-apoptotic) and downregulation expression of *Bcl-2* (anti-apoptotic). Furthermore, zerumbone elevates reactive oxygen species (ROS) levels, which contribute to apoptosis (Memari et al., 2022).

Inhibition of Metastasis and Invasion

Metastasis, the spread of cancer cells from the primary tumor to distant organs, represents the most lethal aspect of cancer and accounts for approximately 90% of cancer-related deaths. For colorectal cancer specifically, metastasis most commonly occurs in the liver, followed by the lungs, peritoneum, and distant lymph nodes. The prognosis is dramatically influenced by metastasis, with five-year survival rates dropping from approximately 90% for localized disease to 14% for metastatic colorectal cancer (Li et al., 2021).

Zerumbone has demonstrated significant anti-metastatic and anti-invasive properties through multiple complementary mechanisms. A fundamental aspect involves its ability to inhibit cancer cell migration. In HT-29 colorectal cancer cells, zerumbone treatment markedly reduced cell migration as demonstrated through scratch wound healing assays. This anti-migratory effect occurred in a dose-dependent

manner, with higher concentrations producing progressively greater inhibition (Memari et al., 2022).

The ability of cancer cells to migrate and invade depends critically on their capacity to degrade the extracellular matrix (ECM). A central aspect of zerumbone's anti-metastatic mechanism involves its ability to modulate matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases that degrade various ECM components. Among these, MMP-2 and MMP-9 play particularly important roles in cancer invasion as they can degrade type IV collagen, the major structural component of basement membranes.

Zerumbone treatment significantly decreases both the expression and enzymatic activity of MMP-2 and MMP-9 in colorectal cancer cells. This reduction preserves the integrity of the extracellular matrix and basement membranes, effectively creating a structural barrier that restricts cancer cell movement (Memari et al., 2022). In SW480 cells, zerumbone effectively disrupted the microfilament network, which comprises actin filaments essential for cell shape and movement (Sithara et al., 2018).

The epithelial-mesenchymal transition (EMT) represents another critical process in cancer metastasis. EMT is a developmental program whereby epithelial cells lose their characteristic features and acquire mesenchymal properties including enhanced migratory capacity and invasiveness. The combination of zerumbone with microRNA-34a (miR-34a) produces enhanced anti-metastatic effects compared to either agent alone. This combination therapy suppresses expression of inflammatory cytokines including TGF-β, SDF-1, and MCP-1, all of which play roles in promoting EMT and creating a pro-metastatic microenvironment (Dehghan et al., 2021).

Furthermore, zerumbone inhibits the FAK/PI3K/NF-κB-uPA signaling pathway, which plays important roles in cell adhesion, migration, and invasion. By modulating this pathway, zerumbone reduces the invasive potential of colorectal cancer cells (Hosseini et al., 2019).

Anti-Angiogenic Properties

Angiogenesis, the formation of new blood vessels from existing vasculature, represents a critical process in tumor growth and metastasis. Without new blood vessel development, tumors typically cannot grow beyond 1-2 mm in diameter. The process is heavily dependent on vascular endothelial growth factor (VEGF), which binds to VEGF receptors on endothelial cells, triggering their proliferation and migration.

Zerumbone has demonstrated potent anti-angiogenic properties through multiple mechanisms. At the level of cancer cells, zerumbone significantly inhibits VEGF expression, thereby reducing the angiogenic stimulus. This inhibitory effect has been documented in various cancer types (Shamoto et al., 2014; Tsuboi et al., 2014). Beyond reducing VEGF production, zerumbone directly interferes with VEGF signaling by disrupting phosphorylation of VEGFR-2, a critical step in transmitting the angiogenic signal. By selectively inhibiting VEGFR-2 phosphorylation, zerumbone blocks pro-angiogenic signals (Park et al., 2015).

Zerumbone also inhibits phosphorylation of fibroblast growth factor receptor-1 (FGFR-1), demonstrating its capacity to target multiple angiogenic pathways. Additionally, zerumbone's inhibition of NF-κB contributes to its anti-angiogenic effects, as NF-κB regulates expression of numerous angiogenic factors (Tsuboi et al., 2014). In vivo studies using the matrigel plug assay demonstrated that zerumbone treatment significantly decreases vascularization and hemoglobin content, providing direct evidence of anti-angiogenic activity (Park et al., 2015).

Table 1. Summary of zerumbone's anti-colorectal cancer effects in preclinical studies

Cell Lines/Model	Mechanism of Action	Key Findings	References
HCT-116	TNF-α inhibition	Concentration-dependent reduction in cell proliferation	Singh et al., 2018
HCT-116, SW-48	FAK/PI3K/NF-κB-uPA pathway inhibition	Suppressed invasion and metastasis	Hosseini et al., 2019

Cell Lines/Model	Mechanism of Action	Key Findings	References
HCT-116, SW-48	Synergy with miR-34a	Enhanced suppression of inflammatory cytokines (TGF-β, SDF-1, MCP-1, IL-33)	Dehghan et al., 2021
HCT-116, SW-48	TRAIL sensitization	Increased DR4/5 expression, decreased c-FLIP; potentiated TRAIL-induced apoptosis	Yodkeeree et al., 2009
SW-480	Multiple mechanisms	G2/M arrest (17.2%-26.66%), apoptosis induction, inhibited migration, disrupted cytoskeleton	Sithara et al., 2018
HT-29	Apoptosis and anti-migration	Upregulated Bax, downregulated Bcl-2, elevated ROS, decreased MMP-2/-9 activity and expression	Memari et al., 2022
ETBF/AOM/DSS mice	Microbiota modulation and anti-inflammation	Restored microbial diversity, increased beneficial Bacteroides, reduced polyps and macroadenomas, suppressed IL-17A, TNF-α, KC, iNOS, and NF-κB signaling	Cho et al., 2020; Hwang et al., 2019, 2020

STRUCTURE-ACTIVITY RELATIONSHIPS ZERUMBONE AND DERIVATES (*IN SILICO* STUDY)

The therapeutic potential of zerumbone is intimately tied to its unique chemical structure, with the α,β-unsaturated carbonyl group being absolutely critical for its biological activities (Figure 1). This functional group acts as a Michael acceptor, enabling covalent interactions with nucleophilic sites in proteins, particularly cysteine residues.

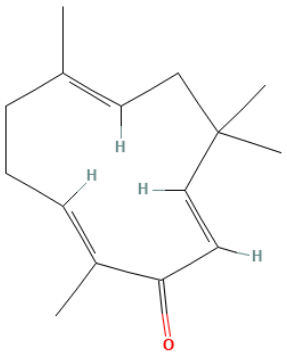

Figure 1. Chemical structure of zerumbone

The Critical Role of the α,β-Unsaturated Carbonyl Group

The importance of this structural feature was definitively demonstrated in a landmark study comparing zerumbone with α-humulene, a structurally similar sesquiterpene that lacks only the carbonyl group. When tested in parallel experiments examining effects on free radical generation, proinflammatory protein production, and cancer cell proliferation, α-humulene proved virtually inactive in all assays, while zerumbone showed potent effects. This dramatic difference despite minimal structural variation unambiguously demonstrates that the α,β-unsaturated carbonyl scaffold is essential for zerumbone's anticancer activity (Murakami et al., 2002). The mechanism involves the ability of this functional group to form covalent adducts with cysteine residues in target proteins through Michael addition reactions, thereby modulating protein function.

Computational Studies of Zerumbone Derivatives for Colorectal Cancer

Building on this fundamental understanding, computational research has

explored how structural modifications might enhance therapeutic efficacy against colorectal cancer. Bioinformatic analysis identified six critical protein targets involved in CRC pathogenesis: AKT1, XIAP-BIR2, XIAP-BIR3, HSP90AA1, MDM2, and EP300 (Fauziyya et al., 2023).

Molecular docking studies comparing zerumbone with twenty structurally related derivatives identified several compounds with potentially superior binding characteristics to these CRC-relevant targets. Notably, derivatives with added functional groups such as amine moieties exhibited enhanced binding affinity, attributed to formation of additional hydrogen bonds with target proteins. For instance, one derivative showed enhanced binding to AKT1 compared to both zerumbone and the clinical AKT inhibitor capivasertib, while another demonstrated strong binding to XIAP-BIR3, a domain that inhibits apoptosis (Fauziyya et al., 2023; Auli et al., 2024).

These computational studies also evaluated pharmacokinetic properties using in silico ADMET prediction tools. Among derivatives examined, twenty-one compounds passed Lipinski's Rule of Five and exhibited favorable predicted ADMET profiles, suggesting they might overcome bioavailability limitations that challenge zerumbone's clinical development. However, these promising in silico predictions require validation through experimental studies, as computational approaches cannot fully capture biological complexity including protein dynamics, cellular uptake, metabolic stability, and potential off-target effects.

EFFECTS ON GUT MICROBIOTA IN COLORECTAL CANCER MODELS

The association between gut microbiota dysbiosis and CRC has been the subject of extensive research. A multitude of studies has underscored the correlations between gut microbiota composition and CRC development (Okuda et al., 2021; Sobhani et al., 2019). Among the implicated microorganisms, *enterotoxigenic Bacteroides fragilis* (ETBF) has been identified as a key contributor to CRC. Furthermore, fungal microorganisms (mycobiota) may also play a role in CRC pathogenesis. Notably, the phyla *Mucoromycota* and *Ascomycota* dominate the mycobiota composition in CRC patient samples (Gao et al. 2022), and *Candida* has been linked to metastatic disease and the disruption of cellular adhesion in colon cancers (Dohlman et al., 2022).

Some microorganisms can assist the development of cancer, create harmful chemicals, and encourage persistent inflammation. The balance between immunological tolerance and anti-tumor immunity is influenced by the microbiome, and certain microorganisms can cause chronic inflammatory conditions that aid in the development of cancer. *Fusobacterium nucleatum*, which is linked to colorectal cancer, is a prominent example. *F. nucleatum* activates the E-cadherin/β-catenin signaling pathway in a FadA-dependent manner, leading to the upregulation of chk2, DNA damage, and increased cell proliferation in colorectal cancer (CRC). Additionally, *F. nucleatum* recruits tumor-infiltrating immune cells, fostering a pro-inflammatory microenvironment that further promotes colorectal carcinogenesis (Rowaiye et al., 2024).

The pharmacological properties of zerumbone have been evaluated through in vivo studies using mice colonized by ETBF and subjected to treatment with azoxymethane (AOM) and dextran sulfate sodium (DSS) to induce colitis-associated CRC. The AOM/DSS treatment resulted in reduced gut microbial diversity in ETBF-colonized mice. However, zerumbone treatment increased the abundance of specific beneficial taxonomic groups, restoring some microbial diversity (Cho et al., 2020). Additionally, in the same mouse model, zerumbone reduced the number of colonic polyps and inhibited the progression of macroadenomas (Hwang et al., 2020).

Another study revealed that zerumbone exerted anti-inflammatory properties on mice colonized by ETBF. Zerumbone treatment notably reduced the levels of pro-inflammatory mediators within colonic tissue, including IL-17A, TNF-α, keratinocyte chemoattractant (KC), and inducible nitric oxide synthase (iNOS). Furthermore, in mice treated with zerumbone, a reduction in NF-κB signaling

was observed, suggesting its role in modulating inflammatory pathways associated with CRC progression (Hwang et al., 2019).

CONCLUSION

Zerumbone has shown significant potential as an anti-cancer agent in preclinical investigations. Its mechanisms of action encompass the initiation of cell cycle arrest, promotion of programmed death, and inhibition of the proliferation, invasion, and metastasis. Furthermore, zerumbone's ability to modulate gut microbiota composition and reduce inflammation highlights its promise in managing colorectal cancer. Despite these encouraging findings, further investigations are necessary to evaluate the efficacy and safety of zerumbone in clinical trials involving human subjects. These promising preclinical findings indicate that zerumbone could emerge as a novel therapeutic agent for CRC.

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