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Review Article

A Pathway to Natural Cancer Therapy; Exploring Zerumbone's Multitargeted Anticancer Actions

Akram Ahmed Aloqbi*

Department of Biological Science, Faculty of Science, University of Jeddah, Jeddah, SAUDI ARABIA.

ABSTRACT

Background: A compound called zerumbone found in gingers rhizome has demonstrated potential in fighting cancer due to its beneficial effects on the body. This thorough examination delves into how zerumbone works to combat cancer by triggering cell death through pathways and controlling cell division while influencing signaling routes, like EGFR and VEGFR as well as NF kappa B. **Materials and Methods:** Zerumbone also shows anti-inflammatory characteristics by decreasing inflammation related proteins and oxidative damage and hampers the formation of blood vessels and spread of cancer cells by focusing on factors such as VEGFR and MMP enzymes along with the transition, between different cell types. **Results:** Moreover, zerumbone shows promise, in tackling drug resistance by reducing the activity of Multidrug Resistance (MDR) proteins and focusing on cancer stem cells which makes it a hopeful addition to chemotherapy. Nevertheless, obstacles like bioavailability, formulation stability issues and insufficient clinical data still hinder its use in therapy. **Conclusion:** More research is needed to tackle these challenges and validate the effectiveness and safety of zerumbone paving the path for its integration, into cancer treatment approaches.

Keywords: Anticancer, Apoptosis, Caspases, Ginger, Targeted therapy, Tumor.

Correspondence:
Dr. Akram Ahmed Aloqbi
Department of Biological Science, Faculty of Science, University of Jeddah, Jeddah-21589, SAUDI ARABIA.
Email: aaaloqbi@uj.edu.sa

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INTRODUCTION

The increasing number of cancer cases necissates the importance of finding methods, for preventing and detecting it on and improving treatment options since current approaches are falling behind the growing rates of occurrence. Cancer takes a toll economically well; the expenses of treatment and the loss of productivity put a significant burden on healthcare systems and economies worldwide. Although there have been advancements in cancer treatments like immunotherapy and customized medications targeted at types of cancer cells; tackling certain cancers remains challenging due to late detection issues as well as problems, with drug resistance and recurrence. Traditional treatments, like chemotherapy and radiation therapy can have side effects that make them less effective over time due to the development of drug resistance in tumors which hinders successful treatment and results in poor survival rates. This highlights the pressing requirement for treatment approaches that're not only efficient but also less harmful to patients' health. Natural remedies sourced from plants have become a topic of interest, for their potential to specifically target cancer cells while also influencing cell signaling pathways and combatting drug resistance. The inclusion of these treatments, in cancer care could open up a new avenue in the battle, against cancer and contribute to easing the increasing worldwide impact of this illness.

Traditional methods, for treating cancer such as chemotherapy and radiation therapy as newer approaches like targeted therapies and immunotherapy encounter obstacles of varying degrees of complexity and difficulty. Chemotherapy is an employed treatment method that lacks precision in its actions by affecting both cells and normal rapidly dividing cells in the body which can cause adverse effects like tiredness, hair loss and stomach issues. Furthermore, cancer cells frequently develop resistance to drugs through processes such, as efflux pumps and genetic mutations resulting in treatment inefficacy and potential relapse (Nikolaou *et al.*, 2018). While radiotherapy proves successful, in treating tumors confined to areas of the body it may harm healthy tissues and its effectiveness is restricted when dealing with tumors that are resistant, to radiation or cancers that have spread to other parts of the body.

Treatment, through surgery is effective when dealing with tumors that are localized; however, its effectiveness decreases when cancer has spread to parts of the body (metastasized) (Klein, 2020). Furthermore, surgeries close to organs may leave behind some cancer cells leading to a recurrence and impacting the patient's quality of life during recovery significantly. Targeted

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therapies are created to combat mutations in cancer cells but face challenges as tumors often develop mutations that make these treatments less effective. High costs and limited applicability also restrict the use of targeted therapies. Immunotherapy shows promise as it uses the system to battle cancer (Dhar *et al*., 2021), however, its success varies from patient, to patient. Tumors often create ways to avoid the system. Certain patients may face serious autoimmune reactions as a result of this phenomenon. Moreover, the Resistance, to Drugs (MDR) and the variety of cancer cells within tumors (known as tumor heterogeneity) make treatment more complex. These obstacles highlight the importance of exploring approaches, such as substances that could provide safer and more efficient ways to support or improve traditional treatments. Substances derived from plants, microbes and marine creatures offer promise in the quest, for anticancer treatments.

Throughout history numerous successful medications, like paclitaxel and vincristine have been discovered in nature showcasing the healing properties of substances. These remedies offer a range of compositions and intricate structures that synthetic compounds find challenging to imitate allowing them to impact various cancer pathways at once. This diverse approach makes natural products especially beneficial in combatting drug resistance, a constraint, in treatments. Natural substances not have anti-cancer effects but also tend to be less harmful, than artificial medications which can enhance patient resilience and minimize adverse reactions (Varghese *et al*., 2018). Elements derived from nature like curcumin and resveratrol have proven their effectiveness in hindering the growth of cancer cells and promoting cell death without harming cells. Additionally natural products play a role in regulating inflammation response to stress and immune functions-all critical factors, in the advancement of cancer. Given the increasing prevalence of Drug Resistance (MDR) and the demand, for safer treatment options in cancer care settings incorporating natural substances into cancer therapy shows significant potential for progress. These natural compounds could be administered independently or alongside treatments to boost effectiveness and mitigate side effects. With research efforts discovering natural compounds and enhancing their absorption using modern drug delivery methods might lead to the development of more efficient long lasting and individualized approaches, to fighting cancer.

Zerumbone (ZMB) is found naturally in the rhizomes of *Zingiber zerumbet* (also known as shampoo ginger) which's part of the ginger family (known as Zingiberaceae) (Chavan *et al*., 2018) (Figure 1). This compound has gained attention for its properties and especially for its strong anticancer effects. This mixture displays a variety of effects, like reducing inflammation and preventing oxidation as well as fighting against microbes and cancer cells making it an important focus for creating new medications. ZBN has presented encouraging outcomes in lab tests and animal studies by blocking the growth of cancer cells effectively and triggering cell death while also curtailing the spread of cancer to other parts of the body (Sut *et al*., 2018). Its diverse approach enables it to regulate pathways involved in cancer development such, as NF kappa B signaling pathway and PI3k/Akt pathway besides MAP kinase pathway. The natural source of ZBN and its low toxicity levels make it a promising option, for combining with cancer treatments to combat drug resistance issues in patients' therapies. Researchers are actively investigating its healing properties. Working on improving how it can be delivered effectively and developing compounds to boost its effectiveness when used in medical treatments. In this review article we aim to discuss the benefits of ginger's active component ZBN, for cancer treatment purposes. We will explore their chemical properties and therapeutic effects to show how ginger and ZBN can provide additional options, alongside cancer therapies.

Phytochemistry and bioavailability

The compound ZBN is classified as a sesquiterpene due, to the presence of an α, β unsaturated carbony1 group in its structure that significantly influences its functions (Sut *et al*., 2018; Ozkur *et al*., 2022). This specific carbony1 group and the connected double bonds contribute to the reactivity of ZBN enabling it to interact with residues found in proteins and enzymes associated with the advancement of cancer (Baptista *et al*., 2022). Additionally, its hydrophobic properties aid in its ability to pass through cell membranes smoothly thereby facilitating interactions with targets, inside cells. ZBN stands out among sesquiterpenes due, to the 11 membered carbon ring it contains which adds to its stability and distinctive structure. In ginger root, compounds such, as gingerols and shogaols are found that have been found to possess anti-inflammatory and antioxidant abilities alongside potential anticancer properties, in the body system of humans or animals when ingested in appropriate quantities or forms (Ozkur *et al*., 2022). ZBN demonstrates effectiveness, in fighting cancer compared to gingerols because of its α and β carbonyl group that allows it to better engage with cellular targets associated with cell death and the spread of cancer cells. This diverse range of actions showcases ZBN as a versatile compound worth exploring further in cancer research as part of gingers array of chemicals (Figure 2).

Anticancer mechanism

Targeting pathways, in cancer treatment is a way to disrupt the progression of the disease and improve the effectiveness of therapies (Figure 2 and Table 1).

Modulation of apoptotic pathways

The compound ZBN has demonstrated an ability to trigger cell death in cancer cells by impacting both the mitochondrial driven and external (death receptor triggered) pathways of programmed cell death or apoptosis process effectively (El Fagie *et al*., 2021). In the pathway of apoptosis induced by ZBN disrupt mitochondrial

Table 1: Summarizing the anticancer properties, target pathway, specific action of ZBN with potential outcomes.

Anticancer Mechanism	Target Pathway	Specific Actions	Potential Outcome
Induction of Apoptosis.	Intrinsic and Extrinsic Apoptotic Pathways.	Activation of caspases (e.g., caspase-3, -8, -9); upregulation of pro-apoptotic proteins (e.g., Bax, p53); downregulation of anti-apoptotic proteins (e.g., Bcl-2).	Promotes programmed cell death in cancer cells.
Cell Cycle Arrest.	Cell Cycle Regulation.	Inhibition of cyclins and CDKs; disruption of cell cycle phases (e.g., G2/M arrest).	Prevents cancer cell proliferation.
Inhibition of Growth Factor Signaling.	EGFR, VEGF signaling pathways.	Downregulation of Epidermal Growth Factor Receptor (EGFR); suppression of Vascular Endothelial Growth Factor (VEGF) expression.	Reduces tumor growth and blood vessel formation.
Anti-inflammatory Effects.	NF-κB and COX-2 Pathways.	Suppression of pro-inflammatory cytokines (e.g., TNF-α, IL-6); inhibition of COX-2 enzyme.	Decreases tumor-promoting inflammation.
Reduction of Oxidative Stress.	ROS and Antioxidant Systems.	Scavenging of Reactive Oxygen Species (ORS); increase in cellular antioxidant levels.	Limits oxidative damage that supports tumor survival.
Inhibition of Angiogenesis.	Angiogenesis Pathways.	Downregulation of angiogenic factors like VEGF and MMPs; suppression of endothelial cell proliferation.	Prevents tumor vascularization, hindering nutrient supply.
Prevention of Metastasis.	EMT and Invasion Pathways.	Inhibition of Epithelial-Mesenchymal Transition (EMT) and metastatic factors.	Reduces cancer cell migration and invasion.
Targeting Cancer Stem Cells.	CSC Signaling Pathways.	Inhibition of self-renewal pathways (e.g., Wnt/β-catenin, Notch, Hedgehog).	Reduces cancer recurrence and metastasis.
Overcoming Drug Resistance.	MDR Protein Regulation.	Downregulation of Multi-Drug Resistance (MDR) proteins, such as P-glycoprotein.	Enhances chemotherapy sensitivity and efficacy.

membrane potential causing cytochrome C release which, in turn initiates signals leading to cell death downstream. This influence is often exerted by altering the permeability of mitochondria and generating Reactive Oxygen Species (ROS). A recent study delved into the effects of ZBN, on human SH SY5Y cells exposed to hydrogen peroxide and its underlying mechanism of action (Moon and Yun, 2023). Hydrogen peroxide treatment at a concentration of 400 μM for 24 hr. It increased the presence of ROS while ZBN treatment notably reduced ROS production. ZBN also effectively hindered the release of nitric oxide induced by H_2O_2 and the activation of inflammation related genes. Additionally, ZBN demonstrated a decrease, in the expression of Mitogen Activated Protein Kinase (MAPK) which is typically induced by hydrogen peroxide exposure. Many signs of cell death, in cells treated with H_2O_2 were reduced as the amount of ZBN decreased the ratio of Bax/Bcl a factor in regulating cell death and survival mechanisms. Additionally, we looked into the role of AMP related Kinase (AMPK) a target for treating conditions. We also studied how the mammalian Target of Rapamycin (TOR) plays a part in the process of autophagy, in SH SY5Y cells treated with H_2O_2. In this research investigation; ZBN increased Sirtuin 1 (abbreviated as SIRT1). Phosphorylated AMPK (pAMPK) both of which were decreased by exposure, to H_2O_2; while also decreasing phosphorylated mTOR (pmTOR). Overall findings suggest that promoting autophagy for apoptotic and anti-inflammatory effects may offer significant neuroprotection, in SH SY5 cells treated with H_2O_2.

On the hand in the pathway of apoptosis, zerumbone activates surface receptors like Fas, on cells leading to a cascade reaction that eventually results in cellular demise (Girisa *et al.*, 2019). ZBN targets both pathways to trigger apoptosis in cells that are resistant, to single pathway activation markers which enhances its promise as a potential anti-cancer treatment option (Barathan *et al.*, 2021).

Caspases and Pro-apoptotic proteins

Enhancing apoptosis is further supported by ZBN as it activates molecules, in the sequence like caspases and pro apoptotic proteins like Bax and p53 (El Fagie *et al.*, 2021). It triggers both initiator caspases like caspase-8 and caspase-9 and executioner caspases like caspase-3 to guide cancer cells through apoptosis. ZBN also boosts apoptotic proteins such as Bax that enhance mitochondrial membrane permeability and p53 a critical tumor suppressant participating in DNA repair and triggering apoptosis. By boosting these proteins functions ZBN effectively stimulates apoptosis and hinders cancer cell survival.

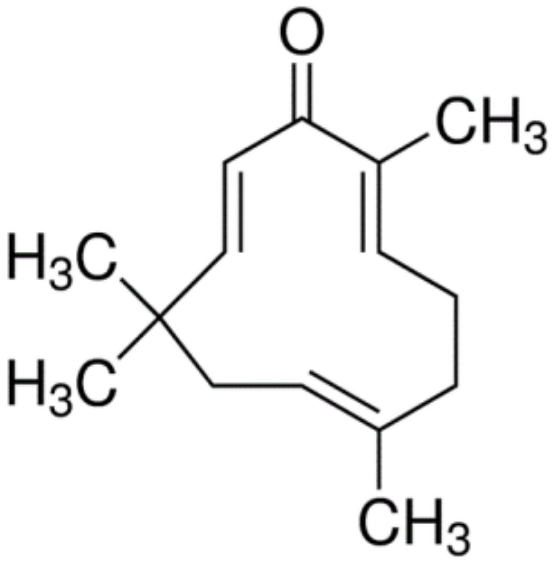

Figure 1: Molecular structure of Zerumbone (CAS #: 471-05-6. Molecular Formula: $C_{15}H_{22}O$. Molecular Weight: 218.3 g/mol.) (Chavan *et al.*, 2018; Girisa *et al.*, 2019).

Effect on cyclins, CDKs and other cell cycle regulators

The specific effect, on the machinery regulating cell growth interferes with the division of cancer cells and encourages cell death naturally occurring in the body. This suggests ZBN holds potential as a substance, in managing cancer. The research has shown that ZBN is able to slow down the growth of cells by interfering with factors that regulate the cell cycle such, as cyclins and Cyclin Dependent Kinases (CDKS) (Zadorozhna and Mangieri, 2021). ZBN reduces the levels of cyclins such as cyclin D and E as CDKs like CDKK and CDKK-2 crucial components for moving cells, between G1 and S phases in the cycle effectively stopping cancer cell growth at these critical stages. Additionally, ZBN affects cell cycle inhibitors, like p21 and p27 by boosting their presence and strengthening cell cycle arrest further (Soroush *et al.*, 2024). This specific influence on cell cycle processes interrupts cancer cells division and encourages programmed cell death.

Downregulation of growth factor signaling pathways

The impact of ZBN, on cancer progression involves reducing the activity of pathways that promote cell growth and blood vessel formation in tumors like the Growth Factor Receptor (EGFR) and Vascular Endothelial Growth Factor (VEGF). By suppressing EGFR signaling pathways in cancer cells ZBN weakens their ability to grow and survive effectively by making them more prone to cell death (Bajalia *et al.*, 2022). Additionally, ZBNs influence over VEGF limits the formation of blood vessels, in the tumor surroundings depriving the tumor of nutrients and oxygen needed for growth Carrera-Aguado *et al.*, 2024) By taking these steps with ZBN in play halts the growth of tumors. It deprives them of vital resources needed for spreading to other parts of the body, thus, showcasing its promise, for treating cancer through multiple avenues.

Suppression of pro-inflammatory cytokines

The compound ZBN has inflammatory effects by reducing the levels of certain inflammatory cytokines, like Tumor Necrosis Factor alpha (TNF a) and Interleukin 1 (IL a). These cytokines are crucial for triggering inflammation, in the tumor environment that promotes the survival and spread of cancer cells. A recent study showed that zerumbone helps reduce sepsis induced Acute Lung Injury (ALI) by reducing inflammation and oxidative stress through blocking the NF-kappa B pathway and promoting the heme oxygenase l pathway activation. The results suggest that using zerumbone before sepsis can help prevent ALI by reducing stress and inflammation suggesting it could be a treatment, for sepsis induced ALI (Chen *et al.*, 2024). The ability to reduce inflammation doesn't just stop tumors from growing but lessens the impacts of long-term inflammation linked to cancer development.

Oxidative stress reduction

ZBN plays a role, in cancer treatment by its properties that help decrease stress in cancer cells. A key factor in cancer development due to high levels of Reactive Oxygen Species (ROS) which can lead to DNA damage and genetic mutations. ZBN works by clearing ROS and adjusting antioxidant defense mechanisms to stress and reduce DNA damage (Nair, 2023; Abu-Izneid *et al.*, 2020). This process weakens the survival pathways of cancer cells while making them more prone, to apoptosis and stopping the buildup of mutations that advance cancer growth. ZBN shows

potential, in fighting cancer by tackling inflammation and oxidative stress on cellular level.

Downregulation of angiogenic factors

ZBN shows properties that hinder the growth of blood vessels, in tumors by decreasing the activity of elements responsible for their formation particularly VEGF and Matrix Metalloproteinases (MMPs) (Kumar *et al*., 2020). VEGFs play a role in creating blood vessels that provide nutrients and oxygen crucial for tumor development and spread. By suppressing VEGFs production levels after exposure, to ZBN starves tumors of resources needed for their growth effectively. Moreover, ZBN also decreases MMP amounts which are enzymes breaking down the matrix that ease cancer cell movement and invasion into areas (Tzeng *et al*., 2016). The combined action of blocking VEGF and MMP enzymes hinders the development and spread of cancer cells effectively showcasing ZBNs promise as a treatment, for cancer.

Prevention of epithelial mesenchymal transition and invasion

The compound ZBN also has a role in stopping Epithelial Mesenchymal Transition (EMT) a process where cancer cells acquire the ability to move and invade by breaking away from tumors and spreading to distant body parts (Ekem *et al*., 2020). ZBN hinders indicators of EMT, like Snail Slug and Twist which are linked to decreased cell adhesion and increased movement. By maintaining traits and blocking the shift to a state zerumbone prevents cancer cell invasion and reduces the chances of metastasis. ZBNs ability to hinder EMT and inhibit angiogenesis positions it as a contender, in managing the growth of tumors and the metastasis of cancer cells.

Effect on cancer stem cell population

The potential of ZBN, in combating Cancer Stem Cells (CSC)s has been evident in studies (Haque *et al*., 2017). CSC are a subgroup of cells within tumors recognized for their resistance to treatments and role in tumor recurrence and spread by interfering with key signaling pathways essential for CSC survival, like the Wnt/beta catenin Notch and Hedgehog pathways. ZBN hampers the self-renewal ability of these cells thereby hindering their capacity to sustain and spread the tumor. Additionally discovering that ZBNs ability to suppress cancer stem cells boosts the tumors responsiveness, to chemotherapy. This decrease in relapse risk could pave the way, for lasting treatment outcomes.

Inhibition of MDR proteins

Treating cancer can be tough, due to drug resistance issues caused by proteins like P glycoprotein (P gp) that work against chemotherapy drugs by pushing them out of cancer cells and making them less effective (Tian *et al*., 2023). ZBN has

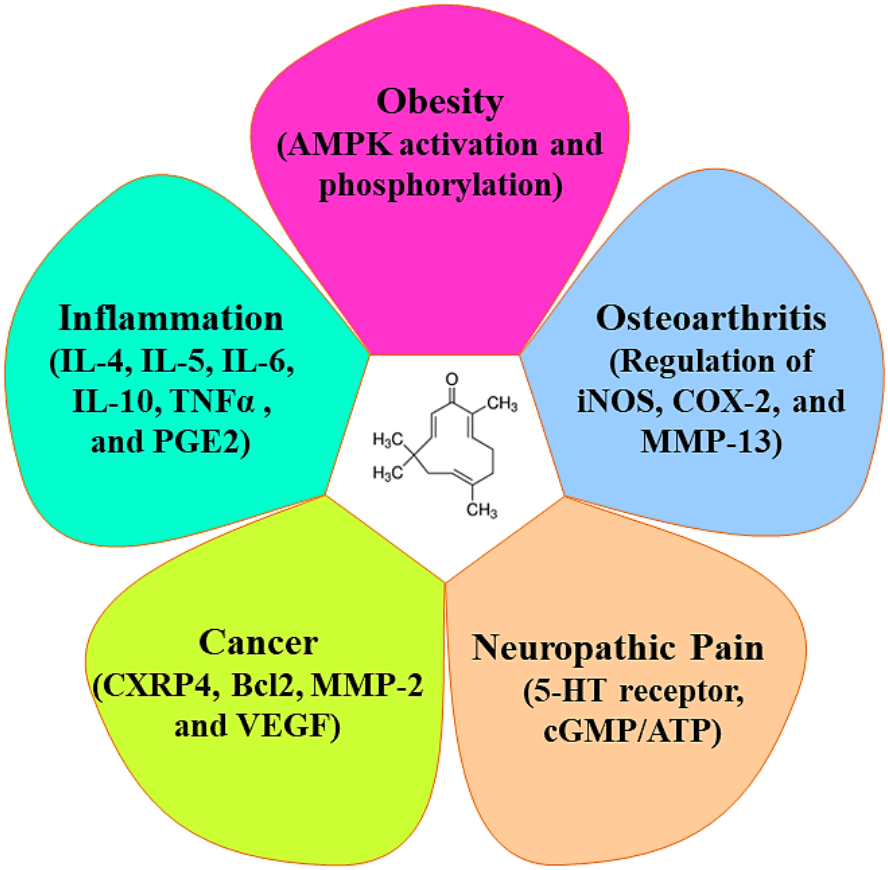

Figure 2: Goals of zerumbone for numerous diseases.

demonstrated the ability to block the function and production of MDR proteins such as P gp (Zadorozhna and Mangieri, 2021). This results in levels of chemotherapy agents within cancer cells. The reduced activity of these proteins makes cancer cells more responsive, to treatment efforts. ZBN provides a strategy to address both CSC and MDR pathways in combatting treatment resistance and improving the efficacy of treatments while potentially reducing the risk of tumor reappearance.

Synergistic/combination effects with chemotherapeutic drugs

The combination of ZBN, with chemotherapy drugs like doxorubicin and cisplatin has shown an impact by boosting the effectiveness of these medications in treating cancer at lower doses while possibly lessening the harsh side effects linked to high dose chemotherapy treatments (Lee *et al*., 2018). For example, ZBNs inherent anti-cancer properties work well with doxorubicins ability to interact with DNA strands resulting in enhanced treatment results, with harmful effects (Manna *et al*., 2020). The dosages positive impact is particularly advantageous, for patients, by decreasing toxicity build up and maintaining the health of normal cells while enhancing the overall tolerability of treatment.

Synergistic/combination effects with natural products

Combining ZBN with compounds, like curcumin (derived from turmeric) and quercetin (found in various fruits and veggies) has shown promise in cancer treatment by exhibiting synergistic effects that enhance the anti-cancer properties through different mechanisms that complement each other effectively. The presence of curcumin amplifies the pro cell death impact of ZBN by affecting similar cellular pathways, like NF Kappa B while also increasing reactive oxygen species production within cancerous cells. One study examined how zerumbone and curcumin work together to combat tumors, in colorectal cancer. The study uses both lab tests and animal models to understand their combined effects (Nobari *et al*., 2023). Colorectal cancer tumors depend on angiogenesis for growth. Spread, with Endothelial Growth Factor A (VEGF A) playing a key role in this process. By combining ZBN the goal is to block tumor promoting pathways and boost factors, like miR-34a. In experiments using cell lines (CT-26 and SW48) the combined treatment notably reduced VEGF-A levels. Raised miRNA-34 expression levels a result that was confirmed through both mRNA and protein analyses. From observations, in mouse models of cancer a 21-day regimen of ZBN and curcumin resulted in a decrease in tumor size; this effect was most pronounced in the group that received both treatments and was associated with minimal signs of toxicity. These results underscore the potential of combining ZBN and curcumin as a well-tolerated therapy, for colorectal cancer (Figure 3).

Quercetin is recognized for its anti-inflammatory qualities and works well with ZBN to offer extra assistance in blocking the growth of new blood vessels and decreasing pro inflammatory proteins (Ahmadabadi *et al*., 2019). This collaboration doesn't just enhance the effectiveness of treatment but also enables the use of amounts of each substance to reduce potential side effects.

The multi-faceted approach disrupts the survival of cancer cells on fronts. Hinders the development of resistance. This approach also offers flexibility in targeting types and stages of cancer because the different mechanisms make it challenging for cancer cells to

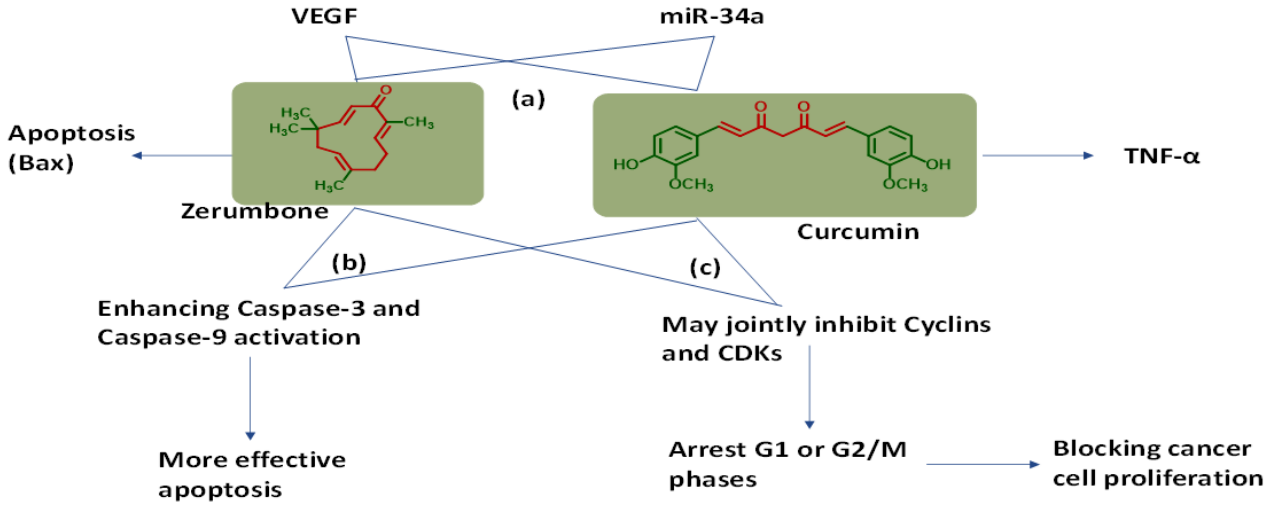

Figure 3: The homologous model demonstrates that combining zerumbone and curcumin effectively targets cancer biology. Zerumbone triggers apoptosis by activating apoptotic proteins and inhibiting anti-apoptotic elements, while curcumin reduces inflammation by blocking inflammatory cytokines. These components can lower VEGF, inhibit cell proliferation and metastasis and potentially enhance tumor suppressing effects. They also boost caspase activity, blocking proteins controlling cell division and halting cell cycle phases.

adjust and survive in response to treatment. This method shows potential, for creating comprehensive treatments, for cancer that are powerful yet less harmful.

Adjuvant potential with Radiotherapy/ immunotherapy

The potential of ZBN, as a treatment to radiotherapy lies in its ability to heighten cancer cells' receptiveness to radiation therapy effects by making them more sensitive to it (Chiang *et al*., 2018). The antioxidant characteristics of ZBN play a role in maintaining the equilibrium of ROS levels; this safeguards cells against harm caused by radiation and boosts ROS production within cancerous cells. This edged mechanism enhances the healing impact of radiation, on cancer cells while minimizing harm to healthy tissues. Moreover, ZBN's ability to trigger cell death via both the mitochondrial and death receptor routes complements the impact of radiotherapy, boosting the removal of tumor cells and possibly enabling the use of lower radiation doses to achieve similar treatment results.

The immunomodulatory properties of ZBN position it, as an option for immunotherapy because it can impact both the adaptive immune responses effectively. Researchers have noted that ZBN enhances the generation and function of T cells and natural killer (NK) cells for identifying and eliminating cancerous cells (Chiang *et al*., 2018; Jorvig and Chakraborty, 2015). Additionally, it plays a role in regulating inflammatory and anti-inflammatory cytokines to create an environment, within tumors that is less supportive of cancer cell growth (Yeh *et al*., 2022). By boosting the systems response, to cancer cells, through ZBN action enhances the effectiveness of immunotherapy by supporting both cell killing and immune monitoring mechanisms simultaneously This approach aims to enhance treatment results and lower the chances of cancer spreading or coming back in the future.

Clinical studies and translational potential

Studies, on ginger and its active components like ZBN are being conducted in trials to explore their potential benefits in fighting cancer. These trials mainly examine gingers inflammatory and antioxidant properties as well as its ability to reduce nausea and vomiting, in cancer patients undergoing chemotherapy. Additionally, research is being done on how ginger may improve the well-being of these patients by managing stress and inflammation (Ballester *et al*., 2022). However, ZBN is still being tested in trials at the stages of development. Studies, before testing have shown that it may help in fighting cancer but there are not large studies testing ZBN as a treatment for cancer yet. More research is needed to understand how well it works and how safe it is, for humans.

Although initial studies show promise, for the cancer fighting properties of ginger and ZBN in a lab setting when it comes to using them for treatments in people there are several challenges that need to be addressed. One significant obstacle is how well these compounds are absorbed by the body, ZBN which might benefit greatly from sophisticated delivery methods like nanoparticles or liposomes to improve its effectiveness in humans (Tan *et al*., 2023). Furthermore, it's essential to establish standards for sourcing and preparing ginger and ZBN since differences, in plant quality and processing techniques can affect their reliability and strength. Additionally in trials there are often challenges when it comes to figuring out the dosages and how long treatments should last for natural products such, as ginger and ZBN because the best time for effective treatment is still uncertainly defined. Completing the scale randomized controlled trials and overcoming regulatory obstacles are important steps to definitively establish whether these natural substances can be safe and effective cancer treatments. Tackling these obstacles through research and clinical trials will play a role in unlocking the full benefits of ginger and ZBN, in cancer treatment.

While there is potential, for ZBN based on preclinical research findings its safety in humans is not yet well established with data at this time. Preliminary studies in animals suggest that ZBN exhibits toxicity; however comprehensive human safety evaluations are still needed to provide an understanding of its effects and tolerance in cancer patients over the long term (Gopalsamy *et al*., 2020). Particularly when it is administered alone or alongside other therapies. Concerns remain regarding the dosage of ZBN, as a result of clinical trials and data collection thus far. Nevertheless, early research, on animals indicates that doses ranging between 10 to 50 mg/kg show encouraging cancer properties with no significant signs of harm; yet further validation is needed through clinical trials involving humans (Chia *et al*., 2021). Determinating the optimal treatment dosage for ZBN will involve evaluating factors like how the body absorbs it (bioavailability) how it moves through the body (pharmacokinetics) and how well patients can tolerate it. It is crucial for studies to establish an effective range of dosages, for both ginger and ZBN. Especially when used alongside existing cancer therapies to enhance treatment outcomes while reducing potential risks.

Developers face a hurdle, in the advancement of ginger and ZBN in terms of how well the body can absorb them effectively when taken orally due to their limited solubility and quick breakdown in the gut caused by metabolism issues. ZBN encounters a challenge in this regard since its molecular size and preference for fats make it tough to achieve appropriate levels in specific body tissues. Moreover, both ginger and ZBN need preparation to guarantee they remain stable and effective, with dosages. The problem is worsened by the differences, in sources that can result in varying strengths across batches of plant extracts. Moreover, both substances encounter obstacles in terms of regulations since they are categorized as supplements than pharmaceuticals, which hinders the stringent regulatory processes necessary for their

endorsement as treatments for cancer. The absence of uniformity in the composition of products adds complexity to the approval procedure because regulatory authorities frequently request clinical trial evidence proving their safety and effectiveness prior to authorizing their use, for therapy.

There are ways to improve how ginger and ZBN work, in our bodies and their effectiveness as treatments for medical conditions like cancer by using different methods to prepare them for use such as encapsulating them in nanoparticles or liposomes which can ensure that more of these compounds reach where they are needed while also making sure they stay stable and don't cause harm to other parts of our body through systemic toxicity effects (Tan *et al*., 2021; Panthi *et al*., 2023). In a study, on how zerumbone's released over time in different conditions research found that the release happened more quickly in acidic environments (Duong *et al*., 2024). This was confirmed by experiments both in a lab setting and in living organisms showcasing destruction of cancer cells inside tumor regions. The systems sensitivity to pH levels suggests promising prospects for cancer treatments for tumors, with blood supply.

Another way could be by using substances, like piperine that have been found to help our bodies absorb curcumin and ginger better which might also help ZBN work more effectively. Furthermore, improving the way ZBN is absorbed and how it interacts within the body through altering its chemical structure could make it more useful, for purposes. In order to overcome the obstacles posed by regulations creating combinations of ginger and ZBN with evidence gathered through thorough testing is essential. Conducting planned clinical trials that prove the effectiveness and safety of these natural substances will be vital in receiving approval, by regulatory bodies and transitioning them out of laboratories into real world medical settings. Collaborations, among academia, industry and regulatory bodies could simplify the development process. Pave the way for using these exciting natural products, in cancer treatment.

CONCLUSION

In short ginger and its bioactive component ZBN show promising cancer properties, by affecting various processes such as cell death initiation (apoptosis) regulation of important signaling pathways in cells and halting cell division progression while reducing inflammation and oxidative stress levels. ZBNs capability to address aspects of cancer development like blood vessel growth (angiogenesis) spread to other body parts (metastasis) and resistance to multiple drugs enhances its potential as a treatment option, for cancer patients. The way it works together with substances such, as curcumin and quercetin and its ability to support radiotherapy and immunotherapy shows how important it is, in comprehensive cancer treatment approaches.

The potential anti-cancer benefits of ginger and zerumbone make them remedies that could work alongside or improve current cancer treatments with fewer side effects, in mind. As promising as these results seem research – both in laboratory and settings– is necessary to confirm their effectiveness and safety for human use. Expanding our understanding of how to administer these compounds their effects on the body, over time and their potential when combined with treatments will play a crucial role in realizing the full benefits of using ginger and zerumbones as part of comprehensive cancer care plans.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

MDR: Multidrug resistance; **ZMB:** Zerumbone; **EGFR:** Epidermal growth factor receptor; **VEGF:** Vascular endothelial growth factor; **ROS:** Reactive oxygen species; **EMT:** Epithelial-mesenchymal transition; **MAPK:** Mitogen activated protein kinase; **AMPK:** AMP related kinase; **TOR:** Target of rapamycin; **CDKS:** Cyclin dependent kinases; **TNFα:** Tumor necrosis factor alpha; Ilα: Interleukin; **ALI:** Acute lung injury; **CSC:** Cancer stem cells.

SUMMARY

Ginger and its bioactive component ZBN show promising cancer properties, affecting cell death initiation, signaling pathways and reducing inflammation. ZBN's ability to address cancer development, blood vessel growth, metastasis and drug resistance enhances its potential as a treatment option. It works well with other substances, supports radiotherapy and immunotherapy. However, further research is needed to confirm their effectiveness and safety for human use.

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