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Zerumbone: Wound healing Efficacy and other Biomedical application- A Review

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Abstract

The review explores the several biomedical applications of Zerumbone, a phytochemical produced from traditional Zingiber Zerumbet. It is being used successfully in ancient medicine to treat wounds, worm infestation in children, rheumatism, sores, stomach-ache, swelling, diarrhoea, loss of appetite, muscular sprain and peptic ulcers. Also, we discussed about wound healing efficacy of Zerumbone along with the possible underlying mechanism of action that enhanced effective wound healing which includes Zerumbone's effects in increasing collagen synthesis, fibroblast proliferation and vascularization in tissue repair. Furthermore, we also addressed various other biomedical applications of Zerumbone including Anticancer, antimicrobial, antioxidant, antiulcer.

Keywords: Zerumbone, Zingiber Zerumbet, wound healing Efficacy, Biomedical application.

Introduction

Wound is continued to be a challenging medical issue in daily life, which can cause late and early difficulties posing a risk of morbidity as well as death [1]. Wound healing is an organism's response to a physical disruption of its cells, tissues, or organs and try to restoring homeostasis and preserving the overall physiology of the organism [2]. Growth factors induce cell proliferation, which results in the inclusion of rapid shifts such as plasma cells, soluble mediators, extracellular matrix synthesis, and parenchymal cell proliferation in a basic linear process of tissue repair [3]. The four highly interwoven and overlapping stages of healing of wounds includes haemostasis, inflammation, proliferation, tissue remodelling or resolution [4].

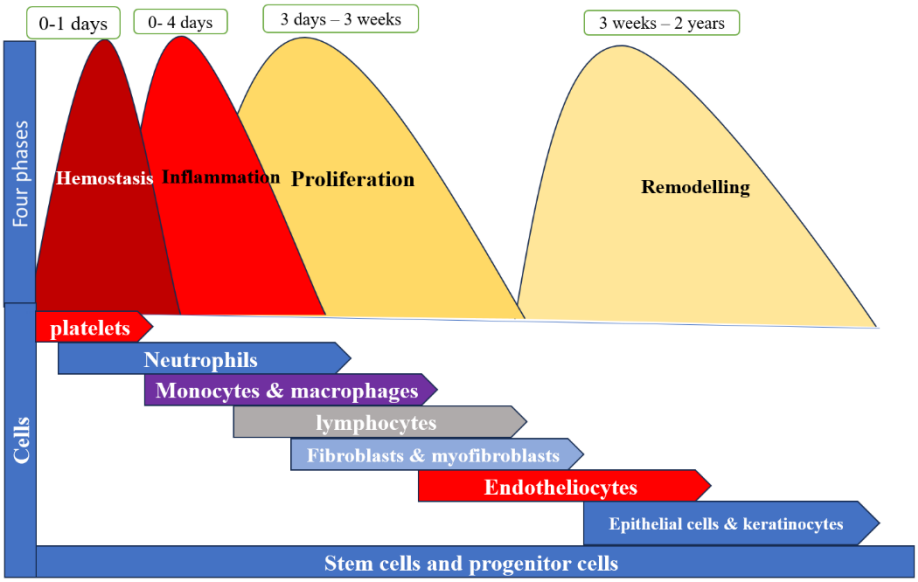

figure :1 Four stages of normal wound healing

A chronic wound may develop due to the abnormal wound healing which is a heavy load on the sick person and also for the health care organisation [5]. Chronic wounds will likewise start to heal, but they will experience prolonged episodes of proliferation or remodelling, which can lead to tissue fibrosis and non-healing ulcers [6]. Therefore, an appropriate clinical treatment can have a beneficial impact on how faster wound heals and decrease the threat of complications.

When wound appears and exposed to the external environment microbes have the potential to infiltrate from the dermis and obstruct the continues healing process [2]. Now a days, numerous antibiotics are presently used in the treatment of wound infections [7]. But because of its adverse effects and increased in bacterial resistance to antibiotic, researchers are focusing on investigating a biologically active compounds that are utilized in ancient herbal medicines.

Among the many ancient herbal remedies, Zerumbone is one such plant derived phytochemical obtained from ancient zingiber zerumbet plant that is commonly referred as a pinecone ginger and bitter ginger [8]. Zingiber zerumbet a wild ginger variation commonly called medicinal ginger is a member of Zingiberaceae family. While in some regions of Asia still uses it as flavouring agents, but interest in its therapeutic potential grown recently. In traditional medicine, it was utilized to cure condition such as, cuts, bruises, swollen areas, toothaches and stomach aches. The bioactivity of zingiber zerumbet is attributed by its primary components "Zerumbone" [9].

When the aromatic oil of edible rhizomes of wild ginger (zingiber zerumbet) was extracted in 1960, crystalline, monocyclic, sesquiterpene phytochemical "Zerumbone" was discovered and identified as a significant component [10]. According to the various earlier research, Zerumbone may possess a broad spectrum of pharmacological actions, which includes, Antiinflammation, antioxidant, analgesic, antibacterial, hepatoprotective, antinociceptive, wound healing and anticancer effects [11-15].

Zerumbone's uses in conventional medicine

Rhizome extract from Z. Zerumbet have anti-hypersensitivity, antiplatelet aggregation, antibacterial, antifungal, anticancer, anti-inflammatory, anti-allergic properties among their biological actions. As a result, traditional medicine has successfully utilized it to treats conditions like wounds, childhood worm infections, rheumatism, sores, stomach ache, swelling, diarrhoea, muscular sprains, and peptic ulcers [16].

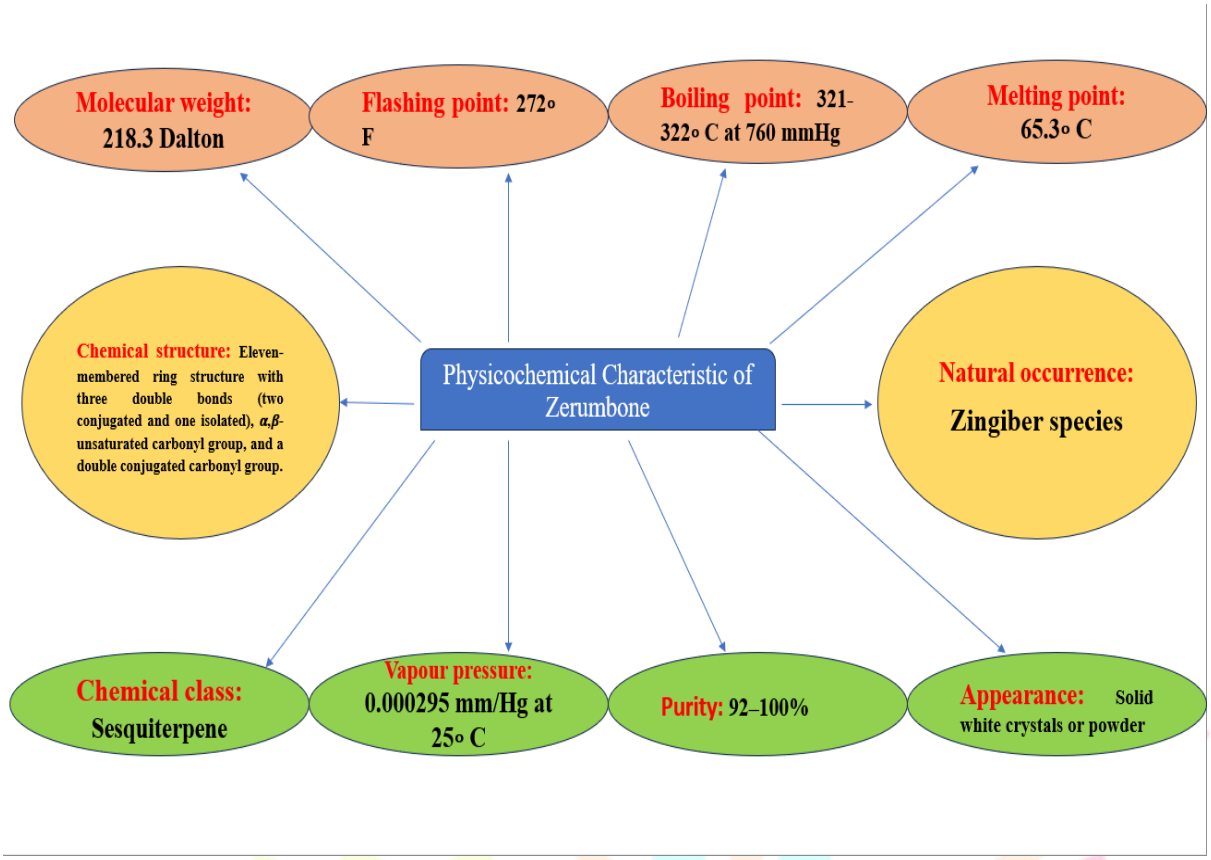

Figure 2: Physicochemical Characteristic of Zerumbone [17]

Wound healing efficacy of Zerumbone

The mechanism of Zerumbone as wound healing agent is not precisely known. However, various studies have indicated that its inherent antimicrobial, anti-inflammatory activity, and antioxidant activity plays important role in its ability to heal the wounds. Additionally, Zerumbone may function directly or indirectly through the generation of collagen and the proliferation of fibroblasts, both of which are essential for wound healing and tissue repair [14,18].

Zerumbone has been found to exhibit antioxidant effects by boosting the antioxidant enzymes expression such as catalase (CAT) and also superoxide dismutase (SOD) while reducing lipid peroxidation (LPO). These properties can assist in minimizing stress and inflammation within the wound area. Oxidative stress is known to hinder the healing process. Zerumbone's robust antioxidant properties may counteract this effect and facilitate healing. Additionally, Zerumbone has demonstrated inflammatory characteristics that can alleviate inflammation in the wound area thereby promoting healing. Chronic inflammation is recognized as an impediment to wound healing making Zerumbone's anti-inflammatory properties valuable in facilitating the natural recovery process. Moreover, Zerumbone exhibits qualities that can effectively prevent infections in the wound area further aiding in the healing process. In wounds particularly infection is a complication; however, Zerumbone's antimicrobial properties may help prevent such complications and support healing [18].

Furthermore, it is believed that Zerumbone may directly or indirectly promote tissue repair and wound healing through proliferation and collagen production— processes, for proper tissue restoration. The Zerumbone treated group exhibited higher expression of VEGF and TGF-β, which is associated with elevated collagen Fiber staining magnitude and fibroblast proliferation [14].

At the first phase of reconstruction of tissue and wound recovery, skin fibroblast is crucial process [19]. The remodelling of granulation tissue into mature skin is influenced by collagens secreted by fibroblasts from newly form granulation tissue [20]. The primary collagen in the extracellular basement that divides various endothelial and epithelial cell types is collagen IV [21]. As per *Wayne young Liu et al.,* the evaluation of collagen IV

production in the injured tissues of both experimental and control wound using immunohistochemical labelling, strongly revealed that Zerumbone therapy increased the new collagen production [18].

The process by which vascular endothelial cells divide and multiply to develop a new blood vessel is known as vascularization. The process provides an essential framework for the healing of wounds. Among the most effective promoters is VEGF, a mitogen exclusive to endothelial cells requires for neovascularization [22]. Extracellular matrix (ECM) structure and synthesis are aided by VEGF, and these processes are critical to the restoration ECM in the vicinity of the injured tissue zone. It has been found that TGF-β1, a multifunctional growth factor secreted from fibroblast, has the broad range of activity and participates in almost all phases of the healing process of wounds. TGF-β1 stimulates angiogenesis, assist in reepithelization, recruits inflammatory cells, enhances collagen deposition during the proliferation phases, and increases macrophage-mediated tissue debridement. The current understanding is that VEGF and TGF- β1, controls and accelerates the process of wound healing [23]. As per *Wayne young Liu et al.,* the group underwent Zerumbone treatment demonstrated higher levels of VEGF and TGF-β1, which is linked to increased collagen Fiber staining strength and fibroblast proliferation [18].

Other biomedical applications of Zerumbone

Anti-inflammatory action

Zerumbone derived from zingiber zerumbet, is known to possess anti inflammatory effects by inhibiting inflammatory processes such as prostaglandin synthesis and endogenous mediator release. Zerumbone has been demonstrated to interfere with the transduction pathway in primary afferent nociceptors, partly by inhibiting lipoxygenase and/or cyclooxygenase in peripheral tissues lowering prostaglandin E2 (PGE2) synthesis [12]. Zerumbone may also block proinflammatory cytokines production and enzymes like COX-2 & iNOS, as well as the initiation of NF-KB, a transcription factor increased inflammation [24].

Sulaiman et al, conducted study, inflammatory action of Zerumbone, a natural bioactive compound from zingiber zerumbet, in both acute as well as chronic inflammation model in mice. The findings of the study suggest that, Zerumbone has promising anti inflammatory properties, effectively decreasing granulomatous tissue development and paw edema caused by carrageenan in a dosage dependent mode. These findings support use of Zerumbone to treat diseases and call for more research in to the processes underlining Zerumbone anti-inflammatory properties [11].

Meanwhile, *chien et al,* investigated Zerumbone's effect on arthritis using both *in-vivo* and *invitro* systems. Zerumbone inhibits the expression of iNOS, COX2, and MMP-13 as well as reduces NO and PGE2 production in LPS- stimulated macrophages and 12-1β- stimulated chondrocytes via, HO 1 induction. Also, they observed that Zerumbone reduced paw edema, pain responses and weight bearing difficulties in rats with MIA- induced Osteoarthritis. These data implies that Zerumbone hold potential as candidate for Osteoarthritis treatment [25].

Antioxidant activity

Zerumbone has been associated to a variety of positive advantages, such as lowered levels of malondialdehyde and reactive oxygen species in the body. It also improves the property of antioxidant enzymes, including catalase, superoxide dismutase and glutathione peroxidase. Additionally, Zerumbone promotes the Nrf2 pathway, which regulates detoxifying and antioxidant expression. These pathways show that Zerumbone has antioxidant capacity and could help to prevent or treat conditions associated with oxidative stress [26, 27].

According to study performed by *mesomo et al,* it was observed that Zerumbone has antioxidant activity, demonstrating its potential to scavenge radicals and reduce peroxidation. Furthermore, Zerumbone reduces oxidative stress and inflammation by restricting the generation of iNOS (inducible nitric oxide synthase) and COX 2 (cyclooxygenase 2). With its anti-inflammatory and antioxidant properties Zerumbone could serve as medical option for various ailments [28].

Assiry et al, have reported on the antioxidant properties of Zingiber Zerumbet a plant which has Zerumbone as one of its bioactive compounds. Several approaches, including HPLC analysis and also DPPH free-radical scavenging test, were used to assess Zerumbone's properties. The results showed that extracts from Zingiber

Zerumbet especially the ethanol extract, had antioxidant benefits by successfully scavenging free radicals, including how it may help to avoid degenerative disorders induced by oxidative stress. the presence of flavonoids and phenolic compound due to which Zingiber Zerumbet possess antioxidant characteristics, making it possible natural source of antioxidants [29].

Anti-microbial activity

Zerumbone is a phytochemical with antibacterial properties against four food borne pathogenic bacteria: *Yersinia Enterocolitica, Bacillus Cereus, Escherichia Coli and Staphylococcus Aureus*[9].

Zerumbone has shown activity against moderate efficacy against *E. coli*, *staphylococcus epidermidis*, and moderate antifungal activity against the *Aspergillus oryzae and niger* [15]. Zerumbone's antibacterial properties are mostly likely to attributed to its composition and interaction with targets. Zerumbone's mechanism of action may include damaging microbial cell membranes, blocking enzymes, or interfering with growth process [30].

As per *Vishwanatha et al*, considerable antibacterial activity against *Staphylococcus epidermidis* was observed in their study on Zerumbone with inhibitory zones detected at concentration from 20 & 10 mg/disc. Also, they found that at a dose of 20mg/disc, it was effective against *E. coli* and also effective against *Aspergillus niger and oryzae* at particular dosages. These findings indicated Zerumbone's potential as an antimicrobial agent and its promise in treating bacterial and fungal diseases [31].

A recent study by *Assiry et al,* demonstrated efficiency against specific endodontic microorganisms, specifically multi- drug resistant gram-positive bacteria. Ethanol extract from zingiber zerumbet shown action against a variety of bacteria examined including, *streptococcus mutans, Enterococcus faecalis and staphylococcus species.* The study emphasized the usefulness of Zerumbone as a bioactive compound against multidrug resistant gram-positive bacteria [32].

Anti-cancer activity

Several studies have demonstrated the potentials of Zerumbone as an anticancer and the possible underlining mechanisms of Zerumbone depends on the types of cancer as well as various biological targets.

Zerumbone activity in oral cancer

Zerumbone inhibits the production of CXCR4, RhoA, proteins and P13K-m TOR signaling pathway, resulting in G2/M cell cycle arrest and eventually death in oral squamous cell cancer. This reduces cell migration, invasion and proliferation. The downregulation of Akt and S6 proteins has been related to the inhibition of the P13K-mTOR signalling pathway [33].

Zerumbone activity in lung cancer

Lung cancer is the most prevalent cause of death that is related to cancer globally. The most frequent kind of lung cancer is NSCLC (non-small cell lung cancer) [34]. Zerumbone triggers apoptosis by reducing the membrane potential of mitochondria, and activating caspases 3 and 9, releasing cytochrome C, increasing P53 and BaX expression, creating more ROS, and making NSCLC cells more sensitive to cisplatin [35].

In a study by *Hseu et al,* Zerumbone was found to suppress Transforming Growth Factor-β-induced EMT by lowering EMT-linked signaling regulators and raising E- cadherin. This highlights the susceptibility of A549 cells to Transforming Growth Factor-β1, which may accelerate EMT process in cancer cells. Additionally, Zerumbone exposures was found to promote Transforming Growth Factor-β-induced cancer cell invasion, migration and formation of colony [36].

Zerumbone activity in Colon cancer

Colon cancer is ranked as second most cause of cancer related death, affecting both male and female. *Murakami et al,* previously revealed that Zerumbone can precisely accelerate programmed cell death in colon cancer cells by upregulating death receptors, hence enhancing TRAIL-induced apoptosis in human colon cancer cells. Also,

Zerumbone has been reported to improve oxidative stress in colon cancer cells by producing reactive oxygen species (ROS), which activate pathways that promote apoptosis and selective cell death. Zerumbone supressed the development of human colon tumor cell lines in vitro by targeting key signaling pathways such as, Wnt/β-catenin pathway, which was necessary for cell survival & proliferation [37].

According to *Islam et al*, Zerumbone may be able to successfully stop colon cancer cells growing by stopping cell division. Zerumbone has demonstrated to inhibit progression of colon cancer by supressing the AKT/STAT3 signaling pathway, which is needed for cancer cell proliferation. This suggests that Zerumbone may affect critical signaling pathways associated with tumor growth [38]. These studies highlight Zerumbone's potential as a therapeutic agent for colon cancer by stressing its ability to affect key biological pathways and target cancer cells.

Zerumbone Activity in breast cancer

Zerumbone exhibits promising anti-cancer potential against breast malignancy. It functions through various pathways to supress proliferation, survival, angiogenesis, and metastasis in Breast cancer cells. Zerumbone targets multiple cellular processes by inhibiting miR-708- BACHI, axis, regulating miR-200, and supressing the epithelial-mesenchymal transition via βcatenin signaling inhibition. Also, Zerumbone interferes with oncogene BACHI, which is crucial for cancer cell formation and proliferation. Studies suggest that Zerumbone's administration down-regulates miR-708, leading to the suppression of breast tumor progression [39].

Various other research has demonstrated that Zerumbone reduces NF-kB activity, which in turn reduces IL-1β-induced cell invasion in TNBC via lowering levels of MMP-3 and IL-8 expression. By supressing the expression of CXCR4, it inhibits invasion and metasis in breast cancer [40-41].

Zerumbone activity in liver cancer

Zerumbone may treat liver cancer in a variety of ways. Hepatocellular carcinoma (HCC) cells create less lactate and utilizes less glucose because it inhibits key enzymes engaged in pentose phosphate cycle and glycolysis. Zerumbone also has an effect on signaling pathways involved in cancer cell proliferation and survival, such as PI3K/AKT/mTOR and STAT3. In addition, Zerumbone inhibits HCC cell metastasis, induce cell cycle arrest, and promotes death. The α, β-unsaturated carbonyl group has lethal effects on cancer cells, disrupting cellular redox equilibrium and selectively targeting cancer cells while sparing normal cells [42].

Zerumbone activity against Gastric cancer

Zerumbone acts against gastric cancer by stopping NF-kB activity, angiogenesis and VEGF expression. It reduces NF-kB activity, causing gastric cancer cells to release less VEGF. Zerumbone inhibits the ability of cancer cells to induce the formation of endothelial tubes, hence preventing, hence preventing angiogenesis. Zerumbone inhibits angiogenesis and cancer by interfering with their mechanism. Furthermore, Zerumbone's anti-angiogenic and anticancer capabilities in gastric cancer are due to these combined actions [43].

As per, *wang et al,* Zerumbone inhibits the growth of human gastric carcinoma cells in a dose-dependent approach and promotes apoptosis, as evidenced by greater apoptotic cell counts. Cyclophilin A (Cyp A) and Bcl-2 causes the activation of caspase-3 through the mitochondrial-mediated apoptosis pathway and liberation of cytochrome C. According to these findings, Zerumbone could constitute a promising new therapy option for gastric cancer, offering a potentially low-cytotoxic technique for addressing metastatic gastric cancer [44].

Zerumbone activity against pancreatic cancer

According to *Zhang et al*, Zerumbone induces apoptosis in pancreatic cancer cells by initiation of the p53 signaling route, resulting in production of p21& p53 proteins, two essential regulators of cell cycle arrest and death. Furthermore, Zerumbone produces higher levels of reactive oxygen species (ROS), thereby improving its pharmacological effects on cancer cells. Furthermore, Zerumbone treatment induces overexpression of miR-34 and p21, both of which are subsequent targets of p53 signaling pathway. By inducing apoptotic cell death

and focusing on key biochemical pathways associated with cancer progression, Zerumbone's combined actions reveal its potential as a lifesaving treatment for pancreatic cancer [45].

Anti-Ulcer Activity

The potential mechanisms of Zerumbone's gastroprotective properties include its ability to improve and boost the complementing action of stomach mucosal protective elements. This process could include a considerable increase in endogenous antioxidant GSH and decrease in lipid peroxidation levels. Zerumbone also increased levels of PEG 2 and NP-SH, which may have contributed to the increased stomach mucus generation. Furthermore, Zerumbone also boosted HSP70 expression in stomach mucosal tissue. In the pylorus ligature model, the study also clearly revels that the Zerumbone molecule has antisecretory activity, which may strengthen the reported gastroprotective effect [46]. Furthermore, Zerumbone has a strong antibacterial action towards *H. Pylori* [47]. As a result, these previously reported studies provide scientific evidence for the Zerumbone compound's stated gastroprotective characteristics.

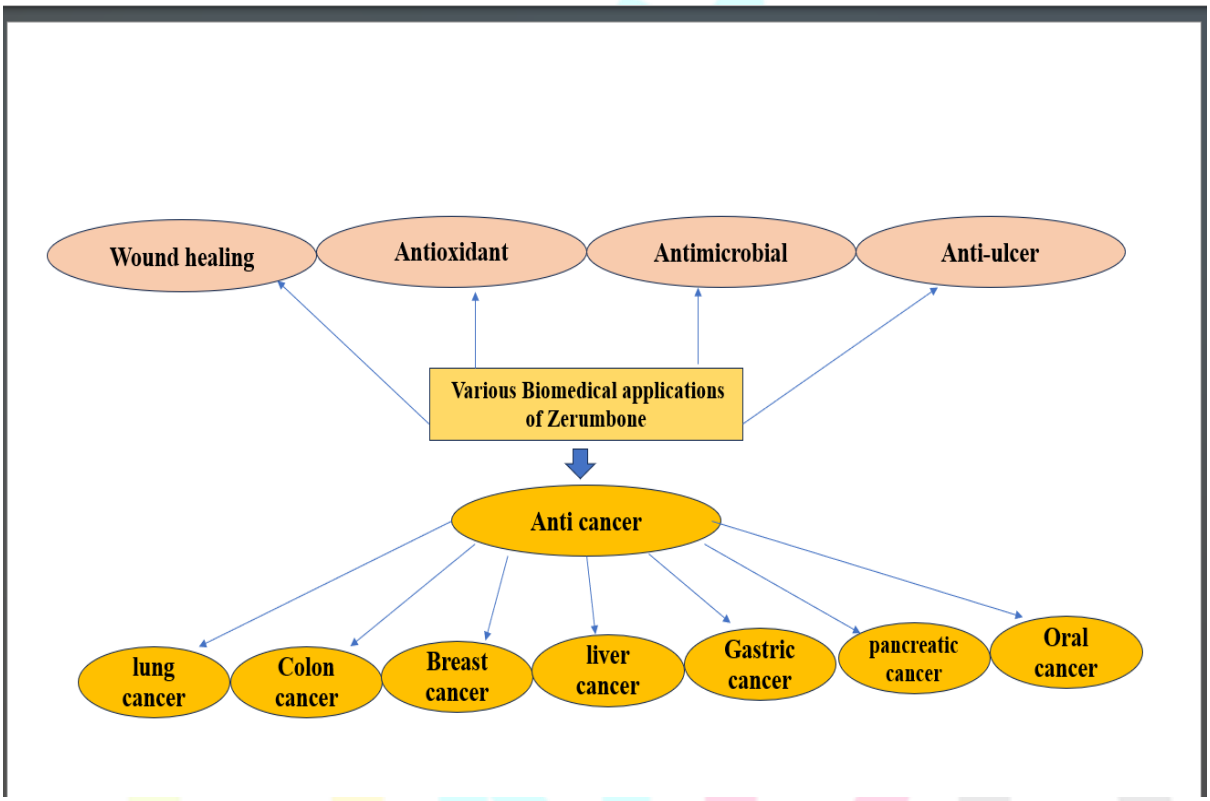

Figure 3: summary flow chart of various biomedical application of Zerumbone

Conclusion

Zerumbone has a wide range of biological properties, making it a feasible candidate for a number of therapeutic applications with low toxicity, including anticancer. Its antioxidant properties, as indicated by increased antioxidant enzyme activity and decreased oxidative stress markers, suggest that it has potential to cure a variety of oxidative stress related disorders. Zerumbone is also a natural antibacterial agent, as proven by its antimicrobial activity against variety of drug resistant microorganisms. Furthermore, Zerumbone's wound healing efficacy may be due to its natural anti-inflammatory, antimicrobial and antioxidant activity, also directly or indirectly through fibroblast proliferation, collagen formation, and vascularization, making it a potential alternative for chronic wound management. Its anticancer mechanisms vary according to the kind of cancer and biological targets. This review articles provides clear evidence that Zerumbone is a beneficial material for the treatment of cancer, wounds, and a variety of other ailments, based on the findings of previous research. However, addition animals' study and human clinical studies are required to determined Zerumbone's efficacy, safety, and utility as a pharmaceutical medication.

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