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Anti-cancer activities of eugenol and potential immunomodulatory effects: a comprehensive review

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Abstract

Diseases such as cancer and inflammatory conditions are on the rise in patients despite advances in early detection methods. Conventional therapeutic techniques such as chemotherapy and common synthetic drugs are facing problems such as serious side effects and drug resistance development which hinders the overall treatment. Traditional medicine involving the use of herbal based products is able to combat against these issues. Eugenol, the major bioactive constituent found in clove has been shown to possess various pharmacological properties that can be used to treat various diseases. This review aims to evaluate the current findings on the therapeutic properties of eugenol against cancer and immune-related conditions. The research has shown that eugenol exerts anti-cancer activities against various cancer cell lines such as colon, breast, lung, skin and cervical cancer, by targeting molecular pathways and genes, such as proto-oncogenic signaling pathways and pro-apoptotic gene expressions, that trigger apoptosis and inhibit cell proliferation and migration. Eugenol has also been shown to affect the immune system by targeting specific immune cells such as T cells and dendritic cells, and pro-inflammatory cytokines including TNF-alpha, IL-6 and PGE2, that leads to an immunosuppressive effect and reduced inflammation, preventing cellular damage which can lead to oncogenesis. The findings support the idea of using eugenol as a therapeutic drug against cancer and inflammation. Further studies focusing on its mechanisms of action and toxicity must be conducted to pave the way to clinical trials to provide more efficient and safer treatment options to cancer and immune related conditions.

Keywords: Eugenol, Cancer, Immune cells, Inflammation, Herbal medicine

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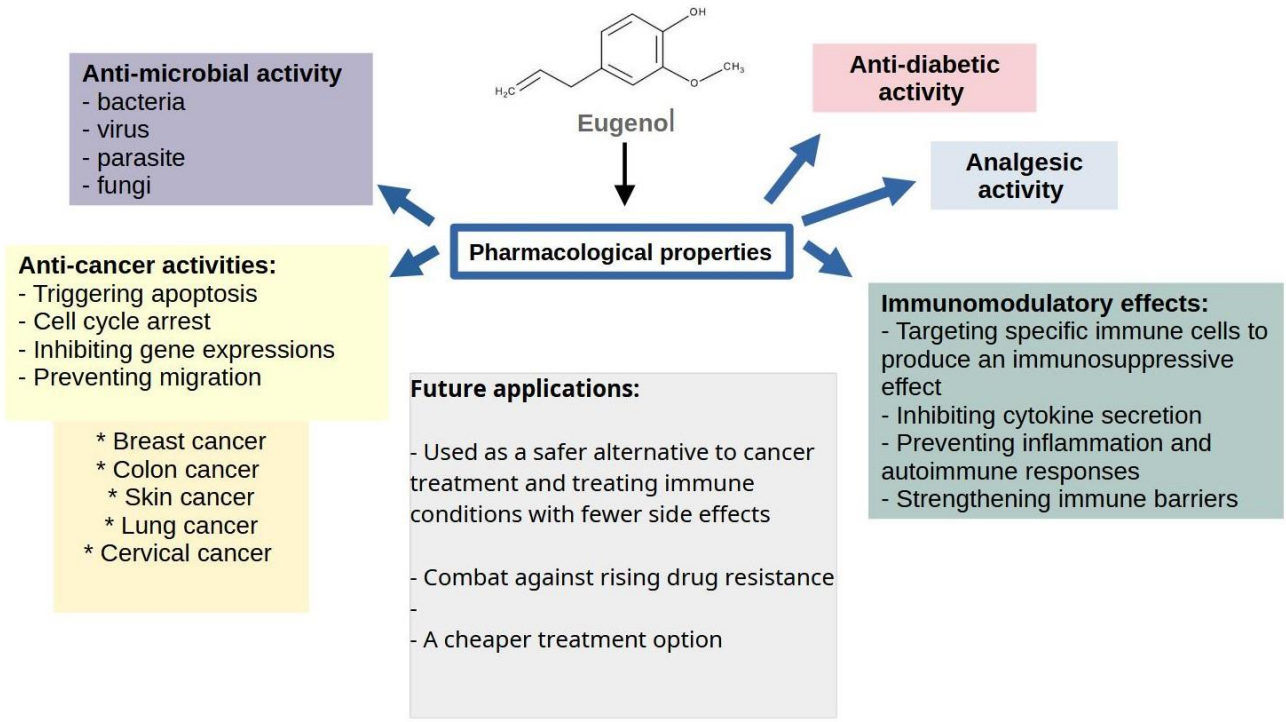
Graphical abstract



Introduction

Cancer is a complex disease that effects millions of people around the world. It results from mutations occurring in genes that control the overall functions of the cell. These genetic mutations can disrupt the normal cellular metabolism, especially in the cell cycle, leading to uncontrollable proliferation, resulting in a tumor (1). It was estimated that in 2020 there were 19.3 million new cases of cancer and 10 million deaths related to the disease (2). During 2015-2019, it was reported that incidence rates have increased by 0.6-3% for breast, kidney, liver and cervical cancers in the United States (3). This alarming rise in cases warrants the need for more effective treatment methods. Conventional methods typically include chemotherapy, radiotherapy and surgery. However these approaches face problems that effect the overall efficiency of the treatment such as serious adverse effects and development of drug resistance (4). Therefore new therapeutic approaches are being studied and developed to treat cancer in a more effective approach. These methods include targeted therapy, stem cell therapy, nanoparticles, chemodynamic therapy and many more (5). The immune system is also said to play important roles that can either promote growth of cancer through factors such as inflammation or target specific cancer cells through targeted therapy.

In the recent years, many therapeutic options now include alternative and herbal medicine due to benefits such as fewer side effects and cheaper cost (6). The use of medicinal plants in healthcare has been an ongoing practice for thousands of years in many societies. Such plants were known to possess various medicinal properties that were utilized to treat diseases such as diabetes, inflammatory conditions and cancer. These pharmacological properties are contributed by secondary plant metabolites called phytochemicals. These compounds can be extracted and modified for drug formulations in the pharmaceutical sector, broadening options available for treating diseases.

The clove (*Syzygium aromaticum*) is an excellent example of a herbal species used for its vast properties. It has been shown to be rich in phytochemicals such as flavonoids, polyphenols, hidroxibenzoic acids and

more (7). These compounds contribute to numerous bioactive properties that have been used in traditional medicine, such as antimicrobial properties, anti-inflammatory, analgesic, anti-cancer activities and many more (8). Eugenol, a major compound present in clove, has been shown to be effective in inhibiting cancer growth in various cell lines. In addition, research has shown that eugenol possess anti-inflammatory activities that can be used to treat inflammatory conditions. This paper presents the current findings on the anti-cancer effects and immunomodulatory actions of the compound eugenol, and evaluates its potential in treating cancer and immune related conditions.

1. The link between cancer and immune activity

The immune system is a defensive system that protects the body against foreign substances that could potentially cause harm. In addition to eliminating infection, it is involved in many other physiological processes such as the development, repair and healing of wounds, thus maintaining tissue homeostasis and integrity (9). The first defense mechanisms involve the innate immune responses, which comprises of white bloods cells such as neutrophils and macrophages that engulf and destroy the foreign substance in a process known as phagocytosis. This first line of defense also involves non-hematopioetic components such as the epithelial linings of the respiratory and gastrointestinal tracts, that rid of the infection through mechanical actions such as mucusal linings (10). If the infection is not resolved, dendritic cells will stimulate he second line of defense, the adaptive immune response, which is long lasting and more specific than the innate immune system (11). It comprises of lymphocytes, such as T helper cells and B cells, that function to produce antibodies leading to immunity against the infecting pathogen. These groups of immune cells, including cytotoxic T cells and natural killer (NK) cells, play an important role in targeting and eliminating cancer cells (12). Some the functions include triggering apoptosis, engulfment and immune cell recruitment and more (13). These responses are triggered by humoural components known as cytokines, which also trigger inflammation. Inflammation is characterized by swelling, redness and pain that removes the infectious substance and initiates the healing process (14). However, inflammation, specifically chronic inflammation, is also the sole source of any problems that involve inflammation mediated tissue injuries, which can occur in organs such as the heart, lungs, brain and other systems, leading to cardiovascular disease, diabetes and cancer (15).

It has been shown that oxidative stress, cancer and chronic inflammation are closely linked together (16). The reactive oxidative species (ROS) released during an inflammation process can promote cell mutations and proliferation, and in turn, the tumor cells may cause the overexpression of pro-inflammatory mediators that could stimulate immune cells for further cytokine production (17) (figure 1). This creates an ‘immune dialogue' between cancer and immune cells. Targeting these interactions could act as a therapeutic option in treating conditions resulting from these factors.

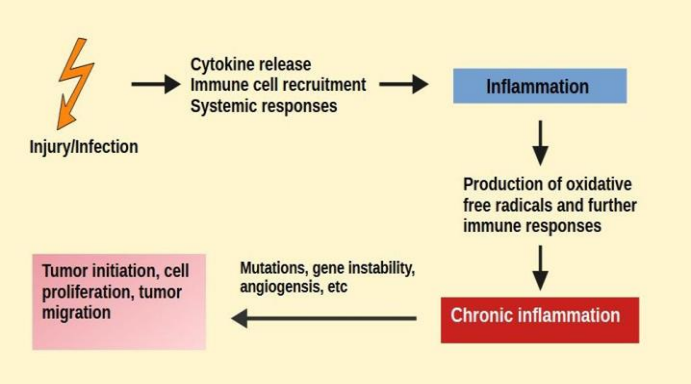


Figure 1. Tumor formations resulting from immune reactions and inflammation.

2. Eugenol

Eugenol, also known as 4-allyl-2-methoxyphenol or eugenic acid, is a natural phenylpropanoid with an allyl chain-substituted guaiacol found in several herbal plant species (18). It is the major bioactive compound found in clove, with concentrations varying between 9 381.70 to 14 650.00 mg per 100 g of the plant (19). Eugenol can be isolated from plant essential oils using extraction methods such as steam distillation and microwave assisted extraction, and was utilized for commercial use by the United States in the 1940s (20). In the industry, eugenol has been used as a food flavoring and preserver, as well to treat toothaches and pulpitis, and acts as a flourishing agent, an allergen, a sensitiser, an anesthetic, a radical scavenger, and many

more roles (figure 2) (21). It has been classified generally recognized as safe (GRAS) chemical by the World Health Organization (WHO) and is labeled as a nonmutant (22).

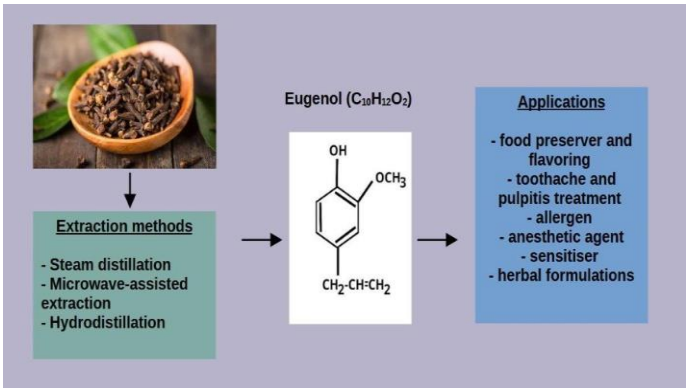


Figure 2. Extraction methods and applications of eugenol compound.

Some of the pharmacological properties that eugenol processes includes antimicrobial activity (anti-bacterial, anti-viral, anti-parasitic and anti-fungal activities), analgesic activity, and many more (18). Studies have shown that eugenol also possesses anti-diabetic effects, such as stimulating glucose uptake and facilitating insulin sensitivity, thus acting as a therapeutic agent in treating type 2 diabetes (23). Due to its structure possessing hydroxyl groups, eugenol is able to scavenge toxic free radicals that can cause cell or tissue damage, leading to mutations (24). Quantitative studies have demonstrated its strong scavenging effect on DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals and inhibition on ROS (25). Thus, eugenol is labeled as a strong antioxidant.

Many research is available demonstrating the beneficial properties of eugenol in treating diseases like cancer (26). The polyphenol has been shown to reduce proliferation and migration in various cancer cell lines by targeting gene expressions and specific molecular pathways which trigger apoptosis (27). Thus, making eugenol an ideal candidate in cancer targeted treatments. Eugenol has also been shown to possess anti-inflammatory properties by reducing the gene expression of pro-inflammatory cytokines, such as cyclooxygenase 2 (COX-2), and cascade reactions that regulate the inflammatory process (28). Therefore, eugenol has potential to used in therapeutic interventions in treating inflammatory mediated diseases.

3. Anti-cancer mechanisms of eugenol

Mutations which trigger oncogenesis can happen in various components of the cell signaling pathway, such as nuclear proteins, cell surface receptors, kinases, phosphatases and cytoplasmic enzymes (29). Targeting these specific genetic mutations and metabolic pathways can lead to the development of targeted therapies in cancer patients. Eugenol has shown to exert anti-cancer activities against different cancer cell lines through various mechanisms of action (table 01). Such anti-cancer activities typically include inhibiting cell proliferation, cell migration, triggering apoptosis and cell cycle arrest, and many more.

3.1 Breast cancer

Breast cancer is the most commonly diagnosed malignant cancer in women worldwide. Despite advances in early detection, mortality rates have not changed (30). Therefore, new therapeutic methods are currently studied to combat against the disease by targeting specific signaling pathways that promote proliferation and malignancy. Such pathways involve proto-oncogenic signaling pathways like Wnt, Notch, SHH, and many more (31).

Research has shown that eugenol is effective against breast cancer cells through various mechanisms of action. A study demonstrated the anti-metastatic effect of eugenol against MDA-MB-231 and SK-BR-3 breast cancer cell lines, where a significant reduction in levels of MMP gene expression was observed, indicating that eugenol may be effective in suppressing triple negative and HER2-positive breast cancer metastasis (32). Another study revealed that eugenol inhibited the proliferation of triple-negative breast cancer cells by targeting the NOD1-NF-κB signaling pathway (33).

An early study revealed that eugenol at low doses (2uM) showed specific toxicity against breast cancer cells, mediated by inducing apoptotic pathway and down-regulation of E2F1/survivin pathway (34). Another study demonstrated that eugenol was able to trigger apoptosis in melanoma breast cancer cells in vitro by causing disruptions of the G2/M phase of cell cycle, and mitochondrial toxicity (35).

3.2 Colon cancer

Colon cancer is the third most most common cancer diagnosed worldwide and the second most common cause of mortality due to cancer (36). Various molecular signaling pathways have been attributed to the development of the cancer. Common mechanisms include Notch, PI3K/AKT pathway, Wnt, mitogen-activated protein kinase (MAPK) cascades and more. Mutations in these signaling pathways has been linked to the progression and development of colon cancer (37).

Many studies support the idea of using eugenol as a chemoprotective agent against colon cancer. It has been demonstrated that eugenol was able to reduce the cell viability of HT-29 colorectal adenocarcinoma cells in a dose-time dependent manner (38). The same study showed that treatment with IC50 of 500uM significantly increased the levels of p53 tumor suppressor genes and APC, and a decrease in KRAS oncogene expression. These genes are generally involved in the colonrectal cancer progression. An early study showed that eugenol suppressed the gene expression of COX-2 in HT-29 human colon cancer cells (39).

3.3 Skin cancer

Skin cancer is the fifth most common cancer diagnosed worldwide, and is expected to rise in cases in the next 20 years (40). It comes in many types such as melanoma, basal cell carcinoma and cutaneous squamous cell carcinoma, and a majority of its cases is caused by exposure to ultraviolet radiation (UV) (41).

Eugenol has been shown to protect against chemically induced skin cancer by inhibiting gene expressions of COX-2 and iNOS, as well as signaling molecules such as NF-kappaB (2). The study also demonstrated an increase in p53 expression and p21(WAF1) levels in epidermal cells after treatment with eugenol, leading to apoptosis. An in vivo study showed that treatment with eugenol reduced the size and incidence of skin tumors at the dysplastic stage in Swiss mice (43). The experiment showed that eugenol treatment led to the downregulation of c-Myc, H-ras and Bcl2 expression, whilst upregulating expressions of P53, Bax and active Caspase-3 in the lesions.

3.4 Lung cancer

Lung cancer is one of the leading cause of death in men with a poor prognosis (44). The common frequently altered genes that occur in 35% of lung cancers are RAS genes that control cell proliferation, NEU gene that is associated with prognosis, p53 and many others that promote the cell proliferation (45).

It has been demonstrated that treatment with eugenol in lung cancer ademocarcinoma A549 cells reduced expressions of phosphate-Akt and MMP-2 activity via PI3K/Akt pathway, inhibiting its cell proliferation, invasion and migration (26). Another study showed that in diethylnitrosamine (DENA)/acetylaminofluorene (AAF) administrated rats, that were then induced with lung cancer, treatment with eugenol exhibited a significant decrease in BcL-2 expression and an increase in p53 and Bax expressions (46). This indicates that eugenol possesses anti-proliferative properties against lung cancer cells.

3.5 Cervical cancer

Cervical cancer is labeled as the second most common cancer diagnosed in women globally, that is linked with infection of the human papillomavirus (HPV) (47). Gene abnormalities that play a role in the pathogenesis of the cancer include c-myc oncogene, ras genes, cyclin dependent kinases and more (48). Targeting these genes and treating HPV infection with vaccines are common therapeutic methods under development for cervical cancer. Eugenol has shown promise in its anti-cancer effects against cervical cancer cell lines. A study demonstrated its anti-cancer effects against HeLa cells, showing a decrease in Snail-1 and vimentin gene expressions, inhibiting cancer migration (49). Another study showed that treatment with eugenol in HeLa cells resulted in a downregulation of Bcl-2, COX-2, and IL-1β genes, triggering apoptosis (50).

Table 1. Summary of anti-cancer mechanisms of eugenol against cancer types.

Cancer type	Treatment dosage	Mechanism of action	References
Breast cancer	2uM	Downregulation of the NOD1-NF-κB signaling pathway and the E2F1/survivin pathway	(33,34)

Colon cancer	500uM	Reduced expressions of COX-2 and KRAS, and increase p53 gene expressions	(38,39)
Skin cancer	1% eugenol in acetone	Inhibited expressions of COX-2, c-Myc, H-ras and Bcl2 genes and increased p53 and p21 expressions	(42,43)
Lung cancer	1000uM	Reduced expressions of MMP-2, BcL-2 and phosphate-Akt activity whilst increasing p53 and Bax expressions.	(26, 46)
Cervical cancer	200 uM	Prevents cell migration by targeting Snail-1 and vimentin gene expressions and triggers apoptosis	(49, 50)

4. Effects of eugenol on immune system

The concept of using materials that establish the immune system's ability to prevent or treat diseases is referred to as immunotherapy. Its aim is to balance the immune responses such that it eliminates cancer cells whilst preventing any autoimmune inflammatory responses (51). This type of therapy is selective and therefore personalized for each patient.

It is widely known that eugenol exerts some effects on the immune responses of the body. Traditionally, it has been used to relieve conditions such as asthma and allergies. A research study investigating its mechanisms of action revealed that eugenol is able to halt T cell proliferation and exerted an immunosuppressive effect on dendritic cells (52). This indicates that eugenol can be used to control autoimmune and hypersensitivity conditions. A group of immune cells called myeloid derived suppressor cells (MDSCs), plays a role in tumor cell progression through their immunosuppressive activity in the tumor environment (53). Eugenol has a selective inhibitory effect on these cells in a dose-dependent manner, triggering apoptosis via the intrinsic pathway (54).

Many research has shown that eugenol possesses significant anti-inflammatory activities that can be unitized to treat inflammatory related diseases. A study by Kaur *et al* demonstrated the anti-inflammatory activity of eugenol in mice by showing a decrease in proinflammatory cytokines (TNF-alpha, IL-6 and PGE2) levels, and COX-2, iNOS and ODC activity (42). Another research study showed that pretreatment with eugenol in procine intestinal epithelial cells with lipopolysaccharide (LPS) induced inflammation inhibited LPS stimulated IL-8 levels and the mRNA of TNF-alpha (55). A recent study showed that eugenol is able to interfere with the NLRP3 inflammasome assembly and IL-1 beta production, and is involved in post-transcriptional mechanisms that regulated the inflammation process (56). These findings suggests that eugenol exerts significant anti-inflammatory actions through different mechanisms of action, which can be used to treat various conditions related to inflammation. For example, an interesting study by Lee *et al* revealed that eugenol was able to suppress pro-inflammatory mediators as well as immune cell infiltration into mice spinal cords induced with autoimmune encephalomyelitis. Thus reducing the symptoms of the autoimmune disease (57). By inhibiting inflammatory actions, eugenol is able to reduce any cellular or tissue damage exerted by the mediators, which could contribute to future tumor development (figure 3).

Eugenol has been shown to effect the immune responses in many other ways as well. For example, an early study suggested that eugenol has a dose-dependent enhancing and suppressive effects on the immune response in mice (28). Eugenol has also been shown to stimulate the production of mucus in mice intestine, strengthening the mucosal barrier against invading pathogens and diseases (58). Overall, the effects of eugenol on the immune system has shown to be beneficial in preventing and treating illnesses.

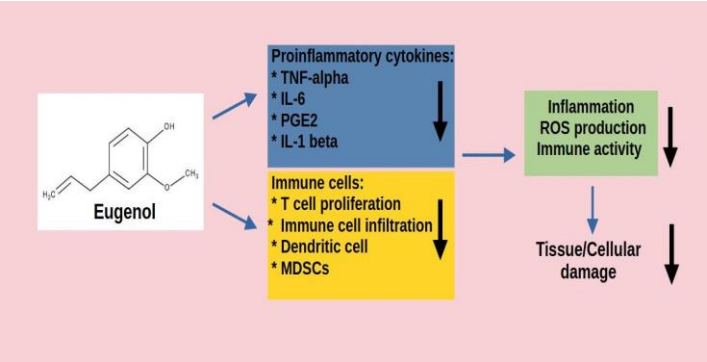


Figure 3. Eugenol inhibiting inflammation and immune activity leading to less cellular damage.

5. Enhancing eugenol therapeutic properties

It is possible through utilizing different methods that the therapeutic properties of a compound can be enhanced to achieve better results. In the recent years, the field of nanotechnology has been incorporated into herbal treatment methods. It involves the use of nanoparticles which are synthesized from biodegradable lipids, polymers and other safe materials, with the purpose of developing dosages within the range of 1 to 100nm (59). Polymetric nanoparticles and solid lipid nanoparticles are common forms nanoparticles used in research studies with advantages such as increased bioavalibility of drug and improved physicochemical stability (60). By using nanoparticle drug delivery systems, the drugs are delivered in a controlled manner to the targeted area of treatment, which reduces the development of resistance and adverse effects whilst increasing the efficiency of the drug (61). A study demonstrated that enzyme-responsive nanoparticles loaded with eugenol was able to prevent the invasion and migration of colorectal cancer cells at high doses whilst maintaining a low concentration among the healthy cells (62).

Another way to enhance the therapeutic properties of a substance is to combine them with other drugs that will act in a synergized manner. Many studies have shown that eugenol combined with other chemotherapeutic drugs can enhance its overall anti-cancer effect (63). Methyl eugenol, when combined with cisplatin, induces apoptosis, cell cycle arrest and anti-cancer activities against HeLa cervical cancer cell lines (64). Another study showed that the combination of eugenol and gemcitabine was able to induce apoptosis and growth inhibition in HeLa cells at lower concentrations, thus minimizing toxicity in healthy cells (50). Eugenol is also able to increase the sensitivity of pancreatic cancer cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) which induces apoptosis (65).

6. The need for alternative therapeutic options

One of the main reasons alternative treatment options are required is due to the rise in drug resistance. It is mentioned that 90% of failures in chemotherapy, the most promising cancer treatment, is related to cancer drug resistance in patients (66). This happens when cancer cells become desensitized towards common drug treatments by altering the drug targets, activating survival defense pathways, and other resistance mechanisms that aid the cancer cell in evading the cytotoxic treatment methods (67). By incorporating different drug formulations derived from herbal plants and the use of nanotransport systems, the resistance mechanisms can be bypassed and allow for a better therapeutic effect with less side effects (61). In addition, the cost of treatment would be cheaper in comparison to synthetic chemotherapeutic drug usage, allowing it to be affordable to more patients. Clinical trails are required to test the long term effects of eugenol on the human body in order to establish the efficacy and safety of the compound.

Conclusion

Eugenol has shown great promise in its potential as an anti-cancer drug and its therapeutic effects against inflammatory conditions. The available research has showed that the bioactive compound acts by targeting specific molecular pathways in different cancer types preventing proliferation and cell migration. Eugenol is also able to effect the immune responses by acting on molecular components such as cytokines and immune cells. Using eugenol provides many benefits such as reduced drug resistance development and serious adverse effects. Therefore, through the utilization of herbal based formulations, more efficient therapy can be developed in the future against diseases which are typically difficult to treat due to treatment cost and complications. Further research must be conducted to pave the way to clinical trails and eventually in the treatment sector.

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Author contribution

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Conflict of interest

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