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Review Article

Eugenol-A Reminder of Its Carcinopreventive Properties

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Abstract

It has long been recognized that herbs and plants can be used as spices in everyday cooking. With time, it became clear that the majority of them had healing characteristics, and they became an important part of traditional medicine. Research revealed that phytochemical are the dominant ingredients in nutrients that exert beneficial effects in cases of pain, inflammation, and even cancer. Eugenol, the principal component of cloves buds (Syzygium aromaticum, Myrtaceae family) has long history with therapeutic properties and gained a respectable position in dental medicine. In addition to its antibacterial, antifungal, antioxidant and antipyretic activities, research with cancer cells has shown that eugenol possesses a considerable potential as a carcinopreventive agent. Oddly, while eugenol targeting cancer cells in vitro provided persuasive and hopeful results, animal models and human trials are scarce. This point inspired the present survey on the effect of eugenol on various types of cancer in expectation of drawing researchers' attention to its anticancer activities and to bring eugenol in front of anticancer drugs adjuvants.

Keywords: foreign body; heart; vessels; The percutaneous retrieval; intravascular foreign bodies

Introduction

Traditional medicine has made extensive use of various herbs and plants. Plant-derived essential oils have been used to treat inflammation, toothaches, and fever [1]. Some of them are utilized as both spices and therapeutic remedies, cloves buds (Syzygium aromaticum, Myrtaceae family) being a suitable example. Cloves' main constituent, eugenol, has been shown to have anti-inflammatory, antioxidant, neuroprotective, anti-diabetic, and antibacterial properties [2,4]. The principal mechanism by which eugenol protects cells from oxidative stress is through the expression of Nrf2 (nuclear factor erythroid 2-related factor) [5]. Inhibition of the oxidative stress prevents inflammation, a process further reinforced by the capacity of eugenol to suppress cyclooxygenase-2 (COX-2) expression, an enzyme possessing both inflammatory and carcinogenic effect [6,7]. The inhibitory activity of eugenol on COX-2 is similar to that of NSAIDs (nonsteroidal anti-inflammatory drugs), but without their undesirable side effects [8]. Eugenol has been demonstrated to have immunomodulatory and anticancer properties [9,10]. While eugenol did not affect the capacity for cytokine production by non-stimulated peripheral blood mononuclear cells, or cells from the HT-29 human carcinoma cell line, co-incubation of immune and cancer cells in the presence of eugenol resulted in reduced secretion of IL-1β, IL-1-ra, and IL-1011. Choudhury et al. [12] investigated the effect eugenol on EAC (Ehrlich Ascites Carcinoma) and MCF-7 (human breast cancer) stem cells and observed enhanced apoptosis accompanied by a decrease in β-catenin overexpression, linked to different malignancies and a reduced mRNA expression of the stem cells' markers. Jaganathan et al. [13] published a detailed review of the ways by which eugenol induces apoptosis of malignant cell and exerts an anti-proliferative effect. Furthermore, eugenol's anti-oxidant action, which predominantly targets hydrogen peroxide, has been shown to decrease matrix metalloproteinase-9 activity in PMA-stimulated HT1080 cells, a fibrosarcoma cell line [14]. In comparison to eugenol, its derivatives showed a stronger antioxidant and anti-proliferative impact on human uterine cancer (HeLa) cells [15]. Through reduction of the PI3K/AKT/mTOR pathway, a key tool for cell cycle regulation, methyl eugenol had beneficial effects on cell viability, enhanced autophagy, and mitotic arrest at the G2/M cycle of RB355 (retinoblastoma) cells [16]. Additional molecular pathways by which eugenol exerts its chemotherapeutic qualities include inhibiting NF-k activation and downregulating prostaglandin production [17]. Given the compelling eugenol carcinopreventive effects observed largely in vitro, it is puzzling that they haven't been tested in more extensive animal and human studies. The aim of this work was to survey the effect and the mechanisms by which eugenol affects different types of cancer, as well as to promote introducing it as an additional tool to the arsenal of anti-cancer medications.

Eugenol and digestive tract cancers

The natural polyphenols contained in everyday foods attracted researchers' attention as for their effect on oral, gastric and colon cancers. When incubated with SCC-25, an oral squamous cell cancer cell line, eugenol was found to induce apoptosis and produce a mitotic arrest at the S-phase [17]. One of the principal mechanisms by which eugenol may prevent the development of gastric cancer is its anti-oxidant propperty [19]. Furthermore, eugenol was found to promote apoptosis and decrease invasion in a rat model of gastric carcinogenesis via regulating Bcl-2 proteins, increasing cytochrome C2 activity and reduced angiogénesis [20]. Through the same paradigm, eugenol decreased cell proliferation and repressed NF-kB expression, resulting in a lower incidence of gastric cancers [21]. The importance of eugenol as an apoptosis inducer was highlighted by Sarkar et al. [22], who found that this function can proceed without the presence of the tumor preventer gene P53 by activating caspase-8 and caspase-3. When AGS (human gastric adenocarcinoma) cells were treated with eugenol, a marked anti- metastatic activity was observed due to inhibition of the TGF-β (transforming growth factor beta) pathway, which occurred independently of P21 (cyclin dependent kinase inhibitor) or P53 (cellular tumor antigen) [3]. The pathways through which eugenol exerts its anti-colorectal cancer characteristics have mostly been studied in vitro. COX-2 overexpression plays a key part in colorectal cancer formation, as it does in other malignancies, hence eugenol's ability to downregulate its activity makes it a useful chemopreventive [23]. Furthermore, because arachidonic acid and COX-2 are strongly linked in the progression of carcinogenesis, eugenol has been demonstrated to suppress colorectal cancer cell growth [24,25]. Eugenol induced apoptosis in human colon cancer lines by generation of reactive oxygen species leading to DNA fragmentation and activation of P53, caspase-3 and diphosphate-ribose-polymerase [26]. Due to the stimulation of reactive oxygen species creation, increased apoptosis was achieved in human HTB [37] colon and HB8065 liver cancer cells when treated with eugenol-loaded nanoemulsions [27]. Based on the findings that patients with colorectal cancer have mutations of the tumor suppressor genes p53 and APC (adenomatous polyposis coli) on one hand, and the tumor promoter gene KRAS on the other [28], Ghodousi-Dehnavi et al. [29] reported that treating HT29 colon carcinoma cells with eugenol increased the expression of p53 and APC genes, while decreasing that of KRAS. Treatment of colon (HTB370 and liver (HB8065) cancer cells with eugenol-loaded nanoemulsions resulted in a significant increase in apoptosis mediated by ROS generation [27]. It is conceivable that eugenol's anti-proliferative properties observed in colorectal cancer cells in vitro could serve as a foundation for more animal and human research.

Eugenol and breast cancer

Breast cancer is a major public health issue, and significant efforts are being undertaken to enhance therapy. Eugenol has been recognized as a possible adjuvant chemotherapeutic for treatment of breast cancer, functioning through a variety of mechanisms, one of which is the activation of apoptosis and decreased proliferation of malignant cells. Eugenol treatment of human MCF-7 breast cancer cells decreased growth and proliferation while increasing apoptosis, with dose and time dependent effects and lowered intracellular glutathione level [30]. Following exposure to eugenol, triple-negative MDA-MB-231 breast cancer cells showed reduced cell proliferation, enhanced apoptosis, and autophagic cell death due to activation of the apoptotic regulators PI3K/Akt and FOXO3a [31]. Ma et al. [32] reported that eugenol was able to inhibit the proliferation MCF-10A breast cancer cells by suppressing the expression of HER2 (human epidermic growth factor) receptor, an important operator in the development of breast cancer. Notable, the proliferation of MCF-10 breast cancer cells with weak HER2 expression did not respond to eugenol. Inhibition of HER2 expression by eugenol had an anti-metastatic effect on MDA-MB-231 and SK-BR-3 breast cancer cells in addition to its anti-proliferative activity [33]. Recent research has detected that semisynthetic isoeugenol derivatives have a strong apoptotic effect on MCF, ER-2 alpha (estrogen receptor) positive breast cancer cells. In addition, cell cycle arrest at G2/M phase and inhibited proliferation were observed [34]. E2F1, a pro-apoptotic transcription factor that functions independently of p53 and ERα and has been shown to be downregulated in a range of malignancies, is one of these transcription factors that influences cell development and apoptosis [35]. According to Al-Sharif et al. [36], eugenol can induce apoptosis and reduce malignant cell proliferation by boosting E2F1 activity in a variety of breast cancer cell lines, including triple negative subtypes. This effect was achieved even with low doses of eugenol (2μM) [37]. The research studies mentioned above give the idea that eugenol could be a beneficial therapeutic strategy in the treatment of breast cancer.

Eugenol and lung cancer

Despite significant attempts to reduce smoking in order to avoid lung cancer, the fatality rate from this tumor remains high. Research with phytochemicals indicates that eugenol might operate as a chemopreventive agent also in this type of malignancy. Choudhury et al. [38] reported that treating A549 human lung cancer cells with eugenol increased their apoptosis and giving it to mice with N-nitrosodiethylamine (NDEA)-induced lung carcinoma suppressed malignant cell proliferation and limited tumor development in its dysplastic stage. According to the authors these findings were connected to a reduction of β-catenin nuclear transportation, which resulted in lower expression of a few cancer stem cell markers implicated in their proliferation. Inhibited expression of PI3K/Akt pathway and MMP (matrix metalloproteinase) activity were found to be additional ways to restrict A549 cell migration and proliferation [39]. Eugenol markedly suppressed xenograft tumor progression in non-small cell cancer bearing mice by inhibited NF-kB (nuclear factor kappa B cells) and TRIM [59] (tripartite motif) pathways which are upregulated in various types of cancer40. Notably, in mice with benzol-pyrene-induced lung carcinogenesis, clove aqueous infusions were observed to reduce the amount of lung lesions, stimulate apoptosis, and decrease malignant cell proliferation. The activation of the pro-apoptosis proteins p53 and BAX, as well as the downregulation of the anti-apoptotic protein Bcl-2, caused these alterations [41]. Despite the small number of data, the overall impression is that eugenol is a potent chemopreventive, also in cases of lung cancer.

Synergistic properties of eugenol.

Treatment of HeLa cells with eugenol alone or in combination with active compounds from green tea and chirata plants caused a stronger anti-proliferative effect, which was explained by downregulation of cyclin D1 and upregulation of cell cycle inhibitors, resulting in cell cycle arrest at the G1/S pase [42]. The anti-cancer effect of conventional medications might be greatly enhanced when combined with eugenol. Eugenol coupled with 5-fluorouracyl increased cytotoxicity against cervical cancer (HeLa) cells with higher number of cell in S and G2/M phases [32], with no negative side effects [43]. Eugenol combined with gemcitabine enhanced dose-dependent cytotoxicity and increased apoptosis in HeLa cells compared to each medication used alone [44]. Similar effects were obtained when HeLa cells were treated with a combination of myricetin and methyl eugenol [45]. When joined with cisplatin and X-rays eugenol revealed a synergistic effect on HeLa cells growth and death, with increased caspase-3 and 9 activity, Bax expression, and decreased synthesis of interleukin-1 beta (IL-1-β) and Cox-

246. Similar results were obtained when HeLa cells were treated with both sulforaphane and eugenol due to downregulation of Bcl-2, COX-2 and IL-1β47. The survival and growth of SKOV3 and OV2774 ovarian cells was markedly constrained when eugenol was added to cisplatin, following inhibition of the Notch-Hes1 signaling pathway. Moreover, treatment of mice with ovarian cancer with eugenol-cisplatin combination was followed by slower tumor progression and increased survival [48]. Eugenol amplified the effect of cisplatin on the apoptosis of triple-negative breast cancer cells by inhibition of the NF-kB signaling pathway and reduced generation of the pro-inflammatory cytokines IL-6 and IL-849.

To summarize, eugenol appears to be a powerful health promoter with a wide range of biological activities that occur via a variety of signaling pathways. Its positive benefits against the proliferation and metastatic ability of numerous types of cancer cells, as well as its strong proapoptotic capacity, should make further extensive animal and human study a challenge. Further research into its anticarcinogenic qualities could result in a valuable treatment tool that can be used alone or in conjunction with conventional anticancer medications.

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