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Review Article

EUGENOL – A REVIEW OF A VERSATILE MOLECULE WITH REMARKABLE PHARMACOLOGICAL PROPERTIES

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ABSTRACT

Eugenol (4-allyl-2-methoxyphenol) is a major volatile component of clove (*Eugenia aromaticum*) essential oil and several medicinal plants. It is a remarkable molecule with broad spectrum of applications extensively in the fields of cosmetic, agricultural and pharmaceutical as it shows slow toxicity, easily available at low cost and rapid metabolism. Recently eugenol has been used for prevention of life threatening diseases like sepsis, Leishmaniasis, Alzheimer's, gingivitis, heart diseases, gastrointestinal diseases and cancer as it possesses wide range of pharmacological activities in addition to analgesic activity including anti-oxidant activity, antimicrobial, anti-inflammatory and anticancer properties. In recent years, eugenol remains a priority in research field due to its broad range of remarkable biological and pharmacological actions. However, there is no overall discussion of versatility and pharmacological action of eugenol elsewhere. In this review, we discuss the overall scenario of pharmacological potential of eugenol.

Keywords: Eugenol, Pharmacological, *Eugenia aromaticum,* Analgesic, Antibacterial.

1. INTRODUCTION

In recent years, potential of phenolic phytochemicals presents in medicinal plants have been widely researched for treatment of life threatening diseases. Eugenol (4-allyl-2-methoxyphenol) is one such interesting molecule which has opened broad range of research. Eugenol, a phenolic phytochemical compound, is an active constituent of most medicinal plants and possesses remarkable spectrum of pharmacological activities like antipyretic, analgesic, anti-inflammatory, antioxidant, antimicrobials, anticancer, central and neuroprotective action and anesthetic effects [1-3]. It has been reported that eugenol usually shows anti-inflammatory and anti-oxidant activity at lower concentration, whereas the generation of free radicals elevates at higher concentration *i.e.* acts as a pro-oxidant [4]. Both the World Health Organization (WHO) and Food and Agriculture Organization (FAO) have allowed a daily intake of eugenol of 2.5 mg/kg body weight for humans [5]. Moreover, the U.S. Food and Drug Administration (FDA) have proclaimed eugenol as safe and it is considered as non-mutagenic and non-carcinogenic [6-8]. In this review, we will discuss the overall scenario of pharmacological potential of eugenol and also deal with other pharmacological activities of eugenol like neuroprotective, anthelminthic and anti- leishmanial.

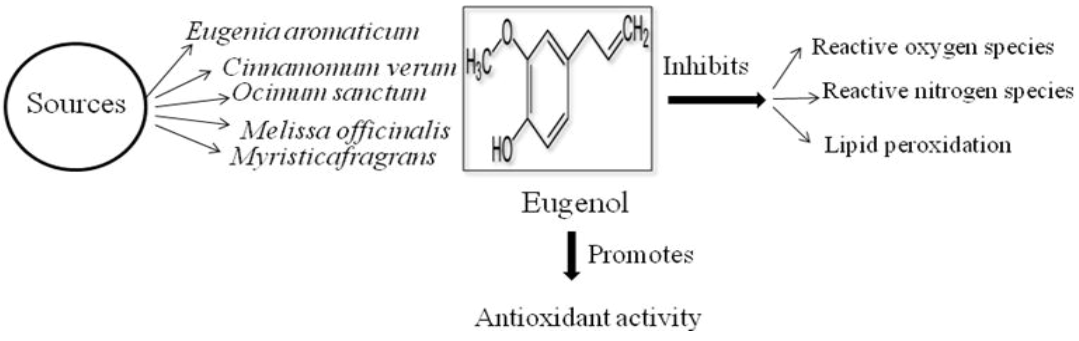

Fig. 1: Mode of action of Eugenol

2. NATURAL SOURCES AND CHEMICAL PROPERTIES OF EUGENOL

The name eugenol originated from the scientific name of cloves, *Eugenia aromaticum* from which it was isolated for the first time. It has also been isolated from other aromatic plants like *Cinnamomum verum*, *Ocimum basilicum*, *Cinnamomum tamala*, *Illicium anisatum, Melissa officinalis*, *Ocimum tenuifloruma* and *Myristica fragrans* which contain 45-90% eugenol as active constituent [9-11]. Eugenol is also isolated from *Rhizoma acori graminei* (RAG), from the fraction of volatile oil [12]. Eugenol ($C_{10}H_{12}O_2$) is 4-allyl-2 methoxy phenol with its phenyl part containing a modified benzene ring and an allyl group attached to it (fig. 1). Phenolic group confers antioxidant property to it. It is weakly acidic, less soluble in organic solvent and more soluble in water [11]. It is a clear, colorless or pale yellow oily liquid [9].

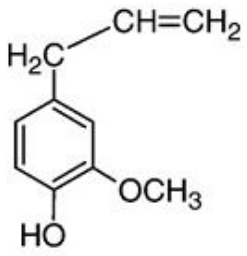

Fig. 2: Structure of eugenol

3. PHARMACOLOGICAL ACTION OF EUGENOL

3.1. Antibacterial activity

Eugenol inhibits the growth of both Gram-positive (*Staphylococcus aureus, Bacillus cereus*, *B. subtilis*) and Gram -negative (*Salmonella typhi*, *Escherichia coli*, *Pseudomonas aeruginosa*) bacteria. Eugenol shows antibacterial activity against various pathogens such as *Helicobacter pylori*, *Streptococcus pneumonia, E. coli*, *S. aureus*, *B. cereus*, *S. epidermidis* and *S. pyogenes.* It has been reported that eugenol affects the bacterial membrane of four strains of bacteria: *Proteus vulgaris, S. pyogenes, Listeria monocytogenes* and *E. coli* [13-19].

3.2. Antifungal potential

Eugenol shows antifungal activity against pathogens such as *Penicillium citrinum*, *Fusarium graminearum*, *C. krusei, F. moniliforme*, *Aspergillus ochraceus*, *P. viridicatum*, *Tricophyton rubrum*, *Candida tropicalis* and *T. mentagrophytes* [17-20]. The antifungal effect of eugenol was evaluated against 38 *Candida* species and 10 collections of *Candida* strains [21]. The minimum concentration of eugenol that inhibits growth of fungus ranged from 0.06 to 0.25% (v/v) [21], while the concentration that inhibits 50% of the isolates (MIC_{50}) ranged from 0.06 to 0.12% (v/v).

Eugenol has been shown to be highly toxic to *C. albicans* (killing 99.9% inoculums) with MIC value of 0.5 mg/mL [22] and exhibited promising inhibitory effect also against *Microsporum gypseum* with the MIC value ranging from 0.01 to 0.03% [23]. Eugenol treatment of 0.5 mg/mL significantly interferes with the development of envelope of *C. albicans* and interferes with adhesiveness and colonizing ability of the fungus [24]. The fluconazole-resistant or multi-drug resistant isolates of *C. albicans* can be treated in combination of eugenol/ methyleugenol with fluconazole or amphotericin B [25].

3.3. Antiviral potential

Eugenol shows antiviral activity against human herpes virus HSV-1 and HSV-2. The effective concentration of eugenol for HSV-I and HSV-II viruses is reported to be 25.6μg/mL and 16.2μg/mL, respectively. Eugenol shows ≥ 90% inhibition against human cytomegalovirus (CMV), murine CMV (MCMV) and hepatitis C virus [26, 27]. Eugenol inhibits autophagy and influenza-A virus replication by inhibiting the activation of IKK/NF-κB, ERK and p^{38}MAPK signal pathways [28].

3.4. Antioxidant activity

Oxidative stress is the hallmark of many chronic diseases. The imbalance of anti-oxidants and pro-oxidants results in the development of such diseases. One study has shown that eugenol acts as both pro-oxidant and anti-oxidant [29]. Thus, this compound may help in prevention of many diseases, including cancer, arteriosclerosis, diabetes and immune deficiency diseases by overcoming oxidative damage. The strong antioxidant activity of eugenol is due to the presence of the phenolic group [2]. Eugenol attributes anti-oxidative property, as it can reduce ROS by trapping hydroxyl radical directly which results in reducing oxidative stress. This property helps in maintaining good health, increasing life span and other biochemical diseases because oxidative stress is the hallmark of such diseases [30, 31]. Cloves and eugenol possess strong antioxidant activity, comparable to synthetic antioxidant. The percentage inhibition ranged from 41 to 93% against the DPPH and from 39 to 62% against hydroxyl radicals, respectively [17]. Eugenol is the most active compound, with an IC_{50} value of 46.6μM [19].

3.5. Lipid per oxidation Activity

Antioxidant property of eugenol and its related compounds inhibits lipid peroxidation and LDL oxidation by forming complexes with reduced metals like- ferrous ion, ferric-ion and cumene-hydroperoxide [31]. Eugenol attributes free radical scavenging effect and it inhibits iron-mediated lipid peroxidation and copper dependent LDL oxidation [32]. It is suggested that eugenol may interfere with fatty acid radical intermediates by scavenging hydroxyl radicals [33].

3.6. Anti-inflammatory and analgesic action

Inflammation is linked with the release of inflammatory mediators by phagocytic cells, which activates cyclooxygenases (COX) 1 and 2 enzymes. COX-2 in turn produces prostaglandin E2 (PGE2), an inflammatory mediator. So, COX-2 is considered as potential pro-inflammatory agent [34]. Eugenol shows potential anti-inflammatory action on COX-2 and 15-lipoxygenase enzyme at 10μg/mL and 25μg/mL, respectively [35]. In addition, eugenol directly inhibits COX-2 enzyme activity in intact cells [34]. Eugenol inhibits nuclear factor-κB (NF-κB) which in turns inhibits tumor necrosis factor (TNFα) which blocks cyclooxygenase activity (COX-2) in LPS stimulated macrophages [36]. Eugenol (50, 100μg/mL) inhibit interleukin (IL)-6 production after addition of LPS and it significantly counteract LPS action [36]. Eugenol has an inhibitory effect on the enzyme 5-LOX with an IC_{50} value of 26.0μM and production of leukotriene-C4 (LTC4) in human polymorphonuclear leukocytes (PMNL) cells with an IC_{50} value of 30.0μM [37]. Eugenol is used in dental clinics as a routine analgesic agent that alleviate tooth pain by blocking Ca^{++}, Na^{+} and K^{+} channels in trigeminal ganglion (TG) neurons [38-40]. Eugenol has shown to exhibit an antinociceptive effect at doses of 50, 75 and 100 mg/kg [35]. It has been reported that eugenol transmit signal for modulation of pain by activating TRPV1 (transient receptor potential vanilloid1) receptors [35].

3.7. Anticancer and Pro-apoptotic Activity

Eugenol is used for prevention and treatment of some cancers like-cervical carcinoma, gastric cancer, prostate cancer, skin cancer and melanoma. Eugenol shows curative effect on prostate cancer when it is used in combination with 2-methoxyestradiol [41]. A study shows that eugenol (150μM) in combination with gemcitabine (15μM) down regulates growth of cancer cells in cervical carcinoma [42]. It is also used for treatment of gastric cancer, skin cancer and melanoma [3]. Eugenol doses varies in different cell lines, it inhibits 50% cell growth at a concentration of 0.5μM in WM3211 and Sbcl2 cell lines while, twice of this dose is required for 50% growth inhibition in WM98-1 and WM1205Lu cell lines [43]. Eugenol reduces proliferation of tumor cells by almost 40% [44]. Eugenol induces apoptotic signal by down regulating the activation of anti-apoptotic protein Bcl-2, Apaf-1 and impelling cytochrome-c release to the cytosol which induces apoptosis through the intrinsic mitochondrial dependent pathway [45, 46]. It has been reported that eugenol present in *Ocimum sanctum* extract decreases the expression of Bcl-2 protein in a dose dependent manner [47].

3.8. Anthelmintic and Anti-insecticidal action

Eugenol shows anthelmintic activity against promastigotes and amastigotes with an IC_{50} value of 135 and 100μg/mL [48, 49]. Study reveals that 100% of *Leishmania amazonensis* parasites were destroyed by eugenol at 100 mg/ml [49]. The anthelmintic activity of the eugenol was also reported against fish parasite *Gyrodactylus* sp. with an LC_{50} value of 42.5 mg/L [50]. These results support eugenol as a potential therapy for parasitic diseases. The anti-insecticidal activity of eugenol was studied on small ruminants of *Haemonchus contortus* at a concentration of 0.5% and *Giardia lamblia* [51]. Eugenol affects on the activity, growth, adherence and ultrastructure of these insects. Eugenol is being used as an effective drug for prevention of giardiasis and verminosis [51].

3.9. Treatment of Alzheimer's disease

Alzheimer's disease is a neurodegenerative disease, caused due to accumulation of amyloid beta protein (Aβ) in the brain which results in memory deficits. Recent studies suggest that efficacy of many medicinal plants containing specific polyphenols or phenols have been evaluated for the prevention and treatment of Alzheimer's disease. Medicinal plant *Rhizoma acori graminei* (RAG) is one of several plants that prevent Alzheimer's disease due to its ability to alleviate amyloid beta peptides (Aβ) accumulation [52]. Eugenol is one of the active constituent of RAG that inhibits excessive influx of calcium ion induced by Aβ protein into neurons. In addition to this, eugenol possesses an antidepressant-like activity [53]. Depression is an

extremely complex disorder and it appears due to many reasons. Biological reason behind it is, a small part of the brain that is responsible for storage of memories *i.e.* hippocampus, appears to be smaller and has fewer serotonin receptors. Serotonin is a neurotransmitter that is involved in processing emotions. It has been reported that eugenol exhibits an antidepressant-like activity, as in hippocampus it elevates the expression of neurotrophic factor, that promotes the growth of neurons [54]. Thus, eugenol can be used as a drug for prevention and treatment of AD and depression. Here, we suggest that eugenol and its analogs can also be used for other central nervous system (CNS) disorders including Parkinson's disease (PD) [55].

4. CONCLUSION

Eugenol is a versatile molecule with potential pharmacological properties. It is widely used as a therapeutic agent as it acts against broad spectrum of pathogens like-bacteria, virus, fungi and other parasites and is also used to treat life threatening diseases. In addition to this, it also has advantage of lesser drawbacks as compared to synthetic compounds due to its lesser toxicity and lower cost. But, the molecular mechanisms for all types of pharmacological actions are not clearly explained. In future, we look forward to find more detailed data related to molecular mechanisms for all types of pharmacological actions of eugenol.

Conflict of Interest

None declared

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