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Review Article

Mechanistic Approach to the Pharmacological Status of a Phenolic Biomarker: Hydroxychavicol

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Abstract

Piper betel Linn. (Family: Piperaceae) is an evergreen perennial vine, native to Southeast Asian countries. Due to its great nutritive, medicinal and economic value it is termed as "Green Gold" in India. Since ages, leaves of *P. betel* have been used as medicine either alone or as adjuvant to other medicine due to various pharmacological activities such as antioxidant, antimicrobial, anti-inflammatory, antidiabetic, hypo-lipidemic, antiplatelet etc. Chemically, leaves of betel vine are reservoir of phenolic compounds. Eugenol and hydroxychavicol are two chief phenolic biomarker compounds isolated from different extracts of *P. betel* L. leaves. Through understanding of the molecular mechanisms through which the phenolic biomarker exerts free radical scavenging activity, hypolipidemic activity, antibacterial activity, antifungal and cytotoxic effects may help various researchers for understanding structural-activity relationship and new drug development. Therefore, in the present review briefly summarizes the current state of knowledge regarding the possible mechanism behind all the pharmacological activities of hydroxychavicol, a phenolic biomarker isolated from *P. betel* leaves.

Keywords: Eugenol; Hydroxychavicol; Antioxidant; *Piper Betel* l; Antifungal

Abbreviations

HC: Hydroxychavicol; *P. betel: Piper betel*; GSH: Glutathione; *S. mutans: Streptococcus mutans; E. coli: Escherichia coli*; TXB2: Thromboxane B2; ROS: Reactive oxygen species; COX: Cyclooxygenase; APC: Allylpyrocatechol; CHB: Chavibetol; CML: *Chronic Myeloid Leukemia*; fMLP/CB: formyl-Met-Leu-Phe and Cytochalasin B.

Introduction

Phenolic compounds are valuable secondary plant metabolites, produced in plants by shikimic acid and pentose phosphate pathway through phenylpropanoid metabolism. Structurally, they contain an aromatic ring with one or more hydroxyl groups. Due to wide structural diversity, they may range from simple low-molecular weight phenolic to complex high-molecular weight phenolic compounds. They are collectively termed as polyphenolic compounds. Due to free radical scavenging activity (antioxidant activity) and ability to bind with proteins (antimicrobial activity) polyphenolic compounds play an important role in the chemical defense mechanism of the plants against predators and pathogens [1]. Scientific research on polyphenolic compounds is gaining more attention due to reported health benefits on their consumption. Epidemiological studies reported that long term consumption of natural sources of polyphenolic compounds provide markable protection against development of various types of tumors such as chronic myloid leukemia, cardiovascular diseases such as hypertension and thrombus formation, diabetes and its complications, ulcer. osteoporosis etc. (Figure 1) [2].

Literature show extensive reports pharmacological status of plant polyphenolic compounds for example, four Piper species namely *Piper crassinervium, P. aduncum L., P. hostmannianum* and *P. gaudichaudianum* shows antifungal activity because of the presence of crassinervic acid, aduncumene, hostmaniane and gaudichaudanic acid phenolic compounds respectively [3]. Mace., *et al*. (2017) reported the antibacterial activity of 25 plant derived phenolic compounds such as phlorizin, naringenin, myricetin, thymol, resveratrol, napthaquinone derivative etc. against *Streptococcus pyogenes* main causative agent for pharyngitis. However, all phenolic compounds show some antibacterial activity but 1,2-naph-

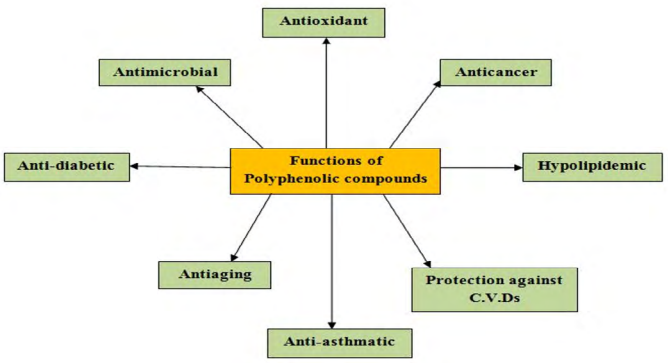

Figure 1: Pharmacological properties of plant polyphenolic compounds.

thoquinone and 5-hydroxy-1,4-naphthoquinone showed more bactericidal activity and can be used as synergistic combination with other antibiotics for the management of *Streptococcal pharyngitis* [4]. Phenolic compounds exhibit strong antioxidant properties and prevent various biomolecules such as DNA, proteins etc. from oxidative stress due to environmental toxins. They behave like reducing agent and oxygen quenchers. In addition to direct antioxidant action, they also show effects on cell signaling pathways, thus modifying gene regulation and cell redox status [5]. Many herbs and spices such as thyme, basil, pepper, cinnamon, clove, ginger, turmeric, rosemery, garlic etc. are rich source of simple and complex phenolic compounds as shown in figure 2 [6].

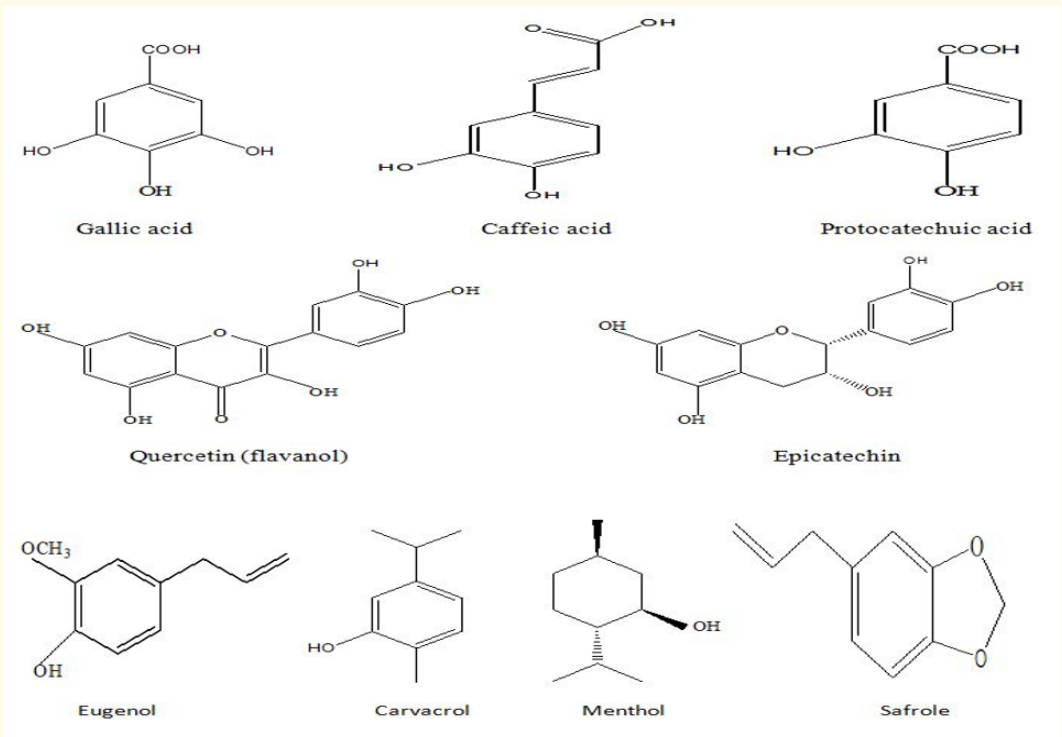

Figure 2: Structure of phenolic compounds.

The present review paper focus on various pharmacological activities of hydroxychavicol (HC) with their mechanism. HC has been extracted from various solvent extracts of *Piper betel* Linn. *P. betel* (Family: Piperaceae) commonly known as "Green Gold" is a tropical, dioecious, shade loving, evergreen creeper, generally grown in hot and damp parts of the Southeast Asian countries. Its main origin is Malaysia. Heart shaped leaves of plant is being popular as Paan [7]. Due to great ethno-medicinal importance, *P. betel* is widely cultivated and used in India, Indonesia and other countries such as Vietnam, Laos, Kampuchea, Thailand, Myanmar and Singapore [8]. The aromatic nature of *P. betel* leaf is due to the presence of essential oils, that chiefly contains phenolics and terpenoids as phyt-

oconstituents. The main active phytoconstituents present in P. betel leaf oil are chavibetol, chavicol, estragole, eugenol, methyl eugenol, isoeugenol, hydroxychavicol, hydroxy catechol, caryophyllene, eugenol methyl ether, carvacrol, sesquiterpenes, cadinene, caryophyllene, dotriacontanoic acid, hentriacontane, pentatriacontane, sitosterol, β-sitosteryl palmitate, γ-sitosterol, stigmasterol, ursolic acid and ursolic acid 3β-acetate [9]. In fact, these constituents are responsible for the medicinal, aromatic and stimulant properties of the leaves. HC has been reported as chief biomarker compound of various leaf extracts of *P. betel*. A number of therapeutic activities of HC have been reported by various researchers. Therefore, in the present paper we try to focus on the mechanism of various pharmacological activities of HC v.i.z. antioxidant, antimicrobial, anticancer, antiplatelet, antidiabetic, antihypertension, antihyperlipidemic etc. However, several paper such as multi-mechanistic approach of antioxidant activity of polyphenolic compounds; resveratrol (3,5,4-trihydroxystilbene), electrochemical properties and mechanistic approach to antioxidant activity of caffeic acid (3,4-dihydroxycinnamic acid), and protocatechuic acid (3,4-dihydroxybenzoic acid) [10], mechanistic insights of eugenol for anti-diabetic action [11] have been published. But, till date, to the best of our knowledge, this is first review on mechanistic approach of various pharmacological activities of hydroxychavicol.

Hydroxychavicol (HC)

HC, found as brown colored solid, (4-allyl-catechol, 1-allyl-3, 4-dihydroxybenzene) is a major phenolic compound in *P. betel* leaves (Figure 3).

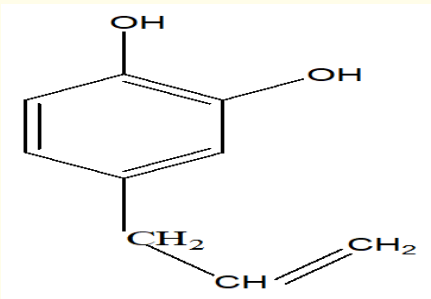

Figure 3: Structure of hydroxychavicol (1-allyl -3, 4-dihydroxybenzene).

It has been reported for various therapeutic activities such as antimicrobial, antioxidant, antiplatelet, anticancer, antiulcer, antidiabetic etc. HC has been reported for induction of cell apoptosis by generation of oxidative stress inside cell membrane which causes disturbance in cell cycle and ultimately cancerous cell death [12].

Mechanism of antimicrobial (including both antibacterial and antifungal) activity of hydroxychavicol

HC has reported for bactericidal and fungicidal properties. Superficial fungal infections are most common skin related problem affecting an average 20-25% of world population. If it gets ignored can be a cause of serious implications. One of the major causes of these infections include dermatophytes, non dermatophytic moulds and yeasts [13]. Sharma., *et al*. isolated HC from aqueous leaf extract of *P. betel* and evaluated its antibacterial potential against oral cavity pathogens. HC has been reported to show bactericidal activity against all tested bacteria *v.i.z. Streptococcus mutans*, *Enterococcus. faecium*, *Enterococcus faecalis*, *Streptococcus sanguis, Actinomyces viscosus* and *Porphyromonas. gingivalis*. HC was reported to exhibit a long post antibiotic affect and prevent the reoccurrence of *S. mutans* and *A. viscosus* associated infection. The probable mechanism of action was confirmed by increased uptake of propidium iodide in the HC-treated cells of *S. mutans* and *A. viscosus which in turn* confirmed alteration in structure of microbial cell membrane. The cell membrane gets disturbed by losing its permeability which further causes cell death by leakage of cytoplasmic content [14]. Thamaraikani., *et al*. studied the antimicrobial potential of HC against *Escherichia coli.* They reported that the antimicrobial activity is due to the inhibition of cell wall growth proteins. HC binds firmly to cell wall protein and causes cell damage. Furthermore, they reported inhibition of the formation of biofilm by *E. coli*. in stomach which in turn prevents their growth [15]. Ali., *et al.* established *in-vitro* antimicrobial action of HC against 58 strains of yeasts, 39 strains of *Aspergillus* species and 27 strains of dermatophytes. Hydroxychavicol has been reported to show lowest MIC value for dermatophytes ranging from 7.81 to 62.5 µg/ml and moderate MIC for yeasts ranging from 15.62 to 500 µg/ml and highest MIC for *Aspergillus* species ranging from 125 to 500 µg/ml. Propidium iodide is a fluorescent nucleic acid stain that is unable to penetrate into normal cell due to rigid membrane structures. However, it gets penetrate into cells with fully and partially damaged cell membranes. Therefore, propidium iodide staining of HC treated cells indicates the disruption of the permeability barrier of microbial membrane structures [16]. Singgih., *et al*. formulated and evaluated some mouthwash preparation containing HC as active ingredients in a concentration of 0.3 and 0.6. HC has been found to show antifungal activity against the mold *Aspergillus niger* and antibacterial activity against bacteria *Staphylococcus*

aureus, *Bacillus cereus, Pseudomonas aeruginosa and E. coli* of both formulations were reported. Thymol has the highest antimicrobial activity toward *S. mutans* but it still found to have higher MIC value than pure hydroxychavicol. The antimicrobial action of HC is due to its favorable physicochemical properties. This may be due to the oily nature of HC, bacteria cannot survive in fat or oil since it needs water for its growth and reproduction [17]. Ali., *et al.* investigated *in-vitro* antifungal activity of hydroxychavicol against onychomycosis causing microorganisms *v.i.z. Epidermophyton floccosum*, *Microsporum gypseum*, *Trichophyton mentagrophytes*, *T. rubrum*, and *Candida. parapsilosis*. Onychomycosis is a fungal infection affecting toe nails and finger nails causing discoloration of nails color and excessive pain and discomfort. HC has been reported to show broad spectrum fungicidal activity against all tested pathogenic fungi. Interestingly, the fungicidal effect of HC was more pronounced for *T. rubrum* having minimum inhibitory concentration (MIC) 30.4 µg/ml. In more than 70% cases, *T. rubrum* is the main fungal agent for chronic dermatophytosis. Further, the study demonstrated that the mechanism of antifungal action of HC is membrane disruption of fungal cell. The antifungal potential of HC was not affected by the presence of keratin or serum because of its lower affinity with both of them, suggesting that hydroxychavicol might exist in the infected skin tissues in a free and active form. For exploring the mechanism of action of HC, on *C. parapsilosis* (ATCC 200954), flow cytometry, confocal microscopy, electron microscopy, and inhibition of ergosterol synthesis studies were performed. From all these studies, it has been confirmed that HC affect the membrane permeability by causing damage of cell wall which finally leads to cell death by leakage of the cytoplasmic content of the cells. Finally, it has been concluded that hydroxychavicol might be an effective alternative topical antifungal agent for the treatment of dermatophytosis (*Tinea corporis*) and cutaneous candidiasis [18]. Jesonbabu., *et al.* (2011), isolated HC from chloroform extract of *P. betel* and evaluated its antibacterial potential against against the pathogenic microbes; *P. aeruginosa, S. aureus, Streptococcus pyogenes, E. coli*, *Salmonella typhi* and *Shigella dysentriea*. It has been reported that HC demonstrated the bactericidal activity towards five bacterial species except the *P. aeruginosa*. The mechanism of bactericidal activity was plasma cell membrane damage and coagulation of the nucleoid on microbial cell [19]. Recently, Singh., *et al.* (2018) investigated the main mechanism of HC for its antibacterial action against *E. coli.* The investigator reported that antibacterial action of HC has been attributed to HC mediated oxidative stress inside the bacterial cell. HC treatment resulted ROS generation that further causes the loss of cell viability. For supporting their finding, they reported that cell lethality has been reduced by treating HC treated bacterial cell with powerful antioxidant like thiourea. In this investigation they showed that HC generates superoxide in *E. coli* cells which induces cell death [20].

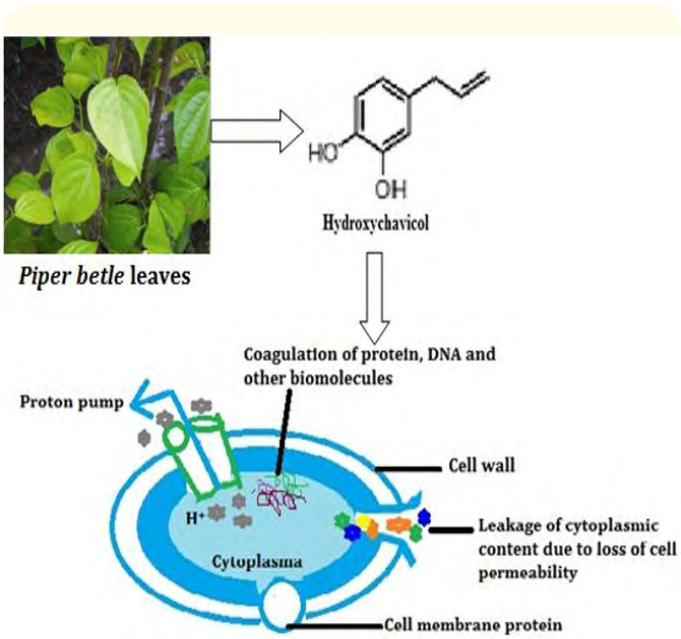

Figure 4: Mechanism of antimicrobial action of hydroxychavicol.

Mechanism of antioxidant and anti-inflammatory activity of hydroxychavicol

Rathee., *et al.* (2006) evaluated the *in-vitro* antioxidant activity of ethanol extract of *P. betel* leaf. They further isolated two biomarker; chavibetol (CHB) and allylpyrocatechol (APC) by column chromatography of ethanol extract of *P. betel* leaf. It has been found that APC (isomer of HC) showed maximum free radical scavenging activity in 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. APC also tested for lipid peroxidation (LPO) and radioprotective activity. The better anti LPO and radioprotective activity of APC is due to ability to scavenge free radical due to more phenolic content [21]. Lin., *et al.* isolated HC from ethanol extract of roots of *P. betel* L. and reported its anti-inflammatory activity. Additionally, they isolated four more compounds namely; 2-(γ'-hydroxychavicol)-hydroxychavicol dimer, aristololactam, piperolactam A and cepharadione A. The anti-inflammatory activity was based on their inhibitory activity against superoxide ion (antioxidant property) and anti-neutrophilic inflammatory assay. HC was reported to exhibit more pronounced anti-inflammatory activity as compare to other isolated compounds as result of significantly

inhibition of superoxide ion generation and elastase release by human neutrophils, in response to formyl-met-leu-phe and cytochalasin B (fMLP/CB). Thus, investigator evaluated the anti-inflammatory and antioxidant potential of HC [22].

Mechanism of ulcer healing activity of hydroxychavicol

Battacharya., *et al*. evaluated the healing effect of allylpyrocatechol (APC); isomer of HC, on indomethacin-induced acute stomach ulceration of rats. Administration of repetitive dose of indomethacin causes markable damage to gastric mucosa which was further evaluated by macroscopic and histopathological examinations. Ulcer healing effect was studied in APC treated rat group as compare to vehicle treated auto-healing control group. The researcher explained the basic principle of HC for anti-ulcer effect is antioxidant activity of HC. As the tissue damage occurs due to excess generation of free radical which causes defects in protein synthesis pathway. Thus, investigator suggest the antioxidant activity of HC is main mechanism for its antiulcer activity in indomethacin induced ulcer model [23].

Mechanism of antiplatelet activity of hydroxychavicol

Chang., *et al.* studied the *in-vitro* antiplatelet activity by platelet aggregation assay, thromboxane B2 (TXB2) assay, COX (cyclooxygenase) inhibition study and ROS scavenging activity. *In-vitro* activity was performed using platelet suspension of rabbits. *In-vivo* platelet plug formation has been evaluated in mice. All studied parameters are play important role in management of cardiovascular disease like hypertension and stroke. It has been reported that HC is a potent COX-1/COX-2 inhibitor, ROS scavenger and inhibits platelet calcium signaling, TXB2 production and aggregation. The mechanism behind antiplatelet activity was found to be inhibition of synthesis of arachidonic acid, inhibition of surface glycoprotein Ia/IIa and VI receptor which stimulates collagen induced platelet aggregation and inhibition of protease-activated receptors (PAR-1, PAR-3 or PAR-4) and glycoprotein Ib which induces THB2 production. Researchers also discussed the prior report of eugenol antiplatelet activity. They specified that eugenol possessed COX-1 inhibiting and partially COX-2 inhibiting activity. In their study, they reported HC as more potent COX1 and COX2 inhibitor than eugenol. They further added more xanthine oxidase inhibiting activity of HC is due to functional -OH group [24].

Mechanism of anticancer activity of hydroxychavicol

Chakraborthy., *et al.* evaluated the cytotoxic effect of alcoholic extract of *P. betel* leaves on *chronic myeloid leukemia (*CML) cell line. Further researchers also reported the anti-CML activity of HC, which is main bioactive compound of alcoholic extract of *P. betel* leaves. Imatinib (Gleevec) has been used as anticancer drug to chronic myeloid leukemia but resistance has emerged against this drug. This study reported apoptosis of CML cells expressing wild type and mutated Bcr-Abl and showed activity against imatinib-sensitive and imatinib-resistant CML xenografts when treated with alcoholic leaf extract of *P. betel*. Recent studies suggest that the alcoholic extract of *Piper betel* leaves induces apoptosis of CML cells expressing wild type and mutated Bcr-Abl and shows activity against imatinib-sensitive and imatinib-resistant CML xenografts. The basic mechanism of HC for cytotoxic effect on CML cell line was reported to be the accumulation of ROS in mitochondria of CML cell and continuous accumulation of nitric oxide which leads to cell damage. The study furher reported that HC have a unique property that ii possessed anticancer activity without any side-effects to normal cells such as GSH depletion was not observed after HC treatment [25]. Similar study was carried out by Gundala., *et al.* investigated anticancer activity of HC on prostate cancer cells. Researchers proved the pro-oxidant nature of HC. HC induced peroxides and superoxides in a time-dependent manner. Basically, HC killed cancerous cells via ROS-mediated mechanism. It was also observed that the HC-induced ROS caused DNA damage, as signified by the increase in the expression of γ-H2AX foci that form around the DNA breakage sites [26]. Paranjpe., *et al.* studied the anticancer activity of methanol leaf extract of betel vine. They fractionated methanol leaf extract using solvent of different polarity and found that F2 fraction containing HC as a chief biomarker compound (26.59%) possessed effective anticancer activity. Mechanism for anticancer activity was found to be HC induced apoptosis in leukemic cells by increasing the levels of mitochondria-derived reactive oxygen species that activated the c-jun N-terminal kinase pathway, thus leading to the loss of mitochondrial membrane potential. Structural activity relationship has been also explained in this study. The presence of a hydroxyl group, an electron-donating moiety at the ortho and para positions of HC enhances its reducing property and antioxidant property. However chavibetol another phenolic biomarker of F2 fraction do not possess free catechol group therefore, have less antioxidant potential as compare to HC [27]. Shwu., *et al.* evaluated the genotoxic potential of HC through oxidative DNA strand breakage. HC was tested positive in *S. typhimurium* TA102 without metabolic activation. In this study, in Chinese hamster ovary (CHO-K1) cells, HC showed chromosome alterations in a dose-dependent manner and the majority was genomic alterations based on structural and content variations. It has been found that HC broke the plasmid DNA strands. Possible mechanism behind this was

found to be generation of ROS such as H_2O_2 which participates in fentone type reaction and induced plasmid DNA strand break. Furthermore, formation of 8-hydroxydeoxyguanosine by HC results in chromosomal aberration and hence cell death [28].

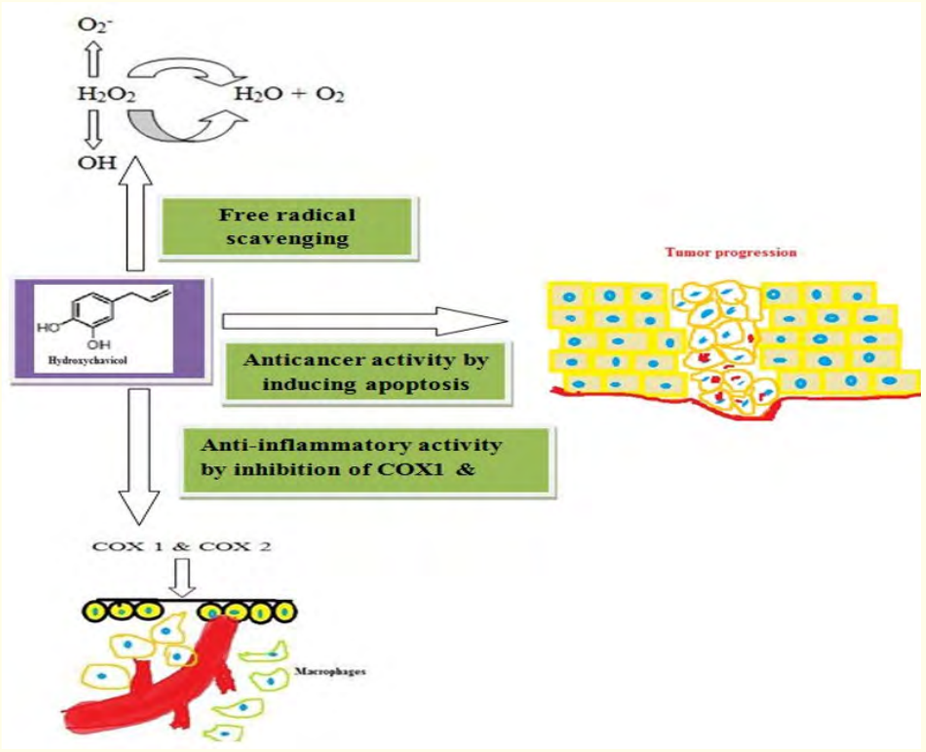

Figure 5: Mechanism of antioxidant, anticancer and anti-inflammatory activities of hydroxychavicol.

Mechanism of antidiabetic and antilipidemic activity of hydroxychavicol

Antidiabetic and antilipidemic activity of HC has been evaluated using type 2 diabetes mellitus (T2DM) rat model. T2DM was induced by high fat diet (HFD) and low dose of STZ administration. It has been found that reduction in body weight of rats treated with STZ occur due to fat and protein catabolism and polyuremia. Increase in weight was observed in HC treated rats. From glucose tolerance test (GST) it has been found that in control group showed more blood glucose level than HC treated group. The mechanism of antidiabetic effect of HC was reported the insulin stimulatory effect of HC. Diabetic rats treated with HC significantly inhibit proteolysis caused by insulin deficiency and improves total protein level to normal value and this mechanism of action of HC is comparable to that of metformin. The anti-lipidemic effect of HC on the levels of total cholesterol, triglycerides and lipoproteins such as high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) in diabetic rats were reported. It has been found that levels of total cholesterol, triglycerides, LDL and VLDL were elevated significantly with simultaneously decline in the levels of HDL in the diabetic group of rats than that of control group of rats. On HC oral administration, all parameters come back to their normal values. Inactivation of hepatic adenosine monophosphate kinase (AMPK) is a key event in the pathogenesis of hypolipidemia in diabetic rats and HC induced phosphorylation of AMPK and increased activity of AMPK thus results in hypo-lipidemic action [29].

Conclusion

On the basis of above study, it can be concluded that hydroxychavicol is a natural derived non-toxic, phenolic compound that can be used as a therapeutic agent for antimicrobial, anticancer and anti-diabetic activities. It can be used alone or with standard antibiotics for synergistic effects for infectious diseases such as dermatophytosis, pharyngitis etc. However, preclinical and clinical trial should be done before its exposure to human beings.

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