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SOURCE, PRODUCTION AND BIOLOGICAL ACTIVITIES OF PICEATANNOL: A REVIEW

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ABSTRACT: Phenolic compounds are group of molecules which contain different families of secondary metabolites. Phenolic compounds, secondary metabolites, are abundantly found in plants and are mostly categorized into two major groups: non-soluble compounds and soluble compounds. Stilbenes which come under the category of soluble compounds of phenolics are small molecules, ranges in their weight from ~200 to 300 g/mol and are found in diverse plants. These compounds are produced in plants via phenylpropanoid pathway. Under unfavourable conditions such as microbial or viral attack, ultraviolet light exposure and disease in plants, stilbenes are synthesized and act as natural agents to protect plants. Piceatannol, a natural stilbene, is found in different plant species and is beneficial for human health. It possesses various pharmacological properties such as antioxidant, antitumor, anti-inflammatory and anti-carcinogenic activities. This review paper focuses on piceatannol, its sources, chemical synthesis mechanism, production and its useful applications in various diseases.

INTRODUCTION: Polyphenols are secondary metabolites in plants, which contain a benzene ring and one or more than one hydroxyl (OH) group in their structure [1]. They are generally categorized as flavonoids, phenolic acids, phenolic alcohols, stilbenes and lignans [2]. Phenylalanine is the precursor molecule which enters in shikimic acid pathway and results in the formation of different types of polyphenols. Usually these polyphenols are produced in plants under stressed conditions and are also called phytoalexins. They help in protection of plants against pathogenic attack or injury.

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These polyphenolic compounds are beneficial for plants as well as humans. They function as antioxidants and improve health status of humans [1].

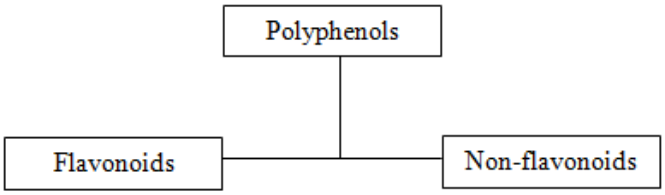

FIGURE 1: TWO MAJOR TYPES OF POLYPHENOLS

Stilbene: soluble polyphenols: Stilbenes are naturally occurring and are small molecular weight (~200-300 g/mol) compounds. These are generally found in several types of plants, plants products and dietary supplements. These exits in two isomeric forms such as in trans (Z) and in cis (E) forms. It has been experimentally proved that the trans and cis forms of stilbenes trigger different beneficial activities [3].

Piceatannol: A stilbene: Piceatannol (3, 5, 3', 4'-tetrahrdroxystilbene) is a naturally occurring polyphenol. It has a melting point of 223-226^{o}C and has a molecular weight 244.24 g/mol. Piceatannol is insoluble in water but dissolve either in dimethyl sulphoxide (DMSO) or in ethanol. It contains two phenolic rings associated by a styrene bond. Presence of styrene double bond in its structure results in trans (E) and cis (Z) isomeric forms. Trans (E) isomeric form is found to be geometrically more stable than cis (Z) form. Piceatannol's absorption spectrum shows that it absorbs maximum light at 322 nm (nanometer) [4].

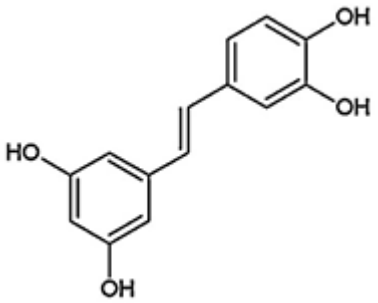

FIGURE 2: PICEATANNOL [4].

Natural sources of piceatannol: Piceatannol has been extracted from *Polygonum cuspidatums* [5]. Montepulciano wine which is produced in Lazio is found to contain maximum amount of piceatannol [6]. Passion fruit (*Passiflora edulis*) [7,8], *Arachis hypogaea* [9], *Vitis thunbergii* [9], and *Ampelopsis brevipedunculaata* [9] are the name of few fruits and plants in which piceatannol concentration has been found. A recent study has verified the presence of piceatannol in Sim fruit (*Rhodomyrtus tomentosa*) [10].

Chemical synthesis of piceatannol: Although piceatannol can be found in several plants and fruits, yet it may be synthesized chemically by two different ways. First way of its chemical synthesis requires benzylphosphonates, which are byproduct of benzylhalides [11]. Alternatively, it may be synthesized by taking 3, 5-dihydoxyacetophenone as a starting chemical agent. 3,5-dihydoxyacetophenone is also cheap and commercially available chemical. Therefore it's a better choice to synthesize piceatannol by the aid of this chemical [12].

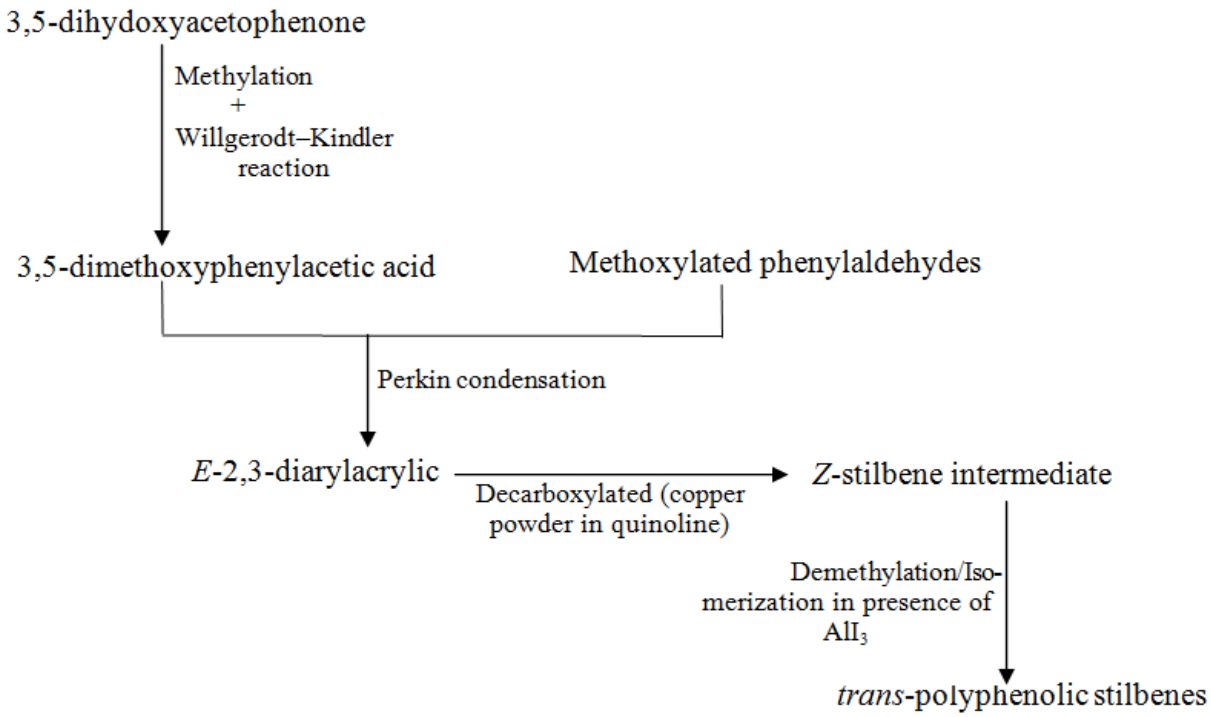

FIGURE 3: CHEMICAL WAY OF SYNTHESIS OF PICEATANNOL BY PERKIN REACTION

Piceatannol bioavailability: The term bioavailability is defined in various ways. But the most preferable definition of bioavailability is the fraction of nutrient which is digested, absorbed and is metabolized by normal pathway [13]. Bioavailability studies are done to determine which polyphenols are absorbed in a better way than others. Polyphenol's chemical structure is the main key factor which determines the extent and rate of absorption of polyphenols and the form of metabolites which circulate in the plasma [2]. Piceatannol's absolute oral bioavailability (F),

when administered orally by using 2-hydroxypropyl-β-cyclodextrin as a carrier vehicle, is found to be 50.7±15.0% [14].

Pharmacokinetics studies of piceatannol: During pharmacokinetics studies of piceatannol, high performance liquid chromatography (HPLC) technique was used to detect the amount of piceatannol and type of its metabolite present in rat [4]. On injecting piceatannol (10 mg/Kg body weight) through intravenous route, it was observed that it gets eliminated (half-life of elimination) through body within 2 hours [15]. Piceatannol was administered in body through two different routes: intravenous and oral route and a comparative study on the half-life of elimination of injected piceatannol through two routes were done by the help of an HPLC method.

Piceatannol when administered through i.v. route, its elimination half life time has been found to be around 313±20 min. Some amount of piceatannol (19±2 ng/ml) was detected in plasma for 12 hours after it was injected through i.v. route. But when it was popped up orally, it was quickly absorbed in body. After oral administration, 28±3 ng/ml of this compound has been detected in the plasma after 12 hours [14]. In a comparative study, the results depicted that this compound has excreted through the body via non-renal pathway [16].

PRODUCTION AND GENERATION OF PICEATANNOL:

Piceatannol's production under lime stressed condition: The presence of high amount of bicarbonate in soil induces iron chlorosis. Iron chlorosis affects the size of fruits and compositions of different compounds in fruits. Iron is the main constituent of many enzymes involved in the synthesis of lignin in plants. Iron deficiency switches the shikimate pathway and results in the production of phenolic compounds including anthocyanins.

When cv. Merlot plants were grown under lime stressed condition, the level of stilbene was found to be increased with respect to plants grown in under-stressed condition. On the basis of berry's fresh weight, a relative increase of 550 % in piceatannol was observed than plants grown under normal conditions. On the basis of berry's skin area, an increase of 406 % in piceatannol's concentration has been observed with respect to normal plants [17].

Piceatannol's production in callus of peanut by using ultraviolet (UV) radiations: Cell culture of *Arachis hypogaea* is used to produce piceatannol because stilbene synthase can easily be induced in cultured tissues under controlled condition; peanuts are inexpensive and can easily be obtained for cell culture experiments. Three major parameters: irradiation power, irradiation time and position of UV-C light, contribute to the induction of piceatannol production in callus culture. One gram callus culture of *Arachis hypogaea* was irradiated with UV radiation under controlled environment. The amount of induced piceatannol content varies from 2.17 µg to 5.31 µg when callus was grown in static culture condition [18].

Generation of piceatannol from resvertraol by using Bacterial Cytochrome P450 BM3: CYP102A1 is one of the mutants of *Bacillus megaterium* P450 BM3. Recent advances suggest that CYP102A1 can be used as biocatalyst for the synthesis of drugs. Mutation in CYP102A1 enzyme enabled it to catalyze hydroxylation reaction. When trans-resveratrol was treated with CYP102A1 enzyme, this enzyme hydroxylated the trans–resveratrol compound and produced piceatannol. The formation of piceatannol, a hydroxylated product of resveratrol, was authenticated by high performance liquid chromatography and GC-MS [19].

Piceatannol's production by the help of chitin in peanut callus: After systematic investigation, Yang et al. has found that chitin component of fungal's cell wall acted as an elicitor and also stimulated the synthesis of piceatannol in peanut callus culture. The amount of trans-piceatannol produced by fungi has found to be 2.55±0.60 µg/g [20].

Picetannol's production by the help of medicinal mushroom in peanut callus culture: *Ganoderma lucidum* is a medicinal mushroom and is generally recognized as safe (GRAS), the elicitor. Moreover, Yang et al. have observed the dose dependent effect of *Ganoderma lucidum* on induction of piceatannol in callus culture of peanut. The total amount of piceatannol produced after 24 hour has been detected.

It has been seen that the amount of piceatannol production has increased with increasing the amount of added viable mycelia upto 10mg in callus culture and also with 80 mg of sterilized mycelia. Maximun amount of trans-piceatannol has been induced by the viable mycelia of *Ganoderma lucidum* and it has found to be 2.88±2.08 µg/g. This amount is about 70% greater than the amount produced b sterilized mycelia [21].

AN EFFECTIVE APPROACH TO DETECT PICEATANNOL: Researchers have been trying to find out plants containing piceatannol because it is present in very low concentration in plants. Therefore, an efficient and sensitive method is required to detect its presence in different plants. An analytical method designed to identify the presence of piceatannol in plants has been mentioned in literature. When a high performance liquid chromatography (HPLC) is attached with ultra violet and fluorescent detectors, the amount of piceatannol can easily be identified in plant samples without the need of standards. This analytical method has found to be effective in identifying amount of piceatannol in different plant species [9].

APPLICATIONS AND MECHANISM OF ACTION OF PICEATANNOL IN DIFFERENT DISEASES:

Inhibit invasion and metastasis of tumor: Matrix metalloproteinases (MMPs) are a part of zinc dependent endopeptidases. Under metastatic state and under normal physical conditions they function in the deterioration of extracellular matrix (ECM). Normally their activities are tightly regulated but deregulation in activities of MMPs is linked to development of cancer and metastasis. One of these, MMP-9 has found to be expressed in tumors of different organs such as prostate, brain and pancreas. Therefore, inhibition of activity of MMP-9 is an effective strategy to treat cancer. The results confirm that piceatannol down regulates TNF (tumor necrosis factor) -α-induced invasion by suppressing the activity of MMP-9 via nuclear factor-κB (NF- κB) pathway in prostate cancer cells of DU145 [22].

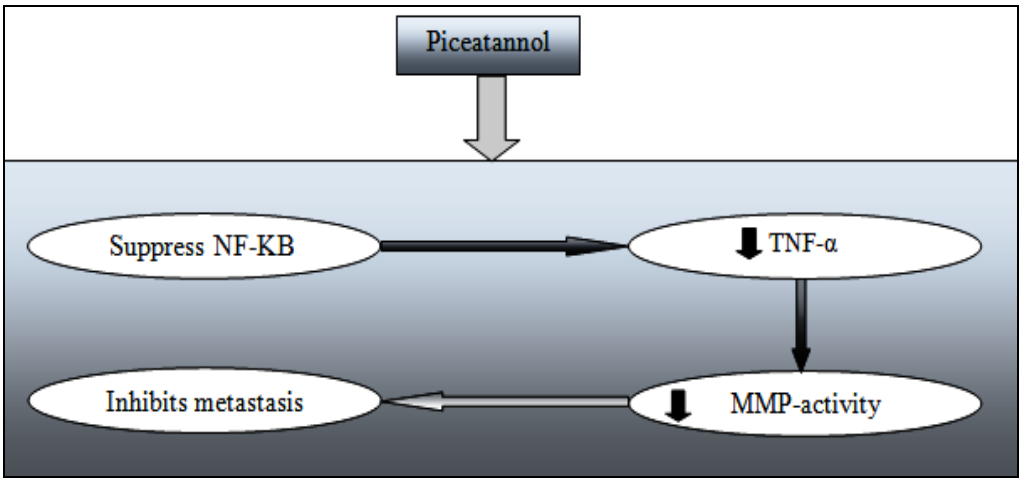

FIGURE 4: EFFECT OF PICEATANNOL ON DU145 HUMAN PROSTATE CANCER CELLS

Promote glucose uptake and repress blood glucose level: Presence of insulin in skeletal muscles, one of the chief site of glucose uptake, facilities diffusion of circulating glucose molecules down its concentration gradient by expression of phosphatidylinositol-3-kinase (PI3K) and guiding the movement of glucose transporter 4 (GLUT4) to the cell's outer membrane. 5' adenosine monophosphate-activated protein kinase (AMPK) is another GLUT4 translocation promoter. It has been found that piceatannol has potential to improve type 2 diabetes mellitus. Piceatannol could prop up activation of AMPK, translocation of GLUT4, aids in glucose uptake in cultured cells and lowers the clinical symptoms associated with diabetes mellitus [23].

Inhibit adipogenesis: Adipogenesis is a process in which formation of adipose tissues takes place. Piceatannol, used at non-cytotoxic concentrations, inhibits the conversion of 3T3-L1 preadipocytes into adipocytes in dose dependent manner. Piceatannol, a novel compound, showed the anti-adipogenetic property.

Piceatannol treated 3T3-L1 preadipocytes also showed a delayed entry into G_2/M phase of cell cycle. Moreover, it also down regulates mitotic clonal expansion [24].

Inhibit metastasis of prostate cancer cells: Prostate cancer is the second major cause of death in males of the United States. It is generally diagnosed in people of old age. The patients of prostate cancer are treated with an androgen deprivation method. But treatment via androgen deprivation method becomes ineffective when prostate cancer reaches to a state known as hormone-refractory state.

Currently existing chemotherapeutic agents, used in the treatment of prostate cancer, has found to be less effective. Piceatannol has recently been used to halt the meatastasis of prostate cancer cells to lungs in mice. Genetically engineered MLL (MAT-Ly-Lu) prostate cancer cells of rat having the capability to stably express firefly luciferase genes were grown and were introduced into tail of nude mice. Piceatannol, administrated orally in mice at a concentration of 20 mg/Kg, has shown to inhibit the metastasis of cells of prostate cancer to lungs via deactivation of STAT3 [25].

As an anti-proliferative and anti-invasive compound against AH109A hepatoma cells: In this experiment, hepatoma cells were grown in in-vitro. Piceatannol, used at a concentration of 25 μM, has found to repress the proliferation of AH109A hepatoma cells. It functions by arresting cells at G_2/M phase of cell cycle. Rate of apoptosis also increases when piceatannol is applied at a higher concentration (100 μM). These results confirm that piceatannol inhibits cell proliferation and induces death of AH109A cells [26].

Anti-carcinogenic and procarcinogneic properties in breast cancer cells: At nanomolar concentrations, piceatannol provokes the activation and expression of c-Myc (proto-oncogene). Therefore, low dose of piceatannol induces proliferation and growth of MCF-7 cells through signaling (PR–Erk1/2–c-Myc).

This shows that low dose of piceatannol increases the rate of occurrence of breast cancer. But at a concentration of 25–50 μM, piceatannol has been demonstrated as an anti-carcinogenic compound and inhibited the growth of MCF-7 cells. High concentration (150 μM) of piceatannol triggered the death of MCF-7 cells. Therefore, it may be concluded that piceatannol has showed both anti-carcinogenic and pro-carcinogenic properties [27].

Bicehmical targets in promyleocytic leukemic cells: Different biochemical targets of piceatannol have been identified by using promyleocytic leukemia cells of human (HL-60). It has also been observed that incubation of leukemia cells with piceatannol led to increase in the number of apoptotic cells by halting cell cycle progression in the G_2-M phase.

Treatment of cells with piceatannol resulted in depletion on intracellular pools of dCTP (dexoy-cytidine triphosphate) and dGTP (deoxy- guanosine triphosphate) and integration of labelled (^{14}C) cytidine into DNA. Combined treatment of cells with piceatannol and Ara-C yielded inhibitory effects on the growth of cells and hence may be used as a life supportive compound in conventional chemotherapies of human diseases [28].

Trigger differentiation of osteoblast: Bone morphogenetic proteins (BMP) play pivotal role in the formation of bone and in the process of bone remodelling. The potential role of piceatannol has been observed in two cell lines, MG-63 and hFOB. Treating these cell lines with piceatannol resulted in the production of bone morphogenetic protein (BMP-2). BMP-2 ultimately triggered the process of bone formation [29].

Antioxidant activity: Antioxidants are compounds that have capability to neutralize free radicals and their negative effects on cells [30].

Antioxidant activity of piceatannol is evaluated by measuring how effectively it protects DNA against hydrogen peroxide (H_2O_2) in leukemic cell lines. Cells were treated with piceatannol and piceatannol's antioxidant activity was investigated after 24 hours of treatment.

It is found that piceatannol is able inhibit the occurrence of breakage in single strand of DNA which is generally induced by H_2O_2 or free radicals. Piceatannol is found to be better antioxidant than its analogue compound resveratrol [31].

As antifungal compound: Recently, antifungal activity of piceatannol has been determined experimentally. *Aspergillus carbonarius* was grown in in-vitro conditions and was supplied with 300 µg/g and 20 µg/g of piceatannol. After certain period of time it inhibited the growth of the fungus.

It acts as a powerful antifungal agent than resveratrol since it is needed in very low concentration than resveratrol to inhibit growth of the fungus [32].

Anti-inflammatory effect of piceatannol in peripheral blood leukocytes: Acute inflammation consists of three steps: initiation, progression and resorption. Inflammation caused due to injury, mechanical stress or pathogen-derived components results in the rapid release of histamin, bradykinin or complements. Prostaglandins E_2 (PGE_2) is the first mediator which is excreted out by the cells infected with bacterial constituents or cytokines. Cytokines produced by activated cells aid in the activation and recruitment of more number of cells to the infected site.

Piceatannol, natural stilbene, affected the biosynthesis of prostaglandins and acted as an anti-inflammatory compound. The anti-inflammatory effect of piceatannol was investigated in peripheral blood leukocytes (PBLs). Piceatannol down regulated the secretion of tumor necrosis factor-α and interleukin-8. It also dose-dependently down regulated the production of PGE_2 in PBLs [33].

Halt the proliferation of bladder cancer cells: Bladder cancer is the cancer of genitor-urinary tract. Po-Lin Kuo and Ya-Ling Hsu have studied the effect of piceatannol on cell cycle progression and apoptosis of bladder cancer cells in two human cell lines, T24 and HT1376. Treatment of T24 and HT1376 cells with piceatannol resulted in increase in the level of p21/WAF1 protein.

Owing to this cells are arrested in the G0/G1 phase of cell cycle. This result has been indicated with the help of flow cytometric analysis. Piceatannol might also increase the expression of Fas/APO-1 and membrane bound Fas ligand system. These apoptotic systems may participate in the death of bladder cancer cells [34].

CONCLUSION: Stilbenes have gained the attention of scientific world and researchers because of their wide spectrum of positive biological properties and applications in health. Piceatannol is a tetrahydroxystilbene and is present in different plants species. It possesses a wide spectrum of activities.

A number of in vitro studies have confirmed its different biological activities such as anti-oxidant, anti-inflammatory, anticancer, anti-adipogenesis and anti-diabetic. Piceatannol inhibits invasion and metastasis of tumor by down-regulating TNF- α and by suppressing the activity of MMP-9 via nuclear factor-κB (NF- κB) pathway in cancer cells. It also improves diabetic mellitus 2 by activation of AMPK and translocation of GLUT4. Piceatannol also delayed the maturation of pre-adipocytes into mature adipocytes by arresting cells in G_2/M phase.

On the basis of pharmacological properties possessed by piceatannol, it may be concluded that this stilbene may be used as a nutritional or pharmacological bio-molecule.

Unfortunately, very few studies with normal cells and animal models have been conducted to assess its clinical applications. More studies are needed to be preformed to uncover the estrogenic activity and hermetic effects of piceatannol in cancer cells. On the other hand, more data should be generated on bioavailability and toxicity of piceatannol in humans.

Moreover, further studies are needed to be performed to find out the mechanism of distribution of this stilbene within cells and tissues.

Competing Interests: Authors disclose no potential conflicts of interest.

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