ISSN: 2279 - 0594

Journal of Biomedical and Pharmaceutical Research 1 (3) 2012, 01-05

SHORT COMMUNICATION

Biological and Clinical Spectrum of Piceatannol – A Hydroxylated Analogue of Resveratrol: A Phytochemical Review.

***Satyanand Tyagi[1], Patel Chirag J[2], Raghvendra[3]**

[1]President, Tyagi Pharmacy Association & Scientific Writer (Pharmacy), Chattarpur, New Delhi, India-110074.

[2]Department of Pharmaceutics, Maharishi Arvind Institute of Pharmacy, Mansarovar, Jaipur, Rajasthan, India-302020.

[3]Department of Pharmaceutics, Aligarh College of Pharmacy, Aligarh, U.P, India-202001.

***Prof. Satyanand Tyagi is a life time member of various pharmacy professional bodies like IPA, APTI and IPGA. He has published various research papers, review articles and short communications. His academic work includes 55 Publications (45 Review Articles, 08 Research Articles and 02 short communications of Pharmaceutical, Medicinal and Clinical Importance, published in standard and reputed National and International Pharmacy Journals; Out of 55 publications, 11 are International Publications). He has published his papers almost in different specialization of Pharmacy fields. His research topics of interest are neurodegenerative disorders, diabetes mellitus, cancer, rare genetic disorders, psycho-pharmacological agents as well as epilepsy.**

ABSTRACT

Resveratrol (3, 4', 5-trans-trihydroxystilbene), a naturally occurring stilbene, is considered to have a number of beneficial effects, including anticancer, anti-aethrogenic, anti-oxidative, anti-inflammatory, anti-microbial and estrogenic activity. Piceatannol (3, 3', 4, 5'-trans-trihydroxystilbene), a naturally occurring hydroxylated analogue of resveratrol, is less studied than resveratrol but displays a wide spectrum of biological activity. Piceatannol has been found in various plants, including grapes, passion fruit, white tea, and Japanese knotweed. Besides antioxidative effects, piceatannol exhibits potential anticancer properties as suggested by its ability to suppress proliferation of a wide variety of tumor cells, including leukemia, lymphoma; cancers of the breast, prostate, colon and melanoma. Although piceatannol has been shown to induce apoptosis in cancer cells, there are examples of its anti-apoptotic pro-proliferative activity. Piceatannol inhibits Syk kinase, which plays a crucial role in the coordination of immune recognition receptors and orchestrates multiple downstream signaling pathways in various haematopoietic cells. Piceatannol also binds estrogen receptors and stimulates growth of estrogen-dependent cancer cells. The pharmacological properties of piceatannol, especially its antitumor, antioxidant, and anti-inflammatory activities, suggest that piceatannol might be a potentially useful nutritional and pharmacological biomolecule; however, more data are needed on its bioavailability and toxicity in humans. The aim of present article is to provide in depth knowledge about clinical and biological activity of Piceatannol. An attempt is also made to focus on various health effects of Piceatannol and brief description of Piceatannol.

KEY WORDS: Resveratrol, Piceatannol, 3, 3', 4, 5'-Trans-trihydroxystilbene, Astringinin.

INTRODUCTION:

Piceatannol is a stilbenoid, a type of phenolic compound. Piceatannol and its glucoside, isorhapontin are phenolic compounds found in mycorrhizal and non-mycorrhizal roots of Norway spruces (*Picea abies*) [1]. It is a metabolite of resveratrol found in red wine. Astringin, a piceatannol glucoside, is also in red wine. LMP2A, a viral protein-tyrosine kinase implicated in leukemia, non-Hodgkin's lymphoma and other diseases associated with Epstein-Barr virus (EBV), were found in a 1989 study to be blocked by piceatannol *in vitro* [2]. In 2003, this prompted research interest in piceatannol as an anti-cancer and anti-EBV drug [3]. Chemically it may be named as 5-[(E)-2-(3'-dihydroxyphenyl) vinyl] benzene-1, 3-diol or 3', 4', 3, 5-tetrahydroxy-trans-stilbene. As seen in the structure, chemically Piceatannol is hydroxylated analogue of resveratrol (Fig.1. & Fig.2.). Injected in rats, piceatannol shows a rapid glucuronidation and a poor bioavailability, according to a 2006 study [4]. A 2012 Purdue University study found that fat cells in culture, in the presence of piceatannol, alters the timing of gene expressions, gene functions and insulin action, resulting the delay or complete inhibition of adipogenesis [5]. The study suggests piceatannol has the potential to control obesity. A compound found in red wine, grapes and other fruits, and similar in structure to resveratrol, is able to block cellular processes that allow fat cells to develop,

*Corresponding author: Satyanand Tyagi / Email: sntyagi9@yahoo.com, Telephone: +91-9871111375/9582025220

opening a door to a potential method to control obesity, according to a Purdue University study. Kee-Hong Kim, an assistant professor of food science, and Jung Yeon Kwon, a graduate student in Kim's laboratory, reported in this week's issue of the *Journal of Biological Chemistry* that the compound piceatannol blocks an immature fat cell's ability to develop and grow. While similar in structure to resveratrol the compound found in red wine, grapes and peanuts that is thought to combat cancer, heart disease and neurodegenerative diseases piceatannol might be an important weapon against obesity. Resveratrol is converted to piceatannol in humans after consumption. "Piceatannol actually alters the timing of gene expressions, gene functions and insulin action during adipogenesis, the process in which early stage fat cells become mature fat cells," Kim said. "In the presence of piceatannol, you can see delay or complete inhibition of adipogenesis." Over a period of 10 days or more, immature fat cells, called preadipocytes, go through several stages to become mature fat cells, or adipocytes. "These precursor cells, ev**1.** though they have not accumulated lipids, have t potential to become fat cells," Kim said. "We consider that adipogenesis is an important molecular target to delay or prevent fat cell accumulation and, hopefully, body fat mass gain." Kim found that piceatannol binds to insulin receptors of immature fat cells in the first stage of adipogenesis, blocking insulin's ability to control cell cycles and activate genes that carry out further stages of fat cell formation. Piceatannol essentially blocks the pathways necessary for immature fat cells to mature and grow. Piceatannol is one of several compounds being studied in Kim's laboratory for its health benefits, and it is also present in different amounts in red grape seeds and skin, blueberries, passion fruit, and other fruits. Kim would like to confirm his current finding, which is based on a cell culture system, using an animal model of obesity. His future work would also include determining methods for protecting piceatannol from degrading so that concentrations large enough would be available in the bloodstream to stop adipogenesis or body fat gain [6].

"We need to work on improving the stability and solubility of piceatannol to create a biological effect," Kim said [7].

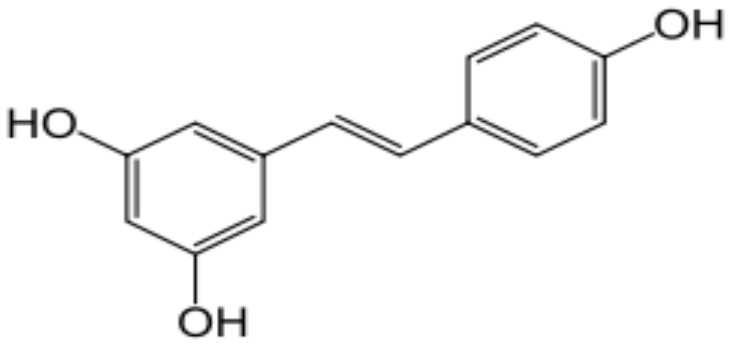

Fig.1. Structure of Resveratrol

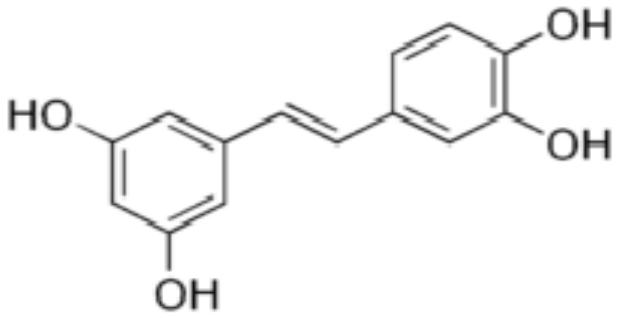

Fig.1.A. Structure of Piceatannol

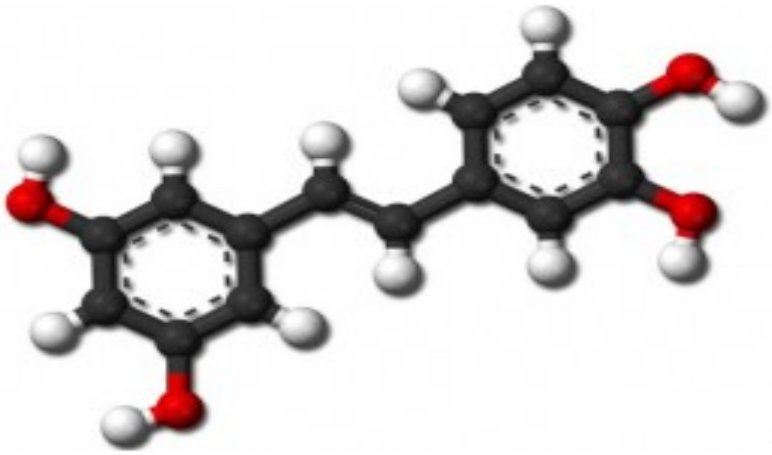

Fig.1.B. Piceatannol Molecule

BIOLOGICAL, PHARMACOLOGICAL AND CLINICAL SPECTRUM OF PICEATANNOL:

Resveratrol (3, 4', 5-trans-trihydroxystilbene), a naturally occurring stilbene, is considered to have a

number of beneficial effects, including anticancer, anti-aethrogenic, anti-oxidative, anti-inflammatory, anti-microbial and estrogenic activity. Piceatannol (3, 3', 4, 5'-trans-trihydroxystilbene), a naturally occurring hydroxylated analogue of resveratrol, is less studied than resveratrol but displays a wide spectrum of biological activity. Piceatannol has been found in various plants, including grapes, passion fruit, white tea, and Japanese knotweed. Besides antioxidative effects, piceatannol exhibits potential anticancer properties as suggested by its ability to suppress proliferation of a wide variety of tumor cells, including leukemia, lymphoma; cancers of the breast, prostate, colon and melanoma. The growth-inhibitory and proapoptotic effects of piceatannol are mediated through cell-cycle arrest; up regulation of Bid, Bax. Bik, Bok, Fas: P21 (WAF1) down-regulation of Bcl-xL; BCL-2, clAP, activation of caspases (-3, -7, - 8, -9), loss of mitochondrial potential, and release of cytochrome c. Piceatannol has been shown to suppress the activation of some transcription factors, including NF-kappaB, which plays a central role as a transcriptional regulator in response to cellular stress caused by free radicals, ultraviolet irradiation, cytokines, or microbial antigens. Piceatannol also inhibits JAK-1, which is a key member of the STAT pathway that is crucial in controlling cellular activities in response to extra cellular cytokines and is a COX-2-inducible enzyme involved in inflammation and carcinogenesis. Although piceatannol has been shown to induce apoptosis in cancer cells, there are examples of its anti-apoptotic pro-proliferative activity. Piceatannol inhibits Syk kinase, which plays a crucial role in the coordination of immune recognition receptors and orchestrates multiple downstream signaling pathways in various hematopoietic cells. Piceatannol also binds estrogen receptors and stimulates growth of estrogen-dependent cancer cells. Piceatannol is rapidly metabolized in the liver and is converted mainly to a glucuronide conjugate; however, sulfation is also possible, based on in vitro studies. The pharmacological property of piceatannol, especially its antitumor, antioxidant, and anti-inflammatory activities, suggests that piceatannol might be a potentially useful nutritional and pharmacological biomolecule; however, more data are needed on its bioavailability and toxicity in humans [8, 9].

OTHER CLINICAL ACTIONS:

Piceatannol (3, 3′, 4′, 5 -tetrahydroxystilbene, astringinin) is a polyphenolic stilbene phytochemical which is rich in the seeds of *Euphorbia lagascae* [10] and is also present in diets of plant-derived foods and beverage such as red wine [11]. Piceatannol was identified as a selective inhibitor of non-receptor Syk tyrosine kinase [12], which plays a critical role in the regulation of immune and inflammatory responses of hematopoietic cells [13, 14], and in maintaining vascular integrity [15] in addition to playing the general physiological functions in a wide variety of non-hematopoietic cells [16]. It was found that piceatannol possesses multiple bioactivities such as anti-cancer [17-19], anti-Epstein-Barr virus [20], and cardio protection associated with antiarrhythmia against ischaemia-reperfusion injury in rat hearts [21-23]. Piceatannol is present in low quantity in grapes [24], peanuts [25], *Euphorbia lagascae* [26] and *Vaccinium* berries [27].

Like Resveratrol, Piceatannol it is a phytoalexin. Piceatannol shows many biological activities. It has known anticancer and antileukaemic properties, inducing apoptosis in several cell lines and animal models; it inhibits a variety of tyrosinase kinases involved in cell proliferation. A recent study has demonstrated that the cancer preventative properties of resveratrol are related to its natural conversion into metabolite piceatannol in living cells by the enzyme CYP1B1 (belongs to the cytochrome P450 enzyme family) that is over-expressed in a wide variety of human tumours. Other experimental evidences showed that piceatannol has a higher level of antioxidant activity compared to resveratrol. This result is according to the evidence that a catechol moiety present in a compound increases the cytotoxic and antioxidant activity *in vitro*.

CONCLUSION:

In the last few years, stilbene-based compounds have attracted the attention of many researchers due to their wide range of positive biological effects. One of the most relevant and extensively Polyphenolic antioxidants of red wine, including resveratrol and piceatannol, are thought to be responsible for the cardiovascular benefits associated with moderate wine consumption. Piceatannol was more potent than resveratrol in cardiac ion channel inhibition which was also in parallel with its potent antiarrhythmic efficacy in ischaemia-reperfused rat hearts. Piceatannol-mediated modulation on cardiac sodium channel may contribute to its antiarrhythmic action at concentrations less than 10 $\mu mol \cdot L^{-1}$. Piceatannol is a metabolite that occurs in the plant Euphorbia lagascae. It is a tetrahydroxystilbene and an analog of resveratrol that has been investigated for its potential antioxidant activities. A report on the cell and enzyme based in vitro screening of potential cancer chemo preventive agents, including piceatannol, has been published. Picetannol has been shown to interfere with the cytokine signaling pathway, notably in the inhibition of the Syk nonreceptor kinases. Picetannol has been shown to interfere with the

antigen presenting capacity of interferonγ treated mouse mast cells. It also inhibits the activation of NFκB in human cultured cells, after treatment of with various inflammatory agents, through inhibition of IκBα kinase and p65 phosphorylation.

ACKNOWLEDGEMENT:

The corresponding author, Prof. Satyanand Tyagi is highly thankful to his Parents, Teachers, wife Pooja, and daughter Tanisha for their moral support and encouragement. Last but not the least, support of all my students and the one above all of us, the omnipresent God, for answering my prayers for giving me the strength to plod on despite my constitution wanting to give up and throw in the towel, thank you so much Dear Lord.

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