Role of Cinnamate and Cinnamate Derivatives in Pharmacology

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Abstract: Cinnamic acid and cinnamate derivatives have gained attention due to their potential protective role against oxidative damage diseases, such as coronary heart disease, stroke and cancers. However, their potential interest for the human health goes far beyond their protective antioxidant behaviour. The present review encompasses the involvement of cinnamate and its derivatives against various chronic diseases of present decade and focuses the elucidation of molecular mechanisms behind their effects.

Key words: Cinnamate • Cinnamate Derivatives • Disease • Human Health • Pharmacology

INTRODUCTION

Plant polyphenols have drawn increasing attention due to their potent antioxidant properties and their marked effects in the prevention of various oxidative stress associated diseases such as cancer. In the last few years, the identification and development of phenolic compounds or extracts from different plants has become a major area of health and medical-related research [1]. Zhiqui et al. [2] says that historically, xenobiotic metabolism was first conceptualized and then demonstrated by feeding cinnamic acid to people and dogs and then isolating hippuric acid from their urine. This landmark study accordingly is said to be therefore, the initiation of synthetic pharmaceutical industry. This also formed the basis for understanding as to how the body of an organism and its chemical response to the externally administered compounds worked, which otherwise was impossible to visualize till that time.

An important pharmaceutical for high blood pressure [3, 4] and stroke prevention [5, 6], known as coumarin or p-hydroxy-cinnamic acid, is a derivative of cinnamic acid, known as storax or balsam of Peru to herbalists and early perfumers for centuries is a cinnamate [7, 8]. In the United States, herbalists, native Americans and early physicians used extractions from the related sweet gum tree to treat coughs, diarrhea and dysentery [9]. Anslow and Stratford [10] refer to a Japanese patent stating that cinnamic acid in combination with other organic acids, such as citric acid found in orange juice and malic acid in apple juice have a greater bactericidal effect. Cinnamic acid and its derivatives, including esters and carboxylic functional derivatives, are important components in flavourings [11, 12], perfumes [7-8, 13, 14], synthetic dyes [15-16] and pharmaceuticals [7, 14]. They have been studied for various pharmacological activities like an antioxidant [17-19], anticarcinogenic [4, 6, 20-24], anti-Alzheimer’s disease [25, 26], hepatoprotective [27, 28], cytotoxic [29], anxiolytic [6], insect repellent [6, 30-33], antidiabetic [6, 34, 35], anti microbial [3, 4, 36], anti-TB [37, 38], antimalarial [39-40], anti-cholesterolemic [3-6] and many more.

Cinnamic acid is a plant production promoter as a lasting-effect fungicide used in high yield, corrosion prevention, metabolite mobilization [41, 42] and freshness preservation of fruits and vegetables [43]. It has extensive applications, but the consumption in the domestic market is very small today. With the development of the aspartame, production and the expansion of its consumption sectors, the consumption of L-phenylalanine will become brisk and the cinnamic acid production will be promoted by many folds. The demand of L-phenylalanine in the world is around 15 thousand tons a year, needing 23 thousand tons of cinnamic acid. The demand of L-phenylalanine in China is around 2 thousand tons a year, needing around 3 thousand tons of cinnamic acid. The output of cinnamic acid in China is only less than 1 thousand tons today and the deficit has to be bridged by imports. Unfortunately the cited author has not been able to source such a data for commerce in India vis a vis cinnamic acid or L-phenylalanine! [44].

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The interest in hydroxycinnamates as bioactive components of the diet, as structural and functional components of plant cell walls and as precursors for flavours in the food industry has expanded rapidly in the last 5-10 years. As a result, the first ever international conference devoted solely to hydroxycinnamates (e.g. ferulate, p-coumarate, sinapate, caffeate), Ferulate ‘98 was held in Norwich (UK) on 9-11 July 1998. There were five sections: Hydroxycinnamates in food-role in nutrition and health; Hydroxycinnamates in plant cell walls; Biosynthesis of hydroxycinnamates; Enzymology of biosynthesis and degradation; Exploitation of hydroxycinnamates. In this review the current state of the art is discussed and suggestions for future research which arose from this conference were given.

The potential interest in cinnamate and its derivatives for the human health goes far beyond their protective antioxidant behaviour [45-48]. Besides their involvement in preventing oxidative protein damages like that of effects on protein carbonyl formation [49, 50] and thiol oxidation of bovine serum albumin [51], These ubiquitous monophenols have been reported to reduce the level of fructosamine, the formation of N-(carboxymethyl)lysine (CML) [52] and that of amyloid cross β-structure thereby assuring the use of these molecules in preventing advanced glycation end products (AGEs)-mediated diabetic complications [53]. The same activity is evidenced by decreasing plasma glucose, elevating glycogen and membrane bound enzymes (Na+ /K+ -ATPase, Ca²⁺-ATPase and Mg²⁺-ATPase) [54] due to these chemicals. Also hypolipidemic effect by these monophenols is evidenced by the decreased levels of total cholesterol, triglycerides, LDL and VLDL-cholesterol and elevated levels of HDL-cholesterol [55,56].

The bio-availabilities of monophenols in plants such as cinnamic acid in cinnamon bark, grape fruit and other and their ability to inhibit and prevent tumor formation after entering blood circulation and absorbing by bowel. These act directly as inhibitors by imposing their effects on protein or control factors which operate active system repairing cell [57,58] and also motivate immune system and increase conformation natural killer cells and effect in the enzymes, responsible of process and complete the cell cycle by hyperexpression arrangement [59-61]. Expression of general antioxidant capability of the hydroxycinnamic acids in vitro might be due to the decrease in malondialdehyde formation in several lipid peroxidation systems; scavenging of O₂ and reduced rates of OH formation [62]. Research studies also suggest that these compounds may also act by other mechanisms in addition to the antioxidant capacity as modulating the activity of some specific enzymes and inhibit cell proliferation [63]. Several common mechanisms- conducive to additive, synergistic, or antagonistic interactions by which these chemicals exert their effects including effects on cellular differentiation, proliferation and apoptosis; on proteins and enzymes that are involved in these processes at a molecular level and other various others through altered immune function and chemical metabolism.

Hydroxycinnamamic acids have been consistently associated with reduced risk of cardiovascular diseases, cancer and other chronic diseases [64-67], partly explained by the ability of these substances in scavenging free radicals and pro-oxidant metals [66,67]. They have also been reported to have a potential inhibitory effect on metastasis and cancer invasion [68-72]. Wu et al. [73] demonstrated that 3,4-dihydroxycinnamic acid (cafeic acid phenethyl ester; CAPE) reduced matrix metalloproteinase (MMP-9) expression induced by Helicobacter pylori (H. pylori) causing multiple genetic and epigenetic alterations by activating nuclear factor-kappa B (NF-kB) [74] and inhibited the invasive capacity of gastric cancer cells stimulated by IL-8 (inflammatory response) [73]. Thereafter, it was Kim et al. [69] who reported the anti- H. pylori activity of varous other natural products like cinamic acids, coumarins. Kim et al. [69] also investigated anti-gastritis activities of Cimicifuga heracleifolia (CH) ethanol extract contains ferulic acid and cafeic acid leading to the fact that hydroxycinnaminic acids exhibit higher free radical scavenging activity [75] than other constituents and inhibited colonization of H. pylori effectively. In addition, the findings of the cytotoxic effects of CH ethanol extract and its constituents using SNU638 and AGS gastric cancer cell lines revealed that cafeic acid have a direct anti-cancer effect and protects against gastric injury induced by H. pylori [69]. Caffeic acid protects against immunoregulation diseases, asthma and allergic reactions [76]. Furthermore, cafeic acid and several of its esters might have some activity against colon cancer [77,78]. Other cafeic acid derivatives like dicaffeoylquinic and dicaffeoyltartaric acids act as potent and selective inhibitors of HIV-1 integrase, currently considered for their potential antiviral therapy [45-46]. Additionally, Kurata et al. [79] isolated diCQA from sweet potato leaf and showed that diCQA (isomer of CGA-chlorogenic acid) depressed Kato III (human stomach carcinoma cell line) cell growth in a dose-dependent manner.
Constant generation of reactive oxygen species (ROS) [80-82], in keratinocytes [83] and fibroblasts [84-85], by skin UV exposure is the main cause of various skin related diseases [86-89]. Phenols like cinnamate and its derivatives rapidly illuminate ROS by their nonenzymic and enzymic antioxidant potential [90-93]. Therefore, prevent harmful effects of ROS and maintain a pro-oxidant/antioxidant balance, resulting in cell and tissue stabilization [90, 94-100]. These molecules are believed to be capable of acting in redox-sensitive signalling cascades [97, 101] to inhibit DNA damage [84, 98, 102,103]. Caffeic acid (3, 4-dihydroxycinnamic acid) and ferulic acid (4-hydroxy-3-methoxycinnamic acid) have been demonstrated to protect phospholipidic membranes from UV-induced peroxidation by inhibiting propagation of the lipid peroxidative chain reaction and to react with nitrogen oxides [103,104]. Also ferulic acid proved effective in protecting human skin from UVB-induced erythema [20, 105,106].

Rastogi et al. [107] reported a non-bactericidal activity of cinnamic acid on Mycobacterium tuberculosis (M.tb.). viability because a synergistic increase in the activity of various antituberculous drugs like isoniazid [108], rifampin [109], ofloxacin [110] or clofazimine [111] by using trans-cinnamic acid [112] along with them even in drug resistant isolates. This activity of augmenting the potential of existing drugs [113] of cinnamic acid and its several hydroxyl derivatives viz., p-coumaric acid [114], caffeic acid [115], ferulic acid [116], sinapic acid [113, 117] lead to a new strategy to circumvent MDR-TB. Cinnamic acid act as hepatoprotective monophenol by suppressing hepatic fibrosis and therefore, prevent liver against several damages [118] prevent or repair oxidation of DNA and protein [119-120] anti-hyperlipidemic activity [121] prevent and escape hydroxyl radical to start lipid peroxidation [122] and by releasing cytokines, histamine, prostaglandins and leukotrenes-the inflammatory mediators [121] so as to protect hepatocyte.

CONCLUSION

Cinnamic acid and its natural analogues or derivatives are important but underutilized class of compounds. In spite of their multi-activities as anti-diabetic, anti-TB, blocking UV radiations, active against solid tumors, cytotoxicity, DNA-damage and many more, their mode of action and understanding of detailed molecular mechanisms remains ambiguous.

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