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Chemopreventive Effect of Sinapic Acid on Head and Neck Squamous Cell Carcinoma

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ABSTRACT

For thousands of years, the natural products have played an important role throughout the world in the treatment and prevention of human diseases. Over 60% of currently used anticancer agents are derived in one way or another from natural sources. Sinapic acid is one of the phenolic acids that widely distributed in edible plants such as cereals, nuts, oil seeds and berries. Sinapic acid shows antioxidant, antimicrobial, anti-inflammatory, anticancer and anxiolytic activity. The present study aimed to evaluate cytotoxicity and chemopreventive efficacy of sinapic acid on head and neck squamous cell carcinoma. It was concluded that sinapic acid induce apoptosis and change cancer cell morphology due to their pro-apoptotic activity and it can be used for cancer prevention and cancer chemotherapy.

Key words: Chemoprevention, sinapic acid, head and neck squamous cell carcinoma, cytotoxicity

INTRODUCTION

Cancer, one of the major causes of death across the world, has shown to be a largely preventable disease, highly susceptible to modulation by dietary factors. Phenolic compounds, abundant in vegetables and fruits ubiquitous in diet, were described to play an important role as chemopreventive agents. Such studies were yielding overwhelming evidence for cellular mechanisms of carcinogenesis to be susceptible to modification by biologically active constituents of food. However, much remains to be learned on the relationships between dietary intake of polyphenol-containing food and cancer[1].

Since conventional therapeutic and surgical approaches have not been able to control the incidence of most cancer types, the development of chemopreventive strategies was an urgent priority in public health. There was an urgent need to develop mechanism-based strategies in order to achieve this goal. Prevention via non-toxic agents may be one such approach[1].

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths) in 2008. Deaths from cancer worldwide were projected to continue to rise to over 11 million in 2030[2]. Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth most common type of cancer worldwide, representing about 6%

of all cancer cases[3]. Laryngeal Squamous Cell Carcinoma (SCC) has the second highest incidence of all head and neck squamous cell carcinomas. In recent years, the incidence of laryngeal cancer is about 160,000 new cases diagnosed per year[4].

The current treatment options involve multimodality approaches that include surgery, γ-irradiation and chemotherapy, depending on the site, size and the stage of the lesions[5]. However, the 5-year survival of patients with HNSCC is about 40-50% despite recent therapeutic advances[6]. Molecular-targeted therapies, based on molecular findings of the last 50 years, are one of the most promising gateways to the development of new strategies in cancer therapeutics[7]. Despite significant advances in surgery and radiotherapy over the last few decades, no treatment has been shown to achieve a satisfactory therapeutic outcome and the mortality rate of laryngeal SCC was still high, with a 5-year survival rate of 64%. Given the high mortality rate of laryngeal SCC, it was a critical need to explore the molecular pathogenesis and develop the new relevant biomarker to increase specificity or sensitivity for early diagnosis and prognosis[8].

Chemoprevention is emerged as a therapy that involves the use of natural, synthetic and semi-synthetic compounds to suppress and inhibit the malignant transformation[9]. Most of the anticancer compounds are in the nature of phenolic acids and these compounds plays a major role in antioxidants as chemoprevention[10]. Natural products are important sources of new bioactive molecules, due to the structural diversity of their constituents. Between 2005 and 2007, thirteen new drugs are derived from phytochemicals and have been approved by FDA, with five of them being the first members of new classes. The discovery of effective anti-cancer drugs from natural products plays an important role in cancer chemotherapy[11].

Natural compounds from various sources including plants, animals and microorganisms offer a great opportunity for discovery of novel therapeutic candidates for the treatment of cancer[12]. Natural products were important sources of new bioactive molecules, due to the structural diversity of their constituents. Though phenolic compounds are present in almost all foods of plant origin, fruits, vegetables and beverages are the major sources of these compounds in human diet. Beverages such as fruit juices and tea are important sources of phenolics in human diet[13].

Phenolic compounds are a group of key plant metabolites found abundantly in fruit and vegetables. Because of their antioxidant properties, they play an important role in preventing various disorders or diseases related to oxidative damage[14]. Phenolic compounds exhibit a wide range of physiological properties, such as antiallergenic, anti-atherogenic, anti-inflammatory, anti-microbial, antioxidant, antithrombotic, cardioprotective and vasodilatory effects[15]. Use of phytomedicines is an effort to combat diseases[16]. Development of such phytomedicines based on ethno medical leads is relatively easier when compared to chemically synthesized drug[17].

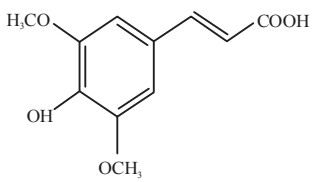

Fig. 1: ChemicalStructure of sinapic acid[20]

Dietary polyphenols may exert their anticancer effects via a variety of mechanisms such as removal of carcinogenic agents, modulation of cancer cell signaling and antioxidant enzymatic activities and induction of apoptosis and cell cycle arrest[18]. Compared to essential vitamins, dietary polyphenols were considered to have a superior amount of antioxidant and anticancer property[19].

One of small naturally occurring hydroxycinnamic acid derivative is sinapic acid. It is a phenolic compound and a member of the phenylpropanoid family, the member of which are assumed as therapeutically beneficial and generally not toxic (Fig. 1). Sinapic acid is widespread in the plant kingdom (fruits, vegetables, cereal grains, oilseed crops and some spices and medicinal plants) and is common in human diet. Derivatives of sinapic acid are characteristic compounds of the *Brassicaceae* family[20].

The important functions of sinapic acid are antioxidant, antimicrobial, anti-inflammatory, anticancerand anxiolytic activity. The 4-vinylsyringol (a decarboxylation product of sinapic acid) is a potent antioxidative and antimutagenic agent, which suppresses carcinogenesis and the induction of inflammatory cytokines. Sinapine (sinapoyl choline) is considered to be an acetylcholinesterase inhibitor which might have therapeutic applications in various disease treatments. Mainly due to their antioxidant activity, these compounds have been suggested for potential use in food processing, cosmetics and the pharmaceutical industry[20].

In colon cancer cells, sinapic acid exerted an inhibitory effect but had a low influence on breast cancer cells. On the other hand, there was anti-proliferative effect of sinapic acid (ability to prevent, or retard, the spread of malignant cells into surrounding tissue) on the human breast cancer (T47D) cell line[21]. Anti-carcinogenic and anti-inflammatory effects of sinapic acid and its derivatives have been well documented.

Macrophages are noted as key mediators of the interaction between inflammation, immunity and cancer. The role of macrophages in cancer has received attention due to the discovery of their tumor-promoting effects[22]. Yun *et al.*[23] reported that sinapic acid inhibits nuclear factor-kappa B (NF-κB) activation in macrophages. NF-κB regulates inflammatory status and plays a key role in immune response to infection; however, incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection as well as improper immune development. Via NF-κB inactivation sinapic acid suppresses the expression of pro-inflammatory mediators such as inducible nitric oxide synthase, cyclooxygenase-2 and tumor necrosis factor-α, as well as interleukin-1β[24].

CONCLUSION

The phenolic constituents of sinapic acid initiate release of H_2O_2 a highly Reactive Oxygen Species (ROS) sources, those can induce damage to proteins, nucleic acids and cell membranes. It was known to cause oxidative DNA damage primarily through the hydroxyl radical which results from Fenton reaction. The H_2O_2 has been reported to cause DNA damage in the form of chromosomal aberrations, single- and double-strand breaks; therefore, sinapic acid possesses cytotoxic effect on cancer cells so can be used for cancer prevention and cancer chemotherapy. Sinapic acid could act as a pro-oxidant and alter the activities/levels of oxidative stress markers. Thus, sinapic acid initiates cancer cell death by inhibiting cell proliferation, lowing antioxidant status, alternating mitochondrial membrane potential, increasing intracellular ROS, lipid peroxidation and inducing apoptosis in cancer cells.

Also, it was recorded that various phytochemicals induce apoptosis and change cancer cell morphology due to their pro-apoptotic activity and they are used for cancer prevention and cancer chemotherapy. This suggests that modes of cell death other than apoptosis may operate in tumor cells following exposure to sinapic acid, or, more generally, to DNA-damaging agents

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