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Editorial

Cancer Prevention Through Restoration of E-cadherin Expression with Promising Natural Products

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Editorial

Cancer is one of the deadliest diseases worldwide. Within the next two decades, annual cancer cases are expected to rise globally from the 2012 figure of 14 million to 22 million, according to the World Health Organization (WHO) [1]. After heart disease, cancer is the second most common cause of death in the US [2]. For the treatment of epithelial cancer (e.g., bladder, breast, colon, lung, ovary, pancreas, prostate, etc.), conventional approaches utilizing radiation, surgery, or chemotherapy have not been entirely successful [3]. The process of development of epithelial cancer in humans may take years to reach its invasive potential [4]. Clinical reports suggest that more than 90% of patient deaths related to solid cancers occur from the metastatic spread of the primary tumor [5-7]. Therefore, pharmacological means that can either arrest or stabilize a preneoplastic lesion can help control the progression of the disease. The current article discusses the potential role of natural products to prevent the metastatic dissemination of the disease to secondary sites.

The primary tumor mass of epithelial cancers can be maintained coherently if the key cell-cell adhesion molecules and inter-cellular structures holding the cells can be retained. Any dysregulation or loss in these key structures, including Adherens Junctions (AJ), Gap Junctions (GJ) and Tight Junctions (TJ), can lead to cancer cell migration into secondary tissue [8,9]. Among these key structures, AJs via E-cadherin-catenin complex provide the most prevailing source of adhesion in epithelial cells. In addition, Epithelial-Mesenchymal Transition (EMT) is widely known to be associated with detachment and dissemination of epithelial cancer cells; in this process, several junctional proteins, including E-cadherin, are lost. Taken together, small non-cytotoxic molecules, which can enhance the expression of E-cadherin, can be an interventional approach to controlling the metastatic dissemination of cancer cells.

Nature has always been instrumental in providing therapies for many human ailments. In fact, traditional medicines from various cultures, such as Chinese medicine, Egyptian medicine, the Indian Ayurvedic system, and Greek and Roman medicine, have been based on the compounds derived from a natural product. The experimental evidence of cancer prevention properties of two natural products, originating from terrestrial and marine environments and targeting specific junctional complex proteins, is discussed below.

Garlic is a member of the family Alliaceae and is often called the 'stinking rose' because of its signature scent [10]. Garlic's odor primarily spreads when it is crushed and organosulfur compounds are produced. In terms of garlic's bulb composition, it contains water (65%), carbohydrates (28%), protein (2%), fiber (1.5%), and fats (0.15%), with less than 5 calories for an average clove of raw garlic [10]. Isolation efforts have yielded several lipid-soluble (Diallyl Sulfide [DAS], Diallyl Disulfide [DADS], Diallyl Trisulfide [DATS]) and water-soluble (S-Allyl Cysteine [SAC], S-Allyl Mercaptocysteine [SAMC]) anticancer compounds from garlic [11,12]. In recent studies, water-soluble derivatives of garlic have significantly inhibited the invasive ability of androgen-independent Prostate Cancer (PC) cells. In particular, treatment with both SAC and SAMC have restored the expression of E-cadherin at both the transcriptional and protein levels in the PC-3 cell line [11,13]. Further studies revealed the induction of Mesenchymal to Epithelial Transition (MET) in the presence of these compounds. The upregulation of the cell-cell adhesion molecule E-cadherin in the presence of SAC and SAMC has also been reported in other cancer types such as esophageal (EC-109 cell line), nasopharyngeal (CNE-3 cell line), and ovarian (Skov-3 cell line) carcinomas. The in vivo studies on the orthotopic PC mouse model with SAMC showed inhibition of the growth of primary tumors by 71%, reduction in the number of adrenal and lung metastases by 85.5%, and reduction of viable circulating tumor cells by 91% [13]. This garlic-derived compound successfully prevented dissemination of tumor cells in vivo, suggesting its potential as an effective anti metastatic treatment option.

During the past 30 years, marine organisms have been extensively studied for their secondary metabolites in search of structurally unique bioactive compounds [14]. Phenyl Methylene Hydantoins (PMH) are marine-derived compounds isolated from the Red Sea sponge *Hemimycale arabica* [15,16]. PMH showed significant augmentation of cell-cell adhesion by enhancing both AJs and TJs in the PC-3M Calcitonin (CT) positive human PC cell line [17,18]. This compound also abolished the destabilizing actions of CT, known to promote PC metastasis by reducing cell-cell adhesion, on these complexes. Furthermore, E-cadherin levels were upregulated in the presence of PMH, even in CT stimulated conditions. In orthotopic PC nude mice models, PMH decreased the orthotopic tumor growth and inhibited the formation of tumor micro metastases in distant organs without apparent cytotoxic effects [17]. Therefore, PMH scaffolds can positively contribute to controlling and preventing the metastatic spread of PC.

In conclusion, this article addresses the contribution of natural products in enhancing cell-cell adhesion to suppress the development and progression of epithelial cancers. A particular emphasis was

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given to molecules that can restore E-cadherin levels in cancer cells. This selective pharmacological approach, via targeting AJs, can also help keep the established metastatic colonies in check.

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