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Natural isothiocyanates of the genus *Capparis* as potential agonists of apoptosis and antitumor agents: Mechanisms and implications

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**Abstract**

In this editorial, we comment on a recent publication, which highlights the important findings from the study, including the antitumor and anti-inflammatory effects of isothiocyanates, their underlying mechanisms, and implications. Additionally, a related perspective is discussed.

**Key Words:** Cancer; Isothiocyanates; Genus *Capparis*; Apoptosis; Autophagy; Inflammation; GC/MS analysis

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**Core Tip:** A growing body of evidence indicates that isothiocyanates derived from natural products possess anticancer and anti-inflammatory properties. This editorial discusses the mechanisms underlying the tumor-suppressing effects of isothiocyanates derived from the genus *Capparis*, their implications, and a related perspective.

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INTRODUCTION

Antitumor effects of isothiocyanates isolated from genus Capparis

Using gas chromatography-mass spectrometry (GC/MS) analysis, Hanuš et al.[1] isolated various isothiocyanates from the yellow and green fruits, seeds, and jam of the scrambling shrub Capparis cartilaginea (C. cartilaginea). They isolated isopropyl isothiocyanate from the fruits, 2-buty1 isothiocyanate from the seeds, isobutyl isothiocyanate from the jam of this genus. Interestingly using the PASS program, they found that these isothiocyanates exhibit apoptotic effects on various cancers, particularly genitourinary cancer, recommending their use in cancer prevention and therapy. They concluded that the discovery of the antitumor activities of these isothiocyanates was unexpected. Furthermore, they found that certain isothiocyanates demonstrated antifungal, antiviral (specifically against arbovirus), and antiparasitic properties. However, the anticancer effects of isothiocyanates found in cruciferous vegetables have been reported in several studies[2-4].

Apoptotic and non-apoptotic mechanisms related to cancer suppression by isothiocyanates

Using the PASS program, the anticancer effects of isothiocyanates were found to be mediated by apoptosis and reduction of cell viability[1]. Apoptosis, a cell death mechanism, is controlled by two signaling pathways. The first, intrinsic apoptosis or the mitochondrial pathway is activated by damage to the outer mitochondrial membrane and enhanced expression of apoptosis genes such as Bax. This results in the release of proapoptotic factors such as caspase-9, from mitochondria into the cytosol, and the activation of executor caspase-3. The second pathway, extrinsic apoptosis, is mediated by Fas-FasL interaction, which releases caspase-8 and activates caspase-3 [5,6]. However, this study does not discuss the signaling pathway of isothiocyanate-related apoptotic effects on cancers cells[1]. This pathway could be related to mitochondrial damage and alteration of apoptotic and antiapoptotic factors, such as Bax and Bcl-2, respectively [2,5,6]. Further studies investigating the Fas-FasL ligand pathway in isothiocyanate-induced apoptosis in cancer cells are required[5,6]. Other mechanisms for the anticancer effects of isothiocyanates include epigenetic modifications such as DNA methylation, and the reduction of cancer cell proliferation, migration, and angiogenesis. Additionally, cancer prevention by isothiocyanates is mediated by several mechanisms, such as the modulation of cytochrome P450 family and activation of the NF-E2-related factor 2 (Nrf2) pathway. The anti-inflammatory effects of isothiocyanates on cancer cells are reported to occur via strong Nrf2 activation, acting as an antioxidant mechanism[2,3,4].

On the other hand, and as an anti-apoptotic mechanism, macroautophagy (hereafter referred to as autophagy) is a lysosomal pathway for the clearance of cellular proapoptotic factors, specifically upregulated as a survival strategy upon exposure to various stressors, such as metabolic insults and cytotoxic drugs. Therefore, activation of autophagy in cancer cells upon exposure to various treatments or hypoxia is a prosurvival mechanism[7,8]. A recent study found that benzyl isothiocyanate induced a prosurvival ER stress-mediated autophagy in lung cancer cells based on in vitro and in vivo studies. Importantly, pretreatment with the autophagy inhibitor 3-MA significantly enhanced the isothiocyanate-induced growth inhibition in lung cancer cells and reduced their viability[3,9]. Therefore, care should be taken when using isothiocyanates in cancer therapy, as they may activate prosurvival autophagy mechanisms. Conversely, activation of autophagy in normal cells by isothiocyanates could prevent tumor formation, as autophagy may clear oncogenic factors, serving as a chemoprotective mechanism[8]. Further studies are required to explore the pro-autophagic effects of isothiocyanates on tumors.

Isothiocyanates isolation and usage in tumor therapy: Safety and challenges for optimal therapy

Although Hanuš et al.[1] isolated various types of isothiocyanates from the yellow and green fruits, seeds, and jam of the scrambling shrub C. cartilaginea using GC/MS analytical methods, the details of this method and the concentration of isothiocyanates used for cancer treatment are not clearly mentioned. Therefore, details regarding sample preparation, extraction methods, and quality control measures are crucial for ensuring the reliability of GC/MS data. Without comprehensive information on these aspects, the robustness of the analytical findings may be questioned. In addition, providing in-silico predictions for an initial screening of volatile components from natural products may oversimplify the complex interactions within biological systems. The predictive accuracy of in-silico models is influenced by the quality of input data, the algorithms used, and the assumptions made, which may not fully capture the intricacies of biological processes [10,11]. Additionally, information on dose-response relationships and concentration-dependent effects of the isothiocyanates on the observed biological activities is essential for determining their pharmacological relevance. Importantly, the safety and toxicological profile of isothiocyanates extracted naturally from genus Capparis are important aspects to consider as high doses may cause unexpected adverse events such as irritation, allergic reactions, and serious harm to certain body systems[11,12]. Thus, extensive toxicological evaluation, consisting of acute and chronic toxicity assays, in addition to potential interactions with medications, is necessary to ensure the safe use of isothiocyanates for therapeutic applications. Without this data, the interpretation of the biological activity results may be limited. More in-depth analyses of individual isothiocyanates extracted from jams, seeds, and fruits of the Capparis genus will offer a clearer understanding of these compounds’ properties and potential therapeutic applications.

CONCLUSION

Isothiocyanates derived from the seeds, jam, and fruits of C. cartilaginea have demonstrated anticancer and anti-inflammatory effects via various mechanisms such as apoptosis induction and suppression of oxidative stress. From this outlook, it will be fascinating to explore the juice of these natural products, as recent plant studies have indicated that the juice contains extracellular vesicles with miRNAs having anticancer capabilities. Further clinical trials are necessary to
specify the doses and types of isothiocyanates for cancer therapy. Additionally, nanotechnology for delivering isothiocyanates into cancer cells could effectively extend their shelf life and improve therapeutic efficacy. Combination therapies involving isothiocyanates with autophagy inhibitors, immunotherapy, and gene therapy could enhance the tumor-suppressing effects of these natural products. Further details regarding sample preparation, extraction methods, and quality control measures for isothiocyanates are needed for optimal cancer therapy.

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**FOOTNOTES**

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