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Short Communication

The Role of Flavonoids as Potential Plant Fungicides in Preventing Human Carcinogenesis: A Short Communication

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Abstract
In the context of the steadily increasing prevalence of malignant disorders all over the world, identification of any novel possibilities for suppressing carcinogenesis is crucial leading to saving human lives. One of the important sources of exposure to potential carcinogens is food products which can be contaminated with different types of mycotoxins. These structurally diverse chemicals are produced by certain fungi, whereas many of them may be associated with the development of malignant neoplasms in distinct organ systems. In this perspective article, the ability of specific plant secondary metabolites from the class of flavonoids to suppress the release of carcinogenic mycotoxins from certain fungi, mostly the members of *Aspergillus* and *Penicillium* genera, is highlighted. This finding might support the development of novel flavonoid-based plant fungicides in the future, to lower the contamination of food products with mycotoxins and thereby also reduce the cancer prevalence in humans. In addition, the application of flavonoids as natural products instead of synthetic chemicals in plant cultivation is probably also more acceptable for final consumers, representing an actual step toward a greener future.

Keywords: plant fungal pathogens, mycotoxins, fungicides, plant-based diet, fruits and vegetables, carcinogenesis, chemoprevention

The importance of ingested food items in affecting the carcinogenesis process in humans is well accepted today, whereas this impact can be either protective or damaging. On the one hand, numerous plant secondary metabolites as constituents of plant-based diets have been shown to exert a wide range of potent antitumoral activities, behaving as antiproliferative, proapoptotic, anti-migratory, anti-invasive, anti-metastatic, and antiangiogenic agents in various models of different cancer types [1]-[3]. Such phytochemicals are widely recognized as chemopreventive compounds [4]. On the other hand, heterocyclic amines formed on the surface of red meat products within their processing at high cooking temperatures are known as carcinogenic and mutagenic chemicals [5]. In addition, several foods can be contaminated with specific mycotoxins which are also able to promote carcinogenesis in human beings after exposure to such dietary products [6][7]. Some of the most frequently occurring and toxicologically significant mycotoxins include aflatoxins, ochratoxins, fusarium toxins, and patulin. Aflatoxins can be detected in foods such as peanuts, spices, pistachios, and maize, whereas aflatoxin B_1 is recognized as the most potent naturally occurring carcinogen being related to the development of liver cancer in many animal species and humans. Aflatoxins B_1, B_2, G_1, and G_2 are currently classified as Group 1 carcinogens by the International Agency for Research on Cancer (IARC) [6][8][9]. Ochratoxin presents as three secondary metabolite forms which can be found in beverages such as beer and wine. Ochratoxin A is identified as a possible human carcinogen inducing damage to DNA and being linked to tumors in the urinary tract [6][10][11]. Fusarium toxins comprise a range of mycotoxins including fumonisins, trichothecenes, and zearalenone, appearing mostly in grains such as wheat and maize. Fumonisins B_1 and B_2 are currently labeled as possible carcinogens by the IARC, based on sufficient evidence of their carcinogenicity in animal models [6][12]. Recent studies with experimental animals have described mutagenicity also for patulin, a mycotoxin found mainly in moldy fruits and vegetables, especially in rotting apples and figs. This chemical can damage DNA and induce severe impairment in the

functioning of the immune system [6]. Despite extensive efforts, the exact molecular mechanisms under the carcinogenesis-promoting action of these mycotoxins are still only poorly understood today.

Mycotoxins are produced by diverse species of fungal pathogens. For example, aflatoxins are generated by *Aspergillus* fungi such as *A. flavus* and *A. parasiticus* [6][8]; ochratoxins are produced by *Penicillium* and *Aspergillus* species, mainly *A. ochraeus* and *A. carbonarius* [6][11]; fusarium toxins are relieved from diverse species of *Fusarium* genus [6][12]; while patulin is produced mostly by *Penicillium*, *Aspergillus* and *Byssochlamys* species, especially by *P. expansum* [6]. Over the past decade, several experimental studies have demonstrated that specific polyphenolic phytochemicals from the class of flavonoids can significantly inhibit the production of such fungal toxins. Low levels of two flavones, apigenin, and luteolin, inhibited aflatoxin B_1 production in *A. flavus* [13]. The *A. parasiticus*-induced aflatoxins contamination in maize was significantly suppressed by citrus flavonoids naringin, neohesperidin, and quercetin [14]. Several citrus flavanones, including naringin, hesperidin, neohesperidin, prunin, and hesperetin glucoside, could inhibit also patulin production from *P. expansum*, *A. terreus* and *B. fulva*, leading to an almost complete decrease in the accumulation of this mycotoxin [15]. In addition, two common flavonols, quercetin, and rutin, reduced the ochratoxin A biosynthesis in *A. carbonarius* [16]. All these data indicate that certain flavonoids may be considered as potential plant fungicides for application in agriculture in the future to prevent the contamination of food products with carcinogenic mycotoxins (Figure 1).

Using natural fungicides instead of synthetic chemicals is more acceptable for final consumers. Furthermore, the added flavonoids might not only suppress the production of mycotoxins in respective food products, thereby preventing the exposure of human beings to these carcinogenic substances but simultaneously also exhibit a wide range of other important health benefits in the human body. Flavonoids have been indeed demonstrated to exert a wide range of advantageous activities, including anti-oxidant, anti-inflammatory, and antihyperglycemic effects [17]-[19]. Nutritionists became interested in these polyphenolic compounds already in the 1930s, when it was demonstrated that flavonoids from citrus fruits reduced capillary permeability and revealed vitamin C sparing properties [20]. Although the initial denomination of flavonoids as vitamin P was abandoned in the 1950s due to a lack of substantive evidence [20]; later on, these compounds drew once again the attention by providing protection against coronary heart diseases and diverse types of cancers in several large-scale epidemiological studies [21] [22]. The exact mechanisms under anticancer bioactivities of flavonoids are currently intensely

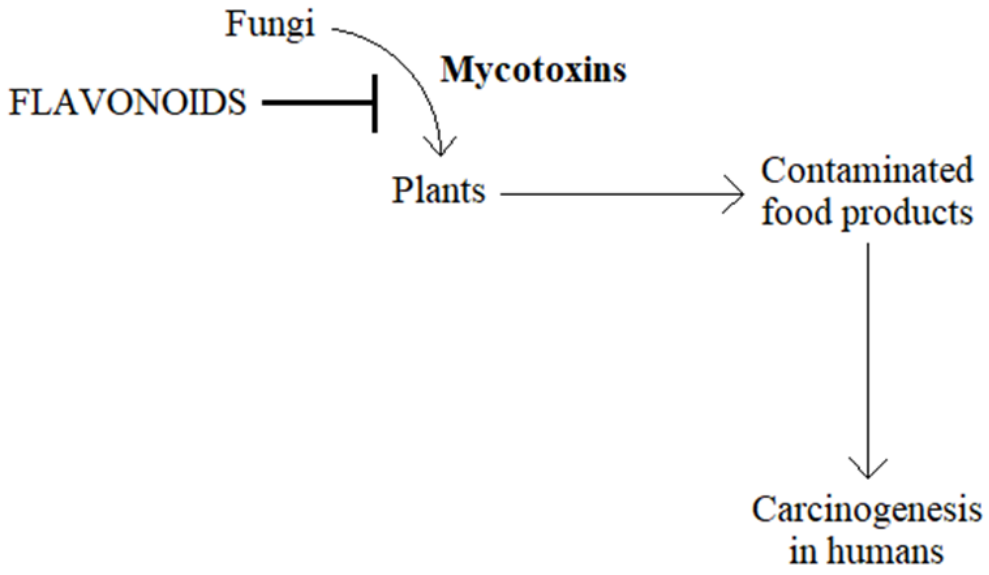

Figure 1. Possibilities to inhibit human carcinogenesis by natural flavonoids through the decrease in the production of mycotoxins in food products.

studied displaying effects on numerous molecular targets and cellular signaling pathways [23]. Such multifaceted action of flavonoids might remarkably contribute to the fight against different types of malignancies, especially considering the ever-increasing incidence of new cancer cases all over the world [24]. As cancerous neoplasms typically develop as a multistage process over many years, each effort to prevent their initiation, and suppress or reverse the progression of already initiated transformed cells to invasive malignancies is of critical relevance [25]. Therefore, although several important steps are still needed to be taken before flavonoids may be applied as potential plant fungicides, such as elaboration of the most efficient formulations and proving their safety, these investigations might contribute to the global fight against cancer, besides leading us toward a greener world in the future.

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Conflicts of Interest

The authors declare no conflict of interest.

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