Cancer Chemopreventive Agents in Plants – A Continuing Challenge

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Why a special issue on plant-derived cancer chemopreventive agents now? For decades the incidence of many solid malignancies has remained stable. Success of treatment of lung, breast, colorectal or pancreas cancer using surgery, radiotherapy or drugs continues to be modest, if not unsatisfactory. In the light of these facts prevention is increasingly an attractive cancer management strategy. Recent figures as to the consequence of smoking cessation for lung cancer incidence (e.g., [1]) emphatically support this notion. Unfortunately, for many cancers, the link between disease and life style habits is not as clear as in the case of lung cancer and smoking. Furthermore, changes in life style habits are not acceptable to many. Such is human nature! In this situation, consumption of cancer chemopreventive agents is an eminently appealing option. Recently, the combination of the anti-inflammatory drug sulindac and difluormethylornithine, an inhibitor of polyamine synthesis, reduced in a dramatic fashion the recurrence of adenomas in polyp patients [2]. This convincing result hints at the potential value of this combination in colorectal cancer prevention and underpins the viability of chemoprevention as a cancer management option. There have been other examples of trials in recent years which support this notion. Nevertheless, cancer chemoprevention is not without problems. Many drugs suspected or known to prevent cancer have unwanted side effects, militating against their use in healthy human beings for extended periods of time. There is clearly an urgent requirement to discover and develop novel safe and efficacious agents. The plant kingdom is an increasingly attractive source of such agents, as phytochemicals tend to have a robust safety record. Many prospective cancer prevention trials in which foodstuffs considered to harbour anti-carcinogenic constituents were explored did not show the positive results expected on the basis of epidemiological findings. We do not know really why this is so. Facing all these issues we felt reviews in this area of scientific endeavour may be a timely and relevant undertaking for the readership of *Planta Medica*.

The first part of this issue is focused on mechanisms by which phytochemicals are thought to exert their chemopreventive efficacy. Review articles from leading experts in the area of cancer chemoprevention provide a thorough introduction into selected mechanisms and models relevant for cancer preventive potential. The second part is dedicated to specific plant sources and compounds of exceptional promise. Readers will find discussions on a fascinating array of plant- and food-derived putative anti-carcinogens, which provide colour, spice, aroma, flavour and tartness to our diet, and at the same time, may promote good health.

Modulation in the expression of enzymes involved in both elimination/inactivation of carcinogens and in cellular antioxidant defence is one of the most important chemopreventive mechanisms of edible phytochemicals. Only recently, the transcription factor nuclear factor-erythroid-2-related factor 2 (Nrf2) has been recognized as a key mediator in the coordinated induction of genes encoding many stress-responsive and cytoprotective enzymes. We are only beginning to understand how chemopreventive agents influence the interaction between Nrf2 and its repressor Keap1, resulting in the release and nuclear translocation of Nrf2 and the transcription of Nrf2-dependent genes [3]. Novel data hint at the possibility that Nrf2 signalling also plays an important role in the defence of acute inflammation, implicating cross-talk between Nrf2 and inflammatory signalling pathways mediated by nuclear factor κB (NF-κB). Intriguingly, combinations of sub-effective doses of anti-inflammatory drugs with natural phytochemicals have been shown to synergistically inhibit carcinogenesis in rodent models [4]. Simultaneous activation of the

received August 18, 2008
accepted August 29, 2008

Bibliografie
DOI 10.1055/s-0028-1088305
Planta Med © Georg Thieme Verlag KG Stuttgart · New York · Published online 2008 · ISSN 0032-0943

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Nrf2/Keap1 pathway concomitantly with anti-inflammatory and immunomodulatory mechanisms has also been indentified as a critical mechanistic property of agents which counteract the damaging effects of UV radiation. Selected alkaloids, flavonoids, carotenoids, and the broccoli-derived isothiocyanate sulforaphane have been shown to work in this way [5]. NF-κB and a second transcription factor, signal transducer and activator of transcription-3 (STAT-3), have emerged as major regulators of inflammation-driven processes involved in carcinogenesis, such as cell survival, hyperproliferation, and angiogenesis. Phytochemicals found in spices may prevent various chronic illnesses including cancerous, diabetic, cardiovascular, pulmonary, neurological and autoimmune diseases through targeting these transcription factors [6]. Organosulfur compounds from *Allium* species (garlic, onion) as well as isothiocyanates such as sulforaphane from cruciferous vegetables are considered to be (indirect) antioxidants which can activate Nrf2 signalling. During the past few years, a novel concept has been established according to which theses agents (at elevated concentrations) generate reactive oxygen species to trigger signal transduction culminating in cell cycle arrest and/or programmed cell death [7]. It has even been speculated that organosulfur compounds may be transformed chemically or enzymatically to form hydrogen sulfide, and that hydrogen sulfide plays an important role as a gaseous transmitter comparable to nitric oxide and carbon monoxide, with essential functions in the brain and cardiovasculature [8]. Metabolites of organosulfur compounds have recently been linked with yet another mechanism: sulforaphane-cysteine and *S*-allylmercaptocysteine, a metabolite of diallyl disulfide derived from garlic, can inhibit histone deacetylase (HDAC) activity. Histone acetylation plays an important role in the regulation of gene transcription and, in addition to DNA methylation, is a major mechanism of epigenetic regulation of gene expression. Epigenetics comprises heritable alteration of gene expression patterns that occur without DNA sequence changes. Epigenetic silencing of tumour suppressor genes through hypermethylation of CpG islands in the promoter region of these genes has been recognized as a very early, potentially initiating event in carcinogenesis. Epigenetics is a fascinating emerging target of dietary phytochemicals in chemoprevention [9].

Almost 20 years ago, Fearon and Vogelstein published a landmark paper describing a genetic model for colon carcinogenesis, which already pinpointed defects in DNA methylation as factors contributing to colon carcinogenesis [10]. In addition, they described several oncogenic genetic changes, including the heritable mutation of the adenomatous polyposis coli (*APC*) gene involved in the development of familial adenomatous polyposis (FAP, a heritable form of colon cancer accounting for about 1% of all colon cancer cases). *APC* is also mutated in about 75% of all sporadic colorectal tumors. Based on this gene defect, the *ApcMin* mouse model was developed which develops multiple intestinal neoplasia (Min) in the small intestine and is frequently used to identify potential chemopreventive agents [11]. Another commonly used animal model is the azoxymethane/1,2-dimethylhydrazine-induced rat colon model. In both models, the cancer chemopreventive efficacy of apple juice has recently been demonstrated. This may not be surprising, since apple juice is rich in polyphenols, particularly in oligomeric proanthocyanidins which are not absorbed and may exert a local chemopreventive effect in the colon. Since quantitative data on the distribution of proanthocyanidins in the diet are limited, the effect of this class of phytochemicals on cancer prevention may have thus far been underestimated [12]. Interestingly, the hitherto relatively unknown chokeberries (*Aronia melanocarpa*) contain an extremely large amount of proanthocyanidins (up to 5 g per 100 g dry weight) as well as coloured anthocyanins, and were identified as a powerfully antioxidant foodstuff. They possess colon cancer preventive efficacy in rats and exert hepato- and cardioprotective as well as antidiabetic activity [13]. Colon cancer-preventive potential has also been reported for other small fruits including blueberries and grapes, which are a rich source of resveratrol and other stilbenes. Resveratrol is an intensely researched compound with anti-inflammatory and anti-aging properties. Overall, pharmacological activities of stilbenes include cancer-preventive and cholesterol-lowering effects, enhanced insulin sensitivity and increased lifespan [14]. The pleiotropic effects of many phytochemicals with chemopreventive activity and recent gene expression data based on DNA array analyses illustrate that understanding the exact molecular mechanism of dietary chemopreventive agents is a continuing challenge. This challenge may be tackled by modern bioinformatic tools such as systems biology [15]. Most importantly, answers concerning clinical efficacy will only emanate from human trials. Such studies will also have to address questions on bioavailability and pharmacokinetics, dose-dependency of metabolism and activity of metabolites, as highlighted in a perspective on resveratrol [16]. Breast cancer treatment and prevention have been revolutionized over the past two decades by the development of synthetic selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifen. The final article of this issue compares actions of clinically approved pharmaceuticals with those of phytoestrogens described as `natural' or `phytoSERMs', such as the isoflavonoids genistein and daidzein abundant in soy products [17].

We do hope that the readers of *Planta Medica* will find the contributions enlightening and stimulating and perhaps inspire some of them to be involved with this exciting area of study.

Acknowledgements

We would like to thank all authors contributing to this issue for their excellent cooperation and we especially acknowledge the help of our reviewers who have ensured high quality with their timely and appropriate suggestions.

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