Drugs based on natural compounds: recent achievements and future perspectives

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This issue has been the focus of the Phytochemical Society of Europe (PSE) Congress on Natural Products in Cancer Prevention and Therapy, Trends in Methods and Modelling, 3rd Edition. The meeting hosted by the University of Naples Federico II on behalf of the PSE was held in Naples, Italy from 4th to 7th of September 2018. The aim of this congress was the presentation of recent results, the discussion of trends, and the exchange of ideas related to the medicinal chemistry aspects of natural products in cancer prevention and therapy with particular attention to the recently developed methods and mathematical modelling. This special issue, based on the contribution of plenary and selected oral speakers presenting lectures at the symposium, deals on the bioactive natural compounds from plants with focus to their activity in cancer prevention and cancer cure.

Multidrug resistance (MDR) is still the main challenge in cancer treatment. Several mechanisms of MDR have been proposed, such as an increased drug efflux due to the overexpression of ABC drug

transporter proteins, or a deregulation of apoptosis. Thus, the development of ABC transporter modulators and the search for effective apoptosis inducers have been considered realistic strategies for overcoming MDR. Exploiting collateral sensitivity is also comprised among the most promising approaches to tackle MDR. Ferreira and Paterna reviewed their work on *Tabernaemontana elegans* that has provided a library of promising monoterpenic indole alkaloids for reversing MDR.

The first step in carcinogenesis is most likely damage to DNA and other macromolecules. Epidemiological studies kept confirming that Mediterranean diet, characterised by a relatively high intake of fruit and vegetables rich in antioxidant compounds, enhances health and provides protection against cancer. Rather than being antioxidants, plant constituents are more likely to act as triggers or inducers of expression of the human antioxidants superoxide dismutase (SOD) catalase (CAT), and reduced glutathione (GSH). Alfa and Arroo reviewed the literature on the relation between dietary flavonoids and their action in the prevention of degenerative diseases.

The paper of Pop et al. focuses on the impact of modified DNA methylation pattern on early carcinogenesis and summarizes the effects/mechanism of phytochemical interventions on epigenetic alterations. This because the potential of phytochemicals to modulate epigenetic events in human health has recently become evident, although their mechanism

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of action is still unclear. Phytochemicals, including dietary compounds, can restore global and gene-specific promoter DNA methylation patterns by reactivating DNA methyltransferases or by providing the provision of methyl groups.

Inflammaging is a low-grade, chronic, asymptomatic, controlled and systemic proinflammatory status that appears during the aging process and it is linked to many age-related diseases. Growing evidence indicates that Mediterranean diet is a reliable instrument to counteract inflammaging, due to its high content of flavonoids, whose main source are *Citrus* fruits. The review by Maugeri et al. is aimed to summarize and critically discuss the rich clinical evidence on the properties of *Citrus* fruits and their derivatives focusing on a series of age-related diseases and their potential use to maintain health in aging populations.

Recently there was an increasing interest in plant derived natural products and their semisynthetic derivatives with potential value as chemopreventive or chemotherapeutic agents. Within the huge class of plant phenolics, prenylated flavonoids show a rich structural variety and pharmacological activity. This make them a prominent potential class of anticancer agents. The aim of the review by Molčanová et al. is to summarize the available data on the in vitro cytotoxicity of C-prenylated flavonoids in solid tumour cell lines assays, extending a previous report published on 2014 by the same research group.

Voller et al. reviewed the literature on the anticancer activity of cytokinin ribosides. Cytokinins are plant hormones playing essential roles in plant growth regulation and development. Whereas cytokinin bases have been studied for cytoprotective activities, cytokinin ribosides have been explored as anti-cancer agents. This because they inhibit growth or cause apoptosis of malignancy cell lines, including those with a mutant p53 gene. Activity against cancer stem cells, anti-angiogenic activity, and the ability to stimulate an immune response to malignant cells in vitro and in vivo have been reported, and in clinical studies on patients with haematological malignancies and solid tumours.

Phytoalimurgy is a term that derives from Greek and Latin by combination of the words *φυτόν*, meaning plant, and *alimenta urgentia*, indicating foods available in case of urgency and necessity. Nowadays, the interest in using the phytoalimurgic

plants has seen an increase because of their rediscovery for use as food ingredients and human health. Among these, common dandelion, *Taraxacum officinale*, is used since ancient times for its curative properties. The aim of the review by Grauso et al. is to contribute to the knowledge of this worldwide-spread phytoalimurgic plant with its botanical, phytochemical and pharmacological description.

The review of Graziani et al. represents an overview of the literature about the taxonomy, distribution and morphology of the *Astragalus* genus along with a comprehensive description of the chemical features and the biological activities of the saponins from it derived. Moreover, to summarise the current mechanistic knowledge on these metabolites, the authors elaborated an overview of the key signalling pathways that are known to be affected by *Astragalus* saponins and dedicated a section to astragaloside IV, the best-characterised cycloartane glycoside from *Astragalus*, to summarise its potential as pharmacological agent.

Garlic has been used as a medicinal food for centuries. Widespread in vitro and in vivo studies reported the mechanism of action of the anticancer activity of garlic organosulfur compounds (OSCs) in a wide range of cancer types. More recently, several studies have reported the ability of garlic-derived OSCs to release hydrogen sulfide (H₂S) and to affect its biosynthesis by altering specific H₂S enzyme activity, such as cystathionine-beta-synthase (CBS) or cystathionine-gamma-lyase (CSE). Yagdi Efe et al. propose here to raise a mechanistic gap in garlic-mediated anticancer activity by documenting current knowledge of the role of H₂S in cancer biology.

The Latin American medicinal plant carqueja got its name from a morphologically similar plant from the Iberian Peninsula. The name indicates all species from section *Caulopterae*, genus *Baccharis*, often difficult to distinguish. Phytochemical studies indicate that different species from this section contain similar compound classes, essential oils, flavonoids and diterpenes, but with variation to individual compounds within species. There are also indications for the existence of different chemotypes within species. The paper by Schripsema et al. gives recommendations for further studies on these plants and increased reproducibility of pharmacological studies.

The paper by Monaco et al. illustrates a unique collection of 189 plant drugs, coming from all continents, based on the original documents, preserved

at MUSA (Museum of Agricultural Sciences), Portici. This collection was produced in 1937 by the company “Carlo Erba”, Milan, on request of prof. G. Catalano, director of the Botanical Institute, Portici. 111 plants were already known as herbal remedies from two ancient books kept in the Historical Library of the Orazio Comes Botanical Museum, dating back fifteenth and seventeenth centuries. 13 plants were selected for their anticancer effects either known in traditional medicine or currently studied.

Recent international developments make access to biological resources across international borders more difficult than in the past. Local access to biological resources, including plant natural products, thus becomes more important. In order to evaluate the opportunities to access bioactive natural products, Zidorn here started a series of dedicated articles assessing the chemical diversity of plant taxa, native and naturalized, in the region of Schleswig–Holstein, Germany with attention to natural products found compared with same plants collected in other regions and analytical GC–MS and/or HPLC–DAD–MS systems used to identify and quantify these compounds.

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This issue of *Phytochemistry Reviews* dedicated to “Natural Products in Cancer Prevention and Therapy, Trends in Methods and Modelling” presents an updated state of art in the field. Much remains to be done with new research especially on the integrated analysis of nutrition and microbiome with the effects of drugs in cancer treatments as well as the novel application of system dynamics modelling to these processes. Being a basis for discussion of new trends and ideas, this publication will stimulate future work on natural products in drug discovery and development.

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