

Editorial

Tannins and related polyphenols: Fascinating natural products with diverse implications for biological systems, ecology, industrial applications and health protection

These two issues of *Phytochemistry* are dedicated to the study of tannins and related plant polyphenols, with contributions largely derived from presentations given at the 4th Tannin Conference – Plant Polyphenols: Chemistry, Biology and Function. The conference was organized as part of the American Chemical Society's Fall 2004 meeting in Philadelphia, hosted by the Cellulose and Renewable Materials Division. More general information about the overall scope of the gathering can be gleaned from the 228th ACS National Meeting Abstract Book. Some selected highlights of the meeting and of the special issues are described below.

Tannin Awards: The Polyphenol Community of Scientists proudly honoured two of its outstanding pioneering research scientists at the meeting for their life-long seminal contributions, and untiring commitment, to this complex field of study. This was done through presentation of the 4th Tannin Conference Awards to *Dr. Richard W. Hemingway* and *Emeritus Professor Takuo Okuda*, respectively.

Dr. Richard (Dick) William Hemingway, Pineville, Louisiana, USA, received the *MARS Inc.-sponsored award*. This appreciation was in recognition of his lifelong prolific contributions to the chemistry and industrial application of condensed tannins (proanthocyanidins), as well as for his sustained abilities to stimulate collaborative research and in establishing productive networking in the tannin field interfacing chemistry, biology and industry.

Dr. Hemingway received his Ph.D. degree from the University of Michigan in 1967, following which he spent six years as a researcher, and then senior researcher, scientist at the Forest Products Division, CSIRO, Melbourne, Australia, while working with Ted Hillis. He subsequently joined the Southern Forest Experiment Station of the USDA Forest Service, Pineville, LA in 1972, where his talents were quickly recognized being

promoted from Technologist, Project Leader to Senior Scientist. Following his retirement from USDA in 2001, he established Plant Polyphenols L.L.C. company in Alexandria, LA, whose research and development focus is on utilization of plant polyphenols for human health applications.

Dick Hemingway has, for many years, been a key figure in the study of the chemistry and application of proanthocyanidins. His most notable contributions involved work on tannin ¹³C NMR spectroscopic properties, conformational behaviours, reactivities under alkaline conditions, and also on industrial applications. He is also greatly appreciated for conceptualising the Tannin Conferences, which, with Dr. J.J. Karchesy, came to fruition through organization of the 1st North American Tannin Conference in 1988 (Port Angeles, Washington). He then untiringly organized, with Dr. P.E. Laks, the 2nd North American Tannin Conference in 1991 (Houghton, Michigan), and most recently, with Professors G.G. Gross and T. Yoshida, the 3rd Tannin Conference in 1998 (Bend, Oregon). Three authoritative tomes emanating from the proceedings of the conferences were published, and this conference followed in this spirit.

Emeritus Professor Takuo Okuda, Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Okayama University, Japan, received the *National Center for Natural Products Research, a University of Mississippi sponsored award*. This appreciation was in recognition of his remarkable legacy, whether for contributions to the chemistry and biology of hydrolyzable tannins, or in training/developing the current/next generation of polyphenol researchers.

Professor Takuo Okuda graduated with a Ph.D. degree from Kyoto University in 1955, following which he spent three years as a postdoctoral research associate at the University of Pennsylvania, Philadelphia, before

returning to join the Kyoto University faculty in 1958. He later moved to Okayama University to take up the position of Professor of Pharmacognosy in the newly opened Faculty of Pharmaceutical Sciences where he now holds Emeritus Professor status.

Professor Okuda's career in hydrolyzable tannin chemistry developed dramatically after isolation and characterization of geraniin from the popular Japanese medicinal plant, *Geranium thunbergii* in 1975. Subsequently, he and his co-workers characterized literally hundreds of very complex hydrolysable tannins and related polyphenols. His collaborations with scientists in the medical and pharmaceutical fields also led to the discovery of many of the most significant biological activities of tannins. Prevalent amongst these discoveries is his work on anti-oxidant properties, especially those from green tea and thus of their human health promoting properties. To date, Professor Okuda has published ca. 280 original research papers, about 40 review articles, as well as six books on natural products and medicinal plants.

The 4th Tannin Conference: The meeting drew together a large contingent of polyphenol researchers, several of whom provided manuscripts for consideration for publication in these special issues. What was readily apparent, from the spirited discussions, was the growing interest in this field from many different perspectives. The following general topics were covered:

- Advances in chemistry and biochemistry – chemical synthesis, biosynthesis, conformational analysis and mechanism of their actions in biological systems.
- Polyphenols as renewable sources of industrial chemicals.
- Polyphenols in plant–plant, plant–animal, plant–insect interactions and other aspects of ecological significance.
- Polyphenols in everyday life, e.g., their properties on health effects in human nutrition and disease prevention.

Before commenting on some of the individual papers in these issues, it is useful to first briefly reflect on the status of past meetings about plant polyphenols and their metabolism. Tannins (polyphenols) have been the subject of extensive research for more than a century, although this exciting area of natural products chemistry was largely neglected scientifically until recently. This was perhaps because of perceived problems concerning definition of other structures, as well as a paucity of detailed information on their biosynthesis and biological functions. However, this situation has rapidly changed, in part because of significant advances in the elucidation of their constitutions and conformations, as well as from the broad recognition of their fascinating biological, pharmacological and physiological activities which have

led to increasing attention to these metabolites. Indeed, today, with the growing realization of their profound health-beneficial effects and emerging specific interactions at the molecular level, tannins (polyphenols) now attract the interests of scientists from many disciplines, and this, in turn, has led to many interdisciplinary studies. Such contemporary developments have also extended the use of 'tannins' beyond the range of this class of metabolites as reflected by a growing adoption of the term 'polyphenols', a change that can also be seen in the contributions to the past Tannin Conferences.

The specific objectives of this particular conference were to promote further collaborations between chemists, biologists and human health related disciplines in order to improve understanding of the chemistry and the biological and physiological significance of polyphenols, and to focus on expanded possibilities for their application in industry and in human health, nutrition and the food industry.

In *Biosynthesis Section*, papers dealt with biochemical and molecular biology approaches directed to elucidation of the pathways to hydrolysable tannins, proanthocyanidins and other phenylpropanoids.

Richard Dixon and his co-workers described our current knowledge of proanthocyanidin biosynthesis at the genetic/molecular level, and in particular, demonstrated that anthocyanidin reductase unexpectedly converts anthocyanidins into their corresponding 2,3-*cis*-flavan-3-ols. Evidence for this very interesting revision of the proanthocyanidin pathway was obtained from studies using *BANYULS* mutants of *Arabidopsis thaliana*.

Ruth Niemetz and Georg Gross reviewed the significant progress made in the enzymology of gallotannin and ellagitannin biosynthesis, highlighting enzymes catalysing the β -glucogallin dependent galloylation of 1,2,3,4,6-penta-*O*-galloyl- β -D-glucopyranose to a variety of higher substituted analogs and formation of cornusinin E via tellimagrandin II, which is catalyzed by laccase-type phenol oxidases.

Norman Lewis' group gave different papers on phenylpropanoid metabolism, with particular emphasis on lignin and lignan formation, highlighting the utility of *Arabidopsis thaliana* to study many of these processes. In particular, he provided an informative description of their systematic approach to identify the structural and mechanistic basis of the enzymes/proteins involved in the various branches of phenylpropanoid metabolism ranging from fundamental biochemistry to X-ray crystallography. The contributions for these particular special issues of *Phytochemistry* describe the comprehensive characterization of the 4-coumarate CoA ligase and cinnamoyl CoA reductase families, and the roles of specific isoforms in lignin and related metabolites. Other presentations reported on regiospecific 8,8'-coupling and polyphenol oxidase enantiospecificity in lignan biosynthesis in *Larrea tridentata*, with the gene encoding

the polyphenol oxidase now cloned. Such details form the basis for modification and genetic manipulation of the lignin/lignan pathways which are of interest due to, for example, the significant antiviral/antitumor activities of some members of these classes of natural products.

In *Chemistry Section*, Daneel Ferreira and his co-workers reviewed studies aimed at stereoselectively synthesizing monomeric flavonoids, especially of the various flavan-3-ols involved in the formation of proanthocyanidins. They also discussed critically the application of circular dichroism for the assessment of absolute configuration of the various classes of flavonoids, and provided a comprehensive analysis of the special case of apparently atypical metabolic pools in plants of the southern hemisphere characterized by the absence of potent flavan-3-ol nucleophiles, which gives rise to the genesis of a vast array of proanthocyanidin prototypes.

Ken Feldman gave a very interesting discussion on development of new synthetic protocols for selective execution of biaryl and diaryl ether bond forming processes in the context of the total syntheses of coriariin A and other ellagitannins. Members of this group of non-cytotoxic dimeric ellagitannins display not only promising new antitumor leads but interesting immunomodulatory activities as well.

Jess Reed and his colleagues summarized the growing application of MALDI-TOF mass spectroscopy for detailed structural characterization of complex proanthocyanidins, with this approach being used by Amy Howell and co-workers on the study of bacterial anti-adhesion activities of cranberries, this being associated with the presence of A-type units in oligomeric procyanidins.

Takashi Yoshida and collaborators reviewed the occurrence, distribution and identification of complex ellagitannin oligomers in Melastomataceae from a chemotaxonomical point of view. Following on from this, Takuo Okuda, the recipient of the 4th Tannin Conference Award, reviewed the impressive contributions made on the isolation and structure elucidation of hydrolysable tannins, as well as on their particular biological activities, i.e. anti-oxidant, anti-cancer, and antiviral properties.

Pharmacological Properties and Health Effects of Tannins/Polyphenols: A number of the papers also addressed pharmacological properties and health effects of polyphenols in human nutrition. These include the following:

J.L. Torres and collaborators described the neuroprotective activity of epicatechin–cysteine conjugates, which have the capability to scavenge intracellular reactive oxygen species, whereas another contribution from Takashi Yoshida's group discussed the significant biological effects of selected hydrolysable tannins on methicillin-resistant *Staphylococcus aureus* strains.

Herbert Kolodziej and collaborators also reviewed the antileishmanial activities of polyphenols. Using parasitised macrophages, incubation with polyphenols induced activation of cytotoxic functions associated with the destruction of amastigotes. RT-PCR analyses showed the expression of a range of cytokine transcripts with notable differences in the IFN patterns.

Hiroshi Sakagami and co-workers discussed the stimulation of macrophages for the release of nitric oxide and production of asparagine by isolated and synthetic lignin-derived preparations, also demonstrating the expression of nitric oxide synthase and asparagine synthase by Western blot and RT-PCR analyses.

Masaaki Nomura reported the inhibition of epidermal growth factor-induced cell transformation by hydrolysable tannins, whereas Ron Prior and his team gave a comprehensive overview of the average daily intake of proanthocyanidins present in the American diet.

The Exciting Future of Tannin (Polyphenol) Research: What might our hopes be for the future? It is essential to continue these meetings with an even stronger emphasis on their interdisciplinary character. Although considerable progress has been made in elucidating the structures and biosynthetic pathways of polyphenols, there are still many important gaps in our knowledge base concerning both their chemistry and biology. Additionally, there is a pressing need to adequately define the structure of these complex polymers, and to gain more fundamental insight into their roles in plants, as well as in establishing the principles of their biological activities in order to benefit human health. In this context, we are looking forward to information emanating from studies of the molecular biology of genomics and proteomics in order to enhance our comprehension of their intricate roles/functions at the molecular level.

Daneel Ferreira
Georg G. Gross
Herbert Kolodziej
Takashi Yoshida