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Editorial

Tannins and related polyphenols: Perspectives on their chemistry, biology, ecological effects, and human health protection

This issue of *Phytochemistry* is dedicated to the study of tannins and related plant polyphenols, with contributions partially derived from presentations read at the 5th Tannin Conference – Plant Polyphenols: Advances and Trends in Basic and Applied Research. The conference was organized as part of the American Chemical Society's Fall 2006 meeting in San Francisco, hosted by the Cellulose and Renewable Materials Division. Additional information about the overall scope of the meeting may be attained from the 232nd ACS National Meeting Abstract Book. Some selected highlights of the meeting and of the special issue are outlined below.

Tannin Awards: The Polyphenol Group of Scientists honored two of its revered research scientists at the meeting for their pioneering contributions and diligent commitment to this challenging field of study. This was done by presentation of the 5th Tannin Conference Awards to *Prof. Dr. George Günter Gross* and *Dr. Gen-ichiro Nonaka*, respectively.

Prof. Dr. George G. Gross, Department of Molecular Botany, University of Ulm, Germany, received the MARS Inc. – Sponsored Award. This award was given in recognition of his seminal contributions to the biosynthesis of both the lignins and the two classes of hydrolyzable tannins, *i.e.*, the gallotannins and ellagitannins in a career spanning almost 40 years, as well as for his enthusiastic dedication towards co-organizing the 3rd (1998), 4th (2004), and 5th (2006) Tannin Conferences in Bend (OR), Philadelphia (PA), and San Francisco (CA), respectively.

Professor Gross earned his *Dr. rer. nat*. degree with Professor Meinhard Zenk at the University of Munich in 1968 for his chemical and biochemical studies of coenzyme A thioesters, the biosynthetic precursors of lignins. He joined the biology faculty at Ruhr-University Bochum and completed his Habilitation there, extending his work on lignification to explore formation of cinnamyl alcohols, the monomeric lignin units. In 1978 he moved to the University of Ulm where he was a Professor in the Plant Biochemistry unit until his retirement in 2006. During his career he collaborated with many leading natural product figures including Professors Joachim Stöckigt, Richard Mansell, and the late Jerry McClure.

Georg Gross will be remembered and appreciated for his cutting-edge contributions (more than 80 publications in top-tier journals) in the areas of lignin biosynthesis, *e.g.*, they synthesis of cinnamoyl coenzyme A thioesters, the first report on the reduction of feruloyl-CoA to coniferyl aldehyde, and the production of hydrogen peroxide in lignifying cell walls; alkaloid biosynthesis, *e.g.* the biosynthesis of tropine and of piperine, the pungent principle of black pepper; and elucidating the pathways from gallic acid to gallotannins and ellagitannins, and the histological and cellular localization of enzymes and metabolites involved in the biosynthesis of hydrolyzable tannins. Highlights of the latter studies involved the biosynthesis of β-D-glucogallin, eventually recognized as the principal activated metabolite in gallotannin biosynthesis, detection of the reactive intermediate in pentagalloylglucose biosynthesis, and elucidating the fundamentals of gallotannin and ellagitannin biosyntheses.

Dr. Gen-ichiro Nonaka, President of the Usaien Pharmaceutical Co., Ltd., Saga, Japan, received the National Center for Natural Products Research (NCNPR), a University of Mississippi-sponsored award. This award was given in recognition of his outstanding contributions to the chemistry and biology of both hydrolyzable tannins and proanthocyanidins.

Dr. Nonaka graduated with a Ph.D. degree from Kyushu University in 1974, for research on the alkaloids of *Corydalis incise.* He served as Assistant Professor at the faculty of Pharmaceutical Sciences, Kyushu University, from 1973 to 1983, was a Research Fellow in the School of Medicine of Johns Hopkins University (1978–1979), and was promoted to Associate Professor Kyushu University in 1984 where he worked until his early retirement from *Academia* in 1993. Since becoming President of Usaien Pharmaceutical Co Ltd., Dr. Nonaka kept close contact with universities as is evident from his extensive involvement as Visiting Professor both in Japan and China.

Dr. Nonaka has published more than 250 original research papers, counting only those written in English. Whereas his first 20 papers mostly dealt with alkaloids, the bulk of the remainder covered the chemistry and biology of the proanthocyanidins and both the gallotannin and ellagitannin classes of hydrolyzable tannins. Remarkably, Dr Nonaka and his coworkers have studied approximately 170 plant species belonging to 47 plant families, as well as herbal products and some commercial extracts. These studies have led to the identification of a large number of new proanthocyanidins of both the A- and B-classes, as well as numerous gallotannins and ellagitannins. Dr Nonaka is also credited with the first demonstration of the oxidative conversion of B- into A-type procyanidins, identification of phenylpropanoid-substituted catechins, and the discovery of the complex tannins, a class of polyphenols in which a flavan-3-ol unit is connected to a gallotannin or ellagitannin via a carbon–carbon bond. That the hexahydroxydiphenoyl moiety, a characteristic feature of ellagitannins, may be linked to residues other than D-(+)-glucose, was demonstrated by characterization of the castanopsinins and casanopsiin with their basic triterpenoid skeleton.

Extensive collaboration with scientists in the medical and pharmaceutical fields enabled Dr. Nonaka to address a wide range of

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the pharmacological properties of tannins. He also worked extensively on the fermentation processes during the manufacturing of tea, a process involving a mind-boggling array of chemical conversions of green tea catechin constituents. Very appropriately, *Professor Takashi Tanaka*, Dr. Nonaka's successor at Nagasaki University, on accepting the NCNPR Tannin Award on Dr Nonaka's behalf, read a paper, *Catechin Oxidation Cascades during Black Tea Production, and Enzyme Inhibition Activities of the Oxidation Products*, describing the complexity and elegance of the research pioneered during Dr Nonaka's illustrious career.

The 5th Tannin Conference: The meeting drew together a significant contingent of polyphenol researchers, representing North America, Japan, Western Europe, Scandinavia, Africa, and Australia. Several of the contributors submitted manuscripts for consideration for publication in this special issue. The remaining manuscripts were selected from regular submissions covering similar classes of naturally occurring polyphenols. The following general topics were covered:

- Polyphenols in plant–plant, plant–animal, plant–insect interactions, and other aspects of ecological significance
- Polyphenols in everyday life, *e.g.*, their role in health effects in human nutrition and disease prevention
- The intricate polyphenolic chemistry of winemaking and the wine industry.

The growing body of evidence in support of the fascinating biological, pharmacological, and physiological activities of polyphenols in general, and proanthocyanidins in particular, has been a considerable catalyst for continuing research into these areas. Indeed, the sharp focus on their profound beneficial effects on human health, and emerging specific interactions at the molecular level, have drawn together a broad interdisciplinary group of scientists addressing problems with a level of sophistication that was unimaginable as recently as 5–10 years ago.

The specific objectives of the 5th Tannin Conference were to advocate and strengthen collaborations between chemists, biologists, and human health related disciplines in order to promote comprehension of the chemistry and the biological and physiological significance of polyphenols, and to target expanded possibilities for their applications in industry, human health, nutrition, and environment.

In the *Biosynthesis Section*, papers dealt with biochemical and molecular biological approaches to a variety of polyphenol classes. In his Award Lecture, *From lignins to tannins: Forty years of enzyme studies on the biosynthesis of phenolic compounds*, Georg Gross reviewed the principal findings and current trends in elucidating the pathways to lignin and lignin precursors, acyl amides, and the gallotannin and ellagitannin classes of hydrolyzable tannins by enzyme studies.

The research group of *Norman Lewis* and *Laurence Davin* discussed the relationship of dirigent protein and 18s RNA localization to heartwood formation in western red cedar. Their *in situ* mRNA hybridization approach facilitated detection of dirigent protein transcripts in cork and vascular cambia, and ray parenchyma cells of the sapwood, but not the heartwood. It thus demonstrated the utility of the technique in identifying specific cell types involved in heartwood formation.

Jianggo Liu and his coworkers demonstrated that stereospecificity (30% atropisomeric excess) of the free radical dimerization of hemigossypol into (+)-gossypol in moco cotton is mediated by a dirigent protein.

Karin Springob and her coworkers described the biosynthesis of pyrone polyketides by a type-III polyketide synthase from *Drosophyllum lusitanicum*. A cDNA with similarity to known type-III polyketide synthases, termed DluHKS, when expressed in *Escherichia coli*, accepted acetyl-CoA as a starter unit and carried out sequential decarboxylative condensations with malonyl-CoA to afford α-pyrones comprising three to six acetate units.

In the *Chemistry Section*, *Takashi Tanaka* read the Award Lecture at the occasion of Dr. Nonaka receiving the NCNPR Tannin Award in *absentia*. He discussed results relevant to the enzymatic oxidation of three catechins with pyrogallol-type B-rings. These oxidations, resulting in the formation of proepitheaflagallin and dehydrotheasinensin C- type dimers, suggested the enzyme-catalyzed oxidation of the pyrogallol B-ring into an *o*-quinone, and subsequent non-enzymatic reactions with a high degree of stereocontrol.

Tsutomu Hatano and *Takashi Yoshida* and their collaborators described the isolation and identification of flavonol glucuronides, C-glucosidic ellagitannins and their oligomers from *Melaleuca squarrosa* as well as phloroglucinol diglycosides, and the new hydrolyzable tannin, kunzeatannin A from *Kunzea ambigua*.

Takashi Tanaka and *Isao Kouno* and their coworkers described the isolation and identification of dunalianosides A-I from the buds of *Vaccinium dunalianum*. Structurally these compounds are caffeoyl esters of arbutin, dunalianosides F–H uniquely representing dimers of *p*-hydroxyphenyl 6-*O*-*trans*-caffeoyl-β-D-glucopyranoside. Dunalianoside I was found to be a conjugate of arbutin and an iridoid glycoside.

Lucia Lopez discussed the structures of two new biflavonoids and a new tetraflavonoid from the leaves of *Aristolochia ridicula*. The biflavonoid comprised a biflavone and a chalcone–flavone, while the structure of the tetraflavonoid contained the structural elements of ridiculuflavone and a chalcone moiety.

In the section dealing with *Pharmacological Properties and Health Effects of Polyphenols, Herbert Kolodziej* and his coworkers explained the effects of interferon (INF-γ), lipopolysaccharide (LPS), and some polyphenols as individual stimuli, and in various combination on nitrous oxide production in infected and non-infected macrophage-like RAW 264.7 cells. The phenolic compounds included gallic acid, 3-*O*-galloylshikimic acid, 3,5-di-*O*-galloylshikimic acid, catechin, epigallocatechin-3-*O*-gallate (EGCG), an ellagitannin, and a procyanidin hexamer with unidentified C-3 configuration of consistent units.

Tsutomu Hatano and his coworkers discussed the enhancement of the antibacterial effects of EGCG by ascorbic acid. Of special significance is the observation that the antibacterial activity of EGCG towards methicillin-resistant *Staphylococcus aureus* was also enhanced in the presence of ascorbic acid, such an enhancement presumably resulting from stabilization of EGCG in solution via the antioxidative effect of ascorbic acid.

Yoshiaki Amakura and his coworkers described the influence of food polyphenols, *e.g.*, daidzein, resveratrol, apigenin, quercetin, baicalein, and naringenin on the aryl hydrocarbon receptor-signaling pathway.

In the *Analytical Chemistry Section, Veronique Cheynier* and her collaborators focused on direct mass spectrometry approaches to characterize polyphenol compositions of complex samples. The utility of direct flow injection electrospray ionization MS analysis was demonstrated in the establishment of polyphenol fingerprints of complex extracts such as wine.

Four contributions focused on identification of Nature's colorful pigments, the anthocyanins. *Fumi Tatsuzawa* and his colleagues described the identification of tetra-acylated cyanidin-3-sophoroside-5-glucosides from the flowers of *Iberis umbetta*, acylating agents involving malonic acid, *p*-coumaric acid, ferulic acid, sinapic acid, and/ or hydroxycinnamic acid β-D-glucopyranosides. *Kumi Yoshida* and his coworkers provided two contributions, *i.e.*, the structure elucidation of cyanosalvianin, a supramolecular blue metalloanthocyanin from the blue petals of *Salvia uliginosa*, and a report discussing the change of color and components in sepals of a chameleon hydrangea (*Hydrangea macrophylla*) during matu-

ration and senescence. Cyanosalvianin was chemically produced by mixing a complex delphinidin, a di-*O*-glucosylated apigenin, and magnesium ions.

Fumio Hashimoto and his colleagues described their meticulous efforts at separation and extensive structure elucidation of five anthocyanins from the red flowers of *Camellia reticulata*. The anthocyanins were all of the cyanidin type, and the attention to detail as far as structure elucidation via utilization of the full array of NMR and MS techniques are concerned, may serve as a standard worth emulating.

In conclusion, it is essential to continue with meetings such as these, especially to foster an even greater interdisciplinary emphasis. In spite of remarkable progress over the past few years, there are still many apparent gaps in our knowledge base, especially as far as the modes of action in human health application of polyphenols are concerned. We also need to emphasize the importance of fully comprehending the roles of these compounds in plants and in the environment, in a broad sense. Information emanating from studies of the molecular biology of genomics and proteomics in order to enhance our understanding of their roles and function at the molecular level is a prerequisite for progress in a research field that is often times hampered by extreme complexity. However, there has never been a better time to be or to become involved with research involving these intricate yet exciting molecules that are such an integral part of Nature's bountiful treasures.

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