

Stéphane Quideau

Editor



Chemistry and Biology of Ellagitannins

An Underestimated Class of
Bioactive Plant Polyphenols



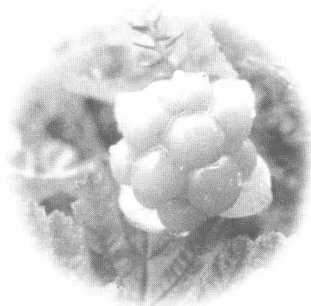
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NEW JERSEY • LONDON • SINGAPORE • BEIJING • SHANGHAI • HONG KONG • TAIPEI • CHENNAI

Published by

World Scientific Publishing Co. Pte. Ltd.

5 Toh Tuck Link, Singapore 596224

USA office: 27 Warren Street, Suite 401-402, Hackensack, NJ 07601

UK office: 57 Shelton Street, Covent Garden, London WC2H 9HE

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

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ISBN-13 978-981-279-740-7

ISBN-10 981-279-740-8

Printed by FulIsland Offset Printing (S) Pte Ltd, Singapore

Preface

Emil Fischer, Karl Freudenberg and Paul Karrer were three iconic figures in the development of organic chemistry in the first half of the twentieth century; they were also pre-eminent amongst those attracted toward the study of vegetable tannins – extracts of plant materials whose use in the conversion of raw animal skins into leather was centuries old. Notwithstanding such efforts it was still possible for the chairman of a symposium dedicated to the subject of vegetable tannins held in Cambridge in 1956 to begin by stating “*After the early encouragement of Emil Fischer’s outstanding contribution to the tannin problem, chemists realised that the problem was still one of great complexity, and tannin chemistry had gradually become one of the disorderly and untidy corners of organic chemistry.*” It was generally recognised [Freudenberg (1920). *Die Chemie der Natürliche Gerbstoffe*, Springer: Berlin] that there was a broad division into condensed or non-hydrolysable and hydrolysable tannins but much else remained vague and uncertain. By contrast the progress made in our understanding of these previously intractable children of nature in the following fifty years has been remarkable. As is often the case in science much of this has been a result of the discovery of new techniques and methods – principally chromatography in its various guises and a panoply of new spectroscopic tools in structure determination. As is also often the case the contributions of particular individuals is frequently critical in charting the way forward. In the case of ellagitannins the efforts of two men in the 1950s were crucial in determining the nature and scope of the subject and its future development. They were the founding fathers of the subject as we know it today.

After the disruption following the second world war and at the age of fifty three, Otto Theodor Schmidt began what was to be the most productive and successful phase of his distinguished career namely the study of the structures of the ellagitannins. Where others before failed he isolated and studied ellagitannins from traditional sources such as *Myrobalans* and *Algorabilla*. It was a classical piece of work and inevitably employed classical techniques (often now long forgotten) such as crystallisation and chemical degradation! By today's standards the number of his publications is very modest but each has depth, the stamp of intellectual rigour and infinite attention to detail and each, without fail, has stood that most important test – the test of time. His work, along with that of his colleague Walter Mayer brought to light for the very first time some of the many characteristic structural groups found in ellagitannins – hexahydroxydiphenic acid, dehydrodigallic acid, dehydrohexahydroxydiphenic acid, valoneic acid, chebulic acid, brevifolin carboxylic acid – all derived from the fundamental building block gallic acid. It is one of the truisms of good scientific practice that one should always set aside time to think and as the work progressed Schmidt and Mayer began to elaborate an eminently satisfying framework and rationale, involving dehydrogenation and hydrolysis, for the biogenesis of the ellagitannins from their presumed galloyl ester precursors. This pioneering work of the Heidelberg school has securely underpinned all the subsequent chemical and biogenetic work in this field over the past half-century.

If Schmidt was a consummate practitioner of organic chemistry then E.C. Bate-Smith was an extraordinary talented polymath whose interests ranged from animal physiology to taste and astringency, to plant systematics and taxonomy. His investigations of astringency in foodstuffs led him to vegetable tannins and to their taxonomic distribution in the plant kingdom. After retirement this became his hobby and his passion, ('Bate-Smithery' as it was occasionally referred to). It constituted the first really serious excursion into the botanical aspects of vegetable tannins and demonstrated unequivocally their presence as normal phenolic metabolites in a much wider range of plants than had hitherto been appreciated. As such it was seminal and its results far-reaching. It opened up the field and has been thoroughly exploited in

subsequent research not only in the search for new tannins but also from the point of view of plant systematics. In the specific case of ellagitannins Bate-Smith suggested that they were to be found in some 75 families of dicotyledonous plants. His methods were deceptively simple, those of the true amateur.

Thus Schmidt and Bate-Smith, in their differing ways, not only laid secure and lasting foundations for many of the developments in the chemistry and biochemistry of ellagitannins that have followed, but they also signposted many of the avenues which were now open to future research. Some measure of the explosion of activity in this field which ensued in the second half of the twentieth century may be gained by comparing Schmidt and Mayer's extensive review [*Natürliche Gerbstoffe, Angewandte Chemie*, (1956), 68, pp. 103–115] and Mayer's appreciation of Schmidt's work and career [*Liebig's Annalen der Chemie*, (1973), pp. 1759–1776] with the 1996 review of Ellagitannin Chemistry by Quideau and Feldman [*Chemical Reviews*, (1996), 96, pp. 475–503]. The present multi-author text now brings the subject right up to date and into the twenty-first century; its contents and the story of achievement it tells would have brought a smile of satisfaction to both Schmidt and Bate-Smith.

Almost inevitably the reader's attention is taken by the enormous range and number of ellagitannin metabolites which have now been isolated from plants – from simple 'monomeric' hexahydroxydiphenoyl esters, dehydroellagitannins, *C*-glycosidic ellagitannins, 'oligomeric' ellagitannins, to macrocyclic 'oligomeric' ellagitannins.....The list seems endless and, in the context of the position fifty years earlier, it represents a monumental achievement, accomplished principally by researchers in Japan – Okuda, Yoshida, Nishioka, and Tanaka. Okuda and Yoshida and their colleagues discuss all of these developments in two chapters and bring order into what might have been chaos by analyzing and classifying the many structural themes within the ellagitannins class of phenolic metabolites. Gratifyingly they also show how each of the structural groups and sub-groups may be derived using the guidelines set out by Schmidt and Mayer in their biogenetic hypothesis, based upon the dehydrogenation of galloyl ester substrates, first elaborated in 1956. Similarly they also comment on the position of

ellagitannins in relation to plant systematics – a topic very dear to the heart of Bate-Smith. Okuda indeed makes a very interesting suggestion linking the progressive oxidation of ‘monomeric’ ellagitannins to Cronquist’s system of plant evolution. These ideas may well repay further attention.

First described by Mayer in the late 1960s, the C-glycosidic ellagitannins represent an intriguing and possibly unique, highly condensed sub-class. They are characterized by the C–C linkage between the C-1 of the open chain form of D-glucose and a carbon of a phenolic nucleus, derived originally from gallic acid. Jourdes, Lefeuvre and Quideau, in a fascinating and wide ranging account of these metabolites, discuss not only their possible biogenetic origins but give an in-depth review of their chemical reactivity. In particular they focus on the striking differences found between the diastereoisomers vescalagin and castalagin. Finally, and in this context, they reflect on the role of compounds such as vescalagin (found in oak) may have on the taste and colour of wines which are aged in oak barrels.

Beautifully complementing these descriptions of the chemistry and taxonomic distribution of ellagitannin metabolites are two chapters dealing with their biosynthesis and strategies aimed at their total chemical synthesis. In the first of these Gross charts the progress made, principally if not exclusively by his own group, towards an understanding of the mechanisms whereby first gallotannins and then ellagitannins are formed from gallic acid and D-glucose. Of particular interest is the recent discovery of an enzyme from *Tellima grandiflora* which is able to convert β -1,2,3,4,6-penta-*O*-galloyl-D-glucose into tellimagrandin II. In doing so the enzyme (probably of the laccase class) oxidatively couples the 4 and 6 galloyl ester groups in the substrate to the (*S*)-hexahydroxydiphenoyl group bridging these same two positions. It is an enormously encouraging first step towards the elucidation of further stages in this pathway. Parenthetically Professor Gross has thus provided welcome affirmation of the early speculations by Otto Schmidt, Mayer and others concerning the biogenesis of these metabolites.

Few would contradict the proposition that the direct chemical synthesis of ellagitannins presents tremendous challenges. Indeed there were no reports of the fruitful outcome of such attempts until the 1990s

and in their 1996 review Quideau and Feldman give an elegant presentation of the possible strategies which may be adopted. These are further developed by Khanbabaee in a chapter on the synthesis of ellagitannins. Feldman was the first to successfully carry out biomimetic syntheses of ellagitannins (*e.g.*, tellimagrandin I and II, pedunculagin) by oxidative coupling of suitably protected preformed galloyl ester precursors and Khanbabaee develops in his essay the possibilities of a second synthetic strategy using as its key step the stereoselective esterification of a diol substrate by hexabenzoyloxydiphenic acid (a compound first described by Schmidt in the 1950s). The example given of the synthesis of strictinin is a persuasive demonstration of this alternative rationale.

Plants have been widely used since antiquity as folk medicines particularly in Asia. The aerial parts of *Geranium thunbergii* are listed in Japan in official pharmacopoeias as an antidiarrhetic. Fruits of *Cornus officinalis* are likewise used as a tonic in traditional Chinese medicine. It has been suggested that the ellagitannins are the principal 'active' components of many of these medicines. Polyphenols such as these have attracted considerable interest in the past fifteen or so years because of possible benefits in human health care and the prevention of diseases such as carcinogenesis and arteriosclerosis. In this context anti-oxidant activity and radical scavenging, antiviral, antimicrobial, anti-inflammatory, and antitumour and anticancer properties have all been variously attributed to specific ellagitannins. These themes occur throughout the text and are also dealt with more specifically and from differing perspectives in chapters by Feldman, Törrönen, Tomás-Barberan and Tanaka. The weight of experimental evidence now available is impressive. For example several ellagitannins exhibit inhibitory action against anticancer targets such as DNA topoisomerases. Others display selective cytotoxicity against human solid tumour lines. The question whether some ellagitannins are not cytotoxic but rather act to enhance the human immune defences is taken up and developed by Feldman in his chapter. Antiviral and antimicrobial activities have also been widely reported and in this area the ability of various ellagitannins to inhibit replication of the *Herpes simplex* virus has attracted particular attention. Since some fruits and fruit juices contain significant amounts

of ellagitannins the question of their effects as part of the diet on human health and their metabolism are also considered by Törrönen and Tomás-Barberán. Both address the vexed but critical question of the bioavailability of ellagitannins which is central to the whole basis of their possible therapeutic action. Tomás-Barberán diplomatically concludes that there are various unresolved issues within this process in humans that still need further research. Tanaka in his chapter makes some beautifully simple but critical observations on the solvation/desolvation processes which must underlie this whole phenomenon and that of complexation with other molecular species. Many questions remain. Thus the C-glycosidic ellagitannin vescalagin is formally derived from β -1,2,3,4,6-penta-O-galloyl-D-glucose by the loss of six hydrogen atoms. Yet it is crystalline and highly water soluble, quite different to its presumed biogenetic precursor. It is a subject which would reward further study. Notwithstanding the final outcome of such studies the reader should certainly follow Törrönen's advice that the consumption of the delicious ellagitannin-rich foods and beverages can be recommended!

The seeming cornucopia of possible medicinal/pharmacological properties associated with ellagitannins has now come right to the fore. It is a complex area and, for the uninitiated, the amount of information can be overwhelming. Perhaps now is the moment for the key underlying issues, such as bioavailability, to be addressed so as to develop a framework of ideas for the future, for as the poet T.S. Eliot wrote:

"Where is the wisdom we have lost in knowledge?

Where is the knowledge we have lost in information?"

Finally it is timely to return to the enigma of gallic acid itself, one to which Bate-Smith repeatedly drew attention. Whilst the occurrence of other hydroxybenzoic acids in the plant kingdom is at best sporadic and idiosyncratic, in certain plant families substantial amounts of polygalloyl and hexahydroxydiphenoyl esters are metabolized. The weight of experimental evidence favours the direct dehydrogenation of 3-dehydroshikimic acid – an intermediate in the shikimate pathway of aromatic amino-acid metabolism – as the route of biosynthesis to gallic acid. As such it is potentially unique for each phenolic group would then derive directly from the aliphatic oxygen functionalities of the substrate. Thereafter the ellagitannins are, *vide supra*, formed by further

dehydrogenation of galloyl ester derivatives, usually of D-glucose. ***Dehydrogenation seems to be the key reaction throughout.*** What is the rationale for this wholesale diversion of intermediate in the shikimate pathway by such means? It is an intriguing question waiting to be answered by investigations at an enzymic/genetic level, for as Eliot also remarked “*What we call the beginning is often the end.*”

E. Haslam, March 2008

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