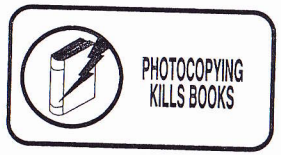
Tel.: +33(0)1 42 65 39 95
Business offices:
14, rue de Provigny
F-94236 Cachan cedex
France
Tel.: +33(0)1 47 40 67 00
Fax: +33(0) 1 47 60 67 02
Telex : TDL 632 020 F
Minitel: 3614 Lavoisier
Web: http://www.Lavoisier.fr
E-mail: export@Lavoisier.fr

and also from :

Intercept Ltd
PO Box 716
Andover SP10 1YG
Hampshire U.K.
SP10 1YG
Tel.: +44 (1264) 334748
Fax: +44 (1264) 334058
E-mail:intercept@andover.co.uk

Lavoisier Publishing Inc.
c/o Springer Verlag
Customers Service
P.O. Box 2485
Secaucus, NJ 07096-2485
U.S.A.
Tel: (800) SPRINGER
Fax: +1 (201) 348 4505
E-mail:orders@springer-ny.com



ISBN : 2-7430-0316-2 (2nd edition, 1999)
(reprint, 2001)
ISBN : 2-7430-0028-7 (1st edition, 1995)
Originally published in French as:
Pharmacognosie, phytochimie, plantes médicinales (3rd edition, 1999)
by Technique & Documentation/Éditions médicales internationales

ISBN : 1-898298-63-7 (2nd edition, 1999)
(reprint, 2001)
ISBN : 1-898298-13-0 (1st edition, 1995)

Jean BRUNETON

Professor of pharmacognosy,
University of Angers (France)
School of Pharmacy

Pharmacognosy
Phytochemistry
Medicinal Plants

2nd edition

Translated by Caroline K. Hatton

Intercept Ltd LONDRES Editions TEC & DOC PARIS NEW YORK LAVOISIER

11, rue Lavoisier
F 75384 Paris Cedex 08

Also available:

Toxic Plants Dangerous to Humans and Animals
J. Bruneton, 1999

Insects and forests: the role and diversity of insects in the forest environment
R. Dajoz, 1999

Illustrations. This book was illustrated by **Annie BRUNETON**, after the following authors:

Berg, O.C. and Schmidt, C.F. (1893-1902). Atlas der officinellen Pflanzen, 4 volumes, Verlag von Arthur Felix, Leipzig; (p. 22, 54, 74, 84, 94, 114, 132, 140, 182, 232, 244, 256, 268, 286, 300, 320, 354, 392, 416, 426, 432, 446, 454, 468, 486, 500, 514, 522, 534, 542, 556, 566, 574, 586, 594, 606, 612, 618, 644, 666, 690, 712, 720, 728, 744, 762, 774, 792, 812, 816, 820, 828, 848, 858, 900, 912, 930, 950, 960, 976, 984, 1002, 1012, 1030, 1044, 1048, 1060, 1070, 1082).

Chaumeton, F.P. (1814 → 1818). *Flore médicale*, 6 volumes, C.L.F. Panckoucke, Paris. (vol. **3** → **6** with the collaboration of Chamberet and Poiret; illustrations by E. Panckoucke and P.J.F. Turpin); (p. 10, 104, 154, 198, 206, 212, 280, 332, 338, 382, 550, 644, 678, 840, 866, 884, 924).

Lamarck, J.B. de Monet, chevalier de (1791 →). *Tableau encyclopédique et méthodique des trois règnes de la nature*, Panckoucke, Paris; (p. 956).

Cover photography: *Papaver rhoeas* L. (Papaveraceae) by Annie BRUNETON

Foreword

In the four years since the publication of the first English edition of "Pharmacognosy, Phytochemistry, Medicinal Plants", the level of interest in plants with potential health benefits has not dropped, quite the contrary.

The therapeutic armamentarium has been augmented, in particular with antimalarial and anticancer compounds that are semisynthetic, but would not exist without the plants that produce their precursors. The future will tell the real impact of these recent additions; the knowledge of the novel mechanism of action of three of them opens new and hopeful research avenues. Novel natural substances have demonstrated potential as antiretroviral agents in experimental conditions. Others that were long known could soon help improve the symptoms of Alzheimer's senile dementia.

*The market for herbal medicines has evolved dynamically. Quantitatively, th Europeans are believed to have spent nearly six billion U.S. dollars in 1995 on plan based pharmaceuticals *. Qualitatively, the release of certain new drugs on the mark has made quite a sensation. Again, the future will tell—I hope—if the excitement that the generate is clinically justified.*

Consumers, who want to see risk minimized in many domains, are becomin increasingly interested in prevention. This is probably why they are interested in foc quality and in plants, for the micronutrients that they contribute to the daily food intak Pharmacognosy cannot ignore this facet of the knowledge of plants. It has a mission t participate in wellness education at the grass-roots level because of the potential impa on public health.

These multiple changes and the accumulation of new data have led to delaying n further the distribution of an updated and expanded version of "Pharmacognos Phytochemistry, Medicinal Plants".

The second edition was revised in the same spirit as that in which the previous one wa written, but not all facets of the knowledge of plants were treated in the same fashion some were developed, others simply maintained. The same is true for the monograph The phytochemical generalities are among the portions that were not expanded: it did no seem desirable to go beyond a general overview—structural or metabolic—of the principa categories of secondary metabolites. In contrast, special attention was devoted to th

biological activity of plants and their constituents, and to the extent that information could be found and used, to clinical data. The approved indications for plants are systematically mentioned for the quasi totality of the species listed in the annex of the French Explanatory Note on "plant-based medicines" ["Médicaments à base de plantes", Les cahiers de l'Agence du médicament, 1998]. It seemed useful to cite, as much as possible, and while awaiting a much-needed European harmonization, the data on plant use as it is presented in the German Commission E monographs. As indicated above, a non negligible place was granted to plant metabolites whose consumption is thought to have an impact on the incidence of certain disorders, particularly cardiovascular disease and cancer.

For the bibliography, I made the choice not to systematically reference all the data: although this would be required for a monograph, perhaps it is not in a general text, considering its breadth and its primary purpose, which is pedagogical. The principle of selecting recent and representative articles and books to list at the end of each chapter was maintained. The vast majority of the selected references were published between 1993 and 1998.

Once more, I am at a loss for words to express my deep gratitude to Michel Lebœuf for his thankless labor, meticulously reading the manuscript, and most of all, for his observations, always pertinent. I give special thanks to Hélène Guinaudeau, Gilbert Fournier, and Jean-François Verbist, who provided useful advice on specific points. I also wish to thank Danièle Piolet for her relentless hunt for spelling and typographical errors.

December 1998

I am especially grateful to Caroline K. Hatton, Ph.D., who provided the translation of the original manuscript with uncommon diligence, efficiency, and competence, and whose pertinent comments gave me food for thought, and to Cindy Angerhofer, Ph.D. (Director of Research and Product Development, Tom's of Maine), who devoted substantial time to reviewing the translation.

July 1999

* This includes the Algae; with rare exceptions (dextran) the substances produced by microorganisms are excluded, the same comment applies to the Fungi (except for ergot and the hallucinogenic species).

Introduction to the 2nd edition (1993)

The concept of phytochemistry is easy to understand, but that of pharmacognosy undoubtedly requires definition and commentary. The phrase "medicinal plants" also deserves a few comments. There is no point in proceeding any further without a good grasp of the meaning of the words which define the scope of this work.

Etymologically, ***pharmacognosy*** is the knowledge (from the Greek *gnosis*) of poisons (*pharmacon*). Note that *pharmacon* not only means poison, but also medication... the difference lies in the dose. Thus one might legitimately think that pharmacognosy treats all drug-like substances: that is not the case. Pharmacognosy limits its field of investigation to natural starting materials: it is simply the descendant of "*materia medica* *", a discipline which, since Dioscorides's treatise by that name, and until the birth of synthetic chemistry, dealt with mineral, animal, and plant starting materials, in other words all of the materials available to prepare remedies, since no others were known!

As time passed, mineral substances lost their appeal. Those that are still in use are now covered as well-defined substances, just like synthetic organic substances and in the same texts. Is pharmacognosy, then, the study of starting materials of plant or animal origin intended for therapeutic use? In fact, a number of French experts and many foreign authors—the former through their lectures, the latter through their writings—treat hormones, enzymes, but also substances elaborated by micro-organisms. Some do not hesitate to include biotechnology and genetic engineering.

Under these conditions, pharmacognosy is *the study of starting materials and substances intended for therapeutics, and of biological origin, in other words obtained from plants, animals, or by fermentation from micro-organisms.*

Although I gladly abide by this definition, this writing will survey a field of applications both narrower and less restrictive. Is this a paradox? No. The field is narrower because it is limited only to plants and to products arising from plants *. It is less restrictive because it is not limited to the sole criterion of therapeutic use: starting materials for the synthesis of drugs, hallucinogenic plants, manufacturing aids, food additives, plants or components for cosmetology, or insecticides of plant origin must be included. The pharmacist—who is not the only one who should be concerned—must

* On the contrary, a plant whose medicinal quality is uncontested, for example Cinchona, may have other applications: a large part of the product is absorbed by food technology (sodas, tonics).

know useful plants, and must also know toxic plants: therefore, these appear prominently in this book. Nature stimulates the creativity of chemists: synthetic analogs, when available, will be mentioned without being fully developed.

Beyond the definition of pharmacognosy, it is important to emphasize what many consider, and they are absolutely correct, one of its major assets: its multidisciplinary character. In pharmacognosy, to study a plant is: to define its identity; to describe its morphology and anatomy; to know its origin and production methods; to appreciate their impact on the plant quality; to determine its chemical composition and the factors that may affect it; to know the structure, physico-chemical properties, and pharmacological activity of the active principles; and, this is a crucial goal, to identify the variables which objectively reflect quality and to develop the methods to control it; finally, to come to grips with all the problems linked to the optimal utilization of plants and plant products: indications, contraindications, side effects, and drug interactions. As noted by V. E. Tyler *et al.* pharmacognosy is "an applied science that deals with the biologic, biochemical, and economic features of natural drugs and their constituents".

To know plants and their uses is also—and this applies mostly to phytotherapy—to be aware of the limits and the dangers of what must be at times no more than a "placebotherapy", but is never completely innocuous: the intoxications reported in 1992 show, if need be, that "natural" does not always rhyme with innocuous. As stated by P. Delaveau, medicinal plants, also known in French as *simples*, are in reality exceptionally complex.

Medicinal Plant. The noun is common, the adjective is commonplace, and their juxtaposition introduces a concept that is not always easy to define. A plant is said to be medicinal when "at least one part possesses therapeutic properties". It may be listed in the French or in other Pharmacopoeias, although this may be true for plants that are of use to pharmacy without being medicinal. In France, a plant not listed in the Pharmacopoeia can be a drug, even if it is not considered a medicinal plant: the only requirement is to present it as having curing or preventive properties for diseases (article 512 of the French public health code. Many medicinal plants are only medicinal (for example the foxglove, used for its leaves), but many are not just medicinal: thyme and other Lamiaceae are herbs as well as medicinal plants, the artichoke is an edible vegetable, as well as a medicinal plant. If these examples are straightforward—the *in vitro* spasmolytic properties of the infusion of thyme are well known, and the fact that it is the artichoke leaf that is medicinal and the inflorescence receptacle that is edible is well known—things are sometimes less clear: what about the onion? What about tea? What about nutmeg? The onion is an edible vegetable *, but do the inhibitory properties toward cyclo-oxygenase of its sulfur-containing compounds make it a medicinal plant? Tea is one of the beverages most widely consumed worldwide, and everybody knows the effects of caffeine: isn't tea also a medicinal plant? Nutmeg is a spice, but is it known in every country that it can be a hallucinogen? And that the neolignans that have been isolated from it are not without pharmacological interest? The French Pharmacopoeia does note that "plants with medicinal properties can also have dietary or culinary uses or also be used in the preparation of refreshing beverages".

These digressions are not aimed at arriving at a precise definition of the concept of medicinal plant: they simply lead to the question of the scope of the present text. First of

* Don't confuse this primary meaning (drug, desiccated) with the meaning, now more common, of narcotic; in English drug applies to the concept of starting material: drug, crude drug, as well as to that of the therapeutic substance or drug of abuse.

all I shall cover *drugs*, in other words "starting materials from which pharmacists prepare medications *" (Littré, 1870). Here, the limits are clear: any plant or plant substance used to prepare a medication must be described. Many of these plants and substances are the subject of a monograph in the 10th edition of the French Pharmacopoeia, and this facilitated my selection. Other plants and substances, described in previous editions or in other national pharmacopoeias, will complete this first list.

What about "medicinal plants" (in the sense of the term accepted by the public at large)? For several years now, the fad for natural therapies has thrust these plants into the limelight. The fact that magistral preparations are no longer covered by the French national health care program or Social Security has not shaken the trust (not always justified) that some still have in them. Although the pace of publication of books on this topic has slowed down a little, bookstores continue to offer recipe books which—to cite P. Delaveau once more—are like old furniture: "too many replicas and not enough authenticity". Need I add that the compilation of errors leads to gross inaccuracies? Under these conditions, it is fully justified to bring to students and professionals the essentials of the information currently available on these plants, even if this raises more questions than it provides answers.

So I shall treat these plants. Very well. But which plants? To select some and eliminate others implicitly grants some value to the former and expresses a doubt about the others! While reserving the right to critically review the activities attributed to a plant, my first step will be to adopt the selection—*which it would have been better to debate*—made by the experts nominated by the French Ministry of Health and of Social Affairs, a choice materialized in 1990 by a list of 174 drugs in the Annex of the French Herbal Remedies, Notice to Applicants for Marketing Authorization. The whole list? No. For several of the plants, there is nearly no scientific literature and for a small number, I have simply not found sufficient information to justify describing them. Overall, relevance does not appear to have been a priority...

In the field of plants as in other fields, it is constructive to look elsewhere: French practices, no matter how clever, are not the whole story. For the key drugs, the question is virtually superfluous: naturally occurring cardiac glycosides or anticholinergics are recognized everywhere, and at most there are marketing differences. For the other plants, one enters the fascinating field of the traditional medicines: one could devote an encyclopedia to this. Therefore I shall cite only a few examples, chosen mainly as a function of the true pharmacological potential of the substances contained in the plants. To look elsewhere is also to look to the future: I will introduce a few examples of plants which may some day make a significant contribution to the therapeutic arsenal.

Of course, pharmacognosy has its prerequisites: I will assume that the reader is somewhat familiar with the language of botany, fluent in organic and analytical chemistry, and has mastered the fundamentals of pharmacology. To assist the reader—and as reflected by the third term in the title: ***Phytochemistry***—I will grant a place of honor to the presentation of the compounds involved in the activity of the plants. The knowledge of their structure and of their behavior is fundamental. It is the underpinning required to understand the nature and details of the quality control methods, to rationalize the extraction procedures, sometimes to envision the pharmacological activity, and often

to predict the pharmacokinetics and bioavailability: it is also a prelude to synthesis, whether this is dictated by the need for freedom from the constraints of an erratic supply, or the desire to design more efficacious structural analogs, or, "like the reason to climb Mount Everest, by the challenge in itself" (R. Mechoulam). These are challenges which constantly expand the horizons of organic chemistry. To study molecular structures is also to understand their origins. The knowledge of the biosynthetic mechanisms guides the hypotheses of the structure elucidator, and inspires the chemist to propose biomimetic syntheses. The more we add to knowledge, the more we are fascinated: a handful of elementary synthons react together to form edifices as complex as they are innumerable. Our awe and wonder before this synthetic cornucopia can only be greater given our virtually complete lack of knowledge of the biological role of these substances. For now, the biosynthetic origin suggests an outline in four parts: primary metabolism products, phenolics (acetates and shikimates), terpenes and steroids, and alkaloids.

Was it necessary to add a fifth part to this work? Was a general introduction really necessary? Yes, probably. But this was a tall challenge. What about covering the production and marketing of medicinal plants? Publication in a periodical is more appropriate than a book in a field which sometimes evolves rapidly, and not only as a function of climatic constraints (consider the market changes induced by political upheavals in eastern and southeastern Europe). What about detailing the origin of the plants? Comparing the harvesting of wild plants with cultivation? Other texts have dealt with this, so there is no need to recopy them. As far as the production and optimization techniques are concerned, they follow the general principles of any agricultural production (with one difference in that the active principle is the criterion by which to select a medicinal plant): the scientific literature on this topic is abundant.

The question which remains (among others) is that of plant quality control. Not so many years ago, the morphologic and anatomical examination of the drugs, together with a few color reactions, was often the essential element of the assay. Back then, it was justified to refer the reader to specialized texts, or to introduce basic concepts in plant anatomy. Today, the chromatographic techniques (TLC, GC, HPLC) permit rapid qualitative and quantitative quality control, and the most sophisticated techniques allow the detection of the most subtle falsifications (for example, NMR of isotopomers). Under these conditions, the only reasonable solution is to refer the reader to analytical chemistry books and periodicals*... and add reminders that before implementing complicated methods, verifying the identity of a sample (morphology, microscopy) is a common sense step which may save time and... money!

Pharmacognosy, Phytochemistry, Medicinal Plants. I shall attempt to provide information to the reader in these specialized fields. In addition, for the reader who wants more, I shall list selected references. To prepare this text, I reviewed more than three thousand references, therefore a selection was in order. This choice, somewhat arbitrary, was made in favor of books, reviews of general interest, more recent and more specialized articles as long as they provided a sufficient introductory or retrospective bibliography. Hopefully, these elements will enable the reader to rapidly and efficiently build a database on the topic of interest [...].

contents

Foreword v
Introduction to the 2nd edition vii
Contents xi
Abbreviations xii

Part 1 **Compounds of Primary Metabolism** 1
Carbohydrates 3
Introduction, 3 . Monosaccharides, 7 . Oligosaccharides, 27 . Polysaccharides, 35 . from microorganisms and fungi, 39 . Algae Polysaccharides, 45 . Homogeneous Polysaccharides, 65 . Heterogeneous Polysaccharides, 81
Lipids 123
Plant Lipids: Generalities, 123 . Vegetable oils, 137 . Alkyne derivatives, 169
Amino Acids and Peptides, Proteins and Enzymes 183
Amino Acids Which are not Constituents of Proteins, 185 . Cyanogenic Glycosides, 189 . Glucosinolates, 199 . Betalains, 213 . Protein Sweeteners, 215 . Lectins, 217 . Enzymes, 221

Part 2 **Phenolics. Shikimates, Acetates** 225
Shikimates - Phenylpropane Derivative-containing Drugs 233
Generalities, 227 . Phenols and Phenolic Acids, 239 . Coumarins, 263 . Lignans, Neolignans, 279 . Drugs Containing Phenylpropane Chain Elongation Derivatives, 295 . Flavonoids, 309 . Anthocyanins, 355 . Tannins, 369
Polyketides 405
Quinones, 409 . Orcinols and Phloroglucinols, (Cannabis, 445)

Part 3 **Terpenoids and Steroids** 461
Introduction 463 . Monoterpenes, 473 . Sesquiterpenes, 479 . Essential Oils, 483 . Oleoresins, 579 . Iridoids, 589 . Pyrethrins, 613 . Sesquiterpenoid Lactones, 619 . Diterpenes, 637 . Triterpenes, 661 . Saponins, 671 . Cardiac Glycosides, 721 . Other Steroids, Other Triterpenes, 751 . Carotenoids, 769

Part 4 **Alkaloids** 781
Generalities 783
Alkaloids Derived from Ornithine and Lysine 801
Tropane Alkaloids, 805 . Pyrrolizidine Alkaloids, 833 . Quinolizidine Alkaloids 849 . Indolizidine Alkaloids, 855 . Piperidine Alkaloids, 859
Alkaloids derived from Nicotinic Acid 867
Alkaloids Derived from Phenylalanine and Tyrosine 875
Phenethylamines, 879 . Simple Isoquinolines, 887 . Benzyltetrahydroisoquinolines, 889 (Curares, 899; Morphinan Alkaloids, 925) . Phenethylisoquinolines, 949 Amaryllidaceae Alkaloids, 957 . Monoterpenoid Isoquinolines, 961
Alkaloids Derived from Tryptophan 967
Tryptamines, β-Carboline Alkaloids, 969 . Esere, 975 . Ergoline Alkaloids, 979 (Ergot of Rye, 983) . Monoterpenoid Indole Alkaloids, 999 (Apocynaceae, 1016 Cinchonas, 1029)
Alkaloids Derived from Anthranilic Acid 1041
Alkaloids Derived from Histidine 1045
Terpenoid Alkaloids 1049
Alkaloids with Miscellaneous Structures 1067
Purine Bases 1071

ABBREVIATIONS

ADI	acceptable daily intake
ADP	adenosine diphosphate
AFNOR	*Association Française de NORmalisation* = French Association for Standardization
AIDS	acquired immune deficiency syndrome
ALAT	alanine aminotransferase
ANDEM	*Agence nationale pour le développement de l'évaluation médicale* = French national agency for the development of medical evaluation
AOCS	American Oil Chemists Society
APRIA	*Association pour la Promotion Industrie Agriculture*
AST	aspartate aminotransferase
ATP	adenosine triphosphate
auct.	*auctorum* (of authors)
A-V	atrium-ventricle
AZT	3'-azido-3'-deoxythymidine
B.C.	before Christ
BHT	butylated hydroxytoluene
BHP	British Herbal Pharmacopoeia
BP	British Pharmacopoeia
BP	boiling point
CNRS	*Centre National de la Recherche Scientifique* = French National Research Council
CNS	central nervous system
CoA	coenzyme A
CSP	Code de la Santé Publique = French Public Health Code
cv.	*cultivar*
DAB	*Deutsches Arzneibuch* = German Pharmacopoeia
DCCC	droplet counter current chromatography
DE	dextrose equivalent
DE	degree of esterification
DHHDP	dehydrohexahydroxydiphenic acid
DM	degree of methylation
DMAPP	dimethylallylpyrophosphate
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EEG	electroencephalogram
e.g.	*exempli gratia* (for example)
et al.	*et allii* (and other authors)
Eur. id. code	European identification code for food colorings and additives
Eur. Ph.	European Pharmacopoeia
ex	after
FAB-MS	fast atom bombardment-mass spectrometry
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FPP	farnesyl pyrophosphate
French Expl. Note	French Explanatory Note
Fr. Ph.	French Pharmacopoeia
GC-MS	gas chromatography-mass spectrometry
GPP	geranyl pyrophosphate
GSH	reduced glutathione
HDL	high density lipoproteins
HFCS	high fructose corn syrup
HHDP	hexahydroxydiphenic acid
HIV	human immunodeficiency virus
HPLC	high pressure liquid chromatography
i.e.	*id est* (that is)
IM	intramuscular (route)
INN	international non-proprietary name
INRA	*Institut National de la Recherche Agronomique*
IP	intraperitoneal (route)
IPP	isopentenyl pyrophosphate
IR	infra-red
ISO	International Organization for Standardization term
IUD	intra-uterine device
IV	intravenous (route)
LD50	lethal dose 50
LDL	low density lipoproteins
LH	luteinizing hormone
LPP	linalyl pyrophosphate
LSD	*lysergic saüre diäthylamide*
MAM	methylazoxymethanol
MAO	monoamine oxidase
MMDA	3-methoxy-4,5-methylenedioxyamphetamine
NADP(H)	nicotinamide dinucleotide phosphate (reduced)
NF	*Norme Française* = French standard
NMR	nuclear magnetic resonance
NSAID	non-steroidal anti-inflammatory drug
OSB	*o*-succinylbenzoic acid = 4-(2'-carboxyphenyl)-4-oxobutanoic acid
PAF	platelet activating factor
PEG	polyethylene glycol
PEP	phosphoenolpyruvate
p.p.	*pro parte* (in part)
ppm	part per million
PUVA	psoralen + 320-400 nm UVA radiation treatment
RNA	ribonucleic acid
SC	subcutaneous (route)
SEITA	*Société d'Exploitation Industrielle des Tabacs et Allumettes* = French manufacturer of tobacco products and matches
sp.	*species*
spp.	various species in the genus
subsp.	*subspecies*
THC	tetrahydrocannabinol
TLC	thin-layer chromatography
TPA	12-O-tetradecanoylphorbol-13-acetate
UDP	uridine diphosphate
UV	ultraviolet

Pa

COMPOUNDS (
PRIMARY METABOLIS