Phytochemistry, Vol. 28, No. 9, pp. 2229–2242, 1989.
Printed in Great Britain.

0031-9422/89 $3.00 + 0.00

REVIEW ARTICLE NO. 46

A BICENTENNIAL OF BETULIN

ERICH W. H. HAYEK, ULRICH JORDIS, WOLFGANG MOCHE and FRITZ SAUTER*

Institute of Organic Chemistry, Technical University of Vienna, Getreidemarkt 9, A-1060 Vienna, Austria

(*Received* 4 *January* 1989)

Key Word Index—Betulin; chemotaxonomy of angiosperms; history; identification; isolation; pharmacology; physical properties; reactivity; review; utilisation.

Abstract—The literature on the history, identification, determination, isolation and distribution in plants of betulin as well as its technological applications and its pharmacology is reviewed and the chemotaxonomy of the angiosperms in relation to betulin is discussed.

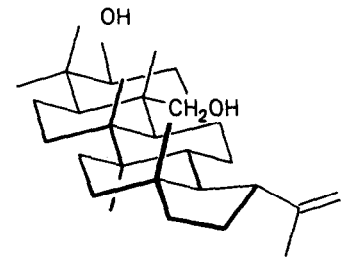
History and Introduction

With the oldest reference on betulin (**1**) dating back to 1788 [1] this substance certainly constitutes one of the first natural products isolated from plants and detailed investigations including elemental analysis were described in 1876 by Hausmann [2]. Betulin, as a pentacyclic triterpene with the lupane skeleton, is also named betulinol, trochton, birkenkampher and (coryli-) resinol. It is referenced in 'Chemical Abstracts' as lup-20(29)-en-3,28-diol, (3β). Systematic names are 5a.5b.8.8.11a-pentamethyl-3a-hydroxymethyl-1-isopropenyl-eicosahydro-1H-cyclopenta[a]-chrysen-9-ol or (3a*S*)-9c-hydroxy-5at.5bc.8.8.11ac.-pentamethyl-3ar-hydroxymethyl-1t-iso-propenyl-(7atH.11btH.13acH.13btH)-eicosahydro-1H-cyclopenta[*a*]chrysen [3]. The latest review on betulin with focus on reactions and uses appeared in 1981 [4].

Isolation and detection

Betulin is isolated primarily from barks [5] either via solvent extraction or sublimation [6] and purified by column chromatography or recrystallization; procedures for the isolation of betulin from birch bark in appreciable amounts [2, 7–15] are well described. Procedures for the isolation from peat [16, 17] lignite [18] and archeological specimens [13, 19] or wood pulp extracts [20, 21] are found as well. For the extractive isolation of betulin on an industrial scale from birch bark waste, various solvents have been compared [21–25]; the azeotrope of 2-butanol–water was found to be the best [22]. Some authors suggest the purification via its diacetate [6, 24] followed by hydrolysis. From our experience methods relying only on recrystallization for purification of betulin are unsufficient. Betulin is also used in geochemistry to trace variations in provenance, fixation and diagenesis of organic matter deposited in sediments along the continental margin [26].

For the detection of betulin combinations of the procedures mentioned below have been utilized:



1

TLC [19, 27–29]. Combined with the use of spray reagents and densitometers [25] were described as well as R_f-structure relationships [30] and TLC using $AgNO_3$–silica gel [29, 31]. From our experience detections of betulin based only on TLC should be critically re-evaluated: far too many triterpenoids exhibit similar R_f-values and behaviour towards spray reagents [30].

HPLC. The use of normal phase as well as C_{18}-reversed phase columns are described in detail [32]. Although betulin can be detected by UV at 205–215 nm and with refractive index detectors, the sensitivities of both methods are low.

GC. The techniques for the separation of betulin, its diacetate and TMSi-ethers have been investigated on packed [29, 33–35] and capillary columns [28, 36].

Droplet Counter Current Chromatography (DCCC). The separation of betulin from betulinic acid, β-amyrin and cholesterol was achieved by this method [37].

Physical properties

Melting points of betulin are reported over a range of 250–261° with the higher values obtained after sublimation of the recrystallized product [2, 38, 39]. The lower values can be explained by the crystallization with 1 mol of ethanol [9, 14]. Some authors further indicate mixed melting points, e.g. of eutectics with saccharin [27].

Table 1. Distribution of betulin in angiosperms

Plant name	Part used	Analysis	Quantity
Acacia modesta [118]	b	IR, mp, TLC	
Acacia nilotica [119]	rb	IR, mp, TLC	
Acacia senegal [120]	r	IR, mp, TLC	
Acacia tortilis [121]	b	IR, mp, TLC	
Acinos thymoides [122]			0.03
Acrotrema arnothianum [183]	l	IR, mp, TLC	0.065
Akebia quinata [123]	st		
Alangium lamarckii [124]	s		
Alnus barata [125]	b	mp, ORD	
Alnus crispa [83]	b	GC	<5
Alnus glutinosa [126]	b	mp	
Alnus maximowiczii [127, 128]	b, r		
Alnus nepalensis [129]	b	mp, MS, ORD	0.23
Alnus rubra [130]	b, w	mp, ORD	0.036
Alnus rugosa [83]	b, f, l	GC	<5
Alnus subcordata [131]	b	mp	
Alphitonia whitei [132]	w	mp	0.0012
Alstonia scholaris [133]	l	IR, mp, TLC	
Amoora canarana [134]			
Amanoa oblongifolia [93]	b	IR, mp, MS, ORD	0.00004
Anisomeles ovata [135]	ae	IR, MS, NMR, TLC	0.001
Aspidixia articulata [136]			
Asteracantha longifolia [137]	r	IR, mp, MS, NMR, UV	
Avicennia alba [138]	b, l	IR, MS, mp, ORD	0.01, 0.012
Avicennia officinalis [138]	b, l	IR, MS, mp, ORD	0.014–0.027, 0.006–0.01
Befaria glutinosa [139]	fl		
Betula [1, 2, 5, 9, 140, 141, 142]	b, ob	mp; IR, mp, ORD	10.0
Betula alba [11, 12, 109, 143]	b, ob	mp	14.0–20.0
Betula alleghaniensis [148]	b	mp	
Betula bojpattra [153]	b	mp	10–20
Betula carpatica [153]	b	mp	10–20
Betula cordifolia [82]	ob	GC/MS	6.8
Betula costata [144, 153]	b	IR, mp	<5
Betula dahurica [145]	b+br		
Betula daurica [127]	b		
Betula ermanii [144]	b	IR, mp	
Betula lenta [148, 153]	b	mp	0.05, <5
Betula luminifera [153]	b	mp	<5
Betula lutea [153]	b	mp	5–10
Betula mandschurica [146]	ob		
Betula maximowicziana [147]	ob	IR, mp, MS	
Betula papyrifera [82, 83, 148, 153]	b, ob	mp, GC, GC/MS	10–20, <30
Betula pendula L. [14, 39]	b, ob	mp	23, 36
Betula pendula [27]	b	IR, mp, TLC	1.08
Betula platyphylla [28, 149]	b, ob	MS, NMR	
Betula populifolia [82, 153]	b, ob	mp, GC/MS	10–20
Betula pubescens [153]	b	mp	10–20
Betula pubescens [27]	b	IR, mp, TLC	0.36
Betula sanbergii [153]	b	mp	5–10
Betula schmidtii [153]	b	mp	⩽10
Betula utilis [78, 107, 150, 151]	b, ob	IR, mp, ORD, TLC	23.5
Betula utilis [153]	b	mp	5–10
Betula verrucosa [22, 25, 152, 153]	b, ob	mp, TLC	10–20
Betula verrucosa [154]	ob	GC/MS	34.0
Betula x *caerulea* [82]	ob	GC/MS	11.4
Buxus microphylla var *intermedia* [155]	b+l	IR, mp	
Buxus microphylla var *suffructiosa* [156]	wp	mp	
Buxus microphylla [57]	l+st		
Buxus papillosa [158]	l	IR, mp, MS, NMR	
Buxus sempervirens [159]	l		
Callistemon lanceolatus [160]	l	mp, ORD	
Canavalia bonariensis [161]	r	IR, mp, NMR, TLC	

Table 1. (*Continued*)

Plant name	Part used	Analysis	Quantity
Capparis sepiaria [162]	l		
Caraipa densifolia [163]	b	IR, mp, TLC	0.003
Carlina corymbosa var *globosa* [164]	a	GC, IR, mp, MS, NMR	
Carpinus betulus [38, 39, 165]	b	mp, ORD	0.04
Cassia holosericae [166]	ae		
Cassia siamea [167]	fl	IR, mp, MS, NMR, ORD	0.0005
Cassia siamea [168]	b	IR, mp, TLC	
Castanea sativa [169, 170]	l	mp, ORD	0.4
Castanopsis concinna [171]	st	IR, mp	0.00067
Castanopsis eyrei [171]	st	mp	0.0009
Ceanothus americanus [134]	rb		
Celtis australis [151]	b	IR, mp, NMR, TLC	0.12
Cistus laurifolius [172]	wp	IR, MS, mp	
Clerodendron inerme [173]	st		
Clinacanthus nutans [174]		IR, MS, NMR	
Clinopodium vulgare [175, 176]	ae, l		
Comptonia peregrina [83]	l, st, r	GC	<5
Cordia obliqua [177]	s		
Cornus capitata [178]	st	IR, MS, NMR, TLC	0.0008
Corylus avellana [39, 179]	b	mp	0.13
Dalbergia sericea [180]	b	mp, ORD	0.0033
Desmodium pulchellum [181]	r	IR, mp	
Dicliptera roxburghiana [182]	l		
Dillenia andamanica [183]	l	IR, mp, TLC	0.082
Dillenia aurea [183]	l	IR, mp, TLC	0.045
Dillenia bracteata [183]	l	IR, mp, TLC	0.07
Dillenia indica [183, 184, 185, 186]	b, fr, l	IR, mp, ORD, TLC	0.105
Dillenia pentagyna [183, 187]	b, l	IR, mp, MS, NMR, TLC	0.15
Dillenia peregrina [186]	b	IR, mp, ORD, TLC	
Dillenia retusa [183]	l	IR, mp, TLC	0.068
Dillenia scabralla [183]	l	IR, mp, TLC	0.12
Diospyros abyssinica [188]	b	TLC	
Diospyros argentea [189]	b	TLC	
Diospyros bioindensis [190]	b	IR, mp, TLC	
Diospyros buxifolia [191,192]	hw	TLC	0.03
Diospyros canaliculata [188]	b	TLC	
Diospyros chevalieri [188]	b	TLC	
Diospyros chloroxylon [193]	r		
Diospyros cinnabarina [188, 190]	b, w	TLC	
Diospyros consolatae [194, 195]	l	GC/MS, mp, NMR, TLC	0.421
Diospyros crassiflora [188]	b	TLC	
Diospyros dendo [188]	b, w	TLC	$\leqslant 0.006$
Diospyros discolor [189, 212]	b, fr, w	IR, mp, ORD, TLC	0.05, 0.08
Diospyros ebenaster [196]	r		
Diospyros ebenum [197, 198, 199]	b, hw, l	IR, mp	$\leqslant 0.053$
Diospyros elliptifolia [200]	b		
Diospyros fragrans [188]	w	TLC	
Diospyros gabunensis [188]	b	TLC	
Diospyros gracilescens [188, 201]	b, w	TLC	$\leqslant 0.012$
Diospyros guianensis [202]	b		
Diospyros hirsuta [203]	b, w, fr	mp, TLC	0.2, 0.11, 0.008
Diospyros hoylena [188]	b, w	TLC	0.011, 0.019
Diospyros ismaili [189]	fl	IR, mp, MS, NMR, UV	0.011
Diospyros iturensis [188]	b, w	TLC	$\leqslant 0.01$
Diospyros kaki [204]	b		
Diospyros kaki var. *sylvestris* [205]	r+w		
Diospyros kamerunensis [188]	b	TLC	
Diospyros kirkii [206]	rb		
Diospyros longiflora [188]	b, w	TLC	$\leqslant 0.009$
Diospyros lotus [189]	b, w	TLC	
Diospyros maingayi [189]	b, w	IR, mp, MS, NMR, UV	0.05, 0.005
Diospyros mannii [207]	b	IR, mp, MS, NMR, ORD, UV	0.005

Table 1. (*Continued*)

Plant name	Part used	Analysis	Quantity
Diospyros maritima [208]	r	IR, mp	0.00026
Diospyros melanoxylon [209–212]	b, f, l, w	IR, mp, ORD	⩽0.5
Diospyros mespiliformis [188]	b	TLC	
Diospyros monobuttensis [188]	b	TLC	
Diospyros montana [213–215]	b, p, w	IR, MS, mp, NMR, UV	0.03
Diospyros moonii [203]	w	mp, TLC	0.056
Diospyros obliquifolia [190]	b	TLC	
Diospyros oblongifolia [203]	fr	mp, TLC	0.1
Diospyros peregrina [212, 215, 216]	fr, l, p	IR, mp, ORD	1.0
Diospyros peregrina [217, 218]	f, l	IR, mp, ORD, TLC	
Diospyros quaesita [203]	b, w	mp, TLC	0.37, 0.05
Diospyros rotundifolia [219]	st		
Diospyros Sanza-Minika [192]	w	TLC	0.035
Diospyros Sanza-Minika [188]	b	TLC	
Diospyros siamang [189]	b, w	IR, mp, MS, NMR, UV	0.03, 0.01
Diospyros siderophylla [220]	b		
Diospyros singaporensis [189]	b, w	IR, mp, MS, NMR, UV	0.02, 0.013
Diospyros spinescens [203]	b, w	mp, TLC	0.16, 0.09
Diospyros sumatrana [189]	b, w	IR, mp, MS, NMR, UV	0.02
Diospyros thwaitesii [203]	w	mp, TLC	0.055
Diospyros tomentosa [191]			
Diospyros variegata [192]	hw	TLC	0.008
Diospyros verrucosa [221]	b+r		
Diospyros walkeri [203]	b, w	mp, TLC	0.08, 0.03
Diospyros wallachi [189]	b, w	IR, mp, MS, NMR, UV	0.05, 0.06
Diospyros zenkeri [188]	b, w	TLC	0.067, 0.007
Dipteryx alata [222]	b	IR, mp, NMR	
Dipteryx odorata [223]	b	IR, mp, MS, NMR	0.0066
Duboisia leichhardtii [224]	l		
Ecbolium linneenum [225]			
Ehretia laevis [226]	b	IR, mp	0.016
Enicostema littorale [227]	wp		
Erica arborea [228]	b+l		
Euclea divinorum [229, 231]	r	IR, mp, MS, NMR, TLC	
Euclea kellau [230]	br	IR, mp, NMR, ORD	
Euclea natalensis [231, 232]		IR, MS, NMR	
Eucommia ulmoides [233]	b	IR, mp, MS	
Euphorbia broteri [234]	ae	IR, mp, MS, NMR, ORD	
Euphorbia lathyris [235]	st		
Euphorbia paralias [236]	pl		
Euphorbia paralias [237]	ae	mp, TLC	0.03
Euptelea polyandra [238]			
Fagonia cretica [134]			
Fagus silvatica [239]	b	mp, ORD	0.0012
Flindersia pimenteliana [240]	b+l		
Fraxinus americana [83]	l, r	GC	20, 5–10
Givotia rottleriformis [241]	b	IR, mp, MS, NMR, TLC, ORD	0.35
Glechoma hirsuta [122]			0.01
Gmelina arborea [242]			
Grewia asiatica [243, 244]	b	IR, NMR, ORD, TLC	0.15
Grewia bicolor [245]	wp		
Grewia flavescens [246]	r		
Grewia tenax [247]	b	IR, mp, TLC	
Guazuma tomentosa [248]	b	mp, MS, NMR, ORD	0.0017
Gymnosporia montana [249]	l	mp, MS, TLC	
Gymnostachyum latifolium [250]	st	IR, mp, TLC	
Haplophyton cimicidum [251]	pl		
Hedyotis lawsoniae [252]	l+t	GC, GC/MS, NMR	0.00012
Helichysum dendroidenum [253]	l	mp	
Holacantha emoryi [254]			
Ilex verticillata [83]	b	GC	20

Table 1. (*Continued*)

Plant name	Part used	Analysis	Quantity
Iris pallassii var. *chinensis* [255]	s	IR, mp, MS, NMR	
Ixora chinensis [256]	l		0.026
Jasminum flexile [257]	l		
Jasminum humile [257]	l		
Jasminum multiflorum [257]	l		
Jasminum sambac [257]	l		
Juglans regia [258]	b		
Klenia articulata [259]	ap	IR, MS	0.005
Lasianthus chinensis [260]	l		
Lawsonia alba [261]	b	MS, mp, ORD	
Leptospermum scoparium [262]	b	mp	
Lithocarpus cornea [43]	st	IR, mp, MS, NMR	0.00016
Lithocarpus elizabethae [263]	l+st		
Lithocarpus haipinii [263]	l+st		
Lithocarpus polystachya [264]	st	mp	0.000044
Lophopetalum rigidum [265]	b		0.013
Lophopetalum toxicum [134]	b		0.7–0.8
Lumnitzera racemosa [266]	b, l	GC, mp, TLC	0.011, 0.25
Macaranga peltata [267]	hw	IR, mp, TLC, UV	0.002
Maytenus octogona [268]	ae		
Melaleuca leucadendron [269]	l, st	IR, mp, TLC	0.0014, 0.0008
Melodinus australis [270]	ae		
Melyanthes trifoliata [72, 134]			0.006
Micromeria benthami [271]		mp	
Mitrephora heyneana [272]	b		
Myrica pensylvanica [83]	st, l	GC	10
Nepeta [117]	wp		0.033
Nepeta aragonensis [273]	ae	GC, IR, mp, NMR, ORD	
Nerium oleander [41]	l	NMR, TLC	0.0004
Neuracanthus sphaerostachys [274]		IR, mp, TLC	
Nuytsia floribunda [134]	ae		
Origanum compactum [275]	ae	IR, mp, MS, NMR	0.009
Orthosphenia mexicana [276]	ae	IR, MS, NMR	
Ougeinia dalbergioides [277, 278]	b	mp, ORD	
Parthenium hysterophorus [279]	l		
Phillyrea latifolia [228]	b+l		
Phlogacanthus thyrsiflorus [116]	l	IR, MS, mp, ORD, TLC	
Phyllanthus reticulatus [280]	r	IR, mp, MS, NMR, UV	
Platanus hybrida [281]	b	mp	
Polygonum perforliatum [282]			
Porteresia coarctata [283]	lc	GC	$\leqslant$11.0
Premna integrefolia [284]	b	IR, mp, NMR	
Psorospermum tenuifolium [285]	rb	IR, mp, MS, NMR, TLC	0.01
Psychotria adenophylla [286]	l		
Pterocarpus santalinus [287]	l	IR, mp, TLC	
Pyrus communis [11]	t		
Quercus bambusaefolia [288]	st	IR, mp	0.00015
Quercus championi [288]	st	IR, mp	0.00067
Quercus myrsinaefolia [288]	st	IR, mp	0.00006
Quercus suber [45]	c	IR, MS, NMR, UV	0.0011
Quercus suber [289–292]	b	mp	0.6–0.7
Rheedia gardneriana [293]			
Rhizaphora mucronata [294]	l	GC	
Rhododendron adamsii [295]	sh		
Rhododendron anthopogon [296]	st		
Rhododendron ledebourii [297]	l+st		
Rhododendron luteum [295]	sh		
Rhododendron schlippenbachii [295]	sh		
Rhodomyrtus tomentosa [298]	l, st	IR, mp, MS	0.002, 0.001
Rosmarinus officinalis [299]		NMR	
Roylea elegans [300]	l		
Rzedowskia tolantoguensis [301]	ae		

Table 1. (*Continued*)

Plant name	Part used	Analysis	Quantity
Saccharum officinarum [302]			
Salvia beckeri [258]	ap		
Salvia mexicana [303]	wp	IR, MS, NMR	
Salvia officinalis [304]	l	GC	0.0015
Sambucus nigra [134, 305]	b	mp	0.011
Sarcococca pruniformis [306, 307]	l, wp	IR, mp, MS, ORD	0.05
Sarracenia flava [114]	r		
Schleichera oleosa [286]	b		
Scirpus fluviatilis [308]	rh	IR, mp, MS, ORD	0.43
Scirpus tuberosus [309]	r	IR, mp, NMR	
Solanum aethiopicum [310]	be	IR, mp	0.0025
Solanum laciniatum [311]	st		
Solanum wrightii [311]	st		
Sorbus aucuparia [134]	b		
Sorbus americana [83]	b, l	GC	10
Stenocereus thurberi [29]	wp	GC, mp, ORD, TLC	
Sterculia foetida [312]	b	mp, ORD	0.005
Sterculia urens [313]	b	IR, mp	0.005
Strobilanthes cusia [314]	r		
Tectona grandis [315]	b	IR, mp, MS, NMR	
Tetracera akara [183]	l	IR, mp, TLC	0.045
Tetracera indica [183]	l	IR, mp, TLC	0.01
Tetracera sarmentosa [183]	l	IR, mp, TLC	0.07
Tetracera scandens [183]	l	IR, mp, TLC	0.03
Thevetia peruviana [316]			
Thymelea hirsuta [317]			
Tricholepis glaberrima [318]	wp	IR, MS, NMR, TLC	
Trochodendron [134]	b, l, w		
Trochodendron aralioides [319]	l		
Viscum album [320]	l+st		
Viscum articulatum [321]	wp	GC, mp, MS, TLC	
Wisteria floribunda [322]	b		
Woodfordia fruticosa [323]	l	IR, mp, ORD	0.004
Zataris multiflora [324]	l+st+fl		
Zizyphus jujuba [134]	s		
Zizyphus mauritiana [325]	st		
Zizyphus sativa [326]	b		
Zizyphus spinosus [327]	s		

ae: Aerial parts; ar: arterial parts; b: bark; be: berries; br: branches; c: cork; fl: flowers; fr: fruit; hw: heartwood; l: leaves; lc: lipid constituents; ob: outer bark; p: pulp; r: roots; rb: root bark; rh: rhizoma; s: seeds; sh: shoots; st: stems; t: twigs; w: wood; wp: whole plant.

NMR. ^{1}H NMR spectra at betulin have been reported [40, 41] and the chemical shifts for the methyl groups have been assigned [42, 43]. ^{13}C NMR spectra were fully interpreted [41, 44, 45].

UV. Reaction products of betulin with concentrated sulphuric acid were analysed by UV [46, 47].

MS. The fragmentation pattern of betulin [48] as well as its diacetate [49] was described. Further information about the mass spectra is found in a review article on pentacyclic triterpenes [50]. Molecular MS results in a simplified fragmentation pattern as expected [51].

Chemical reactivity.

Betulin has a high thermal stability [19]. On distillation at atmospheric pressure a Russia-leather [14] smell is observed. Kinetic investigations indicated a very low reactivity of the hydroxy groups of betulin [52]. Oxidation, reduction and rearrangement reactions with acid catalysis were reviewed [4]. In addition, the homogenous hydrogenation and deuteration [53] as well as an oxidation reaction by air [22] and a dehydrogenation by alkali fusion (NaOH–KOH) [54] are described. Using $Hg(OAc)_2$ in HOAc–$CHCl_3$ as oxidant [55] an isomerisation product is observed [56]. The dehydration with $POCl_3$ leads to a Wagner–Meerwein rearrangement [57]. Catalytic glycosidation of betulin with several catalysts [58, 59] was studied and some betulin glycosides were synthesized [60, 61]. Tetraacetylglycopyranosylorthoesters of betulin have been prepared [62]. Other carbohydrate orthoesters underwent transesterification [63, 64]. The synthesis of betulin glucoside acetates via acyl halides [65] or orthoesters in the presence of $HgBr_2$ was studied [66, 67].

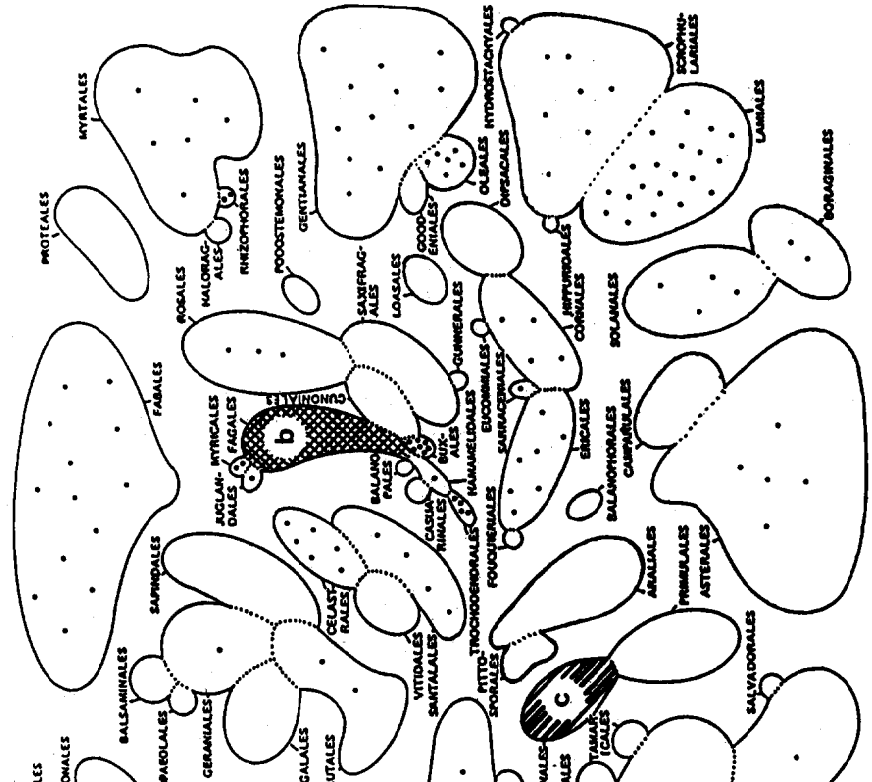


Fig. 1. Reported occurrence of betulin in angiosperms. (a) the number of dots reflects the number of betulin containing species. (b) the occurrence of betulin both quantitatively and qualitatively is concentrated within this order. (c) many investigations are reported for *Diospyros* and betulin was identified in 57 species. (Pedigree adopted from ref. [328].)

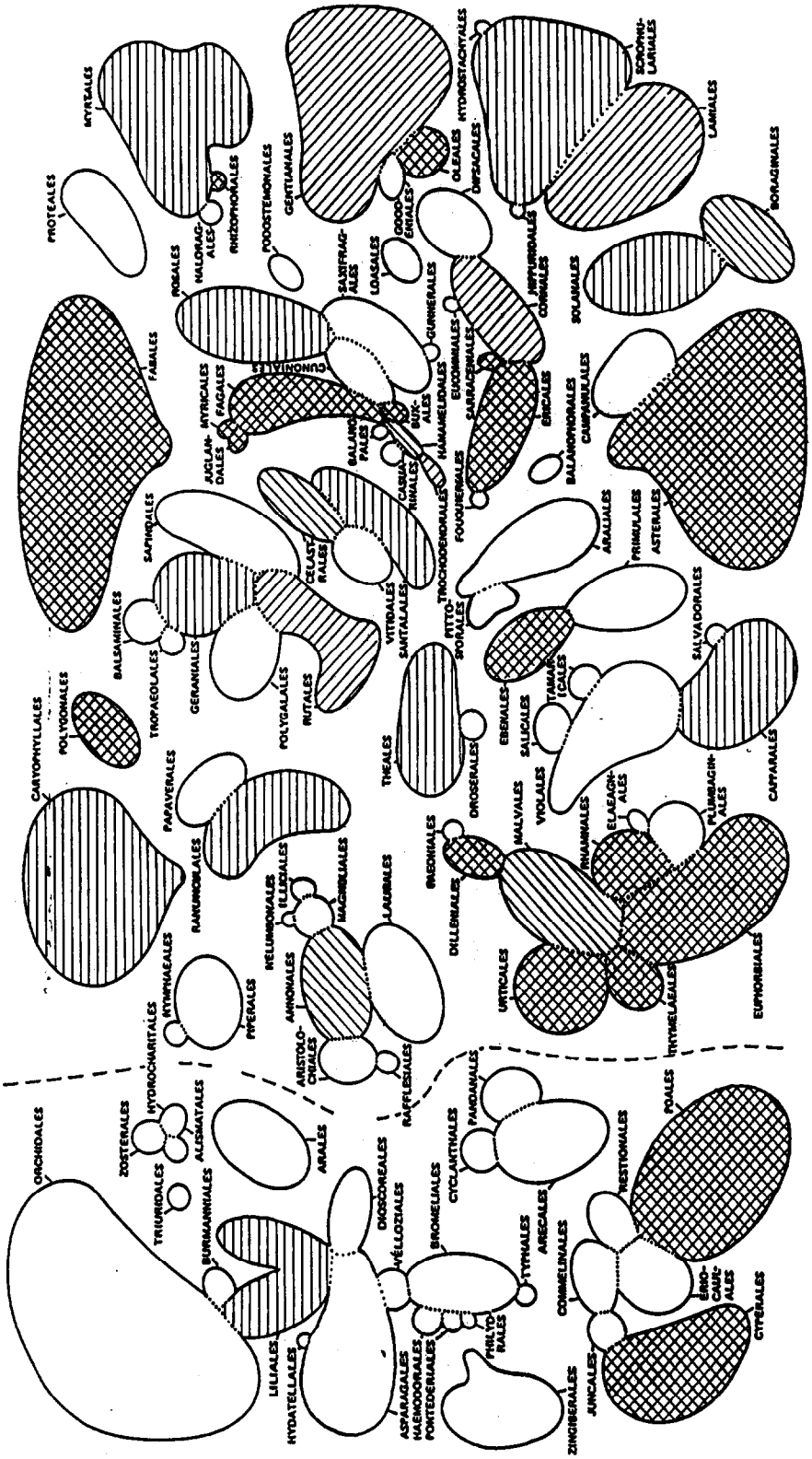


Fig. 2. Distribution of betulin in angiosperm-families (Pedigree adopted from ref. [328].)

The absolute configuration of betulin was assigned by application of the Horeau-method and diastereoisomeric reaction products detected by GC [68, 69]. Betulin is presumed to have isomerized to allobetulin and then oxidized to hydroxyallobetulin in geological samples [70]. The biogenetic pathway to betulin has been shown to proceed via geraniol, farneosol and geranyl-geraniol to squalene [71, 72] which is further converted via lupeol [29] to betulin.

Uses

It has been estimated [22], that a pulp mill with an annual production capacity of 200000 ton birch kraft pulp produces bark waste permitting isolation of *ca* 2500 ton per annum of betulin of 95% purity. Betulin, present in extractives of birchwood and pulp, is assumed to be the main cause of harmful resin deposits on papermaking machines [23] and was the main crystalline compound of the unsaponifiable fraction from hardwood sulphate soap in a Russian pulp mill [73]. It can be isolated from this source and the crude soap of the sulphate process [74]. Addition of 1% betulin solution to groundwood pulp handsheets increased lightfastness and decreased yellowing [75]; thus betulin can be used as light stabilizer for cellulose and wood pulp [76].

Acid betulin diphthalate [77] has been prepared and polyesters of betulin with linseed fatty acids yield quality protective coatings [78]. Furthermore betulin was used in the manufacture of resins, lacquers, emulsifiers, polyurethanes and in cosmetic products [4]. Polymers with rosin have good water resistance [79]. Polyurethanes with Desmondur E22 gave only oligomers [15]. Unsaturated polyesters had improved water and chemical resistance [52]. Polyacrylates of betulin were obtained in quantitative yield [80]. Betulin has inhibitory effects to the curing of a mixture of unsaturated resins [81].

Chemotaxonomy and distribution in the plant kingdom

The variation of the betulin content ranging from 5 to 22% in the leaves of four species of white barked birch is taxonomically useful [82]. Betulin containing plants are systematically widespread within the angiosperms and found predominantly among trees and bushes. An accumulation, both quantitatively and qualitatively, seems to be within the order Fagales; Reports on the occurrence of betulin are mainly dealing with the orders Buxales, Dilleniales, Ebenales and Lamiales as shown in the pedigree adopted from ref. [328] (Fig. 1). The distribution of betulin within families is depicted in Fig. 2.

The only occurence of betulin in gymnosperms was reported for the American *Abies balsamea* [83]. Betulin was also identified in peat [16–18, 84–87], lignite [86] geochemical samples (e.g. kaolin [88] and rock wax [89, 90] as well as in fungi [91–95], kraft black liquors [96, 97], pulp [21, 23, 44, 74–76, 98, 99] and tall oil [100].

The identification of betulin in archaeological specimens gave evidence that tar produced from birch bark was used in prehistoric times as a multifunctional material, e.g. as glue and for paints coating the surface of clay vessels [13, 19, 101, 102]. Among the derivatives of betulin found in nature are betulin-3-caffeate [28, 103], betulin diacetate and the 3α-isomer *epi*-betulin [104] as well as some betulin glycosides [105, 106].

Pharmacology, toxicology, drugs

Birch bark (cortex *Betulae*) containing 10–14% betulin has been used as an antiseptic [107] and in folk medicine against skin diseases, malaria, dropsy and gout [108]. Similarly, birch tar (pix *Betulae*, oleum rusci) was used to treat rheumatism and gout [108] as well as a nematocide antiseptic [107] and against colic and mange in veterinary medicine. Birch bark oil is used as an antirheumatic and disinfectant [109]. Betulin showed inhibitory effects on Epstein–Barr virus activation [110] and bacteriostatic activities against *Escherichia coli, Salmonella typhi, Shigella flexneri* and *Staphylococcus aureus* [111]. It was tested against Walker 256 carcinosarcoma and MCF-7 human mammary adenocarcinoma *in vitro*, and leukemia P 388 *in vivo* and showed activity comparable to inotodiol [92]. Betulin has no effect on the growth of *Phytophthora cactorum* [112]. Betulin glycosides have no cytostatic effect in developing sea urchin embryos [105]. Betulin showed feeding deterrent activity [113]. Tumour inhibition with activity against human epidermoid carcinoma of the nasopharynx *in vitro* [114] and Walker 256 (5WA16) tumour system [115] but not against L-1210 lymphoid leukemia in mice or Walker carcinosarcoma 256 in rats [114] was reported. For betulin and betulin-containing herbs antiseptic [4, 116], antiinflammatory [117] and insecticidal activities have been mentioned.

REFERENCES

1. Lowitz, M. (1788) in *Chemische Annalen* (Crell, L., ed.) Vol. 2, p. 312.
2. Hausmann, U. (1876) *Ann.* **182**, 368.
3. Beilstein, Syst. Nr. 561, E III 6, 5234.
4. Jääskeläinen, P. (1981) *Pap. Puu*, **63**, 599.
5. Fedorishchev, T. I. and Kalaikov, V. G., U.S.S.R. SU 382657, *Chem. Abs.* 137318k.
6. Vesterberg, R. (1932) *Chem. Ber.* **65**, 1305.
7. Steiner, M. (1955) in *Moderne Methoden der Pflanzenanalyse* Vol. 3, (Paech, K. and Tracey, M. V., eds), pp. 128–135. Springer, Berlin.
8. Ruzicka, L., Frame, G. F., Leicester, H. M., Liguori, M. and Brüngger, H. (1934) *Helv. Chim. Acta* **17**, 426.
9. Schulze, H. and Pieroh, K. (1922) *Chem. Ber.* **55B**, 2332.
10. Ikan, R. (1969) *Natural Products—a Laboratory Guide.* Academic Press, London.
11. Ruzicka, L., Brunner, H. and Gustus, G. E. (1932) *Helv. Chim. Acta.* **15**, 634.
12. Ruzicka, L. and Isler, O. (1936) *Helv. Chim. Acta* **19**, 506.
13. Sauter, F., Hayek, E. W. H., Moche, W. and Jordis, U. (1987) *Z. Naturforsch. C: Biosci.* **42**, 1151.
14. Dischendorfer, O. (1923) *Monatsh. Chem.* **44**, 123.
15. Erä, V. A., Jääskeläinen, P. and Ukkonen, K. (1980) *Angew. Makromol. Chem.* **88**, 79.
16. Kaganovich, F. L., Bel'kevich, P. I. and Dolidovich, E. F. (1972) *Vestsi Akad. Navuk Belarus. SSR, Ser. Khim. Navuk*, 110.
17. Ketola, M., Ekman, R. and Luomala, E. (1981) in *Proc. Int. Peat Symp.*, (Fuchsman, Ch. H., ed.), p.221. Bemidji State Univ., Bemidji, Minn.
18. Ikan, R. and McLean, J. (1960) *J. Chem. Soc.* 893.
19. Funke, H. (1969) Ph.D. Thesis. University of Hamburg, F.R.G.
20. Ionova, T. F., Kovalev, V. E., Nekrasova, V. B., Markova, N. P. and Tsybina, L. V., U.S.S.R. *SU* 789481; *Chem. Abs.* 95: 7525v.

21. Hamunen, A., Ger. Offen. *DE* 3226224 A1, *Chem. Abs.* 98: 149584z.
22. Eckerman, C. and Ekman, R. (1985) *Pap. Puu*, **67**, 100, 102, 105.
23. Razumova, L. G. and Stepanov, Yu. I. (1975) *Tr. Vses. Nauchino-Issled. Inst. Tsellyul.-Bum. Prom-sti.* **65**, 162.
24. Parsich, J., Pojda, M. (1974) *Farm. Pol.* **30**, 771.
25. Parsich, J. (1965) *Farm. Pol.* **21**, 861.
26. von der Dick, H. H. (1979) *Erdoel Kohle, Erdgas, Petrochem.* **32**, 467.
27. Rimpler, H., Kuhn, H. and Leuckert, Ch. (1966) *Arch. Pharm.* **229**, 422.
28. Ohara, S., Yatagai, M. and Hayashi, Y. (1986) *Mokuzai Gakkaishi* **32**, 266.
29. Kircher, H. W. (1980) *Phytochemistry* **19**, 2707.
30. Murakami, T., Itokawa, H., Uzuki, F. and Sawada, N. (1965) *Chem. Pharm. Bull.* **13**, 1346.
31. Stahl, E. (1967) *Dünnschichtchromatographie—ein Laboratoriumshandbuch.* Springer, Berlin.
32. Lin, J.-T., Nes, W. D. and Heftmann, E. (1981) *J. Chromatogr.* **207**, 457.
33. Ikekawa, N. (1969) in *Methods in Enzymology* Vol. 15, (Colowick, S., ed.), pp. 200–219. Academic Press, New York.
34. Ikekawa, N., Natori, Sh., Itokawa, S., Tobinaga, S. and Matşui, M. (1965) *Chem. Pharm. Bull.* **13**, 316.
35. Ikan, R. and Gottlieb, R. (1970) *Israel. J. Chem.* **8**, 685.
36. Madani, C. and Chambaz, E. M. (1981) *J. Am. Oil Chem. Soc.* **58**, 63.
37. Domon, B., Hostettmann, M. and Hostettmann, K. (1982) *J. Chromatogr.* **246**, 133.
38. Brunner, O. and Wiedemann, G. (1933) *Monatsh. Chem.* **63**, 368.
39. Brunner, O. and Wöhrl, R. (1934) *Monatsh. Chem.* **64**, 21.
40. Lehn, J. M. and Vystrcil, A. (1963) *Tetrahedron* **19**, 1733.
41. Siddiqui, S., Hafeez, F., Begum, S. and Siddiqui, B. S. (1988) *J. Nat. Prod.* **51**, 229.
42. Dantanarayana, A. P., Kumar, N. S. and Sultanbawa, M. U. S. (1981) *J. Chem. Soc., Perkin I*, 2717.
43. Hui, W.-H., Li, M.-M. (1976) *J. Chem. Soc., Perkin Trans. I*, 23.
44. Sholichin, M., Yamasaki, K., Kasai, R. and Tanaka, O. (1980) *Chem. Pharm. Bull.* **28**, 1006.
45. Patra, A., Chaudhuri, S. K. and Panda, S. K. (1988) *J. Nat. Prod.* **51**, 217.
46. Ponomarev, V. D., Oganesyan, E. T. and Semenchenko, V. F. (1971) *Khim. Prir. Soedin.* **7**, 147.
47. Kartnig, T. and Mikula, G. (1970) *Arch. Pharm.* **303**, 767.
48. Shannon, J. S., MacDonald, C. G. and Courtney, J. L. (1963) *Tetrahedron* **4**, 173.
49. Budzikiewicz, H., Wilson, J. M. and Djerassi, C. (1963) *J. Am. Chem. Soc.* **85**, 3688.
50. Ogunkoya, L. *Phytochemistry* **20**, 121.
51. Huneck, S. and Tuemmler, R. (1968) *J. Prakt. Chem.* **38**, 233.
52. Vasnev, V. V., Konkina, I. N., Korshak, V. V., Vinogradova, S. V., Lindberg, J. J., Jääskeläinen, P. and Piiroinen, K. (1987) *Makromol. Chem.* **188**, 683.
53. Protiva, J., Lepsa, L., Klinotova, E., Klinot, J., Krecek, V. and Vystrcil, A. (1981) *Collect. Czech. Chem. Commun.* **46**, 2734.
54. Hase, T. A., Suokas, E. and Weckman, A. (1981) *Synth. Commun.* **11**, 489.
55. Allison, J. M., Lawie, W., McLean, J. and Taylor, G. R. (1961) *J. Chem. Soc.* 3353.
56. Vystrcil, A., Blecha, Z. (1969) *Chem. Ind.* 418.
57. Anjaneyulu, A. S. R., Rao, M., Narayana Sree, A. and Murty, V. S. (1980) *Indian J. Chem.* **19B**, 735.
58. Odinokova, L. E., Oshitok, G. I., Denisenko, V. A., Anufriev, V. F., Tolkach, A. M. and Uvarova, N. I. (1984) *Khim. Prir. Soedin.* 182.
59. Uvarova, N. I., Atopkina, L. N., Elyakov, G. B. (1980) *Carbohydr. Res.* **83**, 33.
60. Uvarova, N. I., Oshitok, G. I. and Elyakov, G. B. (1973) *Carbohyd. Res.* **27**, 79.
61. Ivanov, A. S., Zakharova, T. S., Odinokova, L. E. and Uvarova, N. I. (1987) *Khim.-Farm. Zh.*, **21**, 1091.
62. Uvarova, N. I., Samoshina, N. F. and Elyakov, G. B. (1975) *Carbohydr. Res.* **39**, 351.
63. Uvarova, N. I., Samoshina, N. F., Novikova, L. E. and Elyakov, G. B. (1975) *Carbohydr. Res.* **42**, 165.
64. Uvarova, N. I., Samoshina, N. F., Oshitok, G. I. and Elyakov, G. B. (1976) *Zh. Org. Khim.* **12**, 1431.
65. Samoshina, N. F., Uvarova, N. I., Oshitok, G. I., Atopkina, L. N. and Elyakov, G. B. (1975) *Tezisy Dokl.—Vses. Simp. Bioorg. Khim.*, p. 19. (Rasskazov, V. A., ed.), Akad. Nauk SSSR, Dal'nevost. Nauchn. Tsentr: Vladivostok, USSR.
66. Samoshina, N. F. and Uvarova, N. I. (1979) *Khim. Prir. Soedin.* 334.
67. Uvarova, N. I., Oshitok, G. I., Isakov, V. V., Dzizenko, A. K. and Ely-Akov, G. B. (1972) *Dokl. Akad. Nauk SSSR*, **202**, 368.
68. Brooks, C. J. W. and Gilbert, J. D. (1973) *J. Chem. Soc., Chem. Commun.* 194.
69. Gilbert, J. D. and Brooks, C. J. W. (1973) *Anal. Letters* **6**, 639.
70. Golovanov, N. G. (1969) *Priroda* (Moscow), 59.
71. Eschenmoser, A., Ruzicka, L., Jeger, O. and Arigoni, D. (1955) *Helv. Chim. Acta* **38**, 1890.
72. Ruzicka, L. (1963) *Pure Appl. Chem.* **6**, 493.
73. Nikulenkova, T. F., Nekrasova, V. B. (1981) *Khim. Mekh. Pererab. Drev. Drev. Otkhodov* **7**, 19.
74. Hamunen, Antti, Ger. Offen. DE 3226225 A1, 3226225, *Chem. Abs.* 98: 149584z.
75. Zakazov, A. N., Leonova, G. V. and Chupka, E. I. (1984) *Bum. Prom-st.* 20.
76. Chupka, E. I., Zakazov, A. N., Kovalev, V. E., Nekrasova, V. B. and Nikulenkova, T. F., U.S.S.R. SU 1079717 A1, *Chem. Abs.* 101: 8985z.
77. Parsich, J., Pol. PL 51129, *Chem. Abs.* 66: 118851u.
78. Aslam, M., Alam, K. and Akhtar, S. (1965) *Pak. J. Sci. Ind. Res.* **8**, 31.
79. Aslam, M. and Alam, K. (1961) *Pak. J. Sci. Ind. Res.* **4**, 62.
80. Er, A. V., Mustonen, T. and Jääskeläinen, P. (1981) *Makromol. Chem., Rapid Commun.* **2**, 283.
81. Lee, C. L., Hirose, Y. and Nakatsuka, T. (1975) *Mokuzai Gakkaishi* **21**, 107.
82. O'Connell, M. M., Bentley, M. D., Campbell, C. S. and Cole, B. J. W. (1988) *Phytochemistry* **27**, 2175.
83. Hooper, S. N. and Chandler, R. F. (1984) *J. Ethnopharmacol.* **10**, 181.
84. Lehtonen, K. and Ketola, M. (1986) VTT Symp., **65** (Turve-Humussymp.), 178.
85. Ketola, M., Luomala, E., Pihlaja, K. and Nyronen, T. (1987) *Fuel*, **66**, 600.
86. Bel'kevich, P. I., Dolidovich, E. F., Kaganovich, F. L., Yurkevich, E. A. and Prokhorov, G. M. (1982) *Khim. Tverd. Topl. (Moscow)*, 57.
87. Ekman, R. and Fagernas, L. (1983) *Finn. Chem. Letters* 129.
88. Falc, Z. (1969) *Acta Univ. Carol., Geol.* 271.
89. Golovanov, N. G., Borisoglebs'kii, V. V., Kuz'menko, E. A.,

Mazira, L. N. and Zinchuk, I. F. (1965) *Khim. Prom., Inform. Nauk.-Tekhn. Zb.* 28.
90. Jarolim, V., Hejno, K. and Sorm, F. (1963) *Collect. Czech. Chem. Commun.* **28**, 2318.
91. Kahlos, K. and Hiltunen, R. (1987) *Acta Pharm. Fenn.* **96**, 85.
92. Kahlos, K., Kangas, L. and Hiltunen, R. (1987) *Acta Pharm. Fenn.* **96**, 33.
93. Fang, X., Nanayakkara, N. P. D., Phoebe, C. H., Jr., Pezzuto, J. M., Kinghorn, A. D. and Farnsworth, N. R. (1985) *Planta Med.* 346.
94. Cambie, R. C. (1978) *N. Z. J. Sci.* **21**, 565.
95. Musgrave, O. C. and Munro, H. D. (1971) *J. Chem. Soc.* C, 685.
96. Ionova, T. F. (1978) *Issled. Obl. Khim. Drev., Tezisy Dokl., Konf. Molodykh Uch.*, 2nd Edn, p. 40. (Karlivan, V. P., ed.) Izd. Zinatne: Riga, USSR.
97. Kitao, K. (1960) *Mokuzai Kenkyu* **24**, 1.
98. Junna, J., Lammi, R. and Miettinen, V. (1982) *Vesientutkimuslaitoksen Julk.* **49**, 17.
99. Holmbom, B. and Lehtinen, K.-J. (1980) *Pap. Puu* **62**, 673, 679, 683.
100. Holmbom, B. and Avela, E. (1971) *Acta Acad. Abo.*, **31B**, 18.
101. Hayek, E. W. H. (1988) Diplomarbeit T. U. Vienna.
102. Moche, W. (1988) Diplomarbeit T. U. Vienna.
103. Bandopadhyay, M., Dhingra, V. K., Mukerjee, S. K., Pardeshi, N. P. and Seshadri. T. R. (1972) *Phytochemistry* **11**, 1511.
104. Das, S. C. (1971) *Chem. Ind.*, 1331.
105. Anisimov, M. M., Shentsova, E. B., Shcheglov, V. V., Strigina, L. I., Uvarova, N. I., Levina, E. V., Oshitok, G. I. and Elyakov, G. B. (1978) *Toxicon* **16**, 31.
106. Jain, A. and Srivastava, S. K. (1984) *Indian J. Pharm. Sci.* **46**, 161.
107. Batta, A. K. and Rangaswami, S. (1973) *Phytochemistry* **12**, 214.
108. Hager, H., List, P. H. and Hörhammer, L. (eds) (1967–1980) *Handbuch der Pharmazeutischen Praxis*, 4th Edn, Springer, Berlin.
109. Nowak, G. A. (1966) *Am. Perfum. Cosmet.* **81**, 37.
110. Konoshima, T., Takasaki, M., Kozuka, M. and Tokuda, H. (1987) *J. Nat. Prod.* **50**, 1167.
111. Liu, J. and Zuo, C. (1987) *Zhiwu Xuebao* **29**, 84.
112. Nes, W. D. and Patterson, G. W. (1981) *J. Nat. Prod.* **44**, 215.
113. Schoonhoven, L. M. and Derksen-Koppers, I. (1973) *Entomol. Exp. Appl.* **16**, 141.
114. Miles, D. H., Kokpol, U., Zalkow, L. H., Steindel, St. J. and Nabors, J. B. (1974) *J. Pharm. Sci.* **63**, 613.
115. Sheth, K., Bianchi, E., Wiedhopf, R. and Cole, J. R. (1973) *J. Pharm. Sci.* **62**, 139.
116. Banerjee, S. K., Biswas, S. and Choudhury, M. K. (1980) *J. Indian Chem. Soc.* **57**, 665.
117. Prokopenko, S. A. and Spiridonov, A. V. (1985) *Farm. Zh. (Kiev).* 70.
118. Joshi, K. C., Tholia, M. K. and Sharma, T. (1975) *Planta Med.* **27**, 281.
119. Prakash, L. and Garg, G. (1981) *J. Indian Chem. Soc.* **58**, 96.
120. Joshi, K. C., Tholia, M. K. and Sharma, M. (1975) *Indian J. Chem.* **13**, 638.
121. Prakash, L. and Singh, M. (1986) *J. Indian Chem. Soc.* **63**, 853.
122. Popa, D. P. and Pasechnik, G. S. (1974) *Khim. Prir. Soedin.* 529.
123. Fujita, M., Itokawa, H. and Kumekawa, Y. (1974) *Yakugaku Zasshi* **94**, 189.
124. Pakrashi, S. C., Bhattacharyya, J., Mookherjea, S., Samanta, T. B. and Vorbrueggen, H. (1968) *Phytochemistry* **7**, 461.
125. Matyukhina, L. G. (1964) *Zh. Obshch. Khim.* **34**, 2796.
126. Zellner, J. (1925) *Monatsh. Chem.* **46**, 309.
127. Matyukhina, L. G., Ryabinin, A. A., Saltykova, I. A. and Shakhvorostova, T. B. (1968) *Khim. Prir. Soedin.* **4**, 387.
128. Sanada, Sh., Inaba, K., Ida, Y. and Shoji, J. (1987) *Shoyakugaku Zasshi* **41**, 80.
129. Talapatra, S. K., Chattopadhyaya, P. and Talapatra, B. (1983) *J. Indian Chem. Soc.* **60**, 203.
130. Jain, M. C. and Seshadri, T. R. (1971) *Indian J. Chem.* **9**, 1026.
131. Matyukhina, L. G., Shmukler, V. S. and Ryabinin, A. A. (1965) *Zh. Obshch. Khim.* **35**, 579.
132. Guise, G. B., Ritchie, E. and Taylor, W. C. (1962) *Aust. J. Chem.* **15**, 314.
133. Banerji, A. and Banerji, J. (1977) *Indian J. Chem.* **15B**, 390.
134. Hegnauer, R. (1962–1973) *Chemotaxonomie der Pflanzen*, Vols 1–5. Birkenhäuser, Basel.
135. Rao, L. J. M., Kumari, G. N. K. and Rao, N. S. P. (1984) *J. Nat. Prod.* **47**, 1052.
136. Lin, J. H. (1981) *Kuo Li Chung-kuo I Yao Yen Chiu So Yen Chiu Pao Kao*, July, p. 86–90.
137. Gupta, D. R., Bhushan, R., Dhiman, R. P. and Ahmed, B. *J. Nat. Prod.* **46**, 938.
138. Majumdar, S. G. and Patra, G. (1979) *J. Indian Chem. Soc.* **56**, 111.
139. Torrenegra, R., Wilches, F., Escarria, S. and Pedrozo, J. (1985) *Rev. Latinoam. Quim.* **16**, 102.
140. Parsich, J. (1964) *Farm. Pol.* **20**, 911.
141. Ruzicka, L. and van Veen, A. G. (1929) *Z. Phys. Chem.* **184**, 80.
142. Hejno, K., Jarolim, V. and Sorm, F. (1965) *Collect. Czech. Chem. Commun.* **30**, 1009.
143. Ekman, R. (1983) *Finn. Chem. Letters*, 162.
144. Kochergina, T. Y., Malinovskaya, G. V., Pokhilo, N. D. and Uvarova, N. I. (1987) *Khim. Prir. Soedin.* 609.
145. Odinokova, L. E., Malinovskaya, G. V., Pokhilo, N. D. and Uvarova, N. I. (1985) *Khim. Prir. Soedin.* 414.
146. Kochergina, T. Y., Malinovskaya, G. V., Pokhilo, N. D., Denisenko, V. A. and Uvarova, N. I. (1986) *Khim. Prir. Soedin.* 647.
147. Pokhilo, N. D., Denisenko, V. A., Baranov, V. I. and Uvarova, N. I. (1986) *Khim. Prir. Soedin.* 650.
148. Seshadri, T. R. and Vedantham, T. N. C. (1971) *Phytochemistry* **10**, 897.
149. Hirota, K., Takano, T., Taniguichi, K. and Igushi, K. (1944) *J. Soc. Chem. Ind. Jpn* **47**, 922.
150. Aslam, M. and Alam, K. (1961) *Pak. J. Sci. Ind. Res.* **4**, 62.
151. Chari, V. M., Neelakantan, S. and Seshadri, T. R. (1968) *Indian J. Chem.* **6**, 231.
152. Constantinescu, E. and Ionescu, A. (1974) *Riv. Ital. Essenze, Profumi, Piante Off., Aromi, Saponi, Cosmet., Aerosol* **56**, 337.
153. Steiner, M. (1936) *Mikrochemie, Festschrift von Hans Molisch*, 405.
154. Ekman, R. (1983) *Holzforschung* **37**, 205.
155. Chou, Ch.-J., Lin, J. and Liu, K.-C. (1973) *T'ai-wan Yao Hsueh Tsa Chih* **25**, 36.
156. Nakano, T., Terao, S. and Lee, K. H. (1965) *J. Pharm. Sci.* **54**, 1201.
157. Men, F. M., Lin, J. H. and Chou, Ch. J. (1983) *Kuo Li Chung-kuo I Yao Yen Chiu So Yen Chiu Pao Kao*, (July), 149.

158. Miana, G. A. (1973) *Phytochemistry* **12**, 470.
159. Abramson, D., Goad, L. J. and Goodwin, T. W. (1973) *Phytochemistry* **12**, 2211.
160. Varma, R. S. and Parthasarathy, M. R. (1975) *Phytochemistry* **14**, 1675.
161. Menichini, F., Delle Monache, F. and Marini Bettolo, G. B. (1982) *Planta Med.* **45**, 243.
162. Juneja, T. R., Gaind, K. N. and Dhawan, C. L. (1970) *Res. Bull. Panjab Univ., Sci.* **21**, 23.
163. Gunasekera, S. P., Cordell, G. A. and Farnsworth, N. R. (1983) *J. Nat. Prod.* **46**, 118.
164. Piozzi, F., Savona, G. and Sprio, V. (1975) *Phytochemistry* **14**, 1662.
165. Zellner, J. (1925) *Monatsh. Chem.* **46**, 621.
166. Yasmin, A., Kapadia, Z. and Badar, Y. (1985) *J. Pharm. (Univ. Karachi)*, **3**, 101.
167. Biswas, K. M. and Mallik, H. (1986) *Phytochemistry* **25**, 1727.
168. Chatterjee, A. and Bhattacharjee, S. R. (1964) *J. Indian Chem. Soc.* **41**, 415.
169. Marsili, A. and Morelli, I. (1972) *Phytochemistry* **11**, 2733.
170. Wagner, H., Iyengar, M. A. and Hörhammer, L. (1972) *Phytochemistry* **11**, 2633.
171. Hui, W.-H. and Li. M.-M. (1976) *Phytochemistry* **15**, 427.
172. De Pascual Teresa, J., Urones, J. G., Basabe, P., Bermejo, F. and Sanchez Marcos, I. (1981) *An. Quim. Ser. C*, **77**, 290.
173. Singh, R. and Prakash, L. (1983) *Pharmazie* **38**, 565.
174. Lin, J., Li, H. and Yu, J. (1983) *Zhongcaoyao* **14**, 337–340.
175. Broda, B., Krolikowska, M. and Kostka, B. (1974) *Acta Pol. Pharm.* **31**, 213.
176. Broda, B., Krolikowska, M. and Kostka, B. (1974) *Acta Pol. Pharm.* **31**, 373.
177. Agnihotri, V. K., Srivastava, S. D., Srivastava, S. K., Pitre, S. and Rusia, K. (1987) *Indian J. Pharm. Sci.* **49**, 66.
178. Bhakuni, R. S., Shukla, Y. N. and Thakur, R. S. (1986) *J. Nat. Prod.* **49**, 714.
179. Feinberg, C., Hermann, J., Röglsperger, L. and Zellner, J. (1923) *Monatsh. Chem.* **44**, 261.
180. Parthasarathy, M. R., Seshadri, T. R. and Varma, R. S. (1976) *Phytochemistry* **15**, 226.
181. Joshi, K. C., Bansal, R. K., Singh, P. and Singh, G. (1975) *Indian J. Chem.* **13**, 869.
182. Bahuguna, R. P. and Jangwan, J. S. (1986) *Herba Pol.* **32**, 71.
183. Dan, S. and Dan, S. S. (1980) *J. Indian Chem. Soc.* **57**, 760.
184. Banerji, N., Majumder, P. and Dutta, N. L. (1975) *Phytochemistry* **14**, 1447.
185. Bhattacharjee, S. R. and Chatterjee, A. (1962) *J. Indian Chem. Soc.* **39**, 276.
186. Sundararamaiah, T., Ramraj, S. K., Rao, K. L. and Vimalabai, V. (1976) *J. Indian Chem. Soc.* **53**, 638.
187. Tiwari, K. P., Srivastava, S. D. and Srivastava, S. K. (1981) *J. Indian Chem. Soc.* **58**, 817.
188. Zhong, S. M., Waterman, P. G. and Jeffreys, J. A. D. (1984) *Phytochemistry* **23**, 1067.
189. Bin Zakaria, M., Jeffreys, J. A. D., Waterman, P. G. and Zhong, S. M. (1984) *Phytochemistry* **23**, 1481.
190. Waterman, P. G. and Mbi, C. N. (1979) *Planta Med.* **37**, 241.
191. Bhakuni, D. S., Satish, S., Shukla, Y. N. and Tandon, J. S. (1971) *Phytochemistry* **10**, 2829.
192. Musgrave, O. C. and Skoyles, D. (1974) *J. Chem. Soc., Perkin Trans. I*, 1128.
193. Rajaram, P., Reddy, V. R. N., Sudhakar, B., Ramaiah, T. S. (1988) *Indian Drugs* **25**, 211.
194. Khan, M. R., Nkunya, M. H. H. and Wevers, H. (1979) *Pak. J. Sci. Ind. Res.* **22**, 301.
195. Khan, M. R., Nkunya, M. H. H. and Wevers, H. (1980) *Planta Med.* **38**, 380.
196. Dominguez, X. A., Cano, R. F. G., Gonzalez, A., Pugliese, O., Dominguez, M. A. and Adolfo Sanchez, G. (1979) *Rev. Latinoam. Quim.* **10**, 92.
197. Gupta, R. K. and Mahadevan, V. (1967) *Indian J. Pharm.* **29**, 289.
198. Gupta, R. K. and Mahadevan, V. (1968) *Indian J. Pharm.* **30**, 93.
199. Sharma, K. and Gupta, R. K. (1985) *Fitoterapia* **56**, 366.
200. Fallas, A. L. and Thomson, R. H. (1968) *J. Chem. Soc.* C, 2279.
201. Mbi, C. N. and Waterman, P. G. (1978) *J. Pharm. Pharmacol.*, **30** (Suppl.; *Brit. Pharm. Conf.* 1978), 86.
202. Bruneton, J. and Moretti, C. (1979) *Plant. Med. Phytother.* **13**, 172.
203. Herath, W. H. M. W., Rajasekera, N. D., Sultanbawa, M. U. S., Wannigama, G. P. and Balasubramaniam, S. (1978) *Phytochemistry* **17**, 1007.
204. Andriamasy, J., Pelissier, Y., Fouraste, I. (1978) *Trav. Soc. Pharm. Montpellier* **38**, 77.
205. Tezuka, M., Kuroyanagi, M., Yoshihira, K. and Natori, S. (1972) *Chem. Pharm. Bull.* **20**, 2029.
206. Seabra, R. M., De Oliveira, C. Qu., Alves, E. A. C. (1979) *Rev. Port. Farm.* **29**, 84.
207. Jeffreys, J. A. D., Zakaria, M. B. and Waterman, P. G. (1983) *Phytochemistry* **22**, 1832.
208. Tezuka, M., Takahashi, C., Kuroyanagi, M., Satake, M., Yoshihira, K. and Natori, S. (1973) *Phytochemistry* **12**, 175.
209. Row, L. R., Rao, C. S. and Ramaiah, T. S. (1966) *Curr. Sci.* **35**. 458.
210. Ramaiah, T. S. and Row, L. R. (1963) *Indian J. Appl. Chem.* **26**, 29.
211. Gupta, R. K., Rao, P. S. (1964) *Proc. Indian Acad. Sci.*, **60A**, 36.
212. Row, L. R., Rao, C. S. and Ramaiah, T. S. (1964) *Curr. Sci.* **33**, 367.
213. Kapil, R. S. and Dhar, M. M. (1961) *J. Sci. Ind. Res.* **20B**, 498.
214. Lillie, T. J., Musgrave, O. C. and Skoyles, D. S. (1976) *J. Chem. Soc., Perkin Trans. I*, 2155.
215. Misra, G., Nigam, S. K. and Mitra, C. R. (1972) *Phytochemistry* **11**, 1508.
216. Misra, P. S., Misra, G., Nigam, S. K. and Mitra, C. R. (1971) *Phytochemistry* **10**, 904.
217. Bhaumik, T., Dey, A. K., Das, P. C., Mukhopadhyay, A. K. and Chatterjee, A. (1981) *Indian J. Chem.* **20B**, 664.
218. Gupta, R. K. and Tiwari, R. D. (1964) *Indian J. Chem.* **2**, 129.
219. Costa, M. A. C., Paul, M. I., Alves, A. C. and van der Vijver, L. M. (1978) *Rev. Port. Farm.* **28**, 171.
220. Lu, R. and Zhang, Y. (1981) *Huaxue Xuebao* **39**, 815.
221. Khan, M. R., Kishimba, M. A. and Locksley, H. (1987) *Planta Med.* **53**, 498.
222. Kaplan, M. A. C., Gottlieb, O. R., Gilbert, B., Guimaraes, I. S. and Magahaes, M. T. (1966) *An. Acad. Bras. Cienc.* **38**, 419.
223 Nakano, T. and Suarez, M. (1969) *Planta Med.* **18**, 79.
224. Kagei, K., Ikeda, M., Sato, T., Ogata, Y., Toyoshima, S. and Matsuura, S. (1979) *Yakugaku Zasshi* **99**, 583.
225. Sahu, N. P., Mahato, S. B. and Chakravarti, R. N. (1973) *J. Indian Chem. Soc.* **50**, 771.
226. Dan, S. and Dan, S. S. (1982) *Fitoterapia* **53**, 51.
227. Rai, J. and Thaker, K. A. (1966) *Curr. Sci.* **35**, 148.
228. Hassan, T. Y., Zorina, A. D., Matyukhina, L. G. and Saltykova, I. A. (1977) *Khim. Prir. Soedin.* 119.
229. Cruz Costa, M. A., Lopes, M. H., Paul, M. I., Ferreira. M. A.

and Correia Alves, A. (1976) *Phytochemistry* **15**, 829.
230. Orzalesi, G., Mezzetti, T., Rossi, C. and Bellavita, V. (1971) *Planta Med.* **19**, 30.
231. Lopes, M. H. and Paul, M. I. (1973) *Rev. Port. Quim.* **15**, 213.
232. Schiaffella, F., Fratini, L., Mezzetti, T. and Bellavita, V. (1975) *Phytochemistry* **14**, 584.
233. Li, D., Wang, H., Chen, J. and Xu, J. (1986) *Zhiwu Xuebao* **28**, 528.
234. De Pascual Teresa, J., Urones, J. G., Marcos, I. S., Basabe, P., Sexmero Cuadrado, M. J. and Fernandez Moro, R. (1987) *Phytochemistry* **26**, 1767.
235. Dutta, P. K. and Chakravarti, R. N. (1971) *Phytochemistry* **10**, 2550.
236. Breton Funes, J. L., Delgado Martin, J., Fraga, B. M. and Gonzalez, A. G. (1969) *An. Quim.* **65**, 61.
237. Khafagy, S. M., Gharbo, S. A. and Abdel Salam, N. A. (1976) *Planta Med.* **29**, 301.
238. Konoshima, T., Takasaki, M., Kozuka, M. and Tokuda, H. (1987) *J. Nat. Prod.* **50**, 1167.
239. Ludwiczak, R. S. and Szczawinska, K. (1965) *Roczniki Chem.* **39**, 583.
240. Bowden, B. F., Cleaver, L., Ndalut, P. K., Ritchie, E. and Taylor, W. C. (1975) *Aust. J. Chem.* **28**, 1393.
241. Reddy, K. D., Reddy, R. P., Raj, S. K. R., Ravindranath, A. and Sundararamaiah, T. (1985) *J. Indian Chem. Soc.* **62**, 411.
242. Ukkonen, K. (1982) *Tappi* **65**, 71.
243. Joshi, K. C., Prakash, L. and Shah, R. (1974) *J. Indian Chem. Soc.* **51**, 830.
244. Chattopadhyay, S. and Pakrashi, S. C. (1975) *J. Indian Chem. Soc.* **52**, 553.
245. Jaspers, M. W. J. M., Bashir, A. K., Zwaving, J. H. and Malingre, T. M. (1986) *J. Ethnopharmacol.* **17**, 205.
246. Prakash, L. and Singh, R. (1981) *Pharmazie* **36**, 576.
247. Prakash, L., Sharma, N. N. and Goyal, G. (1979) *Indian J. Chem.* **17B**, 537.
248. Anjaneyulu, A. S. R. and Murthy, V. S. (1977) *Planta Med.* **32**, 247.
249. Joshi, K. C., Bansal, R. K. and Patni, R. (1978) *Planta Med.* **34**, 211.
250. Govindachari, T. R., Jadhav, S. J., Joshi, B. S., Kamat, V. N., Mohamed, P. A., Parthasarathy, P. C., Patankar, S. J., Prakash, D., Rane, D. F. and Viswanathan, N. (1969) *Indian J. Chem.* **7**, 308.
251. Cava, M. P., Shubber, A. K. and Rao, K. V. (1967) *Phytochemistry* **6**, 1301.
252. Kikuchi, T., Matsuda, S., Kadota, Sh., Sakai, Y., Namba, T., Watanabe, K. and Dissanayake, D. M. R. B. (1984) *Chem. Pharm. Bull.* **32**, 3906.
253. LLoyd, H. A. and Fales, H. M. (1967) *Tetrahedron Letters* 4891.
254. Stoecklin, W., De Silva, L. B. and Geissman, T. A. (1969) *Phytochemistry* **8**, 1565.
255. Wu, S., Zhang, L., Yang, X. and Li, D. (1984) *Zhongcaoyao* **15**, 145.
256. Hui, W. H. and Ho, C. T. (1968) *Aust. J. Chem.* **21**, 547.
257. Dan, S. and Dan, S. S. (1985) *Indian Drugs* **22**, 625.
258. Zorina, A. D., Matyukhina, L. G. and Ryabinin, A. A. (1966) *Khim. Prir. Soedin* **2**, 291.
259. Bohlmann, F., Ahmed, M., Jakupovic, J. and Jeffrey, C. (1981) *Phytochemistry* **20**, 251.
260. Hui, W.-H., Szeto, S. K. and Yee, C. H. (1967) *Phytochemistry* **6**, 1299.
261. Chakrabortty, T., Podder, G. and Deshmukh, S. K. (1977) *Indian J. Chem.* **15B**, 96.
262. Corbett, R. E., McDowall, M. A. and Wyllie, S. G. (1964) *J. Chem. Soc.* 1283.
263. Hui, W.-H., Ko, P. D. S., Lee, Y.-C., Li, M.-M. and Arthur, H. R. (1975) *Phytochemistry* **14**, 1063.
264. Hui, W.-H. and Li, M. M. (1977) *Phytochemistry* **16**, 111.
265. Sainsbury, M. and Webb, B. (1972) *Phytochemistry* **11**, 3541.
266. Majumdar, S. G. and Patra, G. (1980) *J. Indian Chem. Soc.* **57**, 568.
267. Anjaneyulu, A. S. R. and Reddy, D. S. K. (1981) *Indian J. Chem.* **20B**, 1033.
268. Gonzalez, A. G., Amaro, L. J. A. and Gutierrez, L. (1986) *J. Rev. Latinoam. Quim.* **17**, 56.
269. Hui, W.-H. and Li, M.-M. (1976) *Phytochemistry* **15**, 563.
270. Mitscher, L. A. and Vorperian, E. N. (1971) *Phytochemistry* **10**, 1687.
271. Breton Funes, J. L., Fraga, B. M., Jaraiz, I. and Gonzalez, A. G. (1969) *An. Quim.* **65**, 305.
272. Dan, S., Dan, S. S., Mukhopadhyay, P. and Mukherjee, M. K. (1985) *Int. J. Crude Drug Res.* **23**, 73.
273. Von Carstenn-Lichterfelde, C., Rodriguez, B. and Valverde, S. (1973) *Phytochemistry* **12**, 3002.
274. Desai, H. K., Gawad, D. H., Govindachari, T. R., Joshi, B. S., Parthasarthy, P. C., Ramachandran, K. S., Ravindranath, K. R., Sidhaye, A. R. and Viswanathan, N. (1976) *Indian J. Chem.* **14B**, 473.
275. Bellakhdar, J., Passannanti, S., Paternostro, M. P. and Piozzi, F. (1988) *Planta Med.* **54**, 94.
276. Gonzalez, A. G., Gonzalez, C. M., Ravelo, A. G., Dominguez, X. A. and Fraga, B. M. (1986) *J. Nat. Prod.* **49**, 148.
277. Mukherjee, D. K., Barua, A. K. and Bose, P. K. (1963) *Trans. Bose Res. Inst.* **26**, 55.
278. Ghosh, A. C. and Dutta, N. L. (1965) *J. Indian Chem. Soc.* **42**, 831.
279. Gupta, R. K., Dutta, T. R. and Patil, B. D. (1977) *Indian J. Pharm.* **39**, 64.
280. Joshi, K. C., Singh, P. and Mehra, A. (1981) *J. Indian Chem. Soc.* **58**, 102.
281. Aplin, R. T., Halsall, T. G. and Norin, T. (1963) *J. Chem. Soc.* 3269.
282. Lin, Y. L. (1983) *Kuo Li Chung-kuo I Yao Yen Chiu So Yen Chiu Pao Kao*, 103; *Chem. Abs.* **100**: 117811q.
283. Misra, S., Choudhury, A., Chattopadhyay, S. and Ghosh, A. (1988) *Phytochemistry*, **27**, 361.
284. Sundara Ramaiah, T., Laxman Rao, K. and Ramraj, S. K. (1978) *J. Indian Chem. Soc.* **55**, 102.
285. Delle Monache, G., Delle Monache, F., Di Benedetto, R. and Oguakwa, J. U. (1987) *Phytochemistry* **26**, 2611.
286. Dan, S. and Dan, S. S. (1986) *Fitoterapia* **57**, 445.
287. Kumar, N. and Seshadri, T. R. (1976) *Curr. Sci.* **45**, 516.
288. Hui, W.-H. and Li, M.-M. (1976) *J. Chem. Soc., Perkin Trans. I* 897.
289. Seoane, E., Villacorta, E. and de la Villa, M. J. (1971) *An. Quim.* **67**, 329.
290. Duhamel, L. (1963) *Ann. Chim.* **8**, 315.
291. Chretien-Bessiere, Y. and Duhamel, L. (1963) *Bull. Soc. Chim. Fr.* 228.
292. Ribas-Marques, I. and Fernandez-Salgado, J. (1974) *An. Quim.* **70**, 363.
293. Braz Filho, R., Cavalcante de Magalhaes, G. and Gottlieb, O. R. (1970) *Phytochemistry* **9**, 673.
294. Ghosh, A., Misra, S., Dutta, A. K. and Choudhury, A. (1985) *Phytochemistry* **24**, 1725.
295. Belova, N. V. and Fokina, G. A. (1970) *Khim. Prir. Soedin.* **6**, 137.
296. Joshi, Y. C., Dobhal, M. P., Joshi, B. C. and Barar, F. S. K. (1981) *Pharmazie* **36**, 381.

297. Fokina, G. A. and Belova, N. V. (1971) *Khim. Prir. Soedin.*, **7**, 30.
298. Hui, W.-H., Li, M.-M. and Luk, K. (1975) *Phytochemistry* **14**, 833.
299. Arisawa, M., Hayashi, T., Ohmura, K., Nagayama, K., Shimizu, M., Morita, N. and Berganza, L. H. (1987) *J. Nat. Prod.* **50**, 1164.
300. Dobhal, M. P. and Hoshi, B. C. (1979) *Herba Pol.* **25**, 95.
301. Gonzalez, A. G., Bazzocchi, I. L., Ravelo, A. G., Luis, J. G., Dominguez, X. A., Vazquez, G. and Cano, G. (1987) *Rev. Latinoam. Quim.*, **18**, 83.
302. Deshmane, S. S. and Dev, S. (1971) *Tetrahedron* **27**, 1109.
303. Collera, O., Gomora, E. and Garcia Jimenez, F. (1980) *Rev. Latinoam. Quim.* **11**, 60.
304. Brieskorn, C. H. and Kapadia, Z. (1980) *Planta Med.* **38**, 86.
305. Huneck, S. and Snatzke, G. (1965) *Chem. Ber.* **98**, 123.
306. Gopinath, K. W., Kohli, J. M. and Kidwai, A. R. (1962) *J. Sci. Ind. Res.* **21B**, 459.
307. Chatterjee, A., Mukherjee, K. S. and Dutta, C. P. (1966) *J. Indian Chem. Soc.* **43**, 285.
308. Nakajima, K., Taguchi, H., Endo, T. and Yosioka, I. (1978) *Chem. Pharm. Bull.* **26**, 3050.
309. Ahmad, J., Shamsuddin, K. M. and Zaman, A. (1984) *J. Indian Chem. Soc.* **61**, 92.
310. Banerjee, S. K., George, V. and Kapoor, R. (1974) *Planta Med.* **25**, 216.
311. Indrayanto, G., Voelter, W. and Reinhard, E. (1983) *Chem.-Ztg.* **107**, 238.
312. Anjaneyulu, A. S. R. and Murty, V. S. (1981) *Indian J. Chem.* **20B**, 87.
313. Anjaneyulu, A. S. R. and Raju, S. N. (1987) *J. Indian Chem. Soc.* **64**, 323.
314. Chen, R., Lu, Z., Guan, D., Chen, G. and Li, X. (1987) *Zhongcaoyao* **18**, 488; *Chem. Abs.* 108: 101194v.
315. Pathak, N. K. R., Neogi, P., Biswas, M., Tripathi, Y. C. and Pandey, V. B. (1988) *Indian J. Pharm. Sci.* **50**, 124.
316. Chen, R. R. L. and Chen, S.-F. (1974) *T'ai-wan Yao Hsueh Tsa Chih* **26**, 15; *Chem. Abs.* 84: 102337s.
317. Garcia-Granados, A. and Saenz de Buruaga, A. (1980) *An. Quim.* **76C**, 94.
318. Chawla, A. S., Kapoor, V. K., Sangal, P. K., Gupta, A. K. and Evans, F. J. (1976) *Planta Med.* **30**, 151.
319. Shimada, H., Nomura, Sh. and Shimizu, M. (1971) *Yakugaku Zasshi* **91**, 492.
320. Sakurai, A. and Okumura, Y. (1971) *Rep. Fac. Sci., Shizuoka Univ.* **6**, 63; *Chem. Abs.* 77: 58837j.
321. Ray, S., Thakur, T. N., Ghosh, A. and Barua, A. K. (1984) *J. Indian Chem. Soc.* **61**, 727.
322. Tanaka, I., Ohsaki, K. and Takahashi, K. (1975) *Yakugaku Zasshi* **95**, 1388.
323. Dan, S. and Dan, S. S. (1984) *J. Indian Chem. Soc.* **61**, 726.
324. Gupta, G. S. and Gupta, N. L. (1972) *Phytochemistry* **11**, 455.
325. Chauhan, J. S. and Srivastava, S. K. (1978) *Proc. Natl. Acad. Sci., India*, **48A**, 6.
326. Devi, S., Pandey, V. B. and Shah, A. H. (1987) *Fitoterapia*, **58**, 58.
327. Zeng, L., Zhang, R. and Wang, X. (1986) *Zhiwu Xuebao* **28**, 517.
328. Dahlgren, R., Rosendal-Jensen, S. and Nielsen, B. J. (1981) in *Phytochemistry and Angiosperm Phylogeny* (Young, D. A. and Seigler, S., eds), pp. 149–203. Praeger, New York.