Biswanath Dinda

Pharmacology and Applications of Naturally Occurring Iridoids

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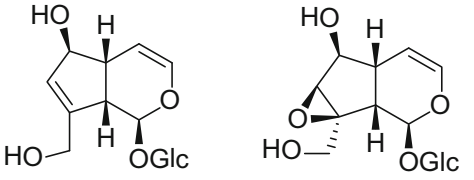
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Pharmacology and Applications of Naturally Occurring Iridoids

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Dedicated
to
my parents, father-in-law
and teacher, Prof. (Mrs) Asima Chatterjee
for her life-time
achievement on herbal drug discovery

Preface

The field of natural products chemistry is immense, fascinating, and interesting because of limitless structural varieties and substitution patterns of natural products, and their specific metabolic origins and fates, cellular transformations, and versatile physiological and other biological activities. Iridoids and their 7,8-seco-derivatives, called secoiridoids, are one of the major classes of secondary plant metabolites, mainly found in a restricted group of plant families. Most of these plant metabolites are found in commonly used folk medicinal plants and edible fruits and vegetables of many countries. Their physiological activities in plants and some specific insects are indispensible in which they occur. The potent and versatile pharmacological activities of some naturally occurring iridoids prompted for in-depth study on their transcriptomes and metabolomes analyses to reveal the specific gene expression in their biosynthesis for utilization of these genes in biotechnological production of these iridoids as raw materials in pharmaceutical industries. Most of the existing monographs and textbooks have a limited coverage on these plant iridoids. Therefore, I have decided to elaborate all the aspects of the naturally occurring iridoids in this book to furnish a comprehensive idea upon this subject and to bring it in the limelight of the students and researchers. In this book, the occurrence and distribution in plant families and insects, methods of isolation, separation and purifications by different chromatographic techniques, structural diagnosis and elucidation by modern spectroscopic methods, methods of partial and total synthesis, biosynthesis of some bioactive iridoids using both transcriptome and metabolome analyses and tracer technique, pharmacological and other biological activities, metabolic fate in microorganisms and animals, pharmaceutical and nutraceutical applications of iridoids in medicine and dietary supplements, and pesticidal applications in eradication of harmful parasitic insect vectors of some diseases have been elaborated. In addition to these, the application of iridoids as chemotaxonomic markers in the study of chemosystematics and phylogeny of plant families is also highlighted.

This book is specifically designed as a textbook for the students of graduate and postgraduate levels of pharmacognosy, pharmacy, and pharmaceutical chemistry. This book will provide a detailed and extensive overview and a unifying concept on

the naturally occurring iridoids. I feel this book will motivate the interest of the students and researchers in this significant area of natural science for the discovery of gene expression in plants for biosynthesis of these metabolites. This book will be a valuable tool in pharmaceutical industry for application of these plant metabolites in various drug formulations.

To the readers of this book, I seek for their valuable suggestions and comments for improvement of this monograph in the next edition.

I am grateful to Prof. I. Calis of Near East University, TRNC, for kindly providing the 2D NMR spectra of lamiide and auroside; Prof. S. R. Jensen of the Technical University of Denmark; Prof. R. Tundis of University of Calabria, Italy; and Prof. A. Viljoen of Tshwane University of Technology, Pretoria, South Africa, for kindly providing some of their research papers on iridoids. I am grateful to my publisher for their support and interest in the publication of this monograph.

I wish to acknowledge the help of the students, Dr. Goutam Kulsi of Seoul National University, Korea; Dr. Arup Kr. Roy of NEIST, India; Dr. Nayim Sepay and Sri Tapas Halder of Jadavpur University, India, for providing some papers on iridoids; Dr. Ankita Chakraborty of Tripura University; my son, Dr. Subhajit Dinda of DDM College, Tripura; Dr. Brajagopal Samanta of Nabajibon Colony Nabajiban Vidyamandir, West Bengal, India; and Sri Goutam Das, City College, West Bengal, for drawing some structures in preparation of this manuscript.

Finally, I wish to express my hearty affections to my wife, Chitralekha, children, Subhajit and Manikarna and son-in-law, Shekhar, and regards to my mother-in-law Mrs. Pravabati Das for their constant encouragement in the completion of this book.

Agartala, Tripura, India Biswanath Dinda
July 2018

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Abbreviations

AA	Adjuvant-induced arthritis
ABTS	2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)
ACC	Acetyl CoA carboxylase
ACD	Anti-convulsant drug
ACh	Acetylcholine
AChE	Acetylcholine esterase
ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropin
ADD	After discharge duration
AGE	Advanced glycation endproduct
AIBN	2,2'-Azobisisobutyronitrite
Akt	Protein kinase B
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMPK	5'-Adenosine monophosphate-activated protein kinase
AP	Acute pancreatitis
AP-1	Activator protein-1
APAP	*N*-Acetyl-p-aminophenol
Ara(f)	D-Arabinofuranosyl
ASK-1	Apoptosis signal-regulating kinase 1
AST	Aspartate transaminase
ATP	Adenosine triphosphate
BACE-1	Beta-site amyloid precursor protein cleaving enzyme-1
BALF	Bronchoalveolar lavage fluid
BAT	Brown adipose tissue
Bax	Bcl-2 associated x
BBB	Blood–brain barrier
Bcl-2	B-cell lymphoma 2
BDNF	Brain-derived neurotrophic factor
BDZ	Benzodiazepine

BHT	Butyrated hydroxytoluene/3,5-diisobutyl-4-hydroxytoluene
Big ET-1	Big endothelin-1
BINAL-H	2,2'-Dihydroxy-1,1'-binaphthyl-lithium aluminum hydride
BiP	Immunoglobulin-binding protein
BMP-2	Bone morphogenetic protein-2
Bn	Benzyl
BSA	Bovine serum albumin
Bu	Butyl
BUP	Bupropion
CAD	Coronary artery disease
Cag A	Cytotoxin-associated gene A
CaMKII	Calcium/calmodulin-dependent protein kinase II
CaMKKβ	Calcuim-/calmodulin-dependent protein kinase kinase beta
CD	Contact dermatitis/ Crohn's disease
C/EBPα	CCAAT/enhancer-binding protein alpha
CEL	N^{ε}-Carboxy ethyl lysine
CerS3	Ceramide synthase 3
CFU	Colony-forming unit
ChAT	Choline acetyl transferase
CK	Creatine kinase
CK-MB	Creatine kinase of types found in muscle and brain
CLP	Cecal ligation and puncture
CMA	Chaperone-mediated autophagy
COPD	Chronic obstructive pulmonary disease
COSY	Correlated spectroscopy
COX-2	Cyclooxygenase-2
CPK	Creatine phosphokinase
CPR	Coronary perfusion rate
CPT	8-Cyclopentyltheophylline
CREB	cAMP response element-binding protein
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CSA	10-Camphorsulfonic acid
CSF	Cerebrospinal fluid
CT_x	C-terminal telopeptide
CYP2E1	Cytochrome P4502E1
DA	Dopamine
DAT	Dopamine transporter
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEET	*N,N*-Diethyl-*meta*-toluamide
DESI	Desipramine
DHP	3,4-Dihydroxyphenethyl/dihydropyran
DIBA-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine

DMAPP	Dimethylallyl pyrophosphate
DMBA	7,12-Dimethylbenz[a]-anthracene
DMSO	Dimethylsulfoxide
DNFB	2,4-Dinitrofluorobenzene
DPPH	2,2-Diphenyl-1-picrylhydrazyl
Drp-1	Dynamin-related protein-1
DSCS	Disodium cromoglycate
DSS	Dextran sulfate sodium
DTH	Delayed-type hypersensitivity
EC_{50}	Equivalent concentration of test sample to scavenge 50% of free radical from the medium
ED_{50}	Effective dose of a drug to produce 50% of the activity
EGF	Epidermal growth factor
EIMS	Electron-impact mass spectrometry
EPM	Elevated plus maze
EPO	Erythropoietin
EPOR	Erythropoietin receptor
ER	Endoplasmic reticulum
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinase
ESIMS	Electrospray ionization mass spectrometry
Et	Ethyl
ET-1	Endothelin-1
FABMS	Fast atom bombardment mass spectrometry
FAS	Fatty acid synthase
Fas	First apoptosis signal
FasL	Fas ligand
FFA	Free fatty acid
FLS	Fibroblast-like synoviocyte
fMLP	*N*-Formylmethionyl-leucyl-phenylalanine
FoxO1	Forkhead box O1
FRAP	Ferric reducing ability of plasma
Fru	D-Fructofuranosyl
FST	Force swimming test
FVP	Flash vacuum pyrolysis
$GABA_A$	Gamma aminobutyric acid receptor A
Gal	β-D-Galactopyranosyl
GAP-43	Growth-associated protein-43
GDNF	Glial cell line-derived neurotrophic factor
GFR	Glomerular filtration rate
GFR-α1	GDNF-receptor alpha-1
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
Glc	β-D-Glucopyranosyl
GLP-1	Glucagon-like peptide-1

GLP-1R	Glucagon-like peptide-1 receptor
GLUT-4	Glucose transporter-4
GP	Glycogen phosphorylase
G6Pase	Glucose 6-phosphatase
G6PD	Glucose-6-phosphate dehydrogenase
GPP	Geranylpyrophosphate
GSR	Glutathione reductase
GRP78	Glucose-regulated protein of 78 kDa
GS	Glutamine synthetase
GSH	Glutathione
$GSH\text{-}P_x/GP_x$	Glutathione peroxidase
GSK-3	Glycogen synthase kinase-3
HA	Hemagglutinating antibody
HBV	Hepatitis B virus
HB_e Ag	Hepatitis B envelope antigen
HB_s Ag	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV_{pp}	Hepatitis C virus pseudoparticles
HEK-293	Human embryonic kidney-293 protein
12-HETE	12-Hydroxyeicosatetraenoic acid
HFD	High-fat diet
5-HIAA	5-Hydroxyindole acetic acid
HMBC	Heteronuclear multiple bond correlation
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
HMGCR	3-Hydroxy-3-methylglutaryl-coenzyme A reductase
HO-1	Heme oxygenase-1
HORAC	Hydroxyl radical averting capacity
Hp	*Harpagophytum procumbens*
HPA	Hypothalamic-pituitary-adrenocortical axis
hPK	Human primary keratinocytes
HSP-70	Heat shock protein-70
HSV-1	Herpes simplex virus-1
5-HT	5-Hydroxytryptamine
HUVEC	Human umbilical vein endothelial cell
hν	Ultraviolet or visible irradiation
HYD	Hydrocortisone
IAP-1	Inhibitor of apoptosis protein-1
IBD	Inflammatory bowel disease
ICAM-1	Intracellular adhesion molecule-1
IDE	Insulin-degrading enzyme
IFN-γ	Interferon gamma
IG	Iridoid glycoside mixture
IκBα	Inhibitor of kappa B activity, alpha form
IKK	Inhibitor of kappa B kinase

IKKβ	Inhibitor of nuclear factor kappa B kinase subunit beta
IMI	Imipramine
IMP	Idiopathic mesenteric phlebosclerosis
iNOS	Inducible nitric oxide synthase
i.p.	Intraperitoneal
IP-10	Interferon gamma-induced protein-10
IPP	Isopentenyl pyrophosphate
i-PrOH	*iso*-Propyl alcohol
IR	Insulin resistance
ISP	Isoproterenol
i.v.	Intravenous
JAK-2	Janus kinase-2
LAMP2A	Lysosome-associated membrane protein type 2A
LC-3II	Microtubule-associated protein-light chain-3-type-II
LC_{50}	Lethal concentration of a drug that causes death of 50% of the tested animal group
LDA	Lithium diisopropylamide
LDH	Lactate dehydrogenase
LLF	*Ligustrum lucidum* fruits
L-NMMA	L-N^G-Monomethyl-arginine
L-02/LO2	Human fetal hepatocytes
LPL-1	Lipoprotein lipase-1
LPS	Lipopolysaccharide
LRP-5	Lipoprotein receptor-related protein-5
LTB_4	Leukotriene B_4
LTC_4	Leukotriene C-4
MALDI-TOF-MS	Matrix-assisted laser desorption ionization-time of flight-mass spectrometry
MAPK	Mitogen-activated protein kinase
MAO-B	Monoamine oxidase B
MATF	Microphthalmia-associated transcription factor
MBC	Minimum bactericidal concentration
MCP-1	Monocyte chemoattractant protein-1
m-CPBA	*meta*-Chloroperbenzoic acid
MDA	Malondialdehyde
Me	Methyl
MEC	Minimum effective concentration
MeJA	Methyl jasmonate
MEP	2-Methyl-D-erythritol-4-phosphate
MES	Maximal electroshock
MFC	Minimum fungicidal concentration
MIC	Minimum inhibitory concentration
MLNL	Mesenteric lymph node lymphocyte
MMI	Macrophage migration index
MMP	Mitochondrial membrane potential

MMP-9	Matrix metalloproteinase-9
MPO	Myeloperoxidase
mPT	Mitochondrial permeability transition
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Mrp-3	Multidrug resistance-associated protein-3
α-MSH	Alpha-melanocyte stimulating hormone
MST	Median survival time
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide
MVA	Mevalonic acid
m/z	Mass-to-charge ratio
NASH	Non-alcoholic steatohepatitis
NBS	N-Bromosuccinimide
NE	Norepinephrine
NEFA	Non-esterified fatty acid
NF-κB	Nuclear factor kappa B
NFT	Neurofibrillary tangles
NGF	Nerve growth factor
NIDDM	Non-insulin-dependent diabetes mellitus
NMP 41/7	Nuclear matrix proteins 41 and 7
NMRI	Naval Medical Research Institute
NOESY	Nuclear Overhauser effect spectroscopy
Nox-4	NADPH oxidase-4
1-NPy	1-Nitropyrene
NQO1	NAD(P)H-quinone acceptor oxidoreductase-1
Nrf-2	Nuclear factor-(erythroid derived-2)-related factor-2
NT-3	Neurotrophin-3
OB-R	Obesity (leptin) receptor
OCN	Osteocalcin
OFT	Open field test
$ONOO^-$	Peroxynitrite anion radical
OPG	Osteoprotegerin
OPLC	Over-pressured layer chromatography
ORAC	Oxygen radical absorbance capacity
ORCA2	Octadecanoid-derivative responsive *Catharanthus* AP2-domain protein-2
ORTEP	Oak Ridge thermal ellipsoid plot
OVA	Ovalbumin
OVX	Ovariectomized
Ox-LDL	Oxidized-low-density lipoprotein
PAI-1	Plasminogen activator inhibitor-1
PBL	Peripheral blood lymphocyte
PC-12	Pheochromocytoma-12
PCA	Passive cutaneous anaphylaxis
PCC	Pyridinium chlorochromate

PIICP	Human procollagen II C-terminal propeptide
PDGF	Platelet-derived growth factor
PDK1	3-Phosphoinositide-dependent protein kinase-1
PDZK1	Protein of four PDZ domains of protein–protein interactions, post-synaptic density protein/protein of Drosophila disks-large/tight-junction protein (ZO1)
PET	Planar electrochromatography
PFC	Plaque-forming cell
PFR-2	Paraflagellar rod-2 protein
PGE_2	Prostaglandin E_2
Ph	Phenyl
PI3K	Phosphoinositide-3-kinase
Piv	Pivaloyl
p-JNK	Phosphorylated-c-Jun-N-terminal kinase
PKC	Protein kinase C
PKDL	Post-kala-azar dermal leishmaniasis
PLA_2	Phospholipase A_2
PMA	Phorbol-12-myristate-13-acetate
p-MAPK AP-2	Phosphorylated mitogen-activated protein kinase-activator protein-2
pMCAO	Permanent middle cerebral artery occlusion
p-MKK	Phosphorylated mitogen-activated protein kinase kinase
PMN	Polymorphonuclear leukocytes
PPAR-α	Peroxisome proliferator-activated receptor alpha
PPAR-γ	Peroxisome proliferator-activated receptor-gamma
p-Smad-2	Phosphorylated protein similar to that of Drosophila gene, mothers against decapentaplegic-homolog-2
PTZ	Pentylenetetrazole
Py	Pyridine
RA	Rheumatoid arthritis
RAGE	Receptor of advanced glycation endproducts
RANKL	Receptor activator of nuclear factor kappa B ligand
RD	Rhabdomyosarcoma
RD_{50}	Effective dose of drug to repel 50% of insect population in an environment
Rha	α-L-Rhamnopyranosyl
RHF	Radiation-induced fibrosarcoma
ROESY	Rotating-frame nuclear Overhauser effect spectroscopy
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
rt	Room temperature
RT-PCR	Real-time polymerase chain reaction
Runx-2	Runt-related transcription factor 2
Rut	Rutinose
SIRT	Sirtuin

α-SMA	Alpha-smooth muscle actin
SNARE	Soluble (N-ethylmaleimide sensitive factor)-activating protein receptor
SOCS	Suppressor of cytokine signaling
SOD	Superoxide dismutase
SRB	Sulforhodamine B
SREBP1/2	Sterol regulatory element-binding proteins one and two
STAT-3	Signal transducer and activator of transcription-3
STZ	Streptozotocin
T_{50}	Time required for 50% tumor induction
T_n-T	Troponin T
TAK1	TGF-beta-activated kinase-1
TAM	Tumor-related macrophages
TBARS	Thiobarbituric acid reactive substance
TC	Total cholesterol
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
TGF-β	Transforming growth factor-beta
TH	Tyrosine hydroxylase
TLJN	Tong Luo Jiu Nao
TLR-4	Toll-like receptor-4
TMS-CHN_2	Trimethylsilyl diazomethane
TNBS	2,4,6-Trinitrobenzene sulfonic acid
TRADD	TNF-receptor-1-associated death domain protein
TRAF-2	TNF-receptor-associated factor-2
TRAP	Tartrate-resistant acid phosphatase
TNF-RSC	Tumor necrosis factor-alpha receptor-associated signaling complex
Ts	Tosyl
TSOD	Tsuma Suzuki obese diabetes
TST	Tail suspension test
TUNEL	Terminal deoxynucleotidyl transferase deoxyuridine-5-triphosphate nick-end labeling
TXB_2	Thromboxane B_2
UCP-1	Uncoupling protein-1
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
VHSV	Viral hemorrhagic septicemia virus
VL	Visceral leishmaniasis
VSV	Vesicular stomatitis virus
WAT	White adipose tissue
wnt	Wingless-type integration site protein
Xyl	β-D-Xylopyranosyl

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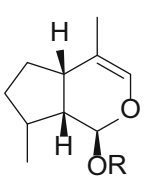
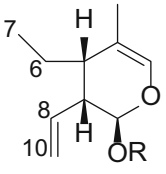
Summary of Contents

The entitled monograph describes the various aspects of naturally occurring iridoids namely their generic name, classification, occurrence and distribution in plants and insects, isolation techniques, characterization by spectroscopic and chemical methods, synthesis of bioactive iridoids and secoiridoids, biosynthesis, methods of identification of transcriptomes and metabolomes involved in their biosynthesis, role as phylogenic markers in plants, pharmacological activities, pharmacokinetics in mammals, insects and microorganisms, and applications in food supplements, herbal medicines, modern medicines and natural pesticides. The entire subject is presented in seven chapters. The emphasis is given in pharmacology of iridoids and their prospective applications in pharmaceutical and insecticidal industries.

The naturally occurring iridoid monoterpenoids 1, and their secoderivatives, known as secoiridoids 2, are widespread in about 56 plant families of dicotyledons (angiosperms)and in one family of monocotyledons (Cyperaceae).Some of these iridoids have been isolated from 8 families of insects. So far about 3000 iridoids of diverse skeletal and substituent pattern have been reported. Many of them possess significant pharmacological activities and have been isolated from several edible plants of folk-lore use.



1: R= H, Glc



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The most of significant aspects of iridoid research are discussed in different chapters.

In Chap. 1, iridoid glycosides, secoiridoid glycosides and their aglycones of different basic skeletons and conjugated patterns are presented.

In Chap. 2, the occurrence and distribution of iridoids in the plant species of different genus in 60 plant families and 8 insect families are discussed.

In Chap. 3, the purification and isolation of iridoids from crude plant and insect extracts using different chromatography techniques have been discussed. In addition, their identification using different spectroscopic techniques including 2D NMR and NMR spectral data of some common iridoids and secoiridoids are presented. These methods could be useful in the identification of iridoids of unknown structures and their quantification in plant extracts and herbal drugs.

In Chap. 4, the synthesis of some bioactive iridoids, secoiridoids and their pharmacologically useful analogues, biosynthesis, and analysis of transcriptomes and metabolomics involved in their biosynthetic pathways are elaborately discussed. Furthermore, their role in the study of phylogeny and evolutionary systematics of plants are discussed. The identified genes involved in their biosynthesis could be useful for commercial production by tissue culture process.

In Chap. 5, about 40 types of pharmacological activities of iridoids including anti-inflammatory, anticancer/antitumor, antiviral, antiprotozoal, neuroprotective and neurogenic, hepatoprotective, cardioprotective, hypoglycemic and hypolipidemic, repellent/antifeedant activities as well as physiological role of iridoids in insects are discussed. Some of these bioactive iridoids could be prospective drugs in pharmaceutical and pesticidal industries.

In Chap. 6, the metabolism of iridoids in microorganisms and mammals and pharmacokinetics in mammals are briefly discussed, Moreover, disposition of some iridoids in animals is highlighted.

In Chap. 7, applications of iridoids as their extracts/ mixture and pure isolates in diet supplements, herbal drugs, modern medicines including cosmetics and dyes, and in pesticides are presented.

Chapter 1
Classification of Iridoids

1.1 Introduction

Iridoids are the highly oxygenated monoterpenes, represented by the cyclopenta[c] pyranoid skeletal structure **1**, based on the structure of monoterpene iridane, 4,8-dimethyl-*cis*-2-oxabicyclo-[4.3.0]-nonane **2** (Fig. 1.1) [1]. These compounds are widespread as secondary plant metabolites in the angiosperm plant families and some ant species [2]. In many plants, these iridoids exist as 7,8-secoderivatives, known as secoiridoids **1a** (Fig. 1.1), which are formed by the cleavage of cyclopentane ring at the C-7–C-8 bond. These compounds are found in about 57 plant families of dicotyledons mainly belonging to the Asterids clade in wide structural diversities [3]. Although these compounds were first isolated from plants in 1800 s, the pioneering work on the structures of this class of compounds started after isolation of iridodial **3**, iridomyrmecin **4**, and isoiridomyrmecin(=iridolactone) **5** (Fig. 1.1) from some species of *Iridomyrmex* (namely *I. detectus*, *I. humilis*, *I. conifer, I. nitidus,* and *I. purpureus*), a genus of ants mostly found in Australia [4]. Later on, iridodial **3** was isolated from an Australian plant of genus, *Myoporum* [5]. Based on these information, the generic name of this class of compounds was adapted as 'iridoids' because of their structural similarity with iridodial **3**, which on intramolecular acylation gives the pyran skeletal structure of iridoid [6]. Application of iridoids, iridodial **3**, and dolichodial **3a** (Fig. 1.1) in defense mechanism of ants of genera, *Iridomyrmex*, *Dolichoderus* (*D. scabridus*), and *Tapinoma* (*T. sessile*), stimulated the interest on the search of more iridoids from plants [7]. Several insects in the orders Coleoptera, Lepidoptera, Hymenoptera, and Hemiptera ingest these iridoid-containing plants and sequester these compounds and use them as defenses against their predators or to increase their reproductive behavior [8]. Iridoids are found in a number of folk medicinal plants that have been used in folk medicine for treatment of various diseases including skin disorders, sedatives, hypotensive, diabetes, and other inflammatory diseases [9]. The active research work on the pharmacology of naturally occurring iridoids revealed that

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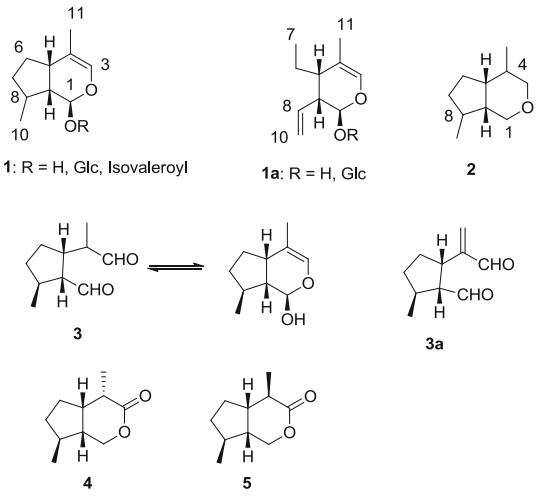

Fig. 1.1 Chemical structures of some representative iridoids

these compounds exhibit a wide range of pharmacological activities such as antidiabetic, hypolipidemic, cardioprotective, hepatoprotective, neuroprotective, wound healing, and antitumor activities [9–13]. In some plant families such as in Bignoniaceae, Oleaceae, and Plantaginaceae, these compounds are used as chemotaxonomic markers for the study of systematics of plants [14–16]. Several plant iridoids and secoiridoid-originated indole alkaloids, such as vincristine and vinblastine, are used in modern medicine for the treatment of inflammatory disorders including tumor [17]. A number of review articles on the isolation and structure elucidation, chemistry, distribution, biosynthesis, biological activity, and listings with spectroscopic data of plant iridoids are available [18–25]. From these review articles, it is evident that about 3000 plant-derived iridoids have been reported. Thus, there is a need to develop the chemistry and pharmacology of these naturally occurring iridoids for their commercial utilization in drug formulations in pharmaceutical industry.

1.2 The Numbering of Substituted Iridoid and Secoiridoid Glucosides

The trivial names of iridoids and secoiridoids are frequently used in the naming of these compounds. In most cases, the naming of the iridoids is done from the genus of the plant source. The numbering of the skeletal structures of iridoid and

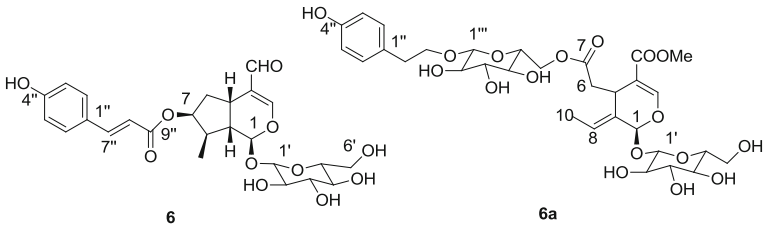

Fig. 1.2 Numbering of substituted iridoid glucosides

secoiridoid glucosides with substituent is shown in **6** and **6a** (Fig. 1.2). The substituent on C-1 is given a single prime (′) designation, while the additional substituents are designated as double prime (″), triple prime (‴), etc., according to their substitution position on the basic carbon skeleton of the iridoid glucoside, except in cases of substituents on other substituents. The substituents on a substituent are designated by successive primes.

1.3 Classification of Iridoids

Iridoids are broadly classified into five groups: iridoid glycosides, iridoid aglycones or non-glycosidic iridoids, secoiridoid glycosides, secoiridoid aglycones, and di- and trimeric iridoid, and secoiridoid glycosides. Iridoid glycosides are divided into five subgroups: iridoid glycosides of eight-carbon basic skeleton, iridoid glycosides of nine-carbon basic skeleton, iridoid glycosides of ten-carbon basic skeleton, iridoid glycosides of fourteen-carbon basic skeleton or iridoid glycosides of plumeria type, and alkaloid-conjugated iridoid glycosides. Iridoid glycosides of ten-carbon basic skeleton are divided into two subgroups: simple iridoid glycosides of ten-carbon basic skeleton and iridoid glycosides of valeriana type. Iridoid aglycones are divided into four subgroups: simple iridoid aglycones and derivatives, rearranged iridoid aglycones, iridoid aglycones of valeriana type, and iridoid aglycones of plumeria type. Secoiridoid glycosides are divided into four subgroups: simple secoiridoid glycosides, terpene-conjugated secoiridoid glycosides, phenolic-conjugated secoiridoid glycosides, and alkaloid-conjugated secoiridoid glycosides. The following iridoids are illustrative of these groups and subgroups (Fig. 1.3).