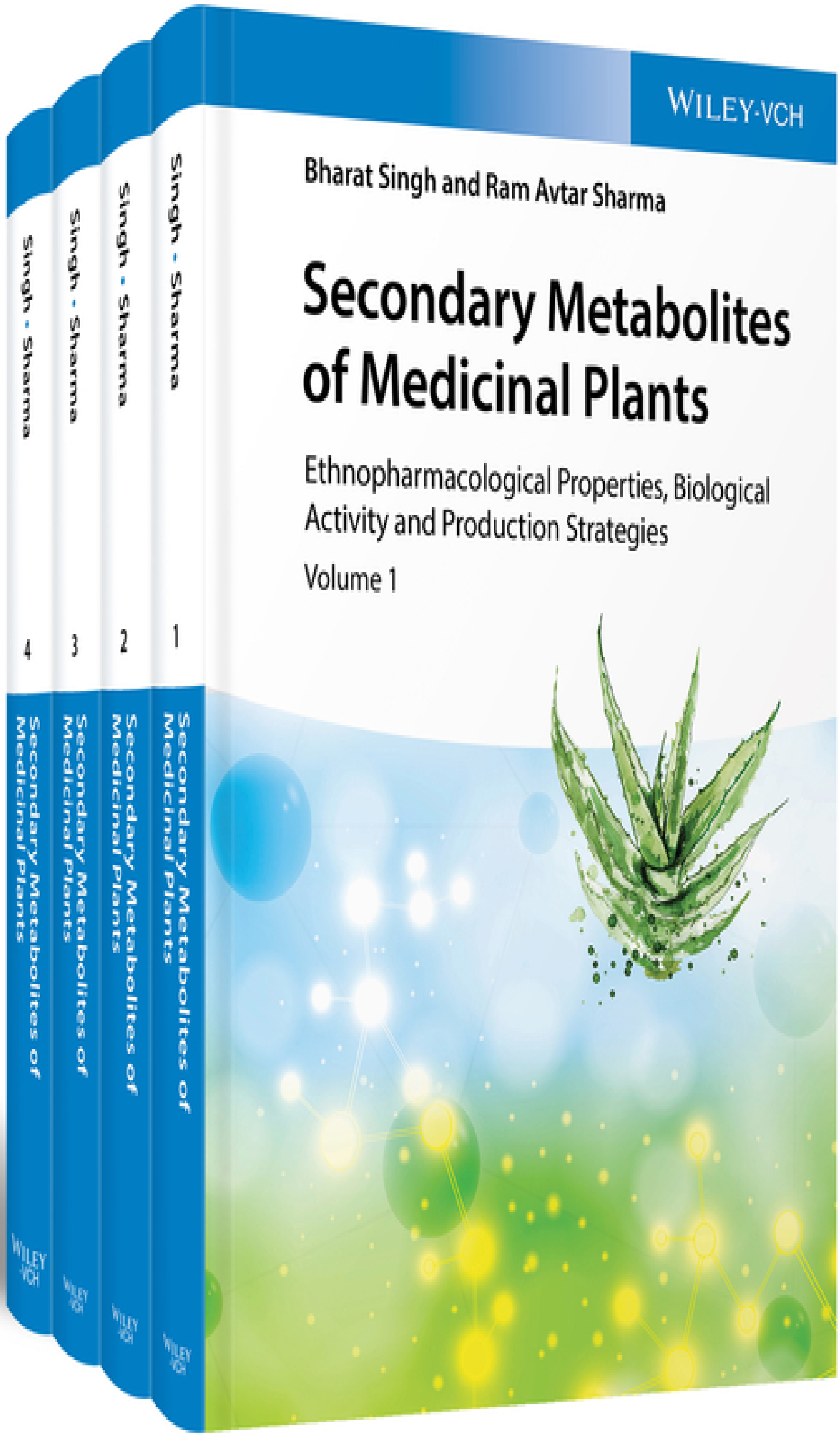

WILEY-VCH
Bharat Singh and Ram Avtar Sharma
Secondary Metabolites of Medicinal Plants
Ethnopharmacological Properties, Biological Activity and Production Strategies
Volume 1
Singh · Sharma
1
2
3
4
Secondary Metabolites of Medicinal Plants
WILEY-VCH

Secondary Metabolites of Medicinal Plants

Secondary Metabolites of Medicinal Plants

Ethnopharmacological Properties, Biological Activity and Production Strategies

Bharat Singh
Ram Avtar Sharma

Volume 1

WILEY-VCH

Authors

Dr. Bharat Singh
Amity University Rajasthan
Institute of Biotechnology
NH 11C, Kant Kalwar
303002 Jaipur
India

Dr. Ram Avtar Sharma
University of Rajasthan
Department of Botany
JLN Marg
302004 Jaipur
India

Cover Images: Aloe vera watercolor © Mokoshka-f/Shutterstock, abstract background © evryka/Shutterstock

Library of Congress Card No.:
applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

Print ISBN: 978-3-527-34732-2
ePDF ISBN: 978-3-527-82558-5
ePub ISBN: 978-3-527-82559-2
oBook ISBN: 978-3-527-82557-8

Typesetting SPi Global, Chennai, India
Printing and Binding

Printed on acid-free paper

10 9 8 7 6 5 4 3 2 1

Contents

Part 1

Introduction

Traditional system of medicine is also known as indigenous medicine system used to maintain our health and to diagnose and treat several complaints based on theories, beliefs, and family experiences. The indigenous system of medicine has been in practice since the last thousands of years; contributions from community practitioners have maintained their popularity at a global level (Sofowora 1982). The traditional knowledge of plants could be attributed to acceptability, affordability, pleasant feeling, and affectivity against any type of disease as compared with modern medicine (Giday et al. 2003; Tolossa et al. 2013). In the case of traditional medicine, the knowledge is transferred from the elders to the younger generation verbally or by just showing the growing plants in the open fields. Several studies have revealed that transfer of medicinal knowledge of plants to the coming generations is adversely affected by development of modern medicine. The interest of younger generation to traditional knowledge is diminishing day by day (Yineger and Yewhalaw 2007). The wide acceptance of indigenous medicine and limited approach to modern healthcare facilities could be considered as main reasons for the continuation of the traditional practices. The documentation of traditional knowledge can be used to support human healthcare system to maintain healthy lives. The documented information will be used in future course of studies to validate biological and pharmacological activities as exhibited by medicinal plants; therefore it is an urgent need of modern time to enhance the affordability and acceptability of plants in rural and modern healthcare systems (Demie et al. 2018).

The secondary metabolites are not considered as energy sources at the cellular level but play important roles in the interaction of plants with surrounding environment. They protect the plants from abiotic (high temperature, drought) and biotic (bacteria, fungi, insects, nematodes) stresses. On the other hand, the secondary metabolites contribute in systematic determination, used as markers in the classification of plants. The biosynthesis of secondary metabolites is organ and individual specific and in low molecular weight compounds. Similarly, the primary metabolites are useful in performing various metabolic activities for growth and development in plants (Piel 2010; Pagare et al. 2015). The secondary metabolites are used as bioactive compounds for the treatment of

Secondary Metabolites of Medicinal Plants:
Ethnopharmacological Properties, Biological Activity and Production Strategies,
First Edition. Bharat Singh and Ram Avtar Sharma.

various diseases. These secondary metabolites can be grouped into three classes based on their biosynthetic pathways, viz. terpenoids, polyketides, and phenylpropanoid (Verpoorte and Alfermann 2000). The alkaloids are nitrogenous molecules, synthesized by amino acids, viz. tyrosine, phenylalanine, and lysine, by using various enzymes (Croteau et al. 2000). Some secondary metabolites (anthocyanins, anthocyanidins, carotenoids, and flavonoids) have specific roles in pollination and seed dispersal; hence, they are involved in reproduction cycles of plants (Winkel-Shirley 2001). Plant-derived secondary metabolites have made an important contribution in the treatment of various diseases including cancer, infections, and inflammations. The immunomodulatory vaccines (edible vaccines) have been obtained from plant sources and are exploring clinically for treatment of viral infections (Woods et al. 2017). Secondary metabolites in plants can be divided into the following chemically defined groups: terpenes, phenolics, nitrogen, and sulfur compounds.

The terpenoids constitute the largest class of natural products, and many interesting products are extensively applied in the industrial sector as flavors, fragrances, and spices and are also used in perfumery and cosmetics. Many terpenoids have biological activities and are also used for medical purposes. In higher plants, the conventional acetate–mevalonic acid pathway operates mainly in the cytosol and mitochondria and synthesizes sterols, sesquiterpenes, and ubiquinones mainly. In the plastid, the non-mevalonic acid pathway takes place and synthesizes hemi-, mono-, sesqui-, and diterpenes along with carotenoids and phytol tail of chlorophyll. The monoterpenes are widely distributed natural products found in herbs, spices, citrus, conifers, and most flowers and fruits. These are C10, short chain compounds, normally found in combination with sesquiterpenes, that play many significant roles, viz. antimicrobial, insect repellant, and pollinator attractants (Davis 2010). Iridoids are characterized by skeletons – in which a six-membered ring, containing an oxygen atom, is combined to an iridane skeleton – and are found in plants combined with sugar as glycosides. The iridoids are classified as iridoid glycosides (aucubin, harpagoside), nonglycosylated iridoids (loganin), secoiridoids (gentiopicroside), and bisiridoids, developed by dimerization of iridoids and secoiridoids (Ludwiczuk et al. 2017). Sesquiterpenes (C15) are less volatile than monoterpenes but have more potential for stereochemical diversities and odors and possess anti-inflammatory and antimicrobial properties (Buckle, 2015). The seed maintenance and bud dormancy are regulated by abscisic acid (sesquiterpene), and it also responded positively to water stress by modifying the properties of cell membrane (Berli et al. 2010). Triterpenoids are widely distributed in plants often accumulated in their glycosylated form. Saponins comprise hydrophobic triterpenoid aglycones called sapogenin and one or more hydrophilic sugar moieties. The triterpenoids possess antimicrobial and anti-inflammatory activities (Vincken et al. 2007).

The phenolic compounds are aromatic benzene ring molecules synthesized by plants mainly as protection against biotic and abiotic stresses (Robles-Sanchez et al. 2009; Velderrain-Rodríguez et al. 2014). These compounds provide structural integrity and scaffolding support to plants. The plant phytoalexins released from wounded sites help in repelling or killing many microbes

(Bhattacharya et al. 2010). The phenolic compounds are widely occurred in the plant kingdom, especially contributing color, flavor, and astringency to flowers and fruits. The accumulation of phenolic compounds may vary from 0.3 to 5.0 g/100 g dry weight of a plant material. These compounds are considered to be by-products of the metabolism of the aromatic amino acid phenylalanine (Swanson 2003). The phenolic compounds are synthesized in plants by two biosynthetic pathways, viz. shikimic acid and pentose phosphate, through phenylpropanoid (Randhir et al. 2004). The glucose moves to pentose phosphate pathway by converting glucose-6-phosphate irreversibly to ribulose-5-phosphate. The reaction catalyzed by glucose-6-phosphate dehydrogenase. In the second pathway, erythrose-4-phosphate along with phosphoenolpyruvate is used for the phenylpropanoid pathway to synthesize phenolic molecules after being channeled to the shikimic acid pathway to produce phenylalanine (Vattem et al. 2005; Lin et al. 2010, 2016). Some coumarins and their derivatives have significant antifungal activity against several soilborne fungi and demonstrate higher stability than original coumarin compounds. Furanocoumarins are found in *Umbelliferae* members known for their use in the treatment of fungal diseases in plants (Brooker et al. 2008; Ali et al. 2008). The flavonoids are chemically polyphenolic in nature and occur in fruits, flowers, and vegetables (Burak and Imen 1999) and have miscellaneous favorable antioxidative effects associated with various diseases such as cancer, Alzheimer's disease, atherosclerosis, etc. (Castañeda-Ovando et al. 2009). They are also associated with a broad spectrum of health-promoting effects and are indispensable constituents in various nutraceutical, pharmaceutical, medicinal, and cosmetic products (Lee et al. 2009).

The quinones are a group of compounds occur in several plant species and are synthesized via the shikimate or polyketide pathways (Scott Obach and Kalgutkar 2010). The benzoquinones, naphthoquinones, and anthraquinones are found in higher plant species. Till today, nearly 600 quinones have been identified from various plant families, viz. *Rubiaceae* (Harborne 1982). These compounds are cyclic α,β-diketones, which can be converted by reduction into hydroquinones (Morrison and Boyd 1973). The oxidized form of conjugated quinones are colorful (yellow color) like *p*-benzoquinone, while reduced forms are colorless. By fusing the second aromatic ring with benzoquinone, the naphthaquinones are formed. Similarly, if both sides of benzoquinone fused with aromatic ring, then the formed molecule is called as anthraquinone. The many quinones are biosynthesized by acetate–malonate pathways, some from shikimic acid pathways, while few are generated by oxidative modification of secondary metabolites from a variety of other pathways (Seigler 1998).

The nitrogen-containing natural products include alkaloids, cyanogenic glucosides, and amino acids. The alkaloids are generally bicyclic, tricyclic, or tetracyclic derivatives of the molecule quinolizidine. The alkaloids are biosynthesized by amino acids (lysine, tyrosine, and tryptophan) and approximately found in 20% plant species of the plant kingdom (Glencross 2016). More than 12 000 alkaloids have been identified from 150 families of plants; alkaloids generally exist as salts of organic acids like acetic acid, malic acid, lactic acid, citric acid, oxalic acid, tartaric acid, tannic acid, and other acids. Some alkaloids are weak and basic in nature while few occur in glycosidic forms as solanine, piperine, and atropine. The alkaloids are used as pharmaceuticals, narcotics, and stimulants (morphine, quinine, codeine, etc.), and their lower doses are pharmacologically significant, while their higher doses may be toxic such as strychnine, nicotine, etc. (Richard et al. 2013). The alkaloids are very complex in their structure; they can be classified on the basis of set of parameters including features of their structure and pathways of biogenesis. They can be grouped as follows (Hussain et al. 2018): pyridine group (piperine, coniine, trigonelline, arecoline, arecaidine, guvacine, cytisine, lobeline, nicotine, anabasine, sparteine, pelletierine), pyrrolidine group (hygrine, cuscohygrine, nicotine), tropane group (atropine, cocaine, ecgonine, scopolamine, catuabine), indolizidine group (senecionine, swainsonine), quinoline group (quinine, quinidine, dihydroquinine, dihydroquinidine, strychnine, brucine, veratrine, cevadine), isoquinoline group (papaverine, narcotine, narceine, pancratistatin, sanguinarine, hydrastine, berberine, emetine, berbamine, oxyacanthine), phenanthrene alkaloids (morphine, codeine, thebaine, oripavine), phenethylamine group (mescaline, ephedrine, dopamine), indole group (serotonin, bufotenine, psilocybin, ergine, ergotamine, lysergic acid), β-carbolines (harmine, harmaline, tetrahydroharmine), yohimbans (reserpine, yohimbine), vinca alkaloids (vinblastine, vincristine), kratom alkaloids (mitragynine, 7-hydroxymitragynine), tabernanthe iboga (ibogaine, voacangine, coronaridine), strychnos nux-vomica (strychnine, brucine), purine group (xanthines, caffeine, theobromine, theophylline), terpenoid group (aconitine, solanidine, solanine, chaconine), and veratrum alkaloids (veratramine, cyclopamine, cycloposine, jervine, muldamine). The secondary metabolites are biosynthesized by three main pathways in plants – the shikimate pathway, the isoprenoid pathway, and the polyketide pathway. The shikimic acid pathway is the major pathway for synthesis of aromatic compounds. This pathway occurs in plants, normally manipulated for targeting the affectivity of antibiotics and herbicides, because this pathway does not occur in animals. The biological reaction of conversion of chorismate into the aromatic amino acids in plants catalyzed by chorismate mutase and anthranilate synthase enzymes. The phenylpropanoid pathway is followed by 20% of plants; the chorismate mutase is a key enzyme that regulates the whole reactions. The important compounds as lignans, alkaloids, flavonoids, and anthocyanins are synthesized by this pathway. The phenylalanine converts to *trans*-cinnamic acid by a non-oxidative deamination and the biochemical reaction catalyzed by phenylalanine ammonia lyase. The isoprenoid pathway is known for synthesis of terpenoids (Behenna et al. 2008; Brooker et al. 2008; da Rocha 2013).

Normally the secondary metabolites of medicinal importance are obtained from their respective plants by growing in the open fields or in green houses. The secondary metabolites extracted from the plant tissues but day by day, so many plant species are getting extinct. Similarly, the relative yield of secondary metabolites from plants is also low. In this context, the cell culture techniques may be explored as an alternative source for increasing the productivity of secondary metabolites (Kirakosyan and Kaufman 2002). The plant cell culture technology is more economically feasible in production of high-value secondary metabolites (paclitaxel, shikonin, atropine, etc.) from rare and/or threatened plants. The formation of valuable products in callus cultures can be optimized by developing suitable bioreactor configurations (e.g. disposable reactors) and the optimization of bioreactor culture environments for improvement yields and bioreactor operational modes (Georgiev et al. 2009). The hairy roots are developed by infection of wounded plants with *Agrobacterium rhizogenes*, which causes neoplastic growth by culturing transformed roots in hormone-free culture medium. The hairy roots produce higher amounts of valuable product than control roots (Pistelli et al. 2010). The accumulation of polysaccharides and phenolic compounds was threefold higher in hairy transformed roots of *Echinacea purpurea* than non-transformed roots (Wang et al. 2006). By application of genetic engineering, the *Atropa belladonna* plants were transformed to encode the enzymes converting L-hyoscyamine into L-scopolamine, and new plants were generated, which produced scopolamine as the major product (Liu et al. 2010; Zhang et al. 2004). Several research papers have already been published on genetic engineering of pharmaceutically important tropane alkaloids (Oksman-Caldentey and Arroo 2000). Therefore, plant cell manipulations can be used efficiently used in increasing the productivity of valuable secondary metabolites.

Part 2

Ethomedicinal and Pharmacological Properties, Chemical Structures, Culture Conditions of Secondary Metabolites

Secondary Metabolites of Medicinal Plants:
Ethnopharmacological Properties, Biological Activity and Production Strategies,
First Edition. Bharat Singh and Ram Avtar Sharma.

2.1

Abutilon Species

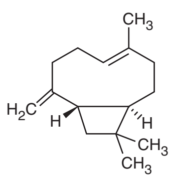
2.1.1 Ethnopharmacological Properties and Phytochemistry

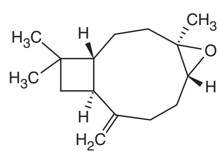
Abutilon indicum L. (Fam. – Malvaceae) aerial parts and roots have been used for treating inflammations, ulcer, diarrhea, pains, stomach ailments, diabetes, and wounds (Jayaweera 2006; Khare 2010; Ushakumari et al. 2012). Traditional practitioners used the plant to treat diseases like gout, tuberculosis, ulcer, jaundice, leprosy, gonorrhea, bronchitis, lumbago malarial fever, piles, dental problems, and other bleeding disorders (Algesaboopathi 1994; Yoganarsimha 2000; Muthu et al. 2006; Nisha and Rajeshkumar 2010). The grounded leaves of this plant species mixed with wheat flour are used for treating uterus in Indian system of medicine (Mohapatra and Sahoo 2008). There are reports of topical application of leaf paste on the spot of scorpion bite to relieve pain (Dinesh et al. 2013). Flowers of this plant are used by tribal population in Southern India to increase the concentration of semen in men (Ramachandran 2008). *Abutilon indicum* is found in tropical and subtropical regions of India–China and has therapeutic uses as febrifuge, anthelmintic, antiemetic, and anti-inflammatory and in urinary and uterine discharges, piles, and lumbago (Nadkarni 1954; Chopra et al. 1958; Subramanian and Nair 1972; Badami, et al. 1975; Gaind and Chopra 1976). Seeds are used in a decoction to treat cough (Yasmin et al. 2008). Ethyl acetate fraction of *Abutilon grandiflorum* showed antimalarial activity (Beha et al. 2004). *A. indicum* demonstrated hypoglycemic (Seetharam et al. 2002), anxiolytic (Tirumalasetty et al. 2011), antiulcer (Malgi et al. 2009), hepatoprotective (Porchezhian and Ansari 2005), antimicrobial (Poonkothai 2006; Edupuganti et al. 2015), anticonvulsant (Golwala et al. 2010), antidiarrheal (Chandrashekhar et al. 2004), antioxidant (Yasmin et al. 2010), antimicrobial, and anti-inflammatory (Tripathi et al. 2012; Kaladhar et al. 2014) activities (Abat et al. 2017).

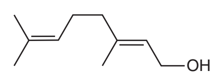
Gossyptin-7-glucoside, cyanidin-3-rutinoside, alantolactone and isoalantolactone, gossypetin-8-glucoside (Subramanian and Nair 1972; Sharma and Ahmad 1989), β-sitosterol, fatty acid esters of stearic and palmitic acid and flavonoids (Yasmin et al. 2008), β-amyrin 3-palmitate, squalene, β-sitosterol and stigmasterol (Macabeo and Lee 2014), fumaric acid, caryophyllene, caryophyllene oxide, geraniol, elemene, methyl indole-3-carboxylate,

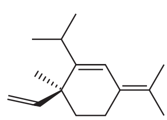
Secondary Metabolites of Medicinal Plants:
Ethnopharmacological Properties, Biological Activity and Production Strategies,
First Edition. Bharat Singh and Ram Avtar Sharma.

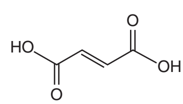
hinesol, cubenol, phytol, γ-sitosterol, lupeol, palmitic acid, 1-lycoperodine, 1-methoxycarbonyl-β-carboline, tetracontane, *n*-tetracosane, 3-hydroxy-β-damascone, 3-hydroxy-β-ionol, scopoletin, scoparone, methyl coumarate, *trans*-*p*-coumaric acid, abutilon A, quercetin, eugenol (4-allyl-2-methoxyphenol), syringic acid, benzoic acid, vanillic acid, gallic acid, *N*-feruloyl tyrosine, caffeic acid, *p*-β-D-glucosyloxybenzoic acid, 4-hydroxy-3-methoxy-*trans*-cinnamic acid methyl ester, methyl caffeate, *p*-hydroxybenzaldehyde, vanillin, syringaldehyde, 4-hydroxyacetophenone, methylparaben, β-sitosterol, stigmasterol, (*R*)-*N*-(10-methoxycarbonyl-20-phenylethyl)-4-hydroxybenzamide, *p*-β-D-glucosyloxybenzoic acid, *p*-hydroxybenzoic acid, and caffeic acid were identified from *A. indicum* (Gaind and Chopra 1976; Kuo et al. 2008; Pandey et al. 2011; Shanthi et al. 2011; Hussain et al. 2012; Khan et al. 2015). Similarly, pakistamide C has been isolated from the ethyl acetate-soluble fraction of the methanolic extract of *Abutilon pakistanicum* (Ali et al. 2014).

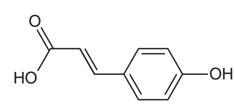

Caryophyllene

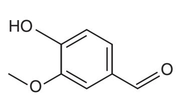

Caryophyllene oxide

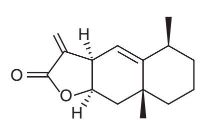

Geraniol

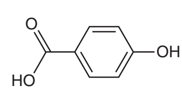

Elemene

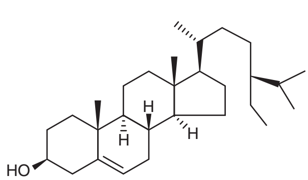

Fumaric acid

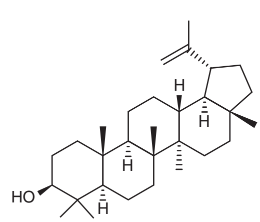

p-Coumaric acid

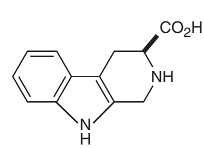

Vanillin

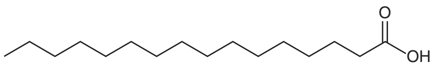

Lactones alantolactone


p-Hydoxybenzoic acid

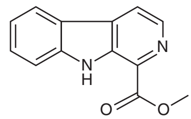

γ-Sitosterol


Lupeol

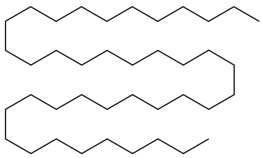

1-Lycoperodine



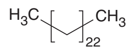
Palmitic acid



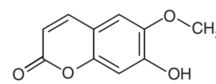
1-Methoxycarbonyl-β-carboline



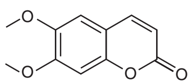
Tetracontane



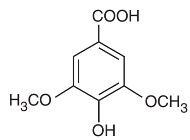
n-Tetracosane



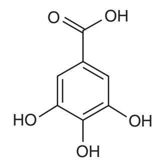
Scopoletin



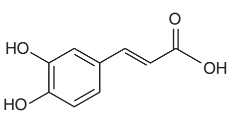
Scoparone



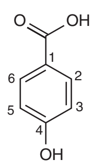
Syringic acid



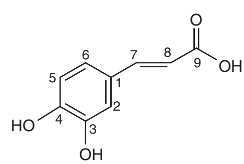
Gallic acid



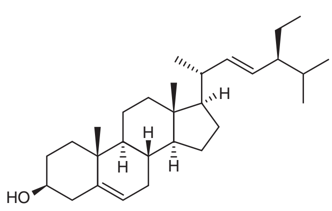
Caffeic acid



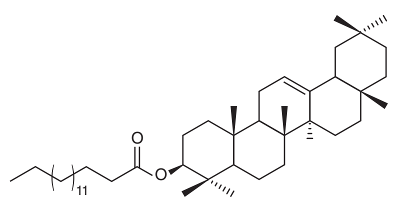
p-β-D-Glucosyloxybenzoic acid



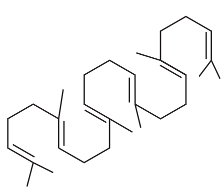
p-Hydroxybenzoic acid



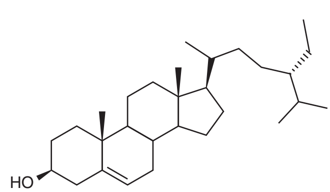
Stigmasterol



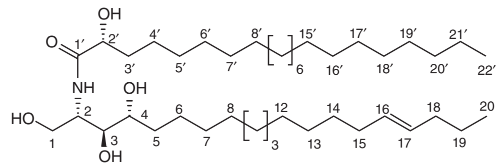
β-Amyrin 3-palmitate



Squalene



β-Sitosterol



Pakistamide C

2.1.2 Culture Conditions

The presence of scopoletin and scoparone has showed a unique pattern of accumulation with higher levels of scopoletin during the earlier stages and scoparone in the later stages of development. The calli contained the highest amount of coumarins followed by regenerated plants developed via somatic embryogenesis (Rao et al. 2016). The callus cultures were induced on Murashige and Skoog (1962) medium supplemented with 2,4-Dichlorophenoxyacetic acid (2,4-D) and kinetin. Flavonoids were found in all callus extracts in comparison with their natural habitat plant parts at various habitats. The secondary metabolites of flavonoid and phenolic acid contents of *A. indicum* were studied at dissimilar habitats and *in vitro* callus culture extract. Among these studies, plants from hills and wet soil habitat showed maximum secondary metabolites than those in the other habitats (Selvam et al. 2012). The supplementation of phenylalanine to callus cultures of *A. indicum* showed threefold increase in quercetin content as compared with control (Sajjalaguddam and Paladugu 2015).

References

Abat, J.K., Sanjay Kumar, S., and Mohanty, A. (2017). Ethnomedicinal, phytochemical and ethnopharmacological aspects of four medicinal plants of Malvaceae used in Indian traditional medicines: a review. *Medicines* 4: E75.

Algesaboopathi, C. (1994). Medico – botanical survey of plans in Kanjamalai hills of Salem, Tamil Nadu. *Anc. Sci. Life* 1: 112–116.

Ali, S.T., Mahmooduzzafar-Abdin, M.Z., and Iqbal, M. (2008). Ontogenetic changes in foliar features and psoralen content of *Psoralea corylifolia* Linn. exposed to SO_2 stress. *J. Environ. Biol.* 29: 661–668.

Ali, B., Ibrahim, M., Hussain, I. et al. (2014). Pakistamide C, a new sphingolipid from *Abutilon pakistanicum*. *Rev. Bras. Farm.* 24: 277–281.

Badami, R.C., Deshpande, G.S., and Shanbhag, M.R. (1975). Minor seed oils, VII. Examination of seed oils by gas–liquid chromatography. *J. Oil Technol. Assoc. India* 7: 76–77.

Beha, E., Jung, A., Wiesner, J. et al. (2004). Antimalarial activity of extracts of *Abutilon grandiflorum* G. Don – a traditional Tanzanian medicinal plant. *Phytother. Res.* 18: 236–240.

Behenna, D.C., Stockdill, J.L., and Stoltz, B.M. (2008). The biology and chemistry of the zoanthamine alkaloids. *Angew. Chem. Int. Ed.* 47: 2365–2386.

Berli, F.J., Moreno, D., Piccolo, P. et al. (2010). Abscisic acid is involved in the response of grape (*Vitis vinifera* L.) cv. Malbec leaf tissues to ultraviolet-B radiation by enhancing ultraviolet-absorbing compounds, antioxidant enzymes and membrane sterols. *Plant Cell Environ.* 33: 1–10.

Bhattacharya, A., Sood, P., and Citovsky, V. (2010). The roles of plant phenolics in defence and communication during Agrobacterium and Rhizobium infection. *Mol. Plant Pathol.* 11: 705–719.

Brooker, N., Windorski, J., and Blumi, E. (2008). Halogenated coumarin derivatives as novel seed protectants. *Commun. Agric. Appl. Biol. Sci.* 73: 81–89.

Buckle, J. (2015). Basic plant taxonomy, basic essential oil chemistry, extraction, biosynthesis, and analysis. In: *Clinical Aromatherapy Essential Oils in Healthcare* (ed. J. Buckle), 37–72. London: Churchill Livingstone.

Burak, M. and Imen, Y. (1999). Flavonoids and their antioxidant properties. *Turk. Klin. Tip Bilim. Derg.* 19: 296–304.

Castañeda-Ovando, A., Pacheco-Hernández, M.L., Páez-Hernández, M.E. et al. (2009). Chemical studies of anthocyanins: a review. *Food Chem.* 113: 859–871.

Chandrashekhar, V.M., Nagappa, A.N., Channesh, T.S. et al. (2004). Anti-diarrhoeal activity of *Abutilon indicum* Linn. leaf extracts. *J. Nat. Remedies* 4: 12–16.

Chopra, R.N., Chopra, I.C., Handa, K.L., and Kapoor, L.D. (1958). *Indigenous Drugs of India*. Calcutta: Dhur UN and Sons Pvt Ltd.

Croteau, R., Kutchan, T.M., and Lewis, N.G. (2000). Natural products (secondary metabolites). In: *Biochemistry and Molecular Biology of Plants* (eds. B.B. Buchanan, W. Gruissem and R.L. Jones), 1250–1318. Courier Companies Inc.

Davis, E.M. (2010). Advances in the enzymology of monoterpene cyclization reactions. In: *Comprehensive Natural Products II: Chemistry and Biology* (eds. H.-W. Liu and L. Mander), 585–608. Elsevier Science.

Demie, G., Negash, M., and Awas, T. (2018). Ethnobotanical study of medicinal plants used by indigenous people in and around Dirre Sheikh Hussein heritage site of South-eastern Ethiopia. *J. Ethnopharmacol.* 220: 87–93.

Dinesh, V., Kashinath Bembrekar, S., and Sharma, P.P. (2013). Herbal remedies used in the treatment of scorpion sting from the Nizamabad District, Andhra Pradesh, India. *Sci. Res. Rep.* 3: 2249–7846.

Edupuganti, S., Gajula1, R.G., Kagitha, C.S., and Kazmi, N. (2015). Antimicrobial activity of *Abutilon indicum*. *World J. Pharm. Pharm. Sci.* 4: 946–949.

Gaind, K. and Chopra, K. (1976). Phytochemical investigation of *Abutilon indicum*. *Planta Med.* 30: 174–185.

Georgiev, M.I., Weber, J., and Maciuk, A. (2009). Bioprocessing of plant cell cultures for mass production of targeted compounds. *Appl. Microbiol. Biotechnol.* 83: 809–823.

Giday, M., Asfaw, Z., Thomas, E., and Woldu, Z. (2003). An ethnobotanical study of medicinal plants used by the Zay people in Ethiopia. *J. Ethnopharmacol.* 85: 43–52.

Glencross, B. (2016). Understanding the nutritional and biological constraints of ingredients to optimize their application in aquaculture feeds. In: *Aquafeed Formulation* (ed. S.F. Nates), 33–73. London: Academic Press.

Golwala, D.K., Patel, L.D., Vaidya, S.K. et al. (2010). Anticonvulsant activity of *Abutilon indicum* leaf. *Int. J. Pharm. Pharm. Sci.* 2: 66–71.

Harborne, J.B. (1982). *Introduction to Ecological Biochemistry*, 2e. London: Academic Press.

Hussain, M.S., Fareed, S., Ali, M., and Rahman, M.A. (2012). Validation of the method for the simultaneous estimation of bioactive marker gallic acid and quercetin in *Abutilon indicum* by HPTLC. *Asian Pac. J. Trop. Dis.* 2: S76–S83.

Hussain, G., Rasul, A., Anwar, H. et al. (2018). Role of plant derived alkaloids and their mechanism in neurodegenerative disorders. *Int. J. Biol. Sci.* 14: 341–357.

Jayaweera, D.M.A. (2006). *Medicinal Plants (Indigenous and Exotic) Used in Ceylon*. Colombo, Sri Lanka: The National Science Foundation.

Kaladhar, D.S.V.G.K., Swathi Saranya, K., Vadlapudi, V., and Yarla, N.S. (2014). Evaluation of anti-inflammatory and anti-proliferative activity of *Abutilon indicum* L. plant ethanolic leaf extract on lung cancer cell line A549 for system network studies. *J. Cancer Sci. Ther.* 6.

Khan, R.S., Senthi, M., Rao, P.C. et al. (2015). Cytotoxic constituents of *Abutilon indicum* leaves against U87MG human glioblastoma cells. *Nat. Prod. Res.* 29: 1069–1073.

Khare, C.P. (2010). *Medicinal and Aromatic Plants*. New Delhi: CBS Publishers and Distributors.

Kirakosyan, A. and Kaufman, P. (2002). New strategies to produce high-value secondary plant metabolites from shoot cultures involving a sustainable photobioreactor system. In: *Natural Products in the New Millennium: Prospects and Industrial Application* (eds. A.P. Rauter, F.B. Palma, J. Justino, et al.), 375–388. Springer.

Kuo, P.-C., Yang, M.-L., Wu, P.-L. et al. (2008). Chemical constituents from *Abutilon indicum*. *J. Asian Nat. Prod. Res.* 10: 689–693.

Lee, Y.K., Yuk, D.Y., Lee, J.W. et al. (2009). (−)-Epigallocatechin-3-gallate prevents lipopolysaccharide-induced elevation of β-amyloid generation and memory deficiency. *Brain Res.* 1250: 164–174.

Lin, D.R., Hu, L.J., You, H. et al. (2010). Initial screening studies on potential of high phenolic-linked plantclonal systems for nitrate removal in cold latitudes. *J. Soils Sediments* 10: 923–932.

Lin, D., Xiao, M., Zhao, J. et al. (2016). An overview of plant phenolic compounds and their importance in human nutrition and management of type 2 diabetes. *Molecules* 21, pii: E1374.

Liu, X., Yang, C., Chen, M. et al. (2010). Promoting scopolamine accumulation in transgenic plants of *Atropa belladonna* generated from hairy roots with over expression of *pmt* and *h6h* gene. *J. Med. Plant Res.* 4: 1708–1713.

Ludwiczuk, A., Skalicka-Woźniak, K., and Georgiev, M.I. (2017). Terpenoids. In: *Pharmacognosy Fundamentals, Applications and Strategies* (eds. S. Badal and R. Delgoda), 233–266. London: Academic Press.

Macabeo, A.P.G. and Lee, C.A. (2014). Sterols and triterpenes from the non-polar antitubercular fraction of *Abutilon indicum*. *Pharmacogn. J.* 6: 49–52.

Malgi, R.A., Hullatti, K.K., Kuppast, I.J., and Singh, S.K. (2009). Antiulcer activity of *Abutilon indicum* (L.), sweet, leaf extract using different experimental models. *Int. J. Chem. Sci.* 7: 1011–1018.

Mohapatra, S.P. and Sahoo, H.P. (2008). An ethno-medico-botanical study of Bolangir, Orissa, India: native plant remedies against gynaecological diseases. *Ethnobot. Leafl.* 12: 846–850.

Morrison, R.T. and Boyd, R.N. (1973). *Organic Chemistry*, 3e. Boston, MA: Allyn and Bacon.

Murashige, T. and Skoog, F. (1962). A revised medium for rapid growth and bioassays with tobacco tissue cultures. *Physiol. Planta* 15: 473–497.

Muthu, C., Ayyanar, M., Raja, N., and Ignacimuthu, S. (2006). Medicinal plants used by traditional healers in Kancheepuram district of Tamil Nadu, India. *J. Ethnobiol. Ethnomed.* 2: 43.

Nadkarni, A.K. (1954). *Indian Materia Medica*. Bombay: Popular Book Depot.

Nisha, M.C. and Rajeshkumar, S. (2010). Survey of crude drugs from Coimbatore city. *Indian J. Nat. Prod. Resour.* 1: 376–383.

Oksman-Caldentey, K.M. and Arroo, R. (2000). Regulation of tropane alkaloid metabolism in plant cell cultures. In: *Metabolic Engineering of Plant Secondary Metabolism* (ed. R. Verpoorte), 254–281. the Netherlands: Kluwer Academic Publishers.

Pagare, S., Manila Bhatia, M., Tripathi, N. et al. (2015). Secondary metabolites of plants and their role: overview. *Curr. Trends Biotechnol. Pharm.* 9: 294–305.

Pandey, D.P., Rather, M.A., Nautiyal, D.P., and Bachheti, R.K. (2011). Phytochemical analysis of *Abutilon indicum*. *Int. J. ChemTech Res.* 3: 642–645.

Piel, J. (2010). The chemistry of symbiotic interactions. In: *Comprehensive Natural Products II: Chemistry and Biology*, vol. 2 (eds. H.-W. Liu and L. Mander), 475–510. Elsevier Science.

Pistelli, L., Giovannini, A., Ruffoni, B. et al. (2010). Hairy root cultures for secondary metabolites production. *Adv. Exp. Med. Biol.* 698: 167–184.

Poonkothai, M. (2006). Antibacterial activity of leaf extract of *Abutilon indicum*. *Anc. Sci. Life* 26: 39–41.

Porchezhian, E. and Ansari, S.H. (2005). Hepatoprotective activity of *Abutilon indicum* on experimental liver damage in rats. *Phytomedicine* 12: 62–64.

Ramachandran, J. (2008). *Herbs of Siddha Medicine/The First 3D Book on Herbs*. Chennai, India: Murugan Pathippagam.

Randhir, R., Lin, Y.T., and Shetty, K. (2004). Stimulation of phenolics, antioxidant and antimicrobial activities in dark germinated mung bean sprouts in response to peptide and phytochemical elicitors. *Process Biochem.* 39: 637–646.

Rao, K., Chodisetti, B., Gandi, S. et al. (2016). Regeneration-based quantification of coumarins (scopoletin and scoparone) in *Abutilon indicum in vitro* cultures. *Appl. Biochem. Biotechnol.* 180: 766–779.

Richard, T., Temsamani, H., Cantos-Villar, E., and Monti, J.-P. (2013). Application of LC–MS and LC–NMR techniques for secondary metabolite identification. *Adv. Bot. Res.* 67: 67–98.

Robles-Sanchez, R.M., Rojas-Grau, M.A., Odriozola-Serrano, L. et al. (2009). Effect of minimal processing on bioactive compounds and antioxidant activity of fresh-cut 'Kent' mango (*Mangifera indica* L.). *Postharvest Biol. Technol.* 51: 384–390.

da Rocha, C.A.M. (2013). Bioactive compounds from zoanthids (Cnidaria: Anthozoa): a brief review with emphasis on alkaloids. *Int. Res. J. Biochem. Bioinf.* 3: 1–6.

Sajjalaguddam, R.R. and Paladugu, A. (2015). Phenylalanine enhances quercetin content in *in vitro* cultures of *Abutilon indicum* L. *J. Appl. Pharm. Sci.* 5: 80–84.

Scott Obach, R. and Kalgutkar, A.S. (2010). Reactive electrophiles and metabolic activation. In: *Comprehensive Toxicology* (ed. C.A. McQueen), 309–347. Elsevier Science.

Seetharam, Y.N., Chalageri, G., Setty, S.R., and Bheemachar (2002). Hypoglycemic activity of *Abutilon indicum* leaf extracts in rats. *Fitoterapia* 73: 156–159.

Seigler, D.S. (1998). Benzoquinones, naphthoquinones, and anthraquinones. In: *Plant Secondary Metabolism* (ed. D.S. Seigler), 76–93. Boston, MA: Springer.

Selvam, K., Arunprakash, S., Selvankumar, T. et al. (2012). Antioxidant prospective and secondary metabolites in *Abutilon indicum* at different environment. *Int. J. Pharm. Sci. Res.* 3: 2011–2017.

Shanthi, K., Gowri, P., and Gopu, M. (2011). Pharmacognosy, analysis of bio-active compounds form *Abutilon indicum* Linn. (Malvaceae) by using gas chromatography and mass spectrometry (GC-MS) in ethanol and hexane solvent. *J. Pharm. Res.* 44: 4795–4797.

Sharma, P.V. and Ahmad, Z.A. (1989). Two sesquiterpene lactones from *Abutilon indicum*. *Phytochemistry* 28: 3525.

Sofowora, A. (1982). *Medicinal Plants and Traditional Medicine in Africa*. New York, NY: Wiley.

Subramanian, S.S. and Nair, A.G.R. (1972). Flavonoids of four malvaceous plants. *Phytochemistry* 11: 1518–1519.

Swanson, B.G. (2003). Tannins and polyphenols. In: *Encyclopedia of Food Sciences and Nutrition* (ed. B. Caballero), 5729–5733. London: Academic Press.

Tirumalasetty, J., Shankar, Nutalapati, C. et al. (2011). Evaluation of anti-anxiety property of alcoholic extract of *Abutilon indicum* leaves in albino mice. *Int. J. Pharm. Phytopharm. Res.* 2: 397–399.

Tolossa, K., Debela, E., Athanasiadou, S. et al. (2013). Ethno-medicinal study of plants used for treatment of human and livestock ailments by traditional healers in South Omo, Southern Ethiopia. *J. Ethnobiol. Ethnomed.* 9: 32.

Tripathi, P., Chauhan, N.S., and Patel, J.R. (2012). Anti-inflammatory activity of *Abutilon indicum* extract. *Nat. Prod. Res.* 26: 1659–1661.

Ushakumari, J., Ramana, V.V., and Reddy, K.J. (2012). Ethnomedicinal plants used for wounds and snake-bites by tribals of Kinnerasani region, A.P., India. *Pharmacogn. J.* 3: 79–81.

Vattem, D.A., Randhir, R., and Shetty, K. (2005). Cranberry phenolics-mediated antioxidant enzyme response in oxidatively stressed porcine muscle. *Process Biochem.* 40: 2225–2238.

Velderrain-Rodríguez, G.R., Palafox-Carlos, H., Wall-Medrano, A. et al. (2014). Phenolic compounds: their journey after intake. *Food Funct.* 5: 189–197.

Verpoorte, R. and Alfermann, A.W. (2000). *Metabolic Engineering of Plant Secondary Metabolism*. Dordrecht, the Netherlands: Kluwer Academic Publishers.