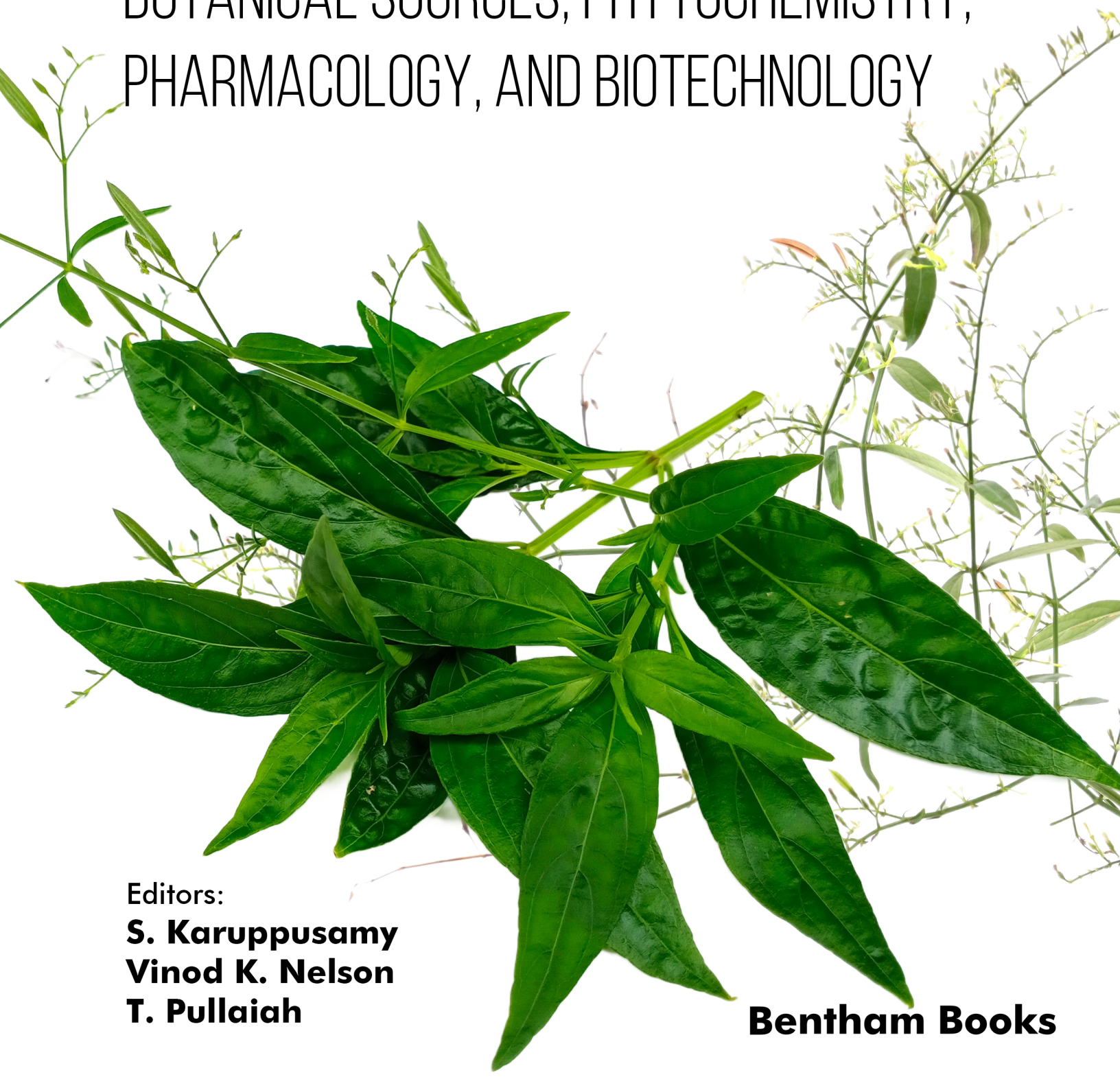
ANDROGRAPHOLIDE AND ITS ANALOGS:

BOTANICAL SOURCES, PHYTOCHEMISTRY, PHARMACOLOGY, AND BIOTECHNOLOGY



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Andrographolide and its Analogs: Botanical Sources, Phytochemistry, Pharmacology, and Biotechnology

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ISBN (Online): 978-981-5256-56-7

ISBN (Print): 978-981-5256-57-4

ISBN (Paperback): 978-981-5256-58-1

First published in 2024.

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PREFACE

In ancient days, human beings mainly depended on plants and plant-derived compounds for various kinds of treatments. In the intricate tapestry of nature's pharmacy, certain compounds emerge as hidden gems, offering a wealth of potential for human health and well-being. One such compound is andrographolide. This compound is well studied and has shown multiple pharmacological effects, such as anticancer, antidiabetic, antifungal, neuroprotective, cardioprotective, and hepatoprotective effects. Hence, we aimed to give a comprehensive review of andrographolide and its analogs in different aspects like chemistry, pharmacology, and biotechnology. The book "Andrographolide and its Analogs: Botanical Sources, Phytochemistry, Pharmacology, and Biotechnology" specifically provides updated information on medicinally important andrographolide and its analogs, sources from various species of *Andrographis* and its botanical identifications, traditional and ethnobotanical uses of *Andrographis* across the world by different cultures, phytochemical extraction and isolation methods, accounts on the pharmacological benefits of andrographolides, and experimental pharmacology of andrographolides against liver diseases and cancer. The book also focuses on biosynthesis, biotechnological production, bioavailability, and pharmacological actions of the andrographolide drug. The book concentrates explicitly on the current experimental research on molecular mechanisms of drug action and target-based drug delivery through phytonanomedicine. The book is a valuable reference source for cancer researchers, pharmacologists, phytochemists, biotechnologists, and those interested in the biomedical field who will benefit from this ready reference for working on andrographolide drugs. We thank all the contributors for their cooperation and erudition.

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CHAPTER 1

Andrographolides – An Overview

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Abstract: The genus *Andrographis* is usually bitter and is the source of several diterpenoids, of which water-soluble labdane diterpenoid is andrographolide. Among the various diterpene lactones reported from most of the species of *Andrographis*, andrographolide is considered one of the major bioactive secondary metabolites. The genus *Andrographis* possesses diverse phytochemical constituents with significantly interesting biological potentials. Diterpenes, flavonoids, xanthoflavones, iridoids, and other groups of miscellaneous compounds have been characterized from the various species of *Andrographis*. Andrographolide has been isolated as a notable major phytochemical compound among the andrographolides, which is a common diterpene flavonoid with phytochemical constituents and therapeutic activities.

Keywords: Andrographolide, *Andrographis*, Anticancer, Ethnobotany, Pharmacology, Propagation.

INTRODUCTION

Plant-derived phytochemicals hold a significant role in cancer drug discovery and chemotherapy, addressing numerous challenging human health problems. Remarkably, phytomolecules like vincristine, vinblastine, paclitaxel, camptothecin derivatives, and epipodophyllotxins have been instrumental in modern medicine. The quest for novel potential therapeutic natural compounds from higher plant sources for cancer treatment is ongoing, with numerous plant species continuously screened for discovering effective therapeutic molecules [1].

Andrographis paniculata (Burm.f.) Wall. ex Nees (Acanthaceae) is one such medicinal plant with a prominent position in the traditional healthcare system and

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modern drug development. It has been effectively used against cancer, diabetes, high blood pressure, ulcers, leprosy, bronchitis, skin diseases, flatulence, colic, influenza, dysentery, dyspepsia, and malaria across the globe [2]. *Andrographis* is a native of the tropical Asian genus and represents 26 taxa in India, of which 20 species are endemic to India; among these, 16 species are endemic to the Western Ghats. Most of the *Andrographis* species are native to Bangladesh, India, Myanmar, Nepal, Sri Lanka, and West Himalaya, mainly distributed in southern India and Sri Lanka, with the majority of the species confined to India except *A. panicualata* [3]. All the *Andrographis* species possess a common medicinal compound known as andrographolide.

Ethnobotany of *Andrographis*

Andrographis species, particularly *A. paniculata*, play a significant role in local traditional systems across several countries, including India, China, Bangladesh, Hong Kong, Pakistan, Philippines, Malaysia, Indonesia, and Thailand. These species are renowned for their therapeutic potential and are utilized for treating a variety of ailments, such as the common cold, diarrhoea, fever, jaundice, tumour, and cancer [4]. In India, *A. paniculata* is a crucial component of traditional medicinal systems like Unani and Ayurvedic medicine [5]. It is employed for managing conditions like snake bites, bug bites, diabetes, dysentery, fever, and malaria. The extensive use of this plant in traditional practices underscores its importance in primary healthcare, which is closely linked to its local abundance and the prevalence of seasonal diseases. Despite its widespread traditional use and the existence of commercial preparations from its extracts, there is a pressing need for standardizing these crude preparations [6]. Establishing phytochemical and pharmacological standards would significantly enhance the efficacy and reliability of these herbal medicines. Moreover, scientific standardization in terms of dosage, mode of administration, and accurate disease diagnosis is essential to validate traditional knowledge, particularly in developing countries. This would ensure the safe and effective use of *A. paniculata* and related species in contemporary medicine.

PHYTOCHEMISTRY OF ANDROGRAPHOLIDES

The genus *Andrographis* contains various phytochemical constituents with significant biological properties, including diterpenes, flavonoids, xanthones, iridoids, and other compounds. Among these, *A. paniculata* is particularly notable for its andrographolides, which are largely responsible for its therapeutic properties [7]. Other significant diterpenoids isolated from the aerial part of *Andrographis* include deoxyandrographolide, neoandrographolide, 20 different diterpenoids, and over 10 flavonoids [8, 9]. These diterpenoids and their glycoside

derivatives often share a similar carbon skeleton, which is reported from different *Andrographis* species. The key bitter compounds among them are andrographolide, neoandrographolide, isoandrographanolide, 14-deoxy 11, 12-didehydroandrographolide, and andrograpanin [10]. Some other major diterpenoids have been reported, such as deoxyandrographolide, neoandrogr-apholide, 14-deoxy-11,12-didehydroandrographide, and isoandrographolide. Four different xanthones *viz* ., 1,8-di-hydroxy-3,7-dimethoxy-xanthone, 4,8-dihydrox--2,7-dimethoxy-xanthone,1,2-dihydroxy -6,8-dimethoxy-xanthone, and 3,7,8-trimethoxy-1-hydroxy xanthone are isolated from the roots of *A. paniculata* [11]. Recent combinatorial chemistry libraries of major andrographolide analogs have been synthesised by tailoring the a,b-unsaturated c-butyrolactone moiety, the two double bonds D8 (17) and D12, (13), and the three hydroxyls at C-3 (secondary), C-14 (allylic) and C-19 (primary) positions [12]. In recent days, andrographolides and their derivatives have been effectively quantified by using HPLC coupled with a DAD detector.

PHARMACOGNOSY

The study on botanical pharmacognosy, especially focusing on the various parts of medicinal plants such as the stem, root, leaves, and other useful parts, is crucial for establishing quality control parameters for crude drugs. The utilization of macro and microscopic analysis, powder characteristics, quantitative measurements, and fluorescence standards of plant extracts help in identifying and authenticating plant drugs [13]. *A. paniculata* exhibits notable morphological and anatomical features. The leaves show eucamptodromous pinnate venation, which is characterized by veins curving towards the margin and not forming a continuous marginal vein. The upper epidermis lacks stomata, while the abaxial surface has diacytic stomata, where a small palisade ratio and less stomatal index are also noted. The presence of large cystoliths in both the upper and lower epidermis is a distinctive feature [14]. The stem of *A. paniculata* is quadrangular, with dense collenchyma strands located at the angles, providing structural support. Medullary rays are uniseriate, containing significant amounts of lignified fibres. There is an abundant deposition of calcium oxalate crystals in the epidermal tissues of the lamina, as well as in the ground tissues of the petiole and stem. Secondary xylem vessels of the root also show significant deposition of calcium oxalate, contributing to the diagnostic characteristic of the species [15]. The anatomical features are specific to *A. paniculata* and serve as diagnostic markers. However, similar detailed characterization for other species within the same genus or related taxa is often lacking. Establishing such standards for a wider range of species would enhance the identification and quality control of medicinal plants and their extracts, ensuring their authenticity and therapeutic efficacy.

CHAPTER 2

Botany of *Andrographis* Wall. ex Nees (Andrographinae: Acanthaceae)

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Abstract: The genus *Andrographis* Wall. ex Nees is recognized for its potential medicinal properties, playing a vital role in traditional and indigenous medicinal systems, particularly in India. It is used for treating various common ailments such as cold, fever, diarrhea, jaundice, cancer, and tumor. In addition, *Andrographis* is valued as a health tonic for fever and cardiovascular health as an antioxidant. Its applications extend to improving sexual dysfunctions and acting as a contraceptive. The therapeutic properties of *Andrographis* are primarily attributed to the major phytochemical andrographolide, although the composition of phytoconstituents can vary significantly among different species. These phytochemical variations are significantly influenced by geographical location, soil types, seasonal changes, and the specific time of harvest. The diversity in chemical composition highlights the importance of understanding the specific context and conditions under which *Andrographis* species are grown and harvested to optimize their medicinal efficacy. This chapter deals with the botany of andrographolide-yielding *Andrographis* species and their taxonomy, identification key, citation, description, and distribution for their availability and conservation.

Keywords: *Andrographis*, Distribution, India, Medicinal importance, Taxonomy.

INTRODUCTION

Andrographis Wall. ex Nees (Andrographinae: Acanthaceae) is a tropical herbaceous genus [1] native to Bangladesh, India, Myanmar, Nepal, Sri Lanka, and West Himalayas, mainly distributed in India and Sri Lanka. In India, it is represented by 26 taxa [2], of which 20 species are endemic [3]; among these, 16 species are confined to the Western Ghats [4, 5]. The current research and review provide a thorough examination of *Andrographis*, relying on a comprehensive field survey reported across their distributional range in India. The descriptions of the majority of species are derived from live collections. The short description, color photographs, distribution, and flowering and fruiting season details are provided here for easy identification and further study.

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Species of the genus *Andrographis* are vastly utilized, effective medicinal plants in the world, especially *A. paniculata*. Plants of this genus are used traditionally to treat a number of ailments like cold, cough, fever, jaundice, diarrhea, and cardiovascular and hepatic diseases in both codified and noncodified medicinal systems. They are also used against jaundice, liver complaints, stomach infections, and external tumors and as antioxidants. Species of this genus have a major medicinal chemical compound, andrographolide, which is responsible for their medicinal potential [6]. Recent studies showed that *A. paniculata* extracts have been proven experimentally against inflammatory and infectious diseases with significant results [7]. Andrographolide is a well-known compound from the genus *Andrographis* with promising therapeutic applications. Many aspects of its bioactivity and mechanisms of action remain to be fully understood. Andrographolide is a major and bioactive diterpene lactone isolated from most species of *Andrographis*, particularly from *A. paniculata*. The compound has garnered significant attention due to its pharmacological potential [8]. Therefore, it has attracted considerable attention in several drug discovery laboratories as a lead molecule that is potentially useful for identifying structurally and functionally novel drugs. This chapter summarizes the taxonomy, distribution, and availability of *Andrographis* species for andrographolide extraction and conservation.

TAXONOMIC TREATMENT

Andrographis Wall. ex Nees in Wall., Pl. Asiat. Rar. 3: 77, 116. 1832. *Neesiella* Sreem. in Phytologia 15: 270. 1967 non Schiffn., 1893. *Indoneesiella* Sreem., Phytologia 16:466.1968; *Andrographis* subgen. *Indoneesiella* (Sreem.) L.H. Cramer, Kew Bull. 51:555. 1996; Gamble, Fl. Madras 2: 1050. 1924; Mathew: Fl. Tam. Car. 1150.1993; Flw. Pl. Ind. 1: 1. 2009; Pullaiah *et al*., Fl. East. Ghats 4:385. 2011.

Herbs or rarely under shrubs; root stock woody; stem and branches terete or angular, glabrous or hairy. Leaves round, lanceolate, ovate, elliptic; apex acute, acuminate, round; margins entire, ciliate, glandular-hairy or revolute; base round, acute, cuneate, base obtuse, subcordate or rarely cuneate. Inflorescence elongate racemes, sometimes subpaniculate, racemes, paniculate, terminal panicles. Calyx lobes 5, glandular-hairy or glabrous, lanceolate or linear, glandular-hairy, pubescent, glabrous. Corolla glabrous, white, with a purple or pink tinge. Anthers bearded or not bearded, glabrous or villous, glandular-hairy. Capsules elliptic or ellipsoid, linear to oblong, glabrous or glandular-hairy, obtuse to attenuate at base, acute at the tip. Seeds ovoid, orbicular, narrowly elliptic to obovoid, rugose, base oblique or rounded, prominently pitted or not pitted, hairy or glabrous.

KEY TO THE SPECIES OF THE GENUS *ANDROGRAPHIS* IN INDIA

1a.. Capsules linear-oblong 2

1b. Capsules elliptic or ellipsoid 24

2a. Procumbent herbs or straggling herbs 3

2b. Erect herbs or undershrubs 8

3a. Racemes longer than 10 cm, many-flowered, unbranched 4

3b. Racemes shorter than 5 cm, few-flowered, little branched 5

4a. Racemes, both axillary and terminal, up to 11 cm long .....***A. rothii***

4b. Racemes always axillary, up to 14 cm ..... ***A. stenophylla***

5a. Inflorescence both axillary and terminal 6

5b. Inflorescence always terminal 7

6a. Racemes up to 3.8 cm long; leaves glabrous; capsules 1.5 cm long, 8-seeded .....***A. beddomei***

6b. Racemes scarcely 2.5 cm long; leaves villous; capsules 1.3 cm long, 4-seeded .....***A. glandulosa***

7a. Anthers conspicuously white-bearded; corolla pale, distinctly ventricose; anthers woolly at base ..... ***A. lobelioides***

7b. Anthers not at all bearded; corolla dark, not distinctly ventricose; anthers glaucous at base..... ***A. lowsoni***

8a. Flowers in elongate racemes, sometimes subpaniculate but the flowers distant 9

8b. Flowers in short racemes, paniculate, terminal, and slender axillary racemes 14

9a. Anthers bearded at the base, filaments more are less hirsute 10

9b. Anthers not bearded at the base, the filaments nearly glabrous 13

10a. Plant erect; leaves lanceolate, glabrescent above ..... ***A. paniculata***

CHAPTER 3

Ethnobotany of the Genus *Andrographis* Wall. ex Nees (Acanthaceae)

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Abstract: Various species of the Genus *Andrographis* are used in multiple tribal and community medicinal systems in India and adjoining countries for more than 20 different local ailments. *A. paniculata* is predominantly used for treating jaundice, liver diseases, fever, cardiovascular diseases, cancer, stomach problems, and common cold and as a blood purifier. This chapter gives an overview of the ethnobotanical uses of various species of *Andrographis* by several tribal communities and local inhabitants in almost all the states of India and other countries.

Keywords: *Andrographis*, Ethnomedicine, Fever, Jaundice, Liver diseases, Snake bites, Traditional medicine.

INTRODUCTION

Species of *Andrographis* Wall. ex Nees (Acanthaceae) are widely used worldwide to treat various human ailments. The plants of different species of *Andrographis* are used as a traditional herbal medicine in Bangladesh, China, Hong Kong, India, Pakistan, Philippines, Malaysia, Indonesia, and Thailand [1]. They are ethnobotanically used to treat snake bites, bug bites, diabetes, dysentery, fever, and malaria [2]. In the Unani and Ayurvedic medicines, *A. paniculata* is a mainly used medicinal plant [3]. Commercial preparations of this plant's extracts have recently been used in certain countries. However, the preparations need to be standardized for the better efficacy of pharmacological standards. The aerial part of *A. paniculata* is most commonly used for various ailments. Whole plant leaves and roots are also used as a folklore remedy for diseases in Asia and Europe [4]. The tribal communities primarily depend on the forest for their livelihood and primary healthcare needs [5]. Indigenous traditional knowledge is integral to local communities' folk culture and history. Ethnic people have rich indigenous conventional wisdom of using local vegetation to remedy and treat several local

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ailments. This knowledge includes the uses, beliefs, management systems, classification systems, and language that modern and traditional cultures attribute to their local ecosystem [6]. Amongst the genus *Andrographis*, *A. paniculata* is widely used for medicinal purposes and is also a pre-clinically and clinically well-studied species. It is a well-known Ayurvedic herb that is medicinally used in various traditional, folklore, unani and homeopathic medicinal systems in India, China, and Thailand [7]. In traditional Chinese medicine, *A. paniculata* treats "heat", especially in the lungs, throat, and urinary tract, and skin-related ailments, such as sores and carbuncles [8]. In China, the herbal formulation derived from the leaves or aerial parts of *A. paniculata* is Chuanxinlian, Yijianxi, or Lanhelian. It treats the common cold and is considered antipyretic, detoxicant, anti-inflammatory, and detumescent. *A. paniculata* is used for the treatment of pharyngolaryngitis, diarrhea, dysentery, cough with thick sputum, carbuncle, sores, and snake bites by the locals of China [9].

Andrographis paniculata extract has been used pharmacologically and experimentally, providing its traditional usage for rheumatoid arthritis, inflammation, cold, fever, and diarrhea [10 - 14]. The World Health Organization (WHO) published the monograph on *A. paniculata* in 2003 that mentioned the uses for prophylaxis and symptomatic treatments of respiratory infection, bronchitis, pharyngotonsillitis, urinary tract infections, and acute diarrhea. This plant species also has other traditionally known medicinal uses mentioned in pharmacopeia [15]. *A. panicaluata* is a multipurpose medicinal plant used widely in Southeast Asia for curing primary ailments, predominantly in remote village areas [16].

ANDROGRAPHIS IN THE INDIAN MEDICINAL SYSTEM

Ayurvedic system of medicine has long been widely practiced in India. In this system, *A. paniculata* is often used in combination with other herbs to treat diverse spectrums of organ pathologies and mental health problems. It is estimated that *A. paniculata* is used in more than 50 different herbal formulations commercialized in India for hepatoprotective treatments [17]. This herb is classified as Rasayana, which helps maintain the digestive system and regulate energy metabolism and immune functions [18, 19]. Rasayana herbs are now pharmacologically classified as herbal adaptogens or adaptogenic and anti-stress activity agents, which has also been proven in *A. paniculata* extracts. The leaves and roots have been used in Ayurvedic medicine as an adjunct treatment for cholera, diabetes, dysentery, enteritis, gastritis, malaria, pneumonia, pyelonephritis, and rabies. The leaf juice has been utilized as a tonic to relieve pain and stomach distress, expel parasites, promote bile flow, and reduce fever, as well as as an antiseptic, antispasmodic, and laxative. As a traditional household

remedy, the leaf juice is used for diarrhea, dysentery, dyspepsia, general debility, and loss of appetite. Two ayurvedic drugs, namely Kalmeghnamayas and Kalmeghashiva, are prepared from *A. paniculata*. Churnas such as Katu churna and Swetradiphala churna, which contain *A. paniculata* as a significant ingredient [20].

Andrographis is Mentioned in Pharmacopeias.

A. paniculata has been used in various medicinal systems, and this herb is mentioned in multiple pharmacopeias for treating several human ailments. These include pharmacopeias like *Indian Pharmacopoeia* (7th edition) [21], *Malaysian Herbal Monograph* (Volume 1) [22], *Medicinal Plants of Myanmar* (Volume 1) [23], *Pharmacopoeia of the People's Republic of China* [24], *Thai Herbal Pharmacopoeia* (Volume 1), *WHO Monographs on Selected Medicinal Plants* [25], and the *United States Pharmacopeia* (USP 37) [26].

Ethnobotany of *Andrographis* Species

A study documented the ethnomedicinal uses of the genus *Andrographis* in the Nilgiri Biosphere Reserve. Nine species of *Andrographis* were used to treat everyday ailments like colds, fever, poisonous bites, and skin diseases by hill tribes of Kotas, Irulas, Kaatunayakkas, Kurumbas, and Todas [27]. Ethnobotany of *Andrographis* is well surveyed in the Eastern Ghats of Tamil Nadu [28]. Tribal people residing in the Eastern Ghats of India used many species of *Andrographis* for treating various ailments like snake bites, colds, coughs, diabetes, fever, malaria, scabies, warts, and skin diseases [29].

Ethnobotany of *A. affinis*

A decoction of the whole plant is administered orally for snake bites, sugar control, and jaundice by the Kota tribes of Nilgiri Hills [27].

Ethnobotany of *A. alata*

The juice of the leaf is mixed with water, which is used to cure snake bites. Fresh leaf juice is given orally twice daily for four to six days for treating fever, diabetes, and diarrhea by Malayalis [30]. Leaf decoction is orally administered for snake bites, scorpion and centipede bites, and heavy fever like malaria and typhoid by Kurumba tribes of Nilgiri hills [27]. Leaf paste is externally used for poisonous bites by the Malayali tribes of Kolli Hills [31].

CHAPTER 4

Andrographolide and its Analogs

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Abstract: Andrographolide is a pharmacologically significant labdane diterpenoid primarily isolated from *Andrographis paniculata*, and later, from many of its allied species. *A. paniculata* is used in many Indian traditional and alternative medicinal systems for treating several human ailments. The phytochemical studies on species has yielded a number of diterpenoids and flavonoids, which have been screened for their pharmacological potential by various scientific groups. The results proved that andrographolides and their analogs have the potential to treat cancer and cardiovascular, hepatic, and various other diseases. In this chapter, the phytochemistry of *Andrographis* and the structure and properties of major andrographolides and their analogs have been reviewed.

Keywords: Andrographolide, anticancer, toxicology, phytochemistry, pharmacology.

INTRODUCTION

Andrographis paniculata (Acanthaceae) is an indigenous medicinal species of India, popularly called “Kalmegh”. Due to its bitterness, it is said to be a king of bitters among medicinal herbs. It is widely distributed all over the Indian states, Sri Lanka, and entire Southeast Asia [1]. *A. paniculata* is traditionally used for treating snake bites, poisonous stings, fever, diarrhea, jaundice, skin diseases, and respiratory problems by local communities in India. This plant species is a well-recognized ingredient in several Indian medicinal systems like Siddha, Ayurveda, Unani, and homeopathy and also in Chinese and Thai traditional systems for treating various human ailments [2 - 5]. The extracts obtained from various parts of *A. paniculata* have been reported to have several pharmacological properties like anticancer, analgesic, antidiabetic, anti-inflammatory, antimicrobial, antiviral, cardioprotective, hepatoprotective, and immunomodulatory [6 - 9]. While, in the extracts of herbs, a major class of phytochemicals such as diterpenoid lactones, flavonoids, phenolic compounds, and xanthones have been reported [10, 11]. The

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relationship between the chemical structure and biological properties was proved by applying modern prediction tools such as pharmacophore modeling and 3D QSAR analysis of andrographolides and their analogs [12].

Phytochemistry of *A. paniculata*

The extracts of *A. paniculata*have been phytochemically profiled with several compounds from various parts, including leaves, stems, and roots. Several traditional medicinal systems use specific parts of the herb due to the active compounds accumulated in the respective plant parts. The major phytochemical compounds isolated from *A. paniculata* are labdane diterpenes, such as andrographolide, which is a bitter alkaloid that accumulates in all the parts of the plant in various proportions. It is only responsible for the major pharmacological properties of the herb. The other class of compounds have also been reported in plants, including flavonoids, iridoids, polyphenols, xantholactones, and some macro-elements. However, andrographolide, a diterpenoid lactone, is a predominant phytochemical principle found in all the parts of *A. paniculata* in higher quantities than other compounds [13]. Some other terpenoid compounds, including deoxyandrographolide and neoandrographolide have been isolated from the aerial parts of *A. paniculata*. Some phytochemical experiments profiled 20 different diterpenoids and 10 flavonoid fractions from the ethanolic and methanolic extracts of various parts of *A. paniculata* [14, 15]. Andrographolide diterpenoids and oxyflavonoids are chemical signatures of *Andrographis,* which is used as a chemotaxonomic marker of the genus. A number of other diterpenoids with common chemical skeletons and stereochemical principles were isolated by the later exploration, including Angrographolide-A, B, C, D, E, and F, neoandrographolide, isoandrographolide, deoxyandrographolide and andrographanin [16 - 18]. Sometimes, these common andrographolide rings are associated with the xanthone group, which is another class of phytochemicals, including 1,8-hydroxy-3,7-dimethoxy-xanthone, 4,8-dihydroxy-2,7-dimethxy-xanthone, 1,2-dihyroxy-6,8-dimehtoxy-xanthine, and 3,7,8-trimethoxy-1-hydroxy-xanthone, and are also characterized from the roots of *A. paniculata* [19]. There are two major flavonoids, 5,7,2,3-tetramethaoxy flavone and 5-hydroxy-7,2,3-trimethoxy flavone, reported from the whole plant of *A. paniculata* [20]. The ethylacetate extracts of aerial parts and roots of *A. paniculata* were reported to have seven major flavonoids, including 7-0-methylwogonin, 1,2-dimethyether flavone, hydroxy tetramethoxy flavone, dihydroxy tetramehtoxy flavone, dihyroxy trimethoxy flavone, dihydroxy-0-methylwogonin, and dimethyl ether [21 - 23].

Phytochemistry of other Species of *Andrographis*

A. affinis

The whole plant extract of *A. affinis* has been isolated with two diterpenoids, andrographanin and 14-deoxy-11,12-didehydroandrographolide, and also three flavonoids, namely 5,7,2,3,4-pentamethoxy flavone, 5-hydroxy-tetramethoxy flavone, and echiodinin-glucopyranoside [18].

A. alata

It is also an endemic herb of Southern India, which is reported to be a source of andrographolide derivatives, including five acetylated flavones and two oxygenated glycopyranosides from the whole plant [24].

A. lineata

The whole plant extract of *A. lineata* fractioned three major flavonoids, including 2,3,4-pentamethoxy flavone, 2-hydroxy, 2,4,6-trimethoxychalcone, and dihydroskullcapflavone. In addition to this, known andrographolide stereomers and six other flavonoid fractions were also reported from the whole plant extract [14]. The phytochemical analysis of the leaf, stems and roots of *A. lineata* extracted with different solvents such as aqueous, ethanol, butanol, methanol and chloroform showed the presence of alkaloids, flavonoids, phenols, coumarins, glycosides, phytosterols, saponins, resins, tannins, terpenoids and steroids [25].

A. wightiana

It is also an endemic herb of Southern India. Three known labdane diterpenoids and two new acetylated diterpenoids including 14-deoxy-3,19-diacetyl-1-,12-didehydroandrographolide with flavones such as echioidinin, skullcapflavone, and 12-methy-ether were isolated from the whole plant extract [26].

Andrographolide

Andrographolide, a common chemical skeleton of labdane diterpenoids as 14-deoxy-11,12-didehydroandrographolide, is a major compound isolated from *A. paniculata*. This compound exhibits varying degrees of the pharmacological spectrum, including antiviral, antibacterial, hepatoprotective, cardioprotective, anti-inflammatory, and anticancer activities in *in vivo* and *in vitro* models. The structure of andrographolide contains a,b-unsaturated, c-butyrolactone moiety (primary, secondary, and allylic) with two double bonds and three hydroxyls at the C3 position, C14, C18, and C19, interacted with the a,b, c-butyrolactones, where the D rings, D12 and D13, with double bonds, interact with hydroxyl and

CHAPTER 5

Pharmacognostic Characterization of *Andrographis paniculata* (Burm. f.) Nees

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Abstract: *Andrographis paniculata* (Burm. f.) Nees is a well-known medicinal plant of the genus *Andrographis* belonging to the family Acanthaceae. This species is widely distributed throughout tropical and sub-tropical Southeast Asia, including India. This herb finds its place not only in the traditional systems of medicine but is also registered under Indian Pharmacopoeia. *A. paniculata* is bestowed with high therapeutic value and is used for the treatment of various ailments. This herb is adulterated with other species like *Andrographis echioides* and *Swertia chirayita* due to the lack of constant supply and less availability of *A. paniculata*. The herbaceous species possess apparent macroscopic similarities, and it is a tedious job to identify the actual raw drug. This chapter will provide in-depth knowledge of the pharmacognostical characterization of *A. paniculata*. Detailed macroscopic evaluation will help in the identification of the species in the field, and the comprehensive microscopic evaluation with the help of a transverse section will help delineate the species from its adulterant. The powder microscopic study will help in the identification of this medicinal plant, even in its

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powder form. The pharmacognostic standards put forward for the correct identification and authentication will prove to be a benchmark standard for this highly potent medicinal herb.

Keywords: Adulteration, Authentication, *Andrographis*, Andrographolide, Pharmacognosy.

INTRODUCTION

Andrographis paniculata (Burm. f.) Nees (AP) belongs to the family Acanthaceae. The other names of this plant are *Justicia latebrosa* Russell. ex Wall. and *Justicia paniculata* Burm.f [1]. *A. paniculata* is one of the biologically active medicinal plants broadly used in alternative medicinal systems in countries like India, China, and Sri Lanka [2]. The vernacular names of *A. paniculata* include Alui, Andrographids, Charita, Cherota, Kalmegh, Halviva, Sambilata, Sinta, and King of Bitters [3]. *A. paniculata* is an annual shrub with immense therapeutic value, and all parts of the plants are used to cure or prevent various diseases both in humans and animals [4]. *Andrographis paniculata* was traditionally used as an antipyretic agent, antibacterial agent, febrifuge, and bitter tonic and was used to treat gastrointestinal disorders, typhoid, and malaria [5]. This herb is used for curing influenza, swellings, itches, gonorrhea, general debility, dyspepsia, bronchitis, and snake bites. The decoction of leaves is the best medicine for infants for curing stomach ailments [6]. According to the Indian Pharmacopoeia, *A. paniculata* is the chief constituent of more than 25 Ayurvedic formulations, and because of its cold potency, *A. paniculata* is used to treat the common cold and fevers as a home remedy [7]. The recent literature points out that *Andrographis paniculata* possesses significant pharmacological activities, including anticancer, anti-inflammatory, antioxidant, hepatoprotective, antidiabetic, and cardioprotective activity [4]. Diterpene lactones are the important phytochemical derivatives of *A. paniculata* among such andrographolides held responsible for biological activity [8]. This plant has been subjected to a wide range of phytochemical, pharmacological, physiological, genetics, microbiological, and seed germination studies [7].

TRADITIONAL MEDICINE

AP has been used as a remedy to cure many diseases for centuries in Asian and European countries. In addition, it is also broadly used for healing purposes by various tribes and traditional practitioners as a folklore remedy in different parts of the world [9]. In Japan, Scandinavian countries, and traditional Thai medicine, it is commonly used to treat the common cold and fever [10]. In traditional Chinese Medicine, AP is widely used to cure diseases like snake bites, viral

infections, dysentery, and respiratory infections like pneumonia and pharyngitis. In the Unani system of medicine, AP is used to treat inflammatory diseases, abdominal infection, scabies, and other skin infections [3].

PHARMACOGNOSTIC STUDIES

The systematic study of crude drugs obtained from natural sources like plants, animals, and minerals is termed pharmacognosy. The pharmacognostical approach deals with the nomenclature, collection, cultivation, habitat distribution, and macro and microscopic studies of the physical and chemical constituents of their therapeutic actions and adulterations of the genuine drug. AP can be grown in all types of soils and is found in diverse habitats like plains, hill slopes, farms, sea shores, and dry and wetlands [11]. *Andrographis* is represented by 26 species that are distributed throughout the Indian subcontinent, with South India showing the highest diversity [12]. These species are also distributed in the tropical and subtropical regions of Asia, the Caribbean Islands, Malaysia, Myanmar, and Thailand [12]. Sometimes, *A. paniculata* is substituted with ' Chirata ' (*Swertia chiravita)* in the market, but it is originally called Kalmegh in Ayurveda preparations, although it possesses anti-malarial properties [13].

The microscopic detailing of the stem showed the presence of glandular and non-glandular hairs, acicular crystals in the phloem region, and ectophloic siphonostele [14]. AP is an annual shrub with branches that grow 90 to 110 cm in height. The leaves are green, simple, opposite, lanceolate, and glabrous, with a short petiole measuring about 3 to 7 cm in length and 1 to 2.5 cm in width. The stems are dark green, reaching up to a height of 0.5 to 1 m and 2 to 6 mm in diameter, with incidence of longitudinal furrows and wings on the angles of young plants. It has many small seeds and is yellowish-brown in color [3]. The powdered microscopy of *A. paniculata* reveals the presence of leaf epidermis with diacytic stomata and lignified fibers with sharp cells. The plant appears grayish black to grayish brown under normal vision and light yellowish to grayish brown under ultraviolet light [3, 15].

PHARMACOGNOSTIC FEATURES OF *ANDROGRAPHIS PANICULATA*

Macroscopic Characteristics

Andrographis paniculata is a herbaceous plant with a quadrangular, woody, glabrous stem that appears green in color and moderately hard with numerous armed branches that are quadrangular. The lower part of the stem gives out adventitious roots, which are thin and slender. The roots are greyish brown in colorfrom the outside with starchy white inside. They appear cylindrical, curved, and tapering, measuring about 6 to 20 cm in length (Fig. **1**). The leaves (5 to 10

CHAPTER 6

Pharmacology of Andrographolide and its Analogs: An Update

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Abstract: *Andrographis paniculata* (AP) is a traditional herb known as "king of bitters" and belongs to Acanthaceae. This plant is used traditionally to treat fever, sore throat, snake bites, and upper respiratory tract infections. The pharmacological effects exhibited by AP are actually due to the presence of several classes of phytocompounds. Among the numerous bioactive compounds generated by *Andrograpahis paniculata*, Andrographolide (AG) is the primary active phytochemical. This compound shows various biological functions, such as anti-inflammatory, anticancer, antimicrobial, neuroprotective, cardioprotective, and organ- and bone-protective activities. On the other hand, AG's structural analogs also showed various potent biological effects

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against different kinds of dreadful diseases. Hence, it is noteworthy to summarize the various pharmacological effects of AG and its analogs to help the researchers focus on this area. Therefore, in this chapter, we elaborated on various biological functions of AG and its derivatives; this review would be a standalone reference for AG's bio-actives and analogs.

Keywords: Andrographolide, Analogs, *Andrographis paniculata*, Bioactive compounds, Pharmacological activities.

INTRODUCTION

Andrographis paniculata (AP) is a traditional herbaceous medicinal plant placed under the family Acanthaceae. This plant is known as Kalmegh and King of Bitters because of its taste. Among the various species of this genus, *A. paniculata* is the primary and well-studied species. This plant species grows well on slopes, paths, and dams and in wet environments in different parts of Asian countries like India, China, Thailand, Malaysia, Myanmar, and Sri Lanka [1, 2]. From ancient times, this plant was traditionally used to treat diseases like jaundice, liver toxicity, cardiotoxicity, sore throat, and flu. Several studies also revealed that this plant extract can be used as a contraceptive in addition to its effects on various sexual disorders [3, 4]. In addition, for a very long time, the whole plant extract and the root extract of AP were recommended for treating various diseases. In earlier times, this plant extract was prescribed by various traditional medicine practitioners for treating diseases like pyrexia, fever, stomachache, intestinal problems, snake bites, dyspepsia, and aggravation [5]. The different kinds of pharmacological effects exhibited by *A. paniculata* extract were due to various classes of phytochemicals in the plant [6]. This plant mainly contains polyphenols, diterpenoids, alkaloids, and flavonoid compounds. Among the various bioactive compounds, andrographolide is the major phytocompound in terms of concentration and pharmacological properties [6]. This compound is highly bitter and belongs to the labdane diterpenoid class. On the other hand, the andrographolide analogs also show various health benefits in different kinds of disease conditions [3]. It was reported that 14-deoxy-11,12-didehydroandro-grapholide, an essential structural analog of andrographolide, possesses various pharmacological benefits like anti-infective, antiatherosclerotic, and immunomodulatory effects [7]. Besides, neoandrographolide also displays multiple biological functions, such as anti-inflammatory, antihepatotoxicity, and anti-infective [8]. In addition, 14-deoxyandrographolide also expresses promising pharmacological functions like hepatoprotective, cardioprotective, and immunomodulatory effects [9, 10]. Besides this, there are a few other minor structural analogs of andrographolide like andrograpanin, 3,19-isopropylidene andrographolide 14-deoxy-14,15-dehydroandrogr, andrographolide, and 14-acetyl

andrographolide [4]. These compounds also show significant benefits on cardiovascular, liver, and cancer health [4]. Other than this structural analog of AG, there are a few different compounds belonging to the flavonoid class, such as 7-O-methyiwogonin, apigenin, insulin, and 3,4-caffeoylquinic acid, which also show various biological functions like cardioprotective and hepatoprotective [11]. Hence, studying the andrographolide and its analogs in detail is noteworthy. This chapter reviewed AG's most significant pharmacological functions and analogs in detail. In this way, this review will become a standalone reference for the research in this area.

Pharmacological Active Compounds of *Andrographis paniculata*

The bioactive compounds in the AP are extracted from several parts of the plant, like the leaf, stem, and root. Among the various available classes of compounds, the diterpenoid compounds (major) were isolated from a methanol fraction of ethanol or methanol extract of the whole plant, leaf, and stem [6, 12]. In the diterpenoids, andrographolide is available in high concentrations like 4%, 1.2%, and 6% in the whole plant, stem, and leaf extract (Shown in Fig. **1**) [13]. In addition, the other essential diterpenoids like neoandrographolide, isoandrographolide, 14-deoxy-11,12-didehydroandrographide, and deoxy andrographolide were also isolated from the methanol fraction of the extract of various parts of the plant (Shown in Fig. **1**) [13]. Similarly, the flavonoid bioactive compounds like 5-hydroxy-7,8,2'-trimethoxyflavone, 5-hydrox--7,8,2',3'-tetramethoxyflavone, 5-hydroxy-7,8-dimethoxyflavone, 5-hydrox--7,8,2',5'-tetramethoxyflavone, 2'-methyl ether, and 7-O-methyl wogonin were separated from ethyl acetate fraction of the methanol or ethanol extract of the whole plant (Shown in Fig. **1**).

Pharmacological Effects of Andrographolide and its Analogs

The extensive use of the *Andrographis paniculata* plant and its parts in various traditional medicines for treating different diseases led the researchers to focus further on this plant to validate its pharmacological efficacy. Hence, the scientists further investigated this plant and found that this plant provides significant health benefits by promoting various pharmacological functions like anticancer, antioxidant, antiangiogenic, antihepatotoxic, antibacterial, antiprotozoal, antiviral, and immunomodulatory effects. Due to the enormous health benefits provided by AP, it is noteworthy to study the medicinal values of the phytocompounds available in this plant [14].

CHAPTER 7

Andrographolide and its Structural Analogs in Parkinson's Disease

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Abstract: Parkinson's disease (PD), a leading movement disorder, is instigated due to the progressive apoptosis of dopaminergic neurons in the substantia nigra pars compacta and due to exhausted levels of dopamine in the striatum of the brain. Currently, all treatments available for PD are palliative rather than curative. Researchers are still investigating the complex interplay of genetic and environmental factors that contribute to the development of PD. Natural product's renaissance is due to their ability to target multiple molecular pathways involved in the disease, as well as due to fewer side effects. A diterpenoid lactone compound, andrographolide, is found in the plant *Andrographis paniculata* and is commonly used in traditional medicine to treat various ailments. It has been discovered to have numerous biological activities, including antioxidant, anti-inflammation, anticancer, and neuroprotective effects. In preclinical studies, andrographolide has been shown to have neuroprotective effects in animal models of PD due to its high antioxidant potential, which can help reduce the impact of inflammation in the brain, and its ability to promote the survival and growth of dopaminergic cells. Several structural analogs of andrographolide have been studied for neuroprotective effects, including 14-deoxy-11-oxoandrographolide, 14-deoxy-11, 12-didehydroandrographolide (DDA), and 14-deoxy andrographolide (DA). Both DDA and DA are analogs of andrographolide that have been shown to have neuroprotective effects in animal models of PD disease. DDA is more potent than andrographolide in

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terms of neuroprotection. The anti-inflammatory and antioxidant properties of 14-deoxy-11, 14-deoxy-11, 12-didehydroandrographolide-19-oic acid (DDAA), and 7--Methyl-andrographolide were found to be more potent than andrographolide. On the other hand, andrographolide derivatives, such as 14-deoxyandrographolide, andrographolide epoxide, and andrographolide sulfonates possess potent anti-inflammatory and anticancer properties. Given that andrographolide and its structural analogs and derivatives have substantial therapeutic potential and have been proven to be neuroprotective, we intend to highlight this promising compound's role in PD disease.

Keywords: Andrographolide, Dopaminergic neurons, Parkinson's disease, Structural analogs.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopamine-producing neurons in the Substantia Nigra pars compacta (SNpc) region of the brain. The exact cause of PD is unknown, but it is believed to be a complex interplay of genetic and environmental factors. Other potential contributing factors include oxidative stress, neuroinflammation, and accumulation of alpha-synuclein, a protein that agglomerates in the brains of PD patients. The characteristics of PD include tremors that are most noticeable at rest and decrease with movement, the rigidity of the muscles, which causes stiffness and resistance to movement, bradykinesia that affects fine motor skills and overall mobility, and postural instability that can lead to falls. The symptoms of PD typically develop slowly over time and progress as the disease advances, leading to a decline in quality of life and decreased independence. Most cases are diagnosed in people over the age of 60, but it can happen at any age. Men are slightly more likely to develop PD than women. Family history also plays a role, with those who have a first-degree relative with the disease being at higher risk. Additionally, certain environmental factors, such as exposure to certain toxins or pesticides, may increase the risk of developing PD [1].

PD prevalence typically ranges from 100 to 300 per 100,000 people [2]. PD is still comparatively rare despite being the second-most prevalent neurodegenerative illness after Alzheimer's. However, the number of Parkinson's disease patients is expected to quadruple by 2030 as the population ages [3]. With age, the frequency of PD dramatically rises. It is uncommon before the age of 50, and both its incidence and prevalence increase steadily after that. According to a meta-analysis of prevalence studies, the prevalence increased from 107 per 100,000 people between the ages of 50 and 59 to 1087 per 100,000 people between the ages of 70 and 79 [2]. Males typically have PD at a rate of around 1.5 times that of females

[4 - 6]. This difference can be explained by X-linked genetic variables, more frequent occupational exposures in men, and neuroprotection from estrogens in women. Although the amount of the risk varied between studies, ranging from 1.26 to 3.79, most investigations discovered a considerably higher risk of mortality in PD cases compared with individuals free of illness of similar age and gender [7, 8]. According to inception cohorts that monitored incident PD cases, the estimated pooled mortality ratio was estimated to be 1.52 (95% CI: 1.23–1.88) with little heterogeneity, a 5% annual decline in survival for PD patients, and a mean median survival of 12.6 years from disease onset compared to 16.0 years in non-PD subjects. Longer follow-ups led to an increase in mortality ratios. There was no credible evidence that mortality declined after levodopa was introduced. Younger PD patients have a higher mortality risk than older PD patients when compared to age-matched PD-free controls [9, 10]. The severity of axial damage [11], the existence of dementia [12], and the decline in motor function all raise the risk of mortality. The three most significant causes of death in PD are heart disease, pneumonia, and stroke [13 - 17].

The current therapeutic strategy against PD primarily relies on restoring the optimum level of dopamine (DA) and its associated signaling pathways, for which levodopa or L-DOPA (L-3, 4-dihydroxyphenylalanine), a precursor of DA, is administered to PD patients [18]. L-DOPA provides an initial benefit by slowing disease progression; however, long-term benefits are unlikely [19]. Moreover, it is also administered in combination with carbidopa, a peripheral decarboxylase inhibitor. This helps alleviate the side effects of L-DOPA, mainly gastrointestinal and cardiovascular problems [18]. Another PD therapy strategy is using monoamine oxidase B (MAO-B) inhibitors. The activity of the MAO-B enzyme is increased on account of DA metabolism, which elevates oxidative stress and mitochondrial dysfunction [19]. Carbidopa decreases the amount of levodopa and prevents or lessens some of the side effects of levodopa medication, including nausea, vomiting, low blood pressure, and restlessness. Levodopa users should never stop taking it without first consulting a physician. Serious adverse effects from abruptly quitting the medication include becoming immobile or having trouble breathing. Levodopa is needed to improve symptoms. Unfortunately, all existing therapies are palliative rather than curative for PD.

Targeting Ionotropic Glutamate Receptors

It is not unusual that blockers of both classifications of metabotropic glutamate receptors have been investigated for neuroprotective potential, albeit with mixed results, given that both AMPA and NMDA receptors are found within the SNPC. Clinical trials have been conducted with NMDA (N-methyl-D-aspartate) receptor antagonists, including those that target receptors that contain the NR2B subunit.

CHAPTER 8

Neuroprotective Potential of Andrographolide (AG) and its Structural Analogs in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a brain disorder that usually has a chronic or progressive nature and results in a reduction in cognitive function that is more than what would be expected from the typical effects of the biological aging process, which is a significant cause of dementia. Even though tau and amyloid-β (Aβ) have been identified as the main components in the formation of tangles and plaques, respectively, there is still little known about the causes of Alzheimer's disease, and no effective treatments are available. It affects an estimated 40 million people worldwide, most of whom are over 60, and is expected to double every 20 years, at least until 2050. Most current efforts at therapeutic intervention are based on the hypothesized pathogenic mechanisms for AD. These include amyloids, inflammatory mediators, excitotoxicity, steroid hormone deficiencies, loss of cholinergic function, dietary fac-

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tors, oxidative stress, band g-secretase effectors, *etc*. Still, these therapies were neither completely effective nor safe for prolonged usage to check this problem. Various natural products have been tested. One such natural product is andrographolide (AG), which has several potential therapeutic benefits, including anti-inflammatory, immunomodulatory, and antiangiogenic properties. It is traditionally used for the treatment of various ailments. AG and its derivatives were found to be effective in the reduction of synaptic proteins associated with Alzheimer's disease by overturning the microglia-mediated growth of pro-inflammatory cytokines, and the research has shown that these compounds decrease amyloid beta aggregation and suppress the neuro-inflammatory response and synaptic dysfunction. In the current review, the therapeutic potential of andrographolide and its analogs is outlined, and its mechanism of action against this disease is examined to explore the possibility of AG for the prevention and treatment of AD.

Keywords: Alzheimer's disease, Andrographolide, Amyloid beta, Dementia, Neurodegenerative disorder.

INTRODUCTION

Dementia is a disorder that typically has a persistent or progressive nature and results in a fall in cognitive capability (*i.e*., the capacity for mental processing) further than what might be predicted from the usual effects of the biological aging process. Memory, thinking, direction, comprehension, computation, language, learning capacity, and judgment are all impacted. Consciousness is not affected. The impairment of cognitive function is frequently accompanied by fluctuations in mood, emotional stability, patterns of behavior, or motivation, but they can also happen before it [1]. One of the primary healthcare challenges of the 21st century is Alzheimer's disease, which is the leading cause of dementia. Three main groups of symptoms make up the chronic, progressive neurodegenerative disorder known as Alzheimer's disease. Memory loss, difficulty speaking and understanding, and executive dysfunction are all included in the first category of cognitive dysfunction. The second category includes behavioral and mental health issues, such as agitation, hallucinations, depression, and delusions, which are collectively referred to as non-cognitive symptoms; the third category consists of people who have trouble performing daily activities of living (considered “basic” for getting dressed and eating by themselves, *etc*.) [2].

In December 2013, the G8 declared that dementia should receive international attention and expressed their hope that a treatment or a cure would be readily accessible by 2025 [3]. Since tau and amyloid β (Aβ) were discovered to be the core elements of plaques and tangles, there has been significant progress in our understanding of molecular pathogenetic events; however, little is known about the causes of AD, and there is no cure. Aβ plaques and NFTs are the disease's two primary pathological markers. As per the amyloid cascade hypothesis, brain

dysfunction and neuronal death are brought on by the buildup of amyloid beta (Aβ) [4]. Furthermore, although the presence of Alzheimer's pathological changes is a requirement for diagnosis and is sufficient in some patients to cause symptoms, patients who develop symptoms after the age of 75 may have multiple causes [3].

Dementia affects an estimated 40 million people worldwide, most of whom are over 60, and is expected to replicate every 20 years, at least until 2050 [5]. AD is the 6th most common cause of mortality in the USA and the 5th most common cause of death for people over 65. Even though deaths from other leading causes have dropped significantly in recent years, the proportion of deaths related to AD has increased sharply. Heart disease, stroke, and prostate cancer deaths as a percentage of all deaths decreased between 2000 and 2008, while AD deaths as a percentage of all deaths increased by 66% [6].

In developing countries with young populations, the projected increase in dementia prevalence is significantly higher than in Western Europe and the USA, where the population is already far older. There are few accurate projections of the incidence of early-onset dementia and Alzheimer's disease (before age 65). Dementia affects fewer than one in 4000 people before they turn fifty, with AD accounting for about 30% of cases [7]. Around 800,000 people with AD live alone (1 in 7), and up to 50% of them lack a caregiver. Dementia patients who live alone are more likely to experience risks such as poor self-care, untreated medical conditions, malnutrition, falls, wandering off unattended, and accidental deaths than those who live with others [6].

Most current efforts at therapeutic intervention are based on the hypothesized pathogenic mechanisms for AD. These include the amyloid cascade, inflammatory mediators [NSAIDs], excitotoxicity (memantine), steroid hormone deficiencies, loss of cholinergic function, dietary factors, oxidative stress (antioxidant therapy), and band g-secretase effectors [8].

It has been discovered that cognitive dysfunction and the loss of cholinergic function are closely related. Inhibition of cholinesterase, postsynaptic cholinergic excitation with muscarinic agonists, precursors of choline, and stimulation of presynaptic cholinergic receptors with nicotinic agonists are some of the therapeutics that have been studied over the past 20 years [9].

It has been known since 1986 that nerve growth factor (NGF) infused into the rat brain stops basal frontal brain cholinergic neuron destruction, both naturally and after injury [10]. However, because the NGF protein cannot cross the blood-brain barrier (BBB), it has a short half-life and a significant impact on biological signals; it has proven difficult to deliver these neurotrophins effectively in the

CHAPTER 9

The Importance of Andrographolide and its Analogs in Prostate Cancer

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Abstract: One of the most common cancers in males is prostate cancer, which frequently appears later in life after 65 years. Prostate cancer is the second most frequent disease in men globally, according to the World Health Organization (WHO), with 1.3 million new cases identified in 2018. Although the composite molecular mechanisms that cause prostate cancer are still not fully understood, certain important

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factors have been identified. These include mutations in the androgen receptor gene and the tumor suppressor gene known as prostate cancer gene 1 (PCA1) or "BRCA1", which are linked to prostate cancer. Furthermore, overproduction of prostate-specific antigen (PSA) and changes in the concentrations or functions of particular proteins, such as cyclin-dependent kinase 4 (CDK4), function as indicators of prostate cancer and aid in its progression. Age, family history, ethnicity, food, obesity, and exposure to specific chemicals and hormones are risk factors. Depending on the stage of the disease and the patient's general condition, the main treatment options for prostate cancer include surgery, radiation therapy, hormone therapy, chemotherapy, immunotherapy, and active surveillance. Examining several strategies, natural products—especially those derived from plants—have shown signs of having anti-cancer qualities and are being researched as possible treatments for prostate cancer. Among these, andrographolide—a diterpenoid lactone compound—has attracted attention. It is extracted from the leaves of the *Andrographis paniculata* plant, traditionally used in Chinese and Ayurvedic medicine. Andrographolide and its analogs are being studied for their potential to treat a variety of malignancies, including prostate cancer, due to their well-known pharmacological actions, which include anti-inflammatory, anticancer, antiviral, and antioxidant qualities. Studies show that they have antiproliferative, pro-apoptotic, and antimetastatic properties in animal models and prostate cancer cell lines, suggesting they may be a valuable treatment for prostate cancer.

Keywords: Andrographolide, analogs, Antioxidants, Anti-cancer activity, Natural products, Prostate cancer.

INTRODUCTION

In 2018, prostate cancer (PC) was placed as the second most widespread cancer in men, after lung cancer. Approximately 1,276,106 new cases were reported every year, out of which, 358,989 deaths were noted, representing 3.8% of all cancer-related deaths in males [1]. Globally, the mean age at diagnosis for prostate cancer is 66, and both the death and prevalence rates of the disease show an age-related relationship [2]. Comparing African American men to their White counterparts, the prevalence of PC was 1.58%, and the fatality rate was nearly twice as high [1]. This discrepancy suggests that social, environmental, and genetic influences vary. By 2040, 2.2 million PC instances are predicted, and variations in death rates are projected [3].

Prostate cancer develops slowly in the early stages and advances silently. Its asymptomatic nature makes the treatment complex and unpretentious. Its symptoms include enlargement of the prostatic gland, increased frequency of urination, and nocturnal urination. As the disease progresses to the bone metastatic stage, urine incontinence and back pain are experienced by the patient. Prostate-specific antigen (PSA > four ng/mL), a glycoprotein that is generally expressed by prostate tissue, is often expressed at increased levels that aid in the

diagnosis of prostate cancer [4]. Tissue biopsy remains the primary method for confirming suspected cancer, even though individuals without cancer may exhibit elevated PSA levels. Unlike many other cancers, the cause of prostate cancer has been broadly researched and remains unclear. Renowned risk factors for PC include higher age, ethnicity, genetic variables, and a family history of cancer, and it is the primary cancer diagnosed in aged men [5]. Increasingly, older men are indeed being screened for prostate cancer as men live longer lives, and PSA screening has become more common. Prevalence rates of PC reveal notable discrepancies across different locations and populations. Globally, 1.2 million new PC cases were reported in 2018, constituting 7.1% of all malignancies among the male population [6]. The occurrence of PC considerably differs among countries. Oceania recorded the maximum age-standardized rate (ASR) at 79.1 per 100,000 persons, followed by North America (73.7) and Europe (62.1) [6]. On the contrary, the prevalence rates in Asia and Africa are relatively lower than those mentioned above, *i.e*., 26.6 and 11.5, respectively [6]. While there are noteworthy racial differences in the occurrence of PC, in the USA, White people have the second-lowest incidence, followed by Alaska Natives and Asian or Pacific Islander people [7, 8]. The frequency and fatality rates for PC are elevated among males of Afro-American descent [7]. This indicates that Afro-American men might hold definite genetic factors that raise their probability of developing prostate cancer mutations. Moreover, these mutations appear to be a more destructive form of cancer. The more prevalent 8q24 variants are known for enhancing the risk of PC among Afro-American men [9]. According to specific research, Afro-Americans cover most gene mutations that govern cell death, including BCL2, or inhibit malignancies, such as EphB2 [1, 10]. Afro-American inheritance is another factor related to hereditary and biological abnormalities, while insufficient surveillance and belated presentation cannot be ruled out. However, a 2007 study by Oliver found that Afro-Americans are notably less prone than Caucasian men to early diagnosis of PC [15]. Additionally, there is a noticeable disparity in prostate cancer mortality rates among the regions. In 2018, Central America reported the maximum death rate at 10.7 per 100,000, with Western Europe and Australia/New Zealand closely following at 10.2 [6]. In Asia, the mortality rates are diverse with regions: South-Central at 3.3, Eastern at 4.7, and South-Eastern Asia at approximately 5.4. Meanwhile, Northern Africa had the lowest mortality rate (5.8) compared to other areas. Asia contributed to 33.0% (118,427) of all prostate cancer fatalities; at the same time, Europe contributed 29.9% (107,315) [11].

About 20% of men diagnosed with PC have a previous family history indicative of the possibility of a potential connection to inherited genes, in addition to exposure to environmental toxins and universal lifestyle choices [1]. Research specifies that the hereditary genetic background contributes to 5% of the risk of

CHAPTER 10

Andrographolide and its Analogs in the Treatment of Lung Cancer: An Update

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Abstract: Lung cancer refers to the changes in the lung tissue and cells that lead to cancer growth due to gene mutations and cellular changes that result in uncontrollable cell growth and division. However, the exact pathophysiology of lung cancer is not yet fully understood. It is a significant cause of mortality worldwide and can be divided

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into two main types: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). The specific subtypes of NSCLC are adenocarcinoma, large-cell carcinoma, and squamous cell carcinoma. Risk factors for lung cancer include exposure to radon, smoking, air pollution, and a family history of lung cancer. Symptoms may include shortness of breath, chest pain, coughing, and weight loss. Early detection and proper treatment, including chemotherapy, radiation therapy, surgery, and targeted therapy, can improve the prognosis and survival rates. However, the deaths and the cases of lung cancer are constantly rising. This increases the need for potential drug treatment for lung cancer. Among the various available sources for identifying novel therapies for multiple diseases, such as cancer, medicinal plants and plant-derived compounds play a significant role. In addition, several studies revealed that *Andrographis paniculata* and its derived compounds have shown various pharmacological effects, including anti-cancer effects. Recently, andrographolide and its structural analogs have also gained attention in lung cancer due to their unique potential. Studies have shown that andrographolide and its analogs can restrict the development of lung cancer cells *via* the induction of apoptosis, a programmed cell death. They have also been shown to target specific signaling pathways that play a role in the development and progression of lung cancer, including the NF-kB and MAPK pathways. Additionally, andrographolide and its analogs have been shown to exhibit low toxicity, making them attractive as potential therapeutic agents for the treatment of lung cancer. Additional investigations are required to thoroughly understand these compounds' mechanisms of action and potential clinical applications in lung cancer treatment. In summary, andrographolide and its structural analogs have shown promising results in both *in vitro* and *in vivo* studies as potential therapeutic agents for lung cancer treatment. Their anti-cancer properties, including inhibition of cancer cell growth and induction of apoptosis, make them of significant interest for further research.

Keywords: Analogs, Andrographolide, Current treatments, Lung cancer, Risk factors, Targets.

INTRODUCTION

The battle against cancer is an enormous challenge. One of the deadliest and most prevalent malignant tumors around the globe is lung cancer [1]. Lung cancer is divided into two types: Small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [2]. SCLC constitutes 10 to 15 percent of all instances of lung cancer; it is characterized by an elevated rate of proliferation and rapid metastatic spread and is strongly associated with the use of products containing tobacco. One-third of SCLC patients are identified with limited-stage illness. Still, most patients suffering from SCLC exhibit extensive-stage (ES-SCLC) metastatic disease (stage IV); SCLC primarily responds extraordinarily well to chemotherapy, which is platinum-based, due to which few patients live for more than a few years. Still, the resistance to that develops quickly [3]. The remaining 85% of cases are affected by NSCLC. The three pathologic subtypes of NSCLC include adenocarcinoma, the most common kind, giant cell carcinoma, and squamous cell carcinoma. NSCLC is typically accompanied by generally poor

outcomes and a high significance of tumor recurrence [4]. In most nations, the most predominant neoplasm is lung cancer, which affects both men and women. According to Globocan 2020, across the globe, lung cancer holds 2nd place as a common type in terms of its incidence and the primary reason for mortality, with 22 lakh newly diagnosed cases and a mortality of 1.8 million [5]. Every day, approximately 350 individuals are killed by lung cancer, which accounts for 2.5 folds higher than colorectal cancer (CRC), as well as the death rate among lung cancer patients is higher than breast, pancreatic, and prostate cancers combined. It is anticipated that around 105,840 deaths, *i.e*., 81 percent of 130,180 lung cancer deaths in 2022, are attributed to smoking, with an additional 3650 mortalities due to passive smoking. It will become the 9th most common cause of cancer-related deaths if an extra 20,700 deaths related to non-smoking-related lung cancer are included separately [6]. While rates of localized-stage lung cancer grew by 4.5% every year, the incidence of advanced illness continued to fall dramatically. Localized-stage diagnoses increased from 17% in the early 2000s to 28% in 2018, and 3-year comparative long-term survival increased to 31% from 21% in 2018 [7]. Further, studies also projected that by 2030, the incidence of cancer is predicted to rise by 50%, with low-and middle-income nations bearing most of the burden [8].

The search for novel therapies and early disease diagnosis in oncology remains imperative despite recent scientific developments that have created new diagnostic and therapeutic techniques. Surgery, radiation, chemotherapy, targeted therapy, anti-microbial peptides (AMPs), immunotherapy, and combinations of these treatments are available for treating lung cancer. While chemotherapy is still the conventional first- and second-line treatment for lung cancer, significant advancements in the therapy and control of lung cancer were made by immunotherapy. Numerous researches have shown that the QOL and overall survival of patients with both preliminary and advanced lung cancer are improved by the usage of chemotherapy, either alone or in addition to other kinds of therapies. Despite the lack of general acceptance for surgery in SCLC, it is an option for tiny biopsy-proven tumors (very restricted disease). A tiny SCLC is most frequently discovered after a lung lesion of uncertain origin has been surgically removed. Surgery was not recommended in a systematic study for certain types of SCLC. Because SCLC spreads quickly and widely throughout the body, it is typically impossible to remove it through surgery. There are several adverse effects after surgery, with pain being the most significant constraint. The standard treatment for LD-SCLC, which aims to cure the disease, involves platinum-doublet chemotherapy of four cycles along radiotherapy. Even in elderly individuals, the overall survival rate is improved when using this treatment compared to chemotherapy. While the previous phase 3 trials preferred radiotherapy twice daily, a large number of patients did not meet the criteria for

CHAPTER 11

Anticancer Potential of Andrographolide and its Analogs in Colorectal Cancer: An Update

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Abstract: Colorectal cancer (CRC) is a highly prevalent and leading cause of death globally. Though well-developed treatment strategies are available, colorectal cancer is still a challenging health problem in developed and developing countries. Despite advanced treatment methods, all may not exterminate the tumor since most cases of CRCs are diagnosed at the last stage, and treatment-associated drug toxicity and resistance are major concerns. Therefore, it is imperative to discover anticancer drugs with less toxicity and no drug resistance. During the process of new drug discovery, medicinal plants and their derivatives play a significant role. This chapter/review

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explores andrographolides and their derivatives as potential anticancer drug candidates to combat colorectal cancer. This chapter describes the molecular mechanisms of colorectal cancer, potential drug targets in cancer, the anticancer potential of andrographolide derivatives in various malignancies, and its specific function in preventing CRC. This review provides concise information and possible clues for researchers to develop andrographolides, their derivatives and anticancer drugs to treat colorectal cancer.

Keywords: Anticancer agents, Andrographolide, Colorectal cancer, Potential targets.

INTRODUCTION

Cancer is an unpleasant disease among non-communicable disorders, and it rapidly deteriorates a person's health. Colorectal cancer (CRC) is a primary cause of death and ranks 3rd among various cancers globally. CRC develops in the inner lining layers of the colonic and rectal mucosa or musculature [1]. Different types of cancers are involved in colo-rectum, like mucus-producing cell adenocarcinoma, gastrointestinal stromal tumors, and carcinoid tumors. The Cancer Survey 2018 reports that CRC in males is 12.8%, and in females, it is 11.3%, which accounts for 700,000 deaths globally. The surveys have predicted that the incidence of CRS will be 3.2 million by 2040 [2]. The United States of America and China recorded the maximum number of CRC cases in 2020, with anticipated new cases increasing by 64% by 2040. However, in India, the incidence of CRC is minimal compared to other countries [3]. Recent WHO reports point out that the increasing speed of CRC occurrence has been an atrocious concern worldwide in the past decade; the triggering factors of this scenario are changing lifestyle factors like dietary habits [4]. The prevalence rate of CRC in Western countries is higher than in Asian countries and least in African countries [5]. The key risk factors involved in developing CRC include inflammatory bowel disease, decreased physical activity, obesity, consumption of alcohol and a diet with low fiber, vegetables, and fruits, and poor gut microflora maintenance. The additional contributory factors, including low socio-economic status, age, and race, determine a role in the progress of CRC [6].

Though well-developed treatment strategies are available, cancer is still a considerable health problem in both urbanized and underdeveloped countries [7]. The foremost action patterns of CRC include chemotherapy, immunotherapy, and surgeries. 5-Fluorouracil (5-FU) is used as an individual drug or combined with other anticancer medications like cisplatin, irinotecan, and capecitabine [8]. These treatment methods may not exterminate the tumor since most cases of CRC are diagnosed at the last stage with significant spread, which increases the mortality rate and economic burden on the families. Despite the advanced drugs available to

treat CRC, treatment-associated drug toxicity and drug resistance are primary concerns [9]. Therefore, it is imperative to discover anticancer drugs with less toxicity and no drug resistance; nevertheless, alternative therapies were explored less for such compounds.

Humans have been associated with plants and their derived materials for treating diseases since ancient times. Ethno-pharmacological reports on various medicinal plants are encouraged to investigate the suitable method of plant selection, isolation of its active principle, and calculation of therapeutic dose to establish and accomplish the benefits of these medicinal plants [10]. Several plant sources, secondary metabolites, and animal and microbial sources confirmed their essential medicinal properties and potential anticancer agents. They are being used in the current treatment strategies for CRC [11 - 13]. With the availability of a unique chemical library and insignificant toxicity, the medicinal plant and its metabolites promise a better alternative drug discovery source for treating dreadful diseases like cancer [14]. FDA disclosed that 40% of drugs have derived from natural origin or its derivative compounds; among those, 74% are merely approved for cancer treatment [15].

Andrographis paniculata (AP) is an inhabitant medicinal plant in India, Bangladesh, China, and Sri Lanka. It is widely practiced in alternative Indian Medicinal systems like Ayurveda, Siddha, and Unani to treat various ailments. *Andrographis paniculata* is called King of Bitters or Kalmegh and is prominent for its traditional or folklore uses, including as a bitter tonic, antipyretic, and febrifuge. It also treats malaria and various gastrointestinal disorders. Traditional Chinese medicine uses *Andrographis paniculata* to treat fever and as a detoxifying agent. At the same time, in Europe, the treatment of common flu is used as a home remedy [16 - 19]. Andrographolides and their derivatives are diterpenoid and terpenoid glycoside compounds of *Andrographis paniculata* with diverse biological actions, including anticancer activity. Chemically, the andrographolide is 3-alfa, 14, 15, 18-tetrahydroxy-5beta, 9beta H, 10α-lambda-8, γ12-dien-16-oic acid γ-lactone with a 350.4 g/mol of molecular weight. Among the identified molecules from AP andrographolide, deoxy andrographolide, 14-deoxy-11, 12-didehydroandrographolide, and neoandrographolide and their derivatives abide by pharmacological actions [20]. The important pharmacological activities of andrographolides include anticancer, bone metabolism, anti-inflammatory, immunomodulatory, anti-viral, anti-hepatitis effects, anti-arthritis, and neuroprotective actions [21 - 23]. The anticancer mechanisms of andrographolides are well-reported. These compounds can arrest the cell cycle and inhibit cytokine, NF-κβ, and angiogenesis [24].

CHAPTER 12

Andrographolide and its Analogs as Cardioprotective Agents

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Abstract: Myocardial infarction is a sudden and fatal disease that causes a significant number of deaths in the world. The current treatment strategy for MI is only for symptomatic relief and cannot cure or reverse the disease condition. Hence, there is a need to identify novel, definitive, and minimal toxic drugs to treat MI. Phytochemicals always draw attention as an alternative and upgraded choice to combat various ailments. Photochemical compounds are non-nutritive biologically active secondary metabolites abundantly found in plants. Andrographolide and its derivatives obtained from a medicinal herb, *Andrographis paniculata*, are broadly utilized in traditional medicinal systems to treat various diseases, including cardiovascular diseases. In the present chapter, we explore andrographolide and its derivatives for its cardioprotective potential both *in vitro* and *in vivo*. Andrographolides show their cardioprotective potential by demonstrating multiple mechanisms, including ERK1/2 inhibition associated with anti-platelet action, PI3K/Akt pathway-associated inflammation inhibition, and activation of Nrf-2/HO-1pathway-associated antioxidant mechanism. Cardioprotection of andrographolide and its derivatives are shown by various animal models' anti-arrhythmic, antihypertensive, anti-inflammatory, and antioxidant mecha-

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nisms. In this way, andrographolide and its derivatives can offer a better choice for developing a novel therapeutic molecule for myocardial infarction.

Keywords: Andrographolide, Antioxidant, Cardioprotection, Myocardial infarction, Nuclear factor erythroid 2-related factor (Nrf-2).

INTRODUCTION

Myocardial infarction (MI) is one of the foremost causes of death. Cardiovascular diseases (CVS) are responsible for approximately 17.9 million deaths each year, which accounts for 31% of all deaths worldwide [1]. Reasons for the increase in the prevalence and incidence of cardiovascular disease (CVD) in developing countries, particularly in urban areas, include changing lifestyles like the adoption of a Western diet (which is typically rich in saturated fats and refined sugars), alcohol and tobacco consumption, and sedentary lifestyle [2]. MI significantly occurs in young adults in South Asian countries, including India, Sri Lanka, and Bangladesh, than in individuals from other countries [3]. Pre-existing diseases like obesity, hypertension, diabetes mellitus, and dyslipidemia significantly contribute to the progression of myocardial infarction [4].

Myocardial infarction is the result of myocardial ischemia and rupture of atherosclerotic plaque, which is reported as the most common cause of acute MI [5]. In MI, there is an initial imbalance between the oxygen supply and demand, which leads to insufficient blood flow to the myocardium (myocardial ischemia) and a series of metabolic or pathological changes. These changes may cause irreversible damage to the heart muscle, lead to impairment in diastolic and systolic function, and make the patient prone to arrhythmias. The pathogenesis of MI includes hyperlipidemia, oxidative stress, peroxidation of membrane lipids, and loss of plasma membrane integrity.

Myocardial infarction is observed as an acute and chronic condition. In acute myocardial infarction, blood flow to myocardial muscles suddenly decreases due to any blockage, leading to muscle damage and elevation of troponin concentration. Chronic myocardial injury is characterized by persistent elevated troponin concentration due to myocardial necrosis [6].

In the last few decades, there has been a significant development in identifying interventions to protect the heart from myocardial infarction. These include the utilization of beta-blockers, calcium antagonists, and antioxidants and inhibition of the angiotensin-converting enzyme, although preventive therapy may lead to severe side effects or require high doses [7].

Numerous treatment approaches have been developed to prevent, treat, and attenuate the risk of myocardial infarction, but the majority of them have their limitations, like adverse effects [8]. Natural products have high universal demands due to their claimed advantage in terms of safety and efficacy against various diseases, including MI. However, most fail when shifted from the bench to the bedside [1]. Therefore, there is a need to find new drugs that are hostile to MI, can be used as suitable therapeutic candidates, and can be translated to clinical use in the future [9].

Chemical characterization of secondary metabolites or new chemical molecules from plants and animals provides a crucial scientific basis for identifying new drug discovery processes [10 - 12]. These compounds are essential for their physiological maintenance [13 - 15].

Pathophysiology of Myocardial Infarction

In myocardial infarction (heart attack), significant irreversible necrosis of the myocardium occurs due to prolonged ischemia. Events trigger MI increase in myocardial oxygen demand or decrease in oxygen supply to the myocardium. Initially, an imbalance between the supply of blood flow to the myocardium and its demand is the critical factor for the cause of myocardial infarction [16]. During myocardial infarction, erosion or rupture of lipids occurs, with loaded coronary atherosclerotic plaque upon its exposure to various factors, including hemodynamic changes, inflammation, and blood vessel injury [17]. This result in a highly thrombogenic core in circulation, which blocks the arterioles or tiny blood vessels to cause ischemia followed by hypoxia. These events typically lead to ST segment elevated myocardial infarction when the thrombus is occluded totally and non-ST segment elevated myocardial infarction (non-STEMI) or unstable angina if it is partially occluded [18].

During ischemic or hypoxic conditions, cardiac myocytes experience an inability to produce intracellular energy to meet their cellular metabolic requirements and eventually undergo necrosis and death. Inflammation is an essential factor in repairing and remodeling the infarcted heart. Chemokines play a vital role, like leukocyte trafficking, during inflammation and myocardial infarction repair [19]. Chemokines-mediated signaling processes uphold leukocyte integrin activation and promote the adhesion process between leukocytes and endothelial cells, which causes the liberation of inflammatory cells in the infarcted area [20]. The clinical manifestations of myocardial infarction range from mild nonspecific to life-threatening and depend on the severity of the attack and the immediate treatment to be initiated. Risk factors contributing to the development of myocardial infarction include social habits, smoking, alcohol consumption [21],

CHAPTER 13

Phytonanomaterials from *Andrographis* Species and their Applications

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Abstract: *Andrographis* (Acanthaceae) is a genus of 26 species native to India, mainly used for the treatment of snake bites, diabetes, fever, cholera, dysentery, gonorrhea, and malaria. Medicinal properties of *Andrographis* are attributed to the presence of phytochemicals such as andrographolide, neoandrographolide, 14-deoxy-11,-2-didehydroandrographolide, 14-deoxy andrographolide, isoandrographolide, 14-deoxy andrographolide 19 β-Dglucoside, homoandrographolide, andrographan, andrographosterin, and stigmasterol. Nanotechnology is a technique capable of achieving a high degree of precision in functions. By creating eco-friendly materials that can be applied to nanomedicine, plants have mediated the synthesis and fabrication of materials in nanotechnology. Mostly, silver nanoparticles biosynthesized using *Andrographis* species showed significant pharmacological activities *viz* ., antimicrobial, antioxidant, anti-inflammatory, antidiabetic, mosquito larvicidal, hepatocurative, and anticancer activity.

Keywords: Andrographolide, *Andrographis* species, Phyto-nanotechnology, Medicinal plants, Pharmacological activities.

INTRODUCTION

Nanoparticles are synthesized using various plant parts in phyto-nanotechnology. The simplicity and cost-effectiveness of this method have made it a non-conventional method that is gaining attention. Through the use of plant-mediated approaches to material synthesis and fabrication, eco-friendly nanotechnology has been developed for use in nanomedicine [1]. Solutes in plant materials are extracted using different solvents depending on the polarity of the bioactive molecules responsible for nanoparticle synthesis. Nanotechnology is a technique capable of achieving a high degree of precision in functions. This can be performed by controlling the reaction conditions of the molecules participating in

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the synthesis of the nanoparticles [2]. Nanoparticles derived from plants are produced using readily available plant materials. Nanoparticles with applications in biomedicine and the environment can be made from plants because of their non-toxic nature.

It has been thousands of years since people started using plants as medicine without proper guidance and scientific knowledge. There are several natural medicinal systems that use plants as medicine. Medicinal plants are now considered an essential source of treating various kinds of diseases. Each plant consists of several important ingredients that can be used in the field of medicine and can be involved in the discovery of drugs. Medicinal plants contain bioactive substances that have definite physiological effects on humans [3, 4]. Traditional medicinal systems are primarily based on herbal treatments. The healthcare system continues to rely heavily on plant-based traditional medicines. Scientific evidence reveals that every part of plants has medicinal properties, including flowers, roots, stems, leaves, fruits, and seeds [5, 6]. Plants have secondary metabolites called phytochemicals, which are active components with numerous therapeutic potentials (alkaloids, flavonoids, saponins, terpenoids, steroids, glycosides, tannins, volatile oils, and others). Additionally, some plants contain toxic compounds that cause adverse effects on the body, which is one reason why they are unsafe for health [7].

Andrographis (family Acanthaceae) is an important genus of 26 species native to India. The southern part of the Eastern Ghats comparatively possesses important ethno-medicinal plant species such as *Andrographis paniculata*, *A. echioides*, *A. serpyllifolia*, *A. lineata*, *A. glandulosa*, *A. affinis*, *A. viscosula*, *A. alata*, *A. nallamalayana*, *A. neesiana*, *A. stenophylla*, *A. ovata*, *A. elongata,* and *A. beddomei*. Only some species have potential medicinal values; while numerous medical systems use *A. paniculata*, including Ayurveda, Homeopathy, Siddha, Unani, and naturopathy [8]. *A. paniculata* is ethnobotanically used for the treatment of snake bites, bug bites, diabetes, influenza, cholera, swellings, dysentery, gonorrhea, fever, and malaria. The decoction is used as a blood purifier and to cure jaundice [3, 9]. *A. alata* and *A. lineata* are traditionally used for treating snake bites, constipation, skin diseases, and lung diseases. The leaf juice of *A. echioides* is used to cure fevers [10]. Leaves and stems of *A. serpyllifolia* possess potent anti-snake and scorpion venom activity. Its leaf extract has been proven to be a highly effective drug to combat bovine mastitis [11]. The phytochemical compounds present in *Andrographis* spp. exhibit different biological activities (Table **1**).

Table 1. Phytochemicals and biological activities of *Andrographis* spp.

Plant Used	Phytochemicals	Activity	References
A. paniculata	Andrographolide	Anti-diabetic activity	[12 - 14]
A. paniculata	Andrographolide	Anti-oxidant activity	[15 - 17]
A. paniculata	Andrographolide	Antiangiogenic activity	[18]
A. paniculata	Andrographolide	Anticancer Activity	[19]
A. paniculata	Andrographolide	Anti-hepatitis C virus	[16]
A. paniculata	Andrographolide	Cardiovascular activity	[15, 20]
A. paniculata	Andrographolide	Antagonistic activity	[21]
A. paniculata	Andrographolide, 14-deoxy andrographolide, 14 – deoxy 12 -hydroxyandrapholide and neoandrographolide	Quorum quenching activity	[22, 23]
		Anticancer Activity	[24]
A. paniculata	andrographiside	Hepato-protective activity	[25]
A. paniculata	19-O-acetyl-14-deoxy-11,12-didehydroandrographolide	Anti-inflammatory activity	[26]

Phytosynthesis of Nanomaterials from *Andrographis* spp.

Various nanoparticles such as silver, zinc oxide, gold, copper, neodymium oxide, lanthanum oxide, ytterbium oxide, and titanium oxide have been synthesized using the *Andrographis* spp. Pharmaceutics and biomedicines are likely to benefit greatly from these nanomaterials. Among different nanomaterials, silver nanoparticles, in comparison, showed significant pharmacological activities like antimicrobial, antioxidant, antidiabetic, mosquito larvicidal, hepatocurative, anti-inflammatory, and anticancer activity.

Andrographolide

As a dietary supplement widely used in herbal medicine because of its diverse biological activities, andrographolide is most abundant in the leaves and stems of *A. paniculata*. This compound has anti-inflammatory, anti-metastatic, anti-angiogenic, anti-proliferative, neuroprotective, and hepatoprotective effects [27]. An andrographolide crystal is a white square prism or flaky crystal made of

CHAPTER 14

Cultivation of *Andrographis paniculata* (Burm. f.) Nees

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Abstract: The present chapter provides different cultivation methods used to propagate *Andrographis paniculata* and other factors that regulate the growth and yield of the bioactive principles of andrographolides. The propagation of the Kalmegh is of two types: vegetative, utilizing stem cuttings, and sexual, through seeds. Much work has been done on the *in vitro* propagation of Kalmegh. The growth and quality of the plant are affected by the following factors: plant geometry, planting density and harvesting time, soil health, fertigation, shading level, endophytes, plant growth regulators, weeding control techniques, different accessions of seeds, plant density, co-cultivation, and aging. The available result revealed plots with 30 × 20 cm, cocopeat-RHA medium, and 50 ppm magnesium composition, and integrated use of chemical fertilizers, biofertilizers, and vermicompost treatments were optimum conditions for better yield. Among different seed cultivars, Pranchiburi cultivars showed a good percentage of germination and growth, and the highest andrographolide content was recorded at 135 DAP in the flowering stage. GA_3 treatment, 25% shading level, and co-cultivation with *Cajanus cajan* exhibited better yield and quality of *A. paniculata*. In dry storage, 1 to 3 months and 25°C temperature were recommended. Further works in vegetative propagation may bring out alternative and rapid multiplication methods for large-scale propagation of *A. paniculata*.

Keywords: *Andrographis paniculata*, Andrographolide content, Growth, Plant growth regulators, Seed cultivars, Vegetative propagation, Yield.

INTRODUCTION

Plant cultivation is accomplished through different propagation methods, *viz* ., sexual propagation and vegetative propagation. Sexual propagation includes seed propagation. It is a cost-effective and satisfactory method of plant propagation. Cuttings, layering, and grafting techniques execute vegetative propagation [1].

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Hydroponics and aeroponics are recent trends in agriculture technology, where plants are cultivated in soil-less cultures under controlled environmental conditions [2].

About 70,000 species of medicinal and aromatic plants are listed worldwide, of which 3,000 are commercially essential plants in trade. Of these, only 900 species are cultivated, and others are exploited from the wild. Annually, India contributes $ 150 million to the present global trade, which is scanty. India recorded 960 medicinal plants that were traded [3]. Among these, 178 species are needed in high volumes of more than 100 tonnes (dry weight) annual requirement. Out of these, only 36 species were cultivated for use. Medicinal and aromatic plants such as mint, basil, chamomile, isabgol, senna, ashwagandha, and opium poppy are cultivated successfully, and India is the largest producer and exporter of these plants [4].

Andrographis paniculata is a member of Acanthaceae and is commonly known as 'Kalmegh'. Various vernacular names also realize it. In north-eastern India, it is known as 'Maha-tita', which means 'King of bitters'. In Tamil, it is known as '*Nila Vembu*'. Among the 26 species of *Andrographis* distributed in tropical Asia, *A. paniculata* is the most popular medicinal plant. Plenty of work has been done to explore the chemical constituents and biological potentials of *A. paniculata* because of its tremendous medicinal importance. *A. paniculata* is mentioned in several countries, such as Materia Medica, and it was mentioned as a widely used medicinal plant in a WHO monograph intended to monitor quality control and herbal medicine usage [5, 6].

Due to the massive demand for *A. paniculata* and *A. paniculata*-based drugs, it is very important and necessary to conserve and cultivate this medicinal plant for sustainable utilization and future use. The tropical and subtropical plains are best for cultivation, and they require clay loam soil to fertile sandy loam soil and a partially shady environment for better growth and yield [7]. In the case of *A. paniculata* cultivation, seed propagation is the most commonly used technique [7, 8]. Vegetative propagation of *A. paniculata* is poor and done by shoot cuttings [9, 10]. Inter-crop cultivation, co-cultivation, integrated nutrient management, ratooning, and fertigation are different methods adopted for the large-scale cultivation of plants [11 - 13]. However, the quality of the plant product, such as the concentration and composition of its phytochemicals, is controlled and affected by different factors, including plant geography, season, soil type, soil health, microbial flora, plant parts, phenological growth stage, harvesting time, time of planting, density of plant growth, shading level, and weeds [14 - 21]. Hence, the present review aims to summarize and provide an idea about the different cultivation methods (Fig. **1**) used to propagate *A. paniculata* and other

factors that regulate the growth and yield of the bioactive principles andrographolides.

Fig. (1). Cultivation of *Andrographis paniculata* [Source: Global Information Hub on Integrated Medicinehttps://globinmed.com/conservation/hempedu-bumi-79366/**]**.

PROPAGATION OF *ANDROGRAPHIS PANICULATA*

Effect of NAA on the Vegetative Propagation of *A. paniculata*

Hossain and Urbi [9] assessed the effect of NAA on the adventitious rooting in shoot cuttings of *A. paniculata*. The slant cuttings were made, and basal cuttings were soaked in different concentrations of NAA at 0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 mM for 4 seconds without plant growth regulators as control. The cuttings were transferred to the planting tray after 10 minutes of soaking. For each treatment, three replicates were done, and the experiment was repeated twice. The treated cuttings were inoculated into peat moss in the planting tray and further incubated for 15 days under complete shade with temperature (25 ± 2° C) and relative humidity (80 ± 5%) for root induction. Water was sprayed once to moisten peat moss. The result showed that root characteristics of *A. paniculata*

CHAPTER 15

Micropropagation of *Andrographis* Species - A Review

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Abstract: The *Andrographis* of the Acanthaceae family is one of the potential sources for many pharmacological drugs with a wide array of essential phytochemicals. The present review summarizes the micropropagation of several *Andrographis* species viz., *A. affinis* Nees, *A. alata* (Vahl) Nees, *A. echioides* (L.) Nees, *A. lineata* Nees, *A. lobelioides* Wight, *A. macrobotrys* Nees, *A. neesiana* Wight, *A. paniculata* (Burm. f.) Wall. ex Nees, and *A. producta* Gamble. Nodal and shoot tip explants were suitable for *in vitro* shoot regeneration, whereas, for callus induction and indirect regeneration studies, cotyledonary leaf and hypocotyl segments were better choices as explants. The major surface sterilants used were alcohol (70%) and mercuric chloride (0.1-0.2%). Murashige and Skoog (MS) medium was the prime choice for *in vitro* regeneration studies of *Andrographis*.

Keywords: *Andrographis*, Acanthaceae family, *In vitro* regeneration, Micropropagation, Phytochemicals, Surface sterilants.

INTRODUCTION

Andrographis – A Medicinal Genus

Andrographis is a crucial medicinal genus of Acanthaceae with 26 species native to India [1]. *Andrographis* spp. possesses some chief phytochemical compounds like andrographolide, neoandrographolide, 14-deoxy-andrographolide, 14-deox--11, 12 -didehydroandrographolide, andrographolide, and serpyllin accountable for several biological and pharmacological activities [1]. *Andrographis* spp. are well known for their pharmacological activities. Their major activities include antidiabetic, anti-inflammatory, antimicrobial, anticancer, anti-venom, antioxi-

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dant, antipyretic, antifertility, anthelminthic, immunomo-dulatory, antiviral, and hepatoprotective [1]. This work aimed to compile several micropropagation works accomplished by various researchers on different *Andrographis* species. The *Andrographis* species to be reviewed are *Andrographis affinis* Nees, *Andrographis alata* (Vahl) Nees, *Andrographis echioides* (L.) Nees, *Andrographis lineata* Nees, *Andrographis lobelioides* Wight, *Andrographis macrobotrys* Nees, *Andrographis neesiana* Wight, *A. paniculata* (Burm. f.) Wall. ex Nees, and *Andrographis producta* (C.B.Clarke) Gamble.

Need for Micropropagation

Plant conservation is an excellent strategy for preventing plants from extinction and maintaining their status in the ecosystems. Increasing commercial and pharmacological demands for these natural resources have degraded their habitats and created a threatened status in this environment. Further, the reproductive status of many plants undergoes various natural and anthropogenic barriers that lead the way toward sterility. Seed and vegetative propagation were influenced by many internal and external factors like predation, desiccation, pathogenic activities, extended dormancy, unfavorable seasons, *etc* [2]. The distribution of *A. lineata* by natural propagation through rootstocks and seeds was restricted due to biotic pressure such as cattle grazing, forest fires, *etc* [3]. Most of the species reported are endemic, but their need in pharmacological aspects is inevitable, so conservation becomes a significant challenge. Overcoming such adversity in conservation and large-scale propagation with minimum period and small area *in vitro* micropropagation can be a better alternative.

Need for Updation in Micropropagation.

Micropropagation is a revolutionary technique for the prompt multiplication of plants [4]. Micropropagation is the large-scale propagation of true-to-type propagules throughout the year in varying climates and with minimized time and space [5]. Micropropagation is an efficient, proven method for commercially exploiting aromatic and medicinal plants [6]. High-quality plant-based medicines can be tremendously achieved through plant tissue cultures *via* micropropagation. The documentation of various advantages of micropropagation over other conventional methods was executed [7]. Some significant benefits are the extensive propagation of plants from a single explant in a short time and space; species can be micropropagated throughout the year. Pathogen-free plant production, increased multiplication rate, and meristem culture yield genetically identical plants, secondary metabolites production, *etc* [7]. Micropropagation is an alternate method to propagate and conserve medicinal plants by selecting high-

yield lines and their efficient cloning. The above-stated works have strongly endorsed that micropropagation can be an alternative to conventional vegetative propagation [7].

MICROPROPAGATION- *ANDROGRAPHIS* SPP.

Explants and Surface Sterilization

Micropropagation works on different *Andrographis* species were studied, and the explants used in these works were given as a compilation. On an MS basal medium, 94 percent of *A. paniculata* seeds germinated within five days of inoculation. Within fifteen days, the seeds had grown into plantlets [8]. Following that, explants from these plantlets were utilized. Pods, leaves, and nodal segments were surface sterilized by first washing them under running tap water for 20 minutes to remove adhering particles such as dust and soil, then rinsing them with a 0.1 percent (v/v) aqueous solution of Tween 20 for 30 minutes. To completely eradicate microbiological contamination over the surface, the samples were rinsed with 70 percent ethanol solution for 2-3 minutes, followed by treatment with 1.2 percent sodium hypochlorite solution (chlorine bleach) for 5-7 minutes. To reduce the effect of chlorine bleach on living plant tissues, all samples were immediately rinsed four times with sterile autoclaved distilled water. After the pods had been sterilized, they were dried on sterilized blotting paper and gently dissected with tweezers to expose seeds for micropropagation. The damaged ends of the leaflets were cut off with a knife. Using a knife, the outer covering of nodal buds and the ends of nodal segments were also removed [9]. Elongated shoots (20-40 mm long) were obtained from Kalmegh plants growing in the field, brought to the lab with the cut ends immersed in distilled water, and then washed in a 2% (w/v) Teepol solution. Surface sterilization was also performed for 5 minutes in a 0.1% (w/v) mercuric chloride solution. The stem (1 to 1.2 cm in length) and leaf segment (2.5 mm 2) were utilized as explants after cleaning the trice with sterile distilled water [10].

For multiple shoot regeneration of *A. paniculata*, shoot tips and nodal segment explants were cultured on MS medium supplemented with varying concentrations of BAP, Kn, and NAA alone or in various combinations [11]. Purkayastha *et al*. [8] devised a speedy and efficient approach for large-scale propagation of *A. paniculata*, using *in vitro* culture of nodal explants obtained from 15-day-old aseptic seedlings. In nodal explants cultivated on MS media supplemented with BAP, high-frequency direct shoot growth was observed. BAP was one of the most efficacious cytokinins (BAP, Kn, TDZ, and 2-iP) examined. The shoot-generating capacity of the nodal explants was impacted by the BAP concentration (1–12.5 M), with 10 M BAP producing an average of 34 shoots in 94% of the cultures

CHAPTER 16

In vitro Production of Medicinally Potential Andrographolides from *Andrographis* Species

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Abstract: *Andrographis* L. (Acanthaceae) is a vital genus that produces the most potential secondary metabolites, such as labdane diterpenoids called andrographolides. Pharmaceutical requirements for andrographolides are sustained through habitat collection and limited cultivation of *Andrographis paniculata*. However, in India, the genus is represented by about 26 species distributed in the southern Peninsula, most of which are endemic to the region. Commercial exploitation for andrographolide extraction is met with *A. paniculata* alone. The low rate of seed production in this plant and enormous variation in andrographolide content were found in the natural population. Tissue culture techniques help us to produce commercially viable andrographolides on a large scale. The present review analyzes the alternative sources of andrographolides from diverse species of *Andrographis*. Also, the review describes *in vitro* culture of callus and suspension cultures, the development of adventitious and hairy root cultures, the addition of biotic and abiotic elicitors for enhancing andrographolide production, and also the production of valuable compounds by utilizing bioreactors, *Agrobacterium*-mediated transformation, and genetic engineering for increasing biosynthesis of andrographolides.

Keywords: Andrographolide, *Andrographis paniculata*, *In vitro* production, Plant tissue culture, Secondary metabolite.

INTRODUCTION

Secondary plant products are low molecular weight compounds with significant pharmaceutical potential. Besides using them as food, humans are constantly exploring and exploiting these natural plant products for use as medicines, cosmetics, dyes, flavors, and food. *Andrographis* (Acanthaceae) comprises 26 species predominantly native to India [1]. This genus displays high diversity, particularly in Peninsular India and the Himalayas, with many species endemic to India. This genus, *Andrographis*, has been highly integrated with the maintenance of the human healthcare system since time immemorial. Several of these species

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are extensively used in ethnomedicinal systems in tribal areas of Western Ghats [2]. Many of the species of *Andrographis* found in India are used in various industries and form an integral part of the traditional system of medicine. The critical compound andrographolide varies within different plants and by geographical location. In wild and conventionally propagated plants, the andrographolide content is typically around 2-3% based on fresh weight. The traditional propagation method through vegetative means needs to be improved to meet the pharmaceutical industry's demand, leading to reliance on wild plants. Variations of phytochemical contents in the wild population and delayed rooting response of seedlings may affect the propagation of this plant only through the seeds [3, 4]. The ever-increasing demand for andrographolides in the pharmaceutical market solely depends on extracting drugs from wild-grown plants. This overharvesting poses a risk of extinction. However, commercial exploitation of andrographolide is hampered due to the limited availability of wild-grown plants [5]. The substantial demand for andrographolide in Indian and international markets has been increasing through commercial cultivation by Indian farmers. Several medicinal potentials of *Andrographis* include carminative, febrifugal, anthelmintic, antirheumatic, antidiabetic, antihyperglycemic, antipyretic, anti-inflammatory, antinociceptive, and antioxidant effects [6]. Sustainable production methods are crucial given the high demand and limited availability of wild plant sources. *In vitro*, producing valuable secondary metabolites using biotechnological methods is a viable alternative for maintaining natural diversity and continuously utilizing plant drugs. In recent decades, *in vitro* techniques have been extensively used to produce secondary metabolites [7] commercially. These techniques used bioreactor, biotic and abiotic elicitors, and cell immobilization for scaling up the production of natural compounds [8]. However, bioreactor trials fail to yield the desired quantities of target compounds due to a lack of understanding of biosynthetic pathways and mechanisms. Enhancing productivity involves overcoming the limitation of precursor availability by adding specific additives to cultured cells or organs. Techniques such as elicitation, immobilization, and metabolic engineering can improve phytocompound production.

SOURCES OF ANDROGRAPHOLIDE – *ANDROGRAPHIS* SPECIES

Andrographis comprises 43 species globally, with 26 species in India [9]. In the southern parts of Eastern Ghats, more than ten species of *Andrographis*, including *A. affinis*, *A. alata*, *A. beddomei*, *A. elongata*, *A. echioides*, *A. glandulosa*, *A. lineata*, *A. ovata*, *A. paniculata*, and *A. serpyllifolia*, are distributed. Among these, *Andrographis paniculata* holds significant potential traditional medicinal value due to its broad spectrum of biological activities. The pharmacological efficacy of *Andrographis* is attributed to their content of flavonoids, terpenoids, and

flavonoid glycosides such as andrographolide, echiodinin, and echiodinin 5-o-β-D-glucopyranoside. Notably, andrographolide, neoandrographolide, and deoxyandrographolide are identified as the most bitter compounds among these. While other *Andrographis* species also contain andrographolides, the rarity of several species has limited their exploration as phytopharmaceutical sources. The primary phytochemical responsible for the medicinal properties of these plants is andrographolide [1].

ANDROGRAPHOLIDE AND ITS ANALOGS

Andrographolide, a labdane diterpenoid, is produced by *A. paniculata*. It is a significant component in over 26 Ayurvedic formulations and is primarily used for treating liver diseases. Among secondary plant products, andrographolides are the most pharmacologically active compounds. However, they are only sourced from conventionally propagated or wild-grown plants, which represent a mere 2-3% of the total, and are insufficient to meet the growing pharmaceutical demand, which is increasing annually by 3.1% [4]. *A. paniculata* also synthesize various other compounds including 5,7-tetramethoxyflavanone, 5-hydroxy-7 trimethoxy-flavone, numerous flavonoids, and polyphenols [10 - 12]. The andrographolide content varies across different plant parts: approximately 4% in the dried whole plant, 0.8-1.2% in the stem, and 0.5-6% in leaf extracts. Other significant diterpenoids in *A. paniculata* include deoxyandrographolide, neoandrographolide, 14-deoxy-11,12-didehydroandrographide, and isoandrogra-pholide [13]. From the EtOAC-soluble fraction of ethanol or methanol extracts, several main flavonoids have been identified, such as 5-hydroxy-7,8-dimethoxyflavone, 5-hydrox--7,8,2',5'-tetramethoxyflavone, 5-hydroxy -7,8,2',3'-tetramethoxyflavone, 5-hydroxy-7,8,2'-trimethoxyflavone, 7-O-methyl wogonin, and 2'-methyl ether [14]. As illustrated in Fig. (**1**), these compounds underscore the chemical diversity and potential therapeutic significance of *A, paniculata*.

A. paniculata is a plant known for its medicinal properties and contains various bioactive compounds. The principal constituent include andrographolide and its derivatives such as andrographiside , neoandrographolide, 6-acetylneo andrographiside , 2,3,14-deoxy-11,12-didehydroandrographolide,14-deoxy-11 ,12-didehydro andrographiside , 14-deoxy andrographolide,14-deox--andrographiside, 4-andrographaninandropanoside, isoandrographolide, andrographato-side, andropanolide, and bis-andrographolides A, B, C and D. Additionally, several 2-oxygenated flavonoids have been identified in *A. paniculata*: 5-hydroxy-7,8,2-trimethoxy-flavone, 5,2-dihydroxy-7-8-dimethoxyflavone, 5-hydroxy-7, 8-dimethoxy-flavone,13 5-hydroxy-7-8-dimethoxyflavanone, and andrographidine A. To date, detailed biological investigations have primarily focused on andrographolide, 14-deoxy-11,-

SUBJECT INDEX

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