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Recent Advances, Traditional Uses and Future Prospects of *Andrographis paniculata*

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ABSTRACT

Andrographis paniculata grows to a height of 60–70 cm and is an annual, branching plant with lanceolate green leaves. Known as Kalmegh in India, it is mostly found in the country's plains and is a common medicinal plant used in Ayurvedic and Unani medical systems. This herb, which belongs to the Acanthaceae family, is frequently found in Southeast Asian nations and is referred to as kalomegh, or "King of Bitters". Phytochemicals such as flavonoids, tannins, and total phenolics were measured and expressed as gallic acid equivalent (GAE), quercetin equivalent (QE), and tannic acid equivalent (TAE) in the root, stem, and leaf of A. macrobotrys, respectively. The plant is said to be rich in flavonoids, lactones, and diterpenoids. Andrographolide has several pharmacological characteristics that make it a possible medicinal substance. Andrographolide's cytotoxic actions against many cancer cell lines are attributed to its α-alkylidene-butyrolactone moiety and three hydroxyls at C-3, C-19, and C-14. Numerous biological activities of andrographolide have been documented, including anti-inflammatory, antiallergic, Anti-Venom Activity, Anti-Oxidant Activity, Hepatoprotective Activity, Antidiabetic Activity and Cytotoxic Activity.

Keywords: *Andrographis paniculata*, Phytochemical Composition, Chemical Properties, Biological Activities, Traditional Uses.

INTRODUCTION

Andrographis paniculata grows to a height of 60–70 cm and is an annual, branching plant with lanceolate green leaves (Figure 1) [1]. In Asian nations including India, Sri Lanka, Pakistan, Java, Malaysia, and Indonesia, it grows profusely. Known as Kalmegh in India, it is mostly found in the country's plains and is a common medicinal plant used in Ayurvedic and Unani medical systems. Because every portion of the plant has an intensely bitter flavor, it is often referred to as the "King of Bitters" [2, 3]. Based on a review of the literature, it has been shown that the aerial portions of plants—their leaves and stems—are most frequently employed to extract the active phytochemicals; however, the entire plant or its roots are only briefly addressed [3]. Hepatoprotective, antibacterial, antifungal, antioxidant, anti-inflammatory, antipyretic, anticancer, and anti-diarrheal properties are just a few of the many highly advantageous pharmacological actions of A. paniculata. It is helpful in treating chronic hepatitis, according to the Unani medical system [4]. Interestingly, there has been conjecture that A. paniculata in Malaysia and Thailand might have originated in India [5]. Two of the roughly 20 species of Andrographis plants—cultivated (A. paniculata) and wild (A. laxiflora var. glomerulifera)—are found in China [6]. More than 90% of China's total production is produced in Guangxi Zhuang Autonomous Region and Guangdong Province, where A. paniculata was first introduced in the 1950s [7] (Figure 2). For generations, "Androghraphis paniculata" has been used in traditional Asian treatments. This herb, which belongs to the Acanthaceae family, is frequently found in Southeast Asian nations and is referred to as kalomegh, or "King of Bitters" [8].

Figure: 1. ***Andrographis paniculata***

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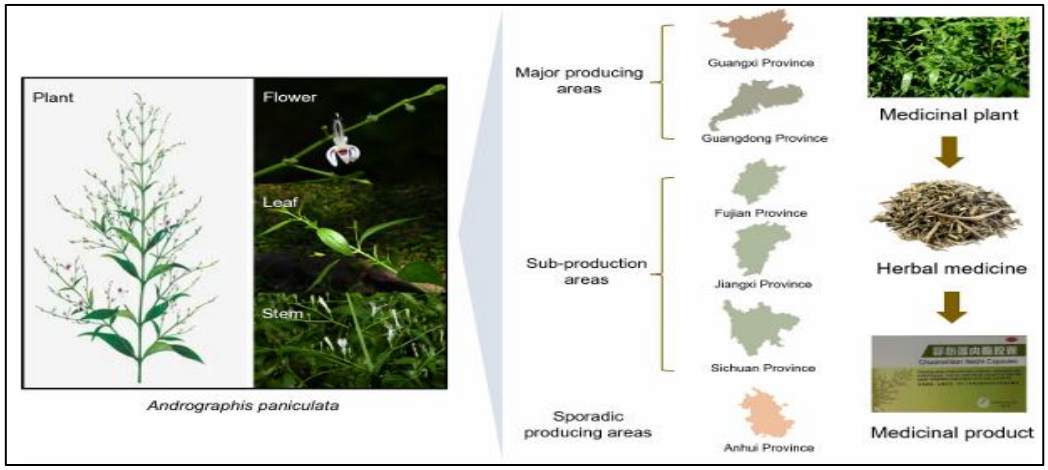

Figure: 2. Schematic Diagram of The Main Origin In China And The Industrialization Process of Andrographis paniculata.

Botanical Description of *Andrographis paniculata*:

Origin and Distribution

Native to Taiwan, Mainland China, and India, Andrographis paniculata is also widely distributed throughout tropical and subtropical Asia, Southeast Asia, and a few other nations, such as Cambodia, Caribbean islands, Indonesia, Laos, Malaysia, Myanmar, Sri Lanka, Thailand, and Vietnam [9,10]. It is also found in various phytogeographical and edaphic zones in China, America, the West Indies, and Christmas Island [11].

Table 1: The Morphology of Andrographis paniculata [12,13,14].

Traits	Values/Characteristics
Plant Height	30-110 cm
Stem	Dark Green
Length	30-100 cm
Diameter	2-6 mm
Shape	Quadrangular with longitudinal furrows and wings on the angles of the young parts, slightly enlarged at the nodes
Leaves	Glabrous
Length	2-12 cm
Width	1-3 cm
Arrangement	Lanceolate
Shape	Pinnate, Acute Apex, Entire Margin
Flowers	White with rose-purple sports on the petals
Size	Small, In lax spreading axillary and terminal racemes or panicles
Seed	Capsules linear-oblong, acute at both ends
Size	1.9 cm × 0.3 cm
Colour	Yellowish Brown
Shape	Subquadrate, Numerous
Flowering and Fruitting	December to April

Table: 2. The Taxonomical Classification of Andrographis paniculata [15,16,17].

Domain	Eukaryota
Kingdom	Plantae
Subkingdom	Tracheobionta
Super-division	Spermatophyta
Division	Angiosperma
Class	Dicotyledonae
Subclass	Gamopetalae

Series	Bicarpellatae
Order	Personales
Family	Acanthaceae
Subfamily	Acanthoideae
Tribe	Justiciae
Subtribe	Andrographideae
Genus	Andrographis
Species	A. paniculata (Burm. f.) Nees

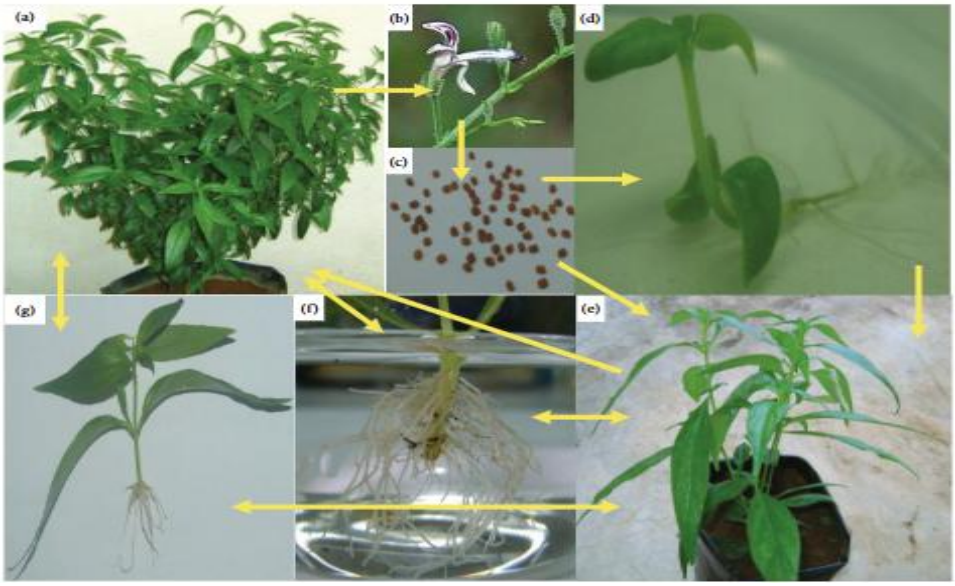

Figure: 3. Morphology of Andrographis paniculata

(a) Mature Andrographis paniculata in Polybag Stage, (b) Flowering Stage, (c) Harvested Seeds, (d) In Vitro Seeding, (e) Young Andrographis paniculata in Polybag, (f) Adventitious Roots of Andrographis paniculata, (g) Vegetative Seedling. Single direction of arrows indicates the developmental stages and both direction of arrow denotes vegetative propagation of plant.

Vernacular Names:

Because of its intensely bitter flavor, the tree is commonly referred to as the "King of Bitters." AP is commonly referred to as "hempedu bumi" (bile of the earth) in Malaysia. Different languages have different names for this plant. **Table 3** lists the AP's colloquial names. Additionally, plant species with colloquial names rather than binomial names are easily recognized by locals.

Table: 3. Vernacular Name of Andrographis paniculata

Languages	**Name**
English	The Creat, King of Bitters
Arabic	Quasabhuva
Hindi	Kirayat, Kalpanath
Urdu	Kalmegh, Kariyat, Mahatita
Sanskrit	Kalmegha, Bhunimba and Yavatikta
Indonesian	Sambiroto, Sambiloto
Azerbaijani	Acılar Şahı, Acılar Xanı (khanı)
Philippines	Aluy, Lekha and Sinta
Russian	Andrografis
Turkish	Acılar Kralı, Acı Paşa, Acı Bey
Vietnamese	Xuyên Tâm Liên
Chinese	Chuan Xin Lian
Scandinavian	Green Chiratta

Spanish	Andrografis
French	Chirette verte
Lao	La-Sa-Bee
Japanese	Senshinren
Kanada	Nelaberu
Burmese	Se-ga-gyi
Konkani	Vhadlem Kiratyem
Thai	Fa-Talai-Jorn, Fah-talai-jon (jone)
Oriya	Bhuinimba
Punjabi	Chooratta
Tamil	Nilavernbu
Bengali	Kalmegh
Assamese	Kalmegh
Gujarati	Kariyatu
Malay	Hempedu Bumi, Sambiloto
Malayalam	Nelavepu, Kiriyattu
Manipuri	Vubati
Marathi	Oli-kiryata, Kalpa
Mizo	Hnakhapui
Persian	Nain-e Havandi
Sinhalese	Hīn Kohomba or Heen Kohomba
Telugu	Nilavembu

Phytochemical Composition

Phytochemicals such as flavonoids, tannins, and total phenolics were measured and expressed as gallic acid equivalent (GAE), quercetin equivalent (QE), and tannic acid equivalent (TAE) in the root, stem, and leaf of A. macrobotrys, respectively. Table 4 displays the total phenolics, flavonoids, and tannins of various plant sections. Out of all the plant parts, the content of phenolics is the highest [22].

Table: 4. Phytochemical Composition of Andrographis Macrobotrys Plant Extracts.

Plant Part	Phenolics (mg GAE/g DW)	Flavonoids mg QE/g DW	Tannins (mg TAE/g DW)
Root	124.28 ± 0.24^{b}	9.06 ± 0.79^{c}	59.49 ± 0.22^{b}
Stem	180.98 ± 0.76^{a}	18.04 ± 0.08^{b}	86.39 ± 0.06^{a}
Leaf	73.01 ± 0.35^{c}	57.04 ± 0.43^{a}	57.33 ± 0.14^{b}

Values are mean ± standard deviation (n = 3). Mean values followed by different superscript in a column are significantly different ($p < 0.05$) according to Duncan's multiple range test.

Chemical Composition

The chemical components of Andrographis paniculata have been thoroughly investigated. The plant is said to be rich in flavonoids, lactones, and diterpenoids. However, region, plant sections, season, and phenological growth stage all affect the concentration and makeup of its phytochemicals [23]. Andrographolide, which is present throughout the entire plant, including the leaves, stem, and roots, is Andrographis paniculata's primary active ingredient. Andrographolide is a colorless, bitter ent-labdane diterpene lactone [24]. In fact, Boorsma was the first to isolate this material and give it the name andrographide. Gorter then established andrographolide's structure in 1911 and gave it that name [24, 25]. Although andrographolide can be isolated from every part of the plant, its concentration is highest in the leaves [26,27,28,29,30].

Chemical Properties

Andrographolide has several pharmacological characteristics that make it a possible medicinal substance. Andrographolide's cytotoxic actions against many cancer cell lines are attributed to its α-alkylidene-butyrolactone moiety and three hydroxyls at C-3, C-19, and C-14 [31]. Leaves contain large amounts of andrographolide, which is easily separated from crude plant extracts as a crystalline solid [32-37]. The total lactone in CM ranged between 9.00 and 14.00 mg/g for both edible components shown in Table

5, whereas KS had the lowest. Between these useful components, there was little variation in the total lactone content. The KS, CM, and RB had much greater phenolic and flavonoid levels (3.00–5.00 mg/g and 2.50–3.00 mg/g, respectively), whereas the stem portion had somewhat higher concentrations. Flavones, which are components of the phenolic group, were found to be more common in fresh A. paniculata. This plant collection's total flavonoid concentration varied from 3.40 to 1.06 mg/g. Approximately 73% of the crude extract had antioxidant activities as measured by DPPH• and ABTS•+, however the activities were much lower in the CM for both edible portions. It is also important to note that, as previously reported [38], ethanol was selected for the extraction process because of its greater solubility.

Biological Activities of Andrographolide

Numerous biological activities of andrographolide have been documented, including anti-inflammatory [39], antiallergic [40], antiplatelet aggregation [41, 42], hepatoprotective [43], and anti-HIV [44]. Furthermore, it has been shown that ethanol or an aqueous extract of A. paniculata can lower blood glucose levels in both normal and streptozotocin-diabetic rats. As a bipolar molecule, rographolide can interact with several intracellular and intercellular components in biological systems, resulting in a variety of biological reactions. A. paniculata polysaccharides in combination with rographolide have been shown in a recent study to facilitate the recovery of diabetic nephropathy [45]. Ayurvedic and allopathic medical literature has documented the advantageous pharmacological properties of A. paniculata with established safety profiles (Jarukamjorn and Nemoto Citation2008; Mehta et al. Citation2021; Intharuksa et al. Citation2022). The features of this plant and its applications in the form of dry powder are described in the World Health Organization (WHO) monograph (WHO Citation 2002). According to the data, a ground powder made from the dried aerial portions of A. paniculata contains a number of flavonoids and diterpenoid lactones, which may be the cause of its biological actions (Song et al. Citation2013; Zhao et al. Citation2014; Wang et al. Citation2018) [46].

Antiviral Effects

Plant extracts' antiviral properties have been revived and are the subject of intense scientific research. A number of extracts from medicinal plants have demonstrated antiviral properties against some DNA and RNA viruses. A. paniculata is one of these plants that has the ability to neutralize the HIV virus [47]. The antiviral activity of andrographolide against HIV [50], herpes simplex virus (HSV) [48,49], flaviviruses, and pestiviruses [51] has been studied. 25 µg/mL of ethanolic extract of A was shown by Lin et al. [52]. During the viral lytic cycle in P3HR1 cells, paniculata and 5µg/mL of andrographolide efficiently suppress the expression of the Epstein-Barr virus (EBV) lytic proteins, Rta, Zta, and EA-D. Among six medicinal herbs tested against DENV1-infected Vero E6 cells, A. paniculata exhibits the most antiviral inhibitory effects, according to a recent study [53].

Antidiabetic Activity

A. paniculata has an active bioactive synthetic component called andrographolide, which may have antidiabetic properties. The main labdane diterpenoid is andrographolide. The antihyperglycemic action was investigated in STZ diabetic rats, and the findings suggested that andrographolide can boost glucose utilization to lower plasma glucose in diabetic rats without insulin. The antihyperglycemic property was also investigated, and it was discovered that ethanolic concentrate may also reduce oxidative pressure in diabetic rodents [54].

Cytotoxic Activity

Further understanding was obtained by employing the MTT test to examine the cytotoxic activities of A. paniculata extract and fractions in CACO-2 cell lines. The assay relies on the introduction of active metabolic cells into the formazan (blue form), which causes mitochondrial dehydrogenase to reduce the MTT reagent. Using an inverted microscope and 40 times magnification, shows the viability of the CACO-2 cell line both before and after treatment with each A. paniculata extract and fraction. The cytotoxic activity of each sample on CACO-2 cell lines is summarized in Figure 4. With the exception of F3, which had values as high as 145.10 µg mL−1, the IC50 values of the samples were generally less than 100 µg mL−1. With an IC50 value of 32.46 µg mL−1, F2 had the strongest CACO-2 cell growth inhibition activity, followed by ME (63.89 µg mL−1) and F1 (61.04 µg mL−1). These results are in line with F2's high amounts of andrographolide, 14-deoxy-11,12-didehydroandrographolide, neo andrographolide, and andrograpanin, as well as its significant anti-inflammatory activity test results. Furthermore, the low activity of F3 is consistent with the low concentration of andrographolide and the lack of andrograpanin, neoandrographolide, and 14-deoxy-11,12-didehydroandrographolide [55].

Anti-Venom Activity

Conventional medicine states that Andrographis paniculata is a natural treatment for snake bites. An intraperitoneal injection of ethanolic leaf extract (25 g/kg body weight) was administered to mice poisoned with cobra venom, which considerably postponed

respiratory collapse and death. The ileum of the guinea pig also contracted at 2 mg/ml of this extract. Antihistamines had no effect on these contractions, whereas physostigmine increased them and atropine stopped them. The study suggests that rather than changing the activation of nicotinic receptors, the extracts' anti-venom capabilities could be explained by a significant increase in muscarinic activity. Ethanolic extract from Andrographis paniculata demonstrated some protection against red scorpion venom in mice [56].

Anti-Oxidant Activity of Andrographis paniculata

The main components of Kalmegh extract include phenolic compounds, glycosides, alkaloids, and flavanoids, according to phytochemical screening. These phenolic compounds have the potential to be the cause of antioxidant activity. The study's findings unequivocally show that kalmegh has strong antioxidant and radical scavenging properties against a variety of antioxidant systems in vitro. Kalmegh is a readily available natural antioxidant and may be used as a dietary supplement. According to our current research, flavonoids, alkaloids, tannins, saponin glycosides, and phenolic chemicals may be responsible for Kalmegh's strong antioxidant properties [57].

Effects on Cardiovascular Disease

Because A. paniculata has been shown to improve blood-clotting time, pre and post treatments with the extract of A. paniculata following surgery greatly reduce the risk of subsequent blood vessel closure following angioplasty operations by preventing blood vessel constriction. The effects of A. paniculata's active ingredients and aqueous extracts before and after experimental myocardial infarction have been studied in a number of animal models. Because the plant's extract relaxed the smooth muscles in blood vessel walls and stopped the blood vessels from constricting and restricting blood flow to the heart, brain, and other organs, it had antihypertensive effects. Pretreatment with andrographolide was found to protect rat cardiomyocytes against hypoxia injury in a time-dependent manner; this effect was linked to an increase in cellular reduced glutathione (GSH) levels and antioxidant enzyme activity [58].

Hepatoprotective Activity

When A. paniculata extract was given orally to Swiss albino mice, it demonstrated hepatoprotective action and recovered serum marker enzymes. Hepatic tissue showed distortion and decreased levels of glutathione, catalase, and glutathione peroxidase, as well as elevated levels of lipid peroxides and superoxide dismutase. In comparison to the control, the levels are restored following the administration of this plant extract (Nagalekshmi et al., 2011). Additionally, Subramaniam et al. (2015) assessed the ethanolic extract of A. paniculata's hepatoprotective efficacy against hepatic cells. In albino rats, the toxicity was evaluated in relation to CCl4-induced hepatotoxicity. Serum glucose, lipid profile, and enzyme levels all decrease following treatment with A. paniculata extract. In albino rats, the plant extract improved the recovery from CCl4-induced hepatotoxicity [59].

Effects on Pneumonia and Lung Injury

Pneumonia is an inflammatory lung disease brought on by bacterial, viral, or fungal infections. When pathogens enter the lungs, they cause alveolar inflammation, fluid buildup, and symptoms like fever, coughing, and respiratory distress. Severe pneumonia can cause lung injury, which is structural damage to lung tissue resulting from a variety of etiologies [60].

In a mouse model of pneumonia, Cui et al. [61] showed that intraperitoneal injection of andrographolide sulfonates successfully reduced airway inflammation and histological alterations. Additionally, the therapy suppressed the expression of mucins MUC5AC and MUC5B in lung tissue and decreased pro-inflammatory cytokine levels in serum and bronchoalveolar lavage fluid (BALF). The suppression of the NF-κB signaling pathway was identified as the cause of these effects. Similar to how andrographolide is used to treat pneumonia [64,65], andrographolide sulfonates also controlled NF-κB to reduce alveolar coagulation, fibrinolysis inhibition [62], and acute lung injury [63]. Proteomic analysis also showed that andrographolide sulfonates reduced acute lung injury caused by LPS in mice by blocking proteases produced by neutrophils, including myeloperoxidase (MPO), cathepsin G (CTSG), and elastase (ELANE) [66].

Additionally, andrographolide sulfonates work in concert with other medications to treat pneumonia [67]. For instance, Zhang et al. [68] found that in mice infected with Klebsiella pneumoniae, the combination of andrographolide sulfonates and imipenem dramatically increased survival rates and decreased MCP-5 levels. In a similar vein, Gu et al. [69] discovered that treating pneumonia brought on by K. pneumoniae was improved by mixing andrographolide sulfonates with azithromycin. Significantly, the combination decreased azithromycin buildup in the liver, indicating that andrographolide sulfonates may enhance azithromycin metabolism, thereby safe guarding the liver and reducing drug resistance. But according to a different study, andrographolide

sulfonates may impede the metabolism of medications like lopinavir and ritonavir in rats by inhibiting CYP3A4 activity, which could be dangerous [70].

Anti-Inflammatory Activity

The albumin denaturation inhibition assay and RAW cell cytotoxicity assays were used to assess the anti-inflammatory efficacy. The Lad et al. method was used to conduct the albumin denaturation inhibition assay. In this experiment, nanoparticle aliquots were incubated for 20 minutes at 37°C with a 1% aqueous solution of cow albumin fraction. Turbidity was determined spectrophotometrically at 660 nm after the reaction mixture was heated to 51 oC for 20 minutes following incubation. The absorbance data was used to calculate the inhibition of albumin denaturation. The standard was acetylsalicylic acid [71].

Traditional Uses

In both Asia and Europe, the aerial portions and roots of A. paniculata are used for various therapeutic purposes in numerous nations. In more than 26 Ayurvedic formulations, the crude medicine from A. paniculata—known as Kalmegh in India—has been frequently employed as a main ingredient [72,73]. Furthermore, the medication has reportedly been used to treat various forms of fever, especially intermittent fevers [74].

For more than a century, A. paniculata, also known as Chuanxinlian in Chinese, has been imported from India and Southeast Asia and utilized in Chinese medicine to eliminate heat and moisture. According to the traditional theory of Chinese medicine, its cooling qualities also prevent fire [75]. It has been used in Malaysian traditional medicine to treat diabetes and hypertension in Southeast Asian nations like Malaysia and Thailand [76]. On the other hand, A. paniculata has been administered to patients with fever and symptoms of the common cold in traditional Thai medicine. In Scandinavian nations, it is also used to treat fevers and cold symptoms [72].

Future Prospects

There is a lot of interest in and promise for future research in the study of Andrographis paniculata. Determining the best uses of this plant for liver problems would require more research on the particular bioactive chemicals and their mechanisms of action. Future research could investigate the possibility of using AP to treat conditions other than liver disease, like inflammation and cancer. Further clinical research is also required to verify the safety and effectiveness of AP in the treatment of human liver problems. All things considered, AP research has bright future potential, and further study of this plant may result in the creation of novel, potent remedies for a number of illnesses [77].

Conclusion

The distribution and variety of phytochemicals were determined by quantitative analysis of different portions of Andrographis macrobotrys. Significant levels of tannins, flavonoids, and phenolics were extracted from the different plant components. This study showed that plant components have strong antioxidative potential since they include phenolic compounds. Several important bioactive phytochemicals, such as 2,4-di-tert-butylphenol, 2-methoxy-4-vinylphenol, 5-hydroxy-7,8-dimethoxyflavone, azulene, salvigenin, squalene, and tetrapentacontane, were identified by GC-MS analysis. Several additional compounds, such as 4,22-stigmastadiene-3-one, acetosyringone, 3,4-dihydro-2(1h)-isoquinoline carboxamidine, and alpha-monostearin, have been identified for biological investigation to determine their significance. Thus, as the current study shown, A. macrobotrys is a source of useful phytochemicals. By using the plants instead of A. paniculata, overuse and extinction can be avoided. The most common species in the genus, A. paniculata, is renowned for its remarkable therapeutic properties. As a result, the pharmaceutical and herbal sectors greatly value it. Asian nations have substituted Western medicine with plant-based remedies. The plant's remarkable capacity to fight viral infections is another well-known feature. As a result, during the COVID-19 pandemic, demand for the products and raw materials made by A. paniculata skyrocketed. In an attempt to lessen the strain, the search for substitutes with potential comparable to A. paniculata has quickened. To verify that, a range of phytochemicals were found in the current phytochemical study, which was conducted on the closely related species A. macrobotrys.

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