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Andrographis Paniculata: A Promising Medicinal Plant

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ABSTRACT

Andrographis paniculata (Burm.F.) Nees, a plant indigenous to South Asian countries like India and China, has been used for the effectively treatment of various diseases. Due to the widespread use of this herb, a number of chemicals have been identified as secondary metabolites. Research reports of diterpenoids with biological activity have been published. These diterpenoids have demonstrated hepatoprotective, immunostimulant, cholerectic, cell differentiation-inducing, anticancer and antiviral properties. Diterpenoids comprises of approximately 11% of methanol extract of *A. paniculata*. We have systematically reviewed the chemical constituents isolated from *A. paniculata* and their pharmacological properties.

KEYWORDS

Andrographis paniculata;
Andrographolide;
Anticancer.

INTRODUCTION

The use of plants as medicines goes back to early man. Certainly the great civilizations of the ancient Indians, Chinese, and North Africans provided written evidence of man's ingenuity in utilizing plants for the treatment of a wide variety of diseases. In ancient Greece, scholars classified plants and gave descriptions of them thus aiding the identification process. It was not until the 19th century that man began to isolate the active principles of medicinal plants and one particular landmark was the discovery of quinine from *Cinchona* bark by the French scientists Caventou and Pelletier. Such discoveries led to an interest in natural products from the New World and expeditions scoured the almost impenetrable jungles and forests in the quest for new medicines[1]. Despite major scientific and technological progress in combinatorial chemistry, drugs derived from natural products still make an enormous contribution to

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drug discovery today[1].

Most of the current drugs are synthesized against the backbone of one or another natural product. *Andrographis paniculata* (Burm.F.) Nees, also known commonly as "King of Bitters", is a member of the plant family Acanthaceae, and has been used for centuries in Asia for the treatment of various diseases. It is found in the *Indian Pharmacopoeia* and is the prominent constituent in at least 26 Ayurvedic formulas; whereas in Traditional Chinese Medicine (TCM), this plant is an important "cold property" herb. In the Scandinavian countries, it is commonly used to prevent and treat common colds[2]. In Malaysian traditional medicine practice, *A. paniculata* drink has been used to alleviate diabetes and fever. Some traditional healers claim that the decoction may be useful in correcting high blood pressure or hypertension[3].

This official herbal medicine is used for the treatment of inflammation, cold, fever, laryngitis and diarrhea[4-6]. This herb commonly used in China by TCM doctors in the treatment of a wide variety of illnesses which include acute hepatitis, bacillary dysentery, meningitis, choriocarcinoma, and many other acute inflammatory conditions[7, 8]. It has been claimed that extracts of this herb are bactericidal to leptospira and to many species of cocci and are also inhibitory to the growth of ECHO virus type II in human cell culture[8]. The leaf forms an ingredient of many patented Indian herbal propriety preparations e.g. *Kalmeghasava* and *Kalmeghnamay Haub* for the treatment of liver ailments[9-11].

A. paniculata is an annual herb branched and erect-running ½ to 1 meter in height. It is cultivated extensively in India, China and South East Asia[12]. Normally grown from seeds, *A. paniculata* is ubiquitous in its native areas. It grows in pine, evergreen and deciduous forest areas, and along roads in villages. Because of its well-known medicinal properties, it is also cultivated-quite easily, since it grows in all types of soil. Moreover, it grows in soil types where almost no other plant can be cultivated, particularly "serpentine soil", which is relatively high in aluminium and copper. Such hardness helps account for its wide distribution. Maximum herb biomass can be obtained in 90-100 days beyond which leaves start shedding. The whole plant is used to extract the active phytochemicals, flavonoids[13-18], labdane diterpenoids[17, 19-24], stigmasterols[25] and xanthones[26]. At the time of flower initiation active principal andrographolide **(1)** (Figure 1) is high in leaves. Also, regional and seasonal variations can also modify the andrographolide **(1)** content in the leaf (0.5% - 2.6%)[4]. Since the whole plant contains active principals, entire harvested material is dried in shade and powdered.

2. Chemical constituents of *A. paniculata*

Andrographolide **(1)**, an extremely bitter compound, the major constituent of the plant *A. paniculata* was first isolated by Gorter[27]. Andrographolide **(1)** chemically designated as 3-[2-[decahydro-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylene-1-napthalenyl] ethylidene] dihydro-4-hydroxy-2(3*H*)-furanone. This compound is found in the whole plant but is most concentrated in the leaves. It is a diterpene containing a γ-lactone ring connected to a decalin ring system *via* an unsaturated C_2 moiety. The crystal structure of andrographolide 1 was determined by Smith et al.[28].

The second diterpene isolated from *A. paniculata* was the minor non-bitter constituent neoandrographolide **(13)**, which was first described by Kleipool [19]. The structure of neoandrographolide **(13)** was described by Chan et al.[20]. Balmain and Connolly[21] reported the isolation and identification of four minor diterpene constituents from *A. paniculata*: 14-deoxy-11,12-didehydroandrographolide **(11)**, andrographiside **(2)**, 14-deoxyandrographolide **(5)** and deoxyandrographiside **(6)** (Figure 1). During investigation of the differentiation inducing agents from *A. paniculata*, Matsuda et al.[23] found six new diterpenoids. They were 14-*epi*-andrographolide **(3)**, isoandrographolide **(4)**, 14–deoxy-11-hydroxyandrographolide **(7)**, 14–deoxy-12-methoxyandrographolide **(8)**, 12-*epi*-14-deoxy-12–methoxyandrographolide **(9)** and 14–deoxy-12-hydroxyandrographolide **(10)** as well as two new diterpene glucosides, 14-deoxy-**(11)**, 12-didehydroandrographoside **(12)**, 6'-neoandrographolide **(14)** and **(4)** new dimers of diterpenoids bisandrographolide A, B, C **(15)** and D **(16)**(Figure 1).

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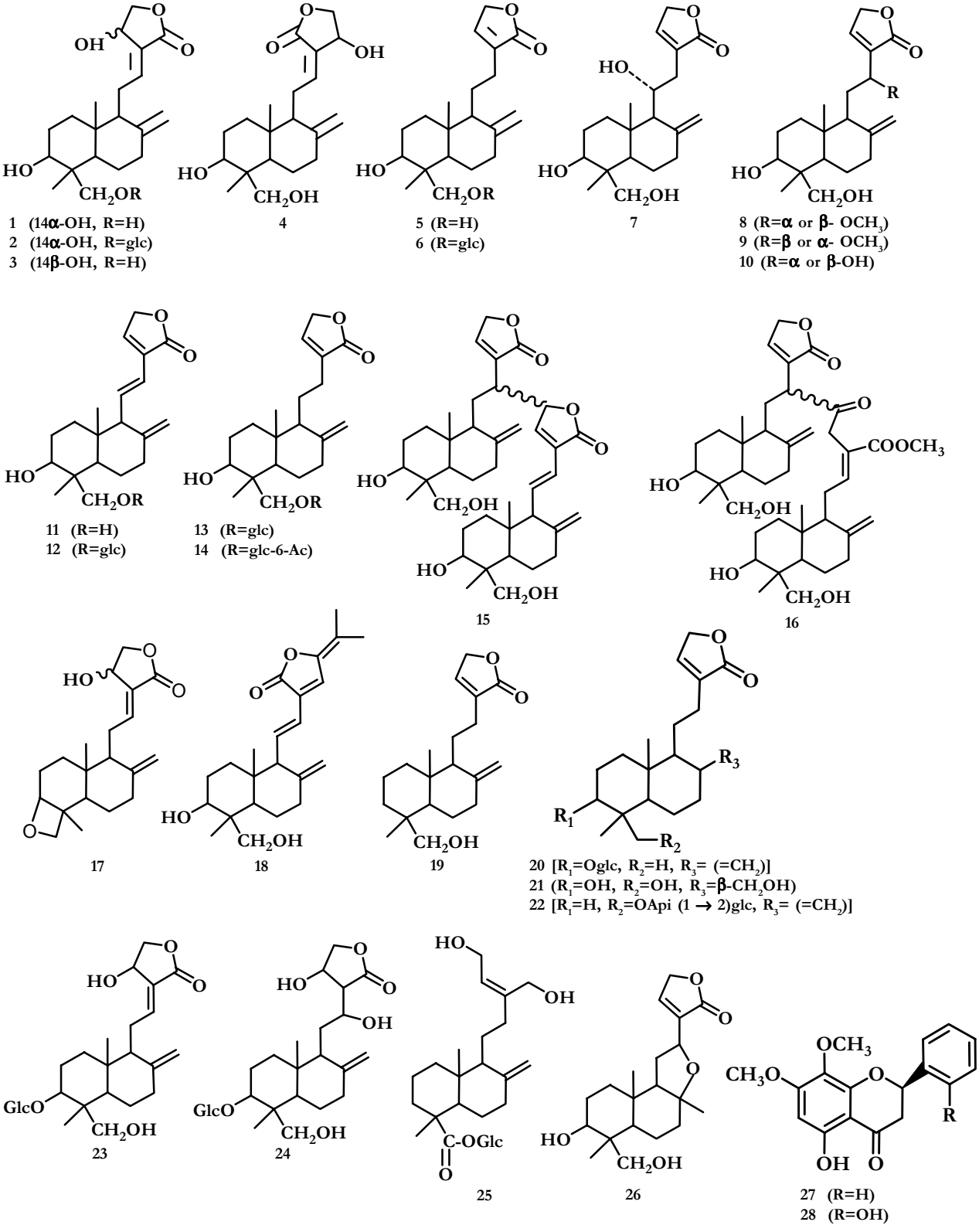

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Figure 1: Chemical constituents of *Andrographis paniculata*.

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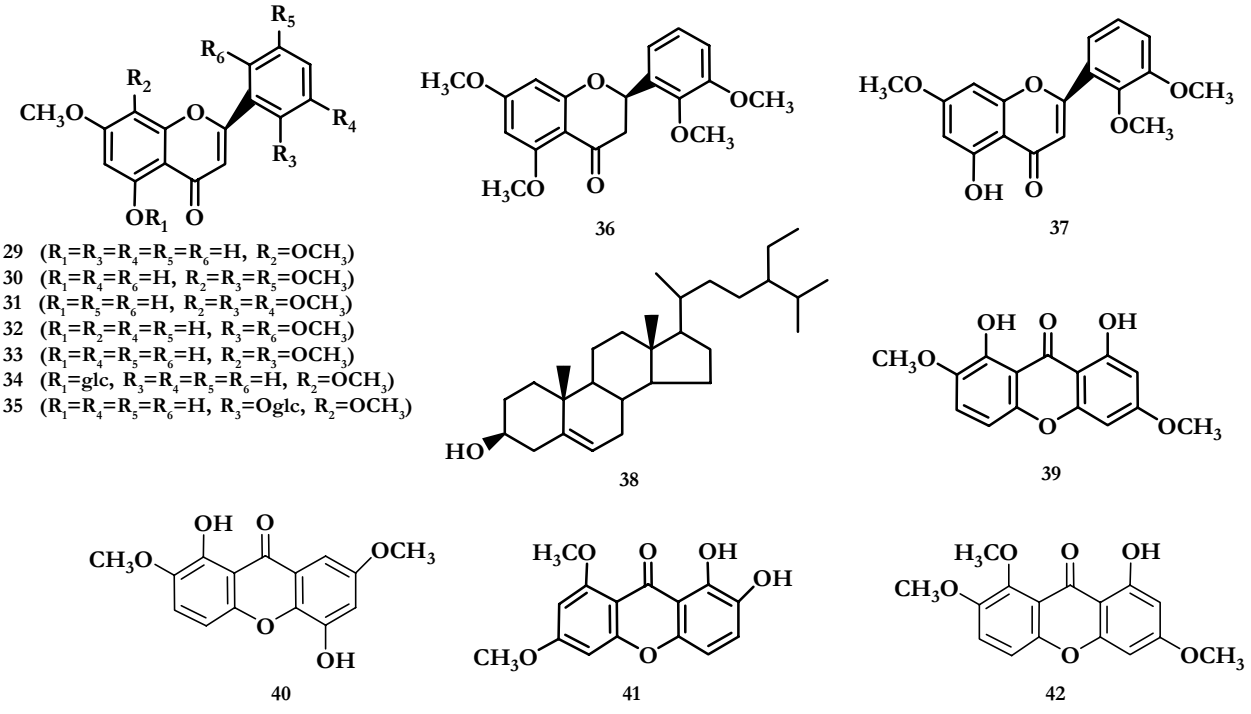

Figure 1: Chemical constituents of *Andrographis paniculata*.

Jantan and Waterman[24] reported ent-14β-hydroxy-8**(17)**, 12-labdadien-16,15-olide-3 β,19-oxide **(17)** from the aerial parts of *A. paniculata*. An unusual 23-carbon terpenoid, 14-deoxy-15-isopropylidene-11,12-didehydroandrographolide **(18)**, from *A. paniculata* was reported by Muntha et al.[17] (Figure 1). Recently, six new *ent*-labdane diterpenoids, 3-*O*-*â*-D-glucopyranosyl-14,19-dideoxyandrographolide **(20)**, 14-deoxy-17-hydroxyandrographolide **(21)**, 19-*O*-[*â*-D-apiofuranosyl(1f2)-*â*-D-glucopyranoyl]-3,14-dideoxyandrographolide **(22)**, 3-*O*-*â*-D-glucopyranosyl andrographolide **(23)**, 12*S*-hydroxyandrographolide **(24)**, andrographatoside **(25)**[29] and a minor diterpenoid andropanolide **(26)**[30] were isolated from *A. paniculata* (Figure 1).

The flavonoids isolated from the whole plant extract of *A.paniculata* were 7-*O*-methyldihydrowogonin **(27)**[15], dihydroskullcapflavone I **(28)**[31], 7-*O*-methyl wogonin **(29)**[16], 5-hydroxy-7,8,2´,5´-tetramethoxyflavone **(30)**[32], 5-hydroxy-7,8,2´,3´-tetramethoxyflavone **(31)**[16], 5-hydroxy-7,2´,6´-tetramethoxyflavone **(32)**[17], skullcapflavone 12´-methylether **(33)**[14], 7-*O*-methylwogonin 5-glucoside **(34)**[16], skullcapflavone I 2´-glucoside **(35)**[33], 5,7,2´,3´-tetramethoxyflavanone **(36)** and 5-hydroxy-7,2´,3´-trimethoxyflavone **(37)**[18] (Figure 1). Siripong et al.[25] isolated β-sitosterol **(38)** from the aerial parts of *A. paniculata*. Recently, Dua et al.[26] isolated four xanthones from the roots of *A. paniculata*. They were, 1,8-dihydroxy-3,7-dimethoxy-xanthone **(39)**, 4,8-dihydroxy-2,7-dimethoxy-xanthone **(40)**, 1,2-dihydroxy-6,8-dimethoxy-xanthone **(41)** and 3,7,8-trimethoxy-1-hydroxy xanthone **(42)** (Figure 1).

3. Secondary metabolites by tissue culture of *A. paniculata*

One of the most remarkable characteristics of the plant tissue cultures is their ability to regenerate organs or intact plants, a property that botanists describes as 'totipotency'[34, 35]. This term implies the notion that even a single de-differentiated cell retains the 'total potency' of the parent plant, and this must include the potential to produce the plant's characteristic secondary metabolites. Nevertheless, it is frequently found that de-differentiated tissues do not produce such metabolites. It is clearly of interest to establish whether the re-differentiation of callus tissues during morphogenesis is accompanied

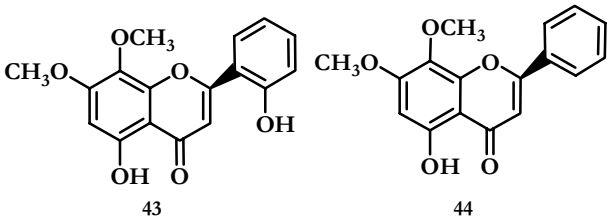

Figure 2: Secondary metabolites by tissue culture of *Andrographis paniculata*.

by reversion to the secondary metabolism of the parent plant, and such a reversion has indeed been previously observed[36].

Previously, it was reported that callus cultures derived from *A. paniculata* produced sesquiterpenoids while intact plants produced diterpenoids[37, 38]. Differentiating tissue cultures of *A. paniculata* produced three new flavones, 5-hydroxy-7,8,2´-trimethoxy flavone **(33)**, 5,2´-dihydroxy-7,8-dimethoxy flavone **(43)** and 5-hydroxy-7,8-dimethoxy flavone **(44)**[14] (Figure 2).

4. Pharmacological properties of *A. paniculata* extract and the compounds isolated from *A. paniculata*

4.1 Anti–HIV property

Among the individual components tested against the clinically important convertases, furin and PC1, neoandrographolide **(13)** exhibited the highest inhibitory action with an IC_{50} of 53.5 μM against furin[39]. Andrographolide **(1)** exhibited a relatively low enzyme inhibition (IC_{50} = 1.0 mM and K_1 = 200 μM) against furin. Upon succinylation, its inhibitory action against the above convertases was enhanced significantly with a K_i in the low micromolar range (< 30 μM), suggesting that a specific structural modification of the andrographolide **(1)** skeleton may be exploited to develop a new class of non-peptide inhibitors of PCs. This potentially interesting observation may be attributed to the reported anti-HIV property of 14-dehydroandrographolide succinic acid monoester (DASM), by virtue of this protease inhibitory property, possibly acts by suppressing the proteolytic cleavage of envelope glycoprotein (gp) 160 of HIV, which is known to be PC-mediated, particularly by furin and PC7[39].

4.2 Cell differentiation-inducing activities

The methanol extract of the aerial parts of *A. paniculata* showed potent cell differentiation-inducing activity on mouse myeloid (M1) cells[23]. The inducibility and cytostatic activity of the eight monomeric diterpenoids, andrographolide **(1)**, 14-deoxyandrographolide **(5)**, 14-*epi*-andrographolide **(3)**, isoandrographolide **(4)**, 14–deoxy-12-methoxyandrographolide **(8)**, 12-*epi*-14-deoxy-12–methoxyandrographolide **(9)**, 14–deoxy-12-hydroxyandrographolide **(10)** and 14–deoxy-11-hydroxyandrographolide **(7)**, towards M1 cells were determined. Of these monomeric compounds, 14-deoxy-12-methoxyandrographolide **(8)**, showed moderate cell differentiation activity and other seven compounds showed potent activity[23].

4.3 Antipyretic and anti-inflammatory activities

Andrographolide **(1)**, 14-deoxyandrographolide **(5)**, 14-deoxy-11,12-didehydroandrographolide **(11)**, and neoandrographolide **(13)**, were investigated for their pharmacological properties in experimental animals including mice, rats, and rabbits. All the compounds exhibited varying degrees of antipyretic and anti-inflammatory activities in animals with fever induced by 2, 4-dinitrophenol or endotoxin, with oedema caused by egg white, or with inflammation caused by croton oil[6]. The antipyretic and anti-inflammatory effects of andrographolide **(1)** and related compounds, however, were lower than those of corticosteroids and of conventionally used non-steroidal drugs. The pharmacological effect was highest with 14-deoxy-11,12-didehydroandrographolide **(11)**, followed by 14-deoxyandrographolide **(5)**, neoandrographolide **(13)** and andrographolide **(1)**. The minimal lethal dose of these compounds by oral administration was greater than 20 g/kg[40]. The anti-inflammatory effect of all four compounds disappeared in adrenalectimized animals, indicating a possible involvement of the pituitary and adrenal systems. Administration of the four compounds did not significantly affect inflammatory hyperplasia and migration of leukocytes into the inflammatory focus. However, andrographolide **(1)** has shown to exhibit diverse anti-inflammatory activities[40-44], although the underlying molecular mechanisms are still unknown.

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Recent report shown the evidence that andrographolide **(1)** inhibits NF-κB action by directly interfering with its binding to DNA[45]. Andrographolide **(1)** prevents both the IκBα degradation and the MAPK phosphorylation following stimulation by PAF or fMLP. Recently, Ji et al.[46] isolated andrograpanin **(19)** from *A. paniculata* could modulate the chemokine pathway. However, in contrast to those inhibitory effects on chemokine pathway, results showed that andrograpanin **(19)** significantly enhanced chemokine SDF-1α-induced Jurkat, THP-1 and PBL cells chemotaxis, which indicated that the effect of andrograpanin **(19)** might contribute to the anti-infectious function of *A. paniculata.* As the other two compounds isolated from *A. paniculata*, andrographolide **(1)** and neoandrographolide **(13)**, have anti-inflammatory function through NO signal pathway, there could be a synergistic effect between andrograpanin **(19)** and these two compounds, which play an important function in the therapeutic effects of *A. paniculata* in the disease of infection combined with inflammation[46].

4.4 Hypoglycemic property

The ethanol extract of *A. paniculata* exhibited a plasma glucose lowering activity in normal and streptozocin-induced diabetic rats[47]. One of the active principle, andrographolide **(1)**, was investigated for its antihyperglycemic action in streptozocin (STZ)-induced diabetic rats[48]. Oral treatment of andrographolide **(1)** decreased the plasma glucose concentrations of STZ-diabetic rats in a dose-dependent manner. Similar treatment with andrographolide **(1)** also decreased the plasma glucose in normal rats and the maximal effect was more marked than that in STZ-diabetic rats[48]. The mechanism of the plasma glucose lowering action of andrographolide may be due to activation of the α_{1A}-AR to enhance glucose uptake into C_2C_{12} cells through the PLC-PKC pathway[49].

4.5 Hepatoprotective properties

Pre-treatment of dogs with an extract of leaves of *A. paniculata* at a dose of 500 mg/kg or with andrographolide **(1)** at a dose of 5 mg/kg prevented the increase in serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) when induced by oral administration of carbon tetrachloride (CCl_4). Simultaneous treatment did not show any effect [10]. Pre-treatment also caused a decrease of CCl_4-induced hepatic microsomal lipid peroxidation but only with a single dose and not with long-term administration of leaf extract or andrographolide **(1)**. The protective action on CCl_4-induced hepatotoxicity of the leaf extract was more significant than that of andrographolide **(1)**[10, 41, 50].

4.6 Immunostimulatory activity

Intragastric administration of ethanol extract of the aerial parts of *A. paniculata* (25 mg/kg body weight) or purified andrographolides (andrographolide **(1)** and neoandrographolide **(13)**) (1 mg/kg body weight) to mice stimulated antibody production and the delayed-type hypersensitivity response to sheep red blood cells[51]. The extract also stimulated a non-specific immune response in mice, measured by macrophage migration index, phagocytosis of [^{14}C]leucine-labelled *E. coli*, and proliferation of splenic lymphocytes. The extract was more effective than either andrographolide **(1)** or neoandrographolide **(13)** alone, suggesting that other constituents may be involved in the immunostimulant response[51].

Andrographolide **(1)**, 14-deoxy-11,12-didehydroandrographolide **(12)** and 14-deoxyandrographolide **(5)** increased human peripheral blood lymphocytes (HPBLs) proliferation[52]. The dose response analysis of these three compounds for IL-2 induction showed that all the three compounds could enhance the IL-2 induction in HPBLs. Andrographolide showed more IL-2 induction when compared to 14-deoxy-11,12-didehydroandrographolide **(12)** and 14-deoxyandrographolide **(5)**. The difference among the three compounds is that andrographolide **(1)** at higher concentrations showed cytotoxicity towards HPBLs, while the other two did not show any signs of toxicity[52]. The pure compounds are less potent compared to dichloromethane or methanolic extract in terms of their immunomodulatory activity, which suggests that molecules other than these diterpenes may also contribute to the immunostimulation, or the synergistic interaction among the different components of the extract that is more active[51,52].

4.7 Antimalarial activity

A 50% ethanol extract of the aerial parts of *A. paniculata* inhibited the growth of *Plasmodium berghei* both *in vitro* (100 mg/mL) and in mice after intragastric administration (1 g/kg body weight)[53]. Andrographolide **(1)** (5 mg/kg body weight) and neoandrographolide **(13)** (2.5 mg/kg body weight) were also effective when administered by gastric lavage[54].

Fractions isolated from *A. paniculata* also exhibited anti-malarial activity[55]. Rehman et al.[56] have also studied *in vitro* and *in vivo* anti-malarial activity of plant extracts of *A. paniculata* and revealed that chloroform extract showed better effect than the methanol extract. Recently, Dua et al.[26] has reported that extract of roots of *A. paniculata* has more anti-malarial activity than the fraction isolated from the leaves. Isolation of the compounds from roots extract revealed that some xanthones exhibited anti-malarial activity[26].

4.8 Anti-diarrhoeal activity

A. paniculata has anti-diarrhoeal activity *in situ*[57, 58]. An ethanol, chloroform or 1-butanol extract of the aerial parts *A. paniculata* (300 mg/mL) inhibited the *E.coli* enterotoxin-induced secretory response in the rabbit and guinea-pig ileal loop assay. However, an aqueous extract of the aerial parts was not active[58]. The constituent diterpene lactones, andrographolide **(1)** and neoandrographolide **(13)**, exhibited potent antisecretory activity *in vivo* against *E.coli* enterotoxin-induced diarrhoea[58]. Andrographolide **(1)** (1 mg per loop) was as active as loperamide when tested against heat-labile *E.coli* enterotoxin-induced diarrhoea and more effective than loperamide when tested against heat-stable *E.coli* enterotoxin-induced diarrhoea[58]. Neoandrographolide **(13)** (1 mg per loop) was as effective as loperamide when tested against heat-labile *E.coli* enterotoxin-induced diarrhoea and slightly less active than loperamide when tested against heat-stable *E.coli* enterotoxin-induced diarrhoea[58].

The mechanism of action involves inhibition of the intestinal secretory response induced by heat-labile *E.coli* enterotoxins, which are known to act through the stimulation of adenylate cyclase, and by inhibition of the secretion induced by heat-stable *E.coli* enterotoxins, which act through the activation of guanylate cyclase[57]. Incubation of murine macrophages with andrographolide (1–50 mmol/L) inhibited bacterial endotoxin-induced nitrite accumulation in a concentration and time dependent manner. Western blot analysis demonstrated that andrographolide inhibited the expression of an inducible isoform of nitric oxide synthase linked to endotoxin-induced circulatory shock[59].

4.9 Cardiovascular activities

Preliminary research in animals has indicated that *A. paniculata* may be useful in preventing coronary heart disease (CHD), and especially in preventing a condition associated with the treatment of CHD that has been very difficult to control: restenosis[59]. It is well accepted that fish oil has beneficial effects in the prevention and management of cardiovascular disease[61]. However, fish oil has not conclusively been shown to reduce restenosis following angioplasty. In an animal model, *A. paniculata* was shown to be twice as effective as fish oil in preventing the incidence and severity of restenosis following angioplasty[60]. The mechanism of this activity may be due to the antithrombotic effects of *A. paniculata*, resulting in the decrease in thromboxane and platelet aggregation[62].

Chewing the fresh leaves of *A. paniculata* has been claimed to be effective against hypertension[63]. The aqueous extract of *A. paniculata* produced a significant decrease in systolic blood pressure of both spontaneously hypertensive rats (SHR) and Wistar Kyoto (WKY) rats when administered as a chronic infusion with osmotic pumps[64]. The cardiovascular activity of 14-deoxy-11,12-didehydroandrographolide **(11)** was elucidated in anaesthetised Sprague-Dawley (SD) rats and isolated rat right atria. In anaesthetised rats, 14-deoxy-11,12-didehydroandrographolide **(11)** produced significant falls in mean arterial blood pressure and heart rate in a dose-dependent manner. Both *in vivo* and *in vitro* tests demonstrate that the hypotensive effect of 14-deoxy-11,12-didehydroandrographolide **(11)** seems to be mediated through β-adrenoceptors, autonomic ganglion receptor and ACE inhibitory activity[64].

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4.10 Antimicrobial activity

The antimicrobial activity of aqueous extract, andrographolides and arabinogalactan proteins from *A. paniculata* were evaluated by Singha et al.[65]. The aqueous extract showed significant antimicrobial activity in comparison to some known antibiotics, which may be due to the combined effect of the isolated arabinogalactan proteins and andrographolides[65].

4.11 Inhibitors of cell cycle progression

The extracts of the dried plant, which contains andrographolide **(1)** compound, have been shown to decrease expression and phosphorylation of $p34^{cdc2}$ kinase, cyclin B and c-Mos for treating or preventing pathogenecity of diseases such as AIDS, Alzheimer's disease and hepatitis (WO 96/17605).

The extract of *A. paniculata* was found to show significant cytotoxic activity against KB and P388 cancer cells. Subsequently, andrographolide, was shown for the first time to have potent cytotoxic activity against KB as well as P388 cells, whereas 14-deoxy-11, 12-didehydroandrographolide **(11)** and neoandrographolide **(13)** failed to show cytotoxic activity in tumour cell lines[25].

A recent study carried out by Rajagopal et al.[66] showed that the anticancer activity may be through the blockage of cell cycle progression by the induction of cyclin dependent kinase inhibitors (CDKI) such as p27 and with a concomitant decrease in cyclin dependent kinase (CDK4) expression. *In vitro* immunomodulatory activity of andrographolide on human peripheral blood lymphocytes demonstrated an increase in cytokine induction (interleukin-2) and enhanced natural killer (NK) cell function. This suggests that andrographolide may exert anticancer activity indirectly by the cytolysis of cancer cells through NK cell activation[66].

A preliminary pharmacokinetics study was carried out to determine the antitumour potential of andrographolide **(1)** in tumour xenografts. It was found that andrographolide **(1)** reaches maximum plasma concentrations in the range of 20-30 μM and has a half life of 1.5 h in nude mice treated with 150 mg/kg of andrographolide. Subsequently shown, andrographolide **(1)** inhibited the growth of MCF-7 tumours in nude mice transplanted with MCF-7 cells, for a period of 14 days[67].

5. Toxicological studies of *A. paniculata* extract and the compounds isolated from *A. paniculata*

5.1 Antifertility and Spermicidal Effect

It should be made clear to all potential users of *A. paniculata* that it has clear antifertility effects in experimental animals, both in males and females. Subchronic toxic effects and inducing infertility in male rats of this plant was described by Akbarsha et al.[68]. A dose of 20 mg (powder) of *A. paniculata* per day for 60 days, resulted in cessation of spermatogenesis, and regression of Leydig cells, suggesting an antispermatogenic and/or antiandrogenic effect of this plant[68]. Female rats become infertile at high doses[69] and may abort[70].

5.2 Testicular toxicity

The testicular toxicity of *A. paniculata* dried extract was evaluated in male Sprague Dawley rats by Burgos et al.[71]. Testicular toxicity was evaluated as by reproductive organ weight, testicular histology, ultra structural analysis of Leydig cells and testosterone levels after 60 days of treatment, with the treatment of 20, 200 and 1000 mg/kg for 60 days. *A. paniculata* dried extract did not induce subchronic testicular toxic effects and did not produce morphological or functional changes in Leydig cells[71].

DISCUSSION

Nature is an attractive source of new therapeutic candidate compounds and has a tremendous chemical diversity found in millions of species of plants, animals, marine organisms and microorganisms. The development of novel agents from natural sources presents obstacles that are not usually met when one deals with synthetic compounds. For instance, there may be difficulties in accessing the source of the samples, obtaining appropriate amounts of the sample, identification and isolation of the active compound in the sample, and problems in synthesizing the necessary amounts of the compound of interest. Isolation, identification, characterization and quantification of potential phytochemicals from natural source, have become

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an important area of pharmaceutical research. Modification of the active pharmacophores from plants by analogue synthesis to improve the therapeutic efficacy has resulted in the development of several therapeutically valuable drugs.

Andrographis paniculata nees is one of the most important medicinal plants, having been used in Chinese and Ayurvedic medicine for colds, gastric disorders, influenza and other infectious diseases. An extract of *A. paniculata*, standardized for its content of andrographolide and deoxyandrographolide and called 'Kan Jang', has been used extensively in Scandinavia for the treatment of common cold[2]. Extracts of this plant and its constituents are reported to exhibit a wide spectrum of biological activities. Andrographolide, an extremely bitter compound, the primary constituent of the plant *A. paniculata*[27]. Besides andrographolide, other related diterpenoid compounds include neoandrographolide, 14-deoxyandrographolide, andrographisside etc.[25].

Andrographolide constitutes 70% of the plant extract and has been subjected for various molecular mechanisms. Andrographolide has the potential to prevent multiple organ dysfunction by inhibiting C5a-induced chemotactic migration of macrophages[72]. This effect is associated with inhibition of intracellular ERK1/2 and Akt signal transduction pathways[72]. As an effective anti-migratory drug against C5a-attracted leukocytes recruitment, andrographolide may be useful in sepsis by limiting the early phases of macrophage infiltration. Andrographolide is also an inhibitor of NF-κB binding to DNA, exhibiting strong potential anti-inflammatory properties and providing tools for cancer treatment and autoimmune diseases[45]. These results suggest that andrographolide is an interesting pharma cophore with anticancer and immunomodulatory activities. This dual activity makes andrographolide an interesting scaffold for analog synthesis and to develop novel anticancer agents with improved therapeutic efficacy[66]. A number of andrographolide analogs has been synthesized and evaluated for anticancer activities. Majority of the analogs has shown improved potency against different cancer cell lines and structure activity relationships of andrographolide analogs as novel cytotoxic agents also evaluated[73-80].

CONCLUSION

Owing to the diversified pharmacological activities of the plant extract and its major constituent, andrographolide, *Andrographis paniculata* has attracted special attention among medicinal plants for the treatment of various diseases. Modification of andrographolide structure has resulted improved potency for anticancer activity. Hence, using andrographolide as a template for further synthesis of its analogs would lead to clinically useful molecules like other natural products, some of which are already in market and some are in clinical trails.

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