



## Review Article

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### AN OVERVIEW ON *ANDROGRAPHIS PANICULATA* (BURM. F.) NEES

Ghosh Kumar Benoy, Datta Kumar Animesh\*, Mandal Aninda, Dubey Kumari Priyanka and Halder Sandip  
Department of Botany, Cytogenetics, Genetics and Plant Breeding Section, University of Kalyani, Kalyani - 741235,  
West Bengal, India

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#### \*Corresponding author

E-mail: dattaanimesh@gmail.com

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#### ABSTRACT

*Andrographis paniculata* (Burm. F.) Nees (Family: Acanthaceae) commonly known as Kalmegh (King of Bitters) is an important plant species in Ayurvedic medicine (prominent in 26 Ayurvedic formulations). An overview is conducted in the species considering all essential aspects namely, therapeutic uses, synonyms, common names, distribution, habitat, soil condition, cultivation, harvest, post harvest and storage, plant description, reproductive biology, cytological aspects, cytogenetical study, molecular genetics, extraction and detection of phytochemicals, assay, phytochemistry, insecticidal activity, clinical trials, contraindications and drug interactions, clinical implications, regulatory mechanism, *in vitro* studies and mutational studies to provide unabridged repository of references to researchers for its effective biological utilization.

**Keywords:** *Andrographis paniculata*; kalmegh; overview

#### INTRODUCTION

*Andrographis paniculata* (Burm. F.) Nees (Family: Acanthaceae) commonly known as Kalmegh (English name: King of Bitters) is an annual herb<sup>1</sup> possessing immense therapeutic uses (mostly used parts are roots, leaves and aerial part of mature twig). The species is also reported to be perennial shrub<sup>2</sup>. It is native to India and Sri Lanka. An overview on *A. paniculata* covering nearly all essential aspects are documented in the text with an objective to provide knowledge for its proper utilization in human welfare and future exploration in the field of genetics and breeding for improvement.

#### Therapeutic Uses

*A. paniculata* is prominent in 26 Ayurvedic formulations as evidenced from Indian Pharmacopoeia; while, in Traditional Chinese Medicine it is an important “cold property” herb used to release body heat in fever<sup>3</sup>. The species is well explored therapeutically and effectively used as immunostimulant<sup>4</sup> and for asthma, gonorrhoea, piles<sup>5</sup>, dysentery and dyspepsia<sup>6</sup>, blood purification<sup>7</sup>, influenza<sup>8</sup>, gastric complaints, diarrhea<sup>9</sup>, pharyngitis<sup>10</sup>, fever<sup>11</sup>, loss of scalp hair<sup>12</sup>, snake bite<sup>13</sup>, myocardial ischemia<sup>14</sup>, common cold<sup>15</sup>, diabetes<sup>16</sup>, respiratory tract infections<sup>17</sup>, jaundice<sup>18</sup> among others. The species also possesses antiulcerogenic<sup>19</sup>, antityphoid<sup>20</sup>, anti snake venom<sup>21</sup>, antiplatelet aggregation<sup>22</sup>, anti HIV<sup>23</sup>, antimalarial<sup>24</sup>, antifertility<sup>25</sup>, anti-inflammatory<sup>26</sup> and antihyperglycemic<sup>27</sup> properties. Bioeffectivity of the species against phytopathogens (bacteria - *Erwinia caratovora*, *Pseudomonas marginales*, *P. syringae*, *P. aeruginosa* and *Xanthomonas compestris*; fungi - *Acremonium strictum*, *Alternaria alternata*, *Aspergillus flavus*, *Bipolaris bicolor*, *Cladosporium herbarum*, *Curvularia lunata*, *Fusarium oxysporum*, *Penicillium expansum*, *Rhizoctonia solani*, *Tiarosporella phaseolina* and *Ustilago maydis*) was noted from methanolic (95%), chloroform (80%) and hexane (65%)

extracts<sup>3</sup>. Ethanolic extract of the leaves of *A. paniculata* was reported to inhibit growth of *Escherichia coli* and *Staphylococcus aureus*<sup>28</sup>; while, methanolic extract was effective against *Proteus vulgaris*<sup>29</sup>. Komwatchara<sup>30</sup> and Rassameemasmaung<sup>31</sup> reported that *A. paniculata* has inhibitory effect against *Porphyromonas gingivalis*. Prajjal *et al.*<sup>32</sup> reported significant antimicrobial activity of aqueous extract of the species containing andrographolide and arabinogalactan proteins. Roy *et al.*<sup>33</sup> also assessed the anti-microbial activity from inhibition zones, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of *A. paniculata* extracts (chloroform and chloroform+HCl) on four gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Enterobacter faecalis*, *S. epidermidis*) as well as five gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Salmonella typhimurium*, *Enterobacter cloacae*) and suggested the utility of the species in development of novel broad spectrum antimicrobial agents.

#### Synonyms

*Andrographis paniculata* Wall ex. Nees<sup>34</sup>, *Justicia latebrosa* Russell ex Wall., *J. paniculata* Burm. f., *J. stricta* Lam. Ex Steud.<sup>35</sup>.

#### Common Names

Kalmegh, Kalafath, Kan-jang, Alui, Charita, Cherota, Chiraita, Cheretta, Kariyat, Green chiretta, Halviva, Kreat, Sinta, Rice bitters, Sambilata, Sambiloto, Andrographidis, Kraut<sup>36-41</sup>.

#### Distribution

Widely found and cultivated in tropical and subtropical Asia, south-east Asia and India<sup>37</sup>. The species is also reported from different phytogeographical and edaphic zones of China, America, West Indies and Christmas Island in Indian Ocean<sup>42</sup>.

### Habitat

The herb is found in a variety of habitat viz. plains, hill slopes<sup>42</sup>, waste lands<sup>43</sup>, farms, dry or wet lands<sup>44</sup>, sea shore and even in the road side.

### Soil Condition

The plant grows well in all types of soil which explains its wide distribution. It grows in soil types where almost no other plant can be cultivated, particularly 'serpentine soil', which is relatively high in metals such as aluminum, copper and zinc<sup>45</sup>. However, soil that is flooded or wet throughout the year may be avoided for its cultivation<sup>46</sup>. The species was also observed to grow luxuriously in mild humid locations with tropical temperature and high rainfall<sup>34,47</sup>. Vijaya et al.<sup>48</sup> recommended the use of vermicompost coirpith for the reclamation of soils from industrial sites for the cultivation of *A. paniculata* in a small scale nursery.

### Cultivation

Cultivation experiments were reported by different authors, namely, Zhou<sup>43</sup>, Nandi<sup>49</sup>, Gupta and Srivastava<sup>50</sup>, Muniramappa et al.<sup>44</sup> among others and they were of the opinion that in general *A. paniculata* prefers sunny condition and is raised from seeds. The seedlings raised in nursery beds should be transplanted to field at a distance of 60 cm × 30 cm with 1 to 3 irrigations during the day periods particularly at flowering stage. In India the seeds of the species are sown in the months of May – June, flowers during August – November and the whole plant starts maturing during February – March. Maximum harvest of total diterpene lactones was noted at blooming from the aerial part.

### Harvest

The best harvesting period of *A. paniculata* leaves<sup>51</sup> is at 3-5 months old or at 50% blossom whereupon the highest quantity of active lactone compound was found followed by final harvesting after next 2-3 months, with an yield of 2-3 ton per hectare (fresh weight) or 0.5-1 tons per hectare (dried weight).

### Post Harvest and Storage

After harvest, the plants were cleaned and dried (cutting the plant into pieces) in hot air oven at 46°C to 50°C for 8 hours or until properly dried. The dried plant parts were stored in airless plastic bags and kept in clean cool place but not more than a year or otherwise there may be a decrease (upto 25%) in quantity of total diterpene lactone<sup>52</sup>.

The stability of andrographolide was determined using a heat-accelerated experiment to reveal a 2<sup>nd</sup> order kinetics of degradation and the rate constant of decomposition was determined to be  $6.58 \times 10^{-6} \text{ d}^{-1}$  at 25°C<sup>53</sup>.

### Plant Description

The plant species is described on the basis of seeds (obtained from Govt. Medicinal Plant Garden, Narendrapur, West Bengal, India) sown in the experimental field of Dept. of Botany, University of Kalyani (22° 99'N, 88° 45'E, elevation 48 feet above mean sea level, sandy loamy soil, organic carbon-0.76%, soil pH 6.85). Voucher specimen deposited in the Herbarium, Dept. of Botany, University of Kalyani, Docket No. – AP01.

Annual branched herb (Figure 1); stem tetragonal, slightly winged, solid, woody, glabrous, green (31264 - color confirmed from British Atlas of Colour, 9<sup>th</sup> Edt., 2007); leaves opposite decussate, simple, 6.0 – 10.0 cm long and 3.5 – 5.0 cm wide, acute to acuminate at apex, entire at margin, often recurved at maturity, cuneate at base, herbaceous, unicostate reticulate with 5 to 6 pairs of usually alternate pinnate secondaries, glabrous on both surface, green (31264) to bottle green (31264) and often with copper shade (84351) coloration above at edge especially during flowering, petiole; petioles slender 0.4 – 0.5 mm long, glabrous, greenish (31260); exstipulate; inflorescence paniculate cyme, both axillary and terminal; upper 5 to 6 axils with peduncles; peduncles 3.0 to 5.0 cm long, tetragonal, angles hairy along the four ridges; hairs dentate to scabrid, glabrescent at maturity, green (31264); bractiate, bracts 2, opposite decussate, linear oblong to lanceolate, lower larger, upper smaller, 2.0 to 3.0 mm long and 0.5 to 1.0 mm wide, often hairy, green (31264), persistent; secondary peduncles 2.0 to 3.0 cm long alike to primary peduncle; bracts of secondary peduncles alike to primary peduncles; flowers complete, bisexual, hypogynous, irregular (zygomorphic), pentamerous, pedicellate; pedicels tetragonal, 2.0 to 3.0 mm long with glandular hairs, dull green (31258) often enlarged up to fruit, 2 mm long; sepals 5, linear dentate with glandular hairs; calyx tube turbinate with glandular hairs on the outer surface, corolla two lipped about 9.0 mm to 10.0 mm long, color pinkish violet (64220), hairy on the outer surface more towards posterior lobe and apex; posterior lip oblong, hooded over the anterior lip; anterior lip 3 lobed, median lobe larger broad, lateral smaller, outer surface with glandular hairs, glabrous within, having purple (64312) oval spot on the median lobe within and two purple (64312) lines to each lateral lobe within (Figure 2); corolla tube narrowed 5.0 mm long (Figure 3); androecium – stamens 2; filaments declinate, epipetalous, alternipetalous, pubescent throughout and more bristly at the base of anther attachment, whitish (00016) with purple (64312) lines; anther 2 celled oblong, dark (Figure 3) purple (643221); gynoecium 2, syncarpous; ovary superior, oblong, slightly 2 lobed, many ovules per chamber in axile placentation, glandular hairy throughout; style 1, terminal, purple (64312), glabrous; stigma shortly 2 fid; fruits simple, dry dehiscent, capsules laterally flat with 2 distinct lobes, marked by central depression along the septation (Figure 4), 12.0 mm to 17.0 mm long and 2.0 mm to 3.5 mm wide, spinous at the apex, narrowed at base, dull brown (44035) color at maturity; dehiscent loculicidal, many seeded (12 – 16); seeds attached on retinacula, seeds flat and often incurved, compressed, translucent, size  $1.4 \text{ mm} \pm 0.34 \times 0.9 \text{ mm} \pm 0.25$  (length × breadth), golden brown (41332) in color (Figure 5) with tumid testal surface.

### Anatomical Studies

Transverse sections (hand sections) of the stem from the basal region (5.0 to 6.0 cm from base at maturity) and root (4.0 to 4.5 cm below base at maturity) were made from fully matured plants (at fruit ripening stage; 110-125 days from sowing), and the sections were double stained using 1.0% Safranin (Merck, AR) dissolved in 50.0%

alcohol and 1.0% Light green (Merck, AR) dissolved in 90.0% alcohol<sup>54</sup>.

**Stem (Figure 6):** Tetragonal in outline; angles shortly winged with projections consisting of 1 cell layer epidermis and groups of parenchymatous cells within; shallow between ridges; thin walled compactly arranged cells cover with thin cuticle and associated with glandular hairs outside; hypodermis 2 to 5 cell layer thick, often variable in the shallow region; cells more or less rounded to polygonal, equal or larger than epidermal cells, thin, compactly arranged, containing chlorophylls; cortical

layers variable, 5 to 6 cell layer thick, up to 10 below the shallow area, rounded, thin walled, compact, parenchymatous without any contents; stele amphipholic siphonostele occupying maximum part of the stem, more spreading to the ridge area; a few sclerenchymatous cell groups of 2 to 4 or even solitary throughout the periphery of the vascular bundles; outer phloem thin layered, inner phloem mostly in patches; xylem interrupted with medullary rays; pith parenchymatous, cells polygonal to rounded, larger in size, thick walled, compactly arranged, without any content.

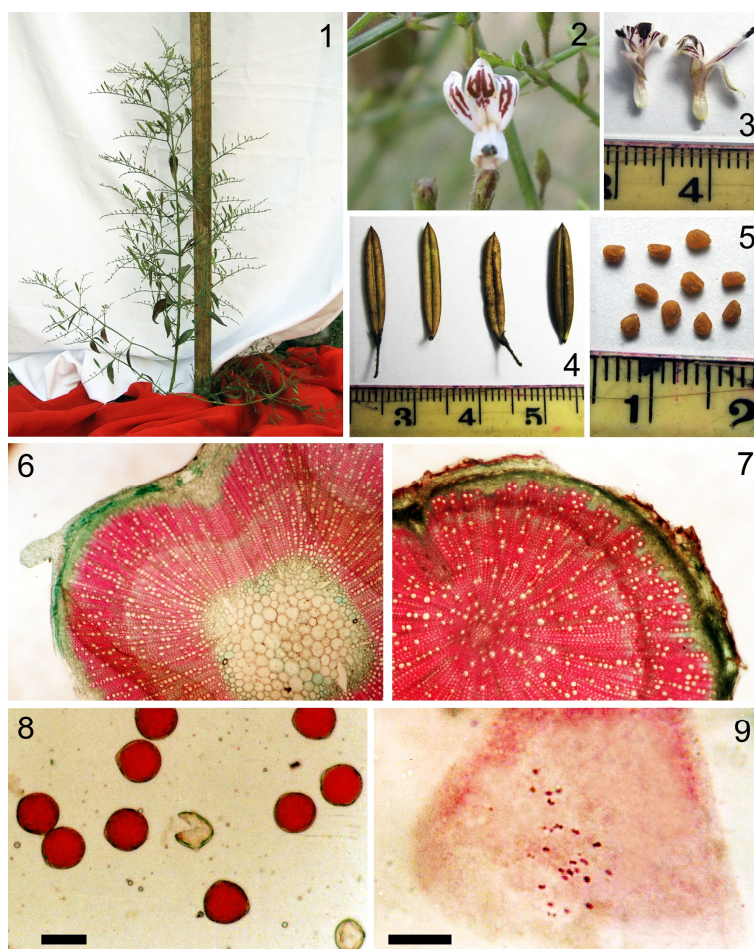


Figure 1-9: *Andrographis paniculata*. 1- Matured erect branched plant. 2- Flower lobes showing pigmentation. 3- Dark purple anther. 4- Fruits. 5- Golden brown seeds. 6- T.S. of stem. 7- T.S. of root. 8- Stained and unstained pollen grains (scale bar = 60 µm). 9- Metaphase I showing 25II (2n=50, scale bar = 20 µm).

**Root (Figure 7):** Secondary growth visible; epiblema not distinct replaced by cork layer, differentiated into 3 distinct zones; peripheral cell layer loosely arranged, inner cells smaller, compactly arranged; stele occupying the maximum part of the root being the secondary growth; xylem and ray cells in distinct rows, primary vascular bundle crushed; pith insignificant having few parenchymatous smaller cells.

#### Reproductive Biology

*A. paniculata* is hermaphrodite self compatible and a habitual inbreeder. Both stigma and anthers are in intimate proximity showing synchronization of anther dehiscence and stigma receptivity respectively thereby providing autonomous selfing in the species<sup>42</sup>. The

present authors analyzed number of features namely, seed set percentage on open pollination ( $80.36 \pm 0.44$ ) and on self pollination ( $82.42 \pm 1.92$ ); seed germinability in petri plates (88.0%) and in field (34.0%), 100 seed weight ( $117.04 \text{ mg} \pm 0.44$ ), seed moisture content (11.55%); number of pollen grains per flower ( $3927.12 \pm 129.62$ ); pollen fertility (73.68% - Figure 8; based on 1% acetocarmine stainability - Marks<sup>55</sup>); pollen size ( $48.26 \mu\text{m}$  to  $75.8 \mu\text{m}$ , mean -  $55.93 \mu\text{m} \pm 2.62$ ), number of ovules/flower (12), number of seeds/fruit (12 to 16); seed protein content (0.065%), leaf protein content (0.0076%), extracted as per Osborne<sup>56</sup> and estimated following Lowry *et al.*<sup>57</sup> These parameters may be useful for breeding endeavor.

### Cytological Aspects

The somatic chromosome number in *A. paniculata* was reported to be  $2n = 50^{58-64}$ . Roy and Datta<sup>64</sup> assessed different biotypes (collected from India and Bangladesh) of the species and suggested variations (chromosome length  $0.50 \mu\text{m} - 1.75 \mu\text{m}$  to  $1.00 \mu\text{m} - 2.00 \mu\text{m}$ ; total diploid chromosome length –  $51.66 \mu\text{m}$  to  $70.00 \mu\text{m}$ ) among the biotypes, which was attributed to minute structural aberrations like translocations, deletions, etc. Chromosomes with secondary constrictions among the biotypes ranged from 4 to 8. The present authors analyzed meiotic chromosomes and confirmed the number as  $2n = 50$  (25 II formation at MI, 23 cells scored; 25 – 25 separation of chromosomes at AI, 39 PMCs analyzed) chromosome in the species (Figure 9).

### Cytogenetical Study

Lattoo *et al.*<sup>42</sup> induced genetic male sterility (6.0 to 14.0%) in *A. paniculata* at  $M_1$  following 20 kR gamma irradiation and the male sterile gene was found to be monogenic recessive to normal. The male sterile gene acted upon the tapetal layer and also affected non sporogenous tissue within the anther locule resulting in encroachment of the locule and thereby, significantly reducing the pollen production and enhancing the formation of abortive pollen. However, female fertility remained unimpaired and fully intact.

### Molecular Genetics

Padmesh *et al.*<sup>65</sup> analyzed 52 accessions (displaying morphological and phytochemical variation) of *A. paniculata* from India, Thailand, Malaysia and Indonesia for intra-specific variability following RAPD analysis. Molecular analysis revealed moderate variation within the species. UPGMA followed by cluster analysis resulted in five major groups among/between genotypes and it was noted that AP-48 (Thailand) had close resemblance to AP-38 (Tamil Nadu) and AP-29 (Assam). Results indicated that RAPD could be effectively used for assessing genetic diversity and provide prospective value in breeding. Lattoo *et al.*<sup>66</sup> also used RAPD (6 highly polymorphic primers) to elucidate genetic diversity among 53 accessions (varied significantly in morphometric traits) of *A. paniculata* belonging to 5 ecogeographic regions. RAPD based UPGMA and D<sup>2</sup> cluster analysis revealed that the accessions might have originated from native places of wild abundance. The authors were of opinion that assessment of both morphometric traits and RAPD marker analysis are complementary approaches to make diversity analysis more explanatory and purposeful for optimum genetic amelioration and effective conservation of genotypic variability. On the contrary, Sakuanrungsirikul *et al.*<sup>67</sup> documented that two molecular marker (ISSR-43 primers used and 391 loci detected, but monomorphic across all accessions; RAPD-41 primers used and 195 loci detected) approaches could not detect genetic variations among 44 accessions (Thailand) of the species.

### Extraction and detection of Phytochemicals

Cheung *et al.*<sup>68</sup> standardized a simultaneous extraction (ethanolic), separation and detection method for andrographolides, deoxyandrographolide and neoandrographolide from the species in fused-silica capillary tube using micellar electrokinetic

chromatography with UV detection at 214 nm. Li *et al.*<sup>69</sup> also standardized a quantitative HPLC method with photodiode array detection using methanolic extract of *A. paniculata* and identified the fractions as methyl, ethyl and propyl esters of  $\beta$ -hydroxybenzoic acid, using high resolution mass spectrophotometry and NMR. Pholphana *et al.*<sup>70</sup> proposed a rapid method for extraction and simultaneous determination of 3 active diterpenoids using isocratic HPLC with methanol and water mobile phase. This method yielded very high purity fractions from crude methanol extracts of dried leaves and stems of *A. paniculata*. Vijaykumar *et al.*<sup>71</sup> also quantitated and validated andrographolide content following HPLC and HPTLC analysis.

### Assay

Assay of andrographolide ( $C_{20}H_{30}O_5$ ) can be successfully performed by extracting total andrographolide by 85% ethanol and precipitation by lead (II) acetate and following the residual titration method using 0.1M NaOH with phenolphthalein as indicator<sup>72</sup>.

### Phytochemistry

The primary medicinal component of *A. paniculata* is andrographolide (diterpene lactone) which is bitter in taste and colorless crystalline in appearance. Analysis of the whole plant (dry basis) yields andrographolides –  $C_{20}H_{30}O_5$ , mp 230 - 239°C, 0.6%<sup>73</sup>; 14-deoxy-11-oxoandrographolide,  $C_{20}H_{28}O_5$ , mp 100°C, 0.12%<sup>74</sup>; 14-deoxy-11, 12-didehydroandrographolide – andrographolide D,  $C_{20}H_{30}O_4$ , mp 203 - 204°C, 0.06%<sup>75</sup>; 14-deoxyandrographolide,  $C_{20}H_{30}O_4$ , mp 175°C, 0.02%, and a non-bitter constituent, neoandrographolide –  $C_{26}H_{40}O_8$ , mp 167 - 168°C, 0.005%<sup>76</sup>. The leaves contain the maximum amount of andrographolide (1.0% to 2.39%), while the seeds contain the lowest<sup>77</sup>. The leaves also possess diterpenoids (bitter principles) viz. deoxyandrographolide, 19 $\beta$ -D-glucoside and neoandrographolide. The roots of the species contains apigenin – 7,4'-di-o-methyl ether, andrographolide and a new natural flavones, 5-hydroxy 7,8,2',3'-tetramethoxy flavones ( $C_{19}H_{18}O_7$ , mp 150 - 151°C, yield – 0.006%). They also contain monohydroxy trimethyl flavones, andrographin ( $C_{18}H_{16}O_6$ , mp 190 - 191°C) and a dihydroxy-di-methoxyflavone, panicolin ( $C_{17}H_{14}O_6$ , mp 263 - 264°C) apart from the presence of  $\alpha$ -sitosterol<sup>78</sup>. Rao *et al.*<sup>79</sup> identified two flavonoids namely, 5,7,2',3'-tetramethoxyflavanone and 5-hydroxy-7,2',3'-trimethoxyflavone as well as several other known flavonoids, andrographolide diterpenoids and polyphenols from the whole plant of *A. paniculata* (MeOH extract was divided into  $CHCl_3$ ,  $Me_2CO$  and MeOH soluble fractions) following spectroscopic method, including analysis by 2D NMR spectroscopy. Kulyal *et al.*<sup>80</sup> reported several diterpenic constituents like andrographolide, 14-deoxy-11, 12-didehydroandrographolide, 14-deoxyandrographolide, 3,14-dideoxyandrographolide, 14-deoxy-11-oxoandrographolide, 14-deoxy-12-hydroxyandrographolide, neoandrographolide, andrographiside and 14-deoxyandrographiside from ethanolic extract of aerial parts of *A. paniculata*. The structure of the compounds were established on the basis of spectral data analysis. Xu *et al.*<sup>81</sup> reported a novel

diterpene (13R, 14R) 3, 13, 14, 19-tetrahydro-ent-labda-8(17), 11-dien-16, 15-olide 1 from ethanolic extract of leaves of the species. The structure of the compound was confirmed by X-ray crystallographic analysis.

#### Insecticidal Activity

Bright *et al.*<sup>82</sup> analyzed bioefficacy of different solvent fraction of *A. paniculata* against cowpea weevil (*Callosobruchus chinensis* L.) during post harvest storage of cowpea (*Vigna unguiculata* L. Walp.) in terms of adult mortality, total egg output and emergence of F<sub>1</sub> adults. Results indicated that adult mortality for methanolic and ethyl acetate extract were 72.01% and 67.69% respectively at the highest concentrations (1000 ppm). Total egg and percentage emergence of F<sub>1</sub> adults were lowest for methanolic fraction. The authors were of opinion that the principle chemical constituents of *A. paniculata* might be responsible for the mortality of the pest along with reduction in egg laying and adult emergence. Zaridah *et al.*<sup>83</sup> reported that aqueous extract of dried leaves of *A. paniculata* possess antifilarial activity when tested *in vitro* against adult worms of subperiodic *Brugia malayi*. The relative movability of the adult worms over the 24 hour observation period was taken as the index of measurement for the study. Uawonggul *et al.*<sup>84</sup> reported that extract of *A. paniculata* may be used as an antidote against scorpion (*Heterometrus laoticus*) venom, and the activity was measured from relative lysis of fibroblast cells.

Kuppusamy and Murugan<sup>1</sup> reported mosquitocidal effect of *A. paniculata* (ethanolic extract of whole plant) against the malarial vector *Anopheles stephensi* Liston (Diptera: culicidae). The ethanolic extract of the species was found to possess larvicidal, pupicidal, adulticidal and ovicidal activities and these were attributed to the toxic impact of andrographolide, 14-deoxy-11,12-didehydroandrographolides, andrographin and homoandrographolide, 19-β-D glucosides, flavonoids and related compounds either singly or jointly. Elango *et al.*<sup>85</sup> revealed that leaf hexane extracts of *A. paniculata* is a potent repellent ovicidal and oviposition deterrent against *Culex tritaeniorhynchus* (Japanese encephalitis vector).

#### Clinical Trials

Thamaree *et al.*<sup>86</sup> reported that *A. paniculata* (500 mg every 6 h and 1 g every 12 h) can reduce both frequency and amount of defecation and also the ORS. It also effective against *Shigella* bacteria compared to tetracycline. Thamlikitkul *et al.*<sup>10</sup> illustrated the comparative efficacy in treatment of Pharyngotonsillitis between powder of *A. paniculata* at dosage of 3, 6 and paracetamol 3 g/day. The results showed that the patients receiving paracetamol and powder of *A. paniculata* at 6 g/day recovered from pyresis and pharyngotonsillitis faster than the patients receiving only powder of *A. paniculata*. Muangman *et al.*<sup>87</sup> showed that *A. paniculata* at dosage of 100 mg three times a day showed equal efficacy as cotrimoxazole at 50 mg twice a day or norfloxacin at 200 mg twice a day in reduction of pus, blood or protein in urine.

Cáceres *et al.*<sup>88</sup> studied the effectiveness of dried extract (SHA-10) of *A. paniculata* in a group of 158 adults of both the sexes divided into equal groups, one of which received the extract (1200 mg/day) and the other a

placebo during a period of five days for evaluation of symptoms like headache, tiredness, ear ache, sleeplessness, sore throat, nasal secretion and intensity of cough. Results obtained were calculated using a logistic regression model and it indicated that the dried extract of the species was much more effective in reducing the prevalence and intensity of the symptoms in uncomplicated common cold beginning at day 2 of treatment with no adverse effect.

Calabrese *et al.*<sup>23</sup> performed a phase I clinical trial of andrographolide in thirteen HIV positive patients and five uninfected volunteers (dosage administered-5 mg/Kg to 10 mg/Kg for the first 3 weeks and 20 mg/Kg for the final 3 weeks; based on body weights, trial interrupted at 6 weeks). Results suggested that andrographolide may inhibit HIV induced cell cycle dysregulation leading to a rise in CD4 (+) lymphocyte levels in HIV-1 infected individuals. No change in mean plasma HIV-1 RNA levels was noted throughout the trials. Amaryan *et al.*<sup>89</sup> andrographolide at 48 mg/day was tested in patients suffered from FMF for 1 month and the results obtained showed reduction of duration, frequency and severity of symptoms in relation to abdominal or chest pain, fever, arthritis and muscle pain. Spasov *et al.*<sup>90</sup> compared the efficacy of Kan Jang (herbal combination containing standardized *A. paniculata*) SHA-10 extract with Immunol, which contains *Echinacea purpurea* (L.) extract, in uncomplicated common cold in 130 children aged between 4 and 11 years over a period of 10 days. The effectivity of Kan Jang over Immunol was much pronounced in controlling nasal secretion and nasal congestion. Agarwal *et al.*<sup>91</sup> studied adverse effects and tolerance to dry powder of aerial part of *A. paniculata* in 20 patients with type 2 diabetes mellitus for a period of 12 weeks (600 mg daily increasing gradually to 1.8 gm daily) using parameters like body weight, blood pressure, lever function tests, renal function tests, cardiac enzymes, haemogram, serum electrolytes, fasting blood glucose, HbA1c, blood cholesterol serum triglycerides and blood hormone levels. It was noted that powdered extract of the species did not induce significant adverse effect based on the parameter studied but significantly lowered HbA1c and fasting serum insulin in patients with type 2 diabetes. Mkrtychyan *et al.*<sup>92</sup> performed phase I clinical study with Kan Jang (SHA-10 extract) and standardized extract of *Valeriana officinalis* and *Panax ginseng* to evaluate the effect of semen quality of healthy males in terms of spermatogenesis. The results of the study revealed no significant negative effect of Kan Jang on male semen quality and fertility, but rather a positive trend was recorded with respect to active number of spermatozooids. The authors were of opinion that Kan Jang, ginseng and valerian were safe with respect to effect on human male sterility at three times the human daily dose. Liu *et al.*<sup>93</sup> reported that oral administration of neoandrographolide (150 mg/Kg) significantly suppressed ear edema in mice; while, vascular permeability enhanced (100-150 mg/Kg). Further, *in vitro* studies revealed that neoandrographolide inhibits nitric oxide (NO) and tumour necrosis factor-α (TNF- α) production in lipopolysaccharide (LPS) induced macrophages, thereby contributing to the anti-inflammatory activity of *A. paniculata*. Sheeja and

Kuttan<sup>94</sup> reported that intraperitoneal administration of ethanolic extract of *A. paniculata* along with whole body hypothermia (WBH) enhanced the total WBC count in cyclophosphamide (CTX) and radiation treated Swiss albino mice in comparison to untreated control animals, thereby suggesting immune response capabilities of the extract. Further, it was also suggested that the elevated level of serum TNF- $\alpha$  after CTX and radiation treatment was lowered significantly after the administration of extract and simultaneous exposure of WBH with respect to untreated tumor bearing animals. Allan *et al.*<sup>95</sup> studied the effect of andrographolide ( $\geq 10.0\%$ ) on male fertility in albino Wistar rat (doses administered orally at 0, 20, 200 and 1000 mg/kg of body weight per day, for 65 days prior to mating and 21 days during mating) considering parameters like testosterone levels and fertility indices (total sperm count and sperm motility). Results suggested no adverse effect of andrographolide up to the level of consumption of 1000 mg/kg per day. Burgos *et al.*<sup>96</sup> studied the effect of Paractin (tablets made from 30% andrographolides) on 60 rheumatoid arthritis patients. The tablets were administered three times a day for 14 weeks, after a 2 week wash out period. Pain intensity was measured using a horizontal visual analogue pain scale (VAPS). Results indicated that intensity of joint pain decreased in the active vs. placebo group at the end of treatment, although not statistically significant.

#### Contraindications and Drug Interactions

*A. paniculata* has been suggested not be used during pregnancy or lactation. It is contraindicated in cases of known allergy to plants of the Acanthaceae family. Extracts of Herba Andrographidis may have a synergistic effect with isoniazid<sup>97</sup>.

#### Clinical Implications

Andrographolide induced DNA fragmentation and enhanced percentage of apoptotic cells in TD-47 human breast cancer cell line by increasing the expression of p<sup>53</sup>, bax, caspase - 3 and concomitantly decreasing bcl-2 in a time and concentration dependent manner<sup>98</sup>. The compound also possesses anticancer activity *in vitro* in many tumor cell lines including leukemia, myeloma, Hela, colon (HT - 29), human peripheral blood lymphocytes (HPBLs) and human breast cancer MCF-7<sup>99</sup> apart from having inhibitory effect on DNA topoisomerase II<sup>100</sup>. Cell cycle inhibition by andrographolide was evidenced in human breast cancer cell (MCF-7) was due to the inhibition of the protein p<sup>27</sup> and reduction in the expression of cyclin-dependent kinase<sup>99</sup>.

Lin *et al.*<sup>101</sup> demonstrated that ethanolic extract (25  $\mu\text{g/ml}$ ) of *A. paniculata* and andrographolide (5  $\mu\text{g/ml}$ ) can effectively inhibit the expression of Epstein-Barr virus lytic protein, RTA, Rta, Zta and EA-D during viral lytic cycle in P3HRI cells thereby suggesting their potentiality as an anti-EBV drug. Woo *et al.* (2008) revealed that the herb *A. paniculata* possesses cardioprotective activities. Andrographolide was reported to protect the cardiomyocytes against hypoxia/reoxygenation injury and up-regulated the cellular-reduced glutathione (GSH) level and antioxidant enzyme activities in neonatal rat cardiomyocytes. The

cardioprotective action of the compound was found to be completely abolished by buthionine sulfoximine, which acts as a specific gamma-glutamyl cysteine ligase inhibitor to deplete cellular GSH levels. Chandrasekaran *et al.*<sup>102</sup> assessed the genotoxicity of the standardized extract of the species through three different *in vitro* tests (Ames, chromosome aberration and micronuclei test) at different concentrations. Results of Ames test confirmed that the species did not induce mutation in *Salmonella typhimurium* (mutant strains TA98 and TA Mix), neither showed clastogenicity in CHO-K1 cells and therefore evident that *A. paniculata* is genotoxically safe. Chao *et al.*<sup>103</sup> reported that ethyl acetate extract of *A. paniculata* significantly inhibited NF- $\kappa\text{B}$  luciferase activity and TNF- $\alpha$ , interleukin 6 (IL-6), macrophage inflammatory protein-2 (MIP-2) and nitric oxide secretion from LPS/interferon- $\gamma$  stimulated Raw 264.7 cells. Pekthong *et al.*<sup>104</sup> studied the ability of *A. paniculata* extract (0.5 and 2.5 g/kg/day) on the expression of cytochrome P450 (CYP) both *in vivo* in rats and *in vitro* in rat and human hepatocyte cultures. The authors concluded from the experiments that both herbal extract and andrographolide can modulate the expression and activities of CYP2C9 and CYP3A4.

#### Regulatory Mechanism

Smith *et al.*<sup>105</sup> identified an active compound bisandrographolide A (BAA) from standardized extract of *A. paniculata* and it was found to potentially activate TRPV4 (transient receptor potential) channel (but not TRPV1, TRPV2 and TRPV3) with an EC<sub>50</sub> of 790 to 950 nm following Ca-imaging assay. It is noteworthy to mention that TRPV4 is a non selective cation channel and its activation causes opening of a pore that allows Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup> ions to cross membrane. Thus, the resulting increase in internal free Ca<sup>2+</sup> and changes in transmembrane voltage potentiality can affect cell signaling apart from its implications in osmoregulation, regulation of vascular tone and heat sensation. Jarukamjorn<sup>106</sup> reported the inductive effect of andrographolide on transcriptional regulatory mechanism by increasing hepatic CYP1A (Cytochrome P450 - role in transcriptional regulation has been postulated through arylhydrocarbon receptor, AhR and AhR nuclear translocator) enzymes including ethoxyresorufin and methoxyresorufin activities.

#### In vitro Studies

Martin<sup>107</sup> studied *in vitro* propagation of *A. paniculata* through somatic embryogenesis and also analyzed the influence of 2,4-dichlorophenoxy acetic acid (2,4-D) on induction, maturation and conversion of somatic embryos. Friable callus was initiated using leaf and internode explants in MS medium supplemented with various concentrations of 2,4-D. Embryos formed from 105 to 185 days after explant establishment, wherein callus subcultured on reduced 2,4-D concentration (2.2  $\mu\text{M}$  and  $\frac{1}{2}$  MS - liquid media) gave rise to highest number of embryos (mean of 312) of which 71% of the embryos underwent maturation out of those 83% developed into plantlets and 88% of the plantlets survived under field condition. Praveen *et al.*<sup>108</sup> induced adventitious roots directly from leaf segment of *A. paniculata* on MS medium with 5.3  $\mu\text{M}$   $\alpha$ -naphthaleneacetic acid (NAA) and 30 gm/l sucrose and highlighted the great potentiality of

adventitious root cultures for the production of andrographolide.

### Mutational Studies

Ghosh *et al.*<sup>109</sup> screened 14 viable macromutants (*viridis*, *lax branching*, *bushy*, *unbranched I* and *II*, *dark green leaf*, *broad leaf I* and *II*, *narrow leaf I* and *II*, *drooping leaf I* and *II*, *dwarf* and *early maturity*) at M<sub>2</sub> following EMS and dES treatments. Mutation frequency over M<sub>2</sub> population was 2.82% and *lax branching* mutant was maximum (0.51%). EMS induced relatively higher (3.12%) frequency of mutation than dES (2.46%). The mutant traits were monogenic recessive mostly (*viridis* showed digenic mode of inheritance). All mutants bred true in M<sub>4</sub> generation. Meiotic analysis revealed 2n=50 chromosome in mutants alike to control. Andrographolide (estimated from matured leaves by HPTLC) content (control: 3.41%, mutants: 0.03 to 3.99%) was significantly higher in *bushy* and *broad leaf I* and *II* than normal plants. The mutants induced were considered to be important genetic resources in the plant species.

### CONCLUSION

Unabridged repository of references has been provided in the text in relation to the comprehensive overview on *A. paniculata* with an objective to update researchers with adequate information for its effective exploration for human benefit.

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