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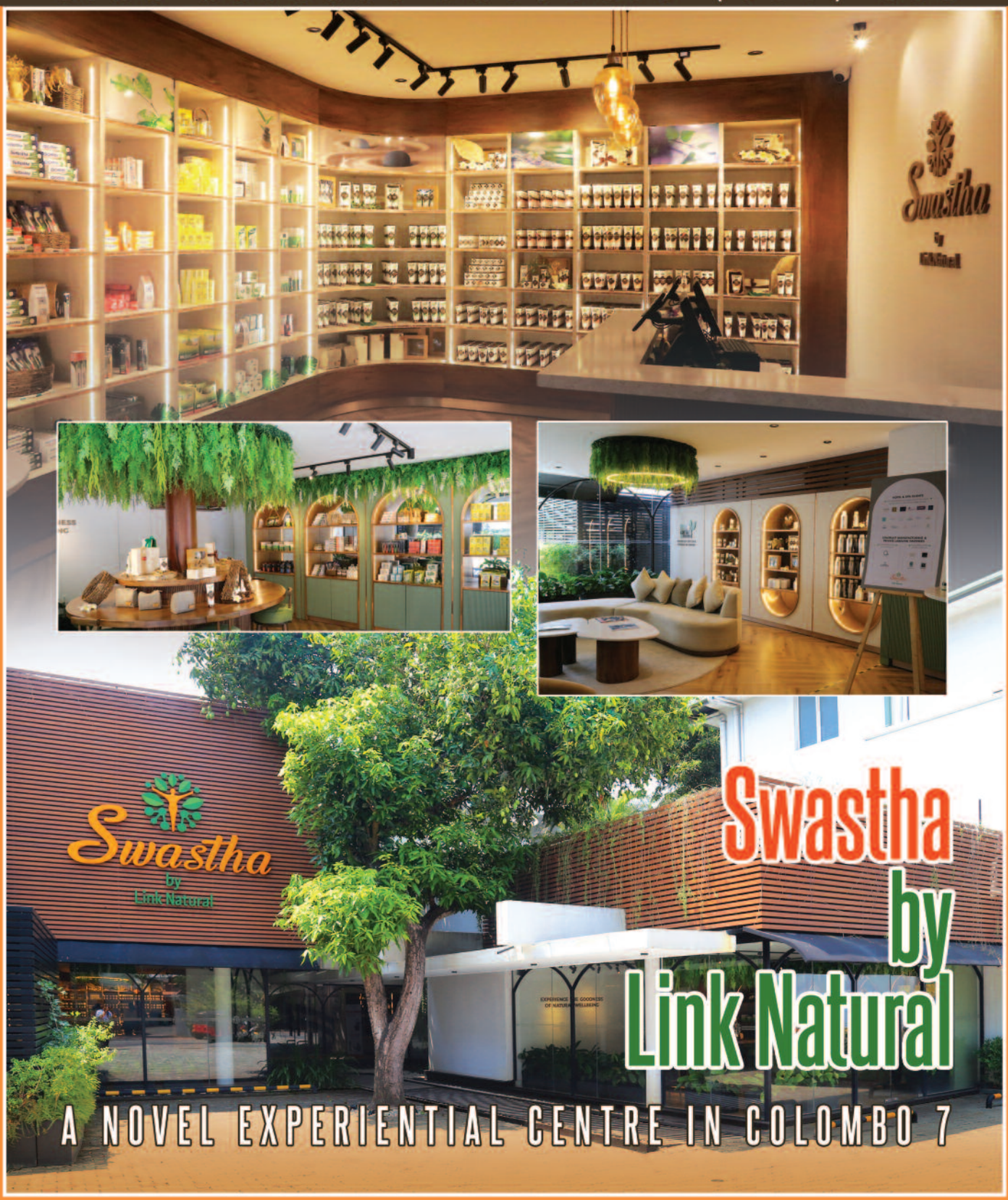

Link Natural DIGEST

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EDITORIAL

We are pleased to introduce a new section in the Link Natural DIGEST which will feature reviews of selected seminars held at our Research and Development facility in the period between the previous issue and the current one. Prof. G. M. K. B. Gunaherath has reviewed the seminar presented by Prof. Leslie Gunatilaka focusing on innovation and multidisciplinary collaboration, in this issue.

Optimizing the harvesting time of medicinal plants used in the manufacture of herbal products has an important bearing on the efficacy of the products and the economy of production. Results of in-house research on optimizing the harvesting time of *Andrographis paniculata* is presented under the Research/Reviews section.

The current issue also features the second part in the three-part series on Arthritis, presenting complementary viewpoints from modern western medicine and Ayurveda. This series in intended to stimulate multi-disciplinary research involving practitioners of the two systems of medicine prevalent in Sri Lanka today.

There is also an account of the recently opened experiential centre, "Swastha", which we hope will enthuse some of our readers to visit the centre, located in Colombo 7.

Ajit Abeysekera

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OPTIMIZING THE HARVEST TIME OF *ANDROGRAPHIS PANICULATA* (Burm.f.) NEES

P.K.V. Ranji

Introduction

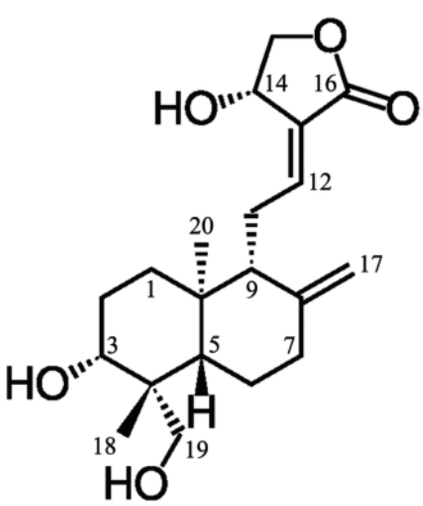
Andrographis paniculata (Burm. f.) Nees (Family Acanthaceae), commonly known as "king of bitters", traditionally known as 'Kalmegh', is an important medicinal plant widely used in Southeast Asian countries. The plant is an annual herbaceous plant (Figure 1) and is extensively cultivated in Southern Asia, China, and some parts of Europe. This species has been used effectively for the treatment of disorders related to liver, immune system, respiratory system, and the cardiovascular system. The plant has been studied widely for its therapeutic effects including anti-inflammatory, immune modulatory, anti-pyretic, analgesic, anti-oxidant, anti-malarial, anti-diarrheal, hypoglycemic, and anti-cancer activity (Jayakumar, T. et al., 2013., Datta K.A. et al., 2012).

Figure 1 : Aerial part and the flowers of *Andrographis paniculata* (Burm. f.) Nees

Figure 2 : *A. paniculata* cultivation at the research fiels at Dambukanda Estate, Link Natural Products (Pvt) Ltd.

In Sri Lanka the plant is famed as "Heen Binkohomba" and is a key ingredient in many of the herbal pharmaceutical formulae in the system of Ayurveda (Compendium of Medicinal plants – A Sri Lankan Study, 2003). At Link natural Products (Pvt.) Ltd. the plant is used widely as a key ingredient in several ayurvedic pharmaceutical formulae. With the high concern for the quality and efficacy of its products and the uninterrupted supply of the authentic plant material, Link Natural Products has initiated the cultivation of *A. paniculata* in its own agricultural lands. (Figure 2)

The plant has been investigated for its bioactive constituents. The major active constituent is the diterpene lactone, andrographolide, (Figure 3) which exhibits several types of pharmacological activities (Mishra S.K. et al., 2007; Ketterman A.J. et al.,2020).



(Figure 3) The Structure of andrographoilde

It is reported that the growing region and the season strongly affects the production of the diterpene lactones in the cultivation (Mishra S.K. et al., 2007). Furthermore, the quality of the drug varies due to variation in environmental conditions at different locations, harvest age, and genetic variation of the material (Bhan M.K. et al.,2006, Mishra S.K. et al., 2007). A study carried out in Jabalpur, India by Parashar R. et. al., 2011 had analyzed the andrographolide content in leaves at different growth stages and found the highest levels of andrographolide in leaves at 120 days. They further carried out a morpho-physiological evaluation of *A. paniculata* at different growth stages up to 120 days, which revealed that growth analytical parameters as well as morpho-physiological parameters increase with crop age (study period up to 120 days), except the specific leaf area which increases up to 90 days and then showed a decline thereafter. In another study carried out in India by Bhan M.K. et al., harvesting at 100 days after transplantation was recommended to obtain the highest content of andrographolide.

To our knowledge, there have been no studies conducted in Sri Lanka on the contents of active constituents at different growth stages from seedling to mature stages of *A. paniculata.* With out this knowledge it is not possible to select the optimum harvest time for obtaining maximum level of active compound, andrographolide. Therefore, we initiated a field study to determine the optimum harvest time of *A. paniculata* by monitoring the variation of the major active principle, andrographolide at different stages of its life cycle, using an analytical HPLC assay method.

Experimental Chemicals and Reagents

All solvents used for HPLC analysis were HPLC grade; acetonitrile was purchased from Honeywell and formic acid was purchased from VWR Chemicals. 0.45 μm Polytetrafluoroethylene (PTFE) membrane filters and C18 cartridge filters were purchased from Agilent. All laboratory chemicals used in the isolation protocol were reagent grade; methanol was purchased from Honeywell, dichloromethane and ethyl acetate were purchased from Merck and n-hexane was purchased from VWR Chemicals. For chromatography, silica gel 60 was purchased from Miles Scientific and pre-coated Aluminum TLC plates (GF 254; 20 x 20 cm) were purchased from Merck.

Plant Materials

Plant Materials for extraction of reference compound and plantlets for field studies were obtained respectively from a previous cultivation and a nursery maintained at the research field at Dambukanda Estate, Link Natural Products (Pvt) Ltd.

Isolation of Andrographolide:

Andrographolide was isolated and purified in the Pharmacognosy Laboratory of Research and Development Centre of Link Natural Products (Pvt.) Ltd. NMR spectroscopic data of isolated andrographolide were obtained from Sri Lanka Institute of Nanotechnology using CD3OD as the solvent and data were recorded at frequency of 400 MHz.

Powdered dried leaves of *A. paniculata* (500 g) were extracted with methanol (1.4 L) using cold extraction with sonication at room temperature. The extract was filtered under suction and residue was re-extracted with 800 mL of methanol with the same method for 6 consecutive extractions (Total volume: 6.2 L). Filtrates were combined and evaporated under suction to obtain crude methanol extract (155.27 g). A sub sample (150 g) of crude extract was dissolved in 50 % methanol/water (600 mL) and filtered through Whatman no. 1 filter paper under suction to remove chlorophyll rich residue. The filtrate was then partitioned with dichloromethane (300 mL X 6 times). The dichloromethane fractions were combined and evaporated under suction to afford a dark brown solid (15.0 g). Repeated re-crystallization of the solid from the dichloromethane extract with dichloromethane: methanol, 2:1 afforded andrographolide (1.5 g) as a white crystalline compound ($C_{20}H_{30}O_5$; M.P. 218-222 ^{0}C, Rec. 218-221 ^{0}C; Fujita, T., et al 1984). The identity and structure of the isolated compound was confirmed by comparison of its 1H-NMR and 13C-NMR spectroscopic data with literature (Liang Cui., et al 2004 and Phattanawasin et al., 2018). The purity was confirmed using melting point, thin layer chromatography (TLC), and high-performance liquid chromatography (HPLC).

Field Experiment

Design: The experiment was carried out at the research field at Dambukanda Estate, Link Natural Products (Pvt) Ltd., Malinda, Kapugoda, Sri Lanka from July – November 2021. The field experiment was performed in a randomized complete block design (RCBD) with three blocks of each containing 120 plants. Healthy 20 - 25 days old plantlets of *A. paniculata* were used for the field experiment. Raised bed plots (width of 105 cm; length of 850 cm; and height of 15 cm) were arranged and culverts in between the plots were made for proper drainage. Planting of the seedlings was done in three rows along the plot length, each row containing 40 plants (30 cm between rows; 20 cm between plants in a row).

The day on which field transferring of plantlets was done, was considered as day zero (0). Harvesting of plants for analysis was carried out on day 30, 60, 90 and 120. Randomization was ensured by selecting the plants using an Excel generated number array. Four plants from each plot were harvested on day 60, 90 and 120, while 16 plantlets from each plot were harvested on day 30 to have sufficient material for analysis. The spaces left after the first harvest (day 30) were filled with plants of the same age maintained in the nursery, (secondary plants) to maintain the uniformity of the plot. Secondary plants were not harvested for future analysis.

Morphometric Analysis: In each plant morphometric observations i.e., plant height (The height of the erect plants from ground surface to shoot apex/cm); number of branches (total number of branches in the plant); leaf length (length of leaf from apex to base of lamina/cm); leaf breadth (measurement of the widest part of

lamina/cm); fresh weight (weight of freshly harvested biomass/g) were recorded. To obtain the leaf dimensions (length and width), the largest ten leaves from each plant were considered.

Plant material Preparation: Plants were segregated into leaves, stems and roots and fresh weights were recorded and oven dried at 60 °C to get the dry plant material. The combined dried parts of 4 plants collected from each plot was ground using a mechanical grinder to afford dry powder. (sieve size - 850μm) and loss on drying (LOD) of the powder was determined by drying a subsample to a constant weight at 105 °C. Quantification of andrographolide was done based on dry weights.

Extraction: Powdered dried plant material (2.000 g) was extracted into 50 mL of methanol by refluxing on a water-bath under a reflux condenser for 15 min. Cooled to room temperature and the methanolic extract by filtration through Whatman no. 1 filter paper. The residue was re-extracted three more times each with 50 mL of methanol. Combined filtrates were evaporated under vacuum. Dry residue transferred quantitatively to a 50 mL volumetric flask with the aid of methanol and made up to the mark with methanol (solution A). Diluted the solution A, 10 was filtered times (1.00 ml: 10.00 ml) with methanol (solution B). The solution B through PTFE (0.45 μm) syringe filter followed by C18 cartridge filter and used as test solution. Extraction was done in duplicate.

Assay: Quantification of the main active ingredient andrographolide was performed using HPLC-DAD (Agilent HPLC 1260 infinity II), on a reversed-phase column (Inert Sustain C-18, 4.6×150mm, 5μm) maintained at 30 ^{0}C. The eluents were acetonitrile (A) and 0.3% v/v formic acid (pH 3.2) (B) with a flow rate of 1.0 mL/min. The gradient condition was as follows: 0-3 min, 10% A; 3-11 min,10-38% A; 11-25 min, 38% A; 25-30 min, 38-50% A. The injection volume was 10μL and detection was based on UV absorption at 223 nm. Standard solutions of andrographolide (0.031, 0.0625,0.125,0.25 and 0.5 mg/ mL) were prepared with methanol and subjected to HPLC analysis using the same method described above. Corresponding peak area (average of triplicated results) was plotted against the concentration to obtain the standard curve for andrographolide.

Results and Discussion

The results of morphometric analysis are given in Table 1 and graphically represented in figure 4. The results revealed that the plant height and total number of branches per plant showed a gradual increase throughout its all-life stages. Accordingly, the minimum plant height and minimum total number of branches per plant were noted at day 30 (19 ± 5.89 cm and 6 ± 2.91), and thereafter it showed a continuous increase, at day 60 and 90 where onset of secondary branching was observed, and maximum was obtained at growth stage at 120 days (69.1 ± 11.11 cm and 83 ± 24.14). *A. paniculata* plants also showed a similar trend in increase of its average total fresh weight from 9.46 ± 3.64 g at day 30 and more than 10-fold increase from that at the final stage, reaching its maximum (107.56 ± 27.80g) at day 120. The fresh weight of leaves showed its minimum at day 30 (7.18 ± 2.57 g) and showed a rapid increase at day 60 (28.12 ± 6.28 g) and day 90 (40.92 ± 13.76 g). Thereafter the rate of increase was not much prominent though, it showed its maximum at day 120 (48.08 ± 12.30). The leaf length and breadth which contribute to the leaf area recorded its minimum value at day 30 (10.4 ± 1.91 and 3.2 ± 0.42 cm respectively) and recorded its highest value at day 60 (14.8 ± 1.56 and 4.0 ± 0.41 cm respectively). Then the leaf length showed a decline at day 90 and thereafter it remained unchanged until day 120 while the leaf breadth showed a gradual decline at day 90 as well as at day 120. These results reveal that the leaf area tend to reduce with the onset of flowering which starts mostly around 90th day onwards.

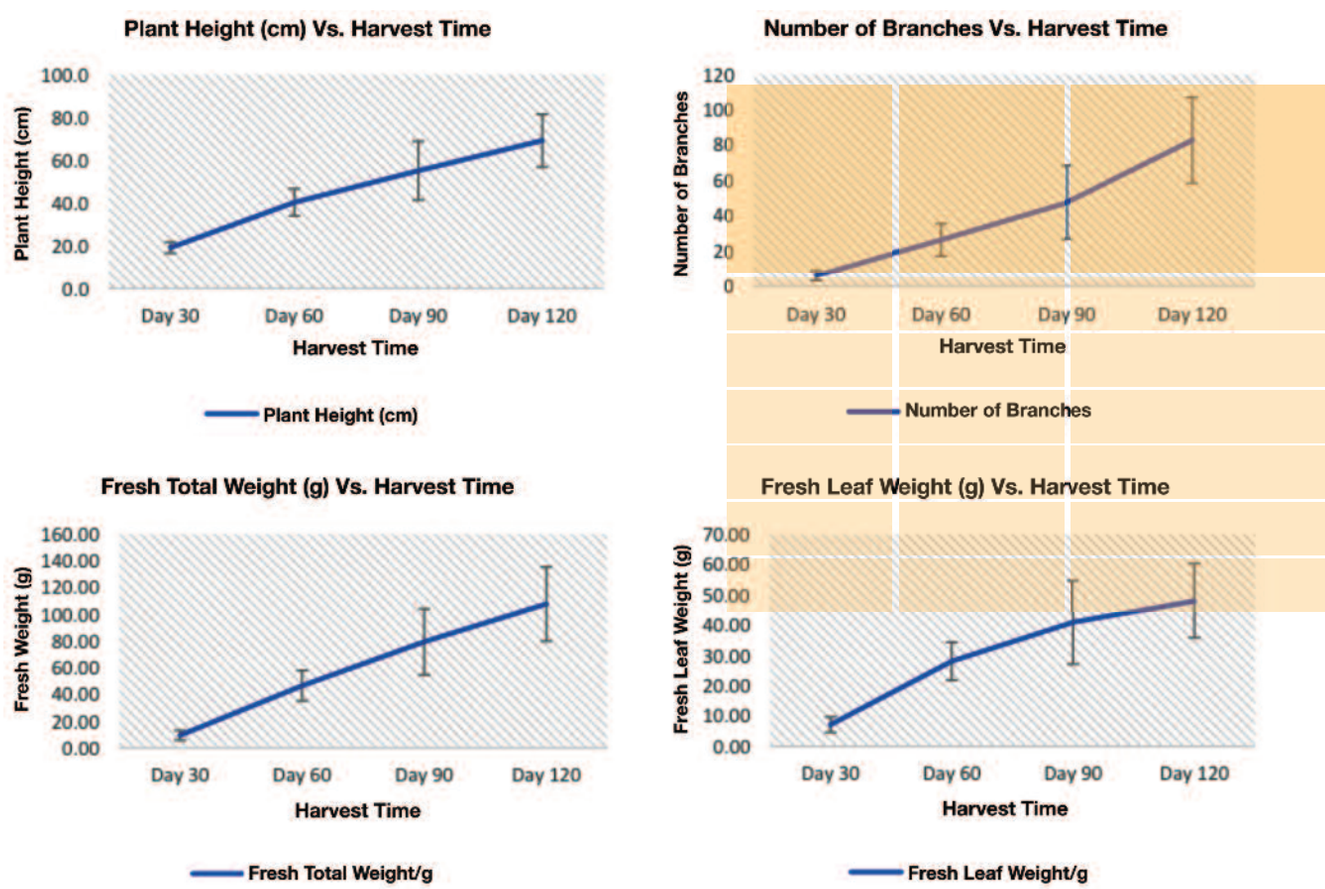
Similar results were recorded from a study carried out in Jabalpur, India to evaluate morpho-physiological parameters of *A. paniculata* at different growth stages and revealed that the growth analytical parameters as well as morpho-physiological parameters increase with crop age (study period up to 120 days), except the specific leaf area which increases up to 90 days and then showed a decline thereafter (by Parashar R. et al., 2011).

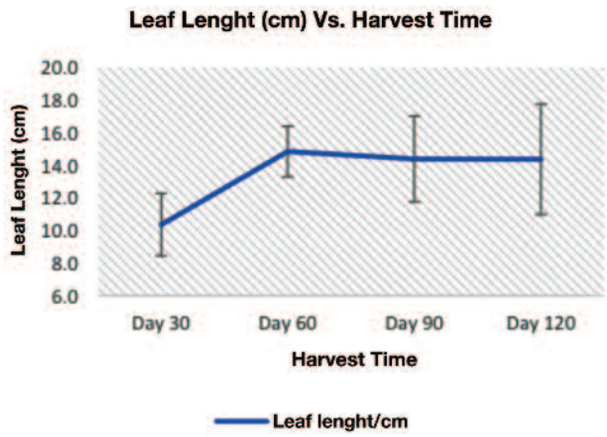
Table 1 Morphometric data of *A. paniculata* at different growth stages

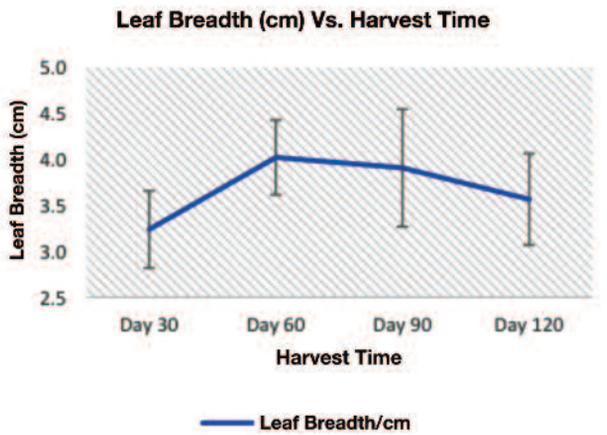
Harvest Time	Plant Height (cm)	No. of Branches	Fresh Total Weight (g/plant)	Fresh Leaf Weight (g/plant)	Leaf length /cm	Leaf Breadth /cm
30 Days	19.0 (± 5.89)	6 (± 2.91)	9.46 (± 3.64)	7.18 (± 2.57)	10.4 (± 1.91)	3.2 (± 0.42)
60 Days	40.3 (± 8.02)	27 (± 9.23)	46.60 (± 11.35)	28.12 (± 6.28)	14.8 (± 1.56)	4.0 (± 0.41)
90 Days	55.0 (± 9.60)	48 (± 20.76)	79.46 (± 24.67)	40.92 (± 13.76)	14.4 (± 2.63)	3.9 (± 0.64)
120 Days	69.1 (± 11.11)	83 (± 24.14)	107.56 (± 27.80)	48.08 (± 12.30)	14.4 (± 3.38)	3.6 (± 0.50)

Note: The data in parenthesis are standard deviations of the corresponding mean values of 12 replicates.

Figure 4. Morphometric data of *A. paniculata* at different growth stages







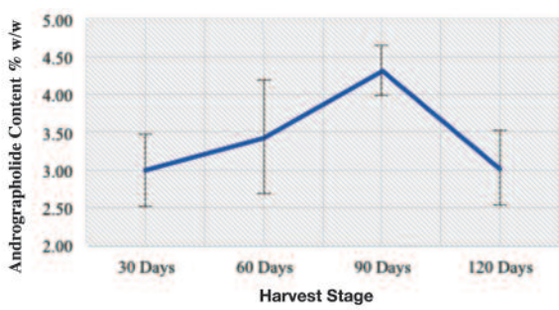
As per the results of the assay carried out (refer Table 1.2 and figure 1.2), the percentage andrographolide content was found to increase with crop age until day 90, by which the maximum value was obtained (4.31 ± 0.33 % w/w on dry basis); and thereafter found to decrease rapidly and at day 120 the value was 3.02 ± 0.49 % w/w on dry basis. This suggests that the optimum harvest time for *A. paniculata* would be 90 days to get maximum andrographolide percentage from the harvest. However, when the andrographolide content in biomass (average amount of andrographolide content that can be obtain from one plant) is considered it reaches its maximum value at day 90 (887.42 ± 224.39 mg) and decline thereafter is not marked and by day 120 it had decreased only marginally to 872.73 (± 208.61) mg.

Table 2. Assay results of *A. paniculata* at different growth stages

Harvest Time	Andrographolide Content (% w/w)	Andrographolide Content per plant (mg)
30 Days	3.00 (± 0.47)	45.28 (± 10.89)
60 Days	3.43 (± 0.75)	346.02 (± 189.14)
90 Days	4.31 (± 0.33)	887.42 (± 224.39)
120 Days	3.02 (± 0.49)	872.73 (± 208.61)

Note: The data in parenthesis are standard deviations of the corresponding mean values of 6 replicates.

Variation of Andrograholide Content % w/w vs Crop Age



Variation of Andrograholide Content (mg/plant) vs Crop Age

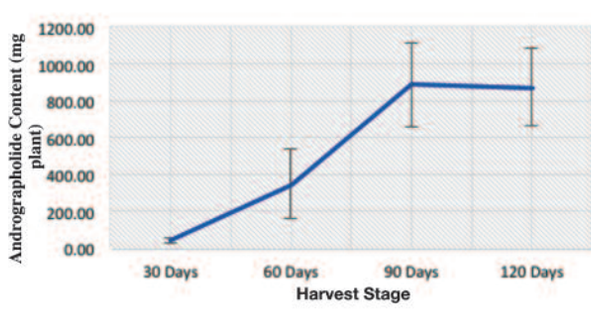


Figure 5. Assay results of *A. paniculata* at different growth stages

Conclusion

The results suggest that the rate of accumulation of andrographolide in the plant is reduced drastically after day 90. Further, our results indicate that the optimum time for harvesting of *A. paniculata* for maximum andrographolide content is from day 90 to day 120 after transferring the plantlets to the field.

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RELEVANCE OF INNOVATION AND MULTIDISCIPLINARY COLLABORATION IN NATURAL PRODUCT RESEARCH AND DEVELOPMENT

Presented by Leslie Gunatilaka
Review by G.M.K.B. Gunaherath

A review by Professor G M K B Gunaherath of the seminar held in March 2023, led by Professor Leslie Gunatilaka, the Director of the Natural Products Center at The University of Arizona (UA NPC), USA. The seminar focused on the significance of innovation and multidisciplinary collaboration in the realm of natural product research and development.

In March 2023, Professor Leslie Gunatilaka, Director, Natural Products Center at The University of Arizona (UA NPC), U.S.A. visited Link Natural Products Research and Development Center and had several interactive sessions with our research scientists and delivered a very informative lecture entitled the above topic. He illustrated the relevance of innovation and multidisciplinary collaboration in natural product (NP) research and development under the following subtopics.

- What are NPs? Major sources of NPs, and why NPs are important?
- Structural diversity and chemical space of known & available NPs
- Advantages and disadvantages of NPs as a source of bioactive molecules
- Fungal-based NP discovery & development program at the Natural Products center (NPC) of the University of Arizona (UA)
- Biologically active & structurally unique metabolites from rhizosphere & endosymbiotic fungal strains
- Plant-based NP discovery & development program at the UA NPC; development of an efficient technique to produce withanolides
- Discovery & development of 17β-hydroxywithanolides as potential agents to treat castration-resistant prostate cancer, metastatic melanoma, and renal carcinoma resulting from multidisciplinary collaborations

This review covers only a limited selection from the subject matter presented by Prof. Leslie Gunatilaka.

Natural products are small molecules produced by terrestrial and marine plant, animal or microbial sources, in response to environmental stress, to defend themselves from predators and for communication. Therefore, NPs exhibit biological activities and are capable of interacting with proteins. Pharmacological activities of medicinal plants used in Traditional Medicines and Herbal Supplements are due to the presence of bioactive NPs and these NPs find applications in pharmaceutical preparations and in agriculture. NPs exhibit enormous structural and chemical diversity and array of pharmacological activities. The significant role played by the NP in the drug discovery is amply exemplified by the fact that, about 4% of all small-molecule drugs approved between 1981 and 2019 are unaltered NPs, 19% are NP derivatives, and 25% are NP mimetics and/or contain an NP pharmacophore, while about 19% are biological macromolecules.[1] A major constraint in the NP based drug discovery is the availability of material for testing. Only about 10% of the more than 250 000 known NPs are readily available from commercial sources and public research institutions for timely experimental testing.[2] It is also important to note that more than 2000 different NPs are represented by at least one X-ray crystal structure in complex with a biomacromolecule in the protein data bank (PDB) relevant in structure-based drug design.[3]

The relevance of innovation and multidisciplinary collaboration in NP discovery and development has been exemplified by the fungal-based natural product discovery program at the UA NPC. Innovative approaches such as one strain many compounds (OSMAC) method, and epigenetic modulations that attempts to induce silent biogenetic clusters that may lead to production of compounds not accumulated during more conventional fermentations were illustrated with some examples.[4] This approach is very useful in NP drug discovery programs because there is a possibility of producing NPs with novel carbon skeletons.[5] Collaboration with scientist in different scientific disciplines also can lead to innovative approaches such as precursor feeding, mutasynthesis, and genetic manipulations to increase chemical diversity.[6,7] Since, it is not possible to develop every required bioassay in one laboratory, it is also important to collaborate with many laboratories to have access to a wide range of bioassays.

Natural products with diverse molecular structures including unique structural types were identified from symbiotic fungi inhabiting higher plants, and previously unexplored sources such as mosses, and lichens, showing an array of biological activities, from this fungal-based natural product discovery program. It is noteworthy that one of the compounds, delitschiapyrone A (Figure 1), identified in this fungal-based natural product discovery program has inspired Japanese scientists to achieve a successful biomimetic synthesis with an overall 37% yield.

Delitschiapyrone A isolated from *Delitschia* sp inhabiting *Serenoa repens* (Saw palmetto) was found to have a novel hybrid carbon skeleton derived from a naphthoquinone and an α-pyrone and a possible biosynthetic pathway has also been proposed from these precursors found to co-occur in this fungal strain (Figure 1).[8] Inspired by this biosynthetic proposal, Kurasawa and co-workers biomimetically synthesized this complex molecule starting with a readily available naphthoquinone and α-pyrone under very mild conditions.[9] This work enables researchers to synthesize an array of compounds with this unique skeleton having diverse substituents and substituent patterns which could enter into different drug discovery programs.

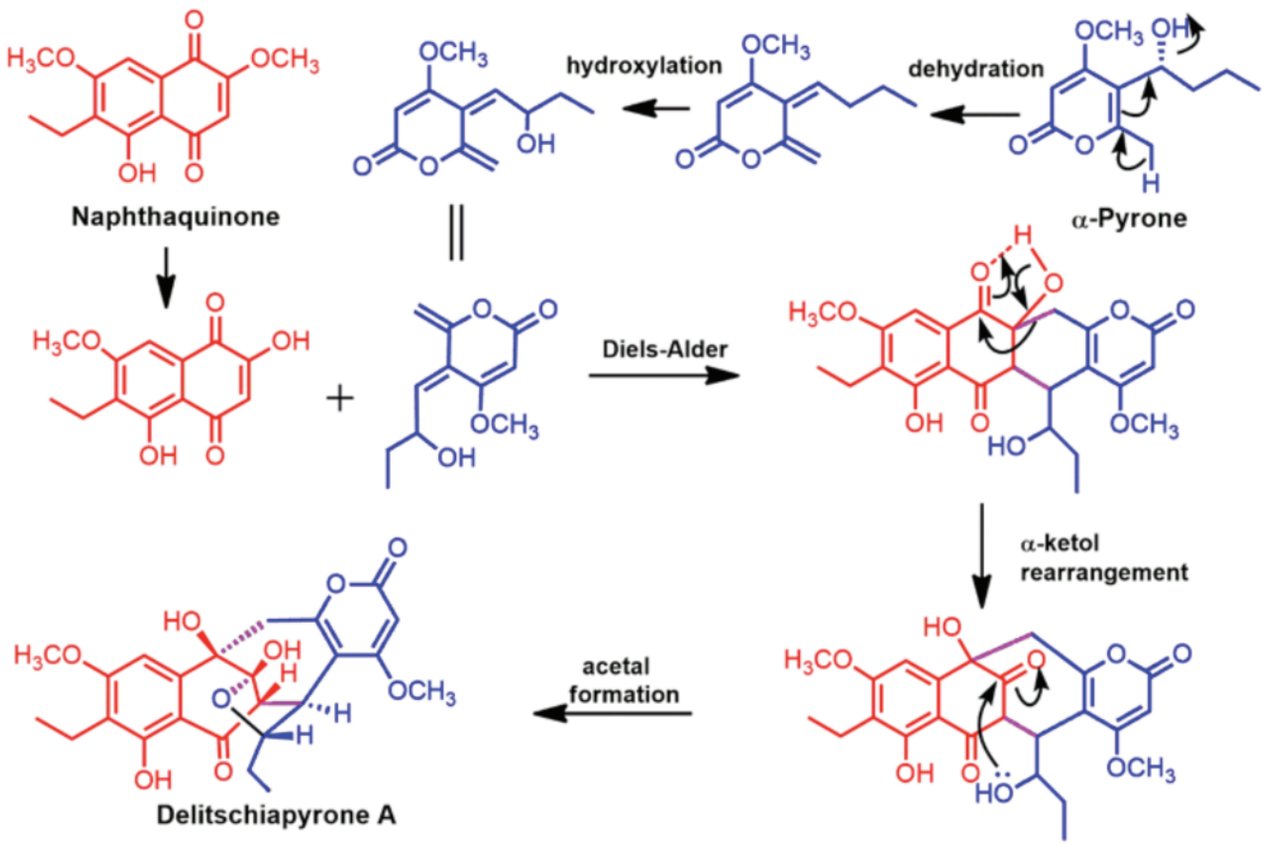
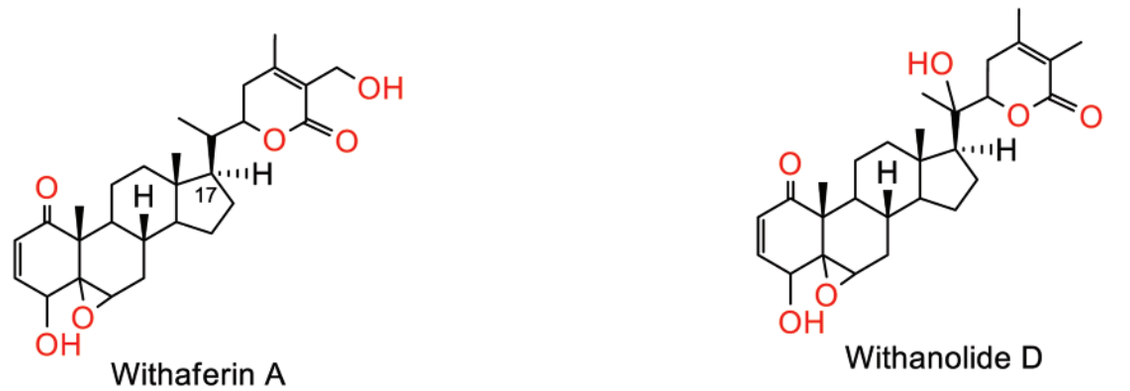


Figure 1. Delitschiapyrone A and its proposed biosynthesis.

Prof. Gunatilaka also illustrated the "plant-based anticancer drug discovery and development program" at the University of Arizona Natural Products Center by the work carried out on *Withania somnifera* and *Physalis crassifolia* both of which belong to the family Solanaceae. The common crop plants belonging to this family are potato and tomato. Many species belonging to the genera, *Withania* and *Physalis*, are used as food and medicine in many countries. The medicinal applications of these plants are attributed to the presence of withanolides. Withanolides are ergostane-type C_{28} steroidal δ-lactones (olides). To date over 1,000 different withanolides are known and they occur mainly in plants of the family Solanaceae (25 Genera). There are two main classes of withanolides. Withanolides with a β-oriented side chain at 17-C, which are mainly produced by *Withania* species and withanolides with an α-oriented side chain at 17-C, are mainly produced by *Physalis* species (Figure 2).



Withanolides with 17β-oriented sidechain

Natural product

Natural product analogue

Withanolides with 17α-oriented sidechain

Figure 2. Withanolides with 17α and 17β sidechains and a withanolide analog LG-134 having *in-vitro* and *in-vivo* activity against melanoma and prostate cancers.

Some members of both classes show anticancer activity in a variety of cancer cell lines, and orientation of their sidechains suggested that they may bind to different cellular targets.

A major challenge in developing plant-based natural products as drugs is lack of availability of the source plants. Conventional methods of obtaining large quantities of plant-based natural products, such as wild crafting, cultivation, and cell culture suffer from many disadvantages as follows.

- Wild crafting – Leads to ecological damage.
- Cultivation – Resource and labor intensive (not environmentally-controlled).
- Cell culture – Not successful with many drug producing plants.

The innovative technique that was developed by Prof. Leslie Gunatilaka's group for the efficient production of withanolides was aeroponic cultivation of withanolide producing plants.[10] This technique has resulted in not only improving the yields of major withanolides in those plants but also increasing the structural diversity of withanolides.[11] The efficient production of withanolides in the family Solanaceae was amply illustrated by the production of withaferin A and its pro-drug, withaferin sulphate on large scale from *Withania somnifera* (Sinhala-Amukkara, Sanskrit

Ashwagandha, English- Winter cherry). It is known that *W. somnifera* is a slow growing plant. It takes 2 – 3 years to mature. Withaferin A is known to occur mainly in roots. Aeroponically grown *W. somnifera* plants mature in 6 – 8 months and withaferin A is produced in areal parts of the plant and occur as its water soluble sulphate.[12] Aeroponic cultivation of Solanaceae plants followed by isolation and identification of withanolides, and preparation of analogs have led to a library of >300 natural and semi-synthetic withanolides at the UA NPC. Bioassay of these compounds in collaboration with scientists at different institutes have led to the identification of withanolides having an array of bioactivities such as selective activity for prostate cancer, activity against multiple myeloma, as anti-nociceptive agents, as potential drugs for immunotherapy of melanoma and renal carcinoma. During this work, physachenolide C (PCC) (Figure 2) was found to be active against castration-resistant prostate cancer by *in-vivo* and *in-vitro* experiments.[13] PCC was found to be the first natural product strongly binding to Bromodomain Extra Terminal (BET) proteins, BRD2, BRD3 and BRD4.[14-16] Physachenolide C and an analog, LG-134 prepared by modifying the substituent at C-18, (Figure 2) were found to have much superior *in-vitro* anti-prostate cancer activity compared to well-known bromodomain inhibitor (+)-JQ1.[17]

During his lecture, Prof. Gunatilaka amply demonstrated the importance of innovative approaches and need for multidisciplinary collaboration in the field of Natural Products Science. The lecture was attended by all staff at the Research and Development center of Link Natural Products (Pvt) Ltd and some outside scientists and was well received.

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ARTHRITIS , PERSPECTIVE FROM MODERN WESTERN MEDICINE , II

Jennifer Perera, MBBS, MD, Emeritus Professor, University of Colombo

Inflammatory Arthritis

Arthritides characterized by synovial inflammation are considered as inflammatory arthritis. Rheumatoid arthritis, spondyloarthritis and crystal arthritis are considered as inflammatory arthritis. Pattern of joint involvement, extra articular manifestations and several other factors help to differentiate the different types of inflammatory arthritis but this may be difficult in early arthritis.

Spondyloarthritis is a broad group of arthritis where spine is mainly involved. Psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease and reactive arthritis which is associated with infections like urethritis etc. belong to the group of spondyloarthritis[1].

Crystal arthritis is characterized by deposition of different kinds of crystals inside the joint cavity. Crystal deposition induces inflammation in the joint. Two main types of crystals that gets deposited are sodium urate and calcium pyrophosphate crystals. Rarely, crystals of calcium apatite and cholesterol also gets deposited.

Rheumatoid arthritis which is more common is described in detail in this article.

Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease (where the immune system reacts against own tissues) of the synovial joints. It is a chronic multi-systemic condition which result in lot of disability and mortality.

Epidemiology and risk factors

The prevalence of rheumatoid arthritis (RA) is about 0.5–1% in the normal population[1]. RA is common among females in the reproductive age group. Female gender, having a first degree relative with RA, and having certain major histocompatibility complex (MHC) genes are risk factors for developing RA[1].

RA are inherited in 50-60% of cases.[2] There is a strong association between susceptibility to RA and MHC genes called HLA genes and this correlates with a poor prognosis. Out of the inherited cases, 10-40% have this HLA association[2]. Examples for associated HLA genes are HLA-DRB1*01 and DRB1*04, some HLA

alleles such as HLA-DRB1*13 and DRB1*15[2]. The environment, including smoking, diet, obesity, infections, and microbiota have been proposed to trigger the disease in genetically predisposed individuals. Cigarette smoking is the most known external factor identified as a trigger of RA.

Pathogenesis

Synovial inflammation is the key feature in RA. Synovial membranes are present in synovial joints, tendon sheaths and bursae. There is formation of autoantibodies against body's own antigens which are called rheumatoid factor (RF). This aberrant immune response involves synovial cells (synoviocytes), osteoclasts, fibroblasts, B cells, T cells, synovial fibroblasts etc[1].

When there are circulating rheumatoid factors, antigen presenting macrophages recognize them and initiate an inflammatory cascade. This inflammatory cascade damages the structures of the joint. Tumor Necrosis Factor (TNF)-alpha is a predominant cytokine in the process and overproduction of this cytokine leads to synovitis and joint damage. Other cytokines involved are IL-1, IL-6, IL-8, TNF-alpha, granulocyte macrophage colony stimulating factor etc[1,4].

Synovium which is usually a thin membrane is thickened during the disease process with the influence of inflammatory cytokines. It also contains inflammatory cell infiltrates. Blood vessels proliferate within the synovium and increased permeability of newly formed blood vessels lead to leaking of fluid into the joint space resulting in joint effusions. This thickened synovium is also called the "pannus". It expands and destroy the underlying cartilage due to cytokine action and block the nutrient supply. The cartilage atrophy exposes the underlying bone. Osteoporosis become evident in the adjacent bone tissue[1]

Clinical presentation

Typically, RA is a symmetrical polyarthritis mainly involving peripheral small joints of the body. It is commonly a relapsing and remitting illness if not controlled properly with medications. Patients will complain of joint pain and early morning stiffness which last about an hour. There can be warmth and tenderness of the affected joints.

Joints of the hand and feet are frequently involved in RA. Other joints affected are wrist, elbows, shoulders, knees, and ankles. In advanced disease there are classic deformities of the hand namely 'swan neck deformity' and 'boutonniere deformity' of proximal interphalangeal joint, ulnar drift and palmar subluxation of metacarpophalangeal joints.

Rheumatoid arthritis is a multi-systemic disease. Inflammatory mediators cause involvement of other organs and cause various complications. This contributes to increased mortality due to this disease. This extra-articular involvement is becoming uncommon due to availability of effective treatment. Lungs, heart, blood vessels, peripheral nerves, eyes, kidneys, and hematological system are involved in RA.

Subcutaneous nodules called 'rheumatoid nodules' over elbows and fingers, wasting of muscles are other clinical features which can be seen in RA.

Diagnosis and investigations

It is important to diagnose RA in early stages and to start treatment to prevent joint damage and permanent disability. Once RA is clinically suspected, initial workup to confirm the diagnosis generally include full blood count, inflammatory markers like ESR and CRP and antibody tests specific to RA like rheumatoid factor and anti-citrullinated protein (anti-CCP)

antibodies. Rheumatoid factor (RF) is present in about 70% of cases of RA. Mere presence of rheumatoid factor is not diagnostic of RA, as it can be present in other conditions. As it has a low sensitivity, absence of RF does not rule out the diagnosis of RA.

X ray also show characteristic features of RA such as periarticular osteopenia, joint space narrowing and joint deformities. Other imaging modalities such as MRI are optional depending on the clinical picture and severity of the disease.

Management

Rheumatoid arthritis is a lifelong condition in most cases. Early diagnosis and treatment is essential to prevent sequele of RA. Most cases need to be managed by a multi-disciplinary team with involvement of rheumatologists, physiotherapists, occupational therapists, nurses, psychologists, and doctors from other specialties such as respiratory physicians and cardiologists depending on the clinical picture and the severity.

Patient education is an important step in the management which will reduce distress to the patient and improve compliance to treatment.

Disease modifying anti-rheumatic drugs are the cornerstone in the management and have significantly improved the outcome of the condition over the years. Examples for these drugs are methotrexate, leflunomide, sulphasalazine. These drugs cause immune modulation. Analgesics such as paracetamol, non-steroidal anti-inflammatory drugs are also given to patients with RA for symptomatic relief.

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ARTHRITIS – PERSPECTIVE FROM AYURVEDA (II)

Dr. J.T.R. Jayakody, D.S.A.C.(Hon), MD (Ayur), Senior Consultant in Ayurveda, Link Natural Products (Pvt) Ltd

It has been observed, that there is currently an increasing incidence of joint diseases in Sri Lanka. Examination of medical records of Ayurveda treatment centres and hospitals indicate that a high percentage of women over fifty years of age, suffer from joint diseases. Currently used foods and the prevalent life styles and food habits as well as the influence of activities related to one's profession, undoubtedly contribute to the rising incidences of joint diseases. Joint diseases have a stressful effect on an individual's daily life, as well as on the individual's family and social life. Therefore, prevention of joint diseases as well as curing them without any complications are important. This is one of the challenges faced by all working in the health sector.

According to the principles of Ayurveda, diseases of joints are classified based on their causative factors and pathogenesis as follows;

* Joint diseases due to *Ama Vata,*
* Joint diseases due to *Vata Raktha*
* Joint diseases related to *Vata Dosha* (*Sandhigatha Vata*)
* Joint diseases due to Trauma
* Joint diseases due to the ageing process (*Jara vata*)

A description of *Ama,* the way it is formed and the bodily and mental basis for its formation has been described within the concepts of Ayurveda pathology. *Ama* is considered a toxic substance produced in the body. For example, it has been noted that *Ama* may be produced by metabolic processes, in the following instances.

1. Consumption of improper food
2. Imperfect digestion
3. Unhealthy life style
4. Situations resulting in physical and mental imbalance

Once *Ama* is generated in the body, it is diffused throughout the body by the body fluids aided by the action of *Vyana Vata* (a variety of *Vata Dosha*). Due to the similarity of *Vyana Vata* to *Kapha Dosha*, it accumulates at joints (which are Kapha locations), thus causing *Ama Vata* joint disease. Since this disease relates to *Ama* which is a toxic substance, it is considered as a systemic disease rather than a localized joint disease. Therefore, the principle behind the treatment of *Ama Vata* joint disease is to reduce and eliminate *Ama* from the body, and to restore the normal functioning of the joint.

Herein, purgation and enema treatments for removal of *Ama* and localized and systemic methods for digestion of *Ama*, are necessary. Locally, heat treatment using *Pottani* (cloth pouches filled with medicinal herbs, which are steamed) and application of medicinal pastes to the joint are done. When *Ama* has been removed from the body, application of medicinal oils is carried out, to pacify *Vata Dosha*. Further systemic methods include reduction of food intake and partaking of light easily digestible food. Medication to improve digestion and appetite are also used. This helps in the reduction of *Ama* & accumilation of *Ama* in the body. Correct diagnosis and implementation of a treatment regime is important in the treatment of joint disease.

LINK NATURAL UNVEILS 'SWASTHA BY LINK NATURAL' A NOVEL EXPERIENTIAL CENTRE IN COLOMBO 7

Link Natural launched its very first novel experiential centre, "Swastha by Link Natural" at No. 6 Maitland Crescent, Colombo 7, with the objective of providing customers, stakeholders and the discerning general public at large, the opportunity of an immersive brand experience.

The experiential centre conceptually showcases what Link Natural does, how it does what it does and why it does it in the way it is done. In short, one can become enthralled with the philosophy and mission of the company by visiting the experiential centre.

Delivering a personalized experience, "Swastha by Link Natural" features several modern facilities enabling customers to discover holistic wellness for good health and longevity in a casual mind-soothing and relaxing environment. They will also have the opportunity to learn about the full range of products manufactured and marketed by Link Natural and conveniently purchase from a range of over 200 options covering herbal health care products, personal care products and generic ayurveda products. It can also be a place to meet, hangout or even enjoy getting some work done in the serene ambience of "Swastha by Link Natural".

This experiential centre show cases Link Natural's safe, efficacious and quality innovative Herbal Healthcare products that cater to many healthcare and wellness needs of consumers, the Herbal Personal Care range of products that encourage customers to pamper themselves from head to toe while the Ayurveda Pharmaceuticals cater to the needs of Ayurveda physicians and their patients. Each category of products is displayed in carefully and creatively curated spaces that allow consumers to learn about and experience each product within a specially demarcated display of the company's unique capabilities.

In addition to the above, together with renowned resource persons, the experiential centre carries out many health and wellness related activities and programs that help people achieve physical, mental and spiritual wellness for the discerning holistic wellness seeker.

The well-trained and customer-friendly staff of "Swastha by Link Natural" help consumers understand the benefits of each product and guide them to purchase what fits their specific needs.

"Swastha by Link Natural" is conveniently located at No. 6, Maitland Crescent in Colombo 7, open to customers daily from 10 a.m. to 7 p.m. and provides plenty of parking spaces.

LINK NATURAL CRAMPGARD PLUS HERBAL CREAM

Janaki Niranjala & Nadeesha Gunasekara

Muscle cramps result in continuous, involuntary, painful, and localized contraction of an entire muscle group, individual single muscle, or selected muscle fibers. It can cause mild to severe pain. Generally, the cramp can last from minutes to a few seconds for idiopathic or known causes with healthy subjects or in the presence of diseases. The specific etiology is not well understood and possible causes depend on the physiological or pathological situation in which the cramps appear.

The mechanism of cramp generation is not completely known but is believed to arise from the spontaneous discharge of the motor nerve rather than directly from the muscle itself. Also, cramps commonly occur in association with a number of conditions, such as dehydration, salt depletion, and electrolyte disturbances. Muscle cramp reduces the quality of life and thereby it is important to address this painful condition since standard treatments are not available.

Link Natural Crampgard Plus Herbal Cream stands out as a fusion of natural ingredients, carefully curated to effectively combat the discomfort of muscle cramps. This unique topical cream brings together a selection of herbal components known for their therapeutic properties. These ingredients include *Trigonella foenum-graecum* L., *Inula racemosa* Hook.f., *Citrus aurantifolia* (Christm. et Panz.) Swingle, *Nigella sativa* L., *Caesalpinia bonduc* (L.) Roxb., along with rock salt, sesame oil, and coconut oil. Each ingredient has been thoughtfully chosen based on a rich heritage of Ayurvedic knowledge and through consultations with experienced Ayurvedic practitioners. This meticulous process ensures that Link Crampgard Plus aligns seamlessly with both traditional wisdom and modern scientific understanding. Link Crampgard Plus Herbal Cream highlights Link Natural Products (Pvt) Ltd's dedication to providing a comprehensive solution for managing muscle cramp discomfort. By blending traditional wisdom with modern science, it offers a well-rounded and scientifically-supported approach to providing fast and effective relief of muscle cramps, thus enhancing the quality of life of those suffering from cramps.


Link Natural
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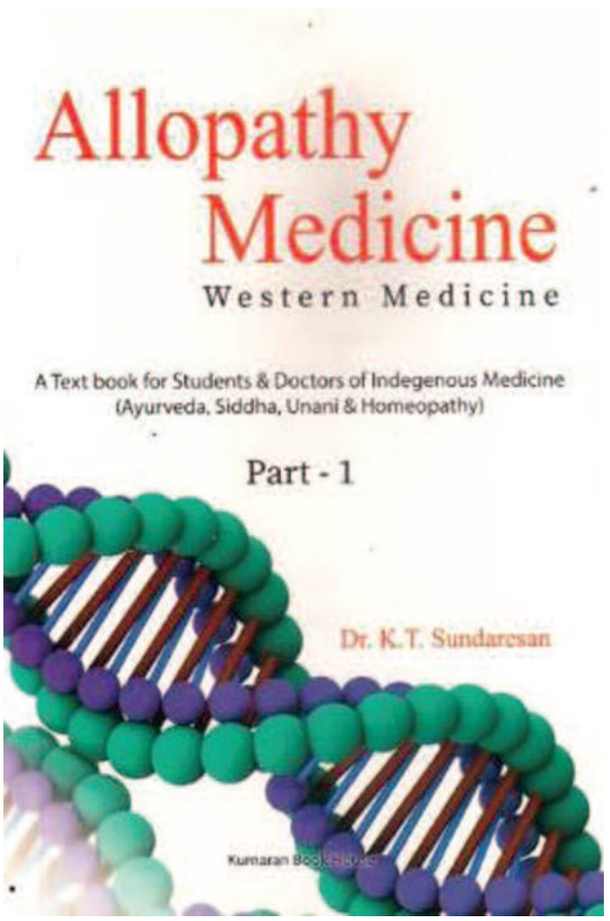

A Text book written for Students pursuing their career in the field of Ayurveda, Siddha, Unani & Homeopathy as well as for the doctors from the same fields.

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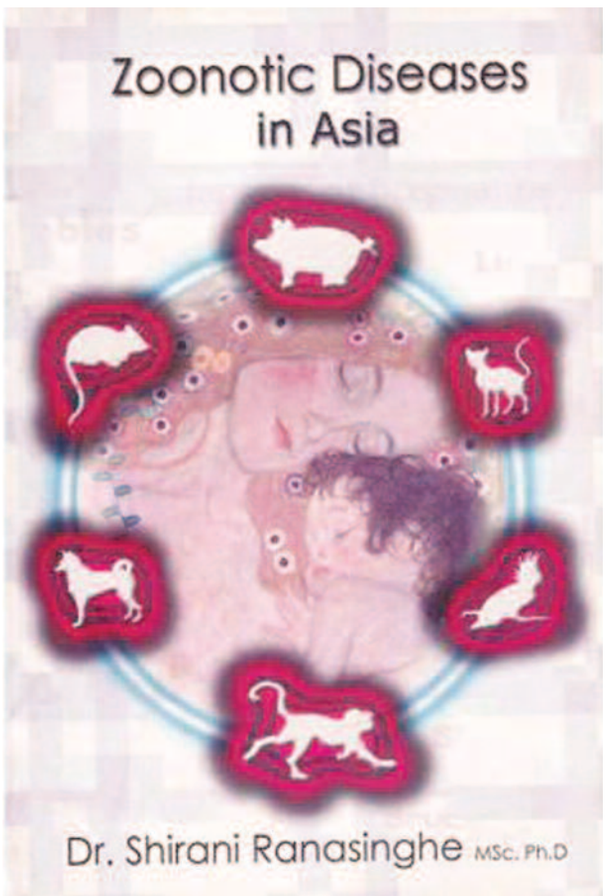
ZOONOTIC DISEASES IN ASIA



Zoonotic disease is an infectious disease transmitted from animals to man and vice versa. There are many small-scale livestock farm holders in the country who are at risk for zoonotic diseases. Most of the zoonotic diseases are preventable but neglected in many developing countries. There is an urgent public need for educating the population in this regard. The author aims to provide a brief overview of key zoonotic diseases in Sri Lanka, focusing on their most significant aspects relevant to both medical and veterinary practices.

Author : Shirani Ranasinghe

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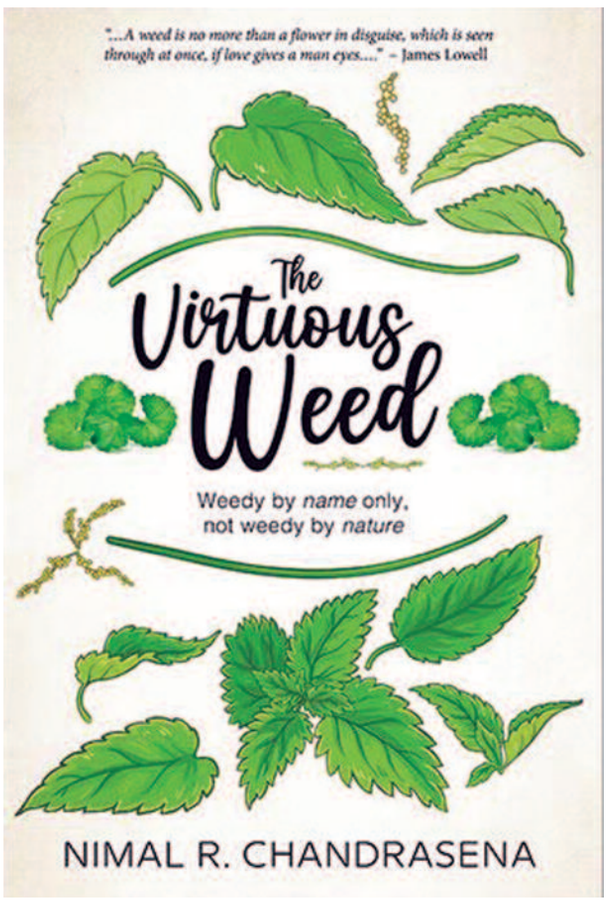
Pages : 105

THE VIRTUOUS WEED



Weedy by name only, not weedy by nature

"A weed is no more than a flower in disguise, which is seen through at once, if love gives a man eyes"

– James Lowell

Weeds, as a group of plants, are unloved by some people. However, this dislike is not universal. Weeds are colonizing, pioneering plants, with special botanical and ecological attributes. They are a critical component of mother earth's rich biodiversity. They are also nature's Gifts from which humans can learn many lessons. This book provides compelling evidence of the virtuous side of weeds and their utilization potential for people's livelihoods and sustainable future societies.

The book will surely open a critical dialogue on weeds, across borders that separate divergent views. Can weeds be appreciated for their critical ecological roles? Can they be managed in situations where they may become problematic? Weeds are shadows of men. The history of weeds is essentially the history of human societies since the agricultural revolution.

A paradigm shift to tolerate the extraordinarily resourceful weedy taxa ('living with weeds') appears prudent as plants and animals, as well as human societies, face uncertain times in a changing global climate.

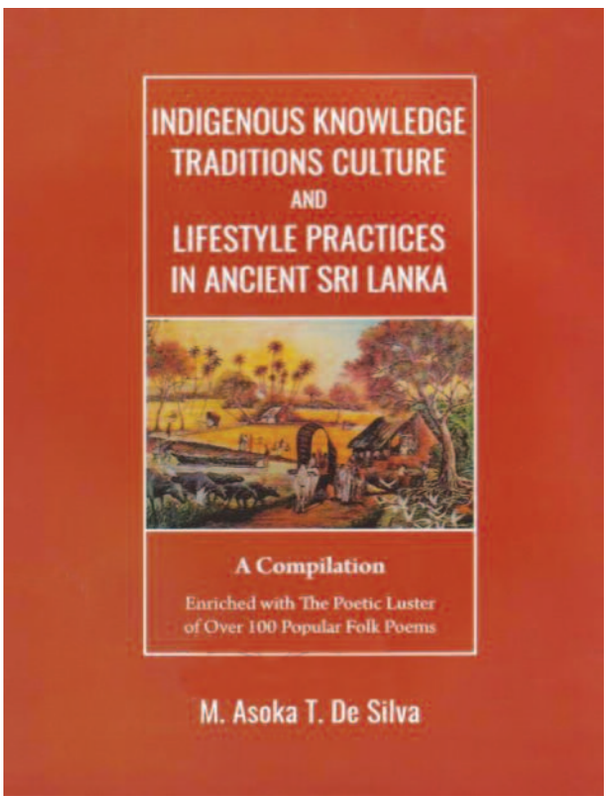
Author : Nimal R Chandrasena

Publisher : Vivid Publishing

ISBN : 978-1-922788-67-2

Pages : 474

INDIGENOUS KNOWLEDGE TRADITIONS CULTURE AND LIFESTYLE PRACTICES IN ANCIENT SRI LANKA



In compiling and writing this book the author has managed to successfully unravel the indigenous knowledge that served the purpose of achieving a sustainable and harmonious development in past.

Author : M. Asoka t. De Silva

ISBN : 9786242050126

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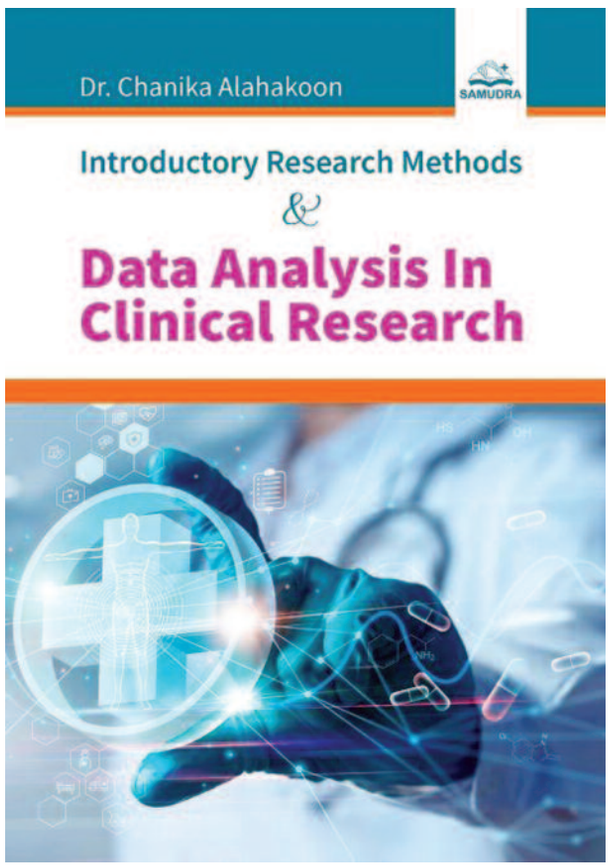
INTRODUCTORY RESEARCH METHODS AND DATA ANALYSIS IN CLINICAL RESEARCH



This book provides a comprehensive overview of two key aspects of research. Firstly, it offers insights into the design of clinical studies. Secondly, it delves into the challenges associated with choosing the right statistical tests based on your data. Understanding the selection of appropriate tests is crucial for effective sample size calculations. Whether you're a medical student or a post-graduate research student, this book is designed to assist anyone grappling with research methods and statistics.

Author : Dr. Chanika Alahakoon

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Link Enriched Paspanguwa	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Link Natural Sudantha	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Link Kesha Hair Oil	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Link Hair Care Cool	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Link Akalapalitha	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Link Swastha Thriphala		✓	✓	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓
Link Swastha Amurtha	✓	✓	✓	✓	✓	✓	✓			✓	✓		✓	✓	✓
Link Five Herbs													✓	✓	✓
Link Gotukola Tea													✓	✓	✓
Link Osupen			✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Link Muscleguaed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Link SP Balm	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Link Crampgard Plus	✓	✓	✓	✓	✓		✓	✓	✓		✓		✓	✓	✓
Link Essentials - Composite Pack				✓											✓
Link Ayurveda Products														✓	✓
Link earth essence products (Cosmetic products)		✓	✓	✓		✓			✓	✓		✓	✓		✓

NOTE TO POTENTIAL CONTRIBUTORS

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