Afr. J. Trad. CAM (2006) **3 (4):** 115 - 120

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Afr. J. Trad. CAM (2006) **3 (4):** 115 - 120

RESEARCH HIGHLIGHTS

Bauhiniastatins: New and Unusual Cancer Cell Growth Inhibitors from *Bauhinia purpurea*

The genus *Bauhinia,* a member of the family Fabaceae, comprises of trees and shrubs that grow in warm climate. The different species of *Bauhinia viz., B. reticulata, B. rufescens* and *B. variegata* have been traditionally used to treat roundworm infections, conjunctivitis, anthrax, ulcerations, dysentery, blood-poisoning, leprosy, lung and skin diseases in Africa; while in India, extracts of the bark of *B. variegata* is used for treatment of cancer. Folklore history emphasizes the use of *B. tomentosa L.* and *B. purpurea* for cancer therapy. The flowers are used as a laxative, while the roots are carminative. The bark is used for treating diarrhoea and other gastrointestinal complaints.

A new flavone rhamnopyranoside has been isolated from this genus. Previous chemical investigations have focussed on the isolated hypoglycemic and antioxidant kaempferol dirhamnoside from *B. forficata,* a traditional antidiabetic treatment in Brazil, while hypoglycemic flavonoid-containing fractions have been isolated from leaves of Egyptian *B. purpurea.* In recent years, *B. purpurea* is best known as a source of a lectin agglutinin that binds to dense cell surface glycoconjugates.

Pettit et al., (2006) have reported the preparation of extracts from the various parts of of *B. purpurea* viz., leaves, stems, roots and pods*.* These workers *have* isolated four new and very remarkable (dibenz[b,f]oxepins) cancer cell growth inhibitors and have designated them as Bauhiniastatins 1-4. In addition, pacharin has also been isolated and structure of Bauhiniastatins and pacharin has been established by spectroscopic techniques like HRMS and 2D NMR. Upon evaluation of anticancer activity, Bauhiniastatins 1 exhibited significant growth inhibition of P388 cancer cell line.

Reference: Pettit. G.R., Numata. A., Iwamoto. C., Usami. Y., Yamada. T., Ohishi. H. and Cragg. G.M. (2006). Antineoplastic Agents. Isolation and Structures of Bauhiniastatins 1-4 from *Bauhinia purpurea*. J. Nat. Prod. **69:** 323-327.

Hepatoprotector from Chamomile: Capitula *of Chamomile recutita* protects against Liver Injury

Chamomile recutita is a reputed medicinal and aromatic plant, and a well known ingredient of several traditional, Unani, Homeopathic medicinal preparations. *Chamomile recutita* (cv. Prashant),L. Rousch, popularly known as Chamomile, belongs to the family of Asteraceae. The oil obtained from the capitula of this plants is a natural source of 'blue oil' (chamazuline) and flavonoids, which are used in pharmaceuticals, perfumery, and cosmetic industries. The anti-inflammatory, wound healing, antiseptic and spasmolytic activities of this plant are well documented in several traditional systems of medicine.

Gupta and co-workers of Amity University, Uttar Pradesh, India have reported the antioxidant activity of methanolic extract of capitula of *Chamomile recutita* by inducing liver injury with CCl_4. The methanolic extract was found to exhibit antioxidant activity with combined hepatoprotective action, and exhibits a synergistic effect by stabilizing cellular membranes of organelles. Since, liver, is one of the most important organs concerned with the biochemical functions like metabolism, breakdown, removal of drugs and

Afr. J. Trad. CAM (2006) **3 (4):** 115 - 120

environmental toxicants, its function can be severely affected due to injury resulting from acute or chronic exposure to toxicants like alcohol, CCl_4 etc. Biotransformation of CCl_4 produces trichloromethyl radical ($CCl_3^{\bullet}$), and subsequently the peroxy radical ($CCl_3OO^{\bullet}$). Hepatoprotection to liver was found to be due to increased activity of the antioxidant enzymes like Glutathione peroxidase (GPX), Glutathione-S-transferase (GST), Glutathione reductase (GRD), Superoxide dismutase (SOD), Catalase (CAT) and Glutathione (GSH).

This study has established that methanolic extract of the capitula of *Chamomile recutita,* can be used for hepatoprotection, in view of its potent antioxidant activity.

Reference: Gupta et al. (2006). Antioxidant activity of *Chamomile recutita* capitula methanolic extracts against CCl_4 induced liver injury in rats. Journal of Pharmacology and Toxicology. **1(2):** 101-107.

Development of a Reliable Source of Plumbagin: A Pharmaceutically Important Drug

Plumbagin (5-hydroxy-2-methyl-1,4-napthoquinone) exhibits a variety of biological activities like anti-microbial, anti-tubercular, anti-asthma, antispasmodic, anticancer abortifacient, chitin synthetase inhibitor, cosmetic, aphrodisiac etc. It has been shown to enhance *in vitro* phagocytosis of human granulocytes, possess antileprosy, antifertility properties. It is also useful for treating bronchial infections and whooping cough. The plant Drosera is used against old age, arteriosclerosis, and is a source of plumbagin and hyperglycaemia.

Pharmacopoeias of European countries include Drosera and dried plants are marketed as 'Herba Droserae, Herba Drosera rotundifoliae'. *D.indica, D.burmanii, D. peltata* is being exported from Southern hemisphere to European countries. In India, many species have been reported e.g., *D.indica* L.., *D. burmanii* Vahl. and *D. peltata* J.E.Sm.ex Willd. However, urbanization, drought, soil erosion, habitat conversion and fragmentation poses a serious threat to their survival.

Jayaram and Prasad of the School of Life Sciences at the University of Hyderabad, India have established *in vitro* protocols for rapid multiplication of *Drosera* shoots and roots on MS basal media and have established *in vitro* fresh material of *D. indica* and *D. burmanii* as a reliable source for plumbagin bioprospection. Therefore, plumbagin and other invaluable phytochemical compound production from *in vitro* produced plants is an alternative viable strategy, which has monetary potential in the international market.

Reference: Jayaram. K. and Prasad, M.N.V. (2005). Rapidly *in vitro* multiplied *Drosera* as reliable source for plumbagin bioprospection. Current Science **89 (3):** 447-448.

Inhibition of Human Telomerase Reverse Transcritptase Gene Expression by Gambogic acid.

Gambogic acid (GA), a major active ingredient of gamboge resin, obtained from *Garcinia hanburyi* tree (Fam. Guttiferae), is an effective telomerase inhibitor and exhibits potent anti-cancerous activity both *in vitro* and *in vivo*. Due to its unique colour and

Afr. J. Trad. CAM (2006) **3 (4):** 115 - 120

cytotoxic activities, Gambogic acid has been used as a coloring material and in folk medicine.

Guo et al. (2006) have shown that Gambogic acid activates the impaired apoptotic pathways in cancerous cells *via* down-regulation of telomerase. It is well known that during cellular immortalization and malignant transformation, a process of human telomerase activation is regulated by the human telomerase Reverse Transcriptase (hTERT). In this paper, the authors have presented the interaction of GA with oncogene c-MYC, a ubiquitous transcription factor of cell proliferation and differentiation. It was observed that GA treatment of a human hepatoma cell line SMMC-7721 reduced the expression of c-MYC in a time and concentration-dependent manner that was associated with the down-regulation of hTERT transcription and finally reduction of telomerase activity. This study shows that hTERT is a molecular target of c-MYC activity and proposes a possible mechanism of action of Gambogic acid *vis-a' vis* anti-cancerous activity.

Reference: Guo. Q.L., Lin. S.S., You. Q.D., Gu. H.Y., Jun Yu., Zhao. L., Qi. Q., Liang. F., Tan. and Z., Wang. X. (2006). Inhibition of human telomerase reverse transcriptase gene expression by gambogic acid in human hepatoma SMMC-7721 cells. Life Sciences **78:** 1238-1245.

Cerebral Protection by *Ginkgo biloba* Extract

Stroke causes disturbances in cerebral function and is a leading cause of morbidity. Ischemic insult results in reduced blood flow that leads to oxygen deficiency and arrest of aerobic metabolism resulting in cell death of CNS via necrosis or apoptosis. *Ginkgo biloba* extract (EGb) is widely used as an antioxidant supplement in Asia and Europe, and contains flavonoids, that exhibit strong free radical scavenging properties, and terpenoids (ginkgolides) which decrease free radical release.

Loh et al. (2006) have investigated the antioxidant cerebroprotective properties of EGb shown its promising therapeutic effects against stroke. The therapeutic effects of Egb, including the role of antioxidant activity and apoptotic interference on cerebral protection in Wistar rats were investigated by studying its effects on apoptosis, and compared with Losartan; a angiotensin II (ANG II) AT 1 receptor blocker.This study shows that reduction occurs in the gene expression level of pro-apoptotic genes (AT2 receptor, Fas, Bax and Bcl-xs) by EGb treatment. The EGb extract has potential for treatment of stroke patients.

Reference: Loh. K.P., Low. L.S., Wong. W.H., Zhou. S., Huang. S.H., Silva. R.D., Duan. W., Chou. W.H. and Zhu. Y. Z. (2006). A comparison study of cerebral protection using *Ginkgo biloba* extract and Losartan on stroked rats. Neuroscience Letters **398:** 28-33.

Afr. J. Trad. CAM (2006) **3 (4):** 115 - 120

REPORT ON A SYMPOSIUM HELD AT THE CENTRAL INSTITUTE OF MEDIC-INAL AND AROMATIC PLANTS (CIMAP), LUCKNOW, INDIA FROM 18-20 NOVEMBER' 2005.

Phytomedicines have been an integral part of civilization since antiquity world-over and have solved several disease problems affecting humans. Modern day biologists being at the verge of new area of merging sciences and technologies on the one hand and traditional, complementary and alternative medicine on the other, have to endeavor to strike a balance so that new accomplishments in drug discovery and development can be made. It is more necessary today to develop the right kind of synergy between traditional and modern medicine, and use modern tools and techniques currently available in the hands of scientists today to validate the traditional systems of medicine. To address some of the issues and firmly establish the role of biotechnological interventions in conservation and improvement of medicinal and aromatic plants used in medicine, the symposium was organized by CIMAP, Lucknow (India) between 18-20 Nov' 2005.

Over six sessions focussing on tissue culture research: new perspectives, plant metabolomics, gene mobilization and genetic modification, molecular markers, genomics and transgenics were held. The welcome address was delivered by Dr. S.P.S Khanuja, Director, (CIMAP) who highlighted the need for the symposia in the national and global context for generating social benefits. The introductory remarks were given by Prof. Sudhir K. Sopoy, International Center for Genetic Engineering and Biotechnology (ICGEB), New Delhi and Secretary, PTCA(I). The Presidential address and keynote lecture entitled " Cutting Edge of New Knowledge: Opening the Door to Plant Genomics" was delivered by Prof. Asis Dutta, Director, National Center for Plant Genome Research, New Delhi.

Several presentations made during the symposium, particularly those that addressed global issues were noteworthy. Dr. A.A. Kulkarni of University of the Pune, highlighted the problems of multi-drug resistance in malaria and diabetes. These workers presented their work on the anti-malarial (growth inhibition with respect to chloroquine in *in vitro* cultures of intra-erythrocytic *(Plasmodium falciparum)* and anti-diabetic potential (assay for inhibition of mouse intestinal glucosidases and porcine μ-amylase with respect to therapeutic drug acarbose) of certain medicinal plants.

Dr. A.K. Mathur presented the contributions made by CIMAP over the last few decades in the area of plant tissue culture of medicinal and aromatic plants utilized in traditional and complementary systems of medicine. Efforts at CIMAP led to success in generating nucleus stock of true-to-type *Dioscorea floribund*a (a diosgenin yielding plant), distribution to farmers and creation of India's first somaclonally improved variety of *Cymbopogon winterians* (CIMAP/BIO-13). Under the dynamic leadership of Dr. P. S. Ahuja at CIMAP, (currently Director, Institute of Himalayan Bioresource Technology (CSIR), Palampur) success was achieved in developing technologies for conservation of endangered Himalayan medicinal herbs, synthetic seed technology and creation of novel somatic hybrids of medicinal and aromatic plants. Dr. A. K. Mathur also highlighted how he steered two important international projects under the aegis of IFS (Sweden) and IAEA (Vienna), on mutation breeding and ginseng research that has put CIMAP on the International arena. Advances in the area of metabolic engineering were also discussed.

As a part of the National Gene Bank facility, micro cloning protocols for more than thirty medicinal plants have been generated, notably on *Artemesia, Catharanthus, Centella, Panax, Rosa, Hypericum, Pelargonium, Pogostemon, Cymbopogon, Veteveria, Mentha, Ocimum, Chlorophytum, Vinca, Rauvolfia, Glycyrrhiza, Bacopa, Acorus, Aloe, Stevia, Psoralea* etc.

Afr. J. Trad. CAM (2006) **3 (4):** 115 - 120

Drs. Samresh Dwivedi and SPS Khanuja of CIMAP, highlighted the importance of investigating natural variation to unlock the allelic richness present in germplasm accession of medicinal and aromatic plants, particularly *Catharanthus roseus* and *Ocimum* species so that marker-assisted selection and genetic engineering can be used to introduce valuable alleles in medicinal and aromatic plants and higher yields obtained.

Dr. Nidhi Bakshi and Padma Kumar of Rajasthan University, Jaipur (India) discussed the bioefficacy of alkaloids from *Solanum dulcamara* like solanine (from unripe fruits) solasodine (from flowers) and solamarine (from roots). These alkaloids were identified by standard methods and screened for antibacterial efficacy utilizing human pathogenic bacteria viz., *Enterobacter aerogens, Escherechia coli, Staphylococcus aureus* etc. and found to be effective except against *E.aerogens*.

Dr. Rajesh Arora's paper discussed the use of *Catharanthus roseus* and *Vinca major* (periwinkle), a producer of terpenoid indole alkaloids vincristine and vinblastine, ajmalicine etc, and vincamine in traditional and modern systems of medicine. The *Catharanthus* alkaloids are produced in miniscule amounts in the plant and their high-value, low volume production, coupled with international demand makes exploration of alternative strategies for their improved production a necessity. The *Catharnathus* alkaloids, particularly vincristine (VCR), vinblastine (VLB) and vinorelbine are used clinically world-over. Vincristine is commonly used in pediatric oncology due to its better tolerance in children and higher sensitivity to pediatric malignancies. Vincristine is useful in treating acute lymphocytic leukemia and Hodgkin's and non-Hodgkin's lymphomas, while vinblastine is effective in treating advanced lymphomas, Kaposis' sarcoma and cancers of breast, brain and bladder. Dr. Arora suggested a novel approach of augmenting secondary metabolites by employing genetic transformation techniques, utilizing *Agrobacterium rhizogenes*.

Dr. Archana Mathur and co-workers of CIMAP, Lucknow described the importance of the plant *Centella asiatica*. *C. asiatica* is a native of Asia and commonly distributed in India, Indonesia , Madagascar, Malaysia, Pakistan and Sri Lanka, and is traditionally used in the treament of leprosy, ulcers, asthma, bronchitis, elephantiasis, anxiety, mental disorders and urethritis. The pharmaceutical potential of the herb is primarily due to the presence of saponins- the most important being the asiaticoside- a triterpene glycoside present in the leaf. These saponins impart anti-spasmodic, diuretic, blood circulation stimulatory and wound healing properties to this plant. Asiaticoside derivatives could also be useful in the treatment of Alzheimer's disease since they can protect cells against β-amyloid induced cell death. The plant is also one of the chief components of the drug 'Geriforte' which is used for senile pruritis. The pharma companies largely depend on natural populations that are getting depleted very fast raising concerns about possible extinction of the plant. The role of tissue culture techniques to develop alternative production systems for Centella metabolites was discussed.

Dr. K.D. Pawar of National Chemical Laboratory, Pune presented his findings on inophyllums B and P. Inophyllums (di-pyranocoumarin derivatives) are anti-HIV compounds that are produced by *Calophyllum inophyllum*. The plant besides producing anti-HIV compounds also produces cancer, chemopreventive agents 4-phenylcoumarins and cytotoxic and antimicrobial compounds like xanthones.

The symposium was quite interesting from both traditional and modern perspective and several papers focussed on studies on plants utilized in traditional medicine, yet less-explored in modern medicine. The organizers wish to get the full papers of the symposium published in the form of a book.