IJPSR (2013), Vol. 4, Issue 2 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 October, 2012; received in revised form, 24 November, 2012; accepted, 26 January, 2013

GREEN PHARMACY: AN ALTERNATIVE AND COMPLEMENTARY MEDICINE

Neeta Shivakumar*, Pushpa Agrawal and Praveen Kumar Gupta

Department of Biotechnology, R V College of Engineering, Mysore Road, Bangalore-560 059, Karnataka, India

Keywords:
Green Pharmacy, traditional medicine, Ayurvedic medicine, Unnani medicine, Nevadensin

Correspondence to Author:

Dr. Neeta Shivakumar

Department of Biotechnology, R V College of Engineering, Mysore Road, Bangalore-560 059, Karnataka, India

E-mail: neeta @rvce.edu.in

ABSTRACT

The people in India have an outstanding knowledge of medicinal plants acquired over centuries. A passion for studying medicinal plants is evident both in folk and scholarly traditions. The indigenous mode of understanding and using plants is different from the modern scientific way. It includes botanical, medical and astrological elements. This is the basis of green pharmacy. Indians obviously care for medicinal plants because they know so many of them, so much about them and have worked extensively on their application. It is a remarkable fact that the use of medicinal plants is still a living tradition in the form of a million village-based folk carriers. These traditional birth attendants, bonesetters, herbal healers and wandering monks are invisible to policy makers and therefore not taken into account as a public health resource. Apart from these specialised folk healers there are also millions of women and elders with traditional knowledge of food and nutrition and herbal home-remedies. However, the revitalisation of this vast and diverse folk tradition does not appear on the Governments agenda. Here is an attempt to introduce these traditional knowledge with an emphasis of Nevadensin that holds a promising substance to cure many of the diseases naturally.

INTRODUCTION: The Indian system of medicine consists of two major tendencies;The folk and the codified traditions. Folk traditions are handed over orally from generation to generation. The codified tradition consists of medical knowledge with sophisticated theoretical foundations expressed in thousands of manuscripts covering all branches of medicine. Examples are ayurveda, *siddha, unani and the Tibetan tradition. Siddha* is one of the oldest systems of medicine in India, largely therapeutic in nature and specialises in pharmacy. The largest number of medicinal plants is used in the folk traditions (4671 species), followed by ayurveda (1769 species), siddha (1121 species), Tibetan (279 species), homeopathy (182 species), modern bio-medicine (105 species) and unani (59 species) [1].

Bridge between Traditions: It is interesting to observe that Indian knowledge about plants and plant products is not based on the application of western categories and approaches like chemistry and pharmacology. Unfortunately, there is a lack of rigorous cross cultural studies and, in fact, a well accepted methodology for such studies is still missing.

Green Pharmacy:

Materia-Medica: The in-depth study required about a plant before it can be admitted into the indigenous Materia-Medica is quite impressive. This includes aspects like nomenclature, parts used, methods of purification, contra- indications, effect on physiological systems, effect on body tissues, effect on organs, effect on excretory system, qualities, metabolic activity, post-

digestive effect, drug therapeutic class and processing strategies. On the basis of these parameters, the pharmaceutical activity and therapeutic applications of thousands of plants have been worked out. In the codified tradition this has resulted in around 25,000 brilliantly designed plant drug formulations. In the folk system it is suggested that over 50,000 herbal drug formulations have been developed for a very wide range of applications by India's 4600 ethnic communities [2,3].

The value of folk knowledge can be illustrated with the example of *Phyllanthus amarus, a plant used in Southern India* for treating jaundice. The effectiveness of this plant in treating viral hepatitis-B was validated by an American Noble prize-winner who later patented this knowledge. Quinine extracted from the cinchona bark was traditionally used in Peru to cure malarial fevers. In South India the jelly of the *Aloe vera plant, known* locally as Korphad Kumari, is applied to burns and wounds and is taken orally for gynaecological problems [2,3].

In the province of Karnataka, a decoction of the bark of the *Alstonia scholaris,* locally called Sapta Parni, is used in virtually every household at the onset of the monsoon to prevent malarial fevers. *Boerhavia diffusa, locally called Punarnava**, is*** commonly used in the treatment of oedema and anaemia, particularly during pregnancy, and is often eaten as a vegetable.

According to an all India Ethnobotanical Survey conducted by the Ministry of Environment (1985-90), there are 6000 species of medicinal plants in India which can be used by traditional practitioners in tribal areas and other village communities. In the local tradition, the internal fleshy mucilaginous jelly of the aloe plant known locally as korphad kumari etc., is used externally on burns and wounds and orally for any gynaecological disorder [4,5].

In Karnataka, a decoction of the bark of the *Astonia scholaris* a flowering branch is used in virtually every household at the onset of the monsoon to prevent malarial fevers. The neck of the turtle is sometimes used for the treatment of a pro-lapsed rectum or uterus. *Adatoda Vassica* or *Adusi Vasa*, as it is locally known, is a common treatment for coughs and to stop bleeding in the case of piles or dysentery.

Case Study:

Nevadensin: Natural sources, Extraction and Isolation, Chemistry and other properties, Synthesis, Bioactivity

NEVADENSIN: Pharmaceutically potent bio-flavonoid.

Nevadensin (5, 7-dihydroxy-6, 8, 4'-trimethoxyflavone) has already established itself as a promising natural bioactive substance that bears the potential to become a novel "natural lead" in drug discovery programmes. The bioflavonoid exhibited a wide range of significant biological activities including hypotensive, anti-tubercular, antimicrobial, anti-inflammatory, anti-tumour and anti-cancer activities.

- **Natural Sources**: Exhaustive literature survey revealed that nevadensin is distributed in several medicinal plants listed below:
- *Iva nevadensis, Acanthopanax trifoliatus*
- *Baccharis* species, *Biebersteinia orphanidis, Esenbeckia almawillia, Helianthus* species
- *Limnophila* species: *Limnophila aromatica, Limnophila geoffrayi, Limnophila rugosa, Limnophila heterophylla, Lysionotus pauciflorus*
- *Ocimum* species: *Ocimum americanum*, *Ocimum x citriodorum, Ocimum minimum*
- *Onions* species: *Onions natrix* ssp. hispanica, *onions natrix* ssp. ramosissima
- *Viguiera* species*: Viguiera mollis, Viguiera procumbens, Viguiera bicolor*
- **Extraction and Isolation**: Typical procedures as reported for the extraction and isolation of nevadensin from few of its natural sources are described herein

From *I. nevadensis*: Ground whole plant of *I. nevadensis* (740g*)* is extracted with chloroform for 2 days; the crude gummy mass (22g) obtained on removal of the solvent under reduced pressure was then chromatographed over 250g of silicic acid . The column was eluted successively with benzene-chloroform (3:1) and benzene-chloroform (5:2).

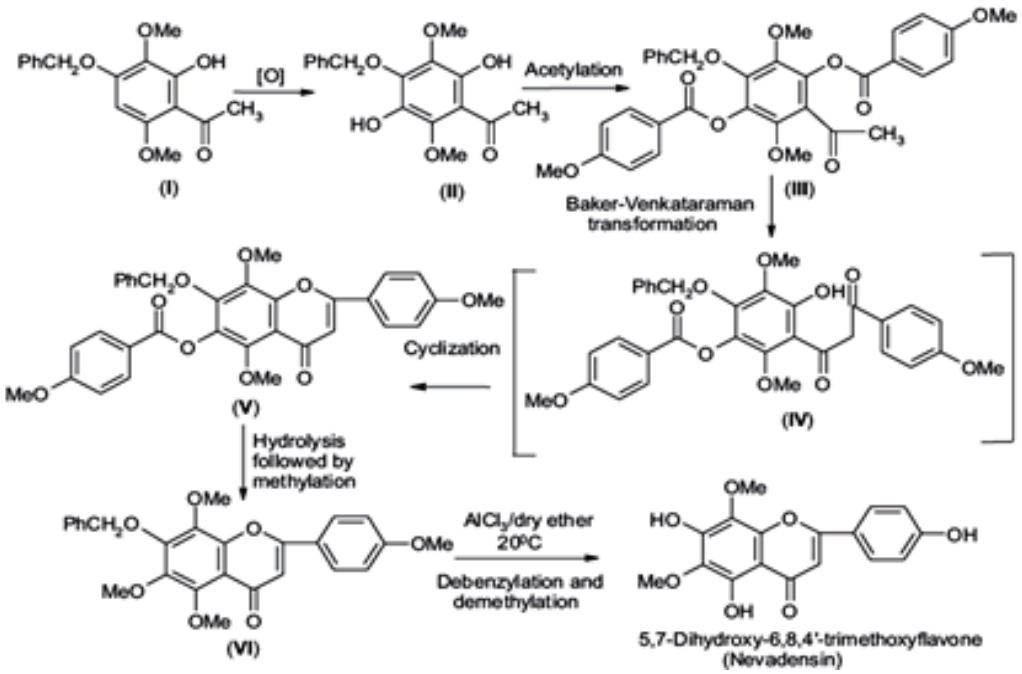
The fractions obtained on elution with benzene-chloroform (5:2) solidified on titration with ether and were recrystallised repeatedly from benzene. This furnished nevadensin (0.2g) exhibited a double melting point of 186-188^{o}C and 193-195^{o}C

From *I. acerosa*: Ground whole plant of *I. acerosa* (950g) is extracted with chloroform for 2 days; the crude gummy mass (30.5g) obtained on removal of the solvent under reduced pressure is then chromatographed over 225g of silicic acid. The column was eluted with benzene. The fractions 22-26 (400ml of benzene each) are solidified on titration with ether and are recrystallised repeatedly from benzene. This furnished nevadensin (0.15g) exhibited a double melting point of 186-188^{o}C and 193-195^{o}C.

From *L. geoffrayi*: The pulverised,dried aerial plant material(615g) are extracted successively with n-hexane, chloroform and methanol in a soxhlet apparatus [6,7].

- The chloroform extract (crude mass of 7.79g) are chromagraphed over silica gel (0.063-0.200mm, 200g), eluted with n-hexane-chloroform, chloroform and chloroform –methanol , with gradually increasing quantity of the more polar solvent.
- Fraction 11 is concentrated (4.99g) and then chromatographed over of silica gel (0.063-0.200mm, 50g) using chloroform and chloroform-methanol as eluents, with increasing percentage of the more polar solvent, to afford 13 sub fractions; the 10th sub fraction (110g) is further chromatographed to furnish nevadensin (15mg)
- Hydrolysis of V, followed by methylation of the hydroxyl function at C-6 as formed, furnished 7-benzyloxy-5, 6, 8, 4'-tetramethoxyflavone (VI).
- Debenzylation and demethylation of VI at 20^{0}c with aluminium chloride in dry ether ultimately afforded 5, 7-didhydroxy-6, 8, 4'-trimethoxy flavone i.e., nevadensin

The schematic representation is given below;



Synthesis of Nevadensin:

Biological activity of Nevadensin: Nevadensin is a therapeutically potential natural flavonoid, and is reported to exhibit a variety of biological activities. The significant phamocological potentials of the bio-flavonoid are presented herein

Hypotensive Activity: Song *et al*., studied the hypotensive effect of nevadensin in dog and cat models. In anaesthetised dogs and cats, intravenous, intramuscular or intraduodenal injections of the drug at doses of 2-40mg/kg body weight lowered the blood pressure(BP) by 64±7mmHg, retaining the heart rate and respiration unchanged.

The BP gradually returned to its original level in next 2-4 hours. In dog model, the BP was found to be lowered more by the test compound (92±7mmHg at a dose of 2.0mg/kg) than reserpine (62±14mmHg at a dose of 1.5mg/kg) or hexamethonium (78±7mmHg at a dose of 2.0mg/kg). The investigators also established that the hypotensive potential of nevadensin was similar to that of total alkaloids of *Rauwvolfia (*94±7mmHg at a dose of 1.0mg/kg). In this study, the mechanism of hypotensive action exerted by nevadensin appeared to be both central and peripheral in nature.

Anti-Inlammatory Activity: *Reddy et al*. studied the anti- inflammatory activity of nevadensin in acute and chronic inflammatory rat model; Carrageenan-induced rat paw edema was compared at 0 to 3 hours with that of control (4% gum acacia mucilage).

In tests for acute inflammatory activity, nevadensin showed significant inhibition by 45.28% at a dosage of 75mg/kg body weight on oral administration.

Anti-Tubercular Activity: Nevadensin and isothymusin (6, 7-dimethoxy -5, 8, 4′ trihydroxyflavone), isolated from the chloroform extract of the aerial parts of *L. geoffrayi*, were reported to exhibit growth-inhibitory activity against *Mycobacterium tuberculosis H37Ra* with equal minimum inhibitory concentration (MIC) value of 200µg/ml; however the efficiency is relatively lower than those of the standard drugs (used during the experiment) rifampicin (MIC 0.003-0.0047µg/ml), ionized (MIC 0.025-0.05µg/ml) and kanamycin sulphate (MIC 1.25-2.5µg/ml). But the flavone, nevadensin, was found to be more effective (MIC values: 100µg/ml for nevadensin; 10µg/ml for streptomycin used as standard) against the H37Ra strain of M. *tuberculosis*. The investigators suggested that the compound shows no toxicity up to 600µg/ml orally in acute toxicity studies. Baxter *et al*., also evaluated the anti-tuberculostatic activity of nevadensin against *Bacillus tuberculosis* at a concentration of 0.2mg/ml *in vitro.*

Anti-Tumor and Anti-Cancer Activity: Nevadensin was evaluated to inhibit markedly the growth of BEL-7404cells-the T/C values [the ratio of cell number of treated (T) to controls (C)] were determined as 87.6, 80.6 and 34.9% at the doses of 1.0,10 and 100mg/ml, respectively. The flavonoid was also reported to show mild cytotoxic activity. It showed 100% cytotoxicity at a concentration of 75µg/ml both in Dalton's lymphoma ascites tumor and Ehrlich ascites tumor. Different concentration of he drug containing nevadensin were used to test the cytotoxic activity. Dalton's lymphoma ascites tumor cells and Ehrlich ascites tumor cells were grown in the peritoneal cavity of swiss albino mice. The compound was found to be more effective than Wogonin (5,7-dihydroxy-8-methoxyflavone) that showed only 24.1% cytotoxicity in both the tumors at the same concentration. Hence, it can be argued that the methoxylated flavones posses' moderate cytotoxic activity, which supports the view of Dong *et al.,* Nevadensin was also reported to possess moderate protein-tyrosine kinase (PTK) inhibitory activity there by expressing its anti-cancer potential.

Anti-Microbial Activity: Nevadensin has also been found to have potent antimicrobial activity against the test organisms -*Escherichia coli* and *staphylococcus aureus*. It showed strong cidal effect on *E. coli* by lysing the cells within 4 hours of treatment; the compound enhanced the activity of fructose bisphosphatase, a gluconeogenic enzyme at sub lethal dose, whereas it decreased the activity of phosphofructokinase and isocitrate dehydrogenase, the key enzyme of Embden-Meyerhof-Parnas and tricarboxylic acid cycle, respectively. Bacteriostatic as well as bactericidal effects of the test compound have been observed on *S. aureus.* The compound inhibits also the growth of a plant pathogenic fungus, *Alternaria solani*, but is unable to inhibit the growth of yeast, Candida *albicans.* MIC of the compound for *E. coli* and *A. solani* were found to be 200 and 250µg/ml, respectively [8, 9].

Nevadensin has been evaluated to exhibit a variety of biological activities, and it demands for more detailed investigations on its pharmacological potentials In depth and systematic studies along with exact mode of action and safety evaluation are also necessary. Studies on their semi-synthetic analogues are also to be considered. :

- **Avenues for Progress toward a "Green Pharmacy":** The last decade has seen tremendous progress in advancing the practice of "green chemistry" (e.g., minimizing the use of ecologically hazardous reagents and designing alternate synthesis pathways, some of which are based on aqueous chemistry) (U.S. EPA Office of Pollution Prevention and Toxics 2002). In fact, the pharmaceutical industry has a strong history of applying environmentally responsible chemistry (which also turns out to be economically advantageous) to drug synthesis and manufacturing. The same principles could be logically extended and applied to drug design, delivery, package design, dispensing, and disposal so that their benefits could accrue to the end user and not just the manufacturer.

Some of these ideas for minimizing the release of PPCPs to the environment have already been put forth (Daughton and Ternes 1999) but are reiterated and expanded on here because all these ideas have never been brought together in one document. Unfortunately, despite the many avenues of advancement that could be and some efforts are already being-made toward a green health care system, the transfer of new knowledge and technology to clinical practice is notoriously slow; as one example, new knowledge gained from clinical trials takes an average of 17 years to become incorporated into routine practice

Drug Design: New drug design (chemical structure and properties) and formulation (combination of the active, therapeutic ingredient with the inert, nonactive ingredients known as excipients) should factor in new considerations for "environmental friendliness" or "environmental proclivity." Such "green" PPCPs would maintain or improve therapeutic or cosmetic efficacy while also maximizing their susceptibility to biodegradation, photolysis, or other physicochemical alterations to yield innocuous end products. Design of more labile drugs (e.g., those that would ordinarily be degraded by or poorly transported across the gut) would further reduce excretion.

Current drugs that do undergo initial structural alterations (e.g., via phase I or phase II metabolism) often yield broad arrays of metabolites, some of which are the actual active drug form and some of which are environmentally persistent; compared with what little is known regarding effects to non target species by parent drugs, even less is known about metabolites. Drugs could be designed with better physiologic sorption characteristics (to lessen direct excretion of the parent compound). Using smaller doses by enhancing the delivery exclusively to the target site or receptor is an objective being pursued on many fronts, including better drug design to accommodate existing membrane transporters (e.g., XenoPort 2002) and "creating" *in situ synthetic transporters (Alper 2002).*

Another design strategy would be "smart" drugs that better emulate the nonanthropocentric, native chemistries of natural products. As examples, consider *the* newer classes of antimicrobial peptides modelled after the endogenous antimicrobials (e.g., defensins, piscidins, and cathelicidins; Toma, *bacteriophages (viruses that infect* only bacteria)and *the enzymes used by phages to destroy their* bacterial hosts [10,11,12].

Alternative medicines missing from the radar*:* The WHO developed a strategy for addressing issues of policy, safety, efficacy, quality, access, knowledge preservation/ protection, and rational use of "traditional, complementary, and alternative medicine" (TM/CAM) (WHO 2002b).

The WHO put forth this first global strategy clearly signals that TM/CAM has gained substantial stature. The popularity of TM/CAM in less developed countries is widely appreciated; its growth in more developed countries over the last two decades is reflected by the proliferation of websites devoted to it. Because many active ingredients in natural medicines are highly bioactive, the same concerns regarding environmental fate and ecologic effects apply (Daughton and Ternes 1999) and should therefore be subject to similar scrutiny. But the WHO strategy does not address any issues concerning disposal or pollution prevention. In many countries, environmental risk assessments of varying degrees are required at least for new drug entities meeting certain criteria.

Although the existing regulations for these assessments as well as those under consideration have the potential to evolve over time in response to new science regarding environmental impacts, similar assessments for dietary supplements, "alternative" medicines, and other personal care products do not exist. Given that the biologic activity of many of these chemicalscan rival that of drugs (e.g., Daughton and Ternes 1999), it would be prudent to also submit these diverse chemical classes to environmental risk assessments; currently, they are completely free of any oversight regarding ecologic hazard, and many escape assessment of human health risk.

Indeed, the fact that nutritional supplements can elicit profound biologic effects is becoming codified in medical references (e.g., PDR 2002a, 2002b) where commonly recognized cross-reactions with conventional drugs have already been noted- for example, with Saint John's wort (a potent inhibitor of certain drug-activating enzymes) [13, 14].

Drug Delivery: Eco-friendly strategies to implement in the area of drug delivery include those relevant to prescribing, dispensing, patient compliance and medication delivery mechanisms. Some advanced ideas regarding delivery mechanisms can be gained from Mort (2000).

Prescribing: Both physicians and the public could be made more aware and better informed as to the medical and environmental consequences of overprescribing medications. Better ways need to be found to engage the medical community and the public in this issue. Guidelines could be developed and promulgated for minimizing inappropriate drug use (misuse, overuse, and abuse) [15].

CONCLUSION: Green pharmacy is necessary for balance between human health and ecology health. Boost the ongoing researches on pharmaceutically potential natural "lead molecules" in drug discovery programmers'. Many people actively engaged in advancing the principles of "sustainability" (sometimes defined as meeting society's needs in ways not diminishing the capacity of future generations to meet theirs) have strongly felt that without empowering people to take charge of the basic aspects of their own lives, sustainable improvements in health are not possible.

REFERENCES:

1. Cutler, Stephen J., Cutler, Horace G. 2000, *Biologically active natural products: pharmaceuticals*. CRC Press. p. 5. ISBN 9780849318870.
2. Newman D J, Cragg G M, *Natural products as sources of new drugs over the last 25 years.* Journal of Natural Products. 2007. 70, 461-477.
3. Dan Bensky, Steven Clavey, Erich Stoger, and Andrew Gamble *Chinese Herbal Medicine:* Materia Medica, Third Edition 2004.
4. Hernan Garcia, Antonio Sierra, Hilberto Balam, and Jeff Connant *Wind in the Blood: Mayan Healing & Chinese Medicine*. 1999"The American Society of Pharmacognosy - Story of Taxol". http://www.phcog.org/Taxus/Taxus_Web.html.
5. El-Shemy HA, Aboul-Enein AM, Aboul-Enein KM, Fujita K *Willow Leaves' Extracts Contain Anti-Tumor Agents Effective against Three Cell Types:* PLoS ONE. 2007,2:e178
6. James Ralph Hanson, Natural Products: The Secondary Metabolites , 2003, *Royal Society of Chemistry*, ISBN 0854044906
7. Xiao-Tian Liang, Wei-Shuo Fang (editors), *Medicinal Chemistry of Bioactive Natural Products* ,2006, *Wiley-Interscience*, ISBN 0471739332
8. Peter B. Kaufman, *Natural products from plants* (1999), *CRC Press*, ISBN 084933134X
9. Meenakshi. Sivakumar, S. Meenakshi, Sujata V. Bhat, Bhimsen A. Nagasampagi, *Chemistry of Natural Products*, 2005, *Springer*, ISBN 3540406697
10. Brahmachari G. Prospects of natural products research in the 21st century: A sketch .In: Brahmachari G, editor. *Chemistry of Natural Products: Recent Trends and developments.*1st ed. Trivandrum: research signpost; 2006.p:1-22.
11. TNS. 2002. The Natural Step. San Francisco, CA: The Natural Step. Available: http://www.detnaturligasteget.se
12. Abramowicz M (ed). 2002, *Drugs past their expiration date*. Med Lett (On Drugs and Therapeutics) 44(W114B):93–94.
13. Available:http://www.medletter.com/freedocs/expdrugs.pdf

14. U.S. EPA Office of Pollution Prevention and Toxics. 2002. EPA's *Green Chemistry Program.* Washington, DC: U.S. Environmental Protection Agency. Available: http:// www.epa.gov/greenchemistry
15. Straub JO. 2002, *Environmental risk assessment for new human pharmaceuticals in the European Union according to the draft guideline/discussion.* January 2001. Toxicol Lett 131(1–2):137–143.
16. Thornton J. 2000, *Beyond risk: An ecological paradigm to prevent global chemical pollution.* Int J Occup Environ Health 6(4):318–330.

How to cite this article:
Shivakumar N, Agrawal P and Gupta PK: Green Pharmacy: An Alternative and Complementary Medicine. *Int J Pharm Sci Res*. 2013; 4(2); 575-581.