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Plants: The Best Synthesizer of Pharmaceutically Important Secondary Metabolites and Nanoparticles

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ABSTRACT

Plants are the renewable resource of majority of existing and novel drugs. It can produce innumerable number of secondary metabolites using raw materials formed during the primary metabolic pathways in response to needs and challenges of its environment. The occurrence of these secondary compounds among plants amounts alkaloids as 20%, flavonoids as 15%, triterpenes and simple phenolics around 10% and others in very low level, with limonoid being the least. Most of these have various applications in the area of pharmaceuticals, food additives, fragrances, pesticides, etc. The total number of natural products produced by plants has been over 600,000.

COMMUNICATION

Each plant contains minimum over 1000 chemical molecules. It implies that plants are highly sophisticated natural chemical factories where a large variety of chemical compounds are manufactured with great precision and ease from simple raw materials. Thus, nature has been carrying out its own combinatorial chemistry and producing structural novelty and molecules with new mode of action [1-3]. Since the isolation of morphine, the first pharmacologically active compound in pure form from the plant *Opium poppy* in 1805 the search for plant derived drugs based on traditional knowledge is a most rewarding area in drug discovery. Perusal of the literature indicate that of the 252 drugs considered as basic and essential by the World Health Organization, 11% are exclusively of plant origin and a significant number are synthetic drugs obtained from natural precursors. About 125 such plant derived compounds are currently in use as drugs and 25% of modern prescription drugs contain at least one compound derived from higher plants [4].

Plant derived secondary compounds are synthesized within the living system in accordance with environmental and other stimuli including the attack of pathogens/pests. These molecules have been interacted with other bio-molecules or chemical constituents in the biological system and ultimately evolved as non-toxic new chemical entities with pharmaceutical properties. The efficacy of such molecules have been tested, modified and evolved through long-term evolutionary process and they can be used as safe drugs, which may cause lesser or no side effects. Generally, natural products particularly plant derived drug molecules have greater number of chiral centers, increased steric complexity, higher number of oxygen atoms, lower ratio of aromatic ring atoms to total heavy atoms, higher number of solvated hydrogen bond donors and acceptors, grater molecular rigidity and broader distribution of molecular properties such as molecular mass, octanol water partition coefficient, and diversity of ring systems [5]. These characteristic features attributed enormous structural and chemical diversity and about 40% of the chemical scaffolds found in natural products are not in today's medicinal chemistry [6]. The forgoing characters are not agreed with drug-likeness criteria proposed by Lipinski's rule of five [7] and rule of three. However, most of the plant derived molecules are biologically active and having favorable ADMET profile (absorption, distribution, metabolism, excretion, and toxicity) and several plant derived drugs currently available in the market are not agreeable with the Lipinski's rule (e.g., paclitaxel). In this backdrop, a biggest challenge is to find alternative drug ability criteria for the compounds of natural origin. The major disadvantages encountered with plant derived drugs are 1) chemical synthesis of certain plant derived compounds is not possible or not economically viable and in such cases its commercial production may depend on the availability of raw materials, 2) complexity in patent laws.

The major challenging factors influencing conventional plant derived drug discovery includes 1) species identification, 2) availability of sufficient quantity of raw materials for compound isolation, 3) collection of a species from wild especially protected, 4) quality and quantity of chemical composition which may depend on season, harvest time, soil composition, altitude, climate, processing, storage condition, extraction and isolation process, association of microorganism, etc., 5) source material export and import issues, 6) accessibility and patent issues, 7) scarcity of raw materials, 8) constraints in high throughput screening and determination of molecular mechanism of action and 9) getting clinical approval [8]. Of the 310,000 plant species [9] only 6% of them have been systematically investigated pharmacologically, and only around 15% phytochemically [10]. Many plant secondary metabolites are genus or species specific and considering the current rate of species extinction, bio prospecting attain *prima face* importance. Furthermore, development of fully automated technology is to be established for facing the drug discovery process in time bound manner.

The conventional administration of plant-derived drugs and herbal extracts has several limitations. Most of the plant-derived compounds are very complex large and these molecules cannot pass through the lipid membrane of the cell. In addition, *in vivo* stability, aqueous insolubility, intestinal absorption and unspecific site of action are the major constraints encountered with conventional drug delivery system. Application of the nanotechnology, the technology of the 21st century may be the best option to overcome these inherent problems related to drug delivery such as site targeted drug delivery, reduce dose, increased solubility, enhanced absorption, reduced elimination and metabolism of drug molecules.

The basic concept of nanotechnology was proposed by Richard Feyman in 1959 in his lecture at American Physical Society. According to him the ability to manipulate individual atoms and molecules might be developed, using one set of precise tools to build and operate another proportionally set, so on down to the needed scale. This concept was evolved as a challenging area of R & D only since 1980s. Today, it has been emerged as a field of applied science and technology, which involves clumps of atoms, molecules, and molecular fragments forms in the range of 1 to 100 nm size. These nanoparticles have applications in various fields such as biosensors, medicines, drug delivery, cosmetics, paint, semi-conductors, packaging, electronics, Nano-Fabrics, bio-engineering, automobiles, catalysts, etc. There are several physical and chemical methods have been employed for the synthesis of nanoparticles in which high radiation and concentrated chemical reductants and stabilizing agents are using. These all induce environmental and health hazards. Moreover, these methods are expensive, labor intensive and time consuming and therefore thinking about alternative methods.

The history of traditional medicine revealed that since time immemorial minerals and metals were integrated with herbal extracts especially in Chinese, Greek and Indian traditional treatment systems. In Ayurveda, the metals such as Pb, Cu, Ag, Au, Li, Fe, Sn and Zn had been used to enhance the effectiveness of herbal preparations [11]. During the course of ayurvedic drug preparation plant materials mixed with minerals/metals and subjected to repeated physical process such as maceration, grinding, crushing, cutting, etc. and in the case of decoction continuous mixing at ambient temperature or preserving in long-term before use and thereby enhance the efficacy of the drug. It is well demonstrated that many organisms such as plants, algae, diatoms, bacteria, yeast, fungi and few types of human cells have the capability to convert inorganic metal ions into metal nanoparticles via reductive capacities of the chemical components present in these organisms. Phytomining has been practiced to remove heavy metal accumulation from the soil [12]. Some plant species such as *Pongamia pinnata* (L.) Pierre, *Adenanthera pavonia* L., etc have the capability of absorbing heavy metals such as Ag, Cu, Cd, etc. from the soil. Phytomining has been also tried in mineral rich area by planting selected plant species, harvested them after maturity and extracted the desired metals. However, the technique was not economical and not popularized. The herbal medicines or the plant extracts contains plethora of chemical constituents and numerous functional groups such as C=C – alkenyl, C=N – amide, O=H – phenolic and alcohol, N=H – amine, C-H and COO- carboxylic acid etc., these functional group may bind with metal ions and form nanoparticles [13]. The different steps in nanoparticle synthesis by plants includes: 1) the activation phase during which the reduction of metal ions and nucleation of the reduced metal atoms occurs, 2) the growth phase during which the small adjacent nanoparticles spontaneously coalesce into particles of a larger size, which is accompanied by an increase in the thermodynamic stability of nanoparticles, and 3) the process termination phase determining the final shape of the nanoparticles and during this stage the nanoparticles acquires the most energetically favorable conformation, which may depend on the ability of the plant extract to stabilizes metal nanoparticles. In addition to the free energy molecules present in the plant extract, other factors such as pH of the reaction mixture, incubation temperature, reaction time, concentration and electrochemical potential of metal ions are also influence nanoparticle formation. Once biosynthesis of nanoparticles have achieved the next step is to analyze the structure by UV-visible spectroscopy and its physicochemical characterization can be determined. By manipulating the constituents of plant extracts as well as influencing factors nanoparticles with desired size and shape can be synthesized, the shape and size has pivotal role in site directed application. Biosynthesis of different metal nanoparticles such as Cu, Co, Ag, Au, Pd, Pt, Zn, Mn, Ti, Ni, Fe, etc. and alloy of Au, Al, Zn were successfully achieved. Synthesis of the foregoing metal nanoparticles derived from over 70 plant species and its pharmaceutical uses were described. Majority of the plant species synthesized Au and Ag nanoparticles, which have wide range of therapeutic property. For examples, Ag nanoparticles obtained from several plant species such as *Acalypha indica* L., *Alternanthera sessilis* (L.) R.Br. ex DC., *Carica papaya* L., *Elettaria cardamomom* (L.) Maton. etc., Au from *Cassia fistula* L., Pd from *Cinamomum zeylanicum* Blume, Pt from *Diospyros kaki* L.f., ZnS and Pb from *Jatropha curcus* L., Fe from *Sorghum* sp., and CuO2 from *Tridax procumbens* L. The biologically synthesized nanoparticles have bactericidal, fungicidal, antiplasmodial, anti-inflammatory, anticancer, antiviral, ant diabetes, antioxidant, cytotoxic and heaptocurative activities. The therapeutic activity of these nanoparticles is depending on the source of plant species [13]. In addition to therapeutic value, biosynthesized nanoparticles have other commercial applications such as waste water treatment, cosmetics, pesticidal, biosensors, etc. Ag, Si, Pt nanoparticles have been used for the manufacturing of water purifier, bone and teeth cement, facial cream, sunscreen, anti-ageing creams, mouthwash, shampoo, soap, detergent, shoes, and perfumes. Silica nanoparticles are also used as pesticide. Ag nanoparticles are used in heat liable instrumentation such as PCR lid and UV-spectrophotometer. It is also used as food preservative. Synthesis of nanoparticles through biological system need low investment, short production time, less effort, safe, and production rate can be easily up-scaled.

Herbal extracts contains a plethora of chemical constituents in balanced form and nanotechnology based drug application method would revolutionized and open a new horizon in plant-derived drug discovery and its usage. It is no doubt that in near future nanotechnology based drug delivery system might be popularised as the best cost effective, safe and effective drug delivery system which will be replaced the present conventional system. Plants are the renewable and best source of therapeutic molecules forever and whatever the technical advancement so far achieved green medicine is in the mainstay.

REFERENCES

1. Ehrman TM, et al. Phytochemical databases of Chinese herbal constituents and bioactive plant compounds with known target specificities. J Chem info Modelg. 2007;47:254-263.
2. Mendelsohn R and Balick MJ. The value of undiscovered pharmaceuticals in tropical forests. Economic Botany. 1995;49:223-228.
3. Verdine GL. The combinatorial chemistry of nature. Nature 1996;384:11-13.
4. Rates SMK. Plants as source of drugs. Toxicon. 2001;39:603–613.
5. Koehn FE and Carter GT. The evolving role of natural products in drug discovery. Nat Rev Drug Disc. 2005;4:206-220.
6. Lahlou M. The success of natural products in drug discovery. phamco Phamcy. 2013;4:17-31.
7. Lipinski CA, et al. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Del Rev. 1997;23:3–25.
8. Atanasov AG, et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Btechnol Advnc. 2015;33:1582-614.
9. http://cmsdocs.s3.amazonaws.com/summarystats/2015_2_Summary_Stats_Page_Documents/2015_2_RL_Stats_Table_1.pdf.
10. Cragg GM and Newman DJ. Natural products: a continuing source of novel drug leads. Biochim Biophys Acta 2013;1830:3670–3695.
11. Pandey A and Pandey G. Nanotechnology for herbal drugs and plant research. RRJPNT 2014;2: 13-16.
12. Makarov VV, et al. Green nanotechnologies: Synthesis of metal nanoparticles using plants. Acta Nature. 2014;6:35-44.
13. Kuppusamy P, et al. Biosynthesis of metallic nanoparticles using plant derivatives and their new avenues in pharmacological applications – An updated report 2016. Saudi Pharma J. 2016;24:473–484.