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Nanotechnology: A Tool to Enhance Therapeutic Values of Natural Plant Products

A. Kumari, V. Kumar and S.K. Yadav
Plant Metabolic Engineering and Nanobiology Laboratory, Biotechnology Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur-176061, India

Corresponding Author: Sudesh Kumar Yadav, Plant Metabolic Engineering and Nanobiology Laboratory, Biotechnology Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur-176061, India

ABSTRACT

Natural product isolation and extraction is full of many technical hitches. In spite of that plant origin natural products have occupied lead positions as drugs in current pharmacopoeia. In this article, problems in natural product drug development and the possibilities of their improvement through nanoformulations using nanotechnology have been reviewed. Known effects and no side effects have made natural products a powerful therapeutic solution to the organisms. But the delivery of plant origin therapeutic molecules as drugs is problematic due to poor solubility, poor permeability, low bioavailability, instabihty in biological milieu and extensive first pass metabolism. These limitations of plant origin drugs can be overcome by attaching or encapsulating them with suitable nanomaterials. Nanomaterials can significantly enhance the pharmacokinetics and therapeutic index of plant origin drugs. Targeted delivery and combination therapy can drastically improve the performance of plant origin drugs.

Key words: Natural products, therapeutic molecules, nanomaterials, nanoformulations, stability, bioavailability

INTRODUCTION

Natural products are serving as vital source of drugs since ancient times. Today, about half of the useful drugs are derived from natural sources. Plant origin drugs have served as the foundation for a large fraction of the current pharmacopoeia (Kingston, 2011). It is astonishing to see that inspite of technical hitches encountered in natural product research 50% of presently marketed drugs owe their origins to natural products. Several latest reviews have tinted the importance of natural products to the drug discovery process (Kingston and Newman, 2002; Baker *et al*., 2007; Gordon *et al*., 2009; Butler, 2008).

This category comprises compounds from plants, microbes and animals, as well as natural products on synthetic or semi-synthetic compounds. They cover variety of therapeutic indications and show a great range of chemical structures (Harvey, 2008). Thirteen natural product drugs have been approved from 2005-2007 (Gibson *et al*., 2007). Another 11 compounds have been listed in chnical use and three in clinical development (Newman, 2008). Importantly, over a 100 natural product-derived compounds are currently undergoing clinical trials. Most of these are derived from plants and microbial sources (Butler, 2008). Scrutinising the chemical properties of the natural products is mandatory for developing them into drugs (Ganesan, 2008). Half of them were found

to be strongly amenable with Lipinski's rule of five for orally available compounds. On an average, natural products are more bioavailable than synthetic drugs. Despite these merits, many large pharmaceutical ventures have decreased the use of natural products in drug discovery screening. This was due to technical hitches of natural products and hopes linked with the use of compounds prepared by methods of combinatorial chemistry (Singh and Barrett, 2006; Lam, 2007; Rishton, 2008).

The interest in applying natural product chemistry to drug discovery is increasing. In addition to plant or microbes, cyanobacteria are receiving attention as a source of natural compounds. Over 120 cyanobacterial alkaloids have been published between 2001 and 2006. They have wide structural diversity and a variety of biological actions, such as cytotoxicity, sodium channel modulation, anti-fungal and protease inhibition activity (Harvey, 2008). The examination of over 1,20,000 exclusive compounds in the dictionary of natural products has shown that 65% of them had no violations of Lipinski's rule of five (Quinn *et al*., 2008).

In addition to their straight use as drugs, many natural products have served as lead compounds for medicinal chemistry. Podophyllotoxin led to the development of clinical drugs as etoposide and teniposide (Srivastava *et al*., 2005). This tool of drug discovery can compete with recently developed technologies such as chemical compound libraries and high throughput screening of combinatorial synthetic efforts (Liu *et al*., 2011). Plants are huge source of natural diversity in the massive amount of compounds that they synthesize. Many plant compounds are known to be useful as therapeutics for treating a variety of human ailments. In fact, approximately two thirds of active ingredients used as drugs for cancer and infectious diseases are derived from plants (McChesney *et al*., 2007). Natural products can offer powerful leads for therapeutic development because they have known effects on organisms. Natural products that demonstrate potent biological activity have poor water solubility, or very short circulating life and face significant developmental challenges. On the other hand, less active natural products may become suitable candidate for drug development. In either case, there is always a degree of compromise and this may inevitably result in the production of less potent drugs (Shi *et al*., 2010). Also, plants extract are being used as a process for the synthesis of silver nanoparticles that may find very important place in drug delivery (Savithramma *et al*., 2011; Mallikarjuna *et al*., 2012).

However, with emerging trends in nanotechnology it has become possible to address the problems associated with potential natural products to be developed as drug. By using nanoscale carriers, therapeutic value of natural products can be drastically improved. In this study, problems associated with the development of drugs from natural products and the possibilities of their improvement through nanoformulations using nanotechnology have been discussed.

Encountered problems in natural products drug development: Most of the natural products are classified as secondary metabolites. Over the past 100 years, secondary metabolites are being chemically isolated and identified. However, commercial production of these biologically active natural products represents an enormous challenge (Kolewe *et al*., 2008). These secondary metabolites are present in extremely low amounts in the plants. Natural products have encouraged many discoveries in organic chemistry (Newman, 2008; Wilson and Danishefsky, 2006). Natural product scaffolds have been used as cores of compound libraries produced by combinatorial chemistry. There are many examples of libraries based on alkaloids, terpenoids (Boldi, 2004) and flavonoids (Yao *et al*., 2007).

Drug discovery within pharma industries is based on the high throughput screening of thousands of compounds. But this approach is not suitable for natural products as the crude

extracts are intricate mixtures containing numerous compounds like tannins. Tannins give false information in high throughput screening (Kingston, 2011). After the identification of lead extract the active compound is isolated by a process of bioactivity directed fractionation which takes weeks or months (Kingston, 2011). In addition to high through put screening isolation of bioactive compounds from plant extracts faces many other challenges like inconsistency of source material, obscurity in isolating active components and the cost of collection. One more problem with natural product research is compound supply. Depending upon the utility of the compound several grams to hundreds of grams are needed for preclinical development. One of the premier concerns in natural product research is that after so much of study many of the compounds in a given extract are known compounds leading to much wasted effort. Dereplication is thus an important part of the process (Kingston, 2011). With development in fractionation techniques to isolate and purify natural products (Wu *et al*., 2007) and in analytical techniques to determine structures (Singh and Barrett, 2006; Harvey, 2007), screening of natural product mixtures is now more well-suited with the expected time scale of high-throughput screening. With advances in NMR techniques, intricate structures can be solved with much less than 1 mg of compound (Harvey, 2008). Newman *et al.* (2003) has described natural products as source of drugs over the period of 1981-2002. Of the 1184 new chemical entities, only 30% were of synthetic origin (Newman *et al*., 2003). They have also tabulated exhaustive list of therapeutic natural products including both natural and their derivatives that are effective against variety of diseases over last 25 years (Newman and Cragg, 2007). The pharmaceutical companies have devoted many years of work to high throughput screening of combinatorial chemistry products. In spite of that natural products field produced 50% of small molecules in the years 2000-2006. Best selling drug atorvastatin is also of plant origin (Newman and Cragg, 2007). Number of other pharmaceutically active natural products has been listed with their clinical status (Shu, 1998). Natural products research as part of drug discovery faces increasing challenges. The most remarkable challenge to this field is how to improve its competitiveness with synthetic and combinatorial libraries. The drawback relative to synthetic and combinatorial molecules can be the time taken to isolate and characterize active molecules from the complex natural product extracts (Shu, 1998).

Despite the challenges many natural products like artemisinin, curcumin, triptolide and capsaicin have been extensively studied and entered into clinical trials (Corson and Crews, 2007). Countless other capable compounds stumble in obscurity. Delivery of natural products using conventional dosage forms is also challenging. The reason for this is widely varying structures of the compounds, their moderate aqueous solubility, poor permeability and instability. Also, natural products undergo fast oxidation under basic conditions and first pass metabolism before reaching to systemic circulation (Haslam, 1996; Anders, 2002).

Nanoformulations to improve therapeutic value of natural products: Nanotechnology had an enormous impact on medical technology, significantly improving the performance of drugs in terms of efficacy, safety and patient compliance. Nanotechnology manifests wide range of materials which can be smartly designed with chemically modifiable surfaces to tag variety of chemical, molecular and biological entities. Modulation of surface properties offers advantageous properties like increased solubility and biocompatibility (McNeil, 2005; Baimark, 2009; Phromsopha and Baimark, 2009; Semwal *et al*., 2010; Saraf *et al*., 2011; Baimark, 2012). Attaching polymers like polyethyleneglycol, polyvinylpyrrolidone and polyvinylalcohol increases the solubility and provide protection to the degradation of proteins during *in vivo* applications (McNeil, 2005). This process

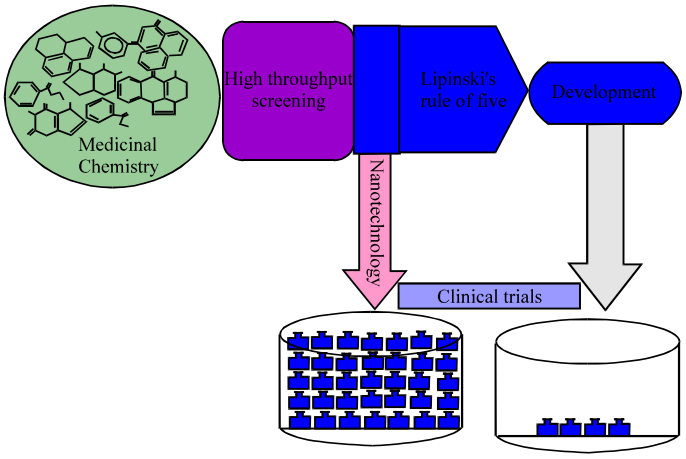

Fig. 1: Natural product drug development pipeline: Plant origin insoluble compounds can be attached or encapsulated in nanoparticles, offering the potential to expand the number of drugs introduced into clinical trials

is very helpful in drug discovery. Although, a large pharmaceutical company may synthesize several million compounds, only a fraction of those new chemical entities become leads for preclinical development as a result of issues associated with their solubility (e.g., Lipinski's Rule of Five). On the contrary, natural products obey Lipinski's rule of five. This is an advantage of natural products over synthetic drug molecules.

Conventional natural product formulations suffer from many limitations and shortcomings. For example in chemotherapy, plant origin drugs causes damage equally to both normal and malignant cells. By carefully designing the nanocarriers, natural product formulation can be targeted to tumour cells (Sahoo and Labhasetwar, 2003). Another problem with natural products formulation is their structural instability in biological milieu and premature drug loss through rapid clearance and metabolism. Their poor solubility and low bioavailability is also the barricade. By smartly using combination of nanocarriers and natural products solubility and bioavailability can be improved significantly. However, nanocarriers may not be suitable for all drugs especially less potent natural products. Because the higher dose of the drug would make the nanocarriers larger, this would be difficult to administered (Sahoo and Labhasetwar, 2003). Nanotechnology allows insoluble compounds to be attached or encapsulated in highly soluble nanoparticles, offering the potential to expand the number of drugs introduced into clinical trials (McNeil, 2005). The procedure for development of drugs from natural products is outlined (Fig. 1).

Nanotechnology approaches have been used to improve the activity, specificity, bioavailability and therapeutic index of various natural products. Number of studies has been carried to elucidate the pharmacokinetics of curcumin as it is poorly absorbed from the gastrointestinal (GI) tract after oral administration due to its low water solubility and low stability against GI fluids. To circumvent this problem curcumin has been encapsulated on liposomes. Liposomal curcumin enhanced the gastrointestinal absorption (Takahashi *et al*., 2009). It has also been found that liposomal curcumin inhibits 70-80% cell proliferation at lower doses compared to free curcumin (Thangapazham *et al*., 2008). The liposomes are larger aggregates, tend to be heterogenous and are larger in size. Nanoparticle formulations of curcumin exhibited increased solubility in water compared to free

curcumin (Bisht *et al.*, 2007). Oral administration of PLGA curcumin enhances curcumin therapy in cystic fibrosis mice (Cartiera *et al.*, 2009). In another study curcumin loaded PLGA nanoparticles showed enhanced cellular uptake, increased bioactivity and superior bioavailability *in vivo* (Anand *et al.*, 2010). Antimicrobial activity and water solubility of curcumin was improved by reducing the size of curcumin to nanorange (Bhawana *et al.*, 2011).

Another plant based drug which has been exploited for nanoformulations is paclitaxel. Paclitaxel was selectively delivered to levulinoyl mannosamine treated HeLa cells by polymeric nanoparticles (Iwasaki *et al.*, 2007). Paclitaxel showed increased antitumor activity when loaded in biodegradable nanoparticles based on linoleic and poly (β-malic acid) (Zhao *et al.*, 2009). Paclitaxel demonstrated antitumor activity comparable to commercial formulation in galactosamine targeted nanoparticles (Liang *et al.*, 2006). Galactosamine targeted nanoparticles showed ligand-receptor interaction with HepG2 cells (Liang *et al.*, 2006). Paclitaxel in core-shell drug nanoparticles retained its activity *in vitro* and induced cell cycle arrest in G2/M phase (Zahr and Pishko, 2007). Heparin-folic-paclitaxel nanoparticles loaded with paclitaxel showed enhanced specific delivery and increased antitumor activity (Wang *et al.*, 2009). Vitamin E –TPGS emulsified nanoparticles containing paclitaxel showed less toxicity and realised sustainable therapeutic time of 168 h as compared to commercial formulation Taxol® (Mo and Lim, 2005). Paclitaxel loaded PEG-PLA nanoparticles also showed reduced toxicity as compared to commercial formulation Taxol® (Danhier *et al.*, 2009b). Paclitaxel loaded in wheat germ agglutinin exhibited superior *in vitro* cytotoxicity than commercial formulation. The stronger cell killing effect was due to enhanced uptake of nanoparticles by receptor mediated endocytosis (Mo and Lim, 2005). In another study, paclitaxel loaded PEG-PLGA nanoparticles showed greater tumour inhibition than commercial Taxol® (Danhier *et al.*, 2009a). RGD grafted PLGA nanoparticles increased the targeting of paclitaxel to tumour endothelium (Danhier *et al.*, 2009b).

Due to low solubility in water and in physiologically acceptable solvents, camptothecin has also been encapsulated on poly(caprolactone-co-lactide)-b-PEG-b-poly(caprolactone-co-lactide) nanoparticles. Camptothecin loaded nanoparticles showed greater blood persistence than free camptothecin (Zhang *et al.*, 2004). Camptothecin loaded in glycol chitosan nanoparticles showed prolonged blood circulation, high stability and high accumulation in tumors than free camptothecin (Min *et al.*, 2008). Other natural products that have been encapsulated on biodegradable nanoparticles are quercetin, quercitrin, epigallocatechin-gallate (Sanna *et al.*, 2011) and catechin (Shutava *et al.*, 2009) to improve their solubility and bioavailability (Kumari *et al.*, 2010, 2011).

Nanotechnology can greatly improve delivery of drugs which are poorly bioavailable due to their unfavourable physicochemical or pharmacokinetic parameters. Apart from improving the bioavailability of the drug candidates, nanotechnology is known for better targeting abilities consequently lowering the required dose considerably. Modification of conventional nanoparticles with ligands has the potential to increase therapeutic index and reduce side effects (Bartlett *et al.*, 2007; Singh *et al.*, 2011; Sekhon, 2012). The ability to actively target specific cells rather than tissues allows ligand coupled nanosystems to smash non-targeted nanosystems. Targeted delivery has countless benefits as documented by many researchers (Bartlett *et al.*, 2007; Davis *et al.*, 2008; Pirollo and Chang, 2008; Farokhzad and Langer, 2009; Gabathuler, 2010). Targeted delivery can be used to enhance the retention and cellular uptake of nanoparticles via receptor mediated endocytosis. It can also be used for transcytosis of nanodrugs across the endothelial and epithelial barriers. Additionally, targeted delivery can be used to combat multidrug resistance. Many targeted delivery systems are in phase I/II clinical trials (Davis *et al.*, 2008). With advances in ligand

engineering and nanoparticle optimization targeted delivery will become a foundation in the next generation therapeutics. Another important strategy utilised is the co-delivery or combination therapy. Later has many advantages and may prove effective than single drug therapy (Greco and Vicent, 2009). Co-delivery of siRNA and chemotherapeutic drugs has been used to overcome multi-drug resistance in cancers (Shi *et al.*, 2010). Another important development in combination therapy is to combine imaging and therapeutic agents with nanosystems allowing us to visualise sites of targeted delivery and therapeutics simultaneously (Debbage and Jaschke, 2008).

CONCLUSION

Natural product research faces many technical hitches like incompatibility of high throughput screening, variability of source material, problems in isolating active constituents, cost of collection, compound supply and dereplication. In spite of all these limitations, over 100 natural products are in clinical trials. Natural product derived drugs also contribute to the profitability of many pharma and biotech companies. These factors have led to renewed interest in natural product research. Delivery of natural products using conventional dosage forms is challenging. These problems can be overcome by attaching or encapsulating natural products with different nanomaterials. Nanomaterials will improve the pharmacokinetics, bioavailability, therapeutic index and specificity of plant origin drugs. By smartly designing nanocarriers, number of plant origin drugs can enter into clinical trials. Targeted delivery can improve the intracellular retention and transcytosis of drugs across the epithelial and endothelial barriers. Combination therapy will help nanosystems efficiently reaching their target sites and enable the effective early detection and treatment of diseases. Current research is focused on design of multifunctional nanosystems. But more extensive studies are needed to establish their *in vivo* fate.

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