

NANOFIBER DEVICES FOR THE TARGETED-DELIVERY OF THERAPEUTICALLY ACTIVE PLANT AND HERBAL INGREDIENTS

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Herbal and plant based remedies have been used since times immemorial for treating illnesses or maladies of variant aetiology, whereas during the past two centuries, the pharmaceutical chemists have discovered many important modern drugs from natural botanicals and microbes. Generally, herbal and plant-derived products containing multiple compounds are administered orally for therapeutic purposes. Currently, targeted drug-delivery systems are being developed and investigated for the treatment of cardio-respiratory disorders, pain relief, wound healing, and life threatening diseases like cancers. A number of novel nanofiber membranes and devices are available for sustained release and to deliver steady supply of natural bioactive ingredients, herbal-based extracts, and a few have been approved by US-FDA and other drug regulatory agencies. The purpose of this mini review is to provide an update on the role of nanofiber devices used for the targeted-delivery of therapeutically active ingredients of plant and herbal origin as well as to underscore the potential for the delivery of cost-effective herbal ingredients and natural plant-based extracts for their biomedical applications in wound healing, inflammation-related diseases and cancer treatment.

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INTRODUCTION

Herbal and natural botanicals have been used for treating human and animals diseases since ancient time in India, China, Egypt, Europe, Latin-America and Africa. Several investigations in experimental animals and a limited number of clinical observations have revealed that oral administration of herbal and plant products produce favorable results for the treatment of non-communicable diseases such as myocardial infarction and stroke, high blood pressure, type 2 diabetes, obesity, insomnia, chronic inflammatory bowel diseases of unknown origin, osteoarthritis, cancer, and postmenopausal symptoms (see Hassanzadeh *et al*, this volume of BMR). Also, herbal based medicines have been used for wound and burn care from ancient times to date. For example, curcumin, the therapeutically active component of turmeric shows anti-inflammatory, anti-bacterial, and wound healing activities and hastens the healing process and reduces the risk of scar formation (1).

In many cases, however, the underlying mechanisms and validation of biologically active ingredients of plant-derived products remain unknown. There is an urgent need of well designed, double-blind, multicentre, clinical trials with adequate number of patients to determine the safety and effectiveness of plant-derived remedies as is done with synthetic pharmaceuticals. Such studies must contain a valid comparator to evaluate the therapeutic potential of herbal and plant products. Mostly, the plant- and food-derived compounds are well-tolerated by the human body, and therefore, their application for the development of alternative therapies may reduce high costs and duration of toxicological studies in drug discovery research, development of new substances, and clinical trials. The plant-based alternative therapies will be highly useful for patients who cannot afford long-term cure with costly synthetic medicines.

THERAPEUTIC POTENTIAL OF HERBALS AND NATURAL BOTANICALS

The most important data concerning the therapeutic potential of active ingredients of herbals and natural botanicals for the treatment of human diseases has originated from Asian countries, especially India and China. Indian Materia Medica includes about 2,000 medications of natural origin almost all of which are derived from different traditional systems and folklore practices (2). Ayurveda, which literally means the science of life, is one of the oldest system of medicines used in India. More than 25,000 single or poly-herbal formulations

are used by the tribal and rural populations in India. But only 6% of all therapeutically important species, which are noted in ancient literature, have been analyzed phytochemically for their therapeutic potential (3). Many important modern drugs have been discovered from natural botanicals and their molecules have been synthesised and/or modified by the pharmaceutical industry. The development of pharmaceutical chemistry and chemical analyses occurred in the early 19th century onward, and consequently led to the extraction, purification, chemical characterization, and modification of plant-derived extracts and/or ingredients into the synthesis of modern drugs (4, 5). Today, herbal medicines in their novel formulations such as nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, and solid lipid nanoparticles (SLNs), nanomicellar system, nanotubes, and colloidal nanogels have been developed to be used either alone or in combination with other chemotherapeutic agents (4, 6, 7). The current focus of pharmaceutical researchers is towards design, characterization and development of targeted-drug delivery systems for synthetic drugs, herbal remedies, and plant-derived medicines to enhance their efficacy, tolerability as well as to deliver required quantity of a medicament to targeted diseased area (8-14).

THE DELIVERY OF SYNTHETIC AND PLANT-DERIVED MEDICINES

The challenges for the systemic delivery of synthetic medicines, herbals and plant-derived products are dissolution and protection of bioactive constituents in the highly acidic pH environment of the stomach, absorption of therapeutically active ingredients from the gastrointestinal tract, reduced biotransformation in the gut and liver, and ultimate delivery of the optimum quantity of bioactive substances to reach the circulating blood (4, 15). Due to their small size and increased surface area, nano-carriers are being promoted for the delivery of synthetic drugs and herbal remedies to maintain therapeutically required amount of drugs and plant medicines to targeted diseased area as well as to overcome all the obstacles experienced for delivering the optimum quantity at the target site. Sharma *et al*. have reported (4) several advantages for the delivery of herbal remedies through nano-systems such as: (i) reduction in bulk doses, (ii) delivery at the targeted diseased area for major life threatening diseases, (iii) ease and comfort to patients over the traditional available formulations such as large doses but lesser effectiveness, (iv) ability to deliver high concentrations of drugs to diseased sites due to their unique

size and high loading capacities and persistence at the sites for the longer periods, (v) enhanced permeation and retention effect, (vi) reduced side effects, and (vii) reduction in the dosage of drug formulations. Considering the significantly successful results obtained with nanomaterials and nanofiber delivery-devices, the US-FDA and other drug regulatory bodies have approved several nanoparticle materials and nanofiber devices for the delivery of synthetic drugs and active herbal ingredients. There is a growing demand for further research to exploit the advantages offered by nanotechnology devices and to enhance their benefits to patients for improving the quality of life. Nanofiber membranes offer unique biomedical potentials for drug incorporation and drug release. Hence, the primary focus of this review is to highlight the biomedical applications of nanofibrous devices for targeted-delivery of cost-effective herbals and plant-derived therapies. The authors have evaluated the most important studies concerning the targeted-delivery of therapeutically active ingredients of plants and herbal remedies.

TARGETED DRUG-DELIVERY SYSTEMS

Over the past two decades, interest for the biomedical applications of nanomaterials and nanotechnology devices have been growing for the targeted-delivery of synthetic and herbal medicines. The ultrasmall size molecules of nanotechnology materials, in the range of 1-100 nanometers, have unique physiochemical properties and interactions with biological systems, and these characteristics of nanodevices help in exploring the controlled delivery and steady supply of therapeutically active substances to targeted sites (16). For the loading of biologically active materials in nano-fabricated devices, a variety of methods are used to incorporate synthetic drugs and plant-derived products with nanoparticles and nanofibers such as non-woven structures, adsorption, and chemical conjugation. The main advantages of nanoparticle-based drug delivery system are: improvement of plasma or serum solubility of xenobiotics; prolongation of systemic circulation half-life; releasing the bioactive substance at a sustained and controlled manner; and preferentially delivering therapy to the targeted tissues and cells. A number of investigators have reported the usefulness of nanotechnology methods for the concurrent delivery of multiple therapeutic agents to the targeted tissues and cells (17, 18). With nanotech devices, the pharmacokinetics and therapeutic efficacy of medicines can be significantly improved in contrast to the conventional drug delivery system, since the drug-loaded

nanoparticles can enter host cells and invading microbial organisms easily as well as through endocytosis drug-payloads can be released to treat microbe-induced infections.

It is recognized that the plant-derived medicines are well tolerated by the human body and they produce lesser side effects compared to synthetic pharmaceuticals. Further, the herbals and plant-derived remedies are less costly for short- and long-term cure in comparison with synthetic drugs. Due to the cost-effectiveness, efficacy and safety, awareness of physicians and patients for their curing benefits, the herbal and plant-derived medicines are gaining popularity worldwide, especially in developing countries. The delivery systems for natural botanicals can be fabricated using biomaterials, namely synthetic biocompatible and biodegradable polymers, microlipids, and polysaccharides (19). Such drug delivery methods would help to increase the therapeutic value of herbal remedies for the treatment of chronic diseases like asthma, diabetes mellitus, obesity, cancer, and other life threatening cardiovascular diseases. Examples of delivery systems of herbal medicines, and their biomedical applications are shown in Table 1.

POLYMERIC NANOFIBROUS-WOVEN DRUG DELIVERY SYSTEMS

Nanofibers of both biopolymers and synthetic polymers have been successfully fabricated (32), which offer high porosity with large surface area-to-volume ratio and are more suitable for cell accommodation, nutrition infiltration, gas exchange and waste excretion (33). Recently, the herbal and plant extracts, powder and nanoparticles intended for biomedical applications have been catching the attention of pharmaceutical researchers. Such therapeutic products are blended with polymers in the form of nano-films or nano-microfibers. Different herbal and plant products are incorporated in nanofibrous-mats with polycaprolactone (PCL) due to their biocompatibility, biodegradability, and substance permeability for wound healing dressings as well as targeted-delivery of medicines and skin tissue engineering. The studies reported in the literature (34-38) are summarized in Table 2.

CONCLUSION

This review summarizes the most recent developments regarding nanofibers loaded with natural botanical extracts and polymeric herbals and plant products incorporated for targeted-delivery of plant-derived remedies. These nano- and macro-structure promote their candidatures for biomedical

Table 1. Herbal and plant products delivery systems

Delivery system	Procedure	Herbal and plant-derived products	Biomedical applications	Ref.
Mouth dissolving tablets	Poly-herbal		Effective for lung problems and other respiratory ailments like asthma , cardiac distress	(20)
Matrix tablets or multi-particulate formulations like microcapsules	Granulated herb and a carrier	Active ingredients from plants consisting hypericin, hyperforin and chinacosides	Steady supply and sustained release of active components for targeted drug delivery to cure diseases	(21)
Microgranules	Extrusion-spheronization, fluid air bed process or a coating-pan method	Gingko biloba	Particularly to supply mixtures of plant extracts to cure diseases	(22)
Mucoadhesive system	Muco-adhesive polymers	Echinacea, Lavender and Mastic gum	Sustained release for the treatment of diseases	(23)
Transdermal films	Transdermal drug- delivery system (TDDS)	Boswellic acid (<i>Boswellia serrata</i>) and curcumin (<i>Curcuma longa</i>)	For continuous administration of medicine through skin into the systemic circulation and to circumvent the first-pass metabolism of the bioactive material, and to avoid pain associated with injection. Offers drug delivery with infrequent dosing via zero-order kinetics, and the therapy can be easily terminated at any time.	(24)
Herbal-based oral composition for periodic retention within the buccal cavity of a human	Consisting of gels, pastes and chewing gums.	Radix Polygoni Multiflori, Rhizoma drynariae, Rhizoma ligustici Chuanxiong, Calculus bovis, Indigo naturalis, Herba eclipiae, Pericarpium trichosanthis, Radix sophorae Flavescentis, Spina gleditsiae, Radix Angelicae sinensis, Fructus mori and Halitum.	To reduce loss of scalp hair and to promote hair growth.	(25)
Shuanghuanglian aerosol (SHLA)	Flos Chrysanthemum indicum, Flos Lonicera, Herba houttuynia, Radix Bupleurum and menthene	Flos Lonicera, Fructus forsythia and Radix scutellaria.	Anti-inflammatory and antiviral effects, a good curative effect in treating infantile upper respiratory tract infections.	(27)
Microparticles	Formulated by different techniques using chitosan, egg albumin, sodium alginate, ethyl cellulose, cellulose acetate, gelatin and beeswax.	Gugulipid extract from the Oleo gum resin of <i>Commiphora wightii</i>	To reduce the levels of harmful serum lipids in the blood stream.	(28)
Microcapsules	Layer-by-layer adsorption of carrageenan and oligochitosan onto calcium carbonate microparticles with their subsequent dissolving after the treatment of EDTA.	Plantain <i>Plantago major</i> and calendula <i>Calendula officinalis</i> L. (PCE)	To accelerates gastric tissue repair.	(29)
Nanoparticles of TCH (traditional Chinese herbs)	Drying, mincing, extracting, crushing into liquid particles with ultrasonic wave, filtering and nanometerizing into nanoparticles soliquid with nanometer collider.	Peach seed, safflower, angelica root, Szechwan lovage rhizome, Rehmannia root, red peony root, leech, gadfly, earth worm and ground beetle,	For quick recovery from arterial embolism and diminution of thrombi.	(30)
Sustained-release implant	Chitosan	dan shen (<i>Radix Salvia miltiorrhiza</i>),	To promote anastomosing and healing on muscles and tissues at the organic incision site in abdominal cavities.	(31)
ArthriBlend-SR	Formulation containing herbal extracts and nutrients	Glucosamine sulfate, Boswellin (<i>Boswellia serrata</i> extract) and Curcumin C3 Complex (<i>Curcuminoids</i> from <i>Curcuma longa</i>)	To support healthy joints and connective tissues in the body; natural actives for joint care applications; to support the management of inflammatory conditions such as arthritis and the continuous management of symptoms of arthritis	(32)

Table 2. Herbal products blended with polymers

Polymer (Nanofibers)	Solvents	Herbals	Biomedical applications	Ref.
PCL/PVP	Chloroform/methanol	Crude bark extract of <i>Tecomella undulata</i> ,	Wound healing and wound dressing	(33)
PCL	Chloroform	Aloe vera	Wound dressing applications	(34)
Gelatin powder	Butanol, dichloromethane, hexane and methanol	Extraction of <i>Centella asiatica</i>	Wound healing ability	(35)
PCL	Dichloromethane (DCM) and N,N-dimethylformamide (DMF)	Shikonin	Wound healing and/or atopic dermatitis	(36)
PCL	Chloroform/ Methanol	<i>Indigofera aspalathoides</i> , <i>Azadirachta indica</i> , <i>Memecylon edule</i> (ME) and <i>Myristica andamanica</i>	Skin tissue engineering	(37)

PCL= Polycaprolactone ; PVP = Poly-vinylpyrrolidone

applications in treating chronic diseases, including wound, and to reduce cure-cost and improve the quality of life of patients. Further work is needed to improve the fabrication and characterization of polymer-herbal blended nanofibers. Future studies should be done with different biocompatible and biodegradable polymer nanofibers either loaded with crude herbal and plant extracts or their active ingredients to explore the therapeutic benefits and safety using the combination of multidisciplinary approach and interdisciplinary research.

Conflict of interest: the authors declare no conflict of interest.

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