Review

DOI: 10.14235/bas.galenos.2022.30502
Bezmialem Science 2022;10(5):666-73

An Overview of Nanofiber Applications for Development of Phytopharmaceuticals

Fitofarmasötiklerin Geliştirilmesi için Nanolif Uygulamalarına Genel Bir Bakış

İmren ESENTÜRK-GÜZEL[1], Lüceyn ABDO[1], Evren ALGIN YAPAR[2], Engin ESENTÜRK[3], Derya BÜYÜKKAYHAN[4], Rakesh K SINDHU[5]

[1]University of Health Sciences Turkey, Hamidiye Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Turkey
[2]Sivas Cumhuriyet University Faculty of Pharmacy, Department of Pharmaceutical Technology, Sivas, Turkey
[3]İstanbul Kent University, Oral and Dental Health Education Application and Research Center, İstanbul, Turkey
[4]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Pediatrics, Division of Neonatology, İstanbul, Turkey
[5]Sharda University, Sharda School of Pharmacy, Uttar Pradesh, India

ABSTRACT

Herbal sources contain a variety of bio-actives, which are also called phytochemicals. Many of the herbal bio-actives have therapeutic effects and distinguished chemical properties that allow them favorable candidates for phytomedicines. The history of traditional herbal medicines, which are the precursors of phytopharmaceuticals, dates back to ancient times. Today, many of the officially approved and widely used medicines are produced by isolating active substances from herbal sources. Although traditional pharmaceutical dosage forms such as tablets, capsules, syrups, solutions, decoctions and ointments are still used today, problems related with the absorption, biotransformation and stability of phytochemicals reduces the efficacy, bioavailability and in some cases safety of herbal medicines. Also, conventional pharmaceutical dosage forms are often providing an immediate release of phytoconstituents. Besides the use of advanced drug delivery systems offer advantages to overcome mentioned problems, they also provide extended release with maximum efficacy associated with minimum side effects. Researches on development of herbal formulations by using novel drug delivery systems have gain attention and the use of nanotechnology-based systems have special attention. One of the nano drug carrier systems is nanofibers which have unique properties making them widely used in different treatments such as infections, allergy, rheumatic diseases, inflammatory diseases, cancers, etc. In this study, the use

ÖZ

Bitkisel kaynaklar, fitokimyasallar olarak da adlandırılan çeşitli biyoaktif maddeler içerirler. Bitkisel biyo-aktiflerin çoğu, bitkisel ilaçlar için uygun aday olmalarını sağlayan terapötik etkilere ve kimyasal özelliklere sahiptirler. Fitofarmasötiklerin öncüsü olan geleneksel bitkisel ilaçların tarihi çok eskilere dayanmaktadır. Günümüzde resmi olarak onaylanmış ve yaygın olarak kullanılan ilaçların birçoğu bitkisel kaynaklardan etken maddelerin izole edilmesiyle üretilmektedir. Tabletler, kapsüller, şuruplar, solüsyonlar, dekoksiyonlar ve merhemler gibi geleneksel farmasötik dozaj formları günümüzde hala kullanılmasına rağmen, fitokimyasalların absorpsiyonu, biyotransformasyonu ve stabilitesi ile ilgili problemler, bitkisel ilaçların etkinliğini, biyoyararlanımını ve bazı durumlarda güvenliğini azaltmaktadır. Ayrıca, geleneksel farmasötik dozaj formları genellikle bitkisel bileşiklerin hemen salınmasını sağlar. Gelişmiş ilaç taşıyıcı sistemlerin kullanılması, bahsedilen sorunların üstesinden gelmek için avantajlar sunmanın yanı sıra, minimum yan etkilerle ilişkili maksimum etkinlik ile uzun süreli salım sağlar. Yeni ilaç taşıyıcı sistemler kullanılarak bitkisel formülasyonların geliştirilmesi üzerine yapılan araştırmalar dikkat çekmiş ve nanoteknoloji tabanlı sistemlerin kullanımına ayrıca önem verilmiştir. Nano ilaç taşıyıcı sistemlerden biri de benzersiz özelliklere sahip olan ve bu sayede enfeksiyon, alerji, romatizmal hastalıklar, enflamatuvar hastalıklar, kanser gibi farklı hastalıkların

Address for Correspondence: İmren ESENTÜRK-GÜZEL, University of Health Sciences Turkey, Hamidiye Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Turkey
E-mail: imrenesenturk@gmail.com **ORCID ID:** orcid.org/0000-0002-4069-2035

Received: 24.12.2021
Accepted: 17.03.2022

Cite this article as: Güzel İE, Abdo L, Algın Yapar E, Esentürk E, Büyükkayhan D, Sindhu RK. An Overview of Nanofiber Applications for Development of Phytopharmaceuticals. Bezmialem Science 2022;10(5):666-73

of the nanofiber-based carrier systems to deliver herbal bio-actives through various drug application routes is overviewed.

Keywords: Nanofibers, herbal bio-actives, phytopharmaceuticals, drug delivery

tedavisinde yaygın olarak kullanılan nanoliflerdir. Bu çalışmada, çeşitli ilaç uygulama yollarıyla bitkisel biyoaktif maddelerin salınması amacıyla nanolif yapısındaki ilaç taşıyıcı sistemlerin kullanımı değerlendirilmiştir.

Anahtar Sözcükler: Nanolifler, bitkisel biyoaktifler, fitofarmasötikler, ilaç salımı

Introduction

Herbal sources contain a variety of bio-actives, which are also called phytochemicals. Many of the herbal bio-actives have therapeutic effects and distinguished chemical properties that allow them to be favorable candidates for phytomedicines. For example, compared to the synthetic active pharmaceutical ingredient, herbal bio-actives carry a larger number of chiral centers in their structures, which makes them sterically more complex and inflexible molecules. The inflexibility increases the receptor-binding ability of the molecules, which gives them more stereospecific biological activity and makes them favorable for medicinal use. Furthermore, herbal molecules contain a higher amount of oxygen and nitrogen atoms rather than synthetic drug molecules. This makes their ability to make hydrogen bonds with receptors better and as a result, increases the affinity and efficacy of the medicines (1,2).

The history of traditional herbal medicines, which are the precursors of phytopharmaceuticals, dates back to ancient times. The usage of herbal sources as healing remedies goes back to the ancient era in China, India, Egypt, Europe, Latin America, and Africa. Since then, many advances have been made in the field of herbal medicine. From the 15th century till the early 19th century, evolutions in phytomedicine reached their peak. Many books that were written in different languages were published, classification and naming systems were developed, and many important herbal active substances were isolated (1-3). Nowadays, many of the officially approved and widely used medicines are produced by isolating phytochemicals from herbal sources, which were used centuries ago, such as morphine, guaifenesin, and digoxin. In recent years, the importance of phytochemicals in modern drug research and development has increased with the use of molecular docking programs to determine biological target binding affinities and interactions. Moreover, it is indicated that around 50% of the current medicines are made from natural resources and over one-third of all new molecular entities are from natural sources and their byproducts (4,5).

Although traditional pharmaceutical dosage forms such as tablets, capsules, syrups, solutions, decoctions, and ointments are still used today, problems related to the absorption, biotransformation, and stability of phytochemicals reduce the efficacy, bioavailability, and in some cases safety of herbal medicines (6). Conventional pharmaceutical dosage forms are also providing an immediate release of phytoconstituents in general. However, the use of advanced drug delivery systems offers advantages to overcome mentioned problems and they also provide extended release with maximum efficacy associated with minimum side effects. Research on the development of herbal formulations by using novel drug delivery systems and the use of nanotechnology-based systems have gained special attention. One of the nano drug delivery systems is nanofibers, which have unique properties and are widely used in the treatment of different diseases such as infections, allergies, rheumatic diseases, inflammatory diseases and cancer (7). Studies to formulate novel drug delivery systems which use new technologies like nanotechnology are still taking place in many places around the world. Some of the recently developed drug delivery systems are nanogels, nanotubes, nanomicelles, microcapsules, nanoparticles, microemulsions, liposomes, niosomes, transfersomes, phytosomes, nanosuspensions, nanofibers, etc. These systems are used to deliver one or more active pharmaceutical ingredients or phytoconstituent with different new pharmaceutical dosage forms such as transdermal systems, buccal or mucoadhesive systems, oral or ocular systems, etc. (8).

In this review article, the use of the nanofiber-based drug carrier systems to deliver herbal bio-actives through various administration routes will be given with the examples of recent studies.

Nanofibers as Drug Delivery Systems

Nanofibers are structures with a diameter smaller than 1,000 nm. Because of having large surface area, high porosity, and being flexible, they are preferred in many applications including drug research and development, drug delivery, burn and wound healing, and tissue engineering. With 3D printing of electrospun nanofibers, models such as neural, mucosal, blood-brain barrier and tumor tissue models that stimulate physiological and pathological tissues can be produced , which have a huge potential to improve *in vivo* simulated tests in drug development studies (9). Additionally, nanofibers play an important role in the field of regenerative medicine, which can recover important tissues such as heart, blood vessels, nerves, bones, cartilages, tendons, and joints. This is possible with the combination of 3D printing and electrospinning techniques to form biomimicking nanofiber scaffolds and patches loaded with stem cells (9,10).

The unique specifications of nanofibers have made them widely used in treatment of different diseases such as infections, allergy, hypertension, rheumatic diseases, inflammatory autoimmune diseases, diabetes, intracranial aneurism, Alzheimer's, cardiovascular diseases, gastrointestinal diseases, AIDS, and cancers (11,12).

Mechanical properties of nanofibers such as high surface area-to-volume ratio, high porosity, amorphous structure, and flexibility

make them useful materials for designing different drug delivery systems (9).

Nanofibers may enhance drug dissolvability. The bioavailability of drugs is directly related to their solubility and dissolution rate (13). Unfortunately, most of the novel drugs are in a lipophilic character which means that they have low water solubility and as a result low bioavailability. To solve this problem, drugs can be loaded into nanofibers produced from water soluble polymers. Due to their high surface area and porosity, the dissolution rate of the drugs may increase significantly (13,14).

Among all advantages, the adjustable properties of nanofibers may be their most important feature. Nanofibers can be designed by modifying their production parameters for controlling polarity, fibers diameter, porosity and nanofiber mat thickness to fit any drug delivery requirement (12,13).

One more advantage is the high loading capacity of nanofibers and their modifiable release ability (14). Drug release is adjusted depending on drug loading methods. Some of these methods are co-electrospinning of drugs and polymers, surface immobilization of the drug on nanofibers, sheath, co-axial and layer-by-layer nanofibers. The most suitable method must be chosen according to the purpose of the medication because this affects the drug release process (15). For example, while the co-axial electrospinning method is used to release drugs immediately, matrix-type nanofiber, Core-shell nanofiber, and sandwich technologies may be used to produce prolonged-release nanofibers (13).

There are various methods to prepare nanofibers and between them, the electrospinning method is the most favorable nanofiber production technique. The other widely used methods can be given as drawing method, template synthesis, phase separation, self-assembly, etc. (16). Electrospinning is a method of producing nanofibers by exposing polymer solution to electrostatic energy, which stretches the polymer and reaches the nanoscale (17). The electrospinning system consists of 4 main parts: syringe pump, power source, needle, and collector (18). While the solution is slowly pumped from the syringe through the needle, the solution surface is electrically charged because of the high electric field in the needle. Due to this charge, the surface tension force of the solution is overcome and as a result, a filament occurs. This filament continuously spins and stretches till it reaches the collector surface where nanofibers are collected (19). The properties of the formed nanofibers may be affected by many parameters such as voltage, needle tip-to-collector distance, molecular weight of the polymer(s) and the flow rate, viscosity, surface tension, and the conductivity of the solution (20). By adjusting these parameters, the properties of the nanofibers can be easily designed to have any intended purpose (21). Morphology of the fibers can also be controlled by the selection of polymer(s) to make many types of nanofibers. Besides being a cost-effective method, the versatility and flexibility of this process make electrospinning the most favored method to produce nanofibers (19).

Nanofiber-based Herbal Drug Carrier Systems for Different Delivery Routes

Nanofiber drug carrier systems can be used to deliver active pharmaceutical ingredients through various routes such as topical, transdermal, oral, and transmucosal routes. Taking advantage of natural substances for mostly their antimicrobial, antioxidant, anti-inflammatory, and wound healing activities and nanofibers with unique properties, a variety of research took place to investigate nanofibers incorporated with natural substances for drug delivery applications. The schematic representation of nanofiber-based herbal drug carrier systems via various drug delivery routes is given in Figure 1. Herbal drugs incorporated

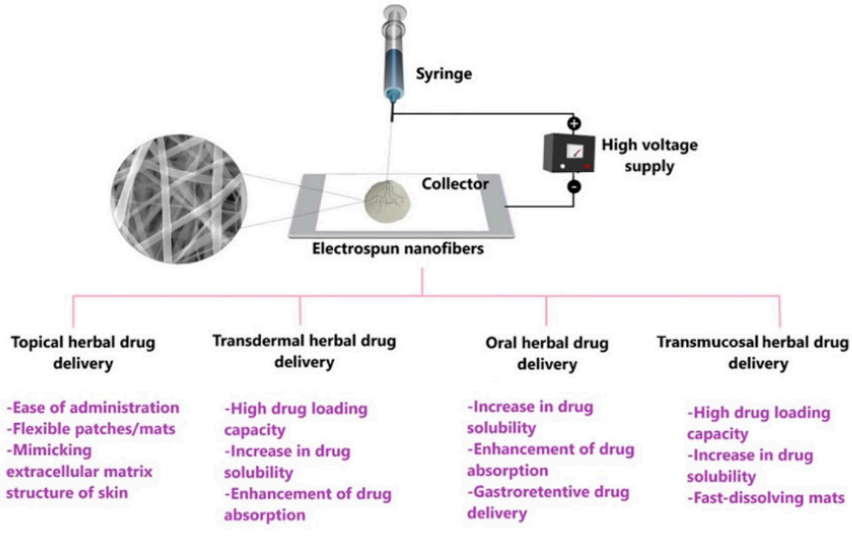

Figure 1. The schematic representation of nanofiber-based herbal drug carrier systems via various drug delivery routes

nanofiber-based carrier systems according to different delivery routes are summarized in this part.

Topical/Transdermal Drug Delivery Route

Topical drug delivery is a local route applied topically to treat skin diseases like bacterial, fungal, and viral infections such as eczema and psoriasis. Transdermal drug delivery differs from topical delivery by being suitable for both local and systemic delivery types. After applying the drug onto the skin, it diffuses through skin layers until reaching blood vessels and joins systemic circulation (22). In the transdermal drug delivery route, the drug does not undergo the first pass metabolism effect of the liver. However, the main challenge of this route is the stratum corneum barrier of the skin. Therefore, nanofiber based drug carrier systems can be used to enhance transdermal drug delivery (23).

Curcumin is a polyphenolic flavonoid that is obtained from the rhizomes of Curcuma longa (turmeric) and has various therapeutic benefits such as anti-inflammatory, antimicrobial, antioxidant, anticancer, antiaging, antidiabetic, and wound healing effects. For this reason, it has been the topic of many recent studies including topical and transdermal delivery (23). Sampath et al. (24) investigated curcumin incorporated poly(lactic-co-glycolic acid) nanofibers to treat squamous carcinoma, which is one of the most deadly skin cancers. *In vitro* release and cell viability studies showed that curcumin incorporated nanofibers had prolonged drug release without initial burst and good anticancer activity against squamous carcinoma cell lines. In another study, curcumin was incorporated into cellulose acetate phthalate electrospun nanofiber transdermal mats by Ravikumar et al. (25). It was shown that the prepared formulations controlled *in vitro* transdermal delivery of curcumin for up to 24 h. Also, Ariamoghaddam et al. (26) evaluated curcumin incorporated gelatin/albumin and PVA nanofibers as transdermal anti-obesity patches. More than 50% of the loaded curcumin was released from the nanofibers after 20 hours and curcumin patches were effective in obesity treatment according to the *in vivo* studies on rats. Tetrahydro curcumin is the major metabolite of curcumin which has similar pharmacological properties with curcumin but is more polar. Ravikumar et al. (27) prepared tetrahydro curcumin into poly(ε-caprolactone)/poly(ethylene glycol) composite electrospun nanofibers and evaluated its *in vitro* drug release properties. It was demonstrated that the prepared nanofibers released the herbal drug according to the Higuchi kinetics model of diffusion mechanism with case II relaxation behavior and anomalous transport for 24 h and it was considered as ideal transdermal patches with the application once daily.

Acne vulgaris is a chronic skin inflammation caused by *Propionibacterium acnes* infection associated with oily skin caused by over release of sebum. Side effects like skin irritation related to drugs used in the treatment of acne vulgaris require advanced pharmaceuticals. In this regard, Tang et al. (28) developed a combination of extracts that incorporated poly(vinyl alcohol)/chitosan nanofibers. *Houttuynia cordata*, *Portulaca oleracea* and *Centella asiatica* extracts were used to inhibit *Propionibacterium acnes*, reduce inflammation, and hydrate the skin, respectively. This combination exhibited good antibacterial activity against *Propionibacterium acnes* and the produced nanofibers showed a rapid efficiency in mild-to-moderate facial acne in a short-term clinical study.

Herbal bio-actives are frequently used for wound or burn healing applications. Propolis is a resinous product collected by honeybees (*Apis mellifera*) from various plant sources, which has antibacterial, antifungal, and antioxidant activities. It was incorporated into poly(lactic acid) nanofibers to enhance its pharmacological activities and bring moisturizing and breathability properties to the wound dressings by Sutjarittangtham et al. (29). While the prepared formulation was able to inhibit *Proteus mirabilis* and *Escherichia coli* at the concentration of 4% (w/v), it was able to suppress *Staphylococcus aureus* and *Staphylococcus epidermidis* at 2% (w/v) concentration. Jin et al. (30) compared efficiencies between polycaprolactone nanofibers loaded with *Indigofera aspalathoides*, *Azadirachta indica*, *Memecylon edule* or *Myristica andamanica* extracts as wound dressings. The results showed that *Memecylon edule* loaded nanofibers exhibited the best metabolic activation in human dermal fibroblasts proliferation assay with the least cytotoxicity. In another study, Sadri et al. (31) found that chitosan/poly(ethylene oxide) nanofibers incorporated with green tea leaf (*Camellia sinensis*) had high potential as a wound dressing. Besides their good antibacterial effect against *Escherichia coli* and *Staphylococcus aureus* strains, these nanofibers have moisturizing, breathable, and highly stable properties, which are suitable for wound healing. Henna (*Lawsonia inermis*) is also one of the herbal drugs which is useful for wound healing due to its antibacterial, antifungal, antioxidant, anti-inflammatory and analgesic activities. In this regard, Yousefi et al. (32) incorporated henna into chitosan/ poly(ethylene oxide) nanofibers to obtain better wound healing results from *Lawsonia inermis* extract. It was demonstrated that henna nanofibers were biocompatible and had good *in vitro* antibacterial activity and accelerated wound healing in *in vivo* studies. Also, Hajilou et al. (33) prepared a wound dressing from *Gamma oryzanol* extract incorporated into poly(ε-caprolactone)/chitosan nanofibers. *Gamma oryzanol* is a crude rice bran oil extraction with antioxidative, antiinflammatory, and antibacterial activities. *In vitro* studies suggested that the prepared dressings had the ability to suppress bacteria, enhance collagen deposition and accelerate wound healing which made it suitable as a wound dressing.

Pineapple (*Ananas comosus*) contains a substance namely bromelain, which has a burn healing effect. Bayat et al. (34) loaded bromelain into chitosan nanofibers and investigated the physicochemical properties and release profile of this delivery system. Chitosan-2% (w/v) bromelain nanofibers were found to be effective in burn injuries with good physicochemical properties and release profile as well as low cytotoxicity. In another study, Motealleh et al. (35) prepared poly(ε-caprolactone)/polystyrene nanofibers loaded with *Chamomilla recutita* (L.) Rauschert extract. Due to the major active substance of chamomile, apigenin, the formulation showed good antibacterial activity against *Staphylococcus aureus* and antifungal activity against

Candida albicans. Moreover, 15% of chamomile-loaded nanofibers reached about 90% of cell proliferation efficiency and gave 10 times better results than unloaded nanofibers. Moreover, *in vivo* studies showed that the nanofibers could treat up to 99±0.5% of wounds in 14-day duration.

Capsaicin is a chemical found in peppers and used as a temporary analgesic for muscle and joint pain. Capsicum extract was loaded into poly(vinyl alcohol) or cellulose acetate nanofibers and *in vitro* drug release, skin permeation, and cytotoxicity characteristics were investigated. Compared to cellulose acetate, poly(vinyl alcohol)-based nanofibers showed better release and skin permeation properties. MTT assay results showed a small decrease in the cell viability via drug loading when compared to blank nanofibers (36).

Blumea balsamifera, or in its other name sambong, was used for centuries in some South-eastern countries as a remedy for different skin diseases such as eczema, beriberi, dermatitis, etc. In a study, Badshah et al. (37) produced electrospun cellulose acetate nanofibers loaded with sambong oil to investigate its wound healing properties. The results confirmed that sambong oil loaded nanofibers had good cell viability and antibacterial activity but inadequate antioxidant properties. Lavender oil majorly contains the compounds linalool and linalyl acetate, which has antibacterial, anti-inflammatory, and antifungal pharmacological effects. Sofi et al. (6) incorporated polyurethane nanofibers with lavender oil and silver nanoparticles. The prepared nanofibers with concentrations of 15% lavender oil and 5% silver nanoparticles exhibited good *in vitro* antibacterial activity against *Escherichia coli* strains. Plai (*Zingiber Cassumunar Roxb.*) has been used extensively as a traditional herbal medicine due to containing antimicrobial, anti-inflammatory, antioxidative and analgesic substances. To improve its efficacy in topical medicines, cosmetics, and skincare products, Tonglairoum et al. (38) prepared Plai oil incorporated poly(vinyl pyrrolidone) nanofibers. *In vitro* release study showed that Plai oil was released from the nanofiber formulations rapidly at first, but then prolonged release was achieved up to 24 hours. In another study, Wongkanya et al. (39) loaded Plai (*Zingiber cassumunar Roxb.*) oil into electrospun poly(lactic acid) nanofibers and examined its properties using (E)-1-(3,4- dimethoxyphenyl) butadiene (DMPBD) as a marker. DMPBD is a compound found in *Zingiber cassumunar Roxb.*, which is exhibiting anti-inflammatory activity. *In vitro* release characteristics and skin penetration and irritation properties were tested. Of DMPBD 80% was released from the nanofibers after 12 hours and 50% of DMPBD permeated through the skin due to the highly lipophilic nature of the substance. Also, Plai oil nanofiber patches did not show any skin irritation.

A food waste, watermelon (*Citrullus lanatus*) peel extract, was formulated as poly(vinyl alcohol) nanofibers to investigate antioxidant and antibacterial effects. The results revealed that watermelon peel extract incorporated nanofibers had better antimicrobial activity against both *Escherichia coli* and *Staphylococcus aureus* strains compared to watermelon peel extract itself. Furthermore, the prepared nanofibers were found to have a 22% enhanced antioxidant activity with a sustained release rate which could reach even 72 hours (40). Also, Lin et al. (41) used green electrospinning to produce poly(ethylene oxide) nanofibers loaded with grape seed extract, which had good antioxidant activity. It was shown that the prepared nanofibers significantly enhanced the proliferation of the skin fibroblasts and protected them against oxidative stress, indicating that they were potential delivery systems to be used in tissue regeneration, wound healing, and cosmetics applications.

Colchicine is a natural substance found in *Colchicum autumnale* and *Gloriosa superba L*. It has cytotoxic effects and can be used efficiently in melanoma, which is the most fatal skin cancer. Morad et al. (42) loaded colchicine into electrospun poly(vinyl alcohol)/chitosan nanofibers to reveal its transdermal performance against melanoma. Both skin permeation and cell viability tests proved the effectiveness of colchicine transdermal nanofiber patches in melanoma management. In another study on the treatment of melanoma, acemannan polysaccharides of aloe vera mediated green synthesized titanium dioxide nanorods loaded resveratrol incorporated poly(vinyl alcohol) nanofibers were produced. By activating apoptosis-promoting caspase enzymes, this formulation exhibited enhanced selective cytotoxicity with fewer side effects (43). Agnes Mary and Giri Dev (44) evaluated the effects of aloe vera loaded nanofibers on the proliferation of human dermal fibroblasts. It was shown that aloe vera nanofibers resulted in a high proliferation rate without any cytotoxic effects. Depending on the results, it was suggested that aloe vera nanofiber scaffolds could be used in skin tissue engineering. In the other study, resveratrol, which was found in grapes and many other plants, was loaded into electrospun poly(vinyl pyrrolidone) and hydroxypropyl-β-cyclodextrin nanofibers to increase its solubility. The results revealed that the nanofiber formulations enhanced water solubility and skin penetration of the drug and exhibited good antioxidant and anti-inflammatory activities (45).

Vitamins are found in many natural nutrients and are used widely as supplementary products. Many studies were carried out to investigate vitamin delivery through the transdermal route to overcome the limitations such as solubility and absorption problems (45-48). Vitamin B12 in poly(ε-caprolactone) based nanofibers, all-trans retinoic acid or vitamin A acid and α-tocopherol or vitamin E in cellulose acetate based nanofibers, ascorbic acid in poly(vinyl alcohol) based nanofibers and folic acid in poly(vinyl alcohol) based nanofibers were investigated for transdermal delivery and all of them showed promising results (49-52).

Oral Drug Delivery Route

Oral route for controlled drug release is usually used to release the drug slowly into the gastrointestinal tract and enable effective drug concentrations for a prolonged period of time (50). Nanofibers are advantageous as oral drug delivery systems due to the properties of improving drug solubility and reducing applied drug dose. Malik et al. (51) evaluated poly(lactic acid) nanofibers loaded with diacerein as a gastroretentive drug delivery system. The results demonstrated that the developed nanofibers exhibited

zero lag time and approximately 61.3% of the herbal drug was released in 30 h, thus facilitating slow drug release with improved drug solubility.

Transmucosal Drug Delivery Route

Transmucosal drug delivery is another systemic and/or local drug application route. All tissues with mucosal membrane are parts of this route, including buccal, ocular, nasal, vaginal, and rectal administrations. The buccal route includes both oromucosal and sublingual applications. Because of the rapid absorption and high bioavailability of drugs in this route, it is commonly used for local and systemic drug delivery and is considered as an alternative to many oral drugs (52). Nanofibers are flexible, mucoadhesive, and stable in oral mucosa depending on the polymer type used in nanofiber production. Due to this, nanofiber-based drug carrier systems are applicable to the buccal cavity either as patches or scaffolds.

Fast dissolving nanofiber formulations composed of poly(vinyl alcohol) and D-a-tocopheryl poly(ethylene glycol) succinate were produced by Nam et al. (53) for oral phloretin delivery against oral cancers. The anticancer activities of phloretin were assessed in oral squamous cell carcinoma cells from the buccal cheek. The antiproliferation efficacy and apoptotic activity of the nanofiber formulations were significantly higher than that of the phloretin solution. Nam et al. (54) also developed poly(vinyl alcohol) and Soluplus based nanofiber mats for the delivery of *Angelica gigas Nakai* extract against oral cancers. The nanofiber formulations showed instant wetting (within 2 seconds) and rapid disintegration (within 3 minutes) properties compared to plain nanofibers, which could be used as a fast-dissolving mat for the treatment of oral cancers.

Tonglairoum et al. (55) developed herbal oil (betel oil or clove oil)-incorporated nanofiber mats with antifungal activity for the prevention and treatment of Candida-associated denture stomatitis. The herbal oils released from the nanofibers rapidly inhibited the growth of Candida species within only a few minutes after contact. Also, George and Varghese (56) formulated *Ocimum sanctum* (Tulsi), which had anti-inflammatory, antimicrobial, antioxidant, and anticancer properties in resorbable poly(vinyl acetate) nanofibers for local periodontal therapy. Then, George et al. (57) evaluated the therapeutic effectiveness of locally delivered electrospun *Ocimum sanctum* nanofibers in patients with periodontitis. *Ocimum sanctum* nanofibers were found to be beneficial in the reduction of interleukin-1β levels, which could be used as an adjuvant in the treatment of periodontitis. In another study, tara extract (*Caesalpinia spinosa*) was loaded into electrospun nanofibers made of poly(ε-caprolactone) and the produced nanofiber membranes indicated a potential of therapeutic application for lesions such as prosthetic stomatitis (58). Moreover, for local drug delivery in bone tissue engineering applications, graphene oxide and zinc-curcumin complex were loaded into coaxial electrospun nanofibers. The shell of the coaxial nanofibers included a blend of carboxymethyl chitosan, poly(vinyl alcohol), and graphene oxide. The prepared nanofibers enhanced the osteogenic performance and had an important antibacterial activity and thus reduced postoperative infections (59). In another study, Zadegan et al. (60) developed silk fibroin nanofibers containing *Urtica dioica L.* (nettle) extract at different concentrations. The prepared nanofibers released nettle in a controlled manner via Fickian diffusion and exhibited osteoblast differentiation in a dose-dependent manner.

Conclusions and Future Perspectives

In conclusion, as a part of nanotechnology, nanofibers have various application alternatives in the medical field, especially promising in drug delivery and regenerative medicine. Due to the high surface area and porosity and also the high drug loading capacity, nanofibers have gained great attention in drug release studies. Although herbal bio-actives have been widely used in various forms of products, most of them have the problems of low stability or water solubility, which can be overcomed by formulating them in nanofiber-based drug carrier systems. For example, resveratrol has increased water solubility in nanofiber formulations, and this enables skin penetration and its activity. Also, extended release can be obtained to enable effective drug concentrations for a prolonged period of time by using nanofibers. This is advantageous especially for oral drug delivery systems in terms of improved drug solubility and reduced applied drug dose in phytopharmaceuticals such as diacerein loaded nanofibers. Although herbal bio-actives including nanofibers have been used mostly in topical/transdermal systems, their use via transmucosal routes such as buccal, ocular, nasal, vaginal, and rectal administrations have increased considerably in recent years. Herbal oils such as clove oil and herbal extracts such as tara extract are widely used via these routes based on the fast-dissolving properties of nanofibers and thus increasing activity. In the light of the previous overviewed studies, nanofibers are promising nanocarriers for the development of phytopharmaceuticals in various drug delivery routes.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: İ.E-G., L.A., E.A.Y., E.E., D.B., R.K.S., Design: İ.E-G., L.A., E.A.Y., E.E., D.B., R.K.S., Data Collection or Processing: İ.E-G., L.A., E.A.Y., E.E., D.B., R.K.S., Analysis or Interpretation: İ.E-G., L.A., E.A.Y., E.E., D.B., R.K.S., Literature Search: İ.E-G., L.A., E.A.Y., E.E., D.B., R.K.S., Writing: İİ.E-G., L.A., E.A.Y., E.E., D.B., R.K.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. Nat Rev Drug Discov 2005;4:206-20.
2. Chen Y, Garcia de Lomana M, Friedrich NO, Kirchmair J. Characterization of the chemical space of known and readily obtainable natural products. J Chem Inf Model 2018;58:1518-32.

3. Sewell RDE, Rafieian-Kopaei M. The history and ups and downs of herbal medicines usage. J HerbMed Pharmacol 2014;3.
4. Islam R, Parves MR, Paul AS, Uddin N, Rahman MS, Mamun AA, et al. A molecular modeling approach to identify effective antiviral phytochemicals against the main protease of SARS-CoV-2. J Biomol Struct Dyn 2021;39:3213-24.
5. Patridge E, Gareiss P, Kinch MS, Hoyer D. An analysis of FDA-approved drugs: natural products and their derivatives. Drug Discov Today 2016;21:204-7.
6. Sofi HS, Akram T, Tamboli AH, Majeed A, Shabir N, Sheikh FA. Novel lavender oil and silver nanoparticles simultaneously loaded onto polyurethane nanofibers for wound-healing applications. Int J Pharm 2019;569:118590.
7. Mandal AS, Biswas N, Karim KM, Guha A, Chatterjee S, Behera M, et al. Drug delivery system based on chronobiology--A review. J Control Release 2010;147:314-25.
8. Sofi HS, Rashid R, Amna T, Hamid R, Sheikh FA. Recent advances in formulating electrospun nanofiber membranes: Delivering active phytoconstituents. J Drug Deliv Sci Technol 2020;60:102038.
9. Chen S, Li R, Li X, Xie J. Electrospinning: An enabling nanotechnology platform for drug delivery and regenerative medicine. Adv Drug Deliv Rev 2018;132:188-213.
10. Kanani GA, Bahrami HS. Review on electrospun nanofibers scaffold and biomedical applications. Trends Biomater Artif Organs 2010;24:93-115.
11. Shahriar SMS, Mondal J, Hasan MN, Revuri V, Lee DY, Lee YK. Electrospinning nanofibers for therapeutics delivery. Nanomaterials (Basel) 2019;9:532.
12. Thakkar S, Misra M. Electrospun polymeric nanofibers: New horizons in drug delivery. Eur J Pharm Sci 2017;107:148-67.
13. Kajdič S, Planinšek O, Gašperlin M, Kocbek P. Electrospun nanofibers for customized drug-delivery systems. J Drug Deliv Sci Technol 2019;51:672-81.
14. Balusamy B, Celebioglu A, Senthamizhan A, Uyar T. Progress in the design and development of "fast-dissolving" electrospun nanofibers based drug delivery systems - A systematic review. J Control Release 2020;326:482-509.
15. Son YJ, Kim WJ, Yoo HS. Therapeutic applications of electrospun nanofibers for drug delivery systems. Arch Pharm Res 2014;37:69-78.
16. Samprasit W, Akkaramongkolporn P, Ngawhirunpat T, Rojanarata T, Kaomongkolgit R, Opanasopit P. Fast releasing oral electrospun PVP/CD nanofiber mats of taste-masked meloxicam. Int J Pharm 2015;487:213-22.
17. Srivastava RK. 16 - Electrospinning of patterned and 3D nanofibers. Electrospun Nanofibers 2017:399-447.
18. Esentürk İ, Erdal MS, Güngör S. Electrospinning method to produce drug-loaded nanofibers for topical/ transdermal drug delivery applications. J Fac Pharm 2016;46:49-69.
19. Zhang W, Ronca S, Mele E. Electrospun Nanofibres Containing Antimicrobial Plant Extracts. Nanomaterials (Basel) 2017;7:42.
20. Alghoraibi I, Alomari S. Different methods for nanofiber design and fabrication. Handb Nanofibers 2018:1-46.
21. Sebe I, Szabó P, Kállai-Szabó B, Zelkó R. Incorporating small molecules or biologics into nanofibers for optimized drug release: A review. Int J Pharm 2015;494:516-30.
22. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: current and future prospects. Drug Delivery 2006;13:175-87.
23. Nair RS, Morris A, Billa N, Leong CO. An Evaluation of Curcumin-Encapsulated Chitosan Nanoparticles for Transdermal Delivery. AAPS PharmSciTech 2019;20:69.
24. Sampath M, Lakra R, Korrapati PS, Sengottuvelan B. Curcumin loaded poly (lactic-co-glycolic) acid nanofiber for the treatment of carcinoma. Colloids Surfaces B Biointerfaces 2014;117:128-34.
25. Ravikumar R, Ganesh M, Ubaidulla U, Young Choi E, Tae Jang H. Preparation, characterization, and *in vitro* diffusion study of nonwoven electrospun nanofiber of curcumin-loaded cellulose acetate phthalate polymer. Saudi Pharm J 2017;25:921-6.
26. Ariamoghaddam AR, Ebrahimi-Hosseinzadeh B, Hatamian-Zarmi A, Sahraeian R. In vivo anti-obesity efficacy of curcumin loaded nanofibers transdermal patches in high-fat diet induced obese rats. Mater Sci Eng C 2018;92:161-71.
27. Ravikumar R, Ganesh M, Senthil V, Ramesh YV, Jakki SL, Choi EY. Tetrahydro curcumin loaded PCL-PEG electrospun transdermal nanofiber patch: Preparation, characterization, and in vitro diffusion evaluations. J Drug Deliv Sci Technol 2018;44:342-8.
28. Tang Y, Liu L, Han J, Zhang Z, Yang S, Li S, et al. Fabrication and Characterization of Multiple Herbal Extracts-loaded Nanofibrous Patches for Topical Treatment of Acne Vulgaris. Fibers Polym 2021;22:323-33.
29. Sutjarittangtham K, Sanpa S, Tunkasiri T, Chantawannakul P, Intatha U, Eitssayeam S. Bactericidal effects of propolis/polylactic acid (PLA) nanofibres obtained via electrospinning. J Apic Res 2014;53:109-15.
30. Jin G, Prabhakaran MP, Kai D, Annamalai SK, Arunachalam KD, Ramakrishna S. Tissue engineered plant extracts as nanofibrous wound dressing. Biomaterials 2013;34:724-34.
31. Sadri M, Arab-Sorkhi S, Vatani H, Bagheri-Pebdeni A. New wound dressing polymeric nanofiber containing green tea extract prepared by electrospinning method. Fibers Polym 2015;16:1742-50.
32. Yousefi I, Pakravan M, Rahimi H, Bahador A, Farshadzadeh Z, Haririan I. An investigation of electrospun Henna leaves extract-loaded chitosan based nanofibrous mats for skin tissue engineering. Mater Sci Eng C Mater Biol Appl 2017;75:433-44.
33. Hajilou H, Farahpour MR, Hamishehkar H. Polycaprolactone nanofiber coated with chitosan and Gamma oryzanol functionalized as a novel wound dressing for healing infected wounds. Int J Biol Macromol 2020;164:2358-69.
34. Bayat S, Amiri N, Pishavar E, Kalalinia F, Movaffagh J, Hahsemi M. Bromelain-loaded chitosan nanofibers prepared by electrospinning method for burn wound healing in animal models. Life Sci 2019;229:57-66.
35. Motealleh B, Zahedi P, Rezaeian I, Moghimi M, Abdolghaffari AH, Zarandi MA. Morphology, drug release, antibacterial, cell proliferation, and histology studies of chamomile-loaded wound dressing mats based on electrospun nanofibrous poly(ε-caprolactone)/polystyrene blends. J Biomed Mater Res B Appl Biomater 2014;102:977-87.
36. Opanasopit P, Sila-On W, Rojanarata T, Ngawhirunpat T. Fabrication and properties of capsicum extract-loaded PVA and CA nanofiber patches. Pharm Dev Technol 2013;18:1140-7.

37. Badshah M, Ullah H, Khan AR, Khan S, Park JK, Khan T. Surface modification and evaluation of bacterial cellulose for drug delivery. Int J Biol Macromol 2018;113:526-33.

38. Tonglairoum P, Chuchote T, Ngawhirunpat T, Rojanarata T, Opanasopit P. Encapsulation of plai oil/2-hydroxypropyl-β-cyclodextrin inclusion complexes in polyvinylpyrrolidone (PVP) electrospun nanofibers for topical application. Pharm Dev Technol 2014;19:430-7.

39. Wongkanya R, Teeranachaideekul V, Makarasen A, Chuysinuan P, Yingyuad P, Nooeaid P, et al. Electrospun poly(lactic acid) nanofiber mats for controlled transdermal delivery of essential oil from Zingiber cassumunar Roxb. Mater Res Express 2020;7.

40. Chemistry T, Soliman WY. Fabrication of Electrospun Nanofibers made of Watermelon Peel Extract and PVA and investigating their antioxidant and antibacterial activities. 2018;77.

41. Lin S, Chen M, Jiang H, Fan L, Sun B, Yu F, et al. Green electrospun grape seed extract-loaded silk fibroin nanofibrous mats with excellent cytocompatibility and antioxidant effect. Colloids Surf B Biointerfaces 2016;139:156-63.

42. Morad H, Jahanshahi M, Akbari J, Saeedi M, Gill P, Enayatifard R. Novel topical and transdermal delivery of colchicine with chitosan based biocomposite nanofiberous system; formulation, optimization, characterization, ex vivo skin deposition/permeation, and anti-melanoma evaluation. Mater Chem Phys 2021;263:124381.

43. Ekambaram R, Saravanan S, Selvam N, Dharmalingam S. Statistical optimization of novel acemannan polysaccharides assisted TiO2 nanorods based nanofibers for skin cancer application. Carbohydr Polym Technol Appl 2021;2:100048.

44. Agnes Mary S, Giri Dev VR. Electrospun herbal nanofibrous wound dressings for skin tissue engineering. J Text Inst 2015;106:886-95.

45. Lin YC, Hu SC, Huang PH, Lin TC, Yen FL. Electrospun Resveratrol-Loaded Polyvinylpyrrolidone/Cyclodextrin Nanofibers and Their Biomedical Applications. Pharmaceutics 2020;12:552.

46. Kim HG, Gater DL, Kim YC. Development of transdermal vitamin D3 (VD3) delivery system using combinations of PLGA nanoparticles and microneedles. Drug Deliv Transl Res 2018;8:281-90.

47. Park SN, Kim JH, Yang HJ, Won BR, Ahn YJ, Kang MK. Preparation of vitamin E acetate nano-emulsion and in vitro research regarding vitamin E acetate transdermal delivery system which use Franz diffusion cell. J Soc Cosmet Sci Korea 2009;35:91-101.

48. Pattama T, Uracha R, Pitt S. Drug-loaded electrospun mats of poly(vinyl alcohol) fibres and their release characteristics of four model drugs. Nanotechnology 2006;17:2317.

49. Parın FN, Yıldırım K. Preparation and characterisation of vitamin-loaded electrospun nanofibres as promising transdermal patches. Fibres Text East Eur 2021;29:17-25.

50. Chaudhary S, Garg T, Murthy RS, Rath G, Goyal AK. Recent approaches of lipid-based delivery system for lymphatic targeting via oral route. J Drug Target 2014;22:87182.

51. Malik R, Garg T, Goyal AK, Rath G. Diacerein-Loaded novel gastroretentive nanofiber system using PLLA: Development and in vitro characterization. Artif Cells Nanomed Biotechnol 2016;44:928-36.

52. Deepak A, Goyal AK, Rath G. Nanofiber in transmucosal drug delivery. J Drug Deliv Sci Technol 2018;43:379-87.

53. Nam S, Lee SY, Cho HJ. Phloretin-loaded fast dissolving nanofibers for the locoregional therapy of oral squamous cell carcinoma. J Colloid Interface Sci 2017;508:112-20.

54. Nam S, Lee JJ, Lee SY, Jeong JY, Kang WS, Cho HJ. Angelica gigas Nakai extract-loaded fast-dissolving nanofiber based on poly(vinyl alcohol) and Soluplus for oral cancer therapy. Int J Pharm 2017;526:225-34.

55. Tonglairoum P, Ngawhirunpat T, Rojanarata T, Kaomongkolgit R, Opanasopit P. Fabrication and Evaluation of Nanostructured Herbal Oil/Hydroxypropyl-β-Cyclodextrin/Polyvinylpyrrolidone Mats for Denture Stomatitis Prevention and Treatment. AAPS PharmSciTech 2016;17:1441-9.

56. George PM, Varghese SS. Electrospun ocimum sanctum loaded fiber with potential biomedical applications - Periodontal therapeutic perspective. Biomed Pharmacol J 2018;11:1731-6.

57. George PM, Jayakumar ND, Kaarthikeyan G. Effectiveness of electrospun Ocimum sanctum nanofibers as an adjunct to scaling and root planning in the management of chronic periodontitis: A randomized controlled clinical trial. J Int Oral Health 2021;13:115-21.

58. Silva JR, Sato TP, Borges ALS. Synthesis and morphological characterization of polycaprolactone (PCL) membranes with tara extract (caesalpinia spinosa). Brazilian Dent Sci 2019;22:163-70.

59. Sedghi R, Sayyari N, Shaabani A, Niknejad H, Tayebi T. Novel biocompatible zinc-curcumin loaded coaxial nanofibers for bone tissue engineering application. Polymer 2018;142:244-55.

60. Zadegan S, Nourmohammadi J, Vahidi B, Haghighipour N. An investigation into osteogenic differentiation effects of silk fibroin-nettle (Urtica dioica L.) nanofibers. Int J Biol Macromol 2019;133:795-803.