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Impact of Modern Technology on the Development of Natural-based Products

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ABSTRACT

Advanced drug delivery systems such as liposomes, niosomes, ethosomes and phytosomes significantly influence the quality of synthetic drug formulations. However, the trend is now shifting towards natural-based moieties, most probably because of their promising therapeutic responses, and considerably lower incidence of side effects and toxicity issues. The effectiveness of herbal plant formulations in nano-sized particles in the delivery of active compounds is increased since nanoparticles offer a larger surface area and promote longer contact time with the surfaces of the targeted sites. Thus, nanoparticles allow the sustained release of small amounts of active compounds and the optimization of the dosing frequency of the drug. The implementation of nanotechnology in the development of natural-based products is able to enhance the delivery of plant extracts and active phytochemicals to the targeted sites. In fact, maximum therapeutic outcomes can be achieved since the herbal formulations are more stable compared to traditional preparations. The development of herbal formulations in modern drug delivery systems will be further discussed in this review. The possible improvement of phytosomes is highlighted in order to give future insights into improvising phytosomes as a targeted drug carrier system. A compilation of evidence-based studies involving the nanotechnology of herbal formulations is summarized accordingly. The use of modern technology in herbal drug delivery systems has been growing in past decades and needs to be further explored by scientists. Hence, at the end of this review, a brief summary is given of a few success stories regarding modern nano formulations that have been commercialized by leading herbal companies and which can be considered as great achievements in this field. Thus, this review is aimed at exploring the use of nanotechnology in drug delivery systems and discusses their contribution to the design of modern herbal formulations.

Keywords: Nanotechnology, Drug delivery, Nanoparticles, Liposomes, Phytosomes, Plant-derived products.

INTRODUCTION: BACKGROUND

Natural-based products continuously attract attention worldwide due to the belief that natural-based products have less hazardous side effects compared to synthetic drugs. This belief has been well embedded in society as a result of its age-old use [1]. In addition, the traditional uses of medicinal plants for treating certain diseases have been proven to produce positive therapeutic outcomes. Some of the most common examples include St. John's Wort for Depression [2], and neem for antiviral, antifungal and anti-inflammatory [3]. This evidence demonstrates possible underlying mechanisms at the molecular level, which contribute to the healing process. Thus, many researches are focusing on the optimization of traditional medicinal plant preparations in modern formulations. The development of medicinal products derived from plants is proving to be very challenging since some active phytochemicals (flavonoids, tannins and terpenoids) are highly soluble in water yet have low absorption due to large molecular size [4], while some suffer from poor solubility in water (curcumin, rutin and quercetin) [5, 6], thus leading to poor bioavailability. In addition, limited knowledge as to their toxic effects and possible harmful interactions between herbal preparations is also a challenge [7].

Despite excellent advancements in the discovery of drugs, there are still frequent reports of therapeutic failures due to drug inefficacy and toxicity effects. Limitations in pharmacokinetic parameters such as poor gastrointestinal absorption and rapid degradation at brush borders, unintended high protein binding, and rapid plasma clearance by major organs namely liver and kidney, are major challenges in drug therapy [8]. These formidable factors greatly affect the effective concentration at the targeted sites, thereby resulting in poor therapeutic responses. An ideal drug delivery system should be capable of delivering an adequate supply of active agents to maintain the efficacy of the drug, and it should precisely deliver the drug to the intended sites. However, conventional drug preparations seem incapable of perfectly overcoming the challenges of pharmacokinetics and are ultimately unable to deliver the drug as desired. Extensive researches in drug delivery systems have been increasing continuously, leading to the emergence of nanotechnology in drug delivery systems.

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As the challenges prevalent in the development of plant-derived products are in line with the rapid development of advanced drug delivery systems, the implementation of nano science in herbal medicines is bound to happen. With the help of nanotechnology, the maximum therapeutic outcomes of plants can be achieved due to the availability of maximum drug concentrations at the targeted sites and also the minimization of the adverse effects of therapy [5, 9]. Eventually, this optimization will strongly contribute to effective drug therapy and better quality of life among patients. A number of advanced drug delivery systems are widely researched across the globe (Fig.1).

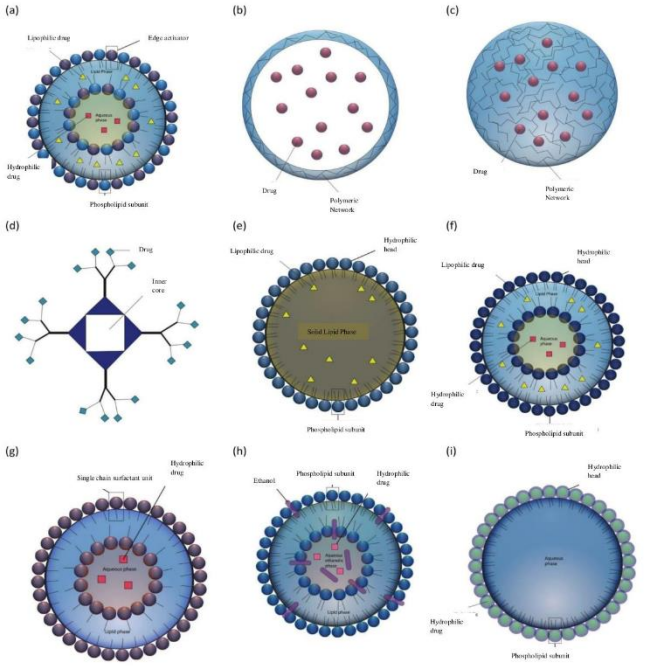

Figure 1: Illustration of advanced drug delivery systems. (a) transferosome, (b) nanocapsule, (c) nanosphere, (d) dendrimer, (e) solid lipid nanoparticle, (f) liposome, (g) niosome, (h) ethosome, and (i) phytosome [10–16].

Revolution of advanced drug delivery systems at a glance

The development of polymers in drug delivery systems has revolutionized the quality of treatment and the therapeutic outcomes of many diseases. Polymer science began with Hermann Staudinger, a German scientist [17], almost 100 years ago in the 1920s. He described the properties and existence of polymers, which he called “macromolecules”. It took a long time for other scientists to accept his macromolecular theory and it was only in 1953 that his hard work was recognized worldwide after he was awarded the Nobel Prize in Chemistry. In 1955, the first attempt to design a polymer-drug conjugate was reported by Jatzkewitz [18]. About 10 years later in 1964, Bangham and Horne described the correlation between surface active agents and the formation of spherulite lipid beads with lamellar structures [19]. Finally, Bangham and his research team discovered spherulite multi-lamellae particles, which are known as liposomes [19, 20].

Eight years later, Gregoriadis, who attempted to encapsulate penicillin and actinomycin D into liposomes, reported the first successful liposomal-drug formulation [21]. In 1974, Kramer discovered that albumin is capable of being a vehicle in drug delivery [22]. Ringsdorf described polymer drug conjugates in 1975 [23], and a year later, the first enzyme-loaded liposome was reported by Gregoriadis and his research team [24]. Duncan and Kopecek reported the biocompatibility of dendrimers and tested their side chain degradability in rat liver tritosomes [25]. In 1985, Krause and his team reported that polylactic acid nanoparticles are suitable for lipophilic drugs [26]. In 1983, the first micelle formulation was approved by the Food and Drug Administration (FDA) [27], followed by the approval of Zoladex in 1989 [28]. These studies were the key to improve drug delivery using nanoparticles by possible enhancing specificity and duration of action of drug.

In 1990, the FDA approved the first polyethylene glycol (PEG) protein conjugate to enter the market [28]. The development of plant-based drug in conjunction with nanoparticles started to flourish as well. In 1992, the plant-based drug, Taxol (Paclitaxel), was approved by the FDA for the treatment of breast cancer [29]. However, due to its toxicity issues, further research done led to the discovery and approval paclitaxel as an albumin bound nanoparticle, Abraxane, in 2005 [30]. Doxorubicin was approved by the FDA in 1994 and a year after that, its liposomal formulation, Doxil, was approved with improved toxicity profile [31]. In 1996, another plant-based drug, Camptothecin analogue was approved by the FDA. The formulation was developed with lipid nanoparticles, namely topotecan and irinotecan [32].

Later, formulation of herbal plants using phytosomes for better drug delivery and refined therapeutic effect was introduced [33]. The impact of nanotechnology has also improvised the formulation of vitamin C in the form of liposomes (Lypo-spheric vitamin C) to improve its delivery [34]. Many successful natural based drugs formulated through the years led to more findings of useful plants. In 2001, the first Traditional Chinese Medicine (TCM), Kanglaite, was approved by the FDA for phase 1 clinical studies for the treatment of cancer [33, 35]. In 2012, the first oral plant-based drugs to be approved by the FDA were antidiarrheal, Fulyzaq [36] and Elelyso for the treatment of Gaucher disease [37]. Many incredible discoveries after that, including the implementation of nanotechnology in herbal medicine formulations, have resulted in numerous commercialized medicinal plants in the form of pharmaceutical dosages. The timeline in Table 1 summarizes the information regarding the development of nanotechnology and the emergence of modern herbal formulations.

Fundamental properties of nano-sized particles in drug delivery

In general, a nanoparticle is defined as any substance with a diameter of 1-100 nm, while from the pharmaceutical perspective of drug delivery, a nanoparticle is referred to as any spherical substance with a diameter of 1-1000 nm [38]. The complexity of the loaded materials and attempts to ensure sufficient amounts of active ingredients may sometimes result in larger nano-sized particles. It has been discovered that the special attributes of particles when observed at the nano-scale level are pronounced and interesting. Nanoparticles are very small in size. Due to this, they have a very large surface area, whereby every single atom is highly exposed to the surrounding environment [38]. The atoms are generally arranged in lattice form and each atom has an intrinsic energy capacity. The vibrations from these atoms contribute to alterations in the physical and chemical properties of the substance. The unique properties of nanoparticles are obvious when these quantum effects significantly override the physicochemical properties of materials [39].

Nanoparticles consist of nanocrystals, nanoemulsion and nanoparticles as drug carriers.

Nanocrystals are crystals either crystalline or amorphous; in a nanometer size range below 1µm. Nanocrystals are 100% drug with enhanced saturation solubility and dissolution velocity. Generation of nanocrystals through precipitation, milling or homogenization can greatly benefit drugs with solubility issues [38]. Meanwhile, nanosuspension is the result of dispersing nanocrystals in liquid media [40, 41]. Nanoemulsions, on the other hand, are basically emulsion with nanoscopic droplet size which can improve drug bioavailability due to its solubilisation capacity [42, 43]. Types of nanoparticle that act as drug carrier are abundant and are used widely. Some of the most popular nanocarriers include dendrimer, liposomes and micelle.

The booming of nanoparticles in research, particularly in drug delivery is due to its major advantages in improving existing drug candidate as well as its versatile and adjustable properties. Nanoparticles are able to improve bioavailability of drugs through due to its small size as well as its ability to modulate the solubility of drugs [44]. The small size of nanoparticle not only can improve bioavailability but it also allows drugs to travel across many biological barriers [45] and prevent aggregation which occurs with parenteral product, thus providing a better distribution profile [46]. Moreover, nanoparticles have greater benefits as it is able to encapsulate abundance of therapeutic agents and diagnostic agents [47]. In addition to that, ligands can also be attached to surface of the nanoparticles thus helping in targeted drug delivery which the application is of utmost importance in cancer therapy [48].

Challenges of modern herbal medicine formulations

Researches on nano-sized materials have been developing at an increasingly fast pace over the past decades. The implementation of nanotechnology in drug delivery systems has led to great advancements in targeted drug therapies specifically in cancer therapy; take for example Doxil/Caelyx which is a liposomal doxorubicin and Abraxane which is a protein-bound paclitaxel [9, 31]. Moreover, the application of nanotechnology in herbal medicines is receiving attention nowadays. The potential of developing herbal medicines as a promising alternative treatment cannot be denied. However, there is a lack of reported scientific evidence regarding the safety and efficacy as well as regulation and standardization of these plant-derived products [49]. Therefore, extensive efforts at formulating herbal plants in modern pharmaceutical formulations have resulted in the standardization of active phytochemicals, and better safety and efficacy profiles. Although medicinal plants have been found to possess promising biological properties, there are various possible hurdles that lie in the path of the development and commercialization of natural products. Natural products derived from medicinal plant sources can succumb to a number of challenges ranging from the active phytochemical retrieval to the commercialization phase. The challenges in the development of natural-based products include, but are not limited to:

- Toxicity issues and limited documentation regarding possible side effects [50, 51]
- Poor bioavailability of active phytochemicals [52]
- Very low yield of active phytochemicals [53] and shortage of medicinal plant resources [54]
- Limited reported evidence on drug-phytochemical interactions *in vitro*, *in vivo* or both [55].

Taxol is a natural alkaloid derived from the bark of the poisonous Pacific yew tree (*Taxus brevifolia*). The discovery of taxol by a United States botanist, Arthur Barcley, in 1962 is priceless. Up until now, taxol (currently referred to as paclitaxel) is used as a fundamental drug in treatment protocols for ovarian cancer, breast cancer and lung cancer. Taxol is a potent natural anti-cancer agent that is capable of reducing the growth rate of tumour cells by blocking the replication of cells during mitosis. In 1992, the FDA approved the use of taxol for ovarian cancer, and two years later it was approved for the treatment of metastatic breast cancer [53]. Despite its remarkable anti-tumour properties, taxol is difficult to isolate, consequently accounting for its very low yield and high cost [56, 57]. Apart from that, the first taxol formulation contained chremophor as an excipient to improve the solubility of the taxol. However, chremophor was later found to be too toxic for living cells, including endothelial and epithelial cells [58, 59].

In terms of the poor bioavailability of natural products, there are diverse reasons contributing to this fact. It can be innate to the phytochemicals such as its chemical structure, solubility, membrane permeability, metabolism or microbial stability. The extrinsic factors that may also affect bioavailability include the processing methods involved, frequency of administration, drugs co-administered or something related to the body system itself such as gender or genetic profile [60, 61]. These problems can be overcome with improved formulation or chemical modification. The bioavailability can be analysed with in vitro models which may mimic how it might act in vivo. However at the end of the day, to confirm bioavailability of these natural products, clinical trial is the most conclusive method [60].

As the popularity of herbal medicines increase, more active phytochemicals are required for development of drugs. Being phytochemicals, it needs to be extracted from plants and the yield obtained from thousand kilograms of plant source is usually minute. A large amount of the active ingredient is required not only during the research period, but even more to commercialize it. For these reasons, shortage of plant sources to extract phytochemicals is becoming a concern [54]. Due to this very reason, fake herbal supplies are becoming more abundant in the market, raising concerns from all parties in regards to the quality, safety and efficacy of natural based products [62].

To develop herbal medicine is already challenging. On top of that, there are also challenges in developing nanoparticles. One of the challenges includes the nanoparticle stability itself. Issues regarding the ability of nanoparticles to retain drug rises because of some nanoparticles have shown to leak its content upon contact with blood components. Another challenge is the survival of nanoparticles through body's metabolism system [63]. Surface modification with PEG has been used to overcome this issue yet disadvantages that come with PEG has not truly overcome this challenge [64]. In the past safety issued regarding nanoparticle was not properly confronted. In respond to that, FDA nanotechnology task force was formed in 2006 to tackle safety issues with nanoparticles and recently they have come up with guidance related to nanotechnology [65]. Despite the existence of this guidance, a lot are still uncertain when it comes to assessments and approvals of nanoparticles. This in turn, negatively affects investors' decision to embark in nanoparticle products. Clearly, there are a lot of obstacles to develop and formulate modern herbal formulations from both the herbs itself and the nanoparticulate delivery system.

Advanced drug delivery systems and herbal medicines

Liposomes, which are made up of phospholipid bilayers, are excellent drug delivery systems [66, 67]. The encapsulation of plant extracts in liposomes helps to contain the drug, whether within the lipid phase or aqueous phase, according to the properties of the compounds, as shown in Figure 1(f). Liposomes behave like solid particles offering secure transportation to herbal formulations until they reach the targeted sites. Drug designers can tailor the release of herbal formulations by modifying the composition of the membranes of liposome vesicles. For instance, with the aid of leucine peptides, a narrow tunnel-like space will be opened to allow the sustainable release of low amounts of the herbal formulation [52, 68]. The same authors explained that another mechanism for controlling drug delivery by liposomes is via the generation of carbon dioxide gas inside the aqueous phase. This will trigger the opening of phospholipid bilayers, hence resulting in the release of the herbal formulation to the targeted sites [52].

It has been reported that liposomal formulations, including proliposomes, protect herbal formulations from being extensively metabolized by the liver, thereby resulting in higher bioavailability [69–72]. Apart from that, liposomes demonstrate strong bio adherence to human cell membranes and also bacterial cell walls. The high cohesion and adhesion to the cell surface can improve the smooth release of herbal formulations into the cells. Niosomes and ethosomes are adapted versions of liposomes. A niosome, as shown in Figure 1(g), is made up of a single non-ionic surfactant unit forming a vesicle. The conversion of herbal formulations into niosomes helps to improve the chemical stability and bioavailability of active phytochemicals [73]. As shown in Figure 1(h), an ethosome is similar to a liposome except for the presence of ethanol in the bilayer membranes, which helps to improve the release of aqueous compounds from the vesicles, especially through the dermal layers [74–76]. Table 2 summarizes the improvements in some herbal medicines through nanotechnology applications.

Another advanced drug delivery system is phytosomes. Basically, a phytosome, as shown in Figure 1(i) has a similar structure to conventional liposomes. It is a nano-sized micelle made up of phospholipids [77]. Phytosome technology helps to improve the absorption of active phytochemicals by offering efficient partitioning between phytochemicals loaded inside the hydrophilic head of phospholipid subunits with lipid layers of cell membranes. When phytosomes are formulated for dermal delivery, a sufficient amount of active phytochemicals is expected to be successfully delivered through the skin layers and to finally accumulate at the intended sites [78]. Meanwhile, after the oral administration of phytosomes, a greater amount of active phytochemicals is expected to be absorbed through the gastrointestinal layer, resulting in higher bioavailability in the plasma [79, 80]. However, it is important to remember that the real challenge in maintaining the bioavailability of phytochemical compounds is to bypass the major metabolism process in the liver and kidneys [81].

In the case of phytosomes, although the high absorption of active phytochemicals can be achieved through the intestinal layers, these compounds will be extensively metabolized by the liver, and this may result in a minimal number of active phytochemicals in the plasma and targeted sites. Based on previous evidence, phytosomes are an impressive drug delivery system and they can be further modified to improve their capability as a phyto-carrier system. There are several possible ways of overcoming the limitations of phytosomes. The formulation of active phytochemicals with a hyaluronic acid-based nanogel conjugate suggests a better drug delivery profile. Nanogels are versatile vehicles that can help to encapsulate active phytochemical molecules, thus forming a compact nanogel containing active phytochemical(s) [82, 83]. The incorporation of compact phytonanogels into phytosomal formulations might be worth considering because nanogels protect active phytochemicals from extensive liver metabolism. Studies have strongly confirmed that the cholesteryl-hyaluronic acid-curcumin nanogel offers longer bioavailability of curcumin up to 96 hours after administration via injection [84].

The numbers of herbal formulation developed with nanoparticles are increasing consistently. The use of nanoparticles in herbal formulation has been found to given spectacular benefits such as enhance solubility profile, increase bioavailability and improve therapeutic efficiency [69]. To further improve and enhance the credibility of herbal medicine, targeted therapy as applied in abundant of cancer therapy may also be implemented. Targeted nanoparticles are divided into three different types which are passive targeting, active targeting and target-activated system. The passive targeting is suitable for tumour due to presence of leaky vasculature in tumours [85] while active targeting can be exploited for modern herbal formulation as it involves attaching ligands to the polymer [86]. Next, nanoparticles that respond to certain condition in target tissue are the target activated systems [64]. These systems can either be activated by pH, usually acidic or presence of certain enzymes which are usually overexpressed [63]. Hence, there are still areas to explore in connection to delivery of natural-based products alongside the advanced delivery systems of nanoparticles.

Natural Products in the Market

Continuous efforts by scientists and researchers over past decades have resulted in fruitful drug developments including natural-based product formulations. Revolutions in drug delivery systems have led to the emergence of a new green trend which focuses on the utilization of natural resources as therapeutic alternatives. Countless natural products are available in the market. Natural products are increasingly in demand in the market, most probably because of their promising therapeutic responses. In fact, the commercialization of natural products in modern pharmaceutical dosage forms offers better safety margins and consistency of active phytochemical amounts in the formulations. The rapid development of advanced drug delivery systems also greatly influences herbal medicine formulations.

Abraxane is an improvised version of taxol and it is less toxic than chremophor-taxol [87]. The formulation of paclitaxel-albumin nanoparticles has modified its pharmacokinetic profiles such that it has a higher solubility and better tissue distribution. The combination of Abraxane with other cytotoxic agents offers more effective chemotherapy than previous formulations and significantly prolongs the survival rate of patients [88]. Indena® is a well-established Italian phyto-pharmaceutical company which focuses extensively on the development of plant-based products. Ninety years of experience in dealing with medicinal plants led to the discovery of a modern herbal delivery system called phytosome [89].

Indena® provides clear halal and kosher certifications in many of their products. Sabinsa® is another leading company in herbal medicines [90]. Both Indena® and Sabinsa® have commercialized a number of patented herbal supplements and pharmaceutical products. Some of the available

pharmaceutical products in the market are listed in Table 3. Another natural-based products company is Tagra® [91]. It is a well-known company in skincare products with a patented microencapsulation technology. It focuses on microencapsulated formulations of vitamins, essential oils, flavonoids and colours for lipsticks and skincare products. Cosmetochem® is a Swiss-based company, which focuses on the development of plant-derived products. Its remarkable achievement in 2010 was Liposome Herbasec, a skincare product [92]. The product consists of five different herbal extracts, namely white and green tea, total polyphenols, white hibiscus, guarana and aloe vera. Herbasec is a standardized liposomal herbal formulation in freeze dried form specifically for skincare.

Table 1: History of nano-based drug formulations and the emergence of modern herbal formulation

Year	Details	Year	Details
1920s	Herman Staudinger pioneered polymer science [17]	**1989**	First controlled-release drug depots approved by FDA (Zoladex) [28]
1955	First polymer drug conjugate designed by Jatzkewitz [18]	**1990**	First PEG-protein conjugate (Adagen) marketed [93]
1960	First vinca alkaloid (Vinblastine) isolation reported [94]	**1992**	Another plant-based drug (Taxol) approved by FDA [95]
1963	FDA approved Vincristine Sulfate (Oncovin) [96]	**1995**	Lipophilic nanoparticles succeeded crossing blood brain barrier reported [97] FDA approved first nano formulation (Doxil) [98]
1964	First polymeric drug carrier reported by Folkman & Long [99]		
1965	Liposomes reported by Bangham & his research team [19, 20]	**2001**	First TCM drug approved by FDA for clinical trial (Kanglaite) [33]
1971	Kulkarni & his team suggested PLA as drug carrier matrix [100]	**2004**	Irinotecan approved by FDA [101]
		2006	First botanical prescription drug approved by FDA (Veregen) [102]
1972	Albumin-based nanoparticle reported by Scheffel & his team [103]	**2008**	Vitamin C oral liposomal formulation reported [104]
1973	First drug-loaded liposomes reported by Gregoriadis [21]	**2011**	Nanoemulsion of plant-derived anticancer reported (Betulinic acid) [105]
1975	Ringsdorf described polymer-drug conjugates [23]	**2012**	First oral botanical drug approved by FDA (Fulyzaq) [36] FDA approved plant-based formulation to treat Gaucher disease (Elelyso)[37] FDA approved plant-derived liposome injection (Marqibo) [106]
1976	First enzyme-loaded liposomes reported [24]		
1980	Dendrimers reported by Duncan & Kopeček [25]		
1983	First micelle formulation approved by FDA (Sandimmune) [27]	**2015**	First conjugation of nanodiamond with plant phytochemicals reported [107]
1985	PLA nanoparticles reported [26]	**2016**	Co-encapsulation of silbinin and glycirrhizic acid into nano-liposomal formulation reported [108]

Table 2: Contributions of Advanced Drug Delivery Systems in Herbal Formulations

Active Phytochemical/ Plant extract	Advanced Drug Delivery System	Improvement	Reference
Rutin	Phospholipid complex	Improved therapeutic efficacy as an antidiabetic than pure rutin Promotes insulin secretion from pancreatic Beta cells	[109]
	Gelatin nanoparticles	Improved antioxidant activity by 74% as compared to free rutin solution	[110]
	Nanocrystal formulation	Increase adhesive force to skin cell membrane (Longer contact time, faster dissolution and diffusion rates across skin layers)	[111]
	Cyclodextrin	Improved solubility profile, heat stability and antioxidant activity	[112]
Silymarin	Liposomes with bile salts	Improved oral bioavailability	[113]
	Porous silica nanoparticles	Improved oral bioavailability	[114]
	Ethosomes	Prolongs blood circulation	[115]
	Phospholipid complex	Improved stability and efficacy	[80]
Curcumin	Lipid vesicles	Better dermal drug delivery than ethosomes and traditional liposomes formulation	[116]
	Micelles	Reduced tumor size and weight	[117]
	Dendrosomes	Up regulated silenced tumor suppressor (Improved chemotherapy)	[118]
	Nanogels	Reduced tumor growth 2- folds than free curcumin	[119]
	Nanoparticles	Improved absorption and solubility profile Increased ameliorative effects against hepatotoxicity	[120]
Ginkgo biloba	Proliposomes	Increased pharmacokinetics profiles of flavonoids & terpenoid lactones than conventional tablets	[121]
	Proliposomes with bile salts	Bioavailability of crude extract increased by 200 -300%	[70]
	Niosomes	Improved stability, Improved biodistribution to major organs	[122]

	Nanoparticles	Increased half-life	[123]
Tea Tree Oil	Liposomes with silver ions	Promote sustained release Increased antimicrobial activity against *Pseudomonas aeruginosa* and *Candida albicans*	[124]
	Liposomes with Tween 80	Enhanced antimicrobial efficacy	[125]
	Nanogel	Minimized skin irritation	[82]
Green Tea	Nanoparticles with magnesium	Improved bioavailability, increased cellular uptake by bladder cancer cells	[126]
	Liposomes	Improved cohesive & adhesion force between formulation and mucosa cell membranes	[127]
Lemon Grass Oil	Nanosponges	Reduced skin irritancy, Increased antifungal activity	[128]
Nigella sativa	Nanoemulsion	Reduced growth of cancer cells, induced cell apoptosis in breast cancer cells	[129]
Ginseng	Proliposomes with sodium deoxycholate	Improved oral bioavailability by 100 – 200%	[130]
	Nanoparticles	Improved oral bioavailability Inhibited oncogenes	[131]

Table 3: Plant-derived Pharmaceutical Products

Product Name	**Plant**	**Therapeutic claim**	**Company**
Ginkgo biloba	*Ginkgo biloba*	Blood circulation improver	Indena® [89] FSC™ [132]
Ginseng	*Panax ginseng CA Meyer*	Adaptogen, Tonic	Indena® [89] Safwa® [133]
Hedge-Mustard	*Sisymbrium officinale Scop*	Expectorant	Indena® [89] Specchiasol® [134]
Horse Chestnut Extract	*Aesculus hippocastanum*	Antiedema, Venotropic	Indena® [89]
Horsetail Extract	*Equisetum arvanse*	Hair / nail fragility reducer	Indena® [89] Kordel's® [135]
Lymphaselect	*Melilotus officinalis Pallas*	Lymphatic circulation improver	Indena® [89]
Myrtocyan	*Vaccinium myrtillus*	Opthalmic, Capillarotropic	Indena® [89]
Paclitaxel	*Taxus brevifolia*	Anti-mitotic/ Anticancer	Indena® [89] Teva® [136]
Passion Flower Extract	*Passiflora incarnata*	Spasmolytic, Mild sedative	Indena® [89]
Prajmaline	*Rauvolfia vomitora* Afz	Antiarrhythmic	Indena® [89]
Reserpine	*Rauvolfia vomitora* Afz	Antihypertensive	Indena® [89] Taj Pharma® [137]
Prunuselect	*Prunus africana*	Anti-Benign Prostatic, Hyperplasia	Indena® [89]
Purselect	*Rhamnus purshiana*	Laxative	Indena® [89]
Rhubarb Extract	*Rheum emodi* Wall	Eupeptic, Laxative	Indena® [89]
Ruscogenins	*Ruscus aculeatus*	Antihaemorrhoidal, Venotropic	Indena® [89]
Saw Palmetto Extract	*Serenoa repens* (Bartr.) Small	Antiandrogen, Anti-Benign Prostatic Hyperplasia	Indena® [89] Otsuka® [138]
Sennosides	*Cassia angustifolia* Vahl	Laxative	Indena® [89] Franco-indian® [139]
Silymarin	*Silybum marianum*	Hepatoprotector	Indena® [89] BiO-LiFE® [140]
St. John's Wort Extract	*Hypericum perforatum*	Anti-depressive	Indena® [89] Sura Vitasan® [141]
Thiocolchicoside	*Gloriosa superba*	Muscle relaxant	Indena® [89]
Forskolin 1% eye drops	*Plectranthus barbatus*	Treatment of open angle glaucoma	Sabinsa® [90]

CONCLUSIONS

Thousands of herbal medicine products in the market can be considered as a great achievement in moving towards a natural-based therapeutic approach. These products have been growing consistently throughout the years. The development of this branch of science has not been hindered despite the challenges that come with herbal formulation such as solubility, safety and efficacy issues. In fact, more researches are

being done in order to overcome these challenges. The use of modern technology in herbal drug delivery systems is one of the most convincing ways of conquering these challenges. Advanced drug delivery systems are obviously capable enough to effectively control the biological fate of active phytochemical and plant extracts. Many studies agree that nanoparticle carrier systems are considerably qualified to overcome the challenges in the development of plant-derived products. This has even been proven by cancer drugs obtained from plants which were initially very toxic yet improved with the help of nanoparticles. In addition to that, continuous development of nanoparticles alone will also be of great advantage in order to improve the establishment of standards, regulations and guidelines surrounding these systems. Challenges that come with nanoparticles including its stability can also be improved which will enable better application of advanced drug delivery systems to natural-based products. This will assure investors to venture, thus allowing modern herbal formulations to flourish as great as conventional therapies.

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