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An overview on natural product drug formulations from conventional medicines to nanomedicines: past, present and future

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Abstract: For decades, naturally produced plants have been studied and used in herbalism (herbal medicines). Despite being natural, these products were not of any interest of any of the major pharmaceutical companies. There are various reasons behind this ignorance but mainly because of the outdated thought, that many people believe about natural products, in which plants are only utilized for their antibiotic benefits since there were successfully used as antibiotics in the post-World War II era. Mainly small pharmaceutical companies have paid attention to natural products and explored their benefits against various diseases such as microbial infection, cancer, cardiovascular diseases, diabetes and other illnesses while big pharmaceutical industries have focused on screening synthetic compounds. Nowadays, natural products and their derivatives have demonstrated their significant impact as therapeutic agents on people health. Accordingly, about one-third of the top-selling products in the pharmaceutical market are natural products which are either derived from plants or microorganisms. The use of such products is highly preferred by people due to their unique advantages of good therapeutic efficacy, low side effects and cheaper than synthetic products. However, many of natural products are not clearing the clinical trials due to their toxicity and problems with biocompatibility. This review will briefly highlight the history of herbal medicine and will cover pharmaceutical formulations prepared from therapeutically active extracts of natural products. In addition, this article will summarise a range of natural products in conventional dosage forms to the most recent nano-medicinal forms.

Keywords: natural products; nanoparticles; liposomes; micelles; natural product dosage forms

1. Introduction

Since the beginning of the time, humans have been contingent on nature to cater for their sustainable requirements. Herbal medicines, sometimes known as phytomedicine or botanical medicine, is one of the nature gifts to humanity [1- 2]. The use of herbal medicine in treating and avoiding of many diseases has long reported history, this started when the archeologists discovered the oldest record of using medicinal plants for remediation engraved on a Sumerian clay slab over more than 5,000 years ago [3-4], and followed by discovering other documents includes the using of natural products across the ages which were reported using different methods depending on the era

of history in which it has been used in like “Ebers Papyrus” of ancient Egyptian, The Chinese Materia Medica of Chinese, Ayurved of Indian, and etc [1,4,5].

For many years, natural products have been used as herbal medicines. The plant kingdom consists of 300,000- 400,000 higher species (sub-groups of one or more plants that share comparable characteristics with each other). Only 5-15 % of these plant species have been reported to have pharmacological effects, and around 150-200 species have been involved into western medicine, and it has been reported that one fourth of prescribed medicines globally are obtained from plants [6]. In the beginning of 19th century the new analysis methods were started to be available, so scientists manage to extract, identify and adapt the active ingredients from the natural products (plants, fungi, alga and microorganisms) which led to transition of the raw materials to synthetic pharmaceuticals [7]. Synthetic drugs are more expensive and produce many unwanted side-effects regardless of their quick medicinal effect and stronger pharmacological action for example [8]. Therefore, public currently are going back to using natural medications [9].

Nowadays, World Health Organization assessed that about 80% of the world's populations still use the old-style medicines for their remediation [10]. There has been an increase in the consumption of herbal medicinal products world-wide. Today, almost one-third of the top-marketing pharmaceuticals are natural products or their derivatives [11]. The increasing request for herbal remedial products crosswise the world has led to the big scale making of these products. Natural products are existing in several dosage forms such as powders, solutions, capsules, tablets, ointments, creams [12-14] and recently formulated in nanoparticulate forms [15].

Natural drug formulation means a dosage form consisting of one or more herbs herbal derivatives. It contains an active herbal substance or preparations or combination of both. It can be obtained by exposing natural substances to certain process such as extraction, distillation, fractionation, or fermentation [16]. Herbal formulae of traditional medicine are often characterized using one or more herbs in an individual formula. Due to sparse publication in this filed, this review was designed to provide an overview on the past and recent advances on application of natural products for their biological activities as medicinal and nanomedicinal products.

2. Biological activities of natural products

Natural products have crucial role in drug discovery. From past eras medicinal plants occurred on earth and with time it become of global and utmost importance. Every plant has its own therapeutic effects due to its unique bioactive compounds, which are usually non-toxic compared to synthetic compounds. Moreover, the nanotechnology field has successful implication on the pharmaceutical formulations of the natural products as will be discussed later.

Bioactive compounds are natural compounds, which have been confirmed to have useful treatment effects. Many biological activities were reported by these compounds [17] such as antimicrobial [18], anthelmintic [19], antioxidant [20], antifungal [21], antispasmodic [22], antitumor [23, 24], antiulcer and hepatoprotective [25,26], anti-inflammatory and anti-arthritic [27] etc. Accordingly, natural products have very important role as direct or indirect sources of therapeutic agents.

3. Overview of natural drugs formulation history

The natural products preparations, formulations and medicinal uses were managed to pass from generation to generation of different historic era verbally or documentary (Figure 1) as explained briefly below.

3.1. Before Christ (BC) Era (Past)

The first medicinal plants information Before Christ (BC) was originated as an oral tradition discovered by the Indian from their 'Ayurveda' which have been traced back to 6,000 BC, since the times of Indus Valley Civilization [28]. The ancient Egyptians priest doctor and pharmacist "Son" reported the using of their herbal knowledge dating to circa 3000 BC in the 'Ebers Papyrus' [29]. Next in series is the ancient Chinese Shen Nung emperor, he wrote the first *Shen-nung Pen-tSao Ching* at 1,100 BC a book on medicinal plants.

Ancient Greece is believed to have started with Hippocrates whom named as "The Father of Medicine" he wrote Hippocratic Corpus 444BC which is a collection of many early medical works and herbal formula written in Ionic Greek [30].

In Mesopotamian, the Assyrians, Babylonians, and Sumerians, recorded herbal remedies in cuneiform inscriptions on numerous clay tablets, and in the Code of Hammurabi at 772 BC [31,32].

3.2. After Christ (AC) Era (Present)

In the beginning of AC era, a grate herbal scientist named Dioscorides wrote the "De Materia Medica" in 60 AC in which he recorded more than 6000 of plants, animals and mineral drugs formulations along with their uses [33].

Islamic era was the most valuable and reproductive reports of natural products herbal formula and their uses by some of talented gifted scantiest such as; Al-Ṭabarī wrote *Firdaws al-ḥikmah* in 820 AC [34], Al-Rhazey (published his a famous book "Alhawi Kabeer in 880 AC [35], Ibn Sina whose name was latinised to Avicenna and his book "Canoon Fi Elteb" in 1010 AC [36]. This book was served as the chief source of herbal formula and medical knowledge for 5 centuries [36]. The contact with the Islamic world in Spain for example permitted Europeans access to scientific Greek and Arabic text books [37]. Some natural products documented over the history were reported in Table 1 in addition to their uses and formulations.

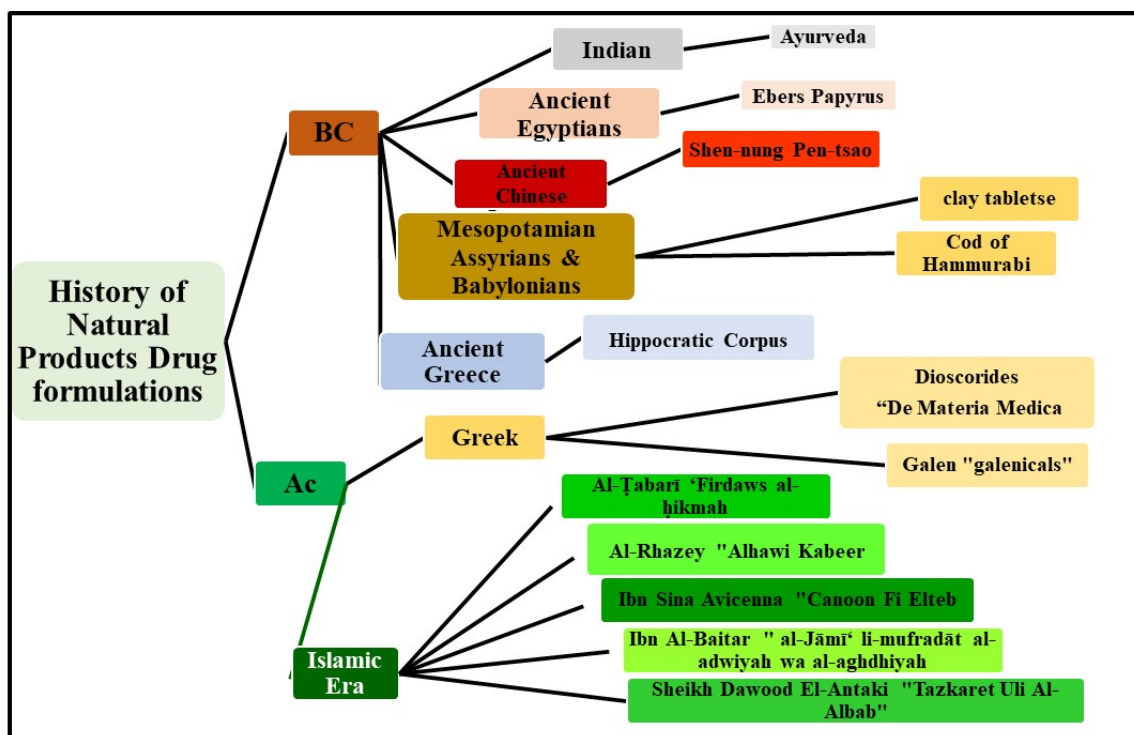


Figure 1. Natural Products Drug formulations History
AC, After Christ; BC, Before Christ

4. Types and efficacy of natural products drug formulations

Natural products are not easy to be formulated due to their special methods of extraction and complicated phytochemical contents which occurs as mixtures. Therefore, formulators faces challenge and difficulties through their work because they must comprehend the chemical behavior and properties of these complex mixtures to reduce the risk of side effects and maximize the efficacy [38]. Hence, for the formulation of natural products into suitable effective dosage forms, the following factors should be taken into consideration solubility, polymorphism, particle size as those factors can affect the bioactivity of the drugs [39].

Cranberry Fruit (*Vaccinium macrocarpon*) is a native plant found mainly in North America, usually formulated as capsules. Due to its effective proanthocyanidins extracts, it is used to prevent urinary tract infections, commonly caused by *Escherichia coli* [40]. Linseed oil (Flaxseed) obtained from herb known as *Linum usitatissimum* Linn. This oil is rich in Omega-3 and alpha-linolenic acid (ALA), accordingly it plays an important role in the management of seizures and ALA may have anticonvulsant effects [41].

Other formulation produced as tablets or oils from *Oenothera biennis* L (good sources of the essential fatty acids, γ -linolenic acid) to treat eczema, asthma, rheumatoid arthritis, premenstrual and menopausal syndrome, and other inflammation-related disorders [42,43].

Valeriana officinalis (Valerian) is a flowering plant formulated in the form of capsules. Valerian extract is currently used as a sedative for the treatment of insomnia and restlessness that would enhance the quality of sleep [44]. Another formula, produced as tablets, capsules and extract named as 5-HTP (5-hydroxytryptophan) was obtained commercially from the seeds of *Griffonia simplicifolia* to be used for treating depression or fibromyalgia [45]. *Ginkgo biloba* leaf extracts have been formulated as liquids, tablets and capsules to treat blood disorders, memory problems, improve eye health cognitive, cardiovascular disorders and ovarian cancer [46].

Aloe vera (*Aloe barbadensis*) contains anthraquinone, acemannan, glycosaminoglycans and carbohydrates in addition to vitamin C, E and aminoacids. *Aloe vera* is the most valuable wild spared plant which have been used in alternative medicine for treating cold sores, itching or rash inside the mouth, or psoriasis and many others health and beauty problems. It was produced in many dosage forms such as; tablets, Soft capsule gels capsules, lotions, ointments, and creams [47]. Horse chestnut is a plant scientifically named as *Aesculus hippocastanum*, the used parts of this plant are seed, bark, flower, and leaves. Saponin escin, extract from the seeds of this plant, is mainly produced in the form of infusions, capsules and tablets to treat varicose veins and chronic venous insufficiency [48].

Allium sativum L., fermented black garlic demonstrated several therapeutic effects such as lowering blood pressure, anti-obesity, hypolipidemic, anticancer, hepatoprotective and immunomodulatory [49]. A liquid of 10% black garlic extract significantly prevented the reduction of glutathione reduced form and retrieved physical stability in addition to high anti-radical efficiencies. This could be effective in protecting skin especially from Ultraviolet B(UVB) photodamage [50]. Propolis extract (PE), a well-known natural extract, is derived by bees which obtain it from plant juices and utilized to cap the openings in the bee hives. It was used in the topical preparation in the folk medicine for its outstanding antioxidant properties. Stable topical formulations loaded with PE were developed to treat the illnesses happening in skin subjected to ultraviolet radiation. Formulations prepared with Polawax® were functionally and physically stable during the whole study. Percutaneous study showed that the antioxidant compounds available in PE were able to reach lower layers in both pig ear skin and the hairless mice skin. *In vivo* study proposed that this preparation could be effective in shielding skin from any photodamage could be caused by UVB photodamage [51].

Pedilanthus tithymaloides (PTL) leaves were prepared in the form of ointment and evaluated for its benefit on wound healing rat models. The results showed that the methanol extract of PTL demonstrated a significant wound management activity of the topical ointment formulations. The histology study exhibited whole epithelialization with increased collagenation [52]. *Evodia rutaecarpa* extract is a commonly used fruit in Traditional Chinese Medicine. Evodiamine and rutaecarpine are

the major active extracts from this fruit which are reported to be depended analgesic agents. The transdermal behavior of both extracts was assessed in addition to *in vivo* investigating the pharmacological outcomes of their topical cream. The *in vivo* study showed a significant inhibitory activity toward a pain induced in a mice pain model response in dose-dependent manner [53].

Citrus maxima is one of the largest citrus fruit among the family *Rutaceae*. It has been safely used for several years in pharmaceuticals and food industries. Piriyaarasarth and Sriamornsak, 2011 reported the possible application of pectin extracted from *Citrus maxima* peels' in pharmaceutical suspensions. Pectin influenced the stability of one of the anti-inflammatory drugs (indomethacin) which was prepared in suspension form. For instance, a low concentration of pectin in addition to ferric ions influenced the stability and redispersibility of indomethacin suspensions. The use of high concentration of pectin successfully worked as a flocculating or suspending agent, suggesting its application as a liquid drug delivery system [54].

Daucus Carota L. (Carrot), extracted materials from this plant, carotenoids, have shown analgesic and anti-inflammatory activities in addition to its effective activity as anticancer, hypoglycemic, antifertility, hepatoprotective, antiulcer and anti-tumor. A soft paraffin cream was applied, in mice models, with the ethanolic extract of *Daucus carota L.* which showed a wound healing activity with no signs of skin irritation [55]. The isolated extracts of *Lichens* have been commonly used in traditional medicine in several countries around the world. *Lichen Usnea* species was found to contain the dibenzofuran derivative usnic acid which is one of the competent antimicrobials and antiviral materials. Usnic acid has been utilized in pharmaceuticals as well as cosmetics [56].

Moreover, alkyl polyglucosides, plant-derived sugars, are biodegradable non-ionic surfactants. They have been utilized as surfactants rather than therapeutics. For instance, a study focuses on assessing topical vehicles based on the use of natural surfactant-mixed emulsifier, specifically alkylpolyglucoside surfactants (cetearyl glucoside and cetearyl alcohol). It was suggested that these surfactants are proposed as "ready to use" bases for several pharmaceuticals [57].

Bougainvillea xbutiana is a plant with an analgesic effect traditionally used in folk medicine. The ethanolic extract of *Bougainvillea xbutiana* was found to reduce the tumour necrosis factor (TNF), increase the levels of interleukin-6 (IL-6), interferon-gamma (IFN- γ) for up to 2 h demonstrating the anti-nociceptive and anti-inflammatory activities of this plant ethanolic extract [27]. Also, *Sechium edule* (*S. edule*) is a plant belongs to the gourd family (*Cucurbitaceae*) which has several diuretics, anti-inflammatory and cardiovascular properties. The mutagenicity, antibacterial and antifungal activities of *S. edule* were also assessed. A topical carbopol acrylic acid based hydrogel loaded with *S. edule* extract was developed in which *S. edule* acted as an antimycotic, antibacterial and antioxidant agent. The formulation was stable for a year without the necessity to add any antioxidant preservative. This study [58] suggested that this topical formulation could be useful as antimycotic and antibacterial for the treatment of cutaneous infections [58].

In field of cosmetic, many natural products drug formulations had been produced including different extracts from the suitable sources. For Example, the ethanolic extract of four plants namely, *Cabernet Sauvignon*, *Pinus pinaster ssp. Atlantica*, *Acacia dealbata*, and *Lentinula edodes* have shown both antioxidants and additives colorant effects [59]. Also, *Saccharomyces cerevisiae* extract (SCE) has a valuable cosmetics activity as it can be effective in oxidative stress and improve skin conditions. The use of cosmetic formulation SCE and/or vitamins (A, C and E) were investigated for its dermatological effects as patches which were tested on back of skin of volunteers. Formulations were tested and the results of this research [60] suggested that vitamins and SCE showed effects in skin microrelief and skin moisture. Also, the formulations which contain SCE had long lasting action enhancing the skin microrelief [60].

Entada Africana leaves is commonly used in Africa for the treatment of wounds, skin infections, and as a tonic for stomach problems in addition to its effective effect against diphtheria-like throat troubles. The extract was used in the form of microcapsules to assess the anti-ulcer effect of the extract on rats' stomach. A significant cytoprotective effect was found for the extract and the microcapsules

against indomethacin and ethanol induced gastro ulceration, suggesting its potential uses as a pharmaceutical formulation for the treatment of peptic ulcer [61].

Polyherbal formulation is commonly used in traditional medicines such as the Indian medicine, as hepatoprotective medicines. The hepatoprotective activity of polyherbal was reported for its significant effect on liver enzymes, lipid profiles, urea and creatinine level [62].

Polytoxinol (PT) is a natural disinfectant used in various formulation. PT is a steam-distilled hydrocarbons extracted from five herbs (*Melaleuca alternifolia* (tea tree), *Eucalyptus globulus*, *Syzygium aromaticum* (clove), *Thymus sp.* (thyme), and *citrus* species). Also, PT was able to inhibit the biofilm formation in the most tolerant isolate at sub-inhibitory concentrations when it has in-vitro tested against clinical isolates of coagulase-negative *staphylococci* [63]. PT in an essential oil-based topical formulation is used to treat postoperative methicillin-resistant *Staphylococcus aureus* (MRSA) infection [64], based on this study the PT formulation is an inexpensive and simple alternative compared to the use of long-term systemic antibiotic therapies.

Artemisia annua and its relative extract artemisinin, poorly water-soluble antimalarial drugs, presented a low and irregular bioavailability upon oral administration (capsule dosage form). However, preparation of artemisinin as agglomerates with β -cyclodextrin made the plant raw material dissolved more rapidly and showed better effect and bioavailability upon oral administration [65].

Table 1. Types, formula type and medicinal uses of the most popular natural products.

Natural product name	Formulation Type	Medicinal use	References
<i>Vaccinium macrocarpon</i> Cranberry Gummies	Capsule or juice	Bladder and kidney diseases, urinary tract infections	[40]
<i>Linum usitatissimum</i> Linn	Capsule	Management of seizures and anticonvulsant effects	[41]
<i>Oenothera biennis</i>	Tablet or oil	Eczema, asthma, rheumatoid arthritis, premenstrual, menopausal syndrome, and inflammation-related disorders.	[42]
<i>Valeriana officinalis</i>	Capsule	Inducing sleep and improving sleep quality	[44]
<i>Griffonia simplicifolia</i>	Tablet, capsules	Treating depression or fibromyalgia	[45]
<i>Ginkgo biloba</i>	Liquid extracts, capsules, and tablets	Blood disorders, memory problems, improve eye health cognitive, cardiovascular disorders and ovarian cancer	[46]
<i>Aloe vera</i>	Tablet, Soft gels capsules, lotions, ointment, cream	Cold sores, itching or rash inside the mouth, or psoriasis and many others health and beauty problems.	[47]
<i>Aesculus hippocastanum</i>	Infusions, capsules and tablets	Treat varicose veins and chronic venous insufficiency	[48]
Black garlic	Powder and supplement pill	Anticancer, anti-obesity, antioxidant, immunomodulatory, hepatoprotective, hypolipidemic, and neuroprotective effects	[49-50]
Propolis	Topical formulations	Prevent and treat the diseases occurring in skin caused by UV radiation	[51]
<i>Pedilanthus tithymaloides L</i>	Ointment	Heal wounds, burn and mouth ulcer	[52]
<i>Evodia rutaecarpa</i>	Cream	Analgesic agent	[53]
<i>Citrus maxima</i>	Suspension	Used as a flocculating or suspending agent in liquid drug delivery system	[54]
<i>Daucus carota Linn</i>	Cream	Wound healing	[55]
<i>Sechium edule</i>	Topical formulation	Antibacterial and antifungal activity	[58]

<i>Saccharomyces cerevisiae</i>	Patch	Skin microrelief	[60]
<i>Entada Africana</i>	Multiparticulate formulation	Antiulcer	[61]
<i>Melaleuca alternifolia</i>	Topical formulation	Antimicrobial and antibiotic	[63-64]
<i>Eucalyptus globulus</i>	Topical formulation	Antimicrobial and antibiotic	[63-64]
<i>Syzygium aromaticum</i>	Topical formulation	Antimicrobial and antibiotic	[63-64]
<i>Thymus species</i>	Topical formulation	Antimicrobial and antibiotic	[63-64]
<i>Citrus species</i>	Topical formulation	Antimicrobial and antibiotic	[63-64]
<i>Artemisia annua</i>	Solution	Antimalarial	[65]

5. Advances in natural product drug formulations via nanotechnology (Future)

From the above, it can be concluded that the loading of natural products extracts into various conventional formulations and dosage forms to be taken orally or applied externally helps in producing therapeutic effects with minimal side effects and less toxicity. Nevertheless, the recent advances in nanotechnology has promising effects on producing the natural products into better effective medicines (nanomedicines) as will be shown in the following sections.

Several challenges concerned with these products (specifically product with large size materials), including poor solubility that would lead to poor absorption and poor bioavailability. In addition to *in vivo* instability and no target-specific delivery that could results on unwanted side effects of the natural pharmaceutical drugs. Advancement in nanotechnology could be the answer for these challenges. Nanotechnology has demonstrated significant role in many aspects of drug delivery such as targeted drug delivery, controlled release profiles of natural products and delivery with immense success. Nanotechnology is one of techniques that used for enhancing drug dissolution, bioavailability and formulations. The use of nanoparticle formulations with specific drug nano-carrier like; liposome, ethosome, phytosomes, nanoemulsion, and nanosphere can enhance natural products drug formulations therapeutic effects and systemic bioactivity.

Nanotechnology has attracted the attention of major pharmaceutical companies as it can bridge the barriers between the main two sciences concerning drug delivery; biology and physics. These nanostructures (particles with sizes ranged between 1-100 nm) have demonstrated significant successes among nanomedicine and nano-based drug delivery systems [66, 67]. Due to their size, nanoparticles can move more freely than larger particles in the human body. In the past years, nanomedicines have become more appreciated. These nanoassemblies can be used as drug delivery vehicles in many ways; incorporating active ingredients within nanoparticles or even attaching the active ingredients to nanostructures. These nanoparticles are able to deliver the active ingredient to an accurate target site with a controlled release manner in the human body [68, 69]. Examples for the most common nanoparticles used in drug delivery are solid lipid and polymeric nanoparticles, crystal nanoparticles, liposomes, micelles, and dendrimers. Each of them has advantages and disadvantages as drug delivery systems. Examples for nanoparticles encapsulating plant-based extracts are presented in Table 2 and also are discussed below in sections 5.1-5.4.

5.1. Polymeric nanoparticles

Polymeric nanoparticles are solid colloidal particles of size range 10 nm–1 μ m, that consist of natural or synthetic biodegradable and biocompatible polymers or copolymers. They are of interest for target drug delivery, biodegradability, nontoxic, water soluble and long shelf life. Drug molecules can be either entrapped or encapsulated within the polymeric nanoparticles, physically adsorbed onto the surface of the carrier or chemically bound to the surface of the polymeric nanoparticles [70]. There are various synthetic and natural polymers which have been utilized for the preparation of

polymeric nanoparticles. Polymers should be biocompatible, biodegradable and are easy to functionalize. Chitosan is a natural polymer that has recently gained growing attention in the delivery of natural products [71, 72].

Quercetin is a bioflavonoid found in the human diet (include: citrus fruits, grapes, apples, cherries, berries, onions, kale, buckwheat, tomatoes, broccoli and black tea) with many biological activities including anti-inflammatory, antihypertensive, antiallergic and antidiabetic effects. Quercetin was characterized with low aqueous solubility, poor permeability, low oral bioavailability, chemical instability (specifically in alkaline aqueous solution) and it undergoes extensive past metabolism before it reaches the systemic circulation. An efficient polymeric carrier prepared with water soluble succinyl chitosan and alginate entrapped quercetin into core-shell nanocarriers via ionic cross linking in order to improve quercetin anti-diabetic effect. The results revealed an efficient hypoglycemic effect for quercetin nanoparticles in comparison to free quercetin after oral administration in diabetic rats [73].

Epigallocatechin-3-gallate (EGCG) was encapsulated into chitosan nanoparticles [74] and evaluated. Epigallocatechin-3-gallate is a major component of green tea has an anti-viral, anti-mutagenic, antitumorigenic, anti-angiogenic, anti-proliferative, and/or pro-apoptotic effects on mammalian cells. The results showed improvement in the efficacy of the nanoparticles as compared to free EGCG [74].

Maity et al developed alginate coated chitosan core-shell nanoparticles encapsulated the flavanone naringenin to enhance its solubility and bioavailability. Naringenin has an antidiabetic action and present in vegetables and citrus fruits such as grapefruit and oranges. In addition to its antidiabetic activity, naringenin has anti mutagenic, anti-inflammatory, antihyperglycemic, and antioxidant activities. It was also found that the nanoparticles were free from any toxicity after histopathology estimation and several blood parameters in streptozotocin-induced diabetic rats [75].

Curcumin-loaded Poly-(lactic-co-glycolic acid)-Polyvinyl-alcohol nanoparticles (PLGA-PVA nanoparticles) were prepared. Curcumin, a derivative of turmeric (*Curcuma longa*), exhibits numerous pharmacological effects including; anti-inflammatory, antioxidant, antimicrobial, and anti-carcinogenic effects [76, 77]. As compared to pure curcumin administration, curcumin-loaded nanoparticles significantly delayed the progression of diabetic cataract which is attributed to the improved bioavailability of curcumin after encapsulation for oral administration in diabetic rats [78].

Poly-(lactic-co-glycolic acid) nanoparticles (PLGA nanoparticles) loaded with a combination of two plant based extracted chemotherapeutic drugs (paclitaxel (PTX) and etoposide (ETP)) for the treatment of osteosarcoma. PTX is derived from the bark of the Pacific yew tree (*Taxus brevifolia*) and ETP belongs to the plant alkaloids. *In vitro* cytotoxicity examinations revealed improvement in the effect of the combined drug-loaded nanoparticles compared with the free drugs alone. *In vitro* cellular uptake studies indicated a considerable uptake in MG63 cells in a time dependent manner suggesting possible application of nanoparticles in chemoprevention within clinical settings [79].

Luteolin (a natural compound found in green vegetables) was encapsulated into polymeric nanoparticles and assessed on H292 cell line (lung cancer cells) and Tu212 cell line (a squamous cell carcinoma of head and neck cells). The results showed higher antiproliferative activity against H292 cells with lower half maximal inhibitory concentration (IC50) values compared to free luteolin [80].

Table 2. Types, formula and medicinal uses of the most natural products in nano-formulations.

Natural product name	Formulation Type	Medicinal use	References
Quercetin	Succinylated chitosan-alginate core-shell-corona nanoparticle	antidiabetic effect	[73]
Epigallocatechin-3-gallate	chitosan nanoparticles, liposomes	anti-viral, anti-mutagenic, antitumorigenic, anti-angiogenic, anti-proliferative, and/or pro-apoptotic effects	[74, 104]
Naringenin	alginate coated chitosan nanoparticles	antidiabetic effect	[75]

Curcumin	Poly-(lactic-co-glycolic acid)-Polyvinyl-alcohol nanoparticles	anti-inflammatory, antioxidant, antimicrobial, and anti-carcinogenic effects	[78]
Curcumin	Liposomes	antitumor, antioxidant, anti-inflammatory, and antihypertensive effect	[99]
Curcumin-doxorubicin combination	Liposomes	antitumor effect	[100]
Curcumin	Pluronic nanomicelles	Antidiabetic effect	[110]
Curcumin	Polymeric micelles	Anticancer activity	[111]
Paclitaxel-etoposide combination	Poly-(lactic-co-glycolic acid) nanoparticles	chemotherapeutic activity	[79]
Paclitaxel	Hyaluronic acid coated Solid lipid nanoparticles	antitumor effect	[84]
Paclitaxel	Hyaluronic coated liposomes	antitumor activity	[102]
β -lapachone- paclitaxel combination	Micelles	antineoplastic and radiosensitizing activities	[112]
Luteolin	Polymeric nanoparticles	Anticancer effect	[80]
Ficus benjamina	Solid lipid nanoparticles	antioxidant, antipyretic, anti-dysentery, anti-inflammatory and hepatoprotective	[82]
Silibinin	Solid lipid nanoparticles	Anticancer effect	[83]
<i>Pentacyclic triterpenediol</i>	Solid lipid nanoparticles	cytotoxic and apoptotic effect	[85]
Myricitrin	Solid lipid nanoparticles	antioxidant and antidiabetic effects	[86]
Berberine	Solid lipid nanoparticles	Antihyperlipidemic, antimicrobial, antihypertensive, and antidiabetic effects	[90]
Vancomycin - Ellagic acid combination	Solid lipid nanoparticles	Broad spectrum antibiotic with antioxidant effect	[91]
Thymoquinone	Nanostructured lipid nanocarriers	Antiproliferative effect	[93]
Resveratrol	Nanoliposomes	antitumor activity, antioxidant, an insulin-like effect, anti-inflammatory, cardioprotective, neuroprotective, vasorelaxant and phytoestrogenic effect	[98]
Cinnamic acid	Liposomes	antibacterial, antiviral, antifungal and antioxidant	[101]
Ursolic acid	Liposomes	Antitumor activity	[102]

5.2. Solid lipid nanoparticles (SLNPs)

SLNPs are nanocarrier systems (size ranging from 10 to 1000 nm) consist of a solid-lipid core which is typically stabilized by emulsifiers. These particles are ideal choice for lipophilic drug delivery due to the ability of the lipid core to solubilize most lipophilic molecules. The most common lipids have been used in SLNPs production includes glycerides (mono-, di-, or tri), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetyl palmitate). They are less toxic than polymeric nanoparticles because of their biocompatibility and biodegradability nature. SLNPs are also more stable than liposomes as they offer less storage and drug leakage problems [81].

SLNPs have been utilized for the delivery of plant-based extracts; for example, *Ficus benjamina*, Silibinin, Paclitaxel, Pentacyclic triterpenediol, Myricitrin, Berberine, Vancomycin, Orcinol glucoside, Thymoquinone and others.

Sharma et al. develop *Ficus benjamina* solid lipid nanoparticles (FBSLNPs) as a therapeutic system against hepatotoxicity caused by alcohol abuse. *Ficus benjamina* (family *Moraceae*) leaves are rich in phenolic and flavonoids compounds which have antioxidant, antipyretic, anti-dysentery and anti-

inflammatory activities. Different formulations of FBSLNPs were prepared and characterized. The results revealed that FBSLNPs have hepatoprotective action and were able to reduce aldehydes levels in the liver tissues of animals [82].

Silibinin (extracted from *Silybum Marianum*) was encapsulated in SLNPs and assessed against MDA-MB-231 breast cancer cells. The results showed improvement in cellular uptake of SLNPs better than free Silibinin [83].

Shen et al. reported the improvement of the anti-tumor effect of paclitaxel encapsulating within SLNPs coated with hyaluronic acid. Paclitaxel loaded SLNPs were prepared by film-ultrasonic method followed by coating with hyaluronic acid (cancer stem cells show presences of CD44 that binds specially to hyaluronic acid). Paclitaxel SLNPs targeted the tumor tissues, consequently, revealed significant antitumor effect with a low dose of paclitaxel compared to the pure drug in mice [84].

Bhushan et al. manufactured *Pentacyclic triterpenediol* as SLNPs by the microemulsion method. *Triterpenediol* (extracted from *Boswellia Serrate*) is reported to be significantly cytotoxic and apoptotic effect in human cancer cell lines. The SLNPs showed a significantly higher antitumor potential as compared with the parent drug in Sarcoma-180 solid tumor in mice. Plain SLNPs did not show any cytotoxic actions on the cancer or in normal mouse peritoneal macrophages [85].

Myricitrin SLNPs produced by cold homogenization method. Myricitrin is a plant-derived compound that has dual action (antioxidant and antidiabetic effects). The effects of myricitrin loaded SLNPs were screened on streptozotocin-nicotinamide- induced Type 2 diabetes mellitus in a mouse and hyperglycemic myotube. The results revealed that Myricitrin SLNPs improved diabetes and hyperglycemia problems in both *in vivo* and *in vitro* studies. The overall results suggested that Myricitrin SLNPs have demonstrated all antiapoptotic, antidiabetic, and antioxidant effects in the mouse and myotube cells [86].

Berberine SLNPs were prepared to enhance drug bioavailability. Berberine is an essential benzylisoquinoline alkaloid found in *Coptis chinensis* [87]. It has been used for the treatment of various conditions, such as hyperlipidemia, intestinal infections, hypertension, cardiac arrhythmia, congestive heart failure, cancer, and diabetes [88,89]. Furthermore, oral administration of Berberine and Berberine-SLNPs significantly reduced body weight gain in mice and fasting blood glucose level [90].

Aldawsari and Hosny articulated Vancomycin and Ellagic acid co-loaded SLNPs (VCEA-SLNPs) by the solvent evaporation-ultrasonication technique. Vancomycin is a broad-spectrum antibiotic characterized with significant nephrotoxicity accordingly it has limited uses. For this reason, authors have used Ellagic acid (has antioxidant effect) as a protective agent against the nephrotoxicity. The results showed VCEA-SLNPs formed with an average size of 164 nm and zeta potential of 14.2 mV. *In vivo* overall results suggested a significant improvement of Vancomycin nephrotoxicity effects by encapsulation with Ellagic acid within VCEA-SLNPs system as the results exhibited that the animals treated with VCEA-SLNPs showed a non-significant difference in all parameters of kidney function as compared to the control group. While, animals treated only with Vancomycin produced a significant difference in tested parameters compared to the control group [91]. Orcinol glucoside (OG) is another herbal extracted molecule which was encapsulated within lipid nanoparticles which showed substantial anticancer activity against hepatoma and gastrointestinal tract cancer cell lines [92].

Haron et al. encapsulated Thymoquinone (TQ) into nanostructured lipid carriers (NLCs). TQ is a bioactive compound found in *Nigella sativa*, has low bioavailability due to its lipophilicity. To overcome this problem, TQ was encapsulated into lipid carrier [93]. This study aimed to assess the antiproliferative actions of both free TQ and the encapsulated TQ (TQNLCs) on liver cancer cells combined with Hep3B (a hepatitis B genome). TQ or TQNLCs treated the Hep3B cells for 24, 48, and 72 hours by MTT assay. The outcomes of this study showed that TQ or TQNLCs prevented Hep3B growth at IC₅₀ <16.7 μ M for a period of 72 hours. Also, TQ nanocarriers showed an antioxidant effect that reduced the level of reactive oxygen species (ROS) [94].

5.3. Liposomes

Liposomes (firstly discovered by Alec Bangham in 1963) are nanosized spherical vesicles, manufactured from naturally derived phospholipid ordered in a bilayer structure. Liposomes are well established for the use in drug delivery in addition to a range of biomedical applications and they are in the market as medicines. Liposomes are able to encapsulate various active pharmaceutical ingredients (APIs) whether they were hydrophobic or hydrophilic drugs [94,95]. Cholesterol works to reduce liposomes fluidity and to enhance the stability of liposomes in the blood [96]. Liposomes were utilized as carriers for several plant based extracted medications; such as Resveratrol, Curcumin, Cinnamic acid, Capsaicin, paclitaxel, Ursolic acid and Epigallocatechin-3-gallate.

Resveratrol is a natural polyphenol usually isolated from the roots of *Veratrum grandiflorum* O. Loes or from *Polygonum cuspidatum* roots. It has several pharmacological impacts such as antitumor activity, antioxidant, has an insulin-like effect, anti-inflammatory, cardioprotective, neuroprotective, vasorelaxant and phytoestrogenic [97]. Yücel et al. developed Resveratrol loaded nanoliposomes to assess its insulin-like effect in streptozotocin (STZ)-induced diabetic animals. Nanoliposomes were PEGylated covalently to increase plasma half-life and residence time of Resveratrol nanoliposomes. Both efficiency of nanoliposomes on diabetes and related oxidative stress were evaluated. The results showed that by comparing Nanoliposomes to unprocessed Resveratrol solution, nanoliposomes managed to significantly reduce the high level of glucose with increase of insulin levels. This is in addition to the prolonged antioxidant activity noticed for nanoliposomes against oxidative stress for a period of 24 hours [98].

Curcumin loaded liposomes (CLPs) were prepared using the thin film hydration method. Then, after the hydration of thin lipid film, the lipid dispersion was sonicated to reduce the size of the obtained liposomes [99]. Milk fat globule membrane (MFGM) phospholipids in addition to soybean lecithin were used in CLPs preparation. It was found that MFGM liposomes revealed higher encapsulation efficiency, higher Zeta-potential, smaller particle size, slower release profile during the *in vitro* studies in addition of being slightly more stable than soybean lecithin liposomes [99]. In addition to curcumin activities, curcumin was able to improve the antitumor efficacy of doxorubicin (DOX) after co-encapsulating into liposomes. The results demonstrated an enhanced antitumor effect of DOX on C26 colon carcinoma by the addition of curcumin in a liposomal system [100].

Cinnamic acid is a slightly soluble in water and can be extracted from cinnamon bark. Three different lipidic materials (phospholipids of docosahexaenoic acid, soya and salmon lecithin) were separately utilised to encapsulate cinnamic acid in nanoliposome forms. The aim of the study [101] was to investigate the potential effect of the three lipids on the entrapment efficiency of cinnamic acid in addition to its membrane permeability. It was found that salmon lecithin containing nanoliposomes had the highest encapsulation efficiency (particle size of 115.2 ± 2.0 and encapsulation efficiency of $91.40 \pm 1.39\%$) and increased membrane rigidity of nanoliposomes thus improved the membrane stability in comparison to nanoliposomes prepared from docosahexaenoic acid or soya lecithin [101].

A new double-functional paclitaxel liposomes which can target both CD44-targeting and mitochondrial-targeting function. The liposomes coated with hyaluronic could be a promising system to enhance the therapeutic efficacy of antitumor agents also overcoming the multidrug resistance in cancer treatment [102].

Ursolic acid is another natural triterpene substance available in numerous fruits and vegetables. Wang et al. developed chitosan (positively charged molecule) coated ursolic acid liposomes that showed significant antitumor targeting ability, low side effects and a control over drug release. Those liposomes were spherical with particle size of ~ 130 nm. Coating with chitosan made liposomes carrying positive charges, which would attract to the negatively charged surface of tumor cells initiating rapid release of ursolic acid. The overall results suggested those liposomes allowed a treatment for localised tumor which suggest an effective tumor therapy [103]. Epigallocatechin-3-gallate (EGCG) is a major catechin in green tea. Liposomes loaded EGCG (EGCGLPs) were manufactures and the results indicated higher insertion degree of EGCG within EGCGLPs leading to

higher encapsulation efficiency especially in the presence of Magnesium chloride (MgCl₂) as compared to calcium ions in both neutral and anionic systems [104].

5.4. Micelles

Micelles (MCLs), core-shell nanostructures, are assemblies of amphiphilic surfactant molecules that extemporaneously agglomerate to form a spherical vesicle in aqueous solutions [105,106]. MCLs core is capable of entrapping both hydrophilic and hydrophobic active ingredients and most of charged substances via electrostatic, hydrogen bonding and hydrophobic interactions in addition to the stereo complex formation [107]. Polymeric MCLs preparation is very simple but how to control the rate of drug release from these MCLs is a dull work. Modification for micelles surface would help in controlling active ingredients release from the MCLs due to the strong chemical bonds on the surface. The administration of MCLs for the treatment of tumor have the advantage of that MCLs activation takes place at the tumor site thus inhibiting active ingredients release in the blood circulation, accordingly, minimizing active ingredients toxicity toward normal cells [108,109]. Several plant-based extracts were developed in MCLs systems, for instance curcumin, β -lapachone and paclitaxel.

Curcumin-loaded pluronic nanomicelles were developed via nanoprecipitation method aiming to enhance curcumin solubility and bioavailability thus achieve its antidiabetic effects. Biological and histological assessments were carried out on nanomicelles in an STZ-induced diabetic model. The nanomicelles exhibited antihyperglycemic effect resulted from the significant up regulation of both Pdx-1 and NKx6.1 genes' expression, which are important transcription factors in gene expression of insulin [110].

Curcumin also was encapsulated within polymeric MCLs which were prepared from methoxy-poly (ethylene glycol)-poly(D/L-lactide) (mPEG-PLA). MCLs were evaluated for their cytotoxicity in B16F10 (melanoma), breast cancer, and murine cancer cells. By comparing micelles with the administration of free curcumin, a higher cellular uptake was reported for micelles over free curcumin uptake in both cell lines. Curcumin cytotoxicity was reported to be more in mPEG-PLA micelles therefore such micelles would be an efficient for curcumin delivery [111].

β -lapachone is an ortho naphthoquinone which is usually isolated from Pau d'arco tree for its potential antineoplastic and radiosensitizing activities. β -lapachone in addition to paclitaxel were encapsulated into micelles containing poly (ethylene glycol)-b-poly (d,l-lactic acid) PEG-PLA copolymer and were assessed against A549 lung cancer cells. The outcomes demonstrated a valuable synergistic effect for the combined β -lapachone and paclitaxel against lung cancer [112].

6. Conclusion and future perspective

The use of herbal medicine in treating and avoiding of many diseases has long reported history. Natural products are not easy to be formulated due to their special methods of extraction and complicated phytochemical contents, which occurs as mixtures. This review reveals that many natural products have therapeutic effects such as anti-inflammatory, anticancer and antibacterial effects within different formulations. It also presented types, effects and efficacy of the plant based extract in suitable dosage forms and formulations.

The recent advances in technology especially nanotechnology will brighten the future of natural remedies as many research in this field is underway. Nano-based drug delivery systems can enhance the efficacy and bioavailability of the natural products and will promote the formulation of those products in more effective way into modern therapeutics; these were also discussed and demonstrated in this review.

The use of plant extracts is highly preferred by people due to their unique advantages of good therapeutic efficacy, low side effects and the cost is cheaper than synthetic products. The review confirmed that many extracts can be formulated in suitable dosage forms and nanomedicinal forms. Hence, there are great promise to have much more natural products, as pharmaceutical products in the market in the near future.

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