HHS Public Access

Author manuscript

Biomed Pharmacother. Author manuscript; available in PMC 2022 March 29.

Published in final edited form as:

Biomed Pharmacother. 2021 November ; 143: 112137. doi:10.1016/j.biopha.2021.112137.

Recent progress in micro and nano-encapsulation of bioactive derivatives of the Brazilian genus *Pterodon*

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Abstract

In the last few decades, utilization of medicinal plants by the pharmaceutical industry has led to the identification of many new bioactive compounds. The genus *Pterodon,* native of the Brazilian Flora, is known for the therapeutic properties attributed to its species, which are widely used in popular medicine for their anti-inflammatory, anti-rheumatic, tonic, and depurative properties. The intrinsic low water solubility of the plant derivatives from the genus, including diterpenes with vouacapane skeletons that are partially associated with the pharmacological activities, impairs the bioavailability of these bioactive compounds. Recent studies have aimed to encapsulate *Pterodon* products to improve their water solubility, achieve stability, increase their efficacy, and allow clinical applications. The purpose of this paper is to review recent research on the use of nanotechnology for the development of new products from plant derivatives of the Pterodon genus in different types of micro- and nanocarriers. Therapeutic properties of their different products are also presented. Finally, an update about the current and future applications of encapsulated formulations is provided.

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CRediT authorship contribution statement

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Declaration of conflicting interests

The authors declare no conflict of interest.

Keywords

Pterodon ; Encapsulation; Polymeric nanoparticle; Lipidic nanoparticle; Terpenes; Natural products

1. Introduction

The use of plants for medicinal purposes for the treatment of various diseases has occurred for thousands of years and the wide structural variability of molecules with biological activity has been appreciated more recently [1–3]. The World Health Organization (WHO) suggests that developing countries, comprising around 80% of the world population, depend on traditional medicine for primary health care [4,5].

In recent years, the search for new natural products has escalated. The number of publications for the term “Natural Products” on Pubmed increased from 452 items in 2000 to more than 5000 in 2021. In addition, plants are of great importance in traditional medicine, cosmetics, and homeopathy, although their use goes far beyond the new drugs approved by regulatory agencies such as the US Food and Drug Administration (FDA) or the Brazilian Health Regulatory Agency (ANVISA) [6]. Plant-derived natural compounds are responsible, directly or indirectly, for approximately one-quarter of the drugs currently available in the world [7].

Synthesis of chemical entities from plants of medicinal importance has been a valuable resource for the development of new drugs [8]. Since these new bioactive compounds can be used either directly as therapeutic agents or as prototypes for the development of new analogs with improved efficacy or reduced toxicity [9–11]. Examples of commercially available plant-derived drugs include salicin (analgesic agent) extracted from *Salix* spp. and later the development of its derivative, the aspirin [12]. Quinine and artemisinin and its derivatives (antimalarial), isolated from *Cinchona officinalis* and *Artemisia annua,* respectively [13,14]; digoxin (muscle relaxant) isolated from *Digitalis lanata,* used for more than 200 years [15,16]; codeine and morphine (analgesic) isolated from opium (*Papaver somniferum*) [17,18]. An antiviral and antitumoral agent, podophyllotoxin, was isolated from *Podophyllum peltatum* [19,20].

The search for new compounds with biological activity is motivated by unmet therapeutic needs. Brazil is a particularly rich source of plants that have undiscovered bioactive compounds having wide biodiversity. However, the use of naturally derived molecules as a source of new medicines also presents some challenges. The isolation, characterization, and purification processes can be costly and time-consuming. In addition, the lipophilicity of the compounds can impair their use *in vivo* [21]. This helps to explain why among the 1562 drugs approved by FDA from 1981 to 2014, 21% were natural product derivatives. However, only 4% were used without alteration [6].

The trees of the genus *Pterodon* are native to, and have an extensive presence in, Brazil. Their extracts and oils contain bioactive compounds, subject to ethnopharmacological use mainly as anti-rheumatic, pain relief or to treat throat infections and respiratory disorders

such as bronchitis [22–24]. The main compounds present in this genus are isoflavones and triterpenes found in the wood [25]; alkaloids, saponins, glycosides, and steroids in the bark [26–29]; sesquiterpenes, isoflavones, and saponins in the leaves [30–33]; terpenoids of furanoditerpenes type, sesquiterpenes, diterpene vouacapanic skeleton in fruit oil [34–40].

Some studies suggest that biological activities of the species of the genus *Pterodon* are directly related to the furan diterpene and sesquiterpene contents [41–43]. *Pterodon*-derived products include oleoresin, an essential oil that can be extracted by cold-pressing and hydro-distillation with no use of solvents [34,40,44,45]. Biological activities have been ascribed to diterpenes from the fruit, especially the vouacapan skeleton, 6α, 7β-dihydroxy-vouacapan-17β-oic acid extracted by the Soxhlet method, using solvents like petroleum ether [46] hexane [47,48], ethanol [49]. Cold extraction using dichloromethane [39,50] and hexane [23,42] were also reported to produce *Pterodon* extracts.

These extracts are complex mixtures of chemicals that might have associated biological properties. A study that evaluated the anti-nociceptive and anti-inflammatory effect, in addition to the suppression of B and T lymphocyte response and nitric oxide production, suggested the therapeutic potential of the genus in controlling exacerbated cellular and humoral immune response in autoimmune diseases and chronic inflammatory processes [51,52]. In another study, antinociceptive activity was attributed to geranylgeraniol and the diterpene 6α,7β-dihydroxyivouacapan-17 α-methyl-oate isolated from the crude seed extract [50]. Analysis of the hydroethanolic extract also demonstrated anti-nociceptive activity in acute and chronic pain models [53].

The oleoresins extracted from the fruit include a blend of lipophilic molecules, including the volatile and non-volatile fractions, while their essential oils are made up of volatile lipophilic substances with antispasmodic and anti-inflammatory actions [41,45,54,55]. However, their therapeutic use is still limited by poor water solubility, which results in low bioavailability and impairs clinical application. To overcome these problems, formulations using micro- and nanotechnology-based systems are being developed (Fig. 1) [56].

Particulate nanocarriers can be used to facilitate the dispersion of lipophilic compounds in water, the encapsulation of hydro and/or lipophilic compounds, protection of the encapsulated compound against degradation, modification of the drug pharmacokinetics, increase in therapeutic efficiency, [57–61]. Recently, studies have shown the promising capacity of micro and nanostructured systems as a delivery platform for vegetable derivatives extracted from the species of the genus *Pterodon,* implying the possible extension of this approach to other bioactive molecules from the same genus.

2. *Pterodon* genus

The plants of the genus *Pterodon* (family Leguminosae/Fabaceae) are native to Brazil and popularly known as “Sucupira-branca” or “Faveiro”, classified into four species: *P. emarginatus* Vogel (synonymy *Sweetia inornata* Mohlenbr.; *Acosmium inornatum* (Mohlenbr.) Yakovlev; *P. polygalaeflorus* (Benth)); *P. pubescens* (Benth.) Benth; *P. abruptus* (Moric.) Benth. (synonymy *Commilobium abruptum* Moric.); *P. apparicioi* Pedersoli, where

the last two are endemic [53,62]. The genus *Pterodon* comprises aromatic trees growing 6–18 m tall and may have alternating or opposite leaflets. Their flowers may be pink or violet with cryptosmara type fruits with well-developed wings, or not. Present in several Brazilian phytogeographic domains, the species are widely distributed in the various North regions (Rondônia e Tocantins), Northeast (Bahia, Ceará, Maranhão e Piauí), Midwest (Distrito Federal, Goiás, Mato Grosso do Sul e Mato Grosso), and Southeast (Minas Gerais e São Paulo) [24, 62].

The literature reports that oils and extracts obtained from fruit or seeds of *Pterodon* genus have a large array of active compounds and are recognized for their therapeutic properties, being widely used in popular medicine [24,49]. Furthermore, a growing scientific interest is observed not only in biological applications and activities, but also in a search for a renewable source of the sample, the seeds, and fruit of *Pterodon* species, in which the supply of drug, extracts or fractions would not be limiting. Moreover, use of native materials is sustainable and may improve ecological conservation efforts.

2.1. Phytochemicals

Phytochemical investigations on the extracts and oil of the fruits and seeds of the *Pterodon* species revealed the presence of compounds such as saponins, phenolics, and terpenes [63,64]. There are several papers referring also to the isolation of di- and sesquiterpenes such as specific compounds of interest within this genus, according to their displayed effects and probably related to biological activities [46,65]. Since the various substances in the class of terpenes are derived from mevalonic acid, their molecular structures are composed of variations of isoprene units (Fig. 2a). Diterpenes contain four isoprene units in their basic structure and may be linear (i.e., geranylgeraniol) (Fig. 2b) or cyclic with vouacapanic structure (also referred to as furan diterpenes) (Fig. 2c) [66].

Other constituents, still of the terpene class, that have been identified as major components in the genus include the sesquiterpenes, with potential antioxidant activities and anti-inflammatory properties [36,45, 53,67]. Compounds from the essential oils of *P. polygalaeflorus* seeds, with a basic structure of three isoprene units such as β-elemene, β-caryophyllene, and α-humulene (Fig. 3) are associated with anti-nociceptive, anti-inflammatory, and antispasmodic effects [41,55,68].

2.2. Therapeutic properties

Although the biological effects of this genus are accepted, there is a lack of analytical methodologies to isolate and quantify furan diterpenes compared to sesquiterpenes. In this scenario, there remains a need to better understand the effects of this complex mixtures. Hydroalcoholic extracts from seeds of *Pterodon pubescens* show an anti-arthritic effect related dependent on the presence of furan diterpenoids and sesquiterpenes [69–71]. Further biological activities were presented for oleaginous extracts obtained from *Pterodon*: antinociceptive [50,51,63,72], anti-inflammatory [23,37,42,73], antileishmanial [31] and antimicrobial [30,74]. Some of the bioactive molecules such as β-caryophyllene and β-elemene are reported as major constituents in the essential oils of *P. emarginatus* comprising ~35% and 17%, respectively, depending on the plant collection site [34,40,75].

Possible therapeutic targets of these compounds seem associated with suppression of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and cell adhesion molecules (MCP-1) [76–78].

In the 1960s, studies of the genus *Pterodon* started when Mors and colleagues demonstrated the chemoprophylactic efficacy of the *P. pubescens* fruit essential oil against *Shistosoma mansoni* cercariae [79]. Later, geranylgeraniol and 14,15-epoxigeranylgeraniol were isolated from the fruits of *P. pubescens* crude oil and the latter demonstrated prophylactic action against the trematode that causes schistosomiasis, by inhibiting the penetration of cercariae into the skin [80].

Subsequently, studies revealed other activities such as the analgesic effect of oleaginous extracts obtained from *Pterodon* species [81–83]. Vouacapan derivatives 6α-7β-dihydroxyvouacapan-17β-oate [81], 6α, 7β-Diacetoxyvouacapane [39] and 6α-7β-Dihydroxyvouacapan-17β-oic acid (DHVA) [43] were previously associated with this activity via activation of the catecholaminergic system or the involvement of central and peripheral opioidergic mechanisms [72,81]. Oral administration of different doses of DHVA (50 and 100 mg/kg) inhibited the second phase of nociceptive behavior of the formalin test, which is dependent on peripheral inflammation and changes in central processing [43,84]. However, there is no evidence that DHVA has any central anti-nociceptive activities. Other than the vouacapan derivatives, linear diterpenes geranylgeraniol and farnesol seem also to contribute to their analgesic actions, through modulation of inflammation [82].

The hexane and methanol extracts of the fruits and seeds of *Pterodon polygalaeflorus* showed larvicidal activity against *Aedes aegypti* [47]. In this study, hexane extracts showed the best activity, which could be related to furanic diterpenes such as methyl 6α,7β-dihydroxyvouacapan-17β-oate, 6β-hydroxyvouacapan-7β, 17β-lactone, 6α-acetoxyvouacapane and DHVA [47,85]. Studies of antiproliferative activities in tumor cells of crude extracts of *Pterodon* seeds also were performed [39,49,86]. Furan diterpene rich fractions were able to induce DNA fragmentation, cell cycle arrest in the G1 phase, change in cyclin D1 and E2-expressing levels, increased cytochrome C release, and apoptosis induction in tumor cells [87,88].

The bioactive molecules of the genus *Pterodon* present in extracts, fractions, as well as the isolated compounds of the species are mostly substances with large hydrocarbon chains of low polarity with enormous structural diversity (Figs. 2 and 3), features that can limit bioavailability. To circumvent this problem, development of pharmaceutical nanotechnology-based formulations has been carried out [89]. Delivery systems from bioactive natural products are considered promising to increase therapeutic efficacy, mask the flavor of plant-derived product and protect it from possible degradation [90–92].

3. Nanotechnology as a drug delivery strategy for encapsulating derivatives from the genus *Pterodon*

Nanotechnology is the manipulation and control of matter on the nanoscale dimension using scientific knowledge [93]. It can be applied in several areas since it is a multidisciplinary

field, including industrial and biomedical applications [94–96]. One significant challenge in developing pharmaceutical products is low water solubility and limited cellular permeability. This limitation can be overcome using nanosystems, exemplified by such marketed products as the liposomal formulations encapsulating the antitumor drugs daunorubicin and cytarabine (Vyxeos®), doxorubicin (Doxil®), vincristine sulfate (Marqibo®), irinotecan (Onivyde®) or antifungal amphotericin (AmBisome®, Abelcet®, Amphotec®), as well as the polymer-based nanoparticles for encapsulating triptorelin (Trelstar™), certolizumab pegol (Cimzia®) and estradiol (Estrasorb®) formulations indicated to treat prostate cancer, moderate vasomotor symptoms and autoimmune inflammatory diseases, respectively [97,98].

Liposomes and polymer-based nanoparticles are the most advanced in terms of clinical translation, cancer therapy being the main application, which may reflect both the levels of funding in the area as well as the suitability of nanocarriers for the drug delivery of antineoplastic. In addition to the encapsulation of drug molecules, research has shown that lipid-based nanoparticles are interesting strategies for the encapsulation of oligonucleotides (RNA, mRNA, siRNA, and DNA) for the treatment and prevention of various diseases [99,100]. Recently, there was FDA approval for Onpattro®, consisting of siRNA encapsulated in lipid nanoparticles for the treatment of polyneuropathy in adults with hereditary transthyretin-mediated amyloidosis [101,102]. Given the current situation regarding the SARS-CoV-2 pandemic scenario, the successful development and fast-tracking of nanotechnology-based vaccines as the delivery vehicle of messenger RNA (mRNA) and DNA have shown notable implications for the future of nanotechnology-enabled for drug and gene delivery. The safety and efficacy data of these nanosystems already available on the market can supply the foundation for the clinical translation on future therapeutic applications. Although each formulation has its challenges to face and overcome [103].

As a drug transport and delivery system, nanocarriers in medicine are colloidal systems that contain an encapsulated active pharmaceutical ingredient (API), integrated into the particle core, or matrix, conjugated on the nanoparticle surface [104]. They can be used as a platform for the diagnosis, prevention, and/or treatment of several diseases [105–107]. Different systems can be used to encapsulate bioactive compounds. Due to their small size and the large surface area, leading to improved pharmacokinetics and site-specific delivery, nanoscale particles have shown promising drug delivery properties [104, 108]. In general, their applications aim to increase a drug’s therapeutic index and safety profile, lowering the required doses used to achieve effective therapy. They, also, can be used to protect unstable substances in the face of early degradation or against possible instabilities in the biological environment. Furthermore, sustained drug release and increased cellular uptake are often associated with the use of nanosystems [89,109].

Nanostructured systems can be categorized as metallic, lipid, or polymeric [110]. Metallic nanoparticles have a core composed of alkali and noble metals [61,111]. They can be classified as hard-nanoparticles whose central core is hardened and may limit drug-loading/appending capacity to the particle’s surface. Soft-nanoparticles refer to those materials whose central core is efficient for drug-loading and provide structural flexibility [112]. The polymeric and lipidic nanoparticles have flexible cores which can deform temporarily by

stress or contact with surfaces [113]. Polymer-based nanoparticles are colloidal particles such as nanocapsules, and nanospheres where the drug can be encapsulated or adsorbed to the polymer [114,115]. While lipid-based systems consist of a lipidic dispersion stabilized by surfactants (phospholipids, proteins, polysaccharides or minerals) and can be represented by liposomes, nano, or microemulsions, nanostructured lipid carriers [116].

They can also be classified as passive or active targeting depending on how they target the desired tissue. In passive targeting, drug-loaded nanocarriers remain sufficiently long in circulation to accumulate in a desired tissue contingent on properties like size, pH, temperature, and charge [117,118]. Drug accumulation in areas with leaky vasculature i. e., tumors, is also exploited for passively targeting [119,120]. The aim is to get selective delivery of drugs into the site of action and low systemic toxicity. Alternatively, in the active targeting (or ligand-based targeting), a biological marker is attached to the nanocarrier surface to be recognized by receptors expressed in the target cell surfaces [119,121]. This strategy is expected not only to improve the affinity and precision of the nanocarriers to the target cells/tissue but also to increase cell uptake [122,123]. Active targeting can lead to better therapeutic effects. Some studies demonstrated that folate receptor–targeted liposomes loaded with antitumor drugs inhibited tumor growth [124,125]. Liposomal formulations showed greater efficacy in MDA-MB-231 and 4T1 mouse models of metastatic breast cancer compared to individual components or current conventional formulations. Highlighting the efficiency of using active targeting for recognition, retention, and cell uptake after accumulation in the target region [126–129]. The development of receptor-targeted systems could, therefore, significantly improve the delivery efficiency of drug-loaded nanocarriers.

For the administration of bioactive compounds from plants, nanosystems have been studied [130]. However, encapsulation of compounds and derivatives from the genus *Pterodon* has produced twenty-three (23) types of formulations that have been reported in the literature. As shown in Fig. 4, nanoemulsions and microemulsions are the most prevalent, followed by polymeric particulate systems, magnetic/metallic, and nanoparticles nanostructured lipid carriers.

Throughout the literature, different combinations of drugs/bioactive ingredients of *Pterodon* spp. loaded in drug-delivery systems can be found and are listed in Table 1.

3.1. Micro and nanoemulsions

Nanoemulsions are colloidal thermodynamically unstable dispersions of oil in water (O/W) or water in oil (W/O) stabilized by an interfacial film of surfactant molecules and sometimes co-surfactants [150–152]. Microemulsions can be differentiated as a colloidal thermodynamically stable dispersion. These nanosystems have the advantage of transporting high loads of lipophilic substances and also protect the encapsulated bioactives from hydrolysis, oxidation, or enzymatic degradation [153]. The main interest for using drug delivery systems based on microemulsions or nanoemulsions is to increase bioactive bioavailability [154,155]. This incorporation can be accomplished through several methods, classified into two primary categories: high-energy and low-energy methods (Fig. 5). Nanoemulsions require the input of some external energy to convert the separate immiscible components into a dispersion. High-energy methods supply intense forces that disrupt and

intermingle the oil and water phases resulting in tiny droplets with high kinetic energy. Mechanical devices such as ultrasonication or high-pressure homogenizers are generally used for nanoemulsion preparations [151,156]. Nanoemulsions formulated through high-energy methods can therefore achieve high stability and small particle size. In contrast, low-energy methods take advantage of the intrinsic physicochemical properties of formulation components that require a little addition of external energy to generate droplets. Phase inversion emulsification (emulsification methods) and self-emulsification are examples of low-energy approaches for the formation of micro and nanoemulsions. In principle, the process consists of mixing two liquid phases, one oily phase containing hydrophilic surfactant (plus drug) and an aqueous phase. When these two liquids are brought into contact, the surfactant molecules rapidly diffuse from the oily phase to the aqueous phase, which causes turbulence creating nano-sized emulsion droplets [154]. Currently, there is a focus on producing nano or microemulsions using low-energy methods once they are considered energetically efficient. In addition, it has a simple implementation and does not require sophisticated and expensive equipment [157].

Once the thermodynamic instability of nanoemulsions is dependent on the preparation method, its optimization appears to be of fundamental importance for the development of successful delivery systems [156] and can lead to safer and more environmentally friendly practices.

Nanoemulsion is also an alternative for the delivery of hydrophobic compounds [158]. In order to increase the pharmacological efficacy of oily extracts from the genus *Pterodon,* several nanoemulsions (NE) have been developed. Among them, NE of the essential oil extracted from *P. emarginatus.* In this context, a study proposed the development of NE (O/W) with essential oils from *P. emarginatus* [131]. NE with the best results were prepared with essential oil and polysorbate 80 (1:1) in concentrations of 0.25% (wt/wt), using a simple organic solvent-free, low-energy method. NE containing essential oil from *P. emarginatus* fruits were able to induce mortality in *Aedes aegypti* larvae. This larvicidal activity may be associated with β-caryophyllene, the main compound corresponding to 25.8% of the relative percentage in the oil. Valentim et al. [135] evaluated the *in vitro* antiparasitic activity of NE containing essential oil of *P. emarginatus* against monogenic parasites of the type *Anacanthorus spathulatus, Notozothecium janauachensis,* and *Mymarothecium boegeri* that usually infect the fish *Colossoma macropomum.* The *in vitro* results showed that NE containing the essential oils at concentrations from 100 to 600 mg/L had 100% antiparasitic activity. As the main constituents present in the essential oil of *P. emarginatus* are the compounds β-elemene, β-caryophyllene, and α-humulene, we can imply that they are responsible for biological activity. Recently, NE loaded *P. emarginatus* essential oil demonstrated high kinetic stability and was non-irritating, estimated by HET-CAM [40]. The results of this study can serve as a lead in determining *in vivo* therapeutic properties of this nanoformulation.

The amber-colored oleoresin from *P. emarginatus* has been widely investigated, where the main components include the volatile essential oils made up of a mixture of terpenoids, e.g., the diterpenes with vouacapan skeleton and the non-volatile components [132]. Recent studies have focused on the development of NE for carrying this oleoresin (NE

P. emarginatus oleoresin) for larvicidal applications against *Aedes aegypti* and *Culex quinquefasciatus,* the main vector of dengue and lymphatic filariasis, respectively [45,133]. The NE were developed using a simple low-energy method with or without heating in solvent-free conditions, remaining stable during storage at room temperature when protected from light [45,132,133]. The formulations proposed in these studies for encapsulation of oleoresin showed activities (at 250–12.5 ppm, relative to oleoresin) against A. *aegypti* having a possible mechanism through the reversible inhibition of acetylcholinesterase [45]. Larvicidal activity against *Culex quinquefasciatus,* indicated morphological changes. However, unlike the larvicidal mechanism of action presented for *A. aegypti,* NE *P. emarginatus* oleoresin does not seem to inhibit acetylcholinesterase in *C. quinquefasciatus* larvae, and further studies are needed to evaluate possible mechanisms of action. In addition to evaluating the activity of a new product, it is essential to assess toxicological profiles, in this case, ecotoxicological risks. Exposing NE *P. emarginatus* oleoresin to an aquatic ecosystem using *Chlorella vulgaris* as a biological indicator, showed this formulation is potentially ecofriendly and non-toxic [133].

Recently, NE prepared with oleoresin from the fruits of *P. emarginatus* showed antioxidant and chemoprotective activity, at 10 μg/mL, against ultraviolet (UV) radiation to human keratinocytes. These activities were related to the presence of phenolic compounds and terpenes present in the extracts of *P. emarginatus.* In parallel to the antioxidant effects, the NE managed to modulate the inflammatory profile of epithelial cells. A reduction in the levels of pro-inflammatory cytokines, IL-6 and IL-8, was observed in keratinocytes after UV irradiation [134]. Despite the high energy emulsification method and heating (at 65 °C) used to produce the nanoformulation, the oil activity was preserved.

The anti-inflammatory effects of *P. emarginatus* oleoresin from fruits Kawakami et al. [136] was evaluated with the topical use of NE oleoresin at 20% (wt/wt) in combination with intraperitoneal (i.p.) meglumine antimoniate in the treatment of lesions caused by *Leishmania (Leishmania) amazonensis.* The results demonstrated the effectiveness of the proposed combination in reducing the parasitic burden and the levels of cytokines (IFN-γ and IL-10) in the lesion. In a study reported by Santos et al. [137] extracts from the fruits of *P. pubescens* presented antileishmanial activity and the nanoemulsions from the optimized extracts were proposed to increase the activity and reduce possible toxicities. The extraction method influenced the pharmacological activities of the extracts (IC_{50}: 40.7 ± 2.9 μg/mL for hexane extract and IC_{50}: 33, 8 ± 4,6 μg/mL for supercritical fluid extract). Although both extracts have high cytotoxicity, supercritical extracts were more effective, showing superior inhibition against L. *amazonensis* promastigotes and amastigotes than extracts obtained by conventional methods. This fact is attributed to the high content of the geranylgeraniol derivative in supercritical extracts. Nanoemulsions showed a better index of selectivity and significant activity against parasite amastigotes *Leishmania amazonensis* (IC_{50}: 2.7 ± 0.1 μg/mL for hexane extract nanoemulsion and IC_{50}: 1.9 ± 0.3 μg/mL for supercritical fluid extract nanoemulsion). The findings of this study show that the developed NE promotes a drastic decrease in the IC_{50} and increase in the selectivity index [137]. In the search for an efficient topical application system, the incorporation of hyaluronic acid in NE with *P. pubescens* fruit extract-loaded was also evaluated and showed an improvement

of rheological properties. The addition of the cross-linked biomaterial resulted in increased viscosity and stability, which might facilitate topical applications [141].

Nanoemulsions containing optimized *P. pubescens* ethanolic extracts of the fruits were developed by Hoscheid et al. [138]. To assess their efficiency and safety, another study by the same group [139], evaluated the anti-inflammatory activities of NE in a model of carrageenan-induced peritonitis. The NE containing ethanolic extracts of *P. pubescens* showed a significant inhibitory effect on leukocyte migration, even after 1 year of storage, indicating potential use in anti-inflammatory therapies, as well as in the treatment of arthritis [142]. The anti-inflammatory potential of the oil extracted from the fruits of *P. emarginatus* and encapsulated in microemulsions was evaluated in the ear edema model induced by the topical application of croton oil [140]. Both the oil extracted and the proposed microemulsion system showed anti-inflammatory potential. However, the microemulsion was more efficient, possibly due to dermal or transdermal permeability improvements [159].

Fundamental differences between micro and nanoemulsion surround the free energy of the system, giving them distinct characteristics in preparation, formulation and stability [160]. However, the use of microemulsions for bioactive compound delivery can be limited by the high concentrations of surfactants, since these agents, at certain levels, might be irritatants [161,162]. On the other hand, nanoemulsions can be potential alternatives in this case since lower concentrations of surfactant are needed when compared to microemulsions [163].

3.2. Polymeric particles

Polymeric particles have been extensively researched as delivery systems. Data in the literature have shown that such systems can modify pharmacokinetics and improve the therapeutic index of many drugs [164]. Some of the advantages of using polymeric systems include easy production, the facility to obtain a solid form that is more stable and marketable, controlled and sustained drug release, ability to modify surfaces with ligands for targeted drug delivery [165]. Differences between micro and nanoparticles relate to their size in micrometers and nanometers, respectively. For structural organization, they can be classified as spheres and capsules. The spheres are formed by a polymeric matrix, where the lipophilic and/or hydrophilic drug can be retained (solubilized or dispersed). The capsules are vesicular systems in which a polymeric wall surrounds the oily liquid core. In this case, the lipophilic drug is usually dissolved in the core, but may also be adsorbed to the polymeric surface [166,167].

Countless synthetic or natural polymers can be used for the development of polymeric nanoparticles. The release profile of the compound can be modulated according to its hydro and lipophilic properties and the nature of the polymers used in the development of the systems [168, 169]. Natural polymers, such as polysaccharides e.g., chitosan, dextran, are well known for their benefits in biodegradability and their negligible toxicity. On the other side, customizable degradation rates and physical and mechanical characteristics benefit synthetic polymers compared to natural polymers. The polymers most commonly used in the production of these carriers are aliphatic polyesters such as polyglycolic acid (PGA), polylactic acid (PLA), poly-lactic-co-glycolic acid (PLGA), and poly--ɛ-caprolactone (PCL) due to biocompatibility and biodegradability [170, 171].

In order to produce microcapsules, the most common techniques used for encapsulation of oils are spray-drying and coacervation [172, 173]. Spray-drying is well-established to produce microparticles by atomizing the liquid suspension into a fine spray-dried by a stream of hot air. This method provides stable dehydrated products in the form of fine powders [174]. The principle behind the coacervation process involves the precipitation of polymers around of active compound, thus encapsulating it. With specific environmental influence (ionic strength, pH, or temperature variation), the liquid phase separates from the polymer-rich (coacervate) phase, forming microspheres or core-shell structured microcapsules [174,175]. This method offers an advantage for encapsulating heat-sensitive compounds. However, depending on the polymer used, a high amount of organic solvent might be required, requiring subsequent evaporation from the product [176,177]. In some cases, the encapsulation by the spray-drying process may be preferred to the coacervation method, as no organic solvents are needed within the preparation and is associated with low process costs allowing large-scale production in a continuous mode [177]. Different polymeric systems were developed from natural or synthetic polymers for the encapsulation of phytochemicals or plant extracts of Pterodon species (Fig. 6), in search of potential therapeutic interventions for future use in many diseases.

The first study to develop polymeric particulate systems employing derivatives of the genus *Pterodon* was reported by Servat et al. [143]. Microcapsules were produced by spray-drying of the biopolymers maltodextrin and gum arabic and the crude extract or vouacapan mixture (6α-hydroxy-7β-acetoxy-vouacapan-17β-oate methyl ester and 6α-acetoxy-7β-hydroxy-vouacapan-17β-oate methyl). Antinociceptive activity after i.p. administration of microcapsules with the crude extract or the vouacapan mixture was confirmed. Subsequently, a study by Alves et al. [44] evaluated the influence of different spray-drying parameters (as dryer inlet and flow injection) and excipient proportions on the production and the stability of microcapsule produced with *P. emarginatus* essential oil. Thus, the proposed system produced microcapsules around 5 μm with encapsulation efficiency higher than 90% and increased stability, in addition to solving the inconvenience of poor water solubility [44,143]. In another study, Reinas et al. [90] microcapsules with oleaginous fractions were obtained from an alcohol extract from the fruits of *P. pubescens* using alginate/chitosan polymers of different molecular weights. Diameters of the microcapsules were between 0.4 and 1.0 μm. The best formulation prepared with alginate and low-molecular-weight chitosan presented high encapsulation efficiency of about 99,5% for vouacapanes methyl 6α-acetoxy-7β-hydroxyvouacapan-17β-oate and methyl 6α-hydroxy-7β-acetoxyvouacapan-17β-oate. Furthermore, *in vitro* release profile of the vouacapanes-loaded microcapsules was close to 75% (acid pH) after 24 h. Recently, PCL-based nanofibers associated with the ethanolic extracts from *P. pubescens* fruits were developed and showed potential *in vitro* activity in wound-healing assays. The extract could inhibit acute inflammatory actions attributed to the presence of voaucapans, limiting the phases of pain response and edema formation [144].

3.3. Magnetic and metallic nanoparticles

Among the various nanosystems, magnetic iron oxide nanoparticles stand out for their high surface area and specific properties related to their magnetism [178,179]. Various

methods have been reported for the synthesis of iron oxide magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) nano-particles. The most common include sol-gel synthesis, co-precipitation, micro-emulsion, and hydrothermal synthesis. However, co-precipitation has advantages of low cost, high product purity, and organic solvent-free conditions, presenting great potential for applications in several technological areas [180].

Silveira et al. [145] proposed the development of maghemite nano-particles conjugated with *sucupira* seed resins produced by co-precipitation methods, without the need for expensive equipment or organic solvents. Molecular traces of iron oxide in the resins extracted from *sucupira* seeds expressed semiconductor characteristics. This system could be further investigated regarding more improved preparation methods and characterization [145]. In addition, the potential applications of maghemite nanoparticles directed against a specific target with the use of an external magnetic field combined with bioactive sucupira resin are of potential interest [181]. More studies are needed on the phytochemical characterization of the resins extracted from the sucupira seeds and the development of colloidal systems with ideal physicochemical characteristics for application *in vivo* [182,183]. Preparation of promising delivery systems phytochemicals-based or plant extracts have also been employed successfully to generate metal nanoparticles with enhanced antimicrobial property (Fig. 7) [184,185]. Within this context, recently Oliveira et al. [146] synthesized silver nanoparticles using aqueous extracts of *P. emarginatus* (AgNPs-PE). Similarly, Toledo et al. [147] demonstrated bactericidal and fungal activity of AgNPs-PE when associated with 1% gentamicin sulfate (AgNPs-PEG) and hyaluronic acid (AgNPs-PEG-AH2).

3.4. Nanostructured lipid carriers (NLCs)

NLCs are systems formed by mixing solid and liquid lipids (oils), generating a less structured lipid matrix with imperfections that lead to greater accommodation of bioactive compounds, stabilized in water solution by surfactants [186]. The NLCs have been developed to enhance the encapsulation efficiency and prevent the expulsion of the drug during storage, a condition that usually can occur with solid lipid nanoparticles [187]. Its advantages compared to other nanosystems include the absence of organic solvents for their production and the ability to modulate the release profile of the encapsulated bioactive compound [188]. Furthermore, lipid nanocarriers can be produced with natural lipids that have the advantage of inherent biological activity [189]. Developed as a promising alternative for liposomes and nano-emulsions, NLCs show advantageous features such as the use of low-cost excipients, ease of preparation, and high-scale production [190]. In this process, different methods have been developed and modified to produce NLCs under stable conditions, capable of reaching the specific target. In general, the most common methods used to manufacture these nanosystems can be divided into three different approaches. The first involves high-energy methods such as high shear homogenization and/or ultrasound techniques performed at elevated temperatures (hot homogenization) or below room temperature (cold homogenization). This approach has the advantage of being a highly effective dispersion technique for large-scale production. The cold homogenization further includes advantages as an absence of drug degradation by temperature or crystalline modification. The second approach involves low-energy methods, in which the commonly used technique is microemulsion formation. The advantage of this method is producing

NLCs spherical and narrow in size [191]. The solvent emulsification-evaporation technique is a third approach for obtaining NLCs [191]. The technique consists of mixing an organic containing oil phase (liquid lipid + solid lipid) and drug dissolved in an organic solvent (water-immiscible) with an aqueous phase. This process allows the formation of nanodispersions, followed by evaporating the organic solvent causing precipitation of lipid nanoparticles in the aqueous phase. Through this method, small and monodisperse particles are obtained with high encapsulation efficiency [192]. However, the drawback of the method is the use of organic solvents, potentially leading to toxicity issues [191].

Outuki et al. [148] optimized the development of NLCs containing *P. pubescens* fruit oil that provided promising activities against human colon adenocarcinoma cell line (HT-29) *in vitro.* In this study, the NLCs formulation containing 5% Precirol® ATO 5, 0.5% P80H, 2.5% PEG-40H castor oil as an aqueous surfactant, and 2% *P. pubescens* oil presented the best physicochemical characteristics. The authors showed that NLC formulations encapsulating *P. pubescens* oil were more effective against HT-29 cells when compared to the free oil, associating the efficiency improvement with the higher cellular uptake of the NLCs. Therefore, a well-designed controlled release system may enhance target specificity, optimizing the activities of compounds perhaps implying further application in colorectal cancer therapy.

The essential oils from fruits of the genus *Pterodon* was also encapsulated in NLCs by [149]. The optimized NLCs in this study consisted of 0.5% (wt/vol) essential oil of *Pterodon,* 4.5% (wt/vol) of glycerol monostearate as a solid lipid, and 1.4% (wt/vol) polyethylene glycol succinate D-α-tocopherol as surfactant. Using Franz diffusion cells, the release kinetics followed first-order, where the variation in concentration over time depends only on the concentration of sucupira oil encapsulated in the NLCs. Additional bioavailability studies are still required, in addition to *in vivo* efficacy.

The development of *Pterodon* genus-derived bioactive-loaded NLC has been extensively investigated showing promising results as drug delivery systems for the treatment of various diseases (Fig. 8).

4. Conclusion

The search for new therapeutic alternatives using flora provides a valuable outlet for new drug discovery in the pharmaceutical industry. However, many new drug molecules have poor water solubility. Overcoming such solubility and/or permeability barriers can be achieved using drug delivery systems such as nano- and micro- structured systems. In this review, we stress the capacity for particulate carriers to encapsulate vegetal derivatives, and detail how their use has shown promising biological activities. This serves to highlight the benefits of encapsulating extracts, oils, and bioactive compounds of the genus *Pterodon* in lipid, polymeric, and hybrid diverse particulate systems with desired performance and functionality. However, such approaches are mostly at the fundamental research stage still focused on the development of micro and nanostructured systems to overcome some potential challenges related to stability, solubility, and bioavailability. Therefore, there are currently no Pterodon genus-derived encapsulated formulations in clinical trials or

commercially available. Although many different combinations of drug carriers and extracts, oils, and bioactive compounds of the genus Pterodon are currently being developed. Further related to the potential of *Pterodon* genus compounds, there is a relative dearth of information about their mechanisms of action and toxicities. Even though particulate carriers have been studied with respect to their application of the genus *Pterodon,* there is a requirement for more robust *in vivo* studies. These could provide a platform for further development of safe and effective therapies using these natural product extracts.

Acknowledgments

The authors are grateful to Fundação de Amparo à Pesquisa do Estado do Amapá (FAPEAP/Decit/SCTIE/MS CNPq/SESA – Brazil - Process nº 250.203.022/2021), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq – Brazil), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES – Brazil), and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG – Brazil) for their financial support. Further supported (DMT) by grants from the National Institutes of Health (NCRR P20RR024485 - COBRE in Oxidants, Redox Balance and Stress Signaling) and from the South Carolina Centers of Excellence program. Some of the research was conducted in a facility constructed with the support from the National Institutes of Health, Grant Number C06 RR015455 from the Extramural Research Facilities Program of the National Center for Research Resources.

References

[1]. Fabricant DS, Farnsworth NR, The value of plants used in traditional medicine for drug discovery, Environ. Health Perspect 109 (2001) 69–75, 10.1289/ehp.01109s169. [PubMed: 11250806]

[2]. Ho TT, Tran QT, Chai CL, The polypharmacology of natural products, Future Med. Chem 10 (2018) 1361–1368, 10.4155/fmc-2017-0294. [PubMed: 29673257]

[3]. Tanaka N, Kashiwada Y, Phytochemical studies on traditional herbal medicines based on the ethnopharmacological information obtained by field studies, J. Nat. Med 75 (2021) 762–783, 10.1007/s11418-021-01545-7. [PubMed: 34255289] .

[4]. Gurib-Fakim A, Medicinal plants: traditions of yesterday and drugs of tomorrow, Mol. Asp. Med 27 (2006) 1–93, 10.1016/j.mam.2005.07.008.

[5]. W.H.O. WHO, The world medicines situation 2011: traditional medicines: global situation, issues, and challenges, Geneva, 2011, pp. 1–13. ⟨http://digicollection.org/hss/en/m/abstract/Js18063en/⟩. (Accessed 25 March 2021).

[6]. Newman DJ, Cragg GM, Natural products as sources of new drugs from 1981 to 2014, J. Nat. Prod 79 (2016) 629–661, 10.1021/acs.jnatprod.5b01055. [PubMed: 26852623]

[7]. Calixto JB, The role of natural products in modern drug discovery, An. Acad. Bras. Cienc 91 Suppl 3 (2019), 20190105, 10.1590/0001-3765201920190105.

[8]. Atanasov AG, Zotchev SB, Dirsch VM, Orhan IE, Banach M, Rollinger JM, Barreca D, Weckwerth W, Bauer R, Bayer EA, Majeed M, Bishayee A, Bochkov V, Bonn GK, Braidy N, Bucar F, Cifuentes A, D'Onoffio G, Bodkin M, Diederich M, Dinkova-Kostova AT, Efferth T, El Bairi K, Arkells N, Fan TP, Fiebich BL, Freissmuth M, Georgiev MI, Gibbons S, Godfrey KM, Gruber CW, Heer J, Huber LA, Ibanez E, Kijjoa A, Kiss AK, Lu A, Macias FA, Miller MJS, Mocan A, Müller R, Nicoletti F, Perry G, Pittalà V, Rastrelli L, Ristow M, Russo GL, Silva AS, Schuster D, Sheridan H, Skalicka-Woźniak K, Skaltsounis L, Sobarzo-Sánchez E, Bredt DS, Stuppner H, Sureda A, Tzvetkov NT, Vacca RA, Aggarwal BB, Battino M, Giampieri F, Wink M, Wolfender JL, Xiao J, Yeung AWK, Lizard G, Popp MA, Heinrich M, Berindan-Neagoe I, Stadler M, Daglia M, Verpoorte R, Supuran CT, Natural products in drug discovery: advances and opportunities, Nat. Rev. Drug Discov 20 (2021) 200–216, 10.1038/s41573-020-00114-z. [PubMed: 33510482]

[9]. Harvey A, Natural products in drug discovery, Drug Discov. Today 13 (2008) 894–901, 10.1016/j.drudis.2008.07.004. [PubMed: 18691670]

[10]. Newman DJ, Natural products as leads to potential drugs: an old process or the new hope for drug discovery? J. Med. Chem 51 (2008) 2589–2599, 10.1021/jm0704090. [PubMed: 18393402]

[11]. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, Ternml V, Wang L, Schwaiger S, Heiss EH, Rollinger JM, Schuster D, Breuss JM, Bochkov V, Mihovilovic MD, Kopp B, Bauer R, Dirsch VM, Stuppner H, Discovery and resupply of pharmacologically active plant-derived natural products: a review, Biotechnol. Adv 33 (2015) 1582–1614, 10.1016/j.biotechadv.2015.08.001. [PubMed: 26281720]

[12]. Desborough MJR, Keeling DM, The aspirin story - from willow to wonder drug, Br. J. Haematol 177 (2017) 674–683, 10.1111/bjh.14520. [PubMed: 28106908]

[13]. Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, Rosenthal PJ, D'Alessandro U, Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria, Malar. J 10 (2011) 144, 10.1186/1475-2875-10-144. [PubMed: 21609473]

[14]. Pandey N, Pandey-Rai S, Updates on artemisinin: an insight to mode of actions and strategies for enhanced global production, Protoplasma 253 (2016) 15–30, 10.1007/s00709-015-0805-6. [PubMed: 25813833]

[15]. Tamargo J, Delpon E, Caballero R, The safety of digoxin as a pharmacological treatment of atrial fibrillation, Expert Opin. Drug Saf 5 (2006) 453–467, 10.1517/14740338.5.3.453. [PubMed: 16610972]

[16]. Virgadamo S, Digoxin: a systematic review in atrial fibrillation, congestive heart failure and post myocardial infarction, World J. Cardiol 7 (2015) 808–816, 10.4330/wjc.v7.i11.808. [PubMed: 26635929]

[17]. Benini F, Barbi E, Doing without codeine: why and what are the alternatives? Ital. J. Pediatr 40 (2014) 16, 10.1186/1824-7288-40-16. [PubMed: 24517264]

[18]. Reed JW, Hudlicky T, The quest for a practical synthesis of morphine alkaloids and their derivatives by chemoenzymatic methods, Acc. Chem. Res 48 (2015) 674–687, 10.1021/ar500427k. [PubMed: 25730681]

[19]. Bedows E, Hatfield GM, An investigation of the antiviral activity of Podophyllum peltatum, J. Nat. Prod 45 (1982) 725–729, 10.1021/np50024a015. [PubMed: 6298369]

[20]. Choi JY, Hong WG, Cho JH, Kim EM, Kim J, Jung C-H, Hwang S-G, Um H-D, Park JK, Podophyllotoxin acetate triggers anticancer effects against nonsmall cell lung cancer cells by promoting cell death via cell cycle arrest, ER stress and autophagy, Int. J. Oncol 47 (2015) 1257–1265, 10.3892/ijo.2015.3123. [PubMed: 26314270]

[21]. Hughes J, Rees S, Kalindjian S, Philpott K, Principles of early drug discovery, Br. J. Pharmacol 162 (2011) 1239–1249, 10.1111/j.l476-5381.2010.01127.x. [PubMed: 21091654]

[22]. Belinelo VJ, Reis GT, Stefani GM, Ferreira-Alves DL, Piló-Veloso D, Synthesis of 6alpha,7beta-dihydroxyvouacapan-17beta-oic acid derivatives. Part IV: mannich base derivatives and its activities on the electrically stimulated Guinea-pig ileum preparation, J. Braz. Chem. Soc 13 (2002) 830–837, 10.1590/S0103-50532002000600016.

[23]. Carvalho JC, Sertié JA, Barbosa MV, Patrício KC, Caputo LR, Sarti SJ, Ferreira LP, Bastos JK, Anti-inflammatory activity of the crude extract from the fruits of Pterodon emarginatus Vog, J. Ethnopharmacol 64 (1999) 127–133, 10.1016/S0378-8741(98)00116-0. [PubMed: 10197747]

[24]. Hoscheid J, Cardoso MLC, Sucupira as a potential plant for arthritis treatment and other diseases, Arthritis 2015 (2015) 1–12, 10.1155/2015/379459.

[25]. de Moraes WF, Galdino PM, Nascimento MVM, Vanderlinde FA, Bara MTF, Costa EA, de Paula JR, Triterpenes involved in the anti-inflammatory effect of ethanolic extract of Pterodon emarginatus Vogel stem bark, J. Nat. Med 66 (2012) 202–207, 10.1007/s11418-011-0547-5. [PubMed: 21643657]

[26]. Filho RB, Gottlieb OR, Viegas Assumpção RM, The isoflavones of Pterodon pubescens, Phytochemistry 10 (1971) 2835–2836, 10.1016/S0031-9422(00)97301-1.

[27]. Galina E, Gottlieb OR, Isoflavones from Pterodon apparicioi, Phytochemistry 13 (1974) 2593–2595, 10.1016/S0031-9422(00)86942-3.

[28]. Marques DD, Machado MIL, de Carvalho MG, da LA, Meleira C, Braz-Filho R, Isoflavonoids and triterpenoids isolated from Pterodon polygalaeflorus, J. Braz. Chem. Soc 9 (1998) 295–301, 10.1590/S0103-50531998000300014.

[29]. Bustamante KGL, Lima ADF, Soares ML, Fiuza TS, Tresvenzol LMF, Bara MTF, Pimenta FC, Paula JR, Evaluation of antimicrobial activity of crude ethanol extract from the bark of "sucupira

branca" (Pterodon emarginatus Vogel) - Fabaceae, Rev. Bras. Plantas Med 12 (2010) 341–345, 10.1590/S1516-05722010000300012.

[30]. Santos AP, Zatta DT, Moraes WF, Bara MTF, Ferri PH, do M, Silva RR, Paula JR, Chemical composition, antimicrobial activity of essential oil and the occurrence of steroids in the leaves of Pterodon emarginatus Vogel, Fabaceae, Rev. Bras. Farmacogn 20 (2010) 891–896, 10.1590/s0102-695x2010005000052.

[31]. Arrais-Silva WW, Nunes PSG, Carvalho JD, Brune MW, Arrais-Lima C, Batalini C, Preliminary phytochemical and antileishmanial studies of the ethanolic extracts of Pterodon pudescens, Rev. Bras. Plantas Med 16 (2014) 561–565, 10.1590/1983-084X/11_146.

[32]. Campos AM, Silveira ER, Braz-Filho R, Teixeira TC, Diterpenoids from Pterodon polygalaeflorus, Phytochemistry 36 (1994) 403–406, 10.1016/S0031-9422(00)97084-5.

[33]. Miranda MLD, Garcez FR, Abot AR, Garcez WS, Sesquiterpenes and other contituents from leaves of Pterodon pubescens Benth (Leguminosae), Quim. Nova 37 (2014) 473–476, 10.5935/0100-4042.20140065.

[34]. Alves SF, Luiz Borges L, de Paula JAM, Vieira RF, Ferri PH, do Couto RO, de Paula JR, Freitas Bara MT, Chemical variability of the essential oils from fruits of Pterodon emarginatus in the Brazilian Cerrado, Rev. Bras. Farmacogn 23 (2013) 224–229, 10.1590/S0102-695X2013005000016.

[35]. Cabral EC, Sevart L, Spindola HM, Coelho MB, Sousa IMO, Queiroz NCA, Foglio MA, Eberlin MN, Riveros JM, Pterodon pubescens oil: characterisation, certification of origin and quality control via mass spectrometry fingerprinting analysis, Phytochem. Anal 24 (2013) 184–192, 10.1002/pca.2404. [PubMed: 23073895]

[36]. Dutra RC, Pittella F, Dittz D, Marcon R, Pimenta DS, Lopes MTP, Raposo NRB, Chemical composition and cytotoxicity activity of the essential oil of Pterodon emarginatus, Rev. Bras. Farmacogn 22 (2012) 971–978, 10.1590/S0102-695X2012005000042.

[37]. Hoscheid J, Bersani-Amado CA, da Rocha BA, Outuki PM, da Silva MARCP, Froehlich DL, Cardoso MLC, Inhibitory effect of the hexane fraction of the ethanolic extract of the fruits of Pterodon pubescens Benth in acute and chronic inflammation, Evid. Based Complement. Altern. Med 2013 (2013), 272795, 10.1155/2013/272795.

[38]. Oliveira LAR, Oliveira GAR, Borges LL, Bara MTF, Silveira D, Vouacapane diterpenoids isolated from Pterodon and their biological activities, Rev. Bras. Farmacogn 27 (2017) 663–672, 10.1016/j.bjp.2017.05.014.

[39]. Spindola HM, de Carvalho JE, Ruiz ALTG, Rodrigues RAF, Denny C, de IM, Sousa O, Tamashiro JY, Foglio MA, Furanoditerpenes from Pterodon pubescens benth with selective in vitro anticancer activity for prostate cell line, J. Braz. Chem. Soc 20 (2009) 569–575, 10.1590/s0103-50532009000300024.

[40]. Zamora LO, Bezerra DC, de Oliveira HNS, Duarte JL, Guisado-Bourzac F, Chil-Núñez I, da Concepção EC, Barroso A, Mourão RHV, de Faria Mota Oliveira AEM, Cruz RAS, Carvalho JCT, Solans C, Fernandes CP, Preparation of non-toxic nano-emulsions based on a classical and promising Brazilian plant species through a low-energy concept, Ind. Crop. Prod 158 (2020), 112989, 10.1016/j.indcrop.2020.112989.

[41]. Leonhardt V, Leal-Cardoso JH, Lahlou S, Albuquerque AAC, Porto RS, Celedônio NR, Oliveira AC, Pereira RF, Silva LP, Garcia-Teófilo TMN, Silva APFS, Magalhães PJC, Duarte GP, Coelho-de-Souza AN, Antispasmodic effects of essential oil of Pterodon polygalaeflorus and its main constituent β-caryophyllene on rat isolated ileum, Fundam. Clin. Pharmacol 24 (2010) 749–758, 10.1111/j.1472-8206.2009.00800.x. [PubMed: 20015227]

[42]. Santos CBR, da Silva Ramos R, Ortiz BLS, da Silva GM, Giuliatti S, Balderas-Lopez JL, Navarrete A, Carvalho JCT, Oil from the fruits of Pterodon emarginatus Vog.: a traditional anti-inflammatory. Study combining in vivo and in silico, J. Ethnopharmacol 222 (2018) 107–120, 10.1016/j.jep.2018.04.041. [PubMed: 29723629]

[43]. Galceran CB, Sertie JAA, Lima CS, Carvalho JCT, Anti-inflammatory and analgesic effects of 6α,7β–dihydroxy-vouacapan-17β-oic acid isolated from Pterodon emarginatus Vog. fruits, Inflammopharmacology 19 (2011) 139–143, 10.1007/s10787-011-0081-9. [PubMed: 21384179]

[44]. Alves SF, Borges LL, dos Santos TO, de Paula JR, Concepção EC,Bara MTF, Microencapsulation of essential oil from fruits of Pterodon emarginatus using gum arabic and

maltodextrin as wall materials: composition and stability, Dry. Technol 32 (2014) 96–105, 10.1080/07373937.2013.816315.

[45]. Oliveira AEMFM, Duarte JL, Amado JRR, Cruz RAS, Rocha CF, Souto RNP, Ferreira RMA, Santos K, da Concepção EC, de Oliveira LAR, Kelecom A, Fernandes CP, Carvalho JCT, Development of a larvicidal nanoemulsion with Pterodon emarginatus vogel oil, PLoS One 11 (2016), 0145835, 10.1371/journal.pone.0145835.

[46]. Mahajan JR, Monteiro MB, New diterpenoids from Pterodon emarginatus vog, J. Chem. Soc. Perkin Trans 1 (1973) 520–525, 10.1039/p19730000520.

[47]. Pimenta ATA, Santiago GMP, Arriaga ÂMC, Menezes GHA, Bezerra SB, Phytotochemical study and evaluation of larvicidal activity of Pterodon polygalaeflorus Benth (Leguminosae) against “Aedes aegypti”, Rev. Bras. Farmacogn 16 (2006) 501–505, 10.1590/S0102-695X2006000400011.

[48]. Arriaga AMC, de Castro MAB, Silveira ER, Braz-Filho R, Further diterpenoids isolated from Pterodon polygalaeflorus, J. Braz. Chem. Soc 11 (2000) 187–190, 10.1590/S0103-50532000000200015.

[49]. Vieira CR, Marques MF, Soares PR, Matuda L, de Oliveira CMA, Kato L, da Silva CC, Guillo LA, Antiproliferative activity of Pterodon pubescens Benth. seed oil and its active principle on human melanoma cells, Phytomedicine 15 (2008) 528–532, 10.1016/j.phymed.2007.08.003. [PubMed: 17913485]

[50]. Spindola HM, Servat L, Denny C, Rodrigues RA, Eberlin MN, Cabral E, Sousa IM, Tamashiro JY, Carvalho JE, Foglio MA, Antinociceptive effect of geranylgeraniol and 6alpha,7beta-dihydroxyvouacapan-17beta-oate methyl ester isolated from Pterodon pubescens Benth, BMC Pharmacol 10 (2010) 1, 10.1186/1471-2210-10-1. [PubMed: 20055987]

[51]. Coelho LP, Reis PA, de Castro FL, Gayer CRM, da C, Lopes S, da MC, Silva CE, de KC, Sabino C, Todeschini AR, Coelho MGP, Antinociceptive properties of ethanolic extract and fractions of Pterodon pubescens Benth. seeds, J. Ethnopharmacol 98 (2005) 109–116, 10.10l6/j.jep.2005.01.014. [PubMed: 15763371]

[52]. Cardoso KCCSCC, Pinto AC, Marques PR, Gayer CRM, Afel MIR, Coelho MGP, Suppression of T and B cell responses by Pterodon pubescens seeds ethanolic extract (2008) 2308–2313.

[53]. Nucci C, Mazzardo-Martins L, Stramosk J, Brethanha LC, Pizzolatti MG, Santos ARS, Martins DF, Oleaginous extract from the fruits Pterodon pubescens Benth induces antinociception in animal models of acute and chronic pain, J. Ethnopharmacol 143 (2012) 170–178, 10.1016/j.jep.2012.06.020. [PubMed: 22728247]

[54]. de VR, Borges A, Tavares MR, da Silva JH, Tajber L, Boylan F, Ribeiro AF, Nasciutti LE, Cabral LM, de Sousa VP, Development and characterization of poly(lactic-co-glycolic) acid nanoparticles loaded with copaiba oleoresin, Pharm. Dev. Technol 23 (2018) 343–350, 10.1080/10837450.2017.1290107. [PubMed: 28145793]

[55]. Rogerio AP, Andrade EL, Leite DFP, Figueiredo CP, Calixto JB, Preventive and therapeutic anti-inflammatory properties of the sesquiterpene α-humulene in experimental airways allergic inflammation, Br. J. Pharmacol 158 (2009) 1074–1087, 10.1111/j.1476-5381.2009.00177.x. [PubMed: 19438512]

[56]. Armendáriz-Barragán B, Zafar N, Badri W, Galindo-Rodríguez SA, Kabbaj D, Fessi H, Elaissari A, Plant extracts: from encapsulation to application, Expert Opin. Drug Deliv 13 (2016) 1165–1175, 10.1080/17425247.2016.1182487. [PubMed: 27139509]

[57]. Kayser O, Lemke A, Hernandez-Trejo N, The impact of nanobiotechnology on the development of new drug delivery systems, Curr. Pharm. Biotechnol 6 (2005) 3–5, 10.2174/1389201053167158. [PubMed: 15727551]

[58]. Rawat M, Singh D, Saraf S, Saraf S, Nanocarriers: promising vehicle for bioactive drugs, Biol. Pharm. Bull 29 (2006) 1790–1798, 10.1248/bpb.29.1790. [PubMed: 16946487]

[59]. Sahoo SK, Labhasetwar V, Nanotech approaches to drug delivery and imaging, Drug Discov. Today 8 (2003) 1112–1120, 10.1016/S1359-6446(03)02903-9. [PubMed: 14678737]

[60]. Wagner V, Dullaart A, Bock A-K, Zweck A, The emerging nanomedicine landscape, Nat. Biotechnol 24 (2006) 1211–1217, 10.1038/nbt1006-1211. [PubMed: 17033654]

[61]. Yetisgin AA, Cetinel S, Zuvin M, Kosar A, Kutlu O, Therapeutic nanoparticles and their targeted delivery applications, Molecules 25 (2020) 2193, 10.3390/molecules25092193.

[62]. Carvalho CS, Cardoso DBOS, Lima HC, Pterodon in Flora do Brasil 2020, Jard. Botânico Do Rio Janeiro, 2020. (http://floradobrasil.jbrj.gov.br/reflora/floradobrasil/FB29840). (Accessed 25 March 2021).

[63]. Negri G, Mattei R, Mendes FR, Antinociceptive activity of the HPLC- and MS-standardized hydroethanolic extract of Pterodon emarginatus Vogel leaves, Phytomedicine 21 (2014) 1062–1069, 10.1016/j.phymed.2014.04.009. [PubMed: 24854569]

[64]. Vila Verde GM, Barros DA, Oliveira M, Aquino G, Santos DM, de Paula J, Dias L, Piñeiro M, Pereira MM, A green protocol for microwave-assisted extraction of volatile oil terpenes from Pterodon emarginatus Vogel. (Fabaceae), Molecules 23 (2018) 651, 10.3390/molecules23030651.

[65]. Dutra RC, Campos MM, Santos ARS, Calixto JB, Medicinal plants in Brazil: pharmacological studies, drug discovery, challenges and perspectives, Pharmacol. Res 112 (2016) 4–29, 10.1016/j.phrs.2016.01.021. [PubMed: 26812486]

[66]. Dewick P, Medicinal Natural Products: A Biosynthetic Approach, Third, John Wiley & Sons Ltd, Chichester, 2009.

[67]. Donati M, Mondin A, Chen Z, Miranda FM, do Nascimento BB, Schirato G, Pastore P, Froldi G, Radical scavenging and antimicrobial activities of Croton zehntneri, Pterodon emarginatus and Schinopsis brasiliensis essential oils and their major constituents: estragole, trans -anethole, β-caryophyllene and myrcene, Nat. Prod. Res 29 (2015) 939–946, 10.1080/14786419.2014.964709. [PubMed: 25280163]

[68]. Souza ANC, Santos CF, Lopes-Filho LN, Holanda FR, Oliveira AC, Gomes-Vasconcelos YA, Oliveira KA, Ferreira-da-Silva FW, Silva-Alves KS, Leal-Cardoso JH, Essential oil of Pterodon polygalaeflorus Benth attenuates nociception in mice, Br. J. Med. Biol. Res 51 (2018) 1–9, 10.1590/1414-431x20187356.

[69]. Sabino KCC, Castro FA, Oliveira JCR, Dalmau SRA, Coelho MGP, Successful treatment of collagen-induced arthritis in mice with a hydroalcohol extract of seeds of Pterodon pubescens, Phytother. Res 13 (1999) 613–615, 10.1002/(SICI)1099-1573(199911)13:7<613::AID-PTR503>3.0.CO;2-D. [PubMed: 10548757]

[70]. Coelho MGP, Sabino KCC, Dalmau SR, Immunomodulatory effects of sucupira (Pterodon pubescens) seed infusion on collagen-induced arthritis, Clin. Exp. Rheumatol 22 (2004) 213–218. http://www.ncbi.nlm.nih.gov/pubmed/15083889. [PubMed: 15083889]

[71]. Coelho MGP, Marques PR, Gayer CRM, Vaz LCA, Nogueira Neto JF, de KC, Sabino C, Subacute toxicity evaluation of a hydroalcoholic extract of Pterodon pubescens seeds in mice with collagen-induced arthritis, J. Ethnopharmacol 77 (2001) 159–164, 10.1016/S0378-8741(01)00288-4. [PubMed: 11535359]

[72]. Duarte IDG, Ferreira-Alves DL, Veloso DP, Nakamura-Craig M, Evidence of the involvement of biogenic amines in the antinociceptive effect of a vouacapan extracted from Pterodon polygalaeflorus Benth, J. Ethnopharmacol 55 (1996) 13–18, 10.1016/S0378-8741(96)01465-1. [PubMed: 9121162]

[73]. Leal LKA, Ferreira AA, Bezerra G, Matos FJ, Viana GS, Antinociceptive, anti-inflammatory and bronchodilator activities of Brazilian medicinal plants containing coumarin: a comparative study, J. Ethnopharmacol 70 (2000) 151–159, 10.1016/S0378-8741(99)00165-8. [PubMed: 10771205]

[74]. Mendes VS, Sant'Anna JB, Oliveira SCC, Maldonade IR, Machado ER, Inhibitory effects of Pterodon emarginatus bean oil and extract on Staphylococcus aureus, Pharmacogn. Res 9 (2017) 348–353, 10.4103/pr.pr_13_17.

[75]. Dutra RC, Fava MB, Alves CCS, Ferreira AP, Barbosa NR, Antiulcerogenic and anti-inflammatory activities of the essential oil from Pterodon emarginatus seeds, J. Pharm. Pharmacol 61 (2010) 243–250, 10.1211/jpp.61.02.0015.

[76]. Yamaguchi M, Levy R, The combination of catechin, baicalin and β-caryophyllene potentially suppresses the production of inflammatory cytokines in mouse macrophages in vitro, Exp. Ther. Med 17 (2019) 4312–4318, 10.3892/etm.2019.7452. [PubMed: 31007758]

[77]. Liu M, Mao L, Daoud A, Hassan W, Zhou L, Lin J, Liu J, Shang J, β-elemene inhibits monocyte–endothelial cells interactions via reactive oxygen species/MAPK/NF-κB signaling pathway in vitro, Eur. J. Pharmacol 766 (2015) 37–45, 10.1016/j.ejphar.2015.09.032. [PubMed: 26415979]

[78]. Liu M, Chen X, Ma J, Hassan W, Wu H, Ling J, Shang J, β-Elemene attenuates atherosclerosis in apolipoprotein E-deficient mice via restoring NO levels and alleviating oxidative stress, Biomed. Pharmacother 95 (2017) 1789–1798, 10.1016/j.biopha.2017.08.092. [PubMed: 28962084]

[79]. Mors WB, Pellegrino J, Santos Filho MF, Ação profilática do óleo dos frutos de sucupira branca, Pterodon pubescens Benth. contra a infecção pelo Schistosoma mansoni, An. Acad. Bras. Cienc 38 (supl.) (1966) 325–330.

[80]. Mors WB, dos Santos Fo MF, Monteiro HJ, Gilbert B, Pellegrino J, Chemoprophylactic agent in Schistosomiasis: 14,15-epoxygeranylgeraniol, Science 157 (1967) 950–951, 10.1126/science.157.3791.950. [PubMed: 5006418]

[81]. Duarte IDG, Ferreira-Alves DL, Nakamura-Craig M, Possible participation of endogenous opioid peptides on the mechanism involved in analgesia induced by vouacapan, Life Sci. 50 (1992) 891–897, 10.1016/0024-3205(92)90208-7. [PubMed: 1545667]

[82]. Silva MCC, Gayer CRM, Lopes CS, Calixto NO, Reis PA, Passaes CPB, Paes MC, Dalmau SR, Sabino KCC, Todeschini AR, Coelho MGP, Acute and topic anti-edematogenic fractions isolated from the seeds of Pterodon pubescens, J. Pharm. Pharmacol 56 (2004) 135–141, 10.1211/0022357022485. [PubMed: 14980011]

[83]. de Moraes WF, de Matos LG, Mariano Nascimento MV, Realino de Paula J, Bara MTF, Carlos da Cunha L, Valadares MC, Alves Costa E, Anti-inflammatory and anti-nociceptive effects of Pterodon emarginatus stem bark alcohol extract, Pharm. Biol 47 (2009) 146–150, 10.1080/13880200802436117.

[84]. Tølsen A, Berge O-G, Hunskaar S, Rosland JH, Hole K, The formalin test: an evaluation of the method, Pain 51 (1992) 5–17, 10.1016/0304-3959(92)90003-T. [PubMed: 1454405]

[85]. De Omena MC, Bento ES, De Paula JE, Sant'Ana AEG, Larvicidal diterpenes from Pterodon polygalaeflorus, Vector Borne Zoonotic Dis. 6 (2006) 216–222, 10.1089/vbz.2006.6.216. [PubMed: 16796519]

[86]. Euzébio FPG, dos Santos FJL, Piló-Veloso D, Ruiz ALTG, de Carvalho JE, Ferreira-Alves DL, de Fátima Â, Effect of 6α,7β-dihydroxyvouacapan-17β-oic acid and its lactone derivatives on the growth of human cancer cells, Bioorg. Chem 37 (2009) 96–100, 10.1016/j.bioorg.2009.03.004. [PubMed: 19394666]

[87]. Pereira MF, Martino T, Dalmau SR, Albano RM, Ferezou J-P, Costa SS, Coelho MGP, Sabino KGC, Terpenic subfraction of Pterodon pubescens induces apoptosis of K562 leukemic cells by modulating gene expression, Oncol. Rep 25 (2011) 215–221, 10.3892/or_00001063. [PubMed: 21109979]

[88]. Martino T, Pereira MF, Gayer CRM, Dalmau SR, Coelho MGP, Sabino KCC, Antitumor screening of Pterodon pubescens terpenic fraction indicates high sensitivity for lymphocytic leukemia cells, 1547-51, Nat. Prod. Commun 9 (2014), 10.1177/1934578X1400901104.

[89]. Ajazuddin S Saraf, Applications of novel drug delivery system for herbal formulations, Fitoterapia 81 (2010) 680–689, 10.1016/j.fitote.2010.05.001. [PubMed: 20471457]

[90]. Reinas AE, Hoscheid J, Outuki PM, Cardoso MLC, Preparation and characterization of microcapsules of Pterodon pubescens Benth. by using natural polymers, Braz. J. Pharm. Sci 50 (2014) 919–930, 10.1590/S1984-82502014000400028.

[91]. Bonifácio B, Silva P, Ramos M, Negri K, Maria Bauab T, Chorilli M, Nanotechnology-based drug delivery systems and herbal medicines: a review, Int. J. Nanomed 9 (2013) 1–15, 10.2147/IJN.S52634.

[92]. Sun M, Su X, Ding B, He X, Liu X, Yu A, Lou H, Zhai G, Advances in nanotechnology-based delivery systems for curcumin, Nanomedicine 7 (2012) 1085–1100, 10.2217/nnm.12.80. [PubMed: 22846093]

[93]. FDA, Nanotechnology—Over a Decade of Progress and Innovation, A Rep. by U.S Food Drug Adm., 2020, pp. 1–26. ⟨https://www.fda.gov/media/140395/download⟩. (Accessed 29 January 2021).

[94]. Porter AL, Youtie J, How interdisciplinary is nanotechnology? J. Nanopart. Res 11 (2009) 1023–1041, 10.1007/s11051-009-9607-0. [PubMed: 21170124]

[95]. Roco MC, Nanotechnology: convergence with modern biology and medicine, Curr. Opin. Biotechnol 14 (2003) 337–346, 10.1016/S0958-1669(03)00068-5. [PubMed: 12849790]

[96]. Carvalho SG, Araujo VHS, dos Santos AM, Duarte JL, Silvestre ALP, Fonseca-Santos B, Villanova JCO, Gremião MPD, Chorilli M, Advances and challenges in nanocarriers and nanomedicines for veterinary application, Int. J. Pharm 580 (2020), 119214, 10.1016/j.ijpharm.2020.119214. [PubMed: 32165220]

[97]. Lee BK, Yun Y, Park K, PLA micro- and nano-particles, Adv. Drug Deliv. Rev 107 (2016) 176–191, 10.1016/j.addr.2016.05.020. [PubMed: 27262925]

[98]. Farjadian F, Ghasemi A, Gohari O, Roointan A, Karimi M, Hamblin MR, Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities, Nanomedicine 14 (2019) 93–126, 10.2217/nnm-2018-0120. [PubMed: 30451076]

[99]. Scioli Montoto S, Muraca G, Ruiz ME, Solid lipid nanoparticles for drug delivery: pharmacological and biopharmaceutical aspects, Front. Mol. Biosci 7 (2020), 587997, 10.3389/fmolb.2020.587997. [PubMed: 33195435]

[100]. Tenchov R, Bird R, Curtze AE, Zhou Q, Lipid nanoparticles—from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement, acsnano.1c04996, ACS Nano (2021), 10.1021/acsnano.1c04996.

[101]. Thi TTH, Suys EJA, Lee JS, Nguyen DH, Park KD, Truong NP, Lipid-based nanoparticles in the clinic and clinical trials: from cancer nanomedicine to COVID-19 vaccines, Vaccines 9 (2021) 359, 10.3390/vaccines9040359. [PubMed: 33918072]

[102]. Kulkarni JA, Witzigmann D, Leung J, Tam YYC, Cullis PR, On the role of helper lipids in lipid nanoparticle formulations of siRNA, Nanoscale 11 (2019) 21733–21739, 10.1039/C9NR09347H. [PubMed: 31713568]

[103]. Milane L, Amiji M, Clinical approval of nanotechnology-based SARS-CoV-2 mRNA vaccines: impact on translational nanomedicine, Drug Deliv. Transl. Res 11 (2021) 1309–1315, 10.1007/s13346-021-00911-y. [PubMed: 33512669]

[104]. Koo OM, Rubinstein I, Onyuksel H, Role of nanotechnology in targeted drug delivery and imaging: a concise review, Nanomed. Nanotechnol. Biol. Med 1 (2005) 193–212, 10.1016/j.nano.2005.06.004.

[105]. Fornaguera C, García-Celma M, Personalized nanomedicine: a revolution at the nanoscale, JPM 7 (2017) 12, 10.3390/jpm7040012.

[106]. de Barros A, Tsourkas A, Saboury B, Cardoso V, Alavi A, Emerging role of radiolabeled nanoparticles as an effective diagnostic technique, EJNMMI Res. 2 (2012) 39, 10.1186/2191-219X-2-39. [PubMed: 22809406]

[107]. Sharma R, Mody N, Agrawal U, Vyas SP, Theranostic nanomedicine; a next generation platform for cancer diagnosis and therapy, Mini Rev. Med. Chem 17 (2016) 1746–1757, 10.2174/1389557516666160219122524.

[108]. Ashraf MA, Peng W, Zare Y, Rhee KY, Effects of size and aggregation/agglomeration of nanoparticles on the interfacial/interphase properties and tensile strength of polymer nanocomposites, Nanoscale Res. Lett 13 (2018) 214, 10.1186/s11671-018-2624-0. [PubMed: 30019092]

[109]. Bozzuto G, Molinari A, Liposomes as nanomedical devices, Int. J. Nanomed 10 (2015) 975–999, 10.2147/IJN.S68861.

[110]. Ding Z, Sigdel K, Yang L, Liu Y, Xuan M, Wang X, Gu Z, Wu J, Xie H, Nanotechnology-based drug delivery systems for enhanced diagnosis and therapy of oral cancer, J. Mater. Chem. B 8 (2020) 8781–8793, 10.1039/D0TB00957A. [PubMed: 33026383]

[111]. Khan SA, Metal nanoparticles toxicity: role of physicochemical aspects, in: Metal Nanoparticles for Drug Delivery and Diagnostic Applications, Elsevier, 2020, pp. 1–11, 10.1016/B978-0-12-816960-5.00001-X.

[112]. Sangtani A, Nag OK, Field LD, Breger JC, Delehanty JB, Multifunctional nanoparticle composites: progress in the use of soft and hard nanoparticles for drug delivery and imaging, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol 9 (2017), e1466, 10.1002/wnan.1466.

[113]. Papakostas D, Rancan F, Sterry W, Blume-Peytavi U, Vogt A, Nanoparticles in dermatology, Arch. Dermatol. Res 303 (2011) 533–550, 10.1007/S00403-011-1163-7. [PubMed: 21837474]

[114]. Mehanna MM, Mohyeldin SM, Elgindy NA, Respirable nanocarriers as a promising strategy for antitubercular drug delivery, J. Control. Release 187 (2014) 183–197, 10.1016/j.jconrel.2014.05.038. [PubMed: 24878180]

[115]. Rao JP, Geckeler KE, Polymer nanoparticles: preparation techniques and size-control parameters, Prog. Polym. Sci 36 (2011) 887–913, 10.1016/j.progpolymsci.2011.01.001.

[116]. Mishra DK, Shandilya R, Mishra PK, Lipid based nanocarriers: a translational perspective, Nanomed. Nanotechnol. Biol. Med 14 (2018) 2023–2050, 10.1016/j.nano.2018.05.021.

[117]. Fernandes RS, Silva JO, Mussi SV, Lopes SCA, Leite EA, Cassali GD, Cardoso VN, Townsend DM, Colletti PM, Ferreira LAM, Rubello D, de Barros ALB, Nanostructured lipid carrier co-loaded with doxorubicin and docosahexaenoic acid as a theranostic agent: evaluation of biodistribution and antitumor activity in experimental model, Mol. Imaging Biol 20 (2018) 437–447, 10.1007/s11307-017-1133-3. [PubMed: 29043471]

[118]. Cavalcante CH, Fernandes RS, de Oliveira Silva J, Ramos Oda CM, Leite EA, Cassali GD, Charlie-Silva I, Ventura Fernandes BH, Miranda Ferreira LA, de Barros ALB, Doxorubicin-loaded pH-sensitive micelles: a promising alternative to enhance antitumor activity and reduce toxicity, Biomed. Pharmacother 134 (2021), 111076, 10.1016/j.biopha.2020.111076. [PubMed: 33341054]

[119]. Hirsjarvi S, Passirani C, Benoit J-P, Passive and active tumour targeting with nanocarriers, Curr. Drug Discov. Technol 8 (2011) 188–196, 10.2174/157016311796798991. [PubMed: 21513482]

[120]. Miranda SEM, de J, Lemos A, Fernandes RS, de J, Silva O, Ottoni FM, Townsend DM, Rubello D, Alves RJ, Cassali GD, Ferreira LAM, de Barros ALB, Enhanced antitumor efficacy of lapachol-loaded nanoemulsion in breast cancer tumor model, Biomed. Pharmacother 133 (2021), 110936, 10.1016/j.biopha.2020.110936. [PubMed: 33254016]

[121]. Silva ATM, Maia ALC, de Oliveira Silva J, de Barros ALB, Soares DCF, de Magalhães MTQ, José Alves R, Ramaldes GA, Synthesis of cholesterol-based neoglycoconjugates and their use in the preparation of liposomes for active liver targeting, Carbohydr. Res 465 (2018) 52–57, 10.1016/j.carres.2018.06.008. [PubMed: 29944996]

[122]. Allen TM, Cullis PR, Liposomal drug delivery systems: from concept to clinical applications, Adv. Drug Deliv. Rev 65 (2013) 36–48, 10.1016/j.addr.2012.09.037. [PubMed: 23036225]

[123]. Sanna V, Sechi M, Therapeutic potential of targeted nanoparticles and perspective on nanotherapies, ACS Med. Chem. Lett 11 (2020) 1069–1073, 10.1021/acsmedchemlett.0c00075. [PubMed: 32550978]

[124]. Monteiro LOF, Fernandes RS, Castro L, Reis D, Cassali GD, Evangelista F, Loures C, Sabino AP, Cardoso V, Oliveira MC, Branco de Barros A, Leite EA, Paclitaxel-loaded folate-coated pH-sensitive liposomes enhance cellular uptake and antitumor activity, Mol. Pharm 16 (2019) 3477–3488, 10.1021/acs.molpharmaceut.9b00329. [PubMed: 31257891]

[125]. de J, Silva O, Fernandes RS, Ramos Oda CM, Ferreira TH, Machado Botelho AF, Martins Melo M, de Miranda MC, Assis Gomes D, Dantas Cassali G, Townsend DM, Rubello D, Oliveira MC, de Barros ALB, Folate-coated, long-circulating and pH-sensitive liposomes enhance doxorubicin antitumor effect in a breast cancer animal model, Biomed. Pharmacother 118 (2019), 109323, 10.1016/j.biopha.2019.109323. [PubMed: 31400669]

[126]. Monteiro LOF, Fernandes RS, Oda CMR, Lopes SC, Townsend DM, Cardoso VN, Oliveira MC, Leite EA, Rubello D, de Barros ALB, Paclitaxel-loaded folate-coated long circulating and pH-sensitive liposomes as a potential drug delivery system: a biodistribution study, Biomed. Pharmacother 97 (2018) 489–495, 10.1016/j.biopha.2017.10.135. [PubMed: 29091899]

[127]. Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC, Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology, Adv. Drug Deliv. Rev 66 (2014) 2–25, 10.1016/j.addr.2013.11.009. [PubMed: 24270007]

[128]. Lammers T, Kiessling F, Hennink WE, Storm G, Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress, J. Control. Release 161 (2012) 175–187, 10.1016/j.jconrel.2011.09.063. [PubMed: 21945285]

[129]. Rosenblum D, Joshi N, Tao W, Karp JM, Peer D, Progress and challenges towards targeted delivery of cancer therapeutics, Nat. Commun 9 (2018) 1410, 10.1038/s41467-018-03705-y. [PubMed: 29650952]

[130]. Watkins R, Wu L, Zhang C, Davis R, Xu B, Natural product-based nanomedicine: recent advances and issues, Int. J. Nanomed 10 (2015) 6055–6074, 10.2147/IJN.S92162.

[131]. Oliveira AEMFM, Bezerra DC, Duarte JL, Cruz RAS, Souto RNP, Ferreira RMA, Nogueira J, da Concepção EC, Leitão S, Bizzo HR, Gama PE, Carvalho JCT, Fernandes CP, Essential oil from Pterodon emarginatus as a promising natural raw material for larvicidal nanoemulsions against a tropical disease vector, Sustain. Chem. Pharm 6 (2017) 1–9, 10.1016/j.scp.2017.06.001.

[132]. Oliveira AEMFM, Duarte JL, Cruz RAS, da Conceição EC, Carvalho JCT, Fernandes CP, Utilization of dynamic light scattering to evaluate Pterodon emarginatus oleoresin-based nanoemulsion formation by non-heating and solvent-free method, Rev. Bras. Farmacogn 27 (2017) 401–406, 10.1016/j.bjp.2016.11.005.

[133]. Oliveira AEMFM, Duarte JL, Cruz RAS, Souto RNP, Ferreira RMA, Peniche T, da Concepção EC, de Oliveira LAR, Faustino SMM, Florentino AC, Carvalho JCT, Fernandes CP, Pterodon emarginatus oleoresin-based nanoemulsion as a promising tool for Culex quinquefasciatus (Diptera: Culicidae) control, J. Nanobiotechnol 15 (2017) 2, 10.1186/s12951-016-0234-5.

[134]. Pacheco MT, Silva ACG, Nascimento TL, Diniz DGA, Valadares MC, Lima EM, Protective effect of sucupira oil nanoemulsion against oxidative stress in UVA-irradiated HaCaT cells, J. Pharm. Pharmacol 71 (2019) 1532–1543, 10.1111/jphp.13148. [PubMed: 31378977]

[135]. Valentim DSS, Duarte JL, Oliveira AEMFM, Cruz RAS, Carvalho JCT, Conceição EC, Fernandes CP, Tavares-Dias M, Nanoemulsion from essential oil of Pterodon emarginatus (Fabaceae) shows in vitro efficacy against monogeneans of Colossoma macropomum (Pisces: Serrasalmidae), J. Fish Dis 41 (2017) 443–449, 10.1111/jfd.12739. [PubMed: 29194663]

[136]. Kawakami MYM, Zamora LO, Araújo RS, Fernandes CP, Ricotta TQN, de Oliveira LG, Queiroz-Junior CM, Fernandes AP, da Concecao EC, Ferreira LAM, Barros ALB, Aguiar MG, Oliveira AEMFM, Efficacy of nanoemulsion with Pterodon emarginatus Vogel oleoresin for topical treatment of cutaneous leishmaniasis, Biomed. Pharmacother 134 (2021), 111109, 10.1016/j.biopha.2020.111109. [PubMed: 33341050]

[137]. da É, Santos S, Garcia FP, Outuki PM, Hoscheid J, Nunes de Goes PR, Cardozo-Filho L, Nakamura CV, Carvalho Cardoso ML, Optimization of extraction method and evaluation of antileishmanial activity of oil and nanoemulsions of Pterodon pubescens benth. fruit extracts, Exp. Parasitol 170 (2016) 252–260, 10.1016/j.exppara.2016.10.004. [PubMed: 27725158]

[138]. Hoscheid J, Outuki PM, Kleinubing SA, Silva MF, Bruschi ML, Cardoso MLC, Development and characterization of Pterodon pubescens oil nanoemulsions as a possible delivery system for the treatment of rheumatoid arthritis, Colloids Surf. A Physicochem. Eng. Asp 484 (2015) 19–27, 10.1016/j.colsurfa.2015.07.040.

[139]. Hoscheid J, Outuki PM, Kleinubing SA, de Goes PRN, Lima MMS, Cuman RKN, Cardoso MLC, Pterodon pubescens oil nanoemulsions: physiochemical and microbiological characterization and in vivo anti-inflammatory efficacy studies, Rev. Bras. Farmacogn 27 (2017) 375–383, 10.1016/j.bjp.2016.08.012.

[140]. Pascoa H, Diniz DGA, Florentino IF, Costa EA, Bara MTF, Microemulsion based on Pterodon emarginatus oil and its anti-inflammatory potential, Braz. J. Pharm. Sci 51 (2015) 117–125, 10.1590/S1984-82502015000100013.

[141]. Kleinubing SA, Outuki PM, Hoscheid J, Pelegrini BL, Antonio da Silva E, de Almeida Canoff J. Renata, de Souza Lima M. Miriam, Carvalho Cardoso ML, Hyaluronic acid incorporation into nanoemulsions containing Pterodon pubescens Benth. Fruit oil for topical drug delivery, Biocatal. Agric. Biotechnol 32 (2021), 101939, 10.1016/j.bcab.2021.101939.

[142]. de Goes PRN, Hoscheid J, Silva-Filho SE, Froehlich DL, Pelegrini BL, de JR, Canoff A, de MM, Lima S, Cuman RKN, Cardoso MLC, Rheological behavior and antiarthritic activity of Pterodon pubescens nanoemulsion, e179108119, Res. Soc. Dev 9 (2020), 10.33448/rsd-v9i10.8119.

[143]. Servat L, Spindola HM, Rodrigues RAF, Sousa IMO, Ruiz ALTG, de Carvalho JE, Foglio MA, Pterodon pubescens benth: stability study of microencapsulated extract and isolated

compounds monitored by antinociceptive assays, J. Braz. Chem. Soc 23 (2012) 1244–1253, 10.1590/SOI03-50532012000700008.

[144]. Salles THC, Volpe-Zanutto F, de Oliveira Sousa IM, Machado D, Zanatta AC, Vilegas W, Lancellotti M, Foglio MA, D'Ávila MA, Electrospun PCL-based nanofibers Arrabidaea chica Verlot – Pterodon pubescens Benth loaded: synergic effect in fibroblast formation, Biomed. Mater 15 (2020), 065001, 10.1088/1748-605X/ab9bb1. [PubMed: 32955022]

[145]. Silveira LB, Martins QS, Maia JC, Santos JG, Preparation of nanocomposites resin from seed Pterodon emarginatus doped maghemite nanoparticles, J. Nanosci. Nanotechnol 12 (2012) 4832–4835, 10.1166/jnn.2012.4946. [PubMed: 22905537]

[146]. Oliveira GZS, Lopes CAP, Sousa MH, Silva LP, Synthesis of silver nanoparticles using aqueous extracts of Pterodon emarginatus leaves collected in the summer and winter seasons, Int. Nano Lett 9 (2019) 109–117, 10.1007/s40089-019-0265-7.

[147]. Toledo ACO, da DP, de Assunção SF, Boscardin PMD, de J, de Paula FP, Biosynthesis and characterization of silver nanoparticles produced with aqueous extract of Pterodon emarginatus Vogel - Fabaceae seeds associated with gentamicin sulfate and hyaluronic acid with potential antimicrobial activity, Braz. J. Dev 6 (2020) 100655–100677, 10.34117/bjdv6n12-526.

[148]. Outuki PM, Kleinubing SA, Hoscheid J, Montanha MC, da Silva EA, do Couto RO, Kimura E, Cardoso MLC, The incorporation of Pterodon pubescens fruit oil into optimized nanostructured lipid carriers improves its effectiveness in colorectal cancer, Ind. Crop. Prod 123 (2018) 719–730, 10.1016/j.indcrop.2018.07.044.

[149]. Vieira R, Severino P, Nalone LA, Souto SB, Silva AM, Lucarini M, Durazzo A, Santini A, Souto EB, Sucupira oil-loaded nanostructured lipid carriers (NLC): lipid screening, factorial design, release profile, and cytotoxicity, Molecules 25 (2020) 685, 10.3390/molecules25030685.

[150]. Talegaonkar S, Azeem A, Ahmad F, Khar R, Pathan S, Khan Z, Microemulsions: a novel approach to enhanced drug delivery, Recent Pat. Drug Deliv. Formul 2 (2008) 238–257, 10.2174/187221108786241679. [PubMed: 19075911]

[151]. Gupta A, Eral HB, Hatton TA, Doyle PS, Nanoemulsions: formation, properties and applications, Soft Matter 12 (2016) 2826–2841, 10.1039/C5SM02958A. [PubMed: 26924445]

[152]. Solans C, Morales D, Homs M, Spontaneous emulsification, Curr. Opin. Colloid Interface Sci 22 (2016) 88–93, 10.1016/j.cocis.2016.03.002.

[153]. Rai VK, Mishra N, Yadav KS, Yadav NP, Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: formulation development, stability issues, basic considerations and applications, J. Control. Release 270 (2018) 203–225, 10.1016/j.jconrel.2017.11.049. [PubMed: 29199062]

[154]. Anton N, Vandamme TF, Nano-emulsions and micro-emulsions: clarifications of the critical differences, Pharm. Res 28 (2011) 978–985, 10.1007/s11095-010-0309-1. [PubMed: 21057856]

[155]. Shukla T, Upmanyu N, Agrawal M, Saraf S, Saraf S, Alexander A, Biomedical applications of microemulsion through dermal and transdermal route, Biomed. Pharmacother 108 (2018) 1477–1494, 10.1016/j.biopha.2018.10.021. [PubMed: 30372850]

[156]. McClements DJ, Nanoemulsions versus microemulsions: terminology, differences, and similarities, Soft Matter 8 (2012) 1719–1729, 10.1039/C2SM06903B.

[157]. Kumar M, Bishnoi RS, Shukla AK, Jain CP, Techniques for formulation of nanoemulsion drug delivery system: a review, Prev. Nutr. Food Sci 24 (2019) 225–234, 10.3746/pnf.2019.24.3.225. [PubMed: 31608247]

[158]. Li Y, Zheng J, Xiao H, McClements DJ, Nanoemulsion-based delivery systems for poorly water-soluble bioactive compounds: influence of formulation parameters on polymethoxyflavone crystallization, Food Hydrocoll. 27 (2012) 517–528, 10.1016/j.foodhyd.2011.08.017. [PubMed: 22685367]

[159]. Hua L, Weisan P, Jiayu L, Ying Z, Preparation, evaluation, and NMR characterization of vinpocetine microemulsion for transdermal delivery, Drug Dev. Ind. Pharm 30 (2004) 657–666, 10.1081/DDC-120039183. [PubMed: 15285339]

[160]. Pavoni L, Pavela R, Cespi M, Bonacucina G, Maggi F, Zeni V, Canale A, Lucchi A, Bruschi F, Benelli G, Green micro- and nanoemulsions for managing parasites, vectors and pests, Nanomaterials 9 (2019) 1285, 10.3390/nano9091285.

[161]. Wilhelm K-P, Cua AB, Wolff HH, Maibach HI, Surfactant-induced stratum corneum hydration in vivo: prediction of the irritation potential of anionic surfactants, J. Investig. Dermatol 101 (1993)310–315, 10.1111/1523-1747.ep12365467. [PubMed: 8370967]

[162]. Froebe CL, Simion FA, Rhein LD, Cagan RH, Kligman A, Stratum corneum lipid removal by surfactants: relation to in vivo irritation, Dermatology 181 (1990) 277–283, 10.1159/000247822.

[163]. Tadros T, Izquierdo P, Esquena J, Solans C, Formation and stability of nano-emulsions, Adv. Colloid Interface Sci 108–109 (2004) 303–318, 10.1016/j.cis.2003.10.023.

[164]. Ekladious I, Colson YL, Grinstaff MW, Polymer—drug conjugate therapeutics: advances, insights and prospects, Nat. Rev. Drug Discov 18 (2019) 273–294, 10.1038/s41573-018-0005-0. [PubMed: 30542076]

[165]. Molavi F, Barzegar-Jalali M, Hamishehkar H, Polyester based polymeric nano and microparticles for pharmaceutical purposes: a review on formulation approaches, J. Control. Release 320 (2020) 265–282, 10.1016/j.jconrel.2020.01.028. [PubMed: 31962095]

[166]. Legrand P, Barratt G, Mosqueira V, Fessi H, Devissaguet J. Polymeric Nanocapsules as Drug Delivery Systems: A Review, ninth ed, S.T.P. Pharma Sci, Paris, 1999.

[167]. Schaffazick SR, Guterres SS, de L, Freitas L, Pohlmann AR, Physicochemical characterization and stability of the polymeric nanoparticle systems for drug administration, Quim. Nova 26 (2003) 726–737, 10.1590/S0100-40422003000500017.

[168]. Chan JM, Valencia PM, Zhang L, Langer R, Farokhzad OC, Polymeric nanoparticles for drug delivery, in: Grobmyer S, Moudgil B (Eds.), 2010, pp. 163–175. 10.1007/978-1-60761-609-2_11.

[169]. Begines B, Ortiz T, Pérez-Aranda M, Martínez G, Merinero M, Argüelles-Arias F, Alcudia A, Polymeric nanoparticles for drug delivery: recent developments and future prospects, Nanomaterials 10 (2020) 1–41, 10.3390/nano10071403.

[170]. Bala I, Bhardwaj V, Hariharan S, Kharade SV, Roy N, Ravi Kumar MNV, Sustained release nanoparticulate formulation containing antioxidant-ellagic acid as potential prophylaxis system for oral administration, J. Drug Target 14 (2006) 27–34, 10.1080/10611860600565987. [PubMed: 16603449]

[171]. Fang Z, Bhandari B, Encapsulation of polyphenols – a review, Trends Food Sci. Technol 21 (2010) 510–523, 10.1016/j.tifs.2010.08.003.

[172]. Bakry AM, Abbas S, Ali B, Majeed H, Abouelwafa MY, Mousa A, Liang L, Microencapsulation of oils: a comprehensive review of benefits, techniques, and applications, Compr. Rev. Food Sci. Food Saf 15 (2016) 143–182, 10.1111/1541-4337.12179. [PubMed: 33371581]

[173]. Mohammed NK, Tan CP, Manap YA, Muhialdin BJ, Hussin ASM, Spray drying for the encapsulation of oils—a review, Molecules 25 (2020) 3873, 10.3390/molecules25173873.

[174]. Ziaee A, Albadarin AB, Padrela L, Femmer T, O'Reilly E, Walker G, Spray drying of pharmaceuticals and biopharmaceuticals: critical parameters and experimental process optimization approaches, Eur. J. Pharm. Sci 127 (2019) 300–318, 10.1016/j.ejps.2018.10.026. [PubMed: 30428336]

[175]. Joye IJ, McClements DJ, Biopolymer-based nanoparticles and microparticles: fabrication, characterization, and application, Curr. Opin. Colloid Interface Sci 19 (2014) 417–427, 10.1016/j.cocis.2014.07.002.

[176]. Lengyel M, Kállai-Szabo N, Antal V, Laki AJ, Antal I, Microparticles, microspheres, and microcapsules for advanced drug delivery, Sci. Pharm. 87 (2019) 20, 10.3390/scipharm87030020.

[177]. Mahdavi SA, Jafari SM, Ghorbani M, Assadpoor E, Spray-drying microencapsulation of anthocyanins by natural biopolymers: a review, Dry. Technol 32 (2014) 509–518, 10.1080/07373937.2013.839562.

[178]. McBain S, Yiu H, Dobson J, Magnetic nanoparticles for gene and drug delivery, Int. J. Nanomed 3 (2008) 169–180, 10.2147/IJN.S1608.

[179]. Cardoso VF, Francesko A, Ribeiro C, Bañobre-López M, Martins P, Lanceros-Mendez S, Advances in magnetic nanoparticles for biomedical applications, Adv. Healthc. Mater 7 (2018) 1–35, 10.1002/adhm.201700845.

[180]. Nazari M, Ghasemi N, Maddah H, Motlagh MM, Synthesis and characterization of maghemite nanopowders by chemical precipitation method, J. Nanostruct. Chem 4 (2014) 99, 10.1007/s40097-014-0099-9.

[181]. Moghimi SM, Hunter AC, Murray JC, Long-circulating and target-specific nanoparticles: theory to practice, Pharmacol. Rev 53 (2001) 283–318. ⟨http://www.ncbi.nlm.nih.gov/pubmed/11356986⟩. [PubMed: 11356986]

[182]. Sandler SE, Fellows B, Mefford OT, Best practices for characterization of magnetic nanoparticles for biomedical applications, Anal. Chem 91 (2019) 14159–14169, 10.1021/acs.analchem.9b03518. [PubMed: 31566353]

[183]. Tran N, Webster TJ, Magnetic nano particles: biomedical applications and challenges, J. Mater. Chem 20 (2010) 8760, 10.1039/c0jm00994f.

[184]. Griffin S, Masood MI, Nasim MJ, Sarfraz M, Ebokaiwe AP, Schäfer K-H, Keck CM, Jacob C, Natural nanoparticles: a particular matter inspired by nature, Antioxidants 7 (2017) 3, 10.3390/antiox7010003.

[185]. Jain S, Mehata MS, Medicinal plant leaf extract and pure flavonoid mediated green synthesis of silver nanoparticles and their enhanced antibacterial property, Sci. Rep 7 (2017) 15867, 10.1038/s41598-017-15724-8. [PubMed: 29158537]

[186]. Han F, Li S, Yin R, Liu H, Xu L, Effect of surfactants on the formation and characterization of a new type of colloidal drug delivery system: nanostructured lipid carriers, Colloids Surf. A Physicochem. Eng. Asp 315 (2008) 210–216, 10.1016/j.colsurfa.2007.08.005.

[187]. Pardeike J, Hommoss A, Müller RH, Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products, Int. J. Pharm 366 (2009) 170–184, 10.1016/j.ijpharm.2008.10.003. [PubMed: 18992314]

[188]. Joshi MD, Müller RH, Lipid nanoparticles for parenteral delivery of actives, Eur. J. Pharm. Biopharm 71 (2009) 161–172, 10.1016/j.ejpb.2008.09.003. [PubMed: 18824097]

[189]. Pivetta TP, Simões S, Araújo MM, Carvalho T, Arruda C, Marcato PD, Development of nanoparticles from natural lipids for topical delivery of thymol: investigation of its anti-inflammatory properties, Colloids Surf. B Biointerfaces 164 (2018) 281–290, 10.1016/j.colsurfb.2018.01.053. [PubMed: 29413607]

[190]. Beloqui A, Solinís MÁ, Rodríguez-Gascón A, Almeida AJ, Préat V, Nanostructured lipid carriers: promising drug delivery systems for future clinics, Nanomed. Nanotechnol. Biol. Med 12(2016) 143–161, 10.1016/j.nano.2015.09.004.

[191]. Ganesan P, Narayanasamy D, Lipid nanoparticles: different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery, Sustain. Chem. Pharm 6 (2017) 37–56, 10.1016/j.scp.2017.07.002.

[192]. Naseri N, Valizadeh H, Zakeri-Milani P, Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application, Adv. Pharm. Bull 5 (2015) 305–313, 10.15171/apb.2015.043. [PubMed: 26504751]

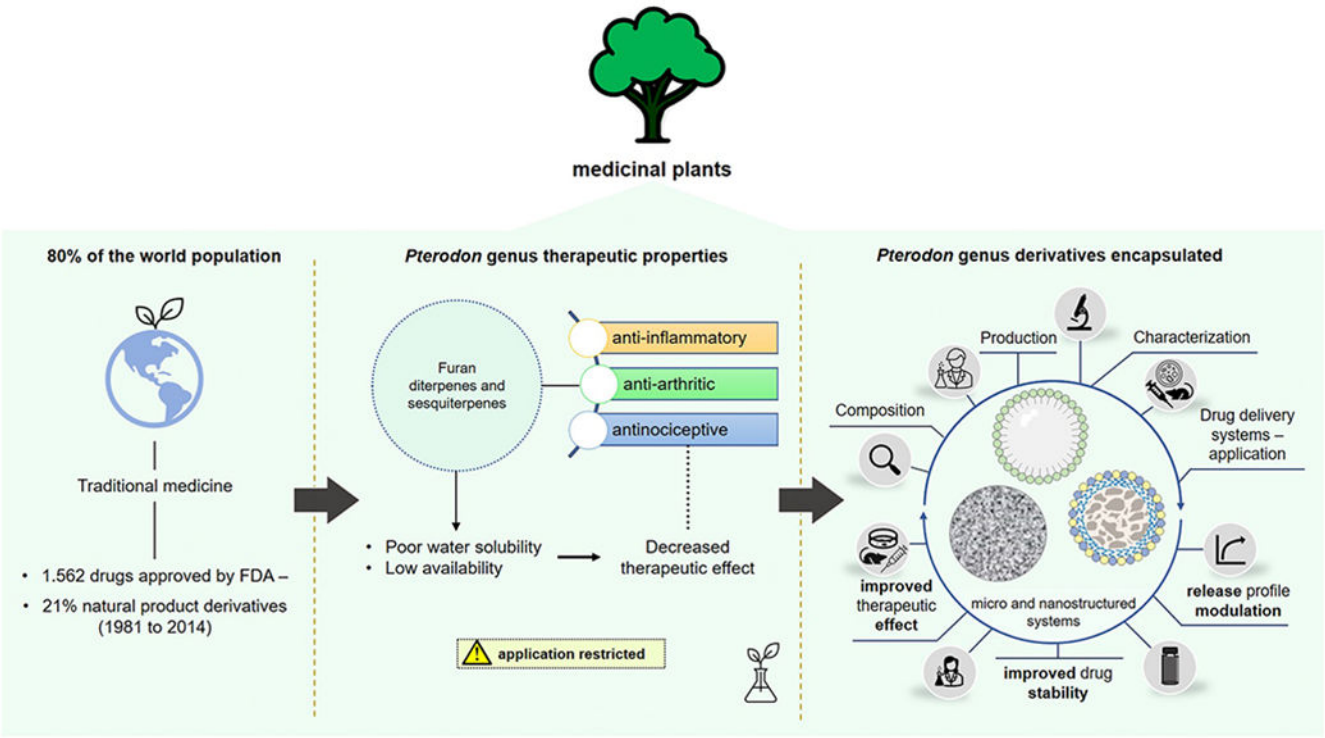

Fig. 1.

Worldwide importance of medicinal plants and their progress towards micro and nano-encapsulation.

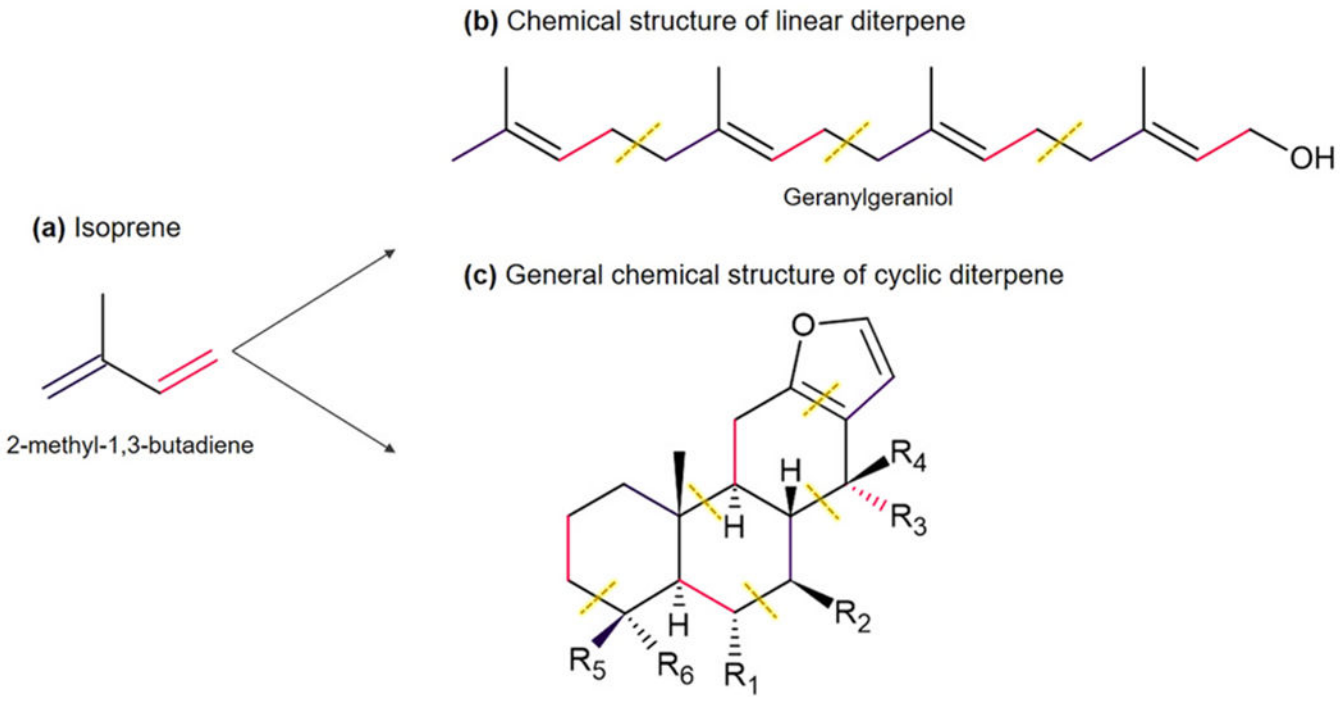

Fig. 2.

Chemical structure of (a) isoprene and isolated diterpenes from *Pterodon* sp. (b) linear structure of Geranylgeraniol and (c) cyclic structure of vouacapane compounds. Dashed lines indicate where the four isoprene units are joined.

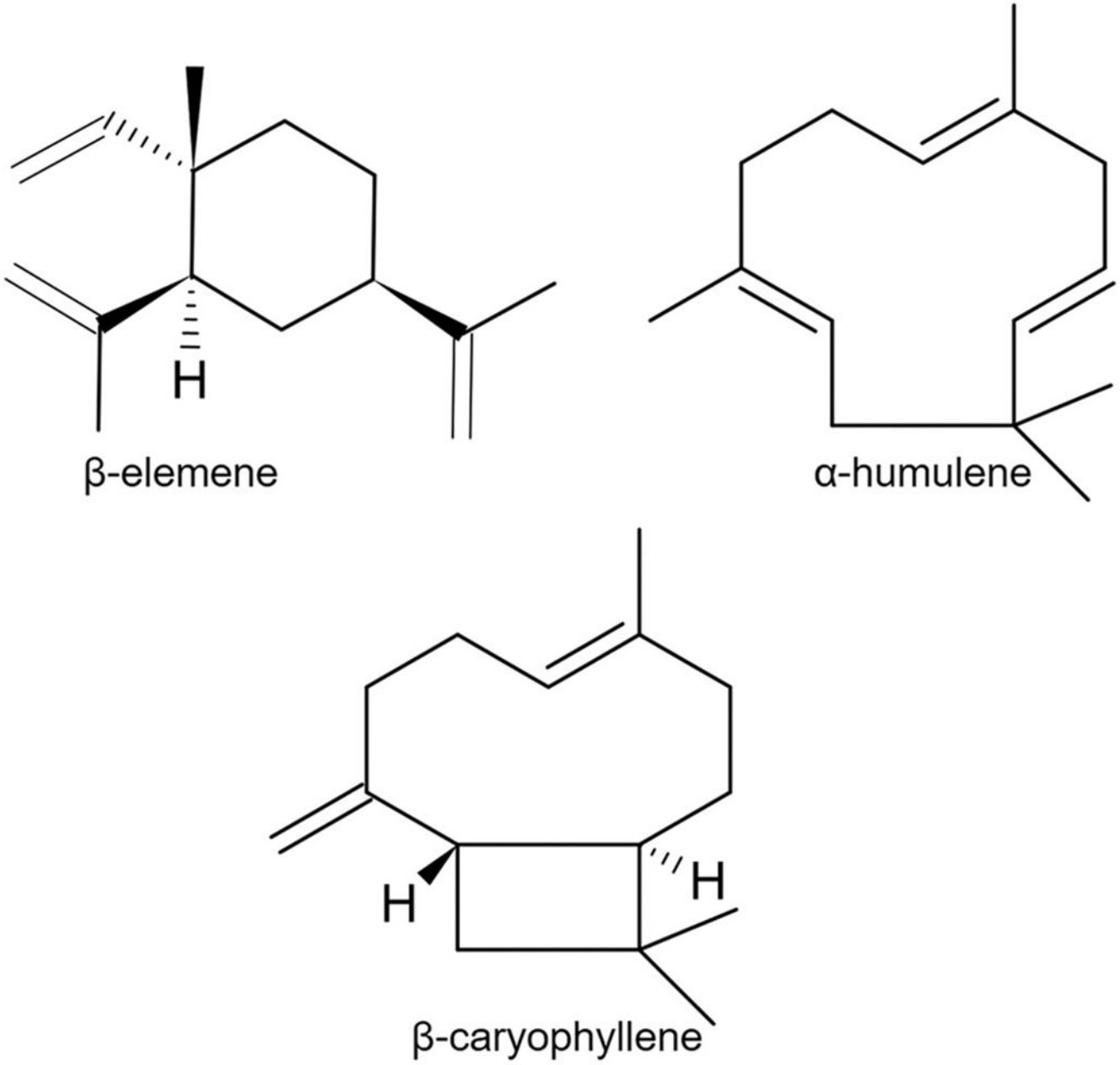

Fig. 3.

Chemical structure of some of the main sesquiterpene compounds isolated from the essential oil seeds and fruits of the genus *Pterodon*.

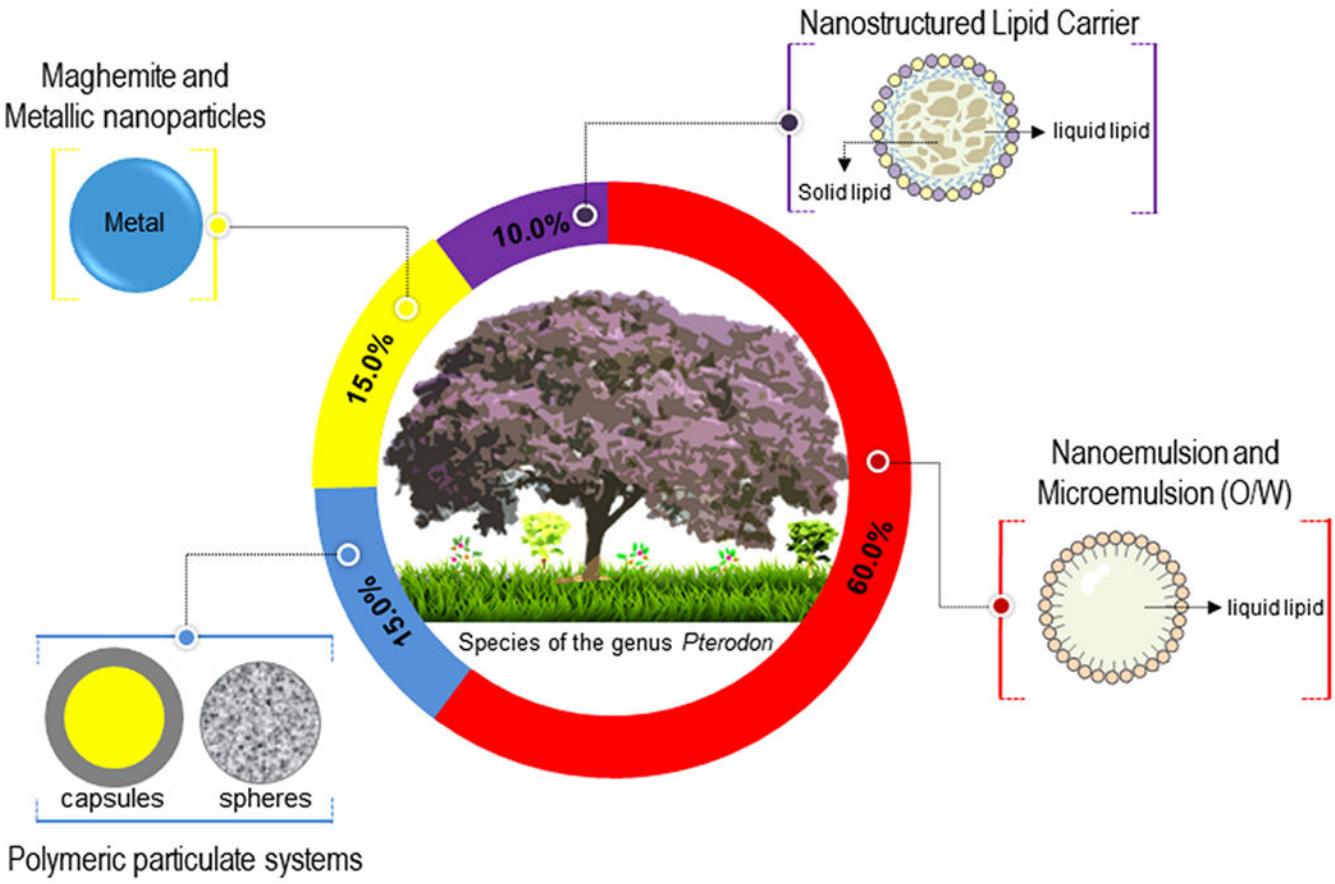

Fig. 4.

Percentage distribution profile of nanostructured systems based on species of the genus *Pterodon*.

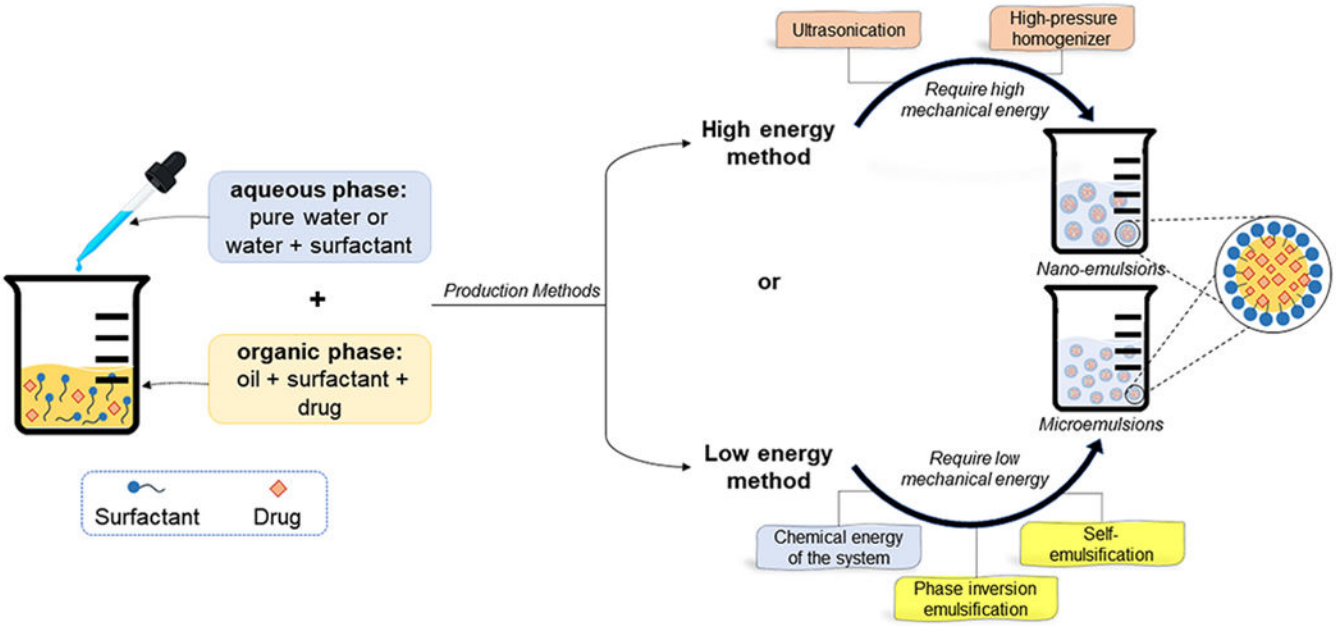

Fig. 5.

Schematic illustration of the high-energy and low-energy methods for obtaining micro and nano-emulsion.

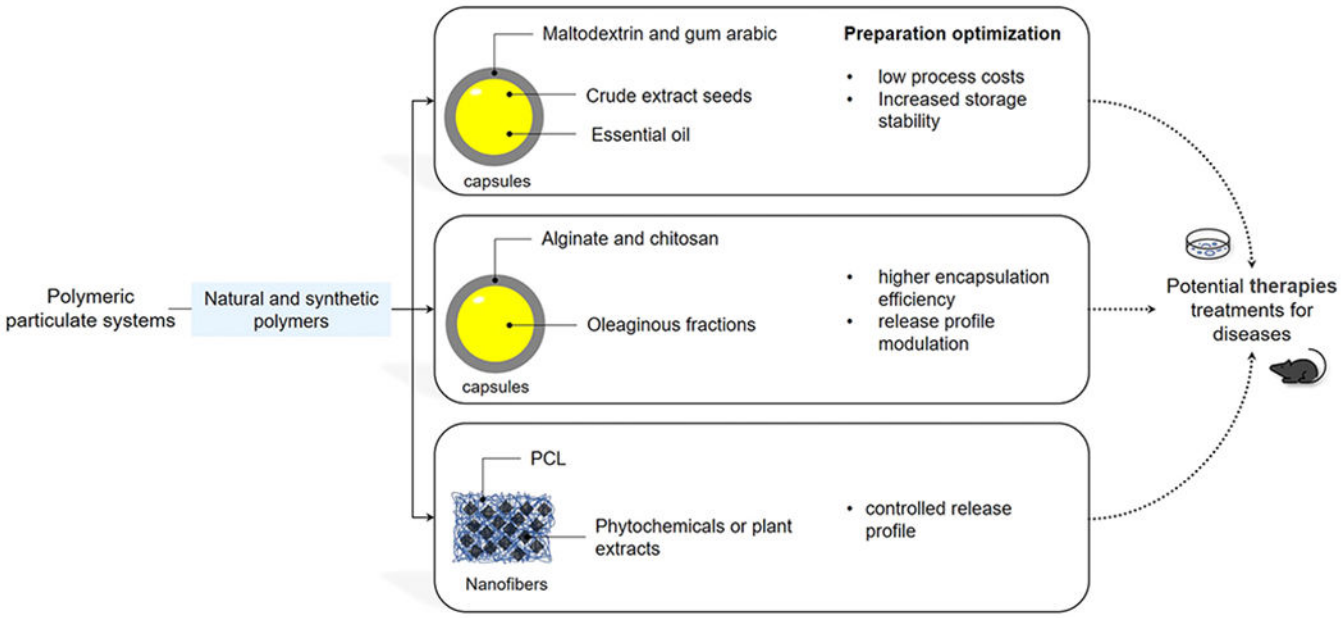

Fig. 6.

Schematic illustration of the use of different polymer systems for encapsulation of phytochemicals or plant extracts of Pterodon species.

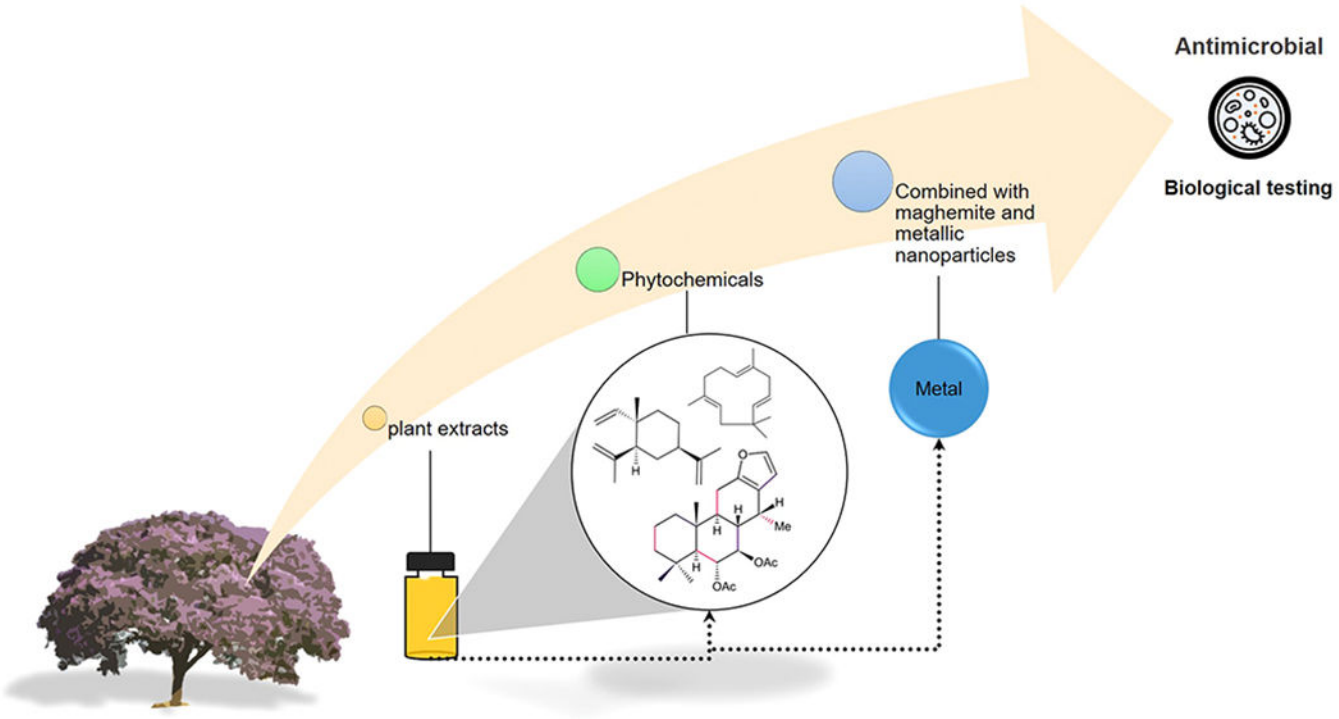

Fig. 7.

Schematic illustration of the association between plant extracts or phytochemicals and their possible biomedical application.

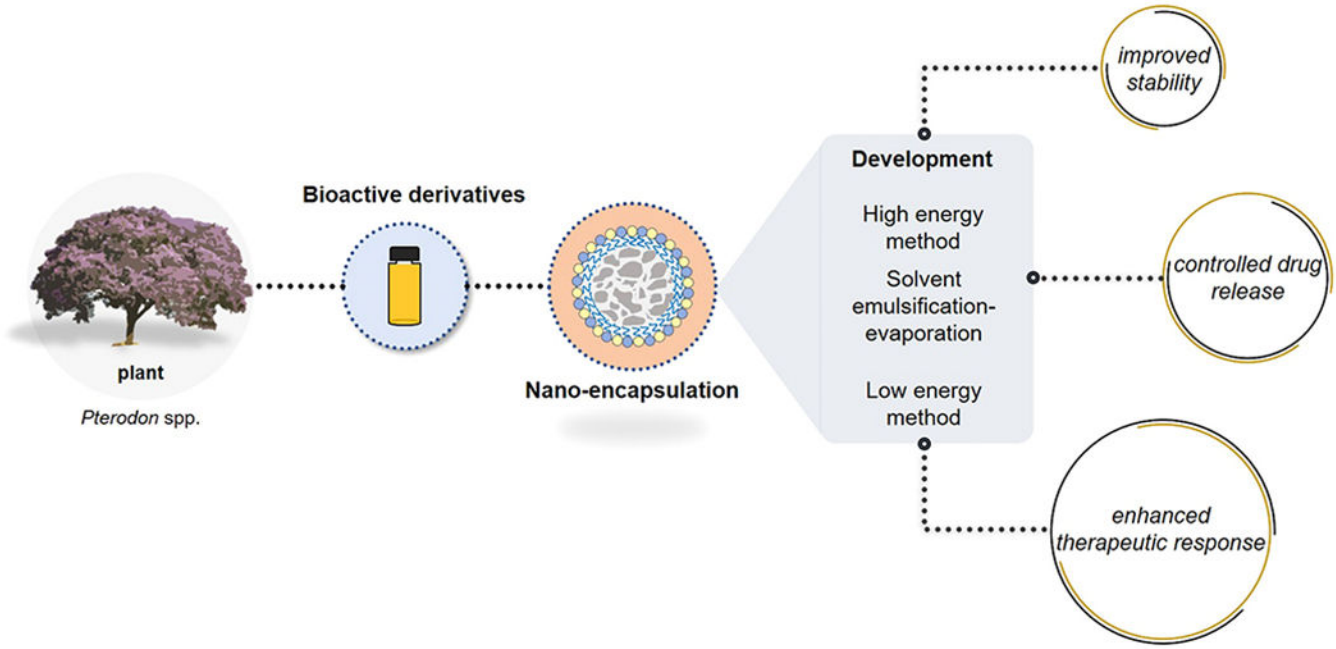

Fig. 8.

Schematic representation of the theoretical upside of developing plant (Pterodon genus) derived bioactive-loaded nanostructured lipid carriers.

Table 1

Drug-delivery systems based on *Pterodon* spp. bioactive products and applications.

***Pterodon* spp.**	**Plants extracts/vouacapan derivative**	**Delivery system**	**Preparation methods**	**Drug-Delivery properties**	**Biological activities**	**References**
P. emarginatus	Oil obtained through the cold pressing of fruits	NE	Emulsification - low energy method	Optimized formulation: 125.1 ± 0.5 nm, PI: 0.175 ± 0.014; dose 250 ppm induces mortality level of 100%; no toxicity for mammals	Larvicidal on *Aedes aegypti*	[45]
P. emarginatus	Essential oil from fruits	NE	Phase inversion emulsification	Optimized formulation: 128.0 ± 6.2 nm, PI: 0.250; Dose 150 μg/mL induces mortality	Larvicidal on *Aedes aegypti*	[131]
P. emarginatus	Oleoresin from fruit	NE	Phase inversion emulsification - with some modifications	Size distribution: < 180 nm, PI: < 0.200; Thermosensitive substances may be efficiently encapsulated by this technique; New perspectives for biological evaluation	Still uninvestigated	[132]
P. emarginatus	Oleoresin from fruit	NE	Emulsification - low energy method	More stable formulation: 151.0 ± 2.3, PI: < 0.3; Doses 500 mg/L, decrease in cell viability; Low toxic effects on environment	Larvicidal on *Culex quinquefasciatus*	[133]
P. emarginatus	Oil obtained through the cold pressing of fruits	NE	Hot high-pressure homogenization	Size distribution: 150 nm, PI: < 0.2 Formulation stability for 90 days	Antioxidant activity	[134]
P. emarginatus	Essential oil from fruits	NE	Phase inversion emulsification - with some modifications	Size distribution: 116.8 ± 0.3606 nm, PI 0.187 ± 0.008	Anthelmintic	[135]
P. emarginatus	Essential oil from fruits	NE	Emulsification - low energy method	Optimized formulation: 130 nm, PI < 0.20; Physical stability in temperature from 25 °C to 80 °C; Formulation classified as non-irritant	Still uninvestigated	[40]
P. emarginatus	Oleoresin from fruit	NE	Phase inversion emulsification - with some modifications	Particle size: < 180 nm; narrow size distribution (PI from 0.136); stable at room temperature	Leishmanicidal	[136]
P. pubescens	Hexanic fruit extracts and Supercritical fluid extract	NE	High shear homogenization	Low particle size (< 200 nm) and narrow distribution PI: < 0.2; Better selectivity index	Leishmanicidal	[137]
P. pubescens	Hexanic fruit extract	NE	High shear homogenization	Optimized formulation: < 200 nm a very narrow size distribution (PI from 0.11)	Anti-rheumatic/anti-arthritic	[138]
P. pubescens	Hexanic fruit extract	NE	High shear homogenization	Unimodal distribution profile; PI: < 0.3; Good stability throughout the study	Anti-inflammatory	[139]
P. emarginatus	Oil obtained through the cold pressing of fruits	ME	Reverse-phase methods	Size distribution: 56.8 ± 6.07 nm; Narrow size distribution (PI < 0.2); Stability at 5 and 25 °C for 30-day	Anti-inflammatory	[140]
P. pubescens	Hexanic fruit extract	NE	High shear homogenization	Size distribution: 16.33 ± 0.30–26.63 ± 0.21 nm; Narrow size distribution (PI < 0.3); Encapsulation efficiency > 90%; Good stability	Still uninvestigated	[141]
P. pubescens	Ethanolic fruit extract	NE	High shear homogenization	Spherical-shaped nanosized structure; Predominantly elastic characteristic; Good stability	Antiarthritic	[142]
P. pubescens	Oleaginous fractions from alcohol extract of the fruit	MC	Phase separation (coacervation)	Size distribution: 0.468–0.903 μm depending on the type of chitosan used in preparing the formulation; Modified oleaginous fractions release profile	Still uninvestigated	[90]

Pterodon spp.	Plants extracts/vouacapan derivative	Delivery system	Preparation methods	Drug-Delivery properties	Biological activities	References
P. pubescens	Crude extract seeds and isomers 6α-hydroxy-7β-acetoxy-vouacapan-17β-oate methyl ester and 6α-acetoxy-7β-hydroxy-vouacapan-17β-oate methyl ester	MC	Spray drying	Good encapsulation efficiency and Its stability can be modified leading to increase shelf lifetime of formulation	Anti-nociceptive	[143]
P. emarginatus	Essential oil from fruits	MC	Spray drying	Size distribution: 1.250 μm; System capable of conserving and protecting essential oil from degradation and evaporation	Still uninvestigated	[44]
P. pubescens	Ethanol fruit extract	Nanofibers	Electrospinning	Size distribution: 1.91 ± 0.71 μm; Controlled release profile; Non-cytotoxic behavior *in vitro*	Wound healing	[144]
P. emarginatus	Resin extracted from the seed	Maghemite NP	Co-precipitation	Size distribution: 84 nm monodisperse size profile; expand applications due to semiconducting properties	Still uninvestigated	[145]
P. emarginatus	Aqueous extract from the seeds/leaves	Metallic NP	Green synthesis	NP in the size range 59–66 nm; predominantly spherical in shape; moderate stability (PI: 0.3)	Antimicrobial	[146,147]
P. pubescens	Oil obtained from hexanic fruit extract	NLC	Melt emulsification	Optimized formulation: 94.47 ± 2.05 nm, PI: 0.197 ± 0.003; The chemical profile of the oil remained unchanged after preparation method	Antitumoral	[148]
Unidentified	Essential oil from fruits	NLC	Hot high-pressure homogenization	Optimized formulation: 148.1 ± 0.1 nm, PI: 0.274 ± 0.029 after preparation; showed no cytotoxic effect against Caco-2 cell line	Still uninvestigated	[149]

Abbreviations: PI: polydispersity index; MC: microcapsules; NP: nanoparticles; NLC: nanostructured lipid carriers; ME: microemulsions; NE: nanoemulsions.