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BIOMEDICAL APPLICATION OF NANOFORMULATED PLANT

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ABSTRACT: An extensive range of studies have shown plant extracts and their phyto-constituents efficacy, proposing them as a promising alternative for treatment or as adjuvants in human diseases such in skin, gastrointestinal, systemic and dental conditions, due to various active components presence, ease of access and reduced side effects. Indeed, depending on solvent used to obtain the extract, its active molecules may vary, including flavonoids, tannins, alkaloids, terpenes, sesquiterpenes, sterols, among others. Extract content (crude/partition/fraction) has pharmacological advantages over isolated compounds, due to pleiotropic activity and synergistic effect between components. Due to factors such as low bioavailability, solubility, and stability, it is difficult to translate its *in-vitro* and *in-vivo* effects into clinical picture, besides that pharmacological effects full potential cannot be exploited. However, in recent decades, extraordinary advances have been made in new drug delivery systems for the encapsulation of active plant metabolites, thus helping to improve different medicinal plant-based therapies and product efficacy. The current review highlights the importance of nanocarriers loaded with plant extracts as an alternative for dental, dermatological, gastrointestinal, and systemic diseases.

INTRODUCTION: According to the World Health Organization (WHO), it is estimated that 80% of world's population depends on traditional medicine for a wide range of respiratory, kidney, skin, inflammatory, and gastrointestinal diseases primary care [1]. Else ways, it is important to mention that plants' potential pharmacological effects have been extensively evidenced in studies both *in-vitro* and *in-vivo* reporting antimicrobial, antioxidant, anticancer, and analgesic activities [2–6].

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However, it is difficult to obtain the same beneficial effects in clinical picture due to factors such as solvent toxicity, conventional dosage form, environmental characteristics, physicochemical stability, pH, *in-situ* bioavailability, among others [7]. Furthermore, recent reports indicate that more than 70% of new formulated drugs have low solubility in water, which becomes the drug's limiting factor for its absorption [8]. Therefore, there is a need to find new dosage forms to take full natural products pharmacological advantage more efficiently.

In recent years, new natural compounds application forms have been adapted through nanotechnology use, which consists of synthesizing particles with a size of 50-500 nm loaded with plant extracts to potentiate their biological activity. Indeed, previous studies report that silver nanoparticles (AgNP) synthesis based on *Justicia glauca* leaf extracts have antibacterial and antifungal activity of dental interest field [9]. Liposomes formulated with Curcumin allow dental pulp stem cells homeostasis restoration [10]. Poly (ε-caprolactone) nano-encapsulated Celastrolhas also been reported with anticancer activity (prostate cancer) [11]; according to Pacheco-Ordaz, polymeric nanoparticles loaded with *Berberis vulgaris* and *Curcuma longa* crude extracts independently have biological activity against *Entamoeba histolytica* [12]. It was verified that polymeric nanoparticles loaded with quercetin (flavonoids) increase their antioxidant activity compared to free bioactive compound [13]. Since, it is possible to modify nanocarriers characteristics such as their constituents (organic, inorganic or hybrid), size (small, medium or large), shape (sphere, rod or cube) and surface properties (charge, functional groups, target union group) to obtain desirable pharmacological effects, nano-technology application is considered a very important tool for medical applications today [8, 14]. Due to aforementioned, this work highlights the relevance of nanotechnological advances in conjunction with natural products potential effects for effective pharmacological use.

Types of Nanoparticles and Their Synthesis: Some characteristics must be considered for NPs synthesis such as bioavailability, better encapsulation, controlled release, and less toxicity, thus, emerging as a biodegradable nanoparticle. Synthesis method is determined according to the nanoformulation application. Biodegradable nanoparticles provide desired characteristic such as controlled release property, subcellular size and biocompatibility with tissue and cells [15]. Nanoparticles carrying a drug can be synthesized by solvent displacement method by adding desired drug in solvent such as acetone along with polymer such as PCL/PLGA, before introducing it into aqueous medium having as a result entrapment of drug within [16]. It has been shown in breast cancer models that when synthesizing tamoxifen-PCL nanoparticles, a higher concentration of the drug is observed intratumorally, increasing its bioavailability [17].

Emulsion/Evaporation Method: Consists of gradually mixing two synthesis phases in order to obtain the nanoformulate (a first consisting in a organic phase containing the drug and the second with a polymer dissolved in an aqueous solution containing an appropriate surfactant). Said mixture induces an emulsion, after which it is subjected to homogenization (magnetic stirring/sonification) at high speed to obtain nanoparticles of desired size. Subsequently, a solvent evaporation is carried out in order to initiate polymer precipitation under reduced pressure or by constant stirring [18].

Dual Emulsion/Evaporation Method: Consist son encapsulating hydrophilic active principles. Initially, an aqueous phase containing drug dissolved in water and an organic phase containing an emulsifier are prepared to form the primary emulsion. Subsequently, primary emulsion is continuously injected into a solution containing a surfactant under constant stirring, to induce a second emulsion. Finally, system is maintained so that solvent is removed to obtain nanoparticles [7].

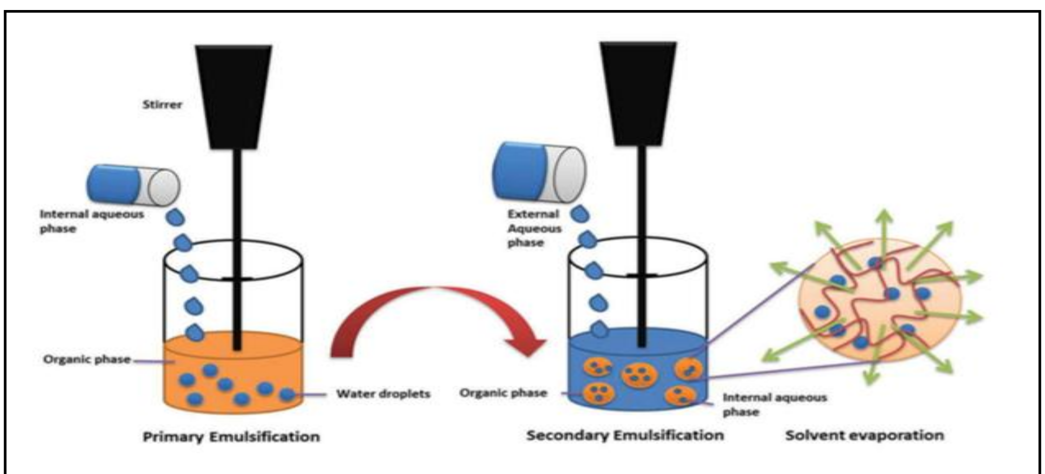

FIG. 1: EMULSION SOLVENT EVAPORATION TECHNIQUE (W/O/W TYPE) [7]

Nanoprecipitation: This method is used massively in hydrophobic and thermo sensitive compounds polymeric nanoparticles encapsulation since heat is not used as energy source, but constant magnetic stirring is, for the purpose of breaking injection drops at phase into nanodroplets. Indeed, obtaining nano formulates using this method consists of injecting an organic phase (solvent, synthesis polymer, and active principle) into an aqueous phase (water and surfactant), under constant stirring. Then, solvent is removed under reduced pressure to obtain a solvent-free NP suspension. It is important to mention that the main solvents used in organic phase are those in which active principle and synthetic polymer can be dissolved. Finally, physical characteristics of nano-formulates are determined by photonic correlation spectroscopy, and encapsulated drug concentration by HPLC, gas chromatography, FT-IR, among others [18].

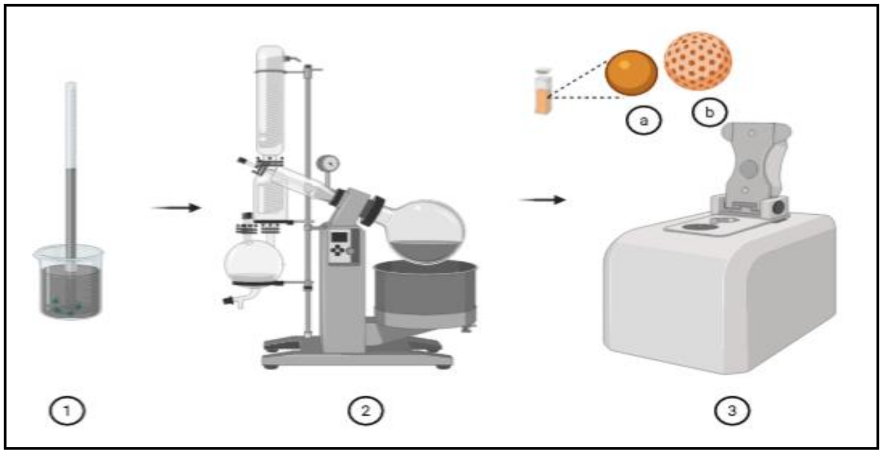

FIG. 2: NANOFORMULATION SYSTEM METHOD AND TYPES OF NANOPARTICLES. 1) ORGANIC PHASE INJECTION INTO AQUEOUS ONE; 2) SOLVENT REMOVAL AT INCREASED PRESSURE; 3) NANOPARTICLES PHYSICAL CHARACTERISTICS DETERMINATION; A) POLYMERIC NANOPARTICLE; B) NANOSPHERE

Green Synthesis of Metallic Nanoparticles: Plant extracts use in green nanoparticles synthesis offers advantages by acting as reducing or stabilizing agents; an environmentally friendly utility, good stability, less toxicity, and rapid synthesis [19]. Indeed, nanoparticles synthesis with metallic materials (Ag, Au, PbS and fularene) is carried out regularly by evaporation/condensation method using a furnace tube [20].

Green Synthesis of Silver Nanoparticles: According to Tollens method, metallic nano-particles synthesis involves the following reaction: $AgNH_3^{2+}$ (aq) + RCHO (aq)→ Ag (s) + RCOOH (aq) The principle of this method is the use of ammonia, which is directly related to controlling nanoparticle size [20]. One of the chemical methods disadvantages is final product possible toxicity [21].

Green Synthesis of Gold Nanoparticles: Gold nanoparticles with palladium-coated orange peel extract use has been reported to improve their solubility, employed in the detection of formaldehyde by colorimetry. It consists on dissolving gold ingots in an aqueous solution, using chloroauric acid ($HAuCl_4$) to obtain $HAuCl_4$ stock solution. Subsequently, plant extract is added under vigorous stirring until a uniform color change is observed. Finally, a H_2PdCl_4 solution is added under constant stirring at 35ºC for 6 h, a color change to brown indicates the successful synthesis of the nanoparticles [19].

Biomedical Application: Among technological advances in recent years, nanoparticles have shown enormous potential for clinical application. In this way, a new discipline called nanomedicine arises, which can be defined as the branch of medicine that applies knowledge and tools of nano-technology to treat and prevent diseases. Within a wide range of diseases that affect humans, such as: dental, dermatological, gastrointestinal system, and systemic conditions.

Odontology: The need to maintain good oral hygiene dates back to ancient times through the use of animal bones, bird feathers, chewing sticks, tree twigs, among other natural materials [22-23]. Today, with medicine advancement and knowledge about medicinal plants, new disciplines have emerged such as "Dentistry" and "Chemistry of Natural Products"; where union of these sciences allows to address problems related to oral diseases through active ingredients of plant origin use. It is important to mention that antiseptic, antimicrobial, antioxidant, antiviral, and analgesic agents derived from plants are of great interest in dentistry due to their high pharmacological potential and low side effects [24]. At present, can be affirm that plant extracts use such as: propolis, burdock and neem, have given excellent results [2-24]. Although medicinal plant-based drugs are gaining popularity due to their high pharmacological potential, their administration is generally done in traditional dosage form. According to Syed and researchers, this form of application has a wide range of disadvantages; among them, low bioavailability of active principle, poor solubility, absorption and instability, thus restricting drug therapeutic effectiveness [25]. Therefore, a need arises to develop new forms of administration of active principles from medicinal plants using nanoparticle systems, not only to increase active compound bio-availability in target organs, but also reducing adverse effects, gaining better therapeutic potential and increase drug half-life [26].

Nanoparticles wide use in dentistry is based on properties such as miniscule size, high contact surface, lower toxicity, and good compatibility, which is often absent in micro and macro materials [27], and sometimes in traditional application forms. These properties make nanoparticle potentially useful as an antimicrobial, in tissue regeneration, oral bone fractures treatment, dental pulp repair, periodontium ligaments regeneration, anticancer, among others [28]. It is known that 10 to 15% of the world population suffers from severe oral infections such as cavities, apical periodontitis associated with inflammatory process [29, 30].

Antimicrobial: Many bacteria and fungi produce diseases that manifest themselves in or around oral cavity; among them, *Lactobacillus*, *Streptococcus*, and *Candida spp*. The greatest susceptibility to tooth decay is found in 20 to 40 age group, being women more susceptible [9]. In the new biologically active molecules dosing system, nanoparticles are included, making it possible to take full advantage of the therapeutic potential. Indeed, according to Emmanuel and researchers [28, 30], silver nano-particles (AgNP) synthesis based on *Justicia glauca* leaf extracts have antibacterial and anti-fungal activity specifically against *Streptococcus mutans, Staphylococcus aureus, Lactobacillus acidophilus*, *Micrococcus luteus*, *Bacillus subtilis*, *Pchericaalugia coli*, and *Candidansomonas coli*, main dental caries and periodontal disease causes, with a Minimum Inhibitory Concentration (MIC) of 25-75 µg/mL. Also, Manojkanna and collaborators reported that silver nanoparticles synthesized from *Plectranthus ambionicus* extract exhibited an antimicrobial potential against *E. faecalis* and *C. albicans* [32]. It is of great importance to mention that other investigations have confirmed antimicrobial effects based on nanoparticles, Niveditha and collaborators confirmed that silver nanoparticles based on *Plectranthus amboinicus* extracts showed antimicrobial effect against *Klebsiella pneumoniae, Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Salmonellaparatyphi* [33]. Nanoparticles from *Chrysopogon zizanioides* leaves aqueous extracts are potentially active against bacteria and has antioxidant activity *in-vitro* [34].

The *Mimusops elengi* fruit extract in silver nanoparticles were proven and confirmed with antioxidant potential compared to standard ascorbic acid, according to Hoskote and Kiran studies [35] Cardamom fruits and *Fructus amomi* dry aqueous extract could be considered a Green resource for easy gold and silver nanoparticles synthesis for various medical ailments [36].

Anti-inflammatory and Antioxidant Activity: Dental caries and periodontitis are one of the most common human diseases in the world. According to World Health Organization (WHO), 3.47 billion people in the world had some oral disorder in 2017. One of the clinical manifestations is inflammatory reaction, due to pathogenic bacteria colonization capable of binding in biofilms [10, 36, 37].

A wide range of bioactive compounds isolated from medicinal plants have been reported to have anti-inflammatory activity; among them, curcumin, which is the main component of *Curcuma longa*, acting through various mechanisms that are not fully understood. According to Sinjari and researchers [10], curcumin formulated in liposomes allows dental pulp stem cells homeostasis restoration at 3 and 5 mmol/L. Thus, favouring cell proliferation decrease, morphological changes and positive regulation of IL-6, IL-8, MCP1, and IFNγ in the presence of 3 and 5 mmol L-1 HEMA treatment. Natural nanocarrier CurLIP influences numerous biochemical and molecular cascades that provoke anti-inflammatory properties in response to HEMA treatment in human dental pulp stem cells, representing an innovative endodontic formulation capable of improving dental care quality with a great human community impact.

Dental Care: In traditional Chinese medicine, a wide range of plants are used in oral care, including Icariin, which strengthens bones, inhibits osteo-penia and inflammation. It was reported that its nanoparticles greatly accelerated dental implants integration, improving success rate of dental implants [39]. Also, it was reported that *Mangifera indica* nanoparticles improve mechanical bonding with considerable antibacterial activity [10].

Anticancer: Among limitations of plant extracts popular application there is active principle solubility, a parameter that considerably limits latter therapeutic action. However, nanocurcumin (curcumin-loaded polymeric nanoparticles) have been shown to have affinity for water without any surfactant. In effect, ease of dispersion gives it a great advantage in systemic application, thus allowing to exponentially take advantage of extract pharmacological potential; According to Laura M. in her work entitled Cardamom fruits as a green resource for easy gold and silver nanoparticles synthesis and their biological applications [40], reports that nanocurcumin are potential anticancer agent due to nuclear factor kappa B and transcription activation in cancer cells. Also, nanoparticles loaded with *S. miltiorrhiza*, *Carthamus tinctorius*, and *Dendropanax morbifera* are conferred anticancer activity due to their ability to inhibit oral precancerous and oral squamous cell carcinoma cell line proliferatios [41, 42]. Following same order ideas, it is important to mention that silver and gold nanoparticles based on extracts of *P. ginseng* Meyer, *Dendropanax mobifera* Le veille, *Tamarix gallica*, *T. chebula* of *M. edule* have proven their antitumor activity *in-vitro* [43].

Dermatology: It has been deeply studied that plants provide beneficial effects to humans due to their antimicrobial [3, 13, 44], antioxidants [45–47], among others properties, which are attributed to their secondary metabolites [48]. However, phytochemical effectiveness on skin can be conditioned by environment characteristics, compound degradation rate or other physicochemical drawbacks [49]. In this manner, nanotechnology is at the forefront in vehicles creation that do not only protect bioactive component against adversity, but also potentiate its beneficial effect, reduces toxicity and increases bioavailability at required site, as well as allows a controlled release for greater effectiveness [7]. It should be pointed out the particle size importance, and to a greater extent, a higher charge concentration to facilitate penetration into the skin barrier and better absorption during dermal administration [50].

Nanoencapsulated Antioxidants: Skin has endogenous antioxidants and enzymes that allow the control of reactive oxygen species; however, such activity is compromised by oxidative stress generated by radiation or pollution, not to mention that with the time passage it deteriorates; therefore, optimal exogenous antioxidants topical use is necessary to strengthen these mechanisms [49, 51].

Several investigation have shown nanotechnology potential in natural extracts applications for dermatological purposes, such is the case of olive leaf extract encapsulation with biodegradable nanoparticles of poly-lactic acid (PLA), desirable characteristics were obtained in particle size (246.3 nm), polydispersity (0.21), and z potential (-27.5 mV), which facilitated its skin permeation; likewise, nanoencapsulate antioxidant capacity against H_2O_2 radical had an IC_{50} = 4.37 mg/mL and showed that extract release reached 100% in 7 days under healthy skin pH conditions. It is noteworthy that the cosmetic formulation with encapsulation proposed presented stability by not generating significant differences in odor, rheology, and emulsion, in comparison with non-encapsulated extract where there were changes in color and pH [49]. In the case of purified compounds, Quercetin, one of the best known flavonoids [52] due to its high antioxidant power [13] has been tested in its encapsulated form with sodium tripolyphosphate and chitosan nanoparticles, obtaining an average particle size of 183.6 nm, and z potential of 37 mV. This polymer has allowed to reduce toxicity, as well as provide it with greater stability and hydrophilicity, greater absorption in assay with spontaneously immortalized human keratinocytes (HaCat); likewise, this way easily penetrated epidermis and was retained in mice skin. It is relevant to mention that mentioned chitosan nanoparticles were able to potentiate the quercetin anti-UVB effect, efficiently inhibiting NF-kB/COX-2 signaling pathway that gives rise to cutaneous edema when activated by this type of radiation [53]. In a similar study, quercetin was encapsulated with a biodegradable copolymer (PLGA-TGPS), observing greater hydrophilicity and anti-UVB effect by significantly blocking COX-2 compared to unencapsulated compound in HaCat cell line; in addition, they corroborated that it penetrated outer layer skin using fluorescent coumarin-6 probe, and it was macroscopically and histopathologically evidenced that skin damage was mitigated in their *in-vivo* study with mice exposed to UVB radiation [54]. On the other hand, through the on sol-gel based platform, nanoparticles composed of silane have advantages over other platforms such as its greater loading capacity compared to liposomes, in addition to providing pores distribution that affect release rate. Likewise, was pointed out that curcumin, another antioxidant compound, when encapsulated solves rapid degradation problems and low solubility [55].

Nanoemulsions with Antioxidants: Regarding the use of nanoemulsions, this technique has been used in order to load pomegranate peel extract ethyl acetate fraction for the reason that it is rich in polyphenols. Baccarin and researchers made two emulsions, one with pomegranate seed oil and other with medium length chain triglycerides, mean size of 201.2 nm and 202.5 nm respectively; likewise, zeta potential was -21.9 and -25.7 mV, and poly-dispersity index was 0.17 and 0.11 respectively; which allowed them to obtain physical stability. Antioxidant activity was observed against H_2O_2-induced hemolysis by IC_{50} of 27.16 μg/mL and 76.05 μg/mL respectively, and compared their protective effect against oxygen radicals induced by azo compound AAPH (2,2 '-Azobis (2-methylpropionamidine) dihydrochloride) on 5 bands of human erythrocyte membrane proteins, reporting values of 59.5% to 88.2% depending on the band and emulsion [56]. Likewise, they showed that nanoemulsions have photoprotective activity against UVB radiation in HaCat cell line in a dose-dependent manner and sun protection factor (SPF) *in-vitro* being fraction and oil concentrations (~25) dependent; furthermore, phototoxicity in Neutral Red uptake test in fibroblast line of Swiss albino 3T3 mice was not observed [57]. In another study, *in-vitro* pomegranate peel main polyphenols skin permeation was evaluated, observing in majority skin retention compared to the free fraction, a 2.2 times higher gallic acid retention in stratum corneum was observed using nanoemulsions [58].

Antimicrobial Effect with Nanotechnology: Skin diseases are very common, almost 900 million people of all ages suffer from these conditions [59]. Likewise, there is a growing interest in natural products use due to microorganisms resistance towards conventional treatments [44]. With regard to fungi, components of the cashew tree walnut shell, as anacardial acid (AA), whose antimicrobial capacity has been proven in bacteria that cause skin infections [60], and cardol (CD), has shown inhibitory capacity *in-vitro* against pathogenic strains that cause candidiasis and cutaneous dermatophytosis. These bioactive compounds encapsulated with chitosan and alginate nanoparticles (NP/AA and NP/CD) showed MIC and CMF values of 0.625 mg/mL and 0.312 mg/mL respectively, against all *Trichophyton rubrum* strains tested; while only NP/AA had activity against a strain of *Candida tropicalis* with MIC/CMF of 2.5 mg/mL.

Authors pointed out that in encapsulated form, inhibitory and fungicidal values were reduced due to dosage-controlled release. Therefore, it is important to highlight that characteristics obtained from nanoparticles not only gave stability and efficiency in encapsulation, but also allowed a prolonged antimicrobial effect [61]. Regarding parasites, use of nanocochleates (nanocarriers) with essential oil of *Artemisia absinthium* (EO-Aa-NC) to treat cutaneous leishmaniasis has yielded results that should be considered. In their research, Tamargo and researchers, managed to obtain EO-Aa-NC with a size of 74.2 nm, a polydispersity index of 0.33, and a zeta potential of -40.8 mV; likewise, tested in murine models infected with *Leishmania amazonensis* on the pad of the foot; intralesional EO-Aa-NC application suppressed infection by approximately 50% compared to untreated mice, and similarly, smaller lesion size was noted compared to mice treated with only essential oil; in addition, it had an efficient inhibitory activity in infection progression like Glucantime, a leishmanicide drug. However, did not show significant difference in relation to parasite load, and there was no full cure in any mice. It should be noted that nanocochletes alone did not show antileishmanial activity [62]. In relation to bacteria, application of silane nanoparticles loaded with curcumin to treat skin lesions, such as infected burns, is promising, since its inhibitory effect has been demonstrated *in-vitro* against common bacteria, such as *Staphylococcus aureus* MRSA (methicillin resistant) and *Pseudomonas aeruginosa*; likewise, in murine model, a significant reduction in bacterial count has been verified when treating burns infected by *S. aureus* MRSA; in addition to reducing burn inflammation extent, and significantly accelerating healing. It should be noted that this type of nanoparticles, by themselves, exhibited antibacterial activity, and with curcumin this effect was enhanced [55]. In this regard, there are infections that are related to antioxidant activity due to free radicals formation, as is the case with acne vulgaris. People who suffer from this disease are under systemic and skin oxidative stress due to reactive oxygen species [63].

In response to this problem, Pan-In and researchers, tested cellulose nanoparticles loaded with α-mangostin, a phytochemical obtained from *Garcinia mangostana*. In previously mentioned work, nano-particles with a size between 300 and 500 nm, polydispersity of 0.11, and the percentage of the bioactive of 41.9% were obtained. Consistent bioactive release in human synthetic sebum at 37 °C and antibacterial activity of the encapsulation against *Propionibacterium acnes*, the main bacteria that causes acne was verified *in-vitro*, obtaining MIC and CMB values of 15,625 µg/mL and >250 µg/mL respectively. Likewise, in irritability tests they showed negligible irritation, excellent fixation, and support in hair follicles on healthy human volunteers. In addition, in their preliminary clinical trial with acne patients, significant improvements in both acne severity index (40%) and inflammatory lesion count (> 50%) were observed, applying gel-nanoparticles loaded with mangosteen 2 times a day [64]. In a subsequent study, efficacy of nanoparticles loaded with α-mangostin (mangosteen bark extract) topical application in a gel 0.5% presentation for the treatment of mild to moderate acne vulgaris in patients between 18 and 40 years of age were evaluated. In this work, researchers observed a significant reduction approximately 70% in comedones and inflammatory lesions at the end of treatment. It should be mentioned that there was no significant difference compared to group treated with 1% clindamycin, but in the group treated with extract a significant improvement in the severity of the disease without presenting severe side effects was observed. Therefore, authors suggested its use for mild to moderate acne vulgaris treatment [65]. Due to the above, natural products beneficial potential with antioxidant and antimicrobial properties, among others, through application of nanotechnological advances are of dermatological relevance for the skin care and protection.

Gastrointestinal Infection: The digestive system main function is directed to digestion, absorption of nutrients and excretion of products such as acids, enzymes, buffers, and salts [66]. In addition to its primary function, intestine constitutes an effective barrier as protection against pathogen micro-organism's invasion and potentially harmful molecules passage to body [67].

Gastrointestinal system diseases are numerous and can occur in various areas of tract, involving mouth, rectum and anus [66]. Among them we have parasitic disorders, bacteria/virus infections, diarrhea, reflux, gastroenteritis, constipation and swelling [68]. Among etiological agents responsible for gastrointestinal disorders are *Entamoeba histolytica* and *Escherichia coli*, main responsible for dysentery in developing countries, where hygiene conditions are very limited; it should be noted that around 25% of gastrointestinal conditions in the world population is caused by *E. histolytica*, [68] another important pathogen is *Helicobacter pylori* [66], a cause of chronic gastritis and a risk factor for gastrointestinal cancer induction [69]. This type of cancer encompasses a variety of diseases, many of which have bad prognosis worldwide [70]. This is why phytotherapy based on herbal preparations has been an important resource in history for the gastrointestinal diseases treatment, many of which have reached modern medicine based on scientific evidence [71]. Pacheco-Ordaz using extracts of *Berberis vulgaris* and *Curcuma longa* loaded in nanoparticles of cationic copolymer Eudragit ® EPO, determined the amoebicidal activity against *E. histolytica* obtaining an IC_{50} of encapsulated *B. vulgaris* extract at 26 ppm compared to free extract that was 34 µg/mL. The *C. longa* extract had an IC_{50} that was 19 ppm corresponding to the encapsulated extract compared to the free extract, which was 38 µg/mL [12]. Polymeric nanoparticles (chitosan and hydroxypropylmethylcellulose) loaded with *Schinopsis brasiliensis* extract by Oliveira and collaborators, allowed to observe a considerable improvement in antimicrobial action of encapsulation compared to free active pharmaceutical ingredient (API), since MIC determined for *E. coli* beta-lactamases Broad spectrum was initially 1,000 µg/mL, while with formulated, a MIC of 7.5 µg/mL of API was obtained, which represents an improvement of 133 times [72]. Pinilla and Brandelli demonstrated that garlic extract and nisin co-encapsulated in phosphatidylcholine nano liposomes, enhanced antimicrobial effect against Gram negative and Gram-positive bacteria. For *E. coli* and *Salmonella enteritidis*, nisin alone at 16 µg/mL resulted in antimicrobial activity of 200 AU/mL (absorbance units per milliliter), while no activity was observed at 8 µg/mL and 4 µg/mL. Meanwhile under analysis conditions garlic extract had no antimicrobial activity against the strains analyzed, combination of nisin 16 µg/mL and 8 µg/mL with garlic extract showed the highest antimicrobial activity (1,600 AU/mL) against *Listeria monocytogenes*, *Staphylococcus aureus*, *S. enteritidis* and *E. coli* [73].

Pan-In and researchers, used *Garcinia mangostana* extract to load ethylcellulose and methylcellulose nanoparticles, shown to improve time- and increase- resistance to damage due to stomach acidic conditions and allowed to determine a MIC against *H. pylori* ATCC 43504 of 62.5 µg/mL, similar to that obtained with metronidazole [74]. Saravanakumar and researchers, developed silver nanoparticles (2-40 nm) loaded with *Toxicodendron vernicifluum* extract and determined their MIC against two enteropathogenic bacteria, obtaining a result of 8.12 µg/mL against *E. coli* STEC and 18.14 µg/mL for *H. pylori* [21]. Similarly, Safarov and researcher susing silver nanoparticles loaded with *Acorus calamus* Linn. extract determined a concentration of 350 µg/mL efficient for *H. pylori* biofilm inhibition [75]. Gold nanoparticles (1 and 2 mM HAuCl4) of 7 nm and 55 nm loaded with extracts of *Tribulus terrestris* by Gopinath and collaborator, allowed to determine MIC and minimum bactericidal concentration (CMB) against *H. pylori* multi-resistant strains, which showed an activity in a size dependent manner. The 55 nm nanoparticles had a MIC of 16.75 µg/mL and a CMB of 18.75 µg/mL, in comparison with those of 7 nm which obtained a MIC of 18 µg/mL and a CMB of 20.50 µg/mL. No cytotoxic effect was found in AGS cell line at concentrations of 50 µg/mL [76]. Swathi and George, using cerium oxide (CeO_2) nanoparticles loaded with *Nelumbo nucifera* flower extract, reported an *in-vitro* cytotoxic effect against human colon cancer cell line HCT 116, with an IC_{50} of 41.6 mg/mL [77]. Rahimivand and researchers., determined *Artemisia ciniformis* extract cytotoxic activity encapsulated in sodium alginate nanogel on the gastric cancer cell line AGS; results showed apoptosis induction in a dose-time-dependent manner with an IC_{50} of 21.5, 18.5, and 15.2 µg/mL, after 24, 48, and 72 h. respectively compared to extract alone 61.9, 40.07, and 28.7 µg/mL after 24, 48, and 72 h respectively [78]. On the other hand, Olea and researchers, analyzed ethyl acetate and ethanolic *Leptocarphari vularis* extracts incorporated in polymeric micelles formed from Pluronic F127 against the cancer cell lines HT-29 (colon cancer) and PC-3 (prostate cancer). The IC_{50} values for encapsulated ethyl acetate extract showed an activity at 0.05 mg/mL compared to unencapsulated extract 10.70 mg/mL for both cell lines, whilst encapsulated ethanolic extract showed an activity against HT-29 at 6.70 mg/mL compared to unencapsulated extract 14.90 mg/mL and an activity at 0.30 mg/mL against 15.60 mg/mL of non-encapsulated extract tested in PC-3 [79].

Systemical Disease/Infection: Several advantages for natural extracts nanoencapsulation can be encounted from therapeutic agents uses at systemic level by virtue of formulation type which provides bioactive compounds extracts protection [80], release control, facilitates site of action binding improving bioavailability and therapeutic activity [81]. An example of this are chitosan nanoparticles that represent a viable vehicle due to its biocompatibility and good stability, reason why it is used in drug delivery, in non-linear vectors development and for vaccines active principle release [82]. There are reports of extracts that function as antioxidants and anti-cancer agents, studies have been carried out to ensure their bioavailability at blood level, which is why nanoencapsulated formulations that fulfill this function have been used, an example is Anthocyanin nanoencap-sulation, which has been reported as a cancer proliferation reducer and tumor formation inhibitor [83], it was encapsulated in whey protein and citric pectin, studies were carried out in healthy volunteers and it was found that there is alarge intestine availability increase compared to other formulations, therefore, this type of encapsulation could optimize bioavailability and concentration at anthocyanins systemic level [84].

A *Prunus cerasus* extracts-beta-lactoglobulin encapsulation report indicates a anthocyanins protection to anthocyanins contained in gastric digestion extract, has a controlled release manner in small intestine, hence extract availability is ensured and administered dose becomes more effective [85]. Polyphenols nanoencapsulation, notwithstanding known for their antioxidant power have been used in inflammatory processes and cancer treatment, however formulations in which it has been tried to administer this type of extracts have not have been able to overcome the disadvantages of this type of compounds, which are low stability, high light sensitivity, low solubility in water and poor bio-availability. Therefore, release systems have been used to improve their chemical or permeability stability. Nanovectors such as cyclodextrins, solid dispersions and liposomes systems have been used, in this way it is ensured that polyphenols reach binding site and their activity is favored by increasing extract-tumor contact area [86]. Thus, guabiroba fruit extracts nanoencapsulation, of which a large number of phytochemicals have been reported with applications in several diseases treatment, among compounds that stand out are polyphenols, for which a study employing guabiroba extract nanoencapsulated with poly (D, L-lactic-acid-co-glycol) (PLGA), its inhibitory activity against *Listeria innocua* was demonstrated in addition to a reduction in reactive oxygen species (ROS) in non-cancer cells in both cases at a low concentration, hence encapsulation allows controlled release and decreases minimum effective concentration of active ingredient, thus preventing side effects [87]. Curcumin nanoencapsulation, used as an anticancer treatment; has also been evaluated with thiolated chitasan and polyientglycol diacrylate hydrogel, results showed that loss of bioactivity is avoided, encapsulation is improved and there is a decrease in side effects due to effective concentration decrease, sustained release profile allows increase its contact surface with tumors in higher concentrations, thus improving its anticancer activity [88]. Celastrol encapsulation, a tripenoid extract obtained from the Chinese herb *Trypterygium wilfordii*, in poly (ε-caprolactone) nanoparticles has been reported, studies on prostate cancer cells were carried out by an *in-vitro* study, different extract concentrations were proved (0.5, 1.0 and 2.0 μM), to subsequently evaluate efficacy of encapsulation for cancer cells inhibition, results showed that capsules inhibited growth in a dose-dependent manner, wherefore this work offers a new area of research for cancer treatment making use of nanoencapasulation formulations [11].

CONCLUSION: Nanotechnological application advances for greater bioavailability and efficacy in natural products therapeutic doses, whose beneficial effects are proven, is undoubtedly of vital importance for the improvement of pharma-cology and human life quality.

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