Chapter 2
Nanotechnology-Inspired Bionanosystems for Valorization of Natural Origin Extracts

Ana Catarina Sousa Gonçalves, Ana Sofia Mendes Ferreira, Alberto Dias, Marisa P. Sárria, and Andreia Castro Gomes

Abstract Medicinal plants are the richest bioresource of drugs on traditional systems of medicine and their use in treating diseases by ancestral societies has caught the attention of the scientific community. Application of these plants in daily diet, cosmetic and pharmaceutical industries is widely implemented for many years. However, with the increasing need for more sustainable and environmentally friendly techniques, substituting chemical processes by plants in the production and enrichment of nanomaterials is certainly a very appealing alternative.

Studies have shown that among many examples of green synthesized drug delivery systems, those that receive the most attention include nanometallic particles, polymers and biological materials. Nanotechnology has enabled the creation of new drug delivery systems with the ability to increase the efficacy and improve the bioavailability of plant-derived bioactive compounds, promoting their release in a controlled manner, requiring a reduced dose, and reducing side effects while potentiating their activity. This review highlights the use of biosynthesized nanomaterials as a viable alternative to conventional techniques, and values plant extracts as a source of new nanomedicines, acting as an ally or alternative to existing therapies.

Authors Ana Catarina Sousa Gonçalves and Ana Sofia Mendes Ferreira have equally contributed to this chapter.

A. C. S. Gonçalves · A. S. M. Ferreira
CBMA – Centre of Molecular and Environmental Biology, Department of Biology, University of Minho, Campus of Gualtar, Braga, Portugal

A. Dias · A. C. Gomes (✉)
CBMA – Centre of Molecular and Environmental Biology, Department of Biology, University of Minho, Campus of Gualtar, Braga, Portugal

IB-S Institute of Science and Innovation for Sustainability, University of Minho, Campus of Gualtar, Braga, Portugal
e-mail: agomes@bio.uminho.pt

M. P. Sárria (✉)
INL – International Iberian Nanotechnology Laboratory, Braga, Portugal
e-mail: marisa.passos@inl.int

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2.1 Introduction

Nanotechnology has been one of the trendiest technologies in the last decades with potential applications at all industrial sectors, from medicine to clean water and energy (Fig. 2.1). Namely, nanotechnology has had tremendous impact in medicine in the synthesis and development of various types of nanomaterials and nanoparticles, used as vehicles of antioxidants, antimicrobials and anticancer agents for therapeutic and diagnostic purposes, and as components of nanosensors (Allafchian et al. 2018). These new nanotechnology tools for medical research and practice are more effective and enable faster response to new diseases, allow continuous patient health control, besides increasing the accuracy of examinations and surgeries (Ocsoy et al. 2018).

Knowledge and use of medicinal plants to treat diseases has had immense relevance along mankind's history. Actually, a large segment of the population in many countries continues to use them solely or as complementary practices to conventional medicines. Although many pharmaceutical products have been implemented in the clinic, the chemical composition of medicinal plants and their popular uses have become focus of intense research by the scientific community, pursuing

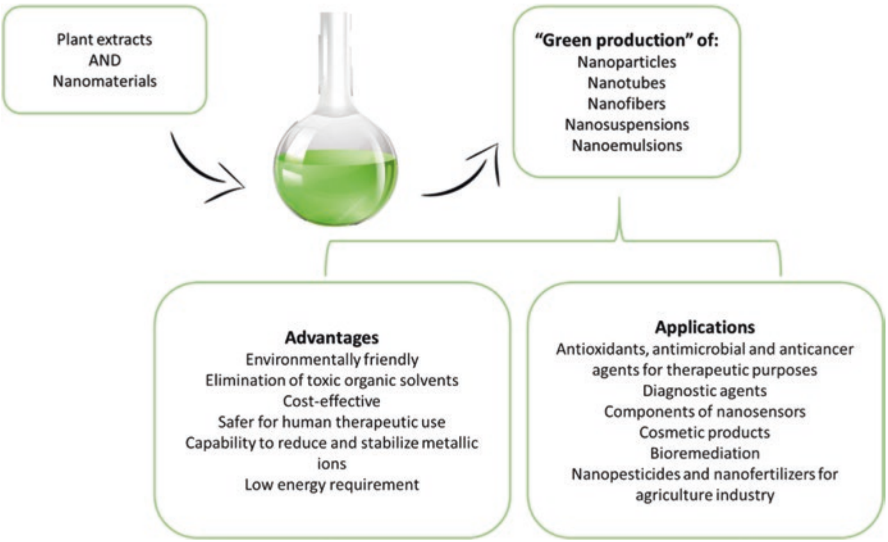


Fig. 2.1 Nanotechnology approach for exploration of plant extracts for biomedical and environmental applications. Use of plant extracts in the production and/or their incorporation in nanotechnology materials has advantages that can be applied to various areas

increasingly innovative products, with fewer side effects, compared to those associated with existing drugs (Islam et al. 2015).

Many bioactive compounds present in plant extracts, such as some alkaloids and phenolic compounds, are highly water soluble and therefore unable to cross lipid membranes. Whereas others, like many terpenoids, are poorly water soluble, making them poorly bioavailable and effective (Afrin et al. 2018). However, several nanotechnological strategies have been developed, such as polymer and solid lipid nanoparticles, liposomes, nanoemulsions, nanosuspensions, nanofibers and nanotubes to try to overcome this limitative feature. These discoveries have revolutionized drug delivery by developing new targeted systems with the ability to increase the efficacy and bioavailability of bioactive compounds, promoting their release in a controlled manner, requiring a reduced dose, reducing side effects and potentiating the activity of the vegetal extracts more efficiently (Afrin et al. 2018).

Multiple strategies of applying nanotechnology to plant extracts have been widely cited in the literature as "green nanoparticles" and "green synthesis". Many original research and review articles focusing on green synthesis of metal nanoparticles, as gold, silver, zinc, copper, iron and others metal oxides report the use of plants extracts rich in secondary metabolites due to their capability to reduce and stabilize metallic ions (Selvam et al. 2017). Furthermore, green synthesis avoid the use of toxic organic solvents and severe reaction conditions, making it an eco-friendly alternative, cost-effective, sustainable and safer for human therapeutic use (Thatoi et al. 2016).

2.2 Methodology

The goal of this review is to provide an overview of the major developments in this field, summarizing the multitude of plant extracts applications in nanotechnology, showing how relevant these natural compounds can be and how it is becoming a trend in nanotherapeutics research.

Literature searching strategy started by pre-selecting keywords related to nanotechnology-inspired bionanosystems using plant extracts and inserting these as search topic into the selected electronic databases, namely PubMed, Scopus and Web of Science.

Two searches were carried out: (1) at PubMed using the following keywords with 205 results: ((plant extract [Title/Abstract]) AND (nanotechnology [Title/Abstract])) and these were being adapted to the syntax and subject headings of the databases; (2) at the three databases, using the keywords: ((plant extract [Title/Abstract] AND (nanoparticles [Title/Abstract])), ((plant extract [Title/Abstract] AND (nanostructures [Title/Abstract])), ((plant extract [Title/Abstract] AND [nanomaterials [Title/Abstract])), and ((plant extract [Title/Abstract] AND (nanocomposites [Title/Abstract])). Results from both searches were merged, resulting in 1060 publications, and after duplicate elimination, just 634 remained.

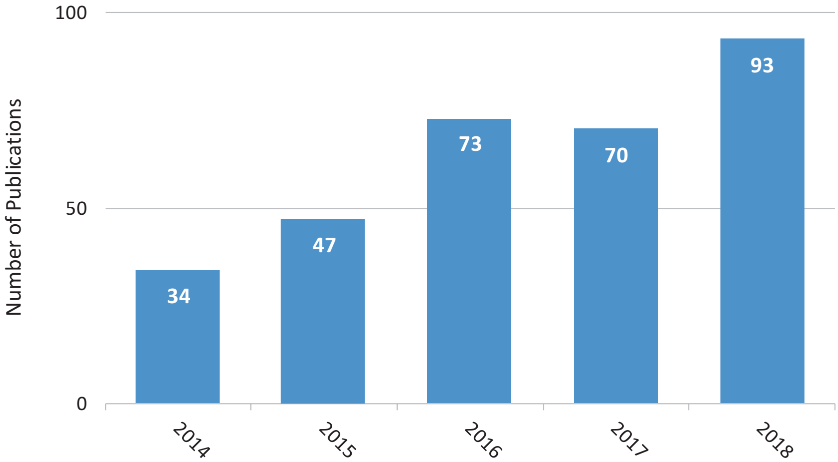


Fig. 2.2 Trend of research articles published from 2014 to 2018, by searching on PubMed, Scopus and Web of Science databases for "plant extract" AND "nanotechnology", "plant extract" AND "nanocomposites", "plant extract" AND "nanostructure", "plant extract" AND "nanoparticles" and "plant extract" AND "nanomaterials", after removing duplicates and reviews

Of these, 317 publications were rejected given that keywords selected were not present in the title or abstract, as or were not written in English language, or were in the format of reviews or book chapters. References in reviews were, however, manually consulted to identify citations that could have been missed in the original database searches. After this step, the collected publications were organized by years, as indicated in Fig. 2.2, demonstrating the increasing trend in this field for the last 5 years. Figure 2.3 shows the intersection between the keywords selected.

The full text of the remaining 182 studies was carefully examined. From this analysis, 51 studies were rejected because either these did not present conclusive results, or had similar or contradictory results.

From this screening and eligibility process, 107 published studies were eligible to be included in this review -see flowchart diagram at Fig. 2.4. The last online search was performed on 13th April 2019.

2.3 Medicinal Plants and Nanotechnology

Medicinal use of plants by mankind is known since ancient times in different contexts. Medicinal plants have historically proved their value as a natural source of molecules with therapeutic potential, and currently represent an important resource for the development of new drugs (Atanasov et al. 2015). Nowadays, the use of natural-derived products as agents for drug discovery has gained considerable attention by the pharmaceutical industry, and is expected to be among the most important sources of new drugs. However, despite their immense potential and considerable availability, only a few medicinal plants have been marketed. This highlights the complexity of

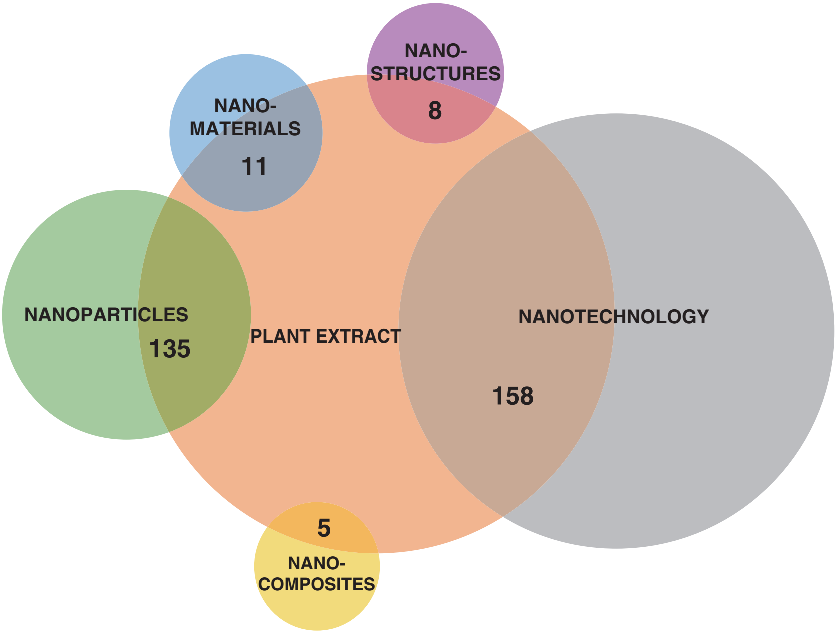


Fig. 2.3 Venn diagram with keywords used in PubMed, Scopus and Web of Science databases, after removing duplicates, reviews and book chapters. The numbers indicate the quantity of publications with the combination of two keywords selected

drug discovery, and the need for an interdisciplinary approach, as well as the valence of considering nanobiotechnology as an ally for the development of new products, that can be used in the treatment of various diseases (Atanasov et al. 2015).

This review aims to recognize how medicinal plants, among of those referred/selected at published articles identified, are distributed throughout the planet. Worldwide distribution of medicinal plants is given in Fig. 2.5. Results show that 45% of the medicinal plants studied are originary from Asia. Countries like China and India have a long tradition in using plants as medicines, apart from being a source of food (Dzoyem et al. 2013). In recent decades, the interest in these plants has increased, with the recognition of their extraordinary pharmacological properties (Dzoyem et al. 2013). Within the search results, 20% of the plants studied were found in Europe, 16% in Africa, 13% in the American continent, and 6% in Oceania. However, it is important to consider that these values are not only related to the number of plants with potential *per* continent, but are also related to the investment that had been made in investigating them.

Plants produce a vast and diverse assortment of organic compounds, such as terpenoids, alkaloids, amino acids, phenolic compounds, glutathiones, polysaccharides, organic acids and quinones, with a vast array of pharmacologic activities like antioxidants, anti-inflammatory and antimicrobial. These substances, traditionally referred as "secondary metabolites" are derived from various parts of plants as leaves, stems, roots shoots, flowers, barks and seeds (Vijayaraghavan and Ashokkumar 2017). Recently, many studies have proven that plant extracts can act as a potential precursor for the

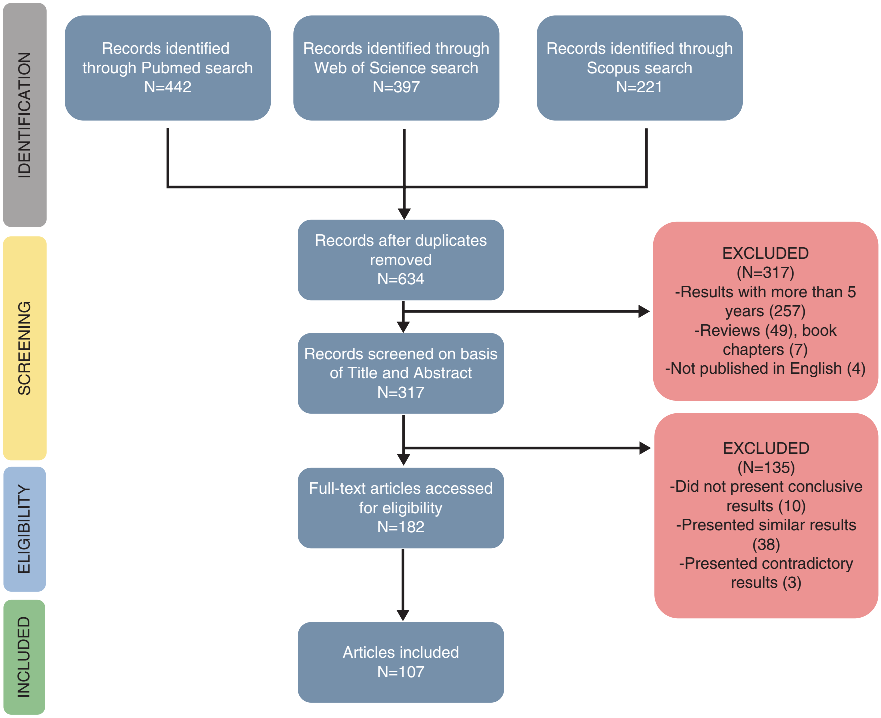


Fig. 2.4 Flowchart diagram of the study selection for this systematic review, from the selection of the keywords in Pubmed, Scopus and Web of Science databases, to the application of filters until the final set of articles

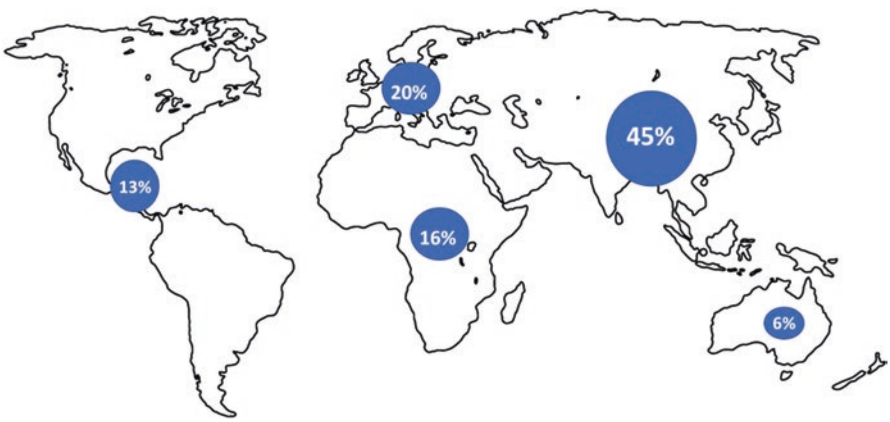


Fig. 2.5 Percentage of worldwide distribution of plant species studied in selected articles. The largest percentage of plants in the studies considered are derivated from Asia, where use and consumption of medicinal plants is significant, as due to their more extensive study

synthesis of nanomaterials in non-hazardous ways, through a process designated green synthesis (Chintamani et al. 2018; Mahendra et al. 2017; Marslin et al. 2015). Balamurugan and colleagues have tested the use of *Eucalyptus globulus* in the biosynthesis of iron oxide nanoparticles, resulting in a reproducibly high yield of about 83% (Balamurugan et al. 2014). Also, Klekotko and his team, in a study of the cytotoxicity of gold nanoparticles found that biological synthesis of these using the extract of *Mentha Piperita* revealed a promising lower cytotoxic profile than those synthesized chemically (Klekotko et al. 2015). Other studies with leaves of lemon and leaves of coriander have been employed for the extracellular biosynthesis of silver nanoparticles. Green leaves were preferably selected for synthesis of these metal-based nanoparticles given that these are photosynthetic organs of the plants, and therefore, H^+ ions to reduce the metal ions are more available (Amooaghaie et al. 2015).

The incorporation of natural products into different forms of nano-scale particles and materials, or the synthesis of these nanosystems with plant extracts has also been explored in nanotechnology. The low insolubility of organic compounds, low stability, poor absorption and rapid systemic elimination causes inherent limitations, impeding the use of these natural phytobioactives *per se* (Marslin et al. 2015). Emergent developments in nanotechnology contribute to surmount some of these obstacles. One of these strategies to circumvent undesirable effects is the incorporation of the natural bioactive agent in nanoparticles, to make its beneficial pharmacological properties more accessible and efficient (Dai et al. 2017).

In addition to the use of plant-based compounds incorporated into nanoparticles, their use for the synthesis of nanomaterials is a fast, economical and easily scalable synthetic route technique, that can enhance the biological activity of the compounds, showed in Fig. 2.6 (Mahendra et al. 2017).

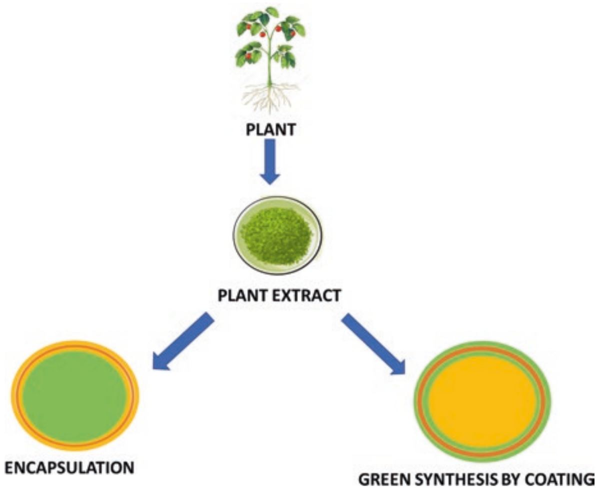


Fig. 2.6 Use of plant extracts in nanotechnology: encapsulation of plant extracts to enhance efficiency for a certain therapeutic target, represented as green core, in the left; and green synthesis of nanoparticles, at which plant derived components nucleate and stabilize nanoparticles formed from a colloidal solution

2.4 Nanomaterials Used in Combination with Plants Extracts

In recent years, nanotechnology has been increasingly used for the synthesis, engineering and design of various nanomaterials. Although the green synthesis is more applied to nanoparticles production, plant extracts have been used to fabricate nanofibers, nanotubes, nanosuspensions and nanoemulsions, as presented in Table 2.1.

Table 2.1 Types of nanostructures used in combination with plant extracts, their composition and advantages

Types of nanomaterials	Composition	Advantages	References
Nanoemulsions	Colloidal particulate system composed of a mixture of water and oil along with a suitable stabilizing surfactant	High biocompatibility, long-time circulation, low toxicity, efficient drug loading efficiency, targeted and sustained drug-release system	Periasamy et al. (2016), Hoscheid et al. (2015), Gumus et al. (2015) and Balestrin et al. (2016)
Nanosuspensions	Sub-micron colloidal dispersions of pure particles of drug, which are stabilized by surfactants	High solubility and bioavailability, drug safety and efficacy; long time circulation	Li et al. (2018), Jahan et al. (2016) and Periasamy et al. (2016)
Nanofibers	Ultra-fine solid fibers with small diameters (lower than 100 nm)	Improvement of drug release, drug loading and drug stability	Ahn et al. (2018), Ajoumshariati et al. (2016), Youse et al. (2017) and Miftahul (2018)
Nanotubes	Nanotubes are cylindrical structures with small diameters (lower than 100 nm)	High biocompatibility, mechanical strength, electrical and thermal conductivity	André et al. (2014), Foo et al. (2018), Tripathi et al. (2017) and Tostado-plascencia et al. (2018)
Nanoparticles	Particles that exist on a nanometer scale, under 100 nm. Nanoparticles types are divided in two main groups: organic and inorganic nanoparticles	High stability, high carrier capacity, feasibility of incorporation of hydrophilic and hydrophobic substances, and variable routes of administration	Riaz et al. (2018), Hassanien et al. (2018), Murad et al. (2018) and Sahni et al. (2015)

2.4.1 Nanoemulsions

Nanoemulsions are dispersions of two immiscible liquids, stabilized by a surfactant or surfactant mixture (Zorzi et al. 2015). Previous studies have suggested that nano-emulsions can be used as carriers of drugs, and may confer long-term validity on carrier drugs for antimicrobial, anticancer, larvicidal and intestinal activities (Zorzi et al. 2015). These can be administered via oral, ocular and intravenous to reduce side effects and potentiate pharmacological effects. A variety of essential oils derived from plants has been used to prepare nanoemulsions, including those derived from neem, basil, lemongrass, clove and kalojeere (Periasamy et al. 2016). Spontaneous emulsification and high pressure homogenization are the most used techniques when associating plant extracts to nanoemulsions (Zorzi et al. 2015). Main advantages of these are high biocompatibility, long-time circulation, low toxicity and efficient drug loading efficiency, targeted and sustained drug-release. Combining these advantages of nanoemulsions with the use of plant extracts, it can be obtained a product with exceptional biological properties that can be used for the production of hydrogels, creams and other products that can be applied at the pharmaceutical industry (Balestrin et al. 2016).

2.4.2 Nanosuspensions

Nanosuspensions are defined as unique liquid submicron colloidal dispersions of nanosized pure drug particles, stabilized by a suitable polymer and/or surfactant (Zorzi et al. 2015). Nanosuspensions represent a potential method for improving bioavailability of hydrophobic drugs (Odei-Addo et al. 2017). In most cases, nanoparticles need to be functionalized by various coating agents before application. Plant extracts act as capping agents and stabilize these (Chung et al. 2016). Nanosuspensions and nanoemulsions have common advantages, just differing between the two types of nanostructures. Nanoemulsions are composed of a mixture of water and oil, together with a suitable stabilizing surfactant, while nanosuspensions are mainly a dispersion of pure particles of a drug, which are stabilized by surfactants (Zorzi et al. 2015). These nanostructures in combination with plant extracts as agents for nanoparticle synthesis, or as a nanoparticle-incorporating bioactive compounds, or even the use at nanoemulsions, have attracted increasing attention by researchers working on targeted and sustained drug-release systems (Li et al. 2018).

2.4.3 Nanofibers

Fibers with diameter size at nanometric range are known as nanofibers. These can be generated from different polymers, and therefore, can have different physical properties and potential applications. Some examples of natural polymers include collagen, silk fibroin, keratin and gelatin (Youse et al. 2017). In addition to these, polymers of vegetable origin such as cellulose and alginate have also been used frequently (Youse et al. 2017). Electrospinning is the most commonly used method for their production (Ghayempour and Montazer 2018). It is a simple, versatile and efficient process to produce ultrafine fibers, as it can be applicable to different polymers (Ghayempour and Montazer 2018). The great advantage of nanofibers lies in their large surface area for volume ratio, as well as their porous structure, that favors cell adhesion, proliferation and differentiation *in vitro*. Functionalized nanofibers with antibacterial and healing properties have been extensively developed (Youse et al. 2017). There has been a growing use of nanofibers containing medicinal compounds from plant extracts for biomedical applications, particularly for wound dressings (Youse et al. 2017).

2.4.4 Nanotubes

Since the discovery and synthesis of carbon nanotubes, these materials have been highly investigated for their peculiar properties. Carbon nanotubes are cylinders made up of carbon atoms that have extraordinary mechanical, electrical and thermal properties, and have been the basis for various applications (Tostado-plascencia et al. 2018). Carbon nanotubes can be made by only one of these cylinders, being classified as single wall nanotubes, and as multi-walled nanotubes, which are formed by several cylinders that are concentrically coiled (Foo et al. 2018). In the field of biomedical applications, because of their extremely small size and lightness, nanotubes can reach the interior of a cell, and therefore, can be used as biosensors on medical diagnostics and therapies (Tostado-plascencia et al. 2018). However, a major inconvenience is though their uncontrolled cytotoxicity. To prevent it, some authors proposed a coating strategy by using a synthetic polymer capable of mimicking cell surface receptors. Although the use of plant extracts is not as widely used in nanotubes, recent studies have shown that their functionalization with plant extracts enhances their biological activity (Foo et al. 2018; Tostado-plascencia et al. 2018).

2.4.5 Nanoparticles

Nanoparticles are the most used nanostructures in combination with plant extracts (P. Sathishkumar et al. 2016). With a particle size between 1 and 100 nm these are composed of synthetic or semi-synthetic polymers with nano- or subnano-sized

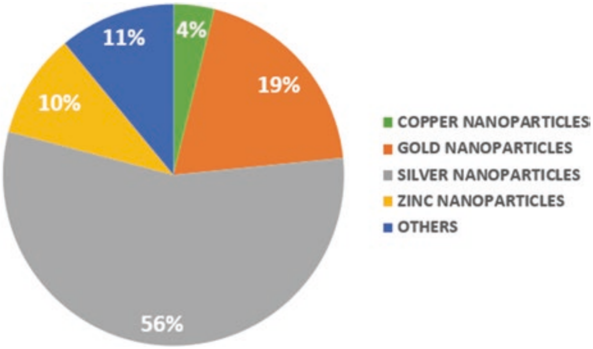


Fig. 2.7 Percentage of different types of nanomaterials used as object of study in articles, for the last 5 years, showing the trend of using metals in nanoparticles fabrication

structures (Zorzi et al. 2015). Encapsulation of plant extracts in nanoparticles is an effective way used to protect compounds against deterioration or interaction with other factors. Besides, several other advantages are of reference, namely increased solubility, efficacy and bioavailability, reduced dosage and improved drug absorption (Zorzi et al. 2015). On the other hand, plant extracts are also used for the production of nanoparticles, being the extract simply mixed with a salt metal solution at room temperature, to promote a reaction that is complete in a few minutes. Most conventional methods for producing nanoparticles are expensive, and environmentally hazardous due to the application of chemicals with high biological risk. (Mittal et al. 2013)

Green synthesis processes have been developed to overcome these disadvantages and are more acceptable for medical applications, due to their high biocompatibility, biodegradability, non-toxicity and green nature of the agents, as well as their cost-effectiveness (P. Sathishkumar et al. 2016). Plant extracts are used for the bioreduction of metal ions to form nanoparticles, and in support of their subsequent stability (Sathishkumar et al. 2016). The most common metal nanoparticles in (bio) medical applications are nanomaterials based on silver and gold, given their biocide effect, showed in Fig. 2.7 (Parveen et al. 2016).

Generally, nanoparticles are prepared by physical and chemical methods. Most of these protocols involve the use of toxic reagents that are potentially hazardous to the environment and relatively expensive (Sathishkumar et al. 2016). Hence, there was a need to develop nanoparticles synthesis techniques that were economically sustainable, environmentally friendly and simple. Secondary metabolites present in plants act as reducing agents towards stabilization of nanoparticles (Lediga et al. 2018). Green synthesis of nanoparticles has demonstrated advantage over chemically synthesized nanoparticles (Pirtarighat et al. 2019). Methods applied do not require any high temperature processing, or relevant toxic chemicals. Instead, these are eco-friendly, time affordable and cost effective procedures. More importantly, these are free of hazardous materials on their surface, and can be coated with bioorganic compounds that make them more biocompatible (Pirtarighat et al. 2019).

Table 2.2 Green-synthesized metal nanoparticles using various plant extracts

Metal nanoparticles	Active compound	Biological activity	References
Silver nanoparticles using *Malva sylvestris* extract	Quercetin, malvidin 3-glucoside and scopoletin	Antibacterial activity	Mahmoodi Esfanddarani et al. (2018)
Silver nanoparticles using *Gymnema sylvestre* extract	Gymnemagenin, gymnemic acids, gymnemanol, and β-amyrin-related glycosides	Anticancer activity	Arunachalam (2014)
Gold nanoparticles and silver nanoparticles using *Stereospermum suaveolens* extract	n-triacontanol, p-coumaric acid, beta-sitosterol, lapachol and cycloolivil	Antioxidant and anticancer activity	Francis et al. (2018)
Magnesium nanoparticles using *Artemisia abrotanum* extract	Aglycones and glycosylates, and hydroxycinnamic derivatives	Catalytic and antioxidant activity	Dobrucka (2018)
Copper nanoparticles using *Punica* granatum extract	Ellagic acid, punicalagins A and B, ellagitannins, gallic acid and gallotannins	Photocatalytic activity	Nazar et al. (2018)

Metallic nanoparticles are of great scientific interest, mainly for biomedical applications, with many of these being used as antibacterial nanoagents (Ocsoy et al. 2018). Several articles have reported the synthesis of metal-based nanoparticles using plant extracts. Some of related examples are listed in Table 2.2.

2.5 Properties and Applications of Plant-Based Nanomaterials

Nanomaterials properties can be very distinct. Their constituents used, as well as their modification, shape and size can give rise to a wide range of useful properties (Al-Huqail et al. 2018; Balalakshmi et al. 2017; Hussain et al. 2018). Also, to standardize production of nanomaterials using plant extracts it is necessary to change the reaction parameters, such as reaction time and temperature, pH, metal ion and plant extract concentrations (Devi et al. 2017). Final products can be characterized by a series of methods as UV-visible spectrophotometer, to validate the reduction of ions; TEM analysis to analyze morphology and size distribution; and X-ray diffraction for crystallographic characterization (Abbasi and Anjum 2016; Judith Vijaya et al. 2017; Thatoi et al. 2016; Yadi et al. 2018).

One of the most used and diverse type of nanoparticles, in terms of properties and applications, are metallic-based nanoparticles, as shown in Fig. 2.7. These are prepared by using various kinds of metals as silver, zinc, iron, copper, gold and titanium (Botha et al. 2019; Saravanan et al. 2016).

There are innumerous reports documenting that these metals are known to have multifunctional bio-applications as antibacterial, antimicrobial, antiproliferative, antifungal, antioxidant, anti-inflammatory, antivirus, antimosquitoes, larvicidal activity and others, as presented in Table 2.3 and Fig. 2.8.

Table 2.3 Applications of metal-based nanomaterials synthesized from plant extract

Metal-based nanomaterials	Applications	References
Silver	Antibacterial; anticancer; antioxidant; antimicrobial; anti-inflammatory; antifungal	Ocsoy et al. (2017), Kotakadi et al. (2014), Amooaghaie et al. (2015) and Rasheed et al. (2017)
Gold	Anticancer; antioxidant; antimicrobial	Rijo et al. (2016), Clemente et al. (2017), Yallappa et al. (2015) and Nambiar et al. (2018)
Copper	Antibacterial; anticancer; antimicrobial; antifungal; antioxidant	Hassanien et al. (2018), Saran et al. (2018), Pansambal et al. (2017) and Yugandhar et al. (2017)
Zinc	Antibacterial; antioxidant; antimicrobial; anticancer	Mahendra et al. (2017), Jafarirad et al. (2016), Suresh et al. (2015) and Vijayakumar et al. (2018)
Nickel	Anticancer; antibacterial; antimicrobial	Ezhilarasi et al. (2016, 2018), Amiri et al. (2018) and Saleem et al. (2017)
Titanium	Antioxidant; antibacterial	Santhoshkumar et al. (2014) and Nadeem et al. (2018)
Magnesium	Antioxidant; antibacterial	Sushma et al. (2016), Dobrucka (2018) and Jamal et al. (2016)

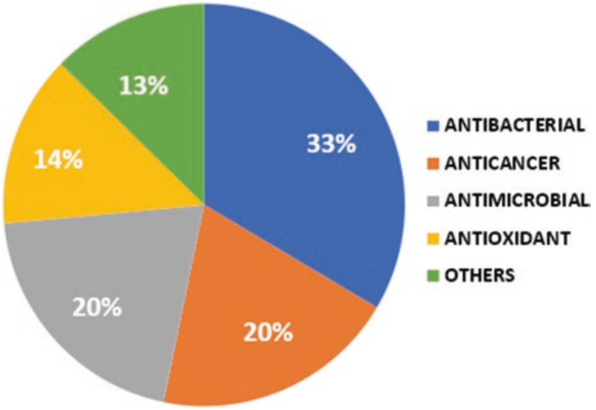


Fig. 2.8 Percentage of biomedical applications of nanomaterials synthesized from plant extracts considering data from the selected articles. It can be concluded that antibacterial, anticancer and antimicrobial are currently their main applications

2.5.1 Silver Nanomaterials

Noble metal nanomaterials have attracted attention because of their structures, as these exhibit better physical, chemical, biological properties and functionalities, due to their ultra-small sizes (Ali et al. 2017). Among the various nanomaterials, silver nanoparticles have been the most studied, given mostly because of their high electrical and chemical conductivity, chemical stability, high catalytic activity and antimicrobial, anticancer and larvicidal activities (Allafchian et al. 2018; Doddapaneni et al. 2018; Zhou and Tang 2018).

Silver nanoparticles can cause cell lyses, inhibit cell transduction, induce changes in cell membrane permeability, affect the microbial genome and cause DNA fragmentation (Ouda Sahar 2014). Oh et al. suggested that the eco-friendly silver nanoparticles prepared with *C. sinensis* were effective as antimicrobial agent against pathogenic *E. coli* and *S. aureus* (Oh et al. 2018).

The unique properties of silver nanoparticles are mainly advantageous, since these also led to an enhanced chemotherapeutic efficacy with minimal toxicity (Adil et al. 2016; Doddapaneni et al. 2018; Jena et al. 2016). Nowadays, nanoparticles-based combinatorial therapies using those with anticancer activity in combination with a chemotherapeutic agent are being translated into nanomedicine, in order to counteract resistance to the standard treatments (Banu et al. 2018; Dehghanizade et al. 2017).

In developing countries, vector-borne diseases are a major public health problem. Suman et al. (2018) indicates that silver nanoparticles synthesized with *H. enneaspermus* are highly stable and had significant mosquito larvicidal activity, having the potential to be used as an ideal ecofriendly approach for vector control programs (Suman et al. 2016).

Less common properties were reported by Sathishkumar et al. wherein silver nanoparticles using *C. sativum* leaf extract showed excellent anti-acne and anti-dandruff against *P. acnes* and *M. furfur*, respectively. Nevertheless, further investigation is still needed to turn it into an effective nano-drug for *in vivo* therapeutic application (Sathishkumar et al. 2016).

2.5.2 Gold Nanomaterials

Biocompatible gold nanomaterials have been studied as biosensors, diagnostic agents, cell targeting vectors, heating mediators for cancer thermotherapy and drug delivery (Yallappa et al. 2015). These stems mainly from their less cytotoxicity, high stability, ability to bind to biomolecules and also their visible light behavior (Guruviah Karthiga Devi and Sathishkumar 2016; Nambiar et al. 2018; Yallappa et al. 2015). Gold nanoparticles have been successfully prepared with *M. foetida* leaves extract and conjugated with folic acid and doxorubicin. Such complex showed low toxicity towards normal epithelial cells, and high toxicity to human cancer cells

(Yallappa et al. 2015). Also, investigation on combined use of *P. emodi* and gold nanoparticles demonstrated enhanced potential for treatment and management of diseases, as is the case of atherosclerosis and myocardial infarction (Ibrar et al. 2018).

Antimicrobial activity of gold nanoparticles has also been widely reported. Oh et al. suggested that gold nanoparticles produced with *C. sinensis,* besides being effective against breast cancer cells, were successful antimicrobial agents against pathogenic *E. coli* and *S. aureus* (Oh et al. 2018).

In addition, the use of gold nanoparticles as catalyst in photocatalytic degradation, and reduction of pollutant, has become a prominent approach for environmental solutions. Choudhary et al. studied a green synthesis approach of gold nanoparticles mediated by *L. speciosa* leaf extract. Obtained nanoparticles showed strong photocatalytic behavior, adequate to be used for treatment of wastewater containing toxic dyes and other organic pollutants (Choudhary et al. 2017).

2.5.3 Zinc Nanomaterials

Zinc nanomaterials have drawn attention for their exclusive optical and chemical behaviors, which are strongly related to their size and morphology (Ambika and Sundrarajan 2015). Zinc nanoparticles combined with *V. negundo* leaves extract were demonstrated to inhibit the growth of *S. aureus* and *E. coli* bacterial cells (Ambika and Sundrarajan 2015). Furthermore, zinc nanoparticles have highly promising prospective on biological functions for sensing, as drug delivery system, or as anticancer, antibacterial, antilarvicidal, antioxidant and antidiabetic agents (Jafarirad et al. 2016; Mahendra et al. 2017; Ovais 2017; Surface et al. 2018; Thatoi et al. 2016; Vijayakumar et al. 2018; Yadi et al. 2018). Zinc nanoparticles produced in combination with *V. Arctostaphylos* have been referred as nano-antidiabetic drugs (Bayrami et al. 2017).

2.5.4 Iron Nanomaterials

Due to the biodegrability, biocompatibility and easy synthesis nature of iron oxide nanomaterials, these have a great potential to be used as treatment agent towards different types of cancer (Zhao et al. 2018). *In vitro* studies revealed that green synthesis of iron nanoparticles with *C. sativum* can be used to enhance cytotoxic effects on HeLa cancer cells, for example (Sathya et al. 2018).

Moreover, iron has been the first choice metal for groundwater treatment due to its high intrinsic reactivity, low toxicity, biodegrability, low cost, abundance and magnetic properties, being considered a universal material for water treatment (Nasiri et al. 2019). It has been used to remediate contaminants such as heavy metals, azo dyes and organic compounds (Carvalho and Carvalho 2017; Nasiri et al. 2019).

Also, iron nanoparticles produced in combination with *C. guianensis* possess a great bactericidal effect against different bacterial human pathogens (Sathishkumar et al. 2018).

2.5.5 Nanofibers

Nanofibers have been mainly recognized for their applications in drug delivery (Charernsriwilaiwat et al. 2013). In this context, these nanomaterials present very large surface area to volume ratios having potential to improve drug release significantly (Ghayempour and Montazer 2018). Furthermore, the small dimension of fibers combined with their microporous structure provided by the polymer, mimics a protective shield, resulting in increased drug loading and stability (Charernsriwilaiwat et al. 2013). Recently, some studies have reported successful development of *Mangosteen pericarp* extract nanofibers intended for various purposes. For instance, it was loaded onto polyvinyl alcohol (PVA) nanofibers for dermal delivery purpose and it was spun in a mixture of chitosan/EDTA/PVA for wound healing (Charernsriwilaiwat et al. 2013; Ghayempour and Montazer 2018).

2.5.6 Nanoemulsions

Main advantages of nanoemulsions compared to conventional emulsions include improved physical stability and absorption/penetration, as high bioavailability, properties that are attributed to their reduced droplet size and great surface area (da Silva Gündel et al. 2018). Besides, these permit the dispersion of lipophilic molecules in aqueous media and can be administered by several vias, from topic, oral, nasal and ocular to intravenous (Zorzi et al. 2015).

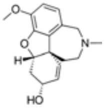
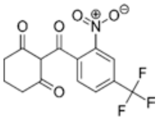
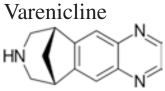
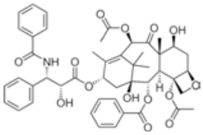
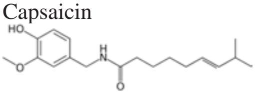
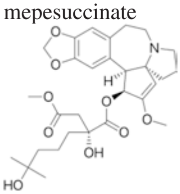
Jaboticaba is a fruit of Jaboticabeira tree (*Myrciaria spp*., *Myrtaceae* family) and highly appreciated in the Brazilian culinary because of its medicinal properties. Pharmacological activities reported include antioxidant, anti-inflammatory, antimicrobial, hypoglycemic and antiproliferative effects (Mazzarino et al. 2017). In a recent study, Mazzarino and colleagues reported that this plant nanoemulsions can be considered a potential antioxidant agent for cosmetic and pharmaceutical applications (Mazzarino et al. 2017).

In another study, microemulsions were fabricated to improve oral bioavailabitilty of the total flavones extracted from *Hippophae rhamnoides*, that exhibits therapeutically significant effects on cardiovascular and cerebrovascular diseases, and showed protective applications in aging, radiation, oxidative injury, myocardial ischemia and cerebral thrombus (Guo and Guo 2017).

2.6 Natural Products from Plants Approved for Therapeutic Use

Over the years, some plant compounds have been integrated into the pharmaceutical industry as drugs for the treatment of various diseases (Afrin et al. 2018; David et al. 2015; Newman and Cragg 2016). Table 2.4 presents some chemical entities derived from plants that are currently used in various therapies.

Table 2.4 Plant-derived natural products approved for therapeutic use

Generic name and chemical structure	Plant species	Commercial name and year of introduction	Therapeutic use
Galantamine 	*Galanthus woronowii Losinsk.* 	Razadyne, 2001	Early-onset Alzheimer's disease
Nitisinone 	*Callistemon citrinus* 	Orfadin, 2002	Hereditary tyrosinemia type 1
Varenicline 	*Cytisus laburnum L.* 	Chantix, 2006	Tobacco dependence
Paclitaxel 	*Taxus brevifolia Nutt.* 	Nanoxelc, 2007	Cancer chemotherapy
Capsaicin 	*Capsicum annum L.* 	Qutenza, 2010	Peripheral neuropathic pain
Omacetaxine mepesuccinate 	*Cephalotaxus harringtonia* 	Synribo, 2012	Oncology

The process of selection and study of bioactive compounds of plants with potential for the development of new drugs is time consuming, since much information is needed about its habitat, abundance, use by population, besides their phytochemical composition that often is quite complex. However, with the development of new technologies and improved instruments, such as high-performance liquid chromatography (HPLC), coupled to mass spectrometry (MS)/MS (liquid chromatography, LC-MS), higher magnetic field-strength nuclear magnetic resonance (NMR) instruments, and robotics to automate high-throughput bioassays, yield study of plants extractives easier and faster (Atanasov et al. 2015).

Several herbal medicines have been released on the market in recent years, and many plant-derived compounds are currently undergoing clinical trials for the potential treatment of various diseases (Atanasov et al. 2015). As there are still many plants that have not been studied and tested as potential sources of bioactive compounds, the discovery of plant-based drugs continues surely to be essential for the release of new and highly competent phytopharmaceuticals, and even more with the development of more sensitive and more versatile analytical methods.

2.7 Usage of Curcumin in Nanoparticles for Periodontal Disease Therapy

Curcumin is a hydrophobic polyphenolic compound derived from the rhizomes of C*urcuma longa*. This natural compound has a long history of use as curry (turmeric) in East Asian countries. India is the largest turmeric producer worldwide, being turmeric a major driver of Indian economy. Data from 2016 estimates that India share in exportations was 65.5% of world exportation, valued at US$186.46 million and estimated to grow yearly above 10% (Tridge. 2019). Demand is driven by increasing awareness of its beneficial characteristics in cosmetics, food and medicine (Sadegh et al. 2019). It is fairly intuitive that, if nanotechnology is to eliminate one of the biggest limitations of curcumin's use in medicine by improving its solubility, and thus bioavailability, this will have a tremendous economical impact on the market and its players, creating opportunities for more business and increased margins of profit (Hatamipour et al. 2019; Sadegh et al. 2019).

Curcumin is "generally recognized as safe" (GRAS) by the Food and Drug Administration (FDA), and is characterized by a wide range of antibacterial, antifungal, antiviral, antioxidative, anti-inflammatory, anticancer and antiproliferative activities (Dai et al. 2017; Loo et al. 2016; Nambiar et al. 2018; Yallapu et al. 2013).

Periodontal disease is a chronic inflammatory condition affecting the tissues that support and protect the teeth, and may lead to the destruction of alveolar bone and periodontal ligament (Preshaw 2015). Its prevalence and severity are highly variable in different populations, but it is estimated that 15–20% of adult individuals are affected by the more severe forms of the disease, while the less severe forms affect 35–60% of the global population (Preshaw 2015).

At literature, there is considerable evidence from both *in vitro* and *in vivo* studies indicating that the anti-inflammatory properties of curcumin attenuate the response of immune cells to periodontal disease-associated bacterial antigens and inhibit periodontal tissue destruction (Zambrano et al. 2018). However, most of these used a systemic route of administration, and their results may be limited by the poor pharmacodynamic properties of curcumin, as well as its high hydrophobicity that conducts to low absorption rates at gastrointestinal tract, besides having extremely short plasma half-life (Pr et al. 2016; Zhou et al. 2013).

Zambrano et al. (2018) reported that local administration of curcumin-loaded nanoparticles effectively inhibited inflammation and bone re-absorption associated with experimental periodontal disease (Zambrano et al. 2018).

A search on U.S. National Institutes of Health Public online database of clinical trials (http://www.clinicaltrials.gov) in May 2019, using the keyword "curcumin", returned 198 registered trials on various clinical conditions such as asthma, multiple myeloma and various other types of cancer, diabetes, Alzheimer's disease, schizophrenia and inflammatory intestinal diseases. Interestingly, this search returned 9 phase IV clinical trials, including 1 on topical use of curcumin as adjunct in treatment of periodontal disease. The primary outcome of this single study was the antioxidant activity in saliva of periodontitis patients, but no results were posted.

2.8 Conclusion

Nanotechnology is in great evolution and has allowed the development of nanomaterials with applications in the most diverse areas, especially in the biomedical field. The variety of existing nanostructures with different properties added different possibilities of treatments that had not existed before, or did not work so effectively. The use of plant extracts allied to nanoparticles, nanoemulsions, nanosuspensions, nanofibers and nanotubes has been shown to improve the efficacy and enhance the biological properties of the phyto-extracts. Although there are many studies of green synthesized nanomaterials and its properties, it is still necessary to continue investigating these derived formulations to validate them as potential agents in new nanotherapies. These technological developments will certainly lead to great economical impact in the plant derived products markets, creating opportunities for more business and increased margins of profit in value added products.

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