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Exploring the Potential of Plant-Derived Natural Products beyond Functional Food: Applications in Nanomedicine

Abstract

The use of plant products as nutritional food and therapeutic agents is immemorial and intimately linked to the human life since its origin. Also, the tanning action of plant extracts has been hugely exploited to transform animal skins into leather from ancient times to present. However, the exploitation of the potential applications of plant biomolecules in some of the modern technologies is rather now emerging. In fact, the antioxidant, reducing and biological activities of the plant metabolites together their chelating and their biodegradable properties, make the plant-derived natural products unique raw materials to design new sustainable approaches to prepare promising hybrid formulations and composite materials at the nanometer scale for innovative diagnostic and therapeutic procedures and nanotechnology applications. In the present contribution, some recent advances and present challenges in this topic are briefly discussed.

Keywords: Phytochemicals; Plant products; Nanomedicine; Nanotechnology

Review Article

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Introduction

Plants naturally generate antimicrobial and antioxidant biomolecules with exceptional biochemical properties that have played crucial roles in the survival of plants and which frequently produce therapeutic effects for the human health. These unique properties have been valued and exploited since immemorial times. For instance, a large variety of plant products have been extensively used as spices, not only for flavoring and coloring food, but also for their beneficial properties for health and because their preserve food with the inhibition of oxidation processes and growth of microorganisms [1]. Furthermore, some of these natural products exhibit notorious analgesic, anti-inflammatory, anticancer, lipolytic and antihyperglycemic activities, among others [2-5], which have constituted the basis of the most traditional medicines and that provide an endless source of active principles for current pharmaceutical drugs [5-7]. Plant biomolecules have a versatile ability to interact with other compounds through a large variety of chemical reactions [8]. In fact, the tanning action of plant polyphenols has been used in the making of leather since antiquity [8,9], and the chelating and antibacterial abilities of algae and plant extracts improve the wastewater treatments [10,11]. However, despite these interesting applications, it is obvious that the exploitation of the immense potential of the plant biomolecules in some of the modern technologies remains in an emerging state notwithstanding the advantages that it offers, including low cost, sustainability and a huge versatility. In this regard, the syntheses of functional colloidal nanoparticles mediated by plant extracts have rapidly become a topic of intensive investigation during recent years [12-14].

Colloidal nanoparticles exhibit fascinating and unique size-dependent physicochemical properties as a consequence of their extremely reduced volume, which are revolutionizing numerous technological fields such as catalysis [15], sensor technology [16] and nano-electro-mechanical systems (NEMS) [17]. Also, they are becoming key pieces in combating cancer, which has remained the major public health problem since decades. In this manner, nanoparticles and quantum dots can improve the cancer imaging with the enhancement of the resolution of magnetic resonance imaging [18] or by fluorescence signals [19], respectively. Also, nanoparticles can serve as nanovectors for drug delivery increasing the efficiency of chemotherapies [20] and as nanoscopic heat sources for hyperthermia therapies in the presence of ac magnetic fields [21] or electromagnetic radiation [22]. However, the technological exploitation of nanomaterials involves two serious problems to be urgently faced:

I. their preparation produces waste products with noxious effects on human health and the environment and

II. nanomaterials themselves can be harmful [23]; in fact, some nanomaterials reduce the cell viability of human healthy cells and produce the inhibition of the metabolism and DNA damage [24], in addition, they can affect to the biological functions of in vivo systems, specially the aquatic ones [25,26].

Both worrying problems could be partially resolved with the use of phytochemicals in the synthesis of the nanomaterials, replacing man-made reagents with harmful effects on human health and the environment by biodegradable and eco-friendly plant metabolites that simultaneously play a dual role as reducing agents and colloidal stabilizers [12-14]. In addition, these "greener" syntheses are quite simple, economically competitive and frequently, "one-pot" processes [13,14,27-32]. The plant metabolites are usually employed in these synthetic methods in the form of concentrated aqueous extracts of fruits [27,28], seeds [29], barks[30], chili peppers [31,32] and leaves [33] with high levels of antioxidant polyphenols. Also, plant metabolites processed by insects have showed astonishing antioxidant physicochemical properties, being aqueous solutions of honey [34-37] and royal jelly [38] excellent reaction media for the crystallization and stabilization of nanoparticles. The "cocktail" of phytochemicals that have these eco-friendly extracts or solutions can synergistically interact with metallic cations from dissolved salts to produce metallic, metal oxide and/or organometallic nanoparticles [12-14,27-38]. Furthermore, the phytochemicals also coat the surface of the resulting nanoparticles providing them colloidal steric and/or electrostatic stabilization and new or enhanced functionalities.

Therefore, these synthetic methods represent novel routes to attach multipurpose biomolecules to nanoparticle surface, providing them improved biological activities exploitable in diverse biomedical applications, including treatments against drug-resistant bacteria [38] and cancer diagnosis and therapy [12]. In this manner, several works have shown that gold nanoparticles capped by photochemicals are more biocompatible that gold nanoparticles capped with other surfactants [39] and also display excellent affinity towards receptors on tumor cells and favor the nanoparticle internalization within cancer cells without affecting the cell viability [12]. This is a promising result for the safe delivery of drugs and cancer imaging [12], and also it could be crucial for the massive use of nanomaterials without jeopardizing human health and the environment.

On the other hand, the well-known broad-spectrum antimicrobial activity of silver nanoparticles [40-42] can be significantly enhanced when they are biosynthesized and coated by biomolecules of plants [43] or metabolites of bee products [38]. In this respect, it is pertinent to remark that the resistance of microbes against silver nanoparticles is generally poor and therefore, Ag nanoparticles could play an essential role in the prevention of epidemics caused by the progressive resistance of pathogens to the available antimicrobial drugs [40]. Given the above-mentioned technological potential [44,45], nanoparticles are increasingly present in the human daily life and their importance in the global market seems unstoppable, being the involved industries strongly competitive. In this framework, the major challenges of the biosynthesis mediated by phytochemicals to become competitive alternatives to obtain nanomaterials at industrial level, is to mass produce stable and very uniform nanoparticles with high reproducibility and engineered sizes and morphologies and controlled uniformity and aggregation states by the facile and reproducible modification of the synthetic parameters, in similar manner to synthetic methods such as co-precipitation [46], sol-gel [47], hydrothermal [48,49], thermal decomposition of salts [50], polyol process [51-53], electro deposition [54] and chemical vapor deposition [55] techniques, which are well-known and widely used.

In this respect, some works have pointed out that the uniformity and size of biosynthesized nanoparticles can be readily modulated with the variation of the pH of the reaction medium [35,56]. Also, the modulation of the concentration ratio between the precursor salt and the organic extract usually allows control of the particle size. Typically, an increment of the extract concentration implies that the reactions occur faster and the particle concentration quickly increases. However, the stabilizing ability of the natural extracts is limited and it can be not enough to prevent particle growth by irreversible aggregation under high particle concentrations. In these conditions, we have found that biosynthesized silver nanocrystals tend to spontaneously form supramolecular structures by oriented attachment [38], coalescence [38] and/or Ostwald ripening [48]. For example, sub-micrometric dendritic- like structures constituted by clusters of Ag nanocrystals that share the same crystallographic orientation have been obtained using aqueous royal jelly solutions and 0.5 M aqueous solutions of silver nitrate ($AgNO_3$) [38]. On the other hand, the variation of the $AgNO_3$/extract weight ratio in the synthesis of Ag nanoparticles mediated by extracts of Illicium verum (star anise) seeds yielded to the variation of the spatial distribution of the obtained nanoparticles:high $AgNO_3$/extract concentration ratios gave rise polydisperse particles randomly positioned, whereas for lower $AgNO_3$/extract ratios, particles of around 100 nm appeared decorated by very fine nanoparticles (with diameters of around 5 nm), displaying these different states of nanoparticle aggregation interesting plasmonic properties [57].

Another challenge to be faced is that the concentration and characteristics of the active bio-molecules in the natural plant extracts and bee products may significantly differ depending on the aging time of the natural product, the environmental conditions of the growing location and the way that they were extracted. Therefore, rigorous quality controls and well-standardized conditions to obtain the natural product extracts should be established to ensure the complete reproducibility of the biosynthetic processes.

Conclusion

In conclusion, green chemistry processes derived from the use of phytochemicals and metabolites of bee products seem very promising due to their effectiveness and their non-requirement of noxious reducing and stabilizing reagents, however, although significant advances have been achieved during the last decade, further investigations are needed to clarify and understand the composition and unique properties of phytochemicals. The progress of this fascinating topic should lead to new approaches to solutions of medical problems and interesting and innovative technologies involving more sustainable processes, nevertheless, the toxicity of the resulting products should be investigated in detail.

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