

Plant Extract Loaded Nanoparticles

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ABSTRACT

Plant extract, a natural source containing complex mixture of compounds, offers many properties such as antiparasitic, antibiotic, antioxidant, anti-hypertensive, antiviral, insecticide, anticancer, antifungal, hypoglycemic properties. Recent research has been focused on developing formulation the plant extracts not only to deliver them safely but also to enhance its therapeutic efficacy. Nanotechnology-based strategies have been proposed as a system that can be used to formulate plant extracts. Plant extract loaded nanoparticles (NPs) is aimed to facilitate in crossing the biological barriers, to increase bioavailability of poorly water-soluble phytochemicals, to encapsulate mixture compounds of different phytochemicals, to provide targeted delivery of phytochemicals to specific organs resulting in low toxicity, to get effective purification process, to mask unpleasant taste and odor, to protect sensitive phytochemicals from biological (e.g. enzyme, pH) and environmental (e.g. light, temperature, humidity) degradation, to control release of encapsulated phytochemicals, and to provide a more flexible control over the size and shape of the NPs. This review is focused on plant extract loaded NPs including its advantages, stages for developing formulation of plant extract loaded NPs, and nanosystem used to loading plant extract. In addition, this review also depicts studies which have been conducted by many researchers in developing plant extract loaded NPs. The data were collected from published journals with 21 and 39 journals as primary and supporting literatures, respectively. Plant extracts loaded NPs could be a promising delivery system for active phytochemical contained in the plant extract which is not only to deliver them safely but also to enhance its therapeutic efficacy.

Keywords: plant, extract, nanoparticle

1. Introduction

Plants have been used for treatment various diseases since long time. Biological active compounds are obtained by extracting mainly the leaves, the fruits, the stems, or roots of medicinal plants (1). The biological active compounds can have antiparasitic, antibiotic, antioxidant, anti-hypertensive, antiviral, insecticide, anticancer, antifungal, hypoglycemic properties (1). To increase the application of plant extracts, a technology must be performed in formulation development of plant extracts (2).

Recently, many studies use nanotechnology to formulate plant extract. By using nanotechnology-based systems, biopharmaceutical and technological properties of plant extracts can be improved (2). The nanosystems used commonly are nanoparticles (NPs) (either polymer or lipid-based NPs), liposomes, and nanoemulsions (2). Formulation development of plant extract loaded NPs has been focused by researchers to combine the benefits offered by nanotechnology and the diversity of biological activities of plant extracts (2).

Plant extract loaded NPs offers numerous advantages because of their size and unique physicochemical characteristics. Moreover, plant extract loaded NPs can be used to decrease plant extracts toxicity, to provide targeted drug delivery and to solve stability related problems (1). There are several stages involved in developing preparation of plant extract loaded NPs (1).

The aim of this review is to describe about plant extract loaded NPs including its advantages, stages for developing formulation of plant extract loaded NPs, and nanosystem used to encapsulate plant extract. In addition, this review also shows many studies which have been investigated by researchers to develop plant extract loaded NPs.

2. Methodology

This review was obtained by using specific keywords “plant extract and nanoparticles,” by following an inclusions criteria (related to specific keywords) and exclusions criteria (opinions and unrelated topics). We collected about 21 journals published in 2010-2021 as a primary literatures and 39 journals published as supporting literature. The flowchart of methodology can be seen in Figure 1.

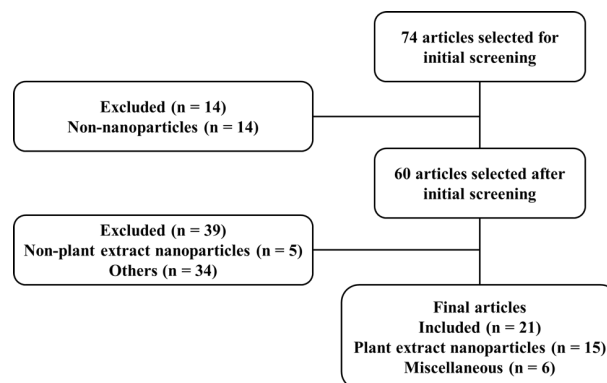


Figure 1. Flowchart of methodology

3. Nanoparticles (NPs)

The rapid development of nanotechnology has good prospect to develop formulation of active compounds loaded NPs. NPs are commonly defined to particulate substances which have diameter in the range of 1 to 100 nm although in principle NPs are described as substances with length of 1-1000 nm in at least one dimension (3-6). NPs have been widely used in many applications such as medications, electronics, manufacturing and materials, environment, mechanical industries, etc. (6). Classification of NPs are polymeric NPs, lipid-based NPs, carbon-based NPs, ceramics NPs, semiconductor NPs, and metal NPs and can be synthesized either top-down or bottom-up method (6). The most common nanoparticle systems used for the delivery of natural products are nanoliposome, polymeric NPs, solid lipid nanoparticle (SLN), dendrimer, nanocrystal, nanoemulsion, micelle, hydrogel, fullerene, and zeolite (7).

In addition, nanotechnology-based systems can be also used to improve biopharmaceutical and technological properties of plant extracts (2). Plant extract loaded NPs can be used for cosmetic, food additives, and phytotherapy (e.g. antioxidant, antiviral, hepatoprotection, antidiabetic, anti-inflammatory, anticholesterolemia, antiulcerolitic, anticancer activity) applications (1, 2).

The nanosystems used commonly are nanoparticles (NPs) (either polymer or lipid-based NPs), liposomes, and nanoemulsions (2). Figure 2 shows the nanosystem used for loading plant extracts. Some techniques which are very frequently used for loading plant extract into NPs are emulsion solvent evaporation, nanoprecipitation, emulsion solvent diffusion, and ionic gelation. These techniques differ by their principles and are also influenced by nature of the encapsulated phytochemicals. Correct selection of the techniques very important to obtain a formulation of plant extract loaded NPs (1).

4. Advantages and disadvantages of plant extract loaded nanoparticle

Many studies reveal that nanotechnology offers many benefits, including for formulation of plant extract loaded NPs. Plant extract loaded nanoparticle have several advantages such as facilitating in crossing the biological barriers, increasing bioavailability of poorly water-soluble phytochemicals, encapsulation of mixture compounds of different phytochemicals, providing targeted delivery of phytochemicals to specific organs resulting in reducing toxicity of phytochemicals, getting effective purification process, masking unpleasant taste and odor, increasing stability of the encapsulated phytochemicals by protection of the sensitive phytochemicals from biological (e.g. enzyme, pH) and environmental (e.g. light, temperature, humidity) degradation or inactivation, controlling the release of encapsulated phytochemicals, and providing a more flexible

control over the size and shape of the NPs during synthesis of NPs using plant extract (1, 7-12).

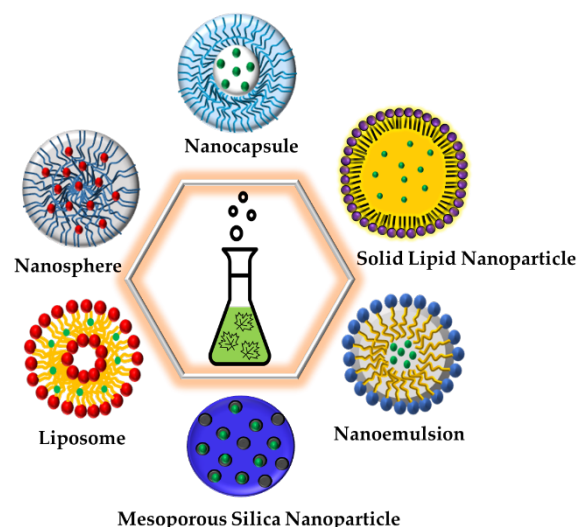


Figure 2. Illustration of nanosystems used for loading plant extract

On the other hand, the drawback of NPs should be a careful consideration in formulation of plant extract loaded NPs such as a tendency to high aggregation in biological system due to high surface area and energy, high immunogenicity, long and expensive cost, and chance of poor targeting (13).

5. Stages for developing preparation of plant extract loaded nanoparticle

Encapsulation of plant extract into NPs can be used to overcome problems such as toxicity risks and extract instability (1). Studies on formulations containing plant extract loaded NPs generally reports about standardizing techniques for NPs formulation, physicochemical characterization of the NPs (size, zeta potential, morphology, etc.), encapsulation/loading efficiency of the active component in the NPs, the release profiles of the active component from the NPs, *in vitro* and *in vivo* evaluations both free extract and embedded extract and stability studies of the formulation (1).

For example, Kamel *et al.* encapsulated both extracts of *Cinnamomum cassia* and *Origanum*

vulgare in solid lipid nanoparticles (SLN) and coated the SLN with chitosan (SLN-Cs) to encapsulate cinnamon and oregano extract, minimize opsonization, and facilitate passive-targeting. This group demonstrated the success of the suggested combination with 5-fluorouracil for treating human colon carcinoma with a low dose leading to decreasing side effects and allowing

uninterrupted therapy. Three phases were applied to develop the SLN-Cs (Figure 3). Phase one was focused on extract standardization. Phase two was aimed to encapsulate both extracts in SLN-Cs to obtain an optimum formulation of SLN-Cs. Phase three was concerned on the cytotoxicity evaluation (14).

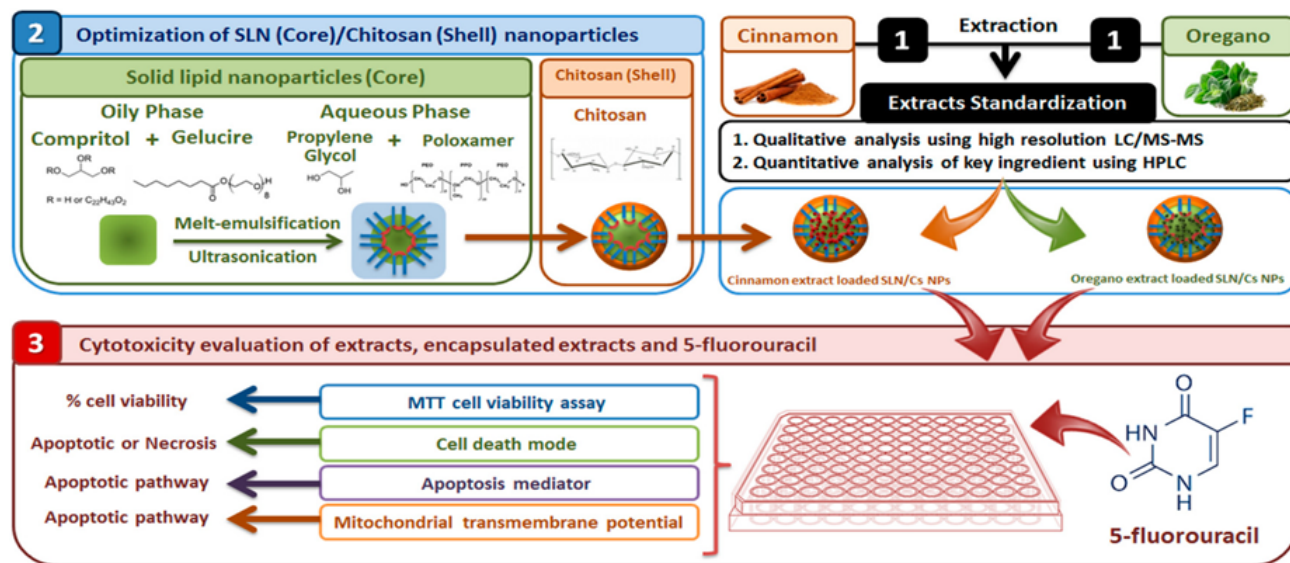


Figure 3. Schematic illustration of the different phases of the study. Reproduced with permission of Kamel KM, Khalil IA, Rateb ME, Elgendy H, Elhawary S., Chitosan-Coated Cinnamon/Oregano-Loaded Solid Lipid Nanoparticles to Augment 5-Fluorouracil Cytotoxicity for Colorectal Cancer: Extract Standardization, Nanoparticle Optimization, and Cytotoxicity Evaluation; published by American Chemical Society, 2017.

Development of plant extract loaded NPs formulation generally have the following stages as depicted in Figure 4. The following stages are summarized from several published studies (1, 2, 7, 14).

6. Nanoparticle loading plant extract

Currently, researchers are interested to develop formulations of plant extract loaded NPs (1). Studies about plant extract loaded nanoparticles formulation are showed in Table 1. According to Table 1, nanoparticle systems used to formulate plant extract are polymeric NPs, nanoliposome, solid lipid nanoparticle (SLN), silica NPs, etc. polymeric-based nanoparticle is the most used as a nanosystem

to load the plant extract. In addition, poly (lactic-co-glycolic) acid (PLGA) is the most used polymer to construct plant extract loaded NPs. Other nanosystems use poly-lactic acid (PLA), xanthan gum-shellac, polyvinyl pyrrolidone (PVP), ethyl cellulose (EC), methyl cellulose (MC), poly(epsilon-caprolactone) (PCL), hydroxypropyl-methylcellulose (HPMC), chitosan, gelatin, hyaluronic acid (HA), etc. for preparing the NPs.

Encapsulation of plant extract can be used for either imaging or therapeutic application. Liu and co-workers prepared turmeric extract encapsulated by PLGA for bioimaging and

Table 1. Studies about formulation of plant extract loaded NPs

Extract name	System	Reference
<i>Cinnamomum cassia</i> and <i>Origanum vulgare</i>	SLN coated with chitosan	(14)
<i>Gelsemium sempervirens</i>	PLGA NPs	(15)
<i>Polygala senega</i>	PLGA NPs	(16)
<i>Vitis sp</i>	PLGA NPs	(17)
	PLA NPs	(18)
	PLGA NPs	(19)
<i>Phytolacca decandra</i>	PLGA NPs	(20)
<i>Syzygium jambolanum</i>	PLGA NPs	(21)
<i>Cinnamomum spp</i>	PLGA NPs	(22)
	Xanthan gum–shellac NPs	(23)
<i>Embllica officinalis</i>	PVP NPs	(24)
<i>Garcinia mangostana</i>	EC NPs	(25)
	EC and MC NPs	(26)
<i>Passiflora serratodigitata</i> L.	PCL NPs	(27)
<i>Lavandula spp</i>	PLGA NPs	(28)
<i>Picrorhiza kurroa</i>	PLA and Pluronic-F-68 (polyoxyethylene–polyoxypropylene block copolymer) NPs	(29)
<i>Uncaria tomentosa</i>	PLGA NPs	(30)
<i>Carum copticum</i>	MnFe ₂ O ₄ NPs coated with PEGylated chitosan	(31)
<i>Malus domestica</i>	Silver NPs	(32)
<i>Elettaria car damomum</i> Maton	Gelatin NPs	(33)
<i>Camellia sinensis</i>	HPMC containing PLA NPs	(34)
<i>Houttuynia cordata</i>	Solid lipid NPs (SLNs) using Stearic acid (SA) and Poloxamer 188 (P188) or poloxamer 407 (P407)	(35)
<i>Ilex paraguariensis</i>	PCL or PLGA NPs	(36)
<i>Annona squamosa</i>	Chitosan NPs	(37)
<i>Beta vulgaris</i>	PEGylated gelatin NPs	(38)
<i>Centella asiatica</i>	Lipid NPs consisting of stearic acid, oleic acid, lecithin, and sodium taurodeoxycholate	(39)
<i>Curcuma longa</i>	Nanoliposomes consisting of phosphatidylcholine	(40)
	Mesoporous silica NPs	(41)
	PLGA NPs	(42)
<i>Dendropanax morbifera</i>	HA or O-carboxymethyl chitosan (CMC)- stabilized zinc oxide nanocomposites (ZnONcs)	(43)
<i>Allium sativum</i>	Solgel NPs consisting of tetramethylorthosilicate	(44)
<i>Glycyrrhiza glabra</i>	Liposomes consisting of soyabean phosphatidylcholine and cholesterol	(45)
<i>Hibiscus sabdariffa</i>	Nanostructured lipid carriers (NLC) composed of solid lipid (Biograpress™ Vegetal BM 297 ATO) and lipid liquid (Soybean oil)	(46)

<i>Hypericum Perforatum</i> L.	PLGA NPs	(47)
<i>Lamium album</i>	Porous hollow silica NPs	(48)
<i>Solanum lycocarpum</i>	Natural lipid-based NPs composed of myristyl myristate	(49)
<i>Camellia sinensis</i>	PCL NPs	(50)
<i>Punica granatum</i>	SLN using precirol or stearic acid, lecithin, and tween 80 or poloxamer 188	(51)
<i>Gynostemma pentaphyllum</i>	Zinc Oxide NPs	(52)
<i>Cordyceps militaris</i>	Nanoemulsion	(53)
	Zinc Oxide NPs	(54)
<i>Amomum longiligulare</i>	Zinc Oxide NPs	(55)
<i>Scutellaria baicalensis</i>	Gold and Silver NPs	(56)
<i>Hippophae rhamnoides</i>	Zinc Oxide NPs	(57)
<i>Stevia rebaudiana</i>	Zinc Oxide NPs	(58)
<i>Suaeda japonica</i>	Zinc Oxide NPs	(59)
<i>Crataegus pinnatifida</i>	Gold and Silver NPs	(60)

antimicrobial applications. Curcumin is the main content in the rhizome of the turmeric. This group proved that Curcumin loaded PLGA NPs (Cur-PLGA NPs) are successfully to be used for not only bioimaging but also antibacterial application (Figure 5) (42).

The release of loaded phytochemicals can be controlled and the stability can be increased when plant extract is loaded in NPs. Sanna *et al.* showed the effectiveness of white tea extract loaded PCL NPs. This nutraceutical application is used to control the release of tea polyphenols and to maintain the antioxidant activity. The release study showed that the polyphenols was released from NPs about 20% at pH 1.2 (simulated gastric medium) and 80% at pH 7.4, respectively (Figure 6). This result proved that NPs can be used to control delivery of the polyphenols. In addition, the encapsulation of the white tea extract into NPs significantly increased stability, thus preventing the losses of TPC and catechins over 30 days of storage (50). In another study, Kim *et al.* developed *Houttuynia cordata* extract-loaded solid lipid NPs (H-SLNs) for oral delivery. This group reported that 92.9–95.9% of quercitrin encapsulated into SLNs. Interestingly, sustained release of quercitrin from *H. cordata* extracts was provided by H-SLNs (35).

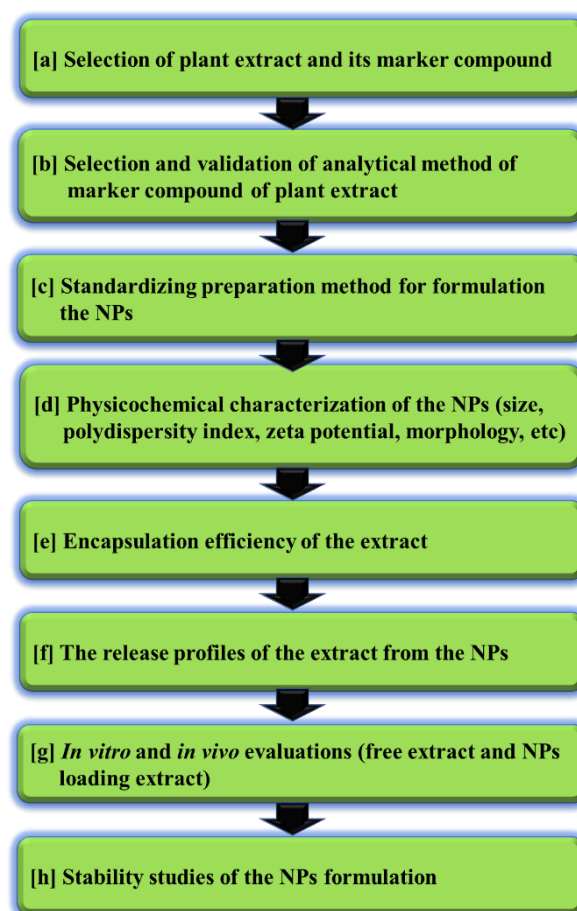


Figure 4. Schematic illustration of stages for developing preparation of plant extract loaded NPs.

In case of the use of plant extract loaded NPs in phytotherapy applications, Paul *et al.* prepared root extract of *Polygala senega* encapsulated

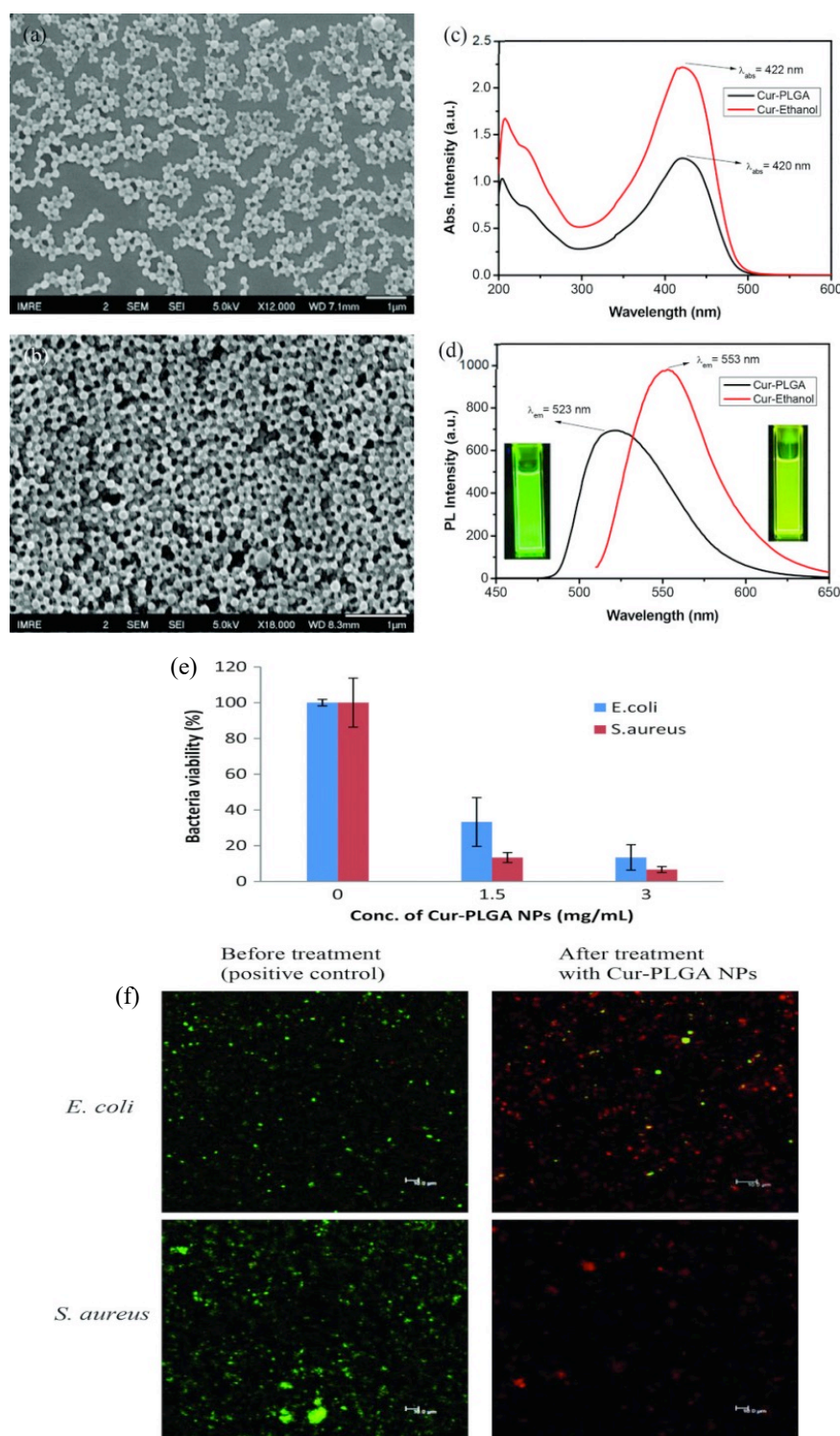


Figure 5. a) SEM image of Cur-PLGA NPs with lower magnification, b) SEM image of Cur-PLGA NPs with high magnification, c) absorption spectra of Cur-PLGA NPs and curcumin solution in ethanol, d) fluorescent spectra of Cur-PLGA NPs and curcumin solution in ethanol, e) Antimicrobial effect of Cur-PLGA NPs against *E. coli* and *S. aureus* bacterial cells. f) Confocal microscopy images showing the antimicrobial effect of Cur-PLGA NPs on *E. coli* and *S. aureus*. Positive controls are bacteria that are not treated with Cur-PLGA NPs. Live bacteria are stained green. Reproduced with permission of Liu M, Teng CP, Win KY, Chen Y, Zhang X, Yang DP, et al., Polymeric Encapsulation of Turmeric Extract for Bioimaging and Antimicrobial Applications; published by John Wiley and Sons, 2019.

PLGA as an anticancer. This group reported that the anticancer activity of the extract loaded PLGA NPs was more effective than extract per se (16). In addition to anticancer activity, Pan-In et al. formulated *Garcinia mangostana* extract-encapsulated EC and a polymer blend of EC and MC NPs. The NPs loading extract successfully improved the bioavailability of *Garcinia mangostana* extract, enhanced cellular uptake, and showed effective anticancer activity (25). In another studies, Strasser et al. constructed nanoencapsulated *Passiflora serratodigitata* L. extracts as an antiulcerogenic activity (27). Other than that in phytotherapy applications, Jia et al. developed nanoencapsulation of *Picrorhiza kurroa* extract as food supplement with hepatoprotective activity (29). Recently, plant extract loaded NPs could be interesting field for research in many areas, such as health, food, cosmetics, medicine, environment, etc.

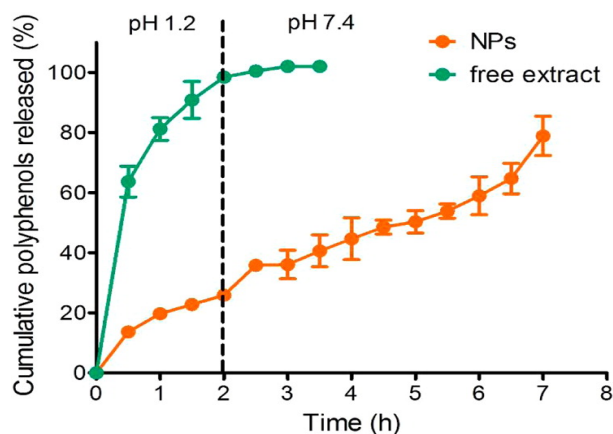


Figure 6. In vitro release profiles of polyphenols (TPC) from free white tea extract and from tea extract-loaded NPs in 0.1 M HCl (pH 1.2) for 2 h, followed by PBS (pH 7.4) for 5 h. Data are means \pm SD, n = 3. Reproduced with permission of Sanna V, Lubinu G, Madau P, Pala N, Nurra S, Mariani A, et al., Polymeric nanoparticles encapsulating white tea extract for nutraceutical application; published by American Chemical Society, 2015.

7. Conclusion

The use of nanotechnology-based systems has been grown rapidly. Plant extract loaded

nanosystems such as nanoparticles (NPs) (either polymer or lipid-based NPs), liposomes, and nanoemulsions can bring many benefits which can be aimed to facilitate in crossing the biological barriers, to increase bioavailability of poorly water-soluble phytochemicals, to encapsulate mixture compounds of different phytochemicals, to provide targeted delivery of phytochemicals to specific organs resulting in low toxicity, to get effective purification process, to mask unpleasant taste and odor, to protect sensitive phytochemicals from biological (e.g. enzyme, pH) and environmental (e.g. light, temperature, humidity) degradation, to control release of encapsulated phytochemicals, and to provide a more flexible control over the size and shape of the NPs. Recent research has been focused on developing formulation the plant extracts not only to deliver them safely but also to enhance its therapeutic efficacy which involves several stages for developing formulation of plant extract loaded NPs.

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