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Anticancer and antibacterial activities of embelin: micro and nano aspects

Mehran Alavi[1,2*], Fleming Martinez[3], Daniel R. Delgado[4], Darío A. Tinjacá[5]

[1]*Department of Biological Science, Faculty of Science, Kurdistan University, Sanandaj, Kurdistan, Iran*
[2]*Nanobiotechnology Department, Faculty of Innovative Science and Technology, Razi University, Kermanshah, Iran*
[3]*Department of Pharmacy, Faculty of Sciences, Universidad Nacional de Colombia, South America, Colombia*
[4]*GRIAUCC Research Group, Department of Engineering, Universidad Cooperativa de Colombia, Neiva, Huila, Colombia*
[5]*Facultad de Ciencias, Universidad El Bosque, Bogotá D. C., Colombia*

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ABSTRACT

There are some reported anticancer and antibacterial effects for embelin, although, it's poor aqueous solubility and bioavailability are main hindrance to apply embelin in therapeutics. In this regard, nanoformulations based on bare or functionalized nanomaterials can overcome these disadvantages. Embelin can be loaded or incorporated in biocompatible polymeric or protein nanoparticles (NPs) such as albumin NPs for improvement of solubility. In addition, targeting specific active sites of some major biological components such as amino acids of efflux pump in multidrug-resistant (MDR) bacteria can be possible by nanoformulation of embelin. The induction of apoptosis processes in cancer cells is also one of the major anticancer mechanisms of embelin, which has exhibited significant *in vitro* and *in vivo* results when nanoformulations are employed. The main aim of this review is to make a discussion about the advantages of these new nanoformulations in comparison with pure embelin. Overlay, embelin may be loaded or incorporated in biocompatible protein or polymeric NPs such as albumin NPs. Specifically, for antibacterial activity, nanoformulation of embelin-loaded chitosan Au-NPs with ciprofloxacin antibiotic exhibited the efficient interactions between embelin and the active sites of the efflux pump. Additionally, hyaluronic acid-coated amphiphilic polymeric NPs have the ability to enhance embelin uptake by triple negative breast cancer cells.

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Introduction

Anticancer and antibacterial activities of various natural materials based on micro and nano formulations have been reported in recent years [1-10]. Specifically, a large class of quinones can be found in a wide range of organisms including in arthropods, plants, and bacteria (Figure 1a-k). Redox, antimicrobial, antifertility, anthelmintic, analgesic, anti-inflammatory, antihelmintic, analgesic, antitumor, and antioxidant activities have been found for embelin ($C_{17}H_{26}O_4$, 2,5-dihydroxy-3-undecyl-1,4-benzoquinone, preferred IUPAC name: 2,5-Dihydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione, CAS number: 550-24-3, PubChem CID: 3218, molar mass: 294.39 $g \cdot mol^{-1}$) as a herbal para-benzoquinone derived from general quinones (Figure 1k), which can be extracted from dried berries of *Embelia ribes*, medicinal plant species used in traditional medicine of China and India [11]. The replacement of the C-11 alkyl chain by other aryl, benzyl, and/or alkyl groups is the common way for preparation of the embelin derivatives [12].

Generally, there are various materials (Figure 2) [13] and methods (Figure 3A) for fabrication and functionalization of nanomaterials (NMs), particularly metal or metal oxide nanoparticles (NPs), with different physicochemical properties (Figure 3B) [14]. Embelin metabolite has the ability to form complexes with metals resulting from their antioxidant property, which make this metabolite desirable to synthesize and modify NMs specifically noble metal NPs. These complexes can have synergistic therapeutic effects as anticancer and antibacterial activity both *in vivo* and *in vitro* [15-17]. Moreover, other organic and inorganic NMs may be used to nanoformulate embelin. Therefore, in this review, we have tried to discuss these activities

*Corresponding author. E-mail: mehranbio83@gmail.com

with related challenges such as the poor aqueous solubility and bioavailability of embelin, according to recent studies. In contrast to a previous review, micro and nano formulations of embelin have been presented and compared in order to obtain a suitable approach of future investigations.

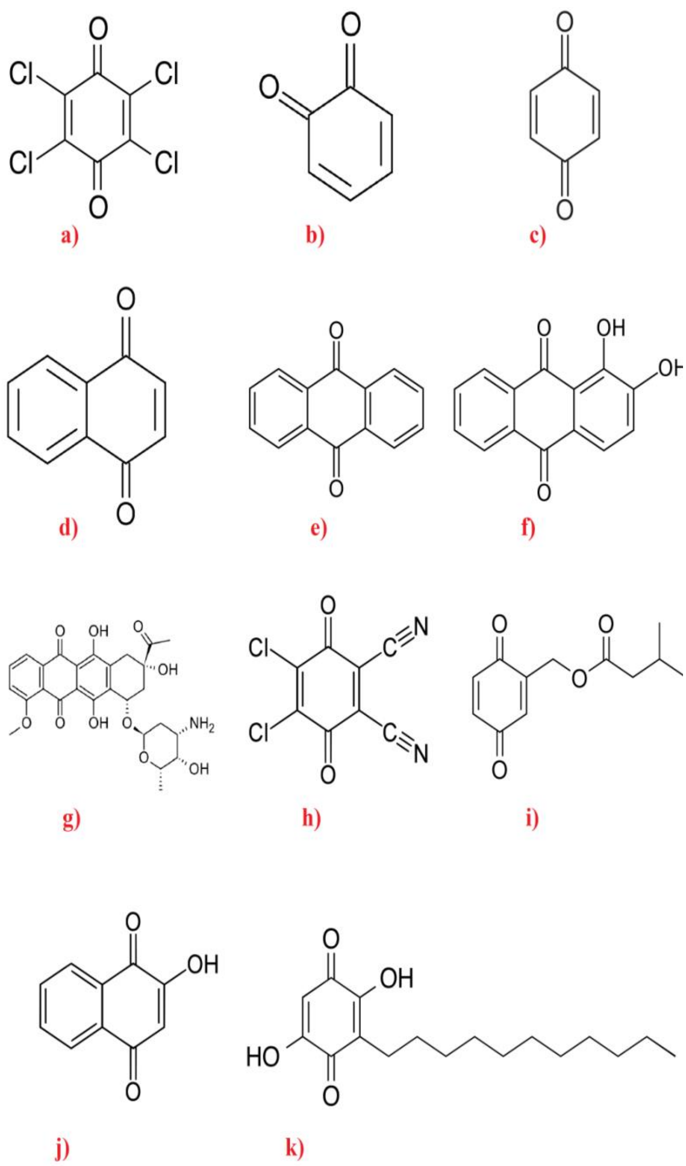

Fig. 1. Molecular structures of some quinones involving a) 2,3,5,6-Tetrachloro-parabenzoquinone or chloranil, b) 1,2-Benzoquinone, c) 1,4-Benzoquinone, d) 1,4-Naphthoquinone, e) 9,10-Anthraquinone, f) 1,2-dihydroxyanthraquinone or alizarin, g) daunorubicin, h) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone or DDQ, i) gentisyl-quinone-isovalerate or blattellaquinone, j) lawsone, and (k) embelin (https://pubchem.ncbi.nlm.nih.gov).

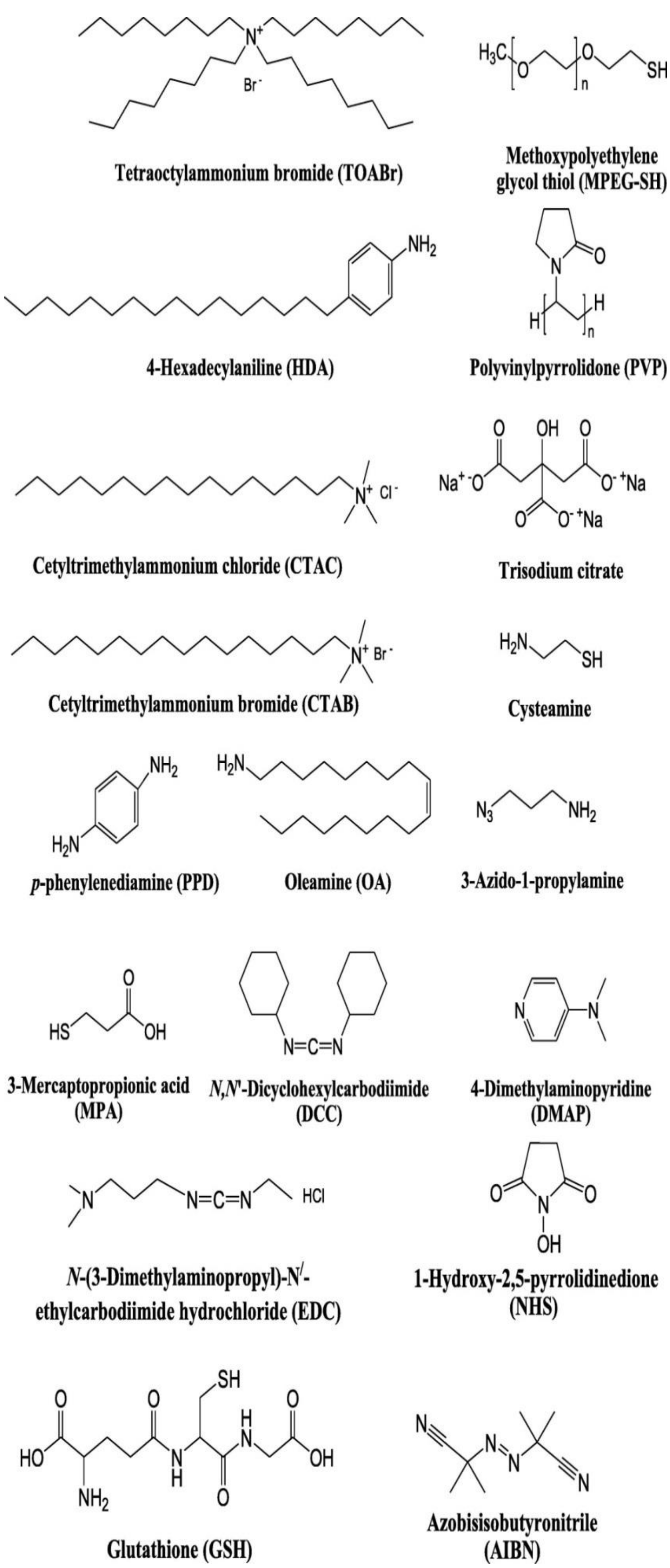

Fig. 2. Common materials suitable for fabrication of noble metal NPs [13].

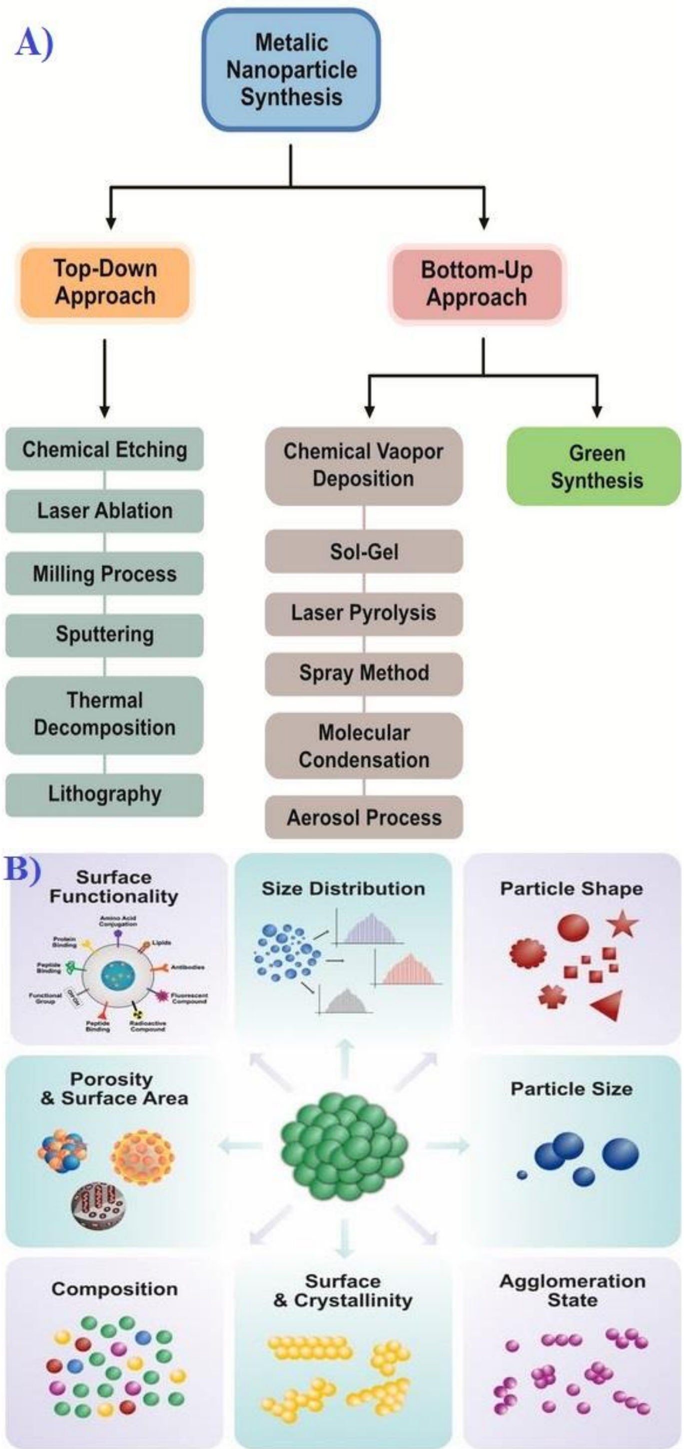

Fig. 3. (A) Various approaches for synthesis of NMs and (B) different physicochemical properties of NMs [14].

Micro aspects

Anticancer activity

In cancer tumor cells, many deregulated cellular processes can be regulated by casein kinase II (CK2) with the functions of changing cellular morphology as well as promotion of angiogenesis cell growth, cellular transformation, cell survival, and cell proliferation [18-20]. Therefore, targeting this protein is critical to hinder cancer cells, wherein two drugs of CX-4945 (an ATP competitive CK2 inhibitor) and CIGB-300 (a peptidic inhibitor) showed acceptable inhibition in clinical trials [12, 21, 22]. Various derivatives of embelin were evaluated against CK2, for instance 4l (2-(tert-butylamino)-3-(furan-3-yl)-5-hydroxy-6-undecyl benzofuran-4,7-dione) as an ATP competitive CK2 inhibitor showed IC_{50} value of 0.63 μM against MCF7 cells, metastatic adenocarcinoma isolated from the breast tissue. Moreover, molecular docking studies confirmed the role of the C-11 alkyl chain in the orientation of this derivative of embelin to get suitable interaction [12]. Embelin has the potential ability to hinder X-linked inhibitor of apoptosis protein (XIAP; inhibitor of apoptosis protein 3) and NF-κB (nuclear factor kappa B), a protein that controls cell survival [23]. Additionally, in the case of breast cancer cell lines including MDA-MB-453, MDA-MB-231, and MCF-7, embelin has the ability to downregulate cellular FADD-like IL-1β-converting enzyme inhibitory protein (cFLIP), and thus, facilitating anti-tumor activity of IL-1β-stimulated human umbilical cord mesenchymal stem cells [24].

Antibacterial activity

There is a plethora of embelin derivatives having antibacterial activity towards various Gram-negative and Gram-positive bacteria. For different dihydropyran and dihydropyridin derivatives of embelin, GI_{50} (concentration that inhibit growth of 50% of bacteria) was in the range of 1.8-35.1 μM, 1.3-35.9 μM, and 5.7-55 μM against of *S. aureus* ATCC25923, *S. aureus* NRS402, and *E. faecalis* ATCC29212, respectively. Among these derivatives, 9-(3,4-Methylenedioxyphenyl)-2-hydroxy-6,6-dimethyl-3-undec-yl-5,6,7,9-tetrahydroxanthene-1,4,8-trione exhibited more antibacterial activity against *S. aureus* NRS402 compared to other derivatives [11]. In similar study, in comparisons with three antibiotics including oxacillin, vancomycin, and mupirocin with minimum inhibitory concentration (MIC) of <1 μg/mL, there were MIC ranges of 1 up to >128 μg/mL and 4 up to >128 μg/mL, respectively against *S. aureus* NRS402 and *S. aureus* ATCC25923 for various dihydropyran embelin derivatives. For two bacteria, cis adduct of

(±)-11-Chloro-2-hydroxy-6,6-dimethyl-3-undecyl-6a,7-dihydrochromeno[3,4-c]chromene-1 , 4 (6 H , 12bH)-dione displayed significant antibacterial activity [25]. Formulation of embelin in conventional ointment is an attractive strategy particularly in large scale. A combination of embelin, emulsifying wax, white soft paraffin, and liquid paraffin in concentrations of 3, 27, 50, and 20 % was used to hinder *S. aureus*, *S. epidermidis*, *E. coli*, and *P. aeruginosa*. 50 mg/mL concentration of modified ointment illustrated 9.33, 8.67, 9.67, and 12 mm inhibition zone diameters (IZDs) towards *S. aureus*, *S. epidermidis*, *E. coli*, and *P. aeruginosa*, respectively [26]. Fiiranylidene benzofuranone and 1,4-dibenzo furandione can be prepared from the irradiation of embelin under microwave oven for 6 min, wherein IZDs of 9, 9, 7, and 7 mm were found for these compounds against *E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. aureus* [27]. In another study, MIC range for three strains of *S. aureus* ATCC25923, *S. aureus* NRS402, and *E. faecalis* ATCC29212 were 1- >128 µg/mL, <1- >128 µg/mL, and 1- >128 µg/mL, respectively. Excellent antibacterial activity was observed for 10-4(4-bromophenyl)-8-hydroxy-3-methy l-7 undecyl pyrano[4,3-b]chromene-1,6,9(10H)-trione towards *S. aureus* NRS402 with MIC value of <1 µg/mL [28].

Nano aspects

Anticancer activity

Paclitaxel is a commonly used chemotherapeutic drug to eradicate various types of cancers including pancreatic cancer, cervical cancer, ovarian cancer, lung cancer, esophageal cancer, Kaposi's sarcoma, and breast cancer [29]. A plethora of drug delivery nano-systems such as lipid NPs, cubosomes, liposomes, and micelles were evaluated to increase bioavailability and active targeting of tumor cells in physiological condition [30]. Polyethylene glycol (PEG) is a hydrophilic polymer with neutral charge, which is employed to augment bioavailability and hydrophilicity of therapeutic agents. Paclitaxel loaded PEG_{3500}-derivatized embelin with the size range of 20−30 nm showed IC_{50} of 13.5 ng/mL compared to neat paclitaxel with 65 ng/mL towards breast cancer cell line of MDA-MB-231 after 72 h incubation. Moreover, there was a very low hemolysis level for these formulations in comparison with cationic polymer of polyethylenimine [31]. In a similar study, loading of paclitaxel by PEG_{5000}-derivatized embelin at molar ratio of 1:1 (size of 21.7 nm and polydispersity index (PDI) of 0.25) showed 13 % and 70.8 % of drug loading capacity and drug loading efficiency, respectively. In addition, this study illustrated complete hindrance of cancer growth in a model of human prostate cancer xenograft with a low toxicity to the animals [17]. Albumin protein having biocompatible and hydrophilic properties is an appropriate option for the embelin formulation in physiological conditions. According to a molecular docking study, free energy and binding constant values were observed as −5.1 $kcal \cdot mol^{-1}$ and 5.9 (±0.1) × 10^4 M^{-1} at 25 °C, respectively. This complex formulated by hydrogen and hydrophobic bond interactions illustrated an induction of 26.3% of apoptosis for HeLa cell line with an IC_{50} value of 29 µM [32]. Hyaluronic acid-coated amphiphilic polymeric NPs including pH-sensitive-polyethyleneimine(PEI)- poly [(1,6-hexanediol)-diacrylate-β-5-hydroxyamylamine] (PBAE) have been used for co-delivery of APO2L or tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) plasmid (pTRAIL), and embelin, against triple negative breast cancer, which is one the most complicated type of breast cancer. Enhanced embelin and APO2L uptake by MDA-MB-231 TNBC cells have been obtained because of the specific binding between hyaluronic acid and CD44 of MDA-MB-231 TNBC cells [33].

Antibacterial activity

There are various inorganic NPs including metal, metal oxide, and metalloid NPs, as well as some organic NPs like liposomes, cubosomes, and solid lipid NPs, suitable to nanoformulate antibiotics and/or natural metabolites with antibacterial activity [34-43]. High molar extinction coefficient, large absorption cross-section, and surface plasmon resonance (SPR) in the near-infrared range are the main properties of noble metal NPs specifically Ag and Au-NPs depending on size and shape, which make these NPs suitable for applications in photodynamic therapy, two-photon luminescence imaging, and surface enhanced Raman scattering [13, 44]. As the major antibacterial mechanisms, these NPs in combination with other natural materials can produce reactive oxygen species, followed by the respective damaging on biological macromolecules, which in turn, could cause inhibition of the efflux pumps of bacteria [45]. As mentioned in the introduction section, embelin has the ability to form complexes with metal resulting from their antioxidant property, which can be helpful in biosynthesis of metal or metal oxide NPs. For example, plasmonic Ag-NPs with bimodal size distribution (~3 and 15 nm) and antibacterial activity against *S. aureus* and *E. coli* were stabilized by embelin. Antibacterial steps specifically in the case of smaller size of Ag-NPs (3 nm at 5 µg/mL) were attachment to cell membrane resulting from binding to thiol groups (-SH) and reduction of the disulfide bonds, disruption of membrane, and leakage of bacterial macromolecules, leading to damaging of biological macromolecules such as proteins and nucleic acids followed by shrinkage of bacteria [16]. The water solubility of embelin may be enhanced by formulation of this metabolite with some surfactant agents. In this way, self-nano-emulsifying drug delivery system containing Capryol 90 as oil, Acrysol EL 135 as surfactant and PEG 400 as co-surfactant provided suitable stability for 6 months and water solubility-increasing for encapsulation of embelin. After 6 months, three parameters of self-emulsifying time, globule size, and release of drug at 15 min were 22.98 sec, 30.22 nm, and 97.06 %, respectively [46]. Antibiotic-resistant bacteria are classified into three categories including MDR, extensively-drug resistant (XDR), and pan-drug resistant (PDR) according to the extent of antibiotic resistance [47]. One major way to escape from antibiotics in these types of bacteria is overexpression of efflux pumps in their envelope. According to a molecular docking study, involving formulation of embelin-loaded chitosan Au-NPs with ciprofloxacin, there were effective interactions between embelin and the active sites of the efflux pump related proteins in EC-r (TolC, AcrB, and AcrA) and PA-r (OprM, MexB, and MexA) [48]. As mentioned above, one of the main compatible NPs with readily solubility in water is albumin NPs, which can be employed to load or incorporate embelin as active ingredient. According to results of MTT assay (that involves the reduction of the tetrazolium dye MTT, chemically known as 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, to its insoluble derivative formazan, which has a purple color), embelin cross-linked albumin NPs at a high concentration of 1500 µg/mL displayed 95% cell viability for NIH3T3 and L929 cell lines [49].

Conclusions

The poor aqueous solubility and bioavailability of embelin can be improved by novel drug delivery systems based on NMs. For improvement of solubility, embelin can be loaded or incorporated in biocompatible polymeric or protein NPs such as albumin NPs. Moreover, in the case of MDR bacteria, one major way to escape from antibiotics is overexpression of efflux pumps in bacterial envelope. In this regard, nanoformulation of embelin-loaded chitosan Au-NPs with ciprofloxacin exhibited the efficient interactions between embelin and the active sites of the efflux pump related proteins in EC-r (TolC, AcrB, and AcrA) and PA-r (OprM, MexB, and MexA). Regarding the anticancer activity, hyaluronic acid-coated amphiphilic polymeric NPs can increase the embelin uptake by triple negative breast cancer cells. As a main conclusion, nanoformulation of embelin can overcome some disadvantages of this plant metabolite observed in physiological conditions. However, future studies should improve or optimize both micro and nano aspects of embelin formulation in the combination with other anticancer and antibacterial activities.

Study Highlights

- The aqueous solubility and bioavailability of embelin can be enhanced by nano drug delivery systems.
- Embelin can be loaded or incorporated in biocompatible polymeric NPs for improvement of its solubility.
- Optimizing both micro and nano aspects of embelin formulation to augment anticancer and antibacterial activities is indispensable.

Abbreviations

NPs: Nanoparticles
MDR: Multidrug-resistant

NMs: Nanomaterials
XDR: Extensively-drug resistant
PDR: Pan-drug resistant
SPR: Surface plasmon resonance
PDI: Polydispersity index
IZDs: Inhibition zone diameters
PEG: Polyethylene glycol

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants.

Authors' contribution

MA: conceptualization, preparing the first draft, and revising; FM, DRD, and DAT: revising of the manuscript.

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