Plant-Derived Nanoparticles for Prostate Cancer Therapy

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Plants have demonstrated potential in providing various types of phytomedicines with chemopreventive properties that can combat prostate cancer. However, despite their promising in vitro activity, the incorporation of these phytochemicals into the market as anticancer agents has been hindered by their poor bioavailability, mainly due to their inadequate aqueous solubility, chemical instability, and unsatisfactory circulation time. To overcome these drawbacks, it has been suggested that the incorporation of phytochemicals as nanoparticles can offer a solution. The use of plant-based chemicals can also improve the biocompatibility of the formulated nanoparticles by avoiding the use of certain hazardous chemicals in the synthesis, leading to decreased toxicity in vivo. Moreover, in some cases, phytochemicals can act as targeting agents to tumour sites.

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1. EGCG-Based NPs

Around 30% of the dry weight of green tea contains antioxidant polyphenolic compounds, and it has been proposed that these compounds are mainly responsible for the chemotherapeutic effects of green tea [1]. Catechins are a major component of green tea polyphenols, of which EGCG is the most abundant [2]. EGCG has a polyphenolic structure (eight hydroxyl groups) that allows for electron delocalization, leading to the neutralization of ROS and nitrogen species. This is the reason why EGCG has protective effects against cancer [3]. EGCG also has potent metal-chelating properties through the presence of the pyrogallol group in its structure, which enable its binding to transition metal ions and function as a proactive antioxidant for cancer treatment [4]. Furthermore, studies have shown that EGCG can prevent cancer progression by affecting several signalling pathways and processes, such as DNA hypermethylation, angiogenesis, apoptosis, and NF-kB activation [5].

It was suggested that the daily consumption of green tea can aid in the treatment and prevention of cancer [6]. However, clinical trials have shown a weaker link between green tea intake and its effectiveness in fighting cancer [7][8][9]. These contradictory observations maybe attributed to the poor bioavailability of EGCG [5]. In fact, it has been shown that systemic levels of EGCG in humans resulting from the oral consumption of green tea catechins are 5 to 50 times lower than the concentrations needed to induce biological effects in vitro [10]. Furthermore, the degradation of EGCG in alkaline and neutral conditions has been attributed to the deprotonation of its hydroxyl functional groups [11]. In addition, the low bioavailability of catechins maybe contributed to their relatively high

molecular weight and the presence of hydrogen-donating hydroxyl groups. Furthermore, the efflux effect of multidrug-resistant proteins on green tea catechins is another reason for their poor bioavailability [12].

Loading EGCG into NPs was used to improve its bioavailability. In this regard, Siddiqi et al. (2009) compared the anticancer effects of the encapsulated and free EGCG on PC3. The study found that encapsulated EGCG was more effective, with an IC_{50} value of 3.74 µmol/L, compared to 43.6 µmol/L for free EGCG. Using flow cytometry techniques, it was found that only a concentration of 2.74 µmol/L of capsulated EGCG was needed to induce apoptosis in around 70% of the cells, while a higher concentration of free EGCG (40 µmol/L) was needed to achieve similar levels of apoptosis. The study also showed that encapsulated EGCG reduced prostate tumour sizes in mouse cancer models more effectively than free EGCG [13]. Similarly, Shafiei et al. (2015) observed the higher cytotoxicity of EGCG loaded into inorganic NPs compared with free EGCG. The positive zeta potential value of the inorganic NPs was suggested to assist in their attachment to the negatively charged cancer cells. The authors also reported increased levels of apoptosis in the cells treated with EGCG-inorganic NPs [14]. Another study described the encapsulation of EGCG in a gum Arabic and maltodextrin matrix, which induced higher cytotoxic effects in androgen-insensitive Du145 cells than free EGCG, as determined via the clonogenic assay [15]. To avoid the degradation of EGCG in the gastric environment, Khan et al. (2014) developed a treatment for oral delivery by encapsulating EGCG in chitosan NPs and showed its controlled release under neutral pH conditions [16]. The oral administration of the chitosan-EGCG NPs to athymic nude mice grafted with human prostate cancer cells (22Rv1) subcutaneously led to a significant reduction in the tumour volumes. The tumour size in mice treated with a dose of 6 mg/kg body weight at day 32 was 216 mm^3. On the same day, the tumour volumes measured for the control group and those treated with free EGCG were 1200 and 514 mm^3, respectively. Immunoblots showed that the treatment with chitosan-EGCG NPs resulted in the initiation of apoptosis via the cleavage of PARP, the overexpression of Bax, the downregulation of Bcl-2, and the activation of caspases [16]. Furthermore, another study reported the encapsulation of EGCG with lipid NPs, which was optimized by varying the lipid content and the amount of co-lipid using an emulsion solvent evaporation method. The study showed that encapsulated EGCG was around four times more cytotoxic to Du145 cells compared to free EGCG, and staining the cells with Hoechst 33,342 dye indicated around a 25% increase in the percentage of apoptotic bodies with the encapsulated EGCG treatments [17].

Other studies utilized prostate cells targeting agents to improve the activity of EGCG-based NPs against Prostate cancer (PC). Sanna et al. (2011) loaded EGCG into polymeric NPs made of poly-e-caprolactone (PCL) and poly-d,l-lactide-co-glycolide/polyethyleneglycol (PLGA-PEG) and introduced a targeting moiety on the NPs by conjugating the NPs with pseudomimetic dipeptide N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-(S)-lysine, which is a PSMA ligand. The in vitro cytotoxicity results exhibited greater antiproliferative activity for the targeting NPs against the PSMA-positive androgen-sensitive human prostate cancer cells (LNCaP) after 48 and 72 h of incubation when compared with the non-targeting NPs [18]. Another interesting synthesis technique reported by Chu and co-workers led to the formulation of PEG-Gelatine-based NPs loaded with EGCG and curcumin to evaluate whether these phytochemicals had synergistic effects [19]. The NPs were conjugated with hyaluronic acid (HA) and fucoidan, which served as CD44 and P-selectin targeting agents, respectively. CD44 is a highly expressed surface protein in solid tumours [20], while P-selectin is a tumour vasculature biomarker [21]. These NPs are pH-sensitive and only

undergo morphological changes in acidic pH conditions, which are comparable to that of the tumour environment. This alteration characteristic represents a form of smart release where the NPs release their therapeutic loads with great precision in the tumour acidic site. Increased cytotoxic effects were demonstrated in PC3 cells for treatments with EGCG- and curcumin-loaded NPs compared to the treatments with free EGCG and curcumin [19]. The same group also reported the incorporation of EGCG (without curcumin) in iron oxide nanoparticles (FeO NPs) using PLGA as a colloidal carrier [22]. However, the IC_{50} values of the PLGA-EGCG NPs observed on PC3 cells were higher than the IC_{50} values observed when EGCG was used in combination with curcumin in their previous study, which clearly indicates the synergistic effects of both EGCG and curcumin [22].

EGCG has been found to have affinity for 67-kDa laminin receptor (67LR), which is overexpressed in several cancers, including PC [23]. Taking advantage of this feature, Shukla et al. (2012) used EGCG and radioactive isotope Au^{198} to synthesize radioactively labelled gold nanoparticles (EGCG-Au^{198}NPs) [24]. The study evaluated the ability of EGCG to increase the targeting effect of the NPs in 67LR-overexpressing PC3 cells. Dark field microscopy confirmed the internalization of the EGCG-Au^{198}NPs in PC3 cells, which could be inhibited by blocking 67LR with a 67LR-blocking antibody. In vivo studies using SCID mice carrying PC3-grafted cells reported in the same study showed a four-fold reduction in the tumour volume in the group treated with EGCG-Au^{198}NPs compared to the control groups (treatments with saline and EGCG alone) [24].

2. Noscapine Based NPs

Noscapine (narcotine) is an alkaloid derived from opium (*Papaver somniferum*). It is a major opioid component of opium, accounting for approximately 10% of its total opioid content, second only to morphine [25]. Although it was originally identified as an antitussive agent, the anticancer properties of noscapine were reported due to its ability to act as a tubulin inhibitor [26]. Unlike other antimicrotubule agents such as taxanes, colchicine, or vinca alkaloids, noscapine can induce cancer cell death with minimal side effects [27]. However, noscapine is a lipophilic compound with average aqueous solubility, making it susceptible to hepatic metabolism. So, despite its potent cytotoxic activity and low toxicity, noscapine is characterized by poor oral bioavailability with a high oral effective dose of ED_{50} 300–600 mg/Kg [28].

Abdalla et al. (2011) developed a triple-conjugated system composed of FeO NPs, a human-type ATF (hATF), uPA, and a fluorescent dye (cy5.5) to deliver noscapine to PC cells. The authors confirmed the binding of the NPs to PC3 cells using Prussian blue staining. Additionally, the crystal violet assay showed a 6-fold increase in cytotoxicity for the loaded noscapine compared to the unmodified compound [29].

3. Curcumin Based NPs

Curcumin, also known as diferuloylmethane, is a major yellow polyphenolic compound found in the spice turmeric (Curcuma longa; Family: Zingiberaceae). It is widely used as a food additive and has been investigated for its potent antioxidant, anti-inflammatory, and anticancer activities [30][31]. Curcumin exerts its anticancer action by

inducing cell death via apoptosis and silencing various cellular signalling pathways that contribute to tumour invasion [32][33]. However, the poor hydrophilicity of curcumin limits its use in medicine due to its inadequate bioavailability and chemical stability in vivo [34]. Additionally, curcumin has poor cellular uptake due to its hydrophobicity, which facilitates its interaction with the cellular membrane rather than the cytoplasm [35]. To overcome these limitations, researchers have sought to load curcumin into NPs to enhance its bioavailability.

Using a wet-milling technique, NPs made entirely of curcumin were produced and reported. The size of these NPs ranged between 34 to 359 nm [36]. Interestingly, in PC3 cells, as shown using MTT assays, the IC_{50} value of the free curcumin was two times higher than the IC_{50} value of the curcumin NPs. The authors suggested that this was due to the increased cellular uptake of the curcumin NPs [36]. However, other reports have highlighted the importance of the NPs' size in cellular uptake, with a suggested size limit of 200 nm [37]. Thus, reducing the size of the curcumin NPs in this study may have led to higher cytotoxicity.

In another study, curcumin was loaded into liposomes with the encapsulation efficiency varying based of the type of lipid used [38]. The treatment of LNCaP cells with 5 to 10 µM of curcumin loaded into liposomes made of dimyristoyl phosphatidyl choline (DMPC) resulted in 70–80% cell death, while free curcumin only achieved similar effects at a much higher dose of 50 µM [38]. In a separate study, Narayanan et al. (2009) loaded curcumin and resveratrol (a phytoalexin from grapes) into separate liposomes and found that the co-administration of these two liposomal NPs had enhanced bioavailability in the serum and prostate tissue in mouse models compared to the free compounds or the naked liposomes [39]. This co-treatment also reduced the prostate weight and the number of adenocarcinomas accompanied by histological changes in prostate-specific PTEN knockout mice. The authors suggested that resveratrol's affinity towards serum albumin enhanced the bioavailability of liposomal curcumin in the blood, thereby increasing its cytotoxic effects [39].

4. Berberine-Based NPs

Berberine, also known as "Natural Yellow 18", is an isoquinoline quaternary alkaloid that has been shown to be present in several medicinal plants of different families, including Berberidaceae, Ranunculaceae, and Rutaceae [40]. The anticancer effects of berberine are well documented in both in vitro and in vivo studies. These effects are related to its regulation of cancer-causing genes and the suppression of different enzymes overexpressed in cancer tissues such as N-acetyltransferase, cyclooxygenase-2, and topoisomerase [41][42][43]. Additionally, berberine treatment has been shown to cause an increase in ROS production and mitochondrial transmembrane potential and stimulate nuclear factor-kappa B. This may explain its apoptotic effects [44]. However, berberine has an absolute bioavailability of less than 1.0%, which hinders its application in its free form as an anticancer treatment [45].

Shen and co-workers increased the solubility of berberine by 300% with a 30-fold increase in its pharmacokinetics by encapsulating it in micelles composed of 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)-2000] (PEG-PE) and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS).

Due to its hydrophobic nature, the incorporation of TPGS increased the loading and stability of berberine. This micelle formulation was three times more toxic to PC cells than the free berberine treatment [46].

5. Eupatorin-Based NPs

The flavonoid eupatorin also displays low pharmacokinetics, which contributes to its poor systemic delivery, short half-life in plasma, insolubility in aqueous media, poor bioavailability and oral absorption, low cellular uptake, and susceptibility to the first-pass effect [47]. One study reported the entrapment of eupatorin in polymeric NPs composed of PEG and PLGA and also then magnetised with FeO NPs [48]. The loaded eupatorin showed sustained release from the polymeric NPs and increased cytotoxicity against Du145 and LNCaP cell lines compared to the free eupatorin. Cell cycle analysis showed that eupatorin-loaded NPs increased the sub-G1 cell population in both prostate cancer cell lines, whereas the free eupatorin increased the G2-M interphase in these cells [48]. This indicates that the eupatorin-loaded NPs can stimulate DNA fragmentation, leading to apoptotic death.

6. Plant-Extract-Based NPs

Due to their high surface-to-volume ratio, nanosized structures exhibit different physicochemical properties compared to bulk structures [49]. Consequently, NPs demonstrate greater activity in various biological applications [50]. Therefore, reducing the size of plant extracts via conventional methods, such as precipitation, can enhance the bioactivity of the phytochemicals present in plant extracts. In most cases, this is accomplished by using plants with known folk medicine uses or those which have been reported to have biological activity. Cherian and co-workers (2015) reported the synthesis of *Baliospermum montanum* NPs (an ingredient of the ayurvedic herbal formulation, with known anticancer properties) via the precipitation method using the aqueous and ethanolic extracts of the plant [51]. The NPs derived from the two extracts exhibited higher cytotoxicity than the crude extract in PC3 cells. However, NPs from the ethanolic extract caused higher levels of cytotoxicity. According to the authors, the reason for this was the presence of anticancer steroids, triterpinoids, and ester compounds in the ethanolic extract, as shown in the FTIR spectrum, which were likely incorporated into the NPs during synthesis [51]. The same authors also reported the synthesis of precipitation-derived NPs using the ethanolic extract of *Leucas aspera*, which is another component of the ayurvedic herbal formulation. Significant cytotoxicity in PC3 cells was also observed after the *L. aspera*-NP treatment, with high levels of NP uptake detected in the treated cells compared to the positive control [52].

7. Plant-Derived Metallic NPs

A study by Bello et al. (2017) demonstrated the biosynthesis of AgNPs from *Hyphaene thebaica* (Doum plant) [53], whose phytochemicals are known to have anticancer activity [54]. The biogenic AgNPs displayed dose-dependent growth inhibition in PC3 cells [53]. A similar study by the authors showed the antiproliferation activity of AgNPs biosynthesized from the aqueous extract of *Guiera senegalensis*, a commonly used medicinal plant in Africa with

reported anticancer activity [55]. These AgNPs displayed anticancer activity in PC3 cells [56]. Indeed, these AgNPs showed selectivity towards PC3 cells compared to other cancer cells lines such as MCF7 (breast cancer cells) and HepG2 (hepatic cancer cells), with IC_{50} values of 23.48, 29.25, and 33.25 µg/mL, respectively. The Chinese *Cornus officinalis*, which is used in Chinese herbal medicine, is another tree known for its antitumour activity [57]. Quasi-spherical AgNPs were biosynthesized from the aqueous fruit extract of this tree within 4 h of incubation with a silver salt solution. The FTIR data indicated that flavonoids and/or anthocyanins of *C. officinalis* play a role in the synthesis and stabilization of AgNPs. An IC_{50} of 25.54 µg/mL was determined for these NPs against PC3 cells using MTT assays, with no observed cytotoxicity for the extract [58]. The IC_{50} values of biogenic AgNPs formulated by Bethu et al. (2018) using *Rhynchosia suaveolens* were, respectively, determined to be 4.35 and 7.72 µg/mL in DU145 and PC3 cells. The authors claimed that the flavonoids and proteins contained in the extract were involved in the NPs' biosynthesis [59]. The flavonoid and protein contents of *Indigofera hisruta* were also suggested to be the reducing and stabilizing agents that allowed for the production of stable AgNPs in another study. An IC_{50} of 68.5 µg/mL was determined for these plant-derived AgNPs against PC3 cells using MTT assays [60]. Zhang and co-workers used the Chinese herb *Salvia miltiorrhiza* to synthesize AgNPs with antiproliferative activity against LNCaP cells. Acridine orange (AO) and propidium iodide (PI) dye staining, as well as the TUNEL assay, demonstrated the apoptotic activity of the NPs. The induction of apoptosis via these AgNPs was also confirmed by an increase in the production of ROS [61].

Zinc nanoparticles (ZnNPs) fabricated using the aqueous leaf extract of *Hyssopus officinalis* showed significantly low IC_{50} values on PC3 (5.0 µg/mL). These NPs also activated apoptosis in cells in a dose-dependent manner [62]. Copper oxide nanoparticles (CuO NPs) were also biosynthesized using the highly nutritious and medicinal plant *Rhus punjabensis*. While the CuO NPs displayed anticancer activity against PC3 as demonstrated by the sulforhodamine B colorimetric assay, the anticancer activity of the plant extract was higher. Furthermore, the CuO NPs showed inhibition to NF-κB signalling, which further highlights their application in fighting cancer [63]. Gold nanoparticles (AuNPs) were also biosynthesized from different extracts of *Euterpe oleraceae* (Acai berry) and *Sambucus nigra* (Elderberry), which showed increased cytotoxic effects against PC3 cells in comparison to the extracts [64].

8. Loading Plant Extracts into NPs

Other approaches were reported when describing the anticancer effects of plant-extract-based NPs such as the direct loading of plant materials into NPs. These NPs are mostly polymeric in nature, which also enhance their overall biocompatibility [65]. These polymeric NPs would also allow the controlled release of phytochemicals to enhance their anticancer action [66]. For example, the anticancer activity of *Nigella sativa* motivated Dawaba and Dawaba (2018) to load this plant's essential oil into NPs composed of chitosan connected to cinnamic acid and benzoic acid in different ratios. Around 90% of the essential oil was released at pH 7.4, indicating the ability of these NPs to release the essential oil into the bloodstream and then to the target site. Further, the MTT results showed significant antiproliferation activity against the PC3 cells (17.95 ± 0.82 µM) as compared to the free oil (43.56 ± 1.95 µM). This activity was attributed to the loaded essential oil as the naked NPs did not exhibit any

cytotoxicity [67]. Another interesting study by Ribeiro et al. (2020) loaded *Uncaria tomentosa* extract, which has known anticancer activity, into different polymeric NPs (PCL and PLGA) [68]. The High Performance Liquid Chromatography analysis for the total alkaloids showed higher drug loading in PLGA NPs than in PCL NPs. This is because of the acidic groups present in PLGA, which facilitate stronger interaction with the amino groups of the alkaloids, as suggested by the authors. The in vitro assay showed higher cytotoxicity for PLGA NPs than PCL NPs against DU145 cells [68].

9. Toxicity of the Reviewed NPs

The reason for incorporating biological materials such as plant extracts in the synthesis of NPs is mainly for the production of biocompatible NPs intended for safe therapeutic applications [69]. However, consideration should be given to the possible side effects of the unknown phytochemicals present in the extracts [70], which may play a role in the synthesis and stabilization of the NPs. The toxic effect of metal ions, especially silver ions [71], is another consideration. Therefore, when reporting on plant-derived NPs, it is vital to evaluate their possible toxicity.

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