Exploring Nanoemulsions for Prostate Cancer Therapy

Authors
Sushmita Srivastava, Md. Faheem Haider, Afroz Ahmad, Usama Ahmad, Muhammad Arif, Asad Ali

Affiliation
Faculty of Pharmacy, Integral University, Lucknow, India

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Md. Faheem Haider
Assistant Professor
Faculty of Pharmacy
Integral University
Lucknow
226026
India
Tel.: + 91-7065237611
fhaider89@gmail.com

ABSTRACT

Prostate carcinoma is typical cancer. It is the second most common cancer globally. The estimated new cases in 2020 was 191 930 and estimated deaths was 33 330. Age, family history, & genetic factors are major factors that drive prostate cancer. Although, for treating metastatic disease, the major therapies available are radiation,bisphosphonate, and palliative chemotherapy. But the major drawback is therapy is disease-driven and later becomes metastatic and requires treatment. The ability to revolutionize cancer treatment by major targeting vehicles via the exploration of nanoemulsion suggests a potential for cancer treatment. The unique property of a biphasic liquid dosage form called nanoemulsion to reach leaky tumor vasculature is due to its nano-meter oil-droplet size of 20–200 nm. Recent reporting on nanoemulsions disclose their embracing and lay alternative for re-purposing herbal and synthetic drugs and their combination especially for targeting prostate cancer formulating an obtainable nanomedicine. So, this article emphasizes the use of nanoemulsions incorporating therapeutic agents for successful and targeted delivery for prostate cancer.

LIST OF ABBREVIATIONS

AR	Androgen receptor
BSA	Bovineserum albumin
CASP7	Caspase-7
CDK1/CDC2	Cyclin-dependent kinase 1/cell-division cycle 2
CDK8	cyclin-dependent kinase 8
CSCs	cancer stem cells
EGCG	Epigallocatechin gallate
EPR	Enhanced permeability and retention effect
G2A	Glycine 2 to Alanine
HLB	Hydrophilic-Lipophilic balance
ICH	International Council for Harmonisation
IL-6	Interleukin-6
LNEs	Lipid nanoemulsions
Mc-1	melanocortin 1
MDK	Midkine gene
MDR	multidrug resistance
mTOR	mammalian target of rapamycin
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
Nrf2/ARE	nuclear erythroid 2-related factor/antioxidant response element
p53	phosphoprotein-53
P-GP	para-glycoprotein
PI3K/AKT	phosphatidylinositol 3- kinase/protein kinase B)
PLA2	Phospholipase A2
PLGA	Poly-Lactic co-Glycolic-Acid

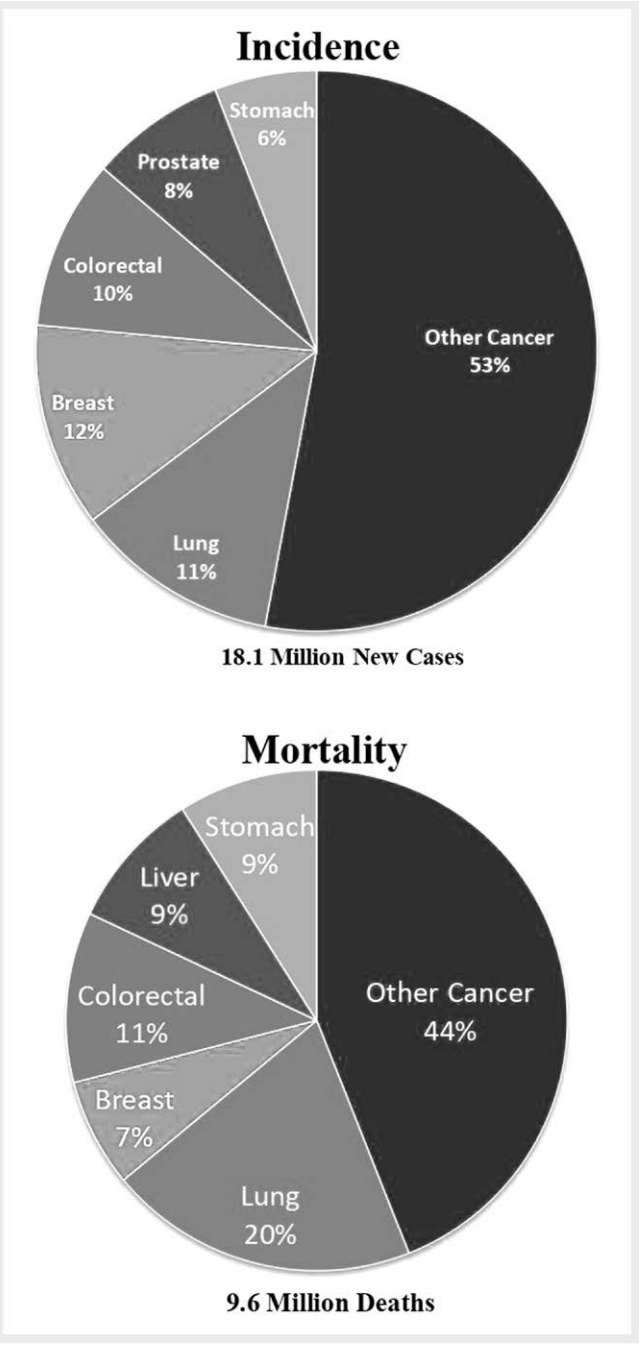
PLK1	polo-like kinase
PTTG1	Pituitary tumor transforming gene 1
RAS/MAPK	Rapidly accelerated Fibrosarcoma/mitogen-activated protein kinase
RGD	Arginine-Glycine-Aspartic
ROS	Reactive oxygen species
STAT3	Signal transducer and activator of transcription 3.
TICs	tumor-initiating cells
Wnt	Wingless-related integration site
ZVAD-FMK	carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluromethylketone

Introduction

The normal growth of cells and malignancy are two different functional alternatives of an organism. The elemental characteristic of normal cells is their division at a particular rate as they have a restricted life-span. Both in vivo and in vitro, normal cells have a limited number of division cycles.

Malignant cell modification appears due to a set of cellular genes called oncogenes by the effect of carcinogens; hormonal factors such as sexual hormones; physical factors thus included in the evolution of neoplasia. Changes in extension rates occur due to the network's functional dysregulation in which tumor suppressor genes (TSGs) and protooncogenes are interconnected. Consequently, by overexpression, protooncogenes are transformed into oncogenes with malignant capacity while TSGs, by loss of their function, are involved in malignant transformation [1]. Cancer is a leading cause of morbidity and mortality across the globe (▶ **Fig. 1**) [2]. The substantial amount of incidences and deaths by cancer is allotted by lung, breast, prostate, colorectum, stomach, and liver (▶ **Fig. 1**) [2] according to data outlined by the International Agency for Research on Cancer with particular bodies such as National Cancer Institute (NCI), American Cancer Society, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention's (CDC's), North American Association of Central Cancer Registries and the International Association of Cancer Registries. In 2018, 9.6 million deaths worldwide occurred due to cancer, and in the next few decades, new cases are projected to grow above 70 %. In 2018, about 18.1 million new cases were diagnosed worldwide [3–5]. In 2019, about 1 762 452 new cases were alone accounted for the U.S, almost equal to 4800 cases per day [6]. To this conclusion, a major part of deaths related to cancer can be prevented through primary prevention by targeted preventive units and screening programs are crucial tools to detect and attenuate adaptable danger personally in a convenient way [7–9]. Moreover, patients with cancer could display longer survival rates at the secondary level of prevention disease management would adjust treatment functions specific to a personal patient profile [10, 11]. ▶ **Figure 1** is based on data published in 2019 [2].

Prostate cancer is second to lung cancer as the primary cause of death and in past years its research interest has increased, so this article emphasizes prostate cancer treatment by use of nanotechnology-based approaches, specifically with nanoemulsion by repurposing herbal and synthetic drugs and their combination targeted to prostate cancer for creating and formulating approachable and attainable nanomedicine.

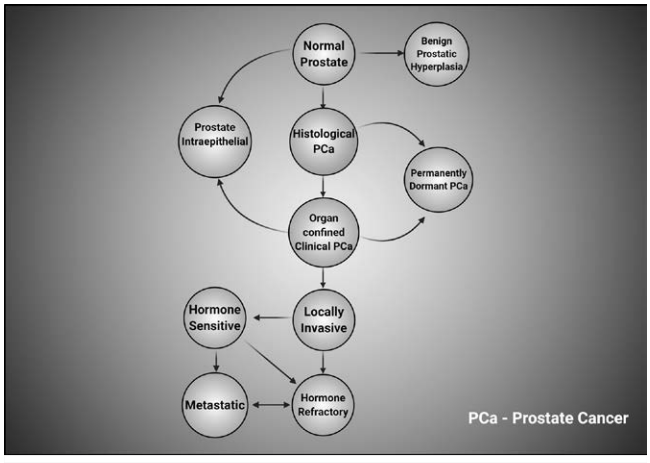


▶ **Fig 1** Global cancer statistics presenting the most prevailing and mortality of different types of cancer.

Carcinoma of the prostate or cancer of the prostate is known as prostate cancer [12]. It is the most typical cancer in men in 84 countries [13]. In men, it is the fifth major cause of death. It is the second most common cancer globally [14]. It was tested in 1.2 million and lead to 359 000 deaths in 2018 [15]. In today's world, the rate is perpetually increasing [16]. It is found in every one out of six American men and is most likely to occur during his life period [17].

There is a variation in rate in different countries, it is most common in New Zealand, North America, Australia, and Europe, and very less common in East and South Asia [18]. It is most likely seen in black men and so less likely seen in Asian men with white in between two [19, 20]. It is the third type of leading cancer in Canadian men, with an estimated 4000 deaths out of 21 600 detected [21]. In Europe, after lung cancer, prostate cancer is the most primeroot of death. Yearly 10 000 deaths out of 35 000 being detected [22]. Until 2040, 2 293 818 new cases are estimated with a small variation in mortality will be observed in 1.05 % [23]. It is calculated that mortality with 379 005 deaths worldwide. The lowest incidence rate will be registered in Europe (+ 58.3 %) followed by Asia (+ 116.7 %) while the highest in Africa(+ 124.4 %) [23]. More often, patients are generally asymptomatic, until their disease becomes metastatic. Indeed, many treatments are available, but they are quite expensive and associated with lots of side-effects. Although, prostatectomy or radiation therapy is most effective for the early-stage treatment of localized prostate cancer, treatment of metastatic disease cancer is often driven by developing a biological mechanism of drug resistance, as prostate cancer arises by the androgen-driven disease [24], the major therapy considered for patients suffering from metastatic or advanced prostate carcinoma is ADT or androgen deprivation therapy to particularly target androgen- receptor axis [25]. Although ADT is effective initially, resistance is still developed in many patients and androgen-independent or develop castration resistance prostate cancer [26, 27]. The etiology of prostate cancer requires an extensive study and remains largely unknown compared to other common types of cancers (▶ **Fig. 2**). Well-known risk factors for advanced prostate cancer are increasing age, family history, and several genetic factors [28–30].

The cells of the prostate are dependent on cell-signaling pathways for their optimal growth, nutrition, and development. However, disturbances in their mechanism lead to the growth of cancerous tissue transformations in the epithelium of the prostate which require treatment strategies (▶ **Fig. 2**). So, [31] reviewed the molecular and functional evidence that inhibiting some of the common pathways involved in a progression such as PI3K/AKT; RAS/MAPK, and STAT3 signaling pathways mediated by growth factor driven receptor tyrosinekinase (RTK) e. g., epidermal growth factor receptor (EGFR) or cytokine (e.g.IL-6). Signaling potentiates the self-renewal capacity of prostate cancer stem cells and their development. In this article, the drugs enlisted below are a major inhibitor of some of these signaling pathways thereby resulting in apoptosis and death of neoplastic transformations.



▶ **Fig 2** Global cancer statistics presenting the most prevailing and mortality of different types of cancer.

There are various types of therapies obtainable for prostate cancer, such as active surveillance, radiation therapy, hormone therapy, radiopharmaceutical therapy, hormone therapy, immunotherapy, bisphosphonate therapy, chemotherapy [32], the risk-benefit relationship should be clearly understood before any sort of treatment after being diagnosed. Patients with unresectable and metastatic cancer may benefit from (palliative) chemotherapy. Although, several studies support curcumin as an anti-cancer drug, yet clinical use is highly restricted because of its low bioavailability and poor absorption of tissue in numerous studies [33, 34]. Different proposals have been accepted to resolve this issue, such as the evolution of delivery systems (for example, nanoparticles, nanoemulsions, and liposomes), etc [35–38].

Since they have unique chemical and physical properties, nanocarrier-based delivery systems are favorable aspirants for the growth of systematic before-time diagnosis and therapeutic tools, frequently incorporated in a theranostic platform to enhance cancerous patient's prospects. A huge diversity of nanostructured materials, such as nanoparticles, nanoemulsions, nanoencapsulation, quantum dots, polymeric nanoparticles, micelles, liposomes, inorganic (titanium, iron- oxide, silver, and gold), ceramic-based carriers, carbon nanotubes, nano-shells, and dendrimers, are nowadays examined as the latest implementation in various anti-cancer treatment [39]. Nanomedicine-based approaches have attracted the attention of researchers due to their tumor-targeting ability [40]. These delivery systems provide Sustained-release action to target cells by an anticancer drug, and normal cells are protected by unnecessary exposure. Through nanomedicine based approaches, drug-related toxicity and therapeutic output are increased [41]. The ability of transferrin-mediated curcumin of solid-lipid nanoparticlesintensifies the anti-cancer effect in breast cancer cells [42]. Polymeric-based drug conjugate (Polyglutamic acid-RGD peptide) targets tumor tissue utilizing enhanced permeability and permeability effects (EPR) effects serving increased anti-tumor activity with decreased toxicity when compared to free paclitaxel-treated mice [43] with amplified anti-angiogenic effect. PEGylated PLGA based nanoparticle attached with RGD peptide-paclitaxel loaded nanoparticle has been outlined for targeting of tumorepithelium [44].

A fascinating and vital evolution in the exploration in the use of nanoemulsion is for targeted drug delivery to cancer as they can be easily targeted to tumor tissue because of their nano-meter oil-droplet size using targeted molecules on the surface of nanoemulsions. Recent studies also designate that they have broad attentiveness as colloidal carriers for the selectedcarriage of many anti-cancer drugs [45–48] and diagnostic agents [49, 50]. Nano-emulsification serves as aninstrument to improve the drug solubility, oral bioavailability of lipophilic compounds, and absorption via lymphatic system with bypassing first passing metabolism and membrane transport [51]. Over many conventional drug delivery systems,available nanoemulsion possesses several advantages: reduced inter-subject differenc-

es, rapid onset of action, and high solubilization capacity [52]. Here is the example of the study conducted by the researchers in which the formation of nanoemulsion increases the encapsulation, which leads to cancer cell apoptosis. Many studies reveal that tumor cells articulatingCSCs markers mainly CD133 and CD4 are correlated with drug resistance and quicken after therapy [53]. Due to the up-regulation of drug efflux transporters, additional structured reactions to DNA damage and repair processes, and anti-apoptotic mechanisms, there is a drug resistance in CSCs [54]. The populations of fast-growing cancer cells are targeted in prostate cancer therapy but exclude subpopulations like CSCs or TICs which is the major problem in therapy. Also, to assess anti-cancer agent's anti-prostate cancer development restricts cell lines with high passage numbers to pre-clinical studies that end with epigenomic or genomic features with very less or no pairing with original cancer [55]. From prostate cancer patient a cell line PPT2 with very low passage number and through this way stem-like properties and immaturity are kept by the team of researchers who conducted this study. Genes of PPT2 cells are connected with anti-apoptotic signaling and drug resistance to a drug being an impeccable model for CSC targeted therapy studies [56]. For therapy of prostate carcinoma one drug that is often used is a paclitaxel-pro drug, Abraxane. It is designed to accelerate its solubility with human serum albumin-bound nanoparticle formation. In MDR cancer cells, Paclitaxel exhibits complications [54]. SBT-1214, is a new generation taxoidthatis potent in case of drug resistance, this taxoid is interfusedwithdocosahexaenoic acid (DHA), a natural polyunsaturated fatty acid (PUFA), with high empathy towards its main bloodstream transporter (human serum albumin) that help direct toxicity to cancer. The Association of DHA with paclitaxel leads to a weak decrease in P-GP and ABC transporters [57]. The nanoemulsion formation of DHA-SBT-1214 in this study holds phospholipids and fish oils. The encapsulation of the drug is increased due to the association of the drug with fish oil. It is told that nanoemulsion formed will function on CSC initiated PPT2 cell line making utilization of EPR effect and ensue in apoptosis of cancer cell [54]. With the use of patient procured CSC enriched PPT2 cells, the formation of drugs that target cells enhanced for tumor initiation can be done. Association of DHA with SBT-1214 increases the blood circulation time of the drug. Encapsulating the associated hydrophobic drug in nanoemulsion formation resulted in effective delivery; Thus, the drug circulation time is enhanced by surface moderation with PEG which accelerates accumulation due to the EPR effect. The nanoemulsionformation can deliver its payload more adeptly as compared to drug solution which can be seen by successful cellular uptake [54].

Nanoemulsion

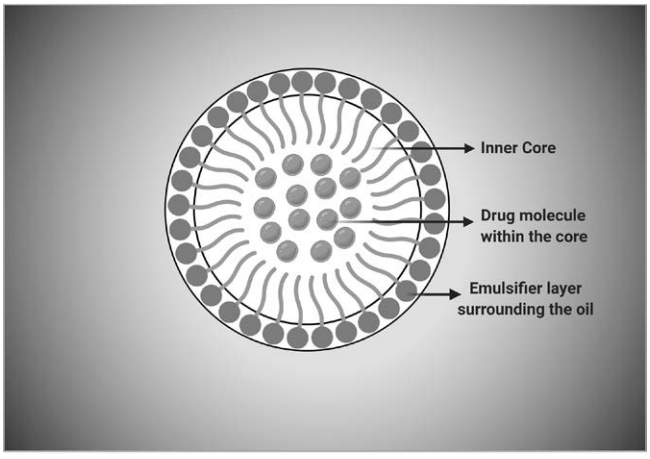
The important framework that differentiates a nanoemulsion ($d < 200$ nm) from a conventional emulsion ($d > 200$ nm) is the proportions of the droplet. As a result, conventional emulsions always have a tendency to degrade over time. [58, 59]. Because of the small particle size, nanoemulsions are much more resistant to gravitational separation and aggregation than conventional emulsions [60, 61]. Nanoemulsions (NE) have a kinetic stability, microemulsions, on the other hand, are thermodynamically stable. In terms of formulation, a microemulsion requires a higher surfactant-to-oil ratio (SOR) than a nanoemulsion. As a result, the particle size of microemulsion is smaller than that of nanoemulsion. For particle size distribution, a single narrow peak is observed in microemulsion, whereas a single or multiple narrow or broad peaks are observed in nanoemulsion. Particles in nanoemulsions are mostly spherical, whereas particles in microemulsions can be spherical or non-spherical [62]. For molecules with low water solubility, nanoemulsion is colloidal dispersion that can be used as a drug vehicle formed with safe grade excipients [62, 63]. It is a heterogeneous dispersion of nano-meter droplets in another liquid which makes them a carrier with high stability and solubility [64]. There are three types of nanoemulsion which are given as under:

(1) Oil in water nanoemulsion in which oil droplets are dispersed in water.
(2) Water in oil nanoemulsion in which water droplets are dispersed in oil.
(3) Bi-continuous phase.

They mainly contain water, surfactant, and oil (▶ **Fig. 3**). The two immiscible phases are separated by surfactants which reduce the interfacial tension between two immiscible phases [65]. For the preparation of oil in water nanoemulsion, surfactants with an HLB value of 8–18 are used whereas for preparation of water in oil-based nanoemulsion the preferred value of HLB is from 3–6 [66].

The absolute emulsifying agent should be rapidly absorbed, reduce the interfacial tension as electrostatic or stearic interaction stabilizes the surface. Surfactants such as amphiphilic proteins like caseinate or phospholipids such as soya lecithin; modified starch in the category of polysaccharide or polymers such as polyethylene glycol [67] and non-ionic surfactants like sorbitan fatty acids ester such as Spans can also be utilized [68].

The oily phase acts as an organic phase and a carrier for active ingredients. The proper selection of the oily phase is a very crucial part of the manufacturing nanoemulsions as it affects the facilitation and solubility of active moieties of nanoemulsion for the preferred cause. Especially in oil in water nanoemulsions, the selection of the oily phase is an important part as it affects various other components in the formulation [69].



▶ **Fig 3** Global cancer statistics presenting the most prevailing and mortality of different types of cancer.

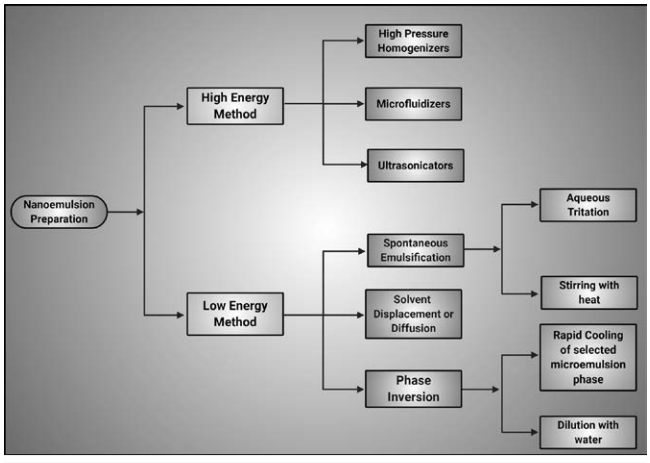
There are various solvents employed for the preparation of the nanoemulsion. Various characteristics of the aqueous phase such as interfacial tension, viscosity, density, and structural properties of the solution of surfactant increase desired curvature and critical micelle concentration [70].

The two phases of nanoemulsion production are mixed and heated phases with optimum temperature and agitation to achieve a homogeneous mixture. To achieve optimum particle size a process of shear force homogenization is achieved. At last, the structure will have a layerof emulsifier separating the lipophilic interior from the aqueous phase. To stabilize the formulation this unique layer acts as a barrier and shows repulsive forces depending on the emulsifier [71].

Nanoemulsion preparation can be divided into two zones which are high energy and low energy methods (▶ **Fig. 4**). High energy requires a power input of 10^7 to 10^9 W/kg and low energy methods require power input of 10^3 to 10^5 W/kg [72]. High shear methods utilize microfluidizers, ultrasonicators, and homogenizers [73]. For perfectly-being scaled up on one side, on the other they reflect a limitation for heat-sensitive drugs. Due to this, low energy and temperature methods must be used like phase inversion methods and self-emulsification phase transition [74].

There are many advantages of nanoemulsion as a structured nano-carrier:-

- Nanoemulsion being structured lipids are manufactured and utilized for increasing the in vivo circulation time [75].
- The capacity of nanoemulsion to solubilize a huge number of both hydrophilic and hydrophobic drugs and their capacity to safeguard the drugs from hydrolysis and enzymatic degradation makes nanoemulsion an ideal platform for the delivery of parentals [76].
- Moreover, they can be used for image-guided delivery of a drug by making use of targeting and imaging components [77].
- They are also being tested extensively for their ability in applications in ophthalmic [78]; pulmonary [79]; and transdermal [80].



▶ **Fig 4** Global cancer statistics presenting the most prevailing and mortality of different types of cancer.

- It can be developed for several formulations such as liquids, sprays, creams, and foams [81].
- They have a larger surface area and wider absorption [82].

Disadvantages:-

- Bioactive components typically have very low bioavailability; however, if their absorption by the human body is significantly increased by incorporation into a nanoemulsion, they may exhibit toxic effects that cannot be predicted using data obtained on the same material in macroscopic form [62].
- Nanoemulsion particles may be able to bind to cellular membrane receptors, disrupting the cell's normal metabolism and function [83].
- The combination of small size, high surface area and high surface energy in nanoemulsion may effect in biological systems that are not predictable from the bulk form of the same materials [84].
- The higher usage of surfactants in nanoemulsions compared to conventional emulsions may have some adverse health effects [62].

Nanoemulsion based Delivery of Various Therapeutic Agents having Activity against Prostate Cancer

Natural Drugs

Catechin

Catechins because of their instability, in-vivo bioavailability remained low [85–87]. Thus, with the help of the preparation of micro or nanoemulsion, bio-active moiety such as catechin can be encapsulated. A study has been displayed by [88],who prepared catechin nanoemulsion constituting cholesterol, phytosterol, glycerol, and water and the average particle size was found to be 300 nm by DLS analysis. Here is a study conducted by [89], in which a nanoemulsion is composed of catechin extract, 0.5 % lecithin, 5 % tween 80, and 94.5 % deionized water was prepared and mean particle size being 11.45 nm, polydispersity index 0.27, encapsulation efficiency 88.1 and zeta potential −66.3 mV. High stability of catechin nanoemulsion was shown at a period of 120 days at 4 °C. Both catechin and catechin extract could inhibit prostate cancer cell PC-3 proliferation with IC_{50} being 15.4 µg/mL and 8.5 µg/mL respectively stating that the nanoemulsion possessed a more pronounced inhibition effect toward the growth of PC-3 tumor cells (▶ **Table 1**).

The anti-cancer activities of EGCG are relevant to be pushed by targeting multiple pathways that are mainly involved in cancer progression, such as mitogen-activated proteinkinase (MAPK); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); the epidermal growth factor receptor (EGFR) and insulin-likegrowth factor receptor (IGF-1) mediated pathways [90].

Curcumin

Recent studies showed that curcumin encapsulated in polymeric nanoparticles could improve the therapeutic efficacy as compared to free curcumin as a result of increased solubility in aqueous media [91–93]. Moreover, different from free curcumin, curcumin nanoemulsions induced more PC-3 cells arrested in the G_2/M phase, which

▶ **Table 1** Nanoemulsion of anticancer agents for prostate carcinoma.

S.No	Category	Active-drug molecules	Drawback with the drug	Purpose of study	Particle size	Zeta potential	Remarks	References
1	Herbal drug	Catechin	Low in-vivo stability and bioavailability	To enhance bioavailability, biological activity and study inhibition effect	11.45 nm	−66.3 mV	Apoptosis of PC-3 cells	[89]
2	Herbal drug	Curcumin	Poor aqueous solubility & low bioavailability	To enhance activity of Cur & oral absorption	34.54 ± 2.2 nm	8.54 ± 0.45 mV	Superior anti- cancer potential of Cur nanoemulsion	[94]
3	Herbal drug	Plumbagin	Sparingly solubility in water	Evaluated anti-proliferative effect on PC-3 cells	135–220 µm	–	Optimal absorption, higher anti-proliferative activity, cytotoxicity & drug loading capacity	[96]
4	Herbal drug	Rutin	Poor oral bioavailability, degradation in aqueous environment	For bio enhancement of rutin, and to increase therapeutic effect	70.09 nm & 88.4 nm	−15 mV to −17 mV	Nanoemulsion was effective against prostate carcinoma cells	[98]
5	Herbal drug	Paclitaxel	Low water solubility	Assess potential of paclitaxel palmitate loaded Anti-Her2 immuno-emulsion	160 ± 30 nm	50 ± 10 mV	Lead to improved metastatic prostate cancer treatment	[99]
6	Synthetic	Docetaxel & Gerainol	Low water solubility	For effective chemotherapy of prostate cancer	–	–	Sustained release formulation with activity against cells of prostate and resulted in effective chemotherapy	[108]
7	Synthetic	Bicalutamide & Bobine serum albumin	Variable bioavailability & pharmacokinetics; poor aqueous solubility and poor absorption	To evaluate effect of BSA on stability of BT- encapsulated LNE particles	50 nm	−40 mV to −30 mV	A suitable DDS carrier for long circulation cancer therapy	[104]
8	Synthetic	Dutasteride	Long term oral administration causes sexual problems in man	To enhance physical and chemical stability	58.83 ± 0.73 to 65.74 ± 0.31 nm	–	Enhanced stability	[106]
9	Combinational drug	Curcumin & Etoposide	Low pharmacokinetic profile	Synergistic effect of drugs by encapsulating in nanoemulsion	< 150 nm	−29.8 mV	Pharmacokinetics profile was improved	[112]
10	Combinational drug	Babassu & Copaiba oils	Severe side effects of pharmacological interventions	Alternative therapeutics for BPH treatment	40–60 nm	−17.0 mV	Synergistic effect reduces appearance of BPH	[115]
11	Combinational drug	Tadalafil & Pumkin seed oil	Poor solubility of Tadalafil	Aimed to improve TDL delivery to prostate	204.8 ± 18.76 nm	7.86 ± 1.21 mV	Improved the efficacy of Tadalafil in management of BPH	[111]

might be due to the slow release of the nanoemulsion [93]. In [94], their study concluded that nanoemulsions could be loaded efficiently with curcumin and therefore increase the solubilization of the drug encapsulated within. Nanoemulsion could increase cellular uptake, cellular cytotoxicity, cell cycle arrest, and apoptosis against prostate cancer cells. Curcumin encapsulated within nanoemulsion was released slowly into the cells thereby resulting in prolonged cytotoxicity and also cell-cycle arrest in PC-3 cells (▶ **Table 1**). Also, in-situ single-pass perfusion studiesshowed a higher effective permeability coefficient for Curcumin nanoemulsion than that of free curcumin.

Through the down-regulation of androgen receptor and epidermal growth factor receptor, curcumin targets prostate cancer metastasis development, and proliferation and also by the induction of cell-cycle arrest. Through the inhibition of pro-inflammatory mediators and the NF-κBsignaling pathway, it mediates inflammatory response. The results also reveal that the molecule potency towards induction of pro-apoptotic proteins and downregulates the anti-apoptotic counterparts [95].

Plumbagin

Plumbagin loaded oleic acid-based nanoemulsion was prepared, using high-pressure homogenization of oleic acid emulsion with polysorbate 80 as an emulsifying agent. The plumbagin-loaded nanoemulsion (135 nm of zeta-potential; 10 % w/w) oleic acid, 3.5 % w/w polysorbate 80) was selected for proper size distribution over time, and polydispersity was selected for further studies of drug release, stability in simulated physiological fluids, and in-vitro cytotoxicity against PC-3 cells. The plumbagin loaded nanoemulsion showed good retention of nano-particulate size, after dispersion in water or media simulating physiological environment. Moreover, the exponential release of plumbagin from nanoemulsionwith half-lives had permit optimal absorption of plumbagin from the gastrointestinal tract is shown by drug-release studies. As compared to free plumbagin, plumbagin encapsulated nanoemulsion displayed higher anti-proliferative activity on PTEN-P2 cells (▶ **Table 1**) [96].

Plumbagin exhibits anti-cancer effects via interaction with multiple targets and modulation of various molecular signaling pathways including CDK1/CDC2, cyclin B1, cyclin D1, AMPK, NF-κB, p53, p21, Cip1/Waf1, p27Kip1, Nrf2/ARE, mTOR/AKT/PI3K &Wnt [97].

Rutin

The percentage of cell viability and cell morphology by rutinnanoemulsion significantly reduces cell viability of prostate cancer cell line PC-3 in a dose-dependent manner [98]. In this, they have also shown that rutinnanoemulsion induces intracellular ROS generation thus provoking cell death. The bioactive encapsulated in rutin nanoemulsion system was found to be more effective against prostate cancer cell line at a very low concentration as compared to the free or purified form of rutin thus inducing apoptosis (▶ **Table 1**). The in-vivo anticancer activity and bio-distribution studieson animal models of cancer are suitable to expand and explore the anticancer potential of rutin nanoemulsion. As compared to pure drug suspension the in-vitro drug release studies from rutinnanoemulsion were significantly higher($p < 0.05$).

Through fluorescent microscopic analysis and intracellular ROS generation explained that significant ROS induction might lead to manipulating apoptosis pathway.

Paclitaxel Palmitate

Anti- HER2 cationic immune-emulsion for treatment of prostate cancer was prepared [99]. Taxanes such as paclitaxel exhibit a wide variety of antitumor activity, its therapeutic application are restricted due to poor solubility. The objective of their study was to assess the efficiency of paclitaxel palmitate loaded anti-HER2 immunoemulsion covalently linked to an anti-HER2 monoclonal antibody (Herceptin) in an in-vivo pharmacologic model of metastatic prostate cancer that overexpresses HER2 receptor. It was noted that cationic emulsion and immune-emulsion did not activate complement compared with commercial and paclitaxel palmitate hydroalcoholic formulations. Moreover, 10 mg/kg of paclitaxel palmitate loaded immune-emulsion once weekly over 3 weeks inhibits tumor growth in severe combined immunodeficient mice much more than the cationic emulsion ($P < 0.05$) and the paclitaxel-palmitate formulation ($P < 0.01$). Histopathologic studies were in favor of immune-emulsion. They concluded that tumor growth was not fully inhibited but actual results are encouraging and lead to an improved therapeutic strategy of metastatic prostate cancer treatment (▶ **Table 1**) [100], suggested paclitaxel a widely used mechanism of action is connected to its potential to arrest cells in mitosis and intrinsic pathway induction. In LNCaP cells, however PTTG1 downregulation prevents mitotic entry and subsequently inhibits mitosis-associated paclitaxel-induced apoptosis. They also identified a role for Mc-1 protein in preventing apoptosis during mitosis in PC-3 cells as alternatively PTTG1 and Mcl-1 silencing enhances mitosis linked apoptosis after paclitaxel treatment.

Synthetic drugs

Bicalutamide

Bicalutamide is a non-steroidal, anti-androgen used for the treatment of prostate cancer [101, 102]. Although it has high in-vitro potency, after oral administration, its absolute bioavailability and pharmacokinetics are highly variable due to poor absorption [103]. For the development of a stable drug carrier for bicalutamide(BT), LNEs (Lipid nano-emulsions) were prepared from a lipid mixture of soyabean oil, phosphatidylcholine, sodium palmitate, and sucrose palmitate(SP) [104]. These Lipid Nanoemulsions had a mean particle size of approximately 50 nm and zeta potential of −4o to 30 mV and their stability was assessed in saline solution and bovine serum by dynamic light scattering method. The droplet size of LNEs hardly increased even after 72 hours placed in bovine serum suggesting bovine serum albumin suppressed their coalescence. The intrinsic fluorescence of BSA was blue-shifted in presence of LNEs. Moreover, zeta potential values of all LNEs increased to around −20 mV according to an increase in BSA concentration. These results stated that BSA interacted with LNE particles and acts as a suitable drug delivery system for bicalutamide and its significant role in cancer therapeutics (▶ **Table 1**).

By demonstrating the exact pathways through which bicalutamide induces its anti-apoptotic effect would help to advance its clinical application.

To identify a specific pathway of action for bicalutamide, [105] pre-treated PC-3 and PWR-1E cells with some specific inhibitors such as calpain 2 inhibitor(caspase-independent pathways and caspase-dependent (zVAD-FMK). Bicalutamide via caspase and calpain independent mechanism induced apoptosis in androgen-dependent PWR-1E cells. This moiety also induced apoptosis by some underlying phenomena that are gradually inhibited by pan-caspase inhibition but were somewhat calpain development.

Dutasteride

Dutasteride, a 5α- reductase inhibitor has been recommended for the treatment of BPH upon oral administration. However, its long-term use can cause sexual problems in men so to enhance physical and chemical stability and remove toxicity [106] formulated nanoemulsion of dutasteride by the aqueous-titration method. Low-surfactant containing nanoemulsion was taken for further study to decrease the toxicity problems. A stability study was performed according to ICH guidelines and the formulation was found to be stable. The droplet size, viscosity, and RI of optimized nanoemulsion show that there were no changes in 3 months of storage stating the nanoemulsion were found to be physically stable. There is slower degradation of dutasteride in nanoemulsion indicating chemical stability (▶ **Table 1**). The shelf-life was found to be 2.18 years at room temperature [107] found out that dutasteride kills PCa cells in vitro, they used the most common prostate cancer cell line LNCaP. Moreover, it reduced viability and proliferation disrupted genes and cellular pathways that are involved in metabolic cell cycle and apoptotic responses besides those that are expected in androgen-signaling pathways. Activation of genes in the FaSL/tumor necrosis factor-alpha (TNF-α) apoptotic and cell-survival pathways correlating with growth and survival effects are revealed by microchip gene array expression analysis. Candidate genes such as PLA2, G2A, CDK8, CASP7, MDK, and NKX3.1 expression level change seen by microarray analysis is confirmed by a real-time polymerase chain reaction.

Docetaxel

A docetaxel nanoemulsion for effective chemotherapy of prostate cancer [108]. DTX-Ger-Nanoemulsionformulation has been designed and developed with desired size and size potential. Pre-formulation studies conducted revealed that the API and excipients were authentic and of standard grade. The formulation has narrow size distribution and spherical shape which is suitable for I.V administration. In the end, it was also concluded that the formulation is sustained release. From the stability studies, it was shown that the formulation is stable at 4 °C and 25 °C for 3 months. Cell uptake studies revealed that the formulation is extensively taken up by cancerous cells so it can be said that the efflux mechanism of the cell is inhibited and formulation is capable of delivering its effect. From in-vitro studies, it is revealed that the formulation is active against cancerous cells. Haemolysis study revealed that the use of Geraniol oil is unsafe for I.V administration but on the other hand shows improved anti-cancer activity (▶ **Table 1**). Therefore, geraniol should be used with caution for I.V administration.

In the study conducted by [109], the apoptotic inhibitory effect of Doc on androgen-independent or androgen-dependent prostate cancer cells was tested and then they tried to demonstrate the regulation of phosphoinositide 3- kinase (PI3K/Akt) signaling pathway in Dox-induced apoptosis. Their studies demonstrated that therapy of three prostate cancer cell lines, with Dox, decreases the level of phosphor-Akt. It has already been reported that the development of Doc resistance is linked to activation of AR [110] which is relevant with the data which thereby confirmed the originality of their data.

Combination drugs

Pumpkin seed oil and Tadalafil

FDA has approved Tadalafil (TDL) for the treatment of benign prostatic hyperplasia (BPH- associated symptoms.) Pumpkin seed oil (PSO) has shown promising results for the relief of prostatitis-related lower urinary tract symptoms [111] aimed to improve the TDL with a PSO-based formula in the management of BPH. PSO, tween 80, and PEG 200 were selected for the optimization of the self nanoemulsified drug delivery system (SNEDDS). SNEDDSs are isotopic mixtures of oil, surfactants, and co-surfactant components that spontaneously form emulsions in the gastrointestinal tract (GIT) fluids. Following dilution, nanoemulsion droplets with sizes less than 20 nm (with 200 nm being the upper limit) are formed. A rat in-vivo study was carried out to investigate the prostate weight and index, histopathology, and pharmacokinetics. The average globule size was 204.8 ± 18.76 nm, the zeta potential was 7.86 ± 1.21 mV. the formulation resulted in a decrease in prostate weight by 35.51 % and prostate index by 36.71 % compared to the testosterone-only group. Also, pharmacokinetic data revealed a 2.3-fold increase of TDL concentration from an optimized formulation in the prostate as compared to the raw TDL group. The study indicated that the combined effect of TDL and PSO in an optimized TDL-PSO SNEDDS formulation improved the efficacy of TDL in the treatment and management of BPH (▶ **Table 1**).

Curcumin and Etoposide

In their investigation [112], encapsulated ETP and CURinnanoemulsion and has been investigated for their effect on cancer. ETP is a well-established chemotherapeutic agent and CUR induces apoptosis in both PC-3 cells [113] and DU-145 cells [114].

The Encapsulation efficiency of ETP & CUR was found to be (490 ± 11.5 ng/ml) (98 ± 2.3 % and 1480 ± 11.5 ng/ml) 99 ± 1.7 % respectively. The in-vitro drug release profile showed biphasic release behavior with an initial burst effect followed by sustained release. The particle size was less than 500 nm. Pharmacokinetics of CUR and ETP was not affected significantly either separately or in combination. However, F5 formulation resulted in a dramatic increase in AUC of both CUR & ETP and the trough concentration of both the drugs was higher than that of their native form of ETP & CUR. This resulted that nanoemulsion improved absorption of both CUR & ETP. Nanoemulsion containing solubilized hydrophobic drugs ETP & CUR allowed for efficient intracellular delivery. In their study, they have not found any synergistic effect of CUR & ETP against prostate cancer cells, and an instead lower degree of antagonism of CUR & ETP was observed. Also, the degree of antagonism of ETP & CUR was different for DU-145 cell lines. They attributed the aberrant response of DU-145 to its inherent differences from PC-3 cells. The developed nanoemulsion could enhance the bio-availability of both CUR & ETP. The formulation increased the response of CUR & ETP

significantly in both cell lines. They assumed that the antagonistic effect of ETP and CUR which was more prominent in the case of the plain drug was somehow subdued by enhanced bio-availability imparted by formulation (▶ **Table 1**).

Babassu oil (BBS) and Copaiba oil (COP) resin

The use of copaiba-oil resin (COP) and babassu oil (BBS) and incorporated into self-emulsifying drug delivery systems (SEDDS) [115]. The physical characteristics of the resulting nanoemulsion were next analyzed to identify the preparation suitable for in-vitro toxicity and in-vivo tests. The two most promising formulations containing BBS and with and without COP were thermodynamically stable with a zeta potential less than − 20 mV and droplet size around 30 nm. These formulations in the rat model of BPH showed promising potential to reduce the onset of this process. The SEDDS formulation developed served as an alternative incorporating BBS and COP for the treatment and prevention of BPH. The accumulation of SEDDS in hyperplastic tissues, which is a characteristic of other herbal medicine. At the same time, the synergistic effect of two oils in the association was detected, since no protective activity was observed for the use of copaiba oil alone its BBS improved outcomes (▶ **Table 1**). Also, the droplet size and zeta-potential suggested that SEDDS formulation would be suitable for oral administration. Altogether, these highlighted the promising potential to use phytochemicals in a SEDDS formula for control of BPH.

Future Perspectives

Nanoemulsions are used as a targeted drug delivery system in various cancer therapeutics and act as a carrier system for many anticancersbecause of their nano-meter-oil droplet size and ability to cross inside leaky tumor vasculatures. Many therapeutic agents are effective against prostate cancer but their nanoemulsionis not yet made. Hence, a nanoemulsion formulation of these drugs could be a possible treatment regimen for different types of cancer including prostate.

Different types of drugs include Lycorine which is already revealed that lycorine leads to apoptosis & anti-proliferation in several prostate cancer cell lines. A mannosylated lipid nanoemulsion formulation loaded with lycorine-oleic complexwas prepared and assessed on the A549 cell line [116]. Thelipophilicity of lycorine was greatly enhanced which resulted in high encapsulation efficiency of the particular formulation.

Resveratrol is also a potent therapeutic in prostate cancer cell death. A resveratrol nanoemulsion was made for reducing nicotine toxicity in the lungs of rats [117]. The protective effects were seen. So, resveratrol incorporation in nanoemulsion for prostate cancer therapy will provide use in clinical applications.

Flutamideis a non-steroidal antiandrogenic poorly water-soluble drug and binds to the androgen receptor in the prostate gland. Flutamide is practically insoluble in water (9.45 mg/L); log P (2.6). thus this type of nano-based system incorporating flutamide in nanoemulsion will be a good treatment in near future [118].

Thalidomide is a drug that is highly potent in many cancers such as myeloma, pancreatic, prostate, and lung. It actuates angiogenesis and advances apoptosis. Its incorporation into nanoemulsion through suitable emulsifiers can be a powerful treatment of cancers including prostate [119, 120].

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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