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REVIEW

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Next-generation strategies against prostate cancer: natural products and nanomedicine targeting prostate cancer stem cells

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Abstract

Recurrence, metastasis, and treatment resistance are significant issues in prostate cancer management. Evidence increasingly substantiates the notion that prostate cancer stem cells (PCSCs) initiate cancer, facilitate its progression, and complicate therapy. Thus, targeting PCSCs may provide a feasible strategy for addressing incurable or recurrent illnesses. Research indicates that natural compounds derived from medicinal plants and foods may combat cancer, particularly by targeting cancer stem cells via modulation of signals from the Wnt/β-catenin, Notch, Hedgehog, and Phosphoinositide 3-kinase (PI3K)/Protein kinase B (AKT)/Mechanistic target of rapamycin (mTOR) signaling pathway. Nonetheless, the majority of these bioactive chemicals exhibit low solubility in water, inadequately penetrate the circulation, and are rapidly eliminated by the body before they can be effectively used in medical applications. Nanotechnology has enhanced the delivery, production, and targeting of certain natural products. Phytochemicals may be effectively administered to PCSCs inside tumours using liposomes, polymeric nanoparticles, dendrimers, micelles, and exosomes. Moreover, stimuli-responsive nanoplatforms may be constructed to concurrently administer several pharmaceuticals. This review analyses the function of PCSCs in prostate cancer, identifies key natural chemicals that target PCSCs, and evaluates the potential of nanotechnology to amplify the efficacy of these natural products. Furthermore, we examine current obstacles, unresolved enquiries, and anticipated trajectories for the implementation of natural nanomedicine therapies in PCSCs.

Keywords

Prostate cancer stem cells; Natural products; Nanomedicine; Phytochemicals; Drug delivery; Cancer recurrence; Tumor resistance; Precision oncology

1. Introduction

Prostate cancer (PCa) is one of the most common cancers in men around the world, with a significant impact on the health of the population [1–3]. It is the second most reported cancer and the fifth killer-cancer of men in the whole world. As indicated by the Global Cancer Observatory (GLOBOCAN), over 1.46 million estimated cases of prostate cancer were recorded in 2022 alone, and about 396,000 of them died [4]. Prostate cancer incidence is highly variable in different parts of the world, with those in the West, especially North America, Northern, and Western Europe as well as Australia recording high incidences [3, 5]. The causes of such disparities remain widely spread, including variations in healthcare accessibility, genetics, environment, and the popularity of using the prostate-specific antigen (PSA) test [5]. In low- and middle-income countries, the reported incidence is low, but the mortality rates are unbalanced as people are not diagnosed timely, screening programs are insufficient, and treatment facilities are weak. Since there is a tendency of life expectancy going up, the increasing burden of prostate cancer all over the world is inevitable, hence the need to come up with the best prevention and treatment methods [6].

Though there have been tremendous innovations in the diagnosis and treatment of prostate cancer, especially with the advent of androgen deprivation therapy (ADT), radiations, and surgery, as well as newer generation anti-androgen based drugs, there has not been a long term disease management in a high number of patients [7]. Therapeutic resistance, culminating in poor outcomes, is one of the major challenges of prostate cancer arising in the form of recurrence and its progression to a disease-resistant condition, castration-resistant prostate cancer (CRPC), which is fatal [8]. Recent studies have increasingly pointed to a minor fraction of tumor-initiating cells, the so-called prostate cancer stem cells (PCSCs), creating resistance to conventional therapies [3, 9]. These PCSCs have distinguishing features like self-renewal, multi-lineage differentiation, and quiescence, with the possibility to rise

therapeutic attacks that normally wipe millions of bulk tumor cells away. They are able to re-seed the tumor and enable the occurrence of metastasis that leads to treatment failure and illness relapse [10]. In addition, PCSCs are resistant to chemotherapeutic drugs and radiation therapy due to high expression of drug efflux pump, resistance paths, and increased DNA repair [11].

Since PCSCs are so instrumental in the progression of prostate cancer, as patients develop resistance to treatment, it follows that an attack on this persistent subpopulation is highly promising to break therapeutic resistance and enhance patient outcomes [12]. But the straightforward destruction of the PCSCs is a significant challenge because they are resistant, with a unique microenvironment, and their molecular pathways are complex [13]. There has been a growing interest recently in the use of natural products as the future agents of targeted cancer stem cells. Natural products, including c-curcumin, resveratrol, epigallocatechin-3-gallate (EGCG), and quercetin, which are used as diets, and medicinal plants; have displayed anticancer activity in numerous malignancies, including prostate cancer [14, 15]. The known targets of action of these compounds include modulation of important signaling pathways that relate to stemness, including Wnt/β-catenin, Notch, Hedgehog, and PI3K/AKT [16]. Unlike other synthetic drugs, natural products tend to be less toxic and can be used long term with negligible side effects. They have a potential to be used as combination drugs with the current therapeutic methods because they can modulate the tumor microenvironment, which helps in interfering with the self-renewal machinery of PCSCs [17].

However, many of these potential natural-derived compounds have suffered limitations due to very low solubility, low bioavailability, and rapid metabolism accompanied by systemic clearance when attempting clinical reality [18]. These pharmacokinetic shortcomings limit their therapeutic effectiveness and bench to bedside translation. Nanotechnology has offered a good option to mitigate these hurdles by means of targeting bioactive constituent delivery to cancer cells and specifically to shred cancer stem cells [19]. Nanoparticle-based drug delivery systems, including liposome, polymeric nanoparticles, dendrimers, micelles, and solid lipid nanoparticles, have been developed to improve the aqueous solubility, loading capacity, and targeted delivery of natural products [20]. The recognition of surface markers on PCSCs is possible by ligands or antibodies in functionalizing these nanosystems and thus guarantee specificity and reduce the off-target effect [21]. In addition, nanoparticles are able to be tuned to react to the appropriate stimuli within the tumor environment, *e.g.*, pH or tissue enzymatic activity, to provide a controlled and enhanced delivery and gathering of therapeutic loads at the tumor location [22].

The combination of natural compounds and nanocarrier systems is a synergistic integration of strategy to combat cancer cells and target PCSCs as it manages both mechanistic and pharmacological weaknesses of conventional treatment regimens [23]. This innovative strategy allows enhancing bioavailability and suitability index of natural agents and helps them break the process of tumor initiation driven by PCSC, tumor progression, and resistance. As our body of knowledge of PCSC biology and tumor microenvironment broadly expounds, the fact that phytochemicals in conjunction with highly developed nanotechnologies may transform the landscape of the therapeutic market in prostate cancer cannot be ignored. This review, thus, seeks to discuss the existing knowledge of PCSCs in prostate cancer, the potentials of using natural compounds against these cells, as well as how nanotechnology can be used as the tool to deliver these agents and make them more effective, ultimately providing a bright prospect on how drug resistant prostate cancer can be overcome and its long-term outcomes improved.

2. Prostate cancer stem cells: biology and therapeutic resistance

2.1 Definition and characteristics of prostate cancer stem cells

Prostate cancer stem cells (PCSCs) are a small, specific population of cells in prostate tumors which have stem-like qualities (self-renewal, differentiation, and even the ability to cause cancer) [12]. This type of cells are thought to be on the top of the chain in the tumor cells, and it is core to the creation, preservation, and growth of prostate cancer [3]. In contrast to bulk tumor, the PCSCs have the capacity to regenerate new tumors upon transplantation into immunodeficient mice, and are thus central to the development of cancer [3].

The PCSCs have much in common with normal stem cells: they can develop asymmetrically, *i.e.*, give way both to similar unilateral stems (self-renew) and to differentiated progenitors that add to tumor heterogeneity [24]. This dynamic ability permits PCSCs, in this way, to keep a supply of tumor-initiating cells, even as non-stem cancer cells proceed with the proliferation. These features add to the plasticity and flexibility of tumors, and PCSCs are especially risky in the context of clinical practice [24]. Notably, PCSCs are defined by their non-sensitivity to standard treatment approaches that include chemotherapy, radiotherapy, and androgen deprivation therapy (ADT) [25, 26]. Although such therapies are successful in shrinking tumor mass they do not always eliminate PCSCs which are capable of survival and repopulation, resulting into tumor recurrence and metastases. These resistances are because PCSCs are characterized by some inherent factors, such as quiescence (low proliferation status), the presence of efficient repair mechanisms of a DNA strand break (DNA damage), high expression rate of drug efflux pumps (like the ATP-binding cassette transporters (ABC)), and considerable neutralization of reactive oxygen species (ROS) [27].

Another aspect that makes stem cells resilient is the PCSC niche, which is the special microenvironment in which they are sustained [28]. The factors that maintain the PCSC phenotype include hypoxia, stromal support, inflammatory cytokines, and the components of extracellular matrix. Besides that, PCSCs are capable of responding to environmental stressors, and can live even in the presence of nutrient deprivation or therapeutic insult [29].

The oncogenic transformation of normal prostate stem/progenitor cells may be a foundation source of PCSCs, or PCSCs may be developed by the acquisition

of stem-like properties by more differentiated cancer cells in the same manner, such as an epithelial to mesenchymal transition (EMT) [30]. In whatever way they appear, PCSCs presence in prostate tumors is characterized by poor prognosis, aggressive nature of disease development, as well as decreased effectiveness of treatment. To target PCSCs, a full picture of their biological characteristics and regulatory networks is needed. The latest findings aim toward perturbation of important signaling pathways, particular surface markers, and methods of treatment, which can destroy the PCSCs without destroying the normal stem cells. The understanding of the peculiarities of PCSCs presents a rewarding way out in the treatment and prevention of prostate cancer relapse.

2.2 Prostate cancer stem cells surface markers

The isolated PCSCs identification and isolation strongly depend on the application of surface and functional markers. Such markers can be used in differentiating PCSCs with bulk tumor cells as well as normal prostate cells and have been useful in elucidating their biology, in addition to being used in the development of precision medication. The cluster of differentiation 44, 133 (CD44, CD133) and aldehyde dehydrogenase (ALDH) are some of the most widely-researched PCSC markers, but others, including integrin 21, Epithelial Cell Adhesion Molecule (EpCAM) and ATP-Binding Cassette Sub-Family G Member 2 (ABCG2), have also been suggested [31].

CD44 is a plasma membrane glycoprotein primitively in cell-cell cooperation, cell adhesion, and movement [32]. CD44-positive cells are more tumorigenic and have clonogenic capacity besides being chemoresistant and ADT resistant in prostate cancer [33]. CD44 is linked to epithelial-to-mesenchymal transition (EMT) which augments cell mobilities and invasions, thus facilitating metastasis [33]. CD44+ and PCSCs are more flexible to drug stress and more expressive of stemness related genes [33]. CD133 (Prominin-1) has also been found to be another important marker that has been extensively used to define PCSCs. CD133+ prostate tumor or prostate cell line-derived cells have much better *in vitro* formation of prostaspheres and form tumors much earlier in xenografts than parental or CD133-negative cell lines [34]. CD44 is frequently co-expressed with these cells and the CD44+/CD133+ phenotype has been demonstrated to purify population of highly tumorigenic PCSCs. CD133 is associated with resistance to therapy, especially in CRPC and can be viewed as a possible prognostic marker [35].

Aldehyde dehydrogenase (ALDH), and specifically Aldehyde Dehydrogenase 1 Family Member A1 (ALDH1A1) isoform, is an intracellular aldehyde oxidase that takes part in the cellular detoxification and retinoic acid biosynthesis [3]. The most characteristic feature of stem-like cancer cells, such as PCSCs, is the high activity of ALDH that leads to greater resistance to radiation and chemotherapeutic drugs, as a result of an increased ability to detoxify and regulate reduction and oxidation processes [3]. Another indicator is integrin alpha 2 beta 1 which is a receptor of laminin and is involved in cell attachment and invasion. Higher expression of integrin alpha 2 beta 1, especially when combined with CD44, imparts improved stem cell characteristics and displays tumor-initiating potential by cells [36]. Enrichment of epithelial-like PCSCs can also be done by epithelial cell adhesion molecule (EpCAM), which has been shown to be associated with enhanced proliferation and metastasis [37]. Nevertheless, all of them are limited to the therapeutic targeting of PCSCs, yet they are not specifically PCSCs-related. The specificity and the effectiveness of PCSC isolation can be enhanced by combining several markers and functional assays (side population analysis, dye exclusion, or sphere formation) [3]. These markers are significant research tools portraying a hope of dynamic benefits in diagnosis and treatment of prostate cancer.

2.3 Tumor initiation, metastasis and therapy resistance role

The PCSCs are considered to be central to the whole chain of the development of prostate cancer: initiation of the tumor, its growth and development, metastasis, and re-development during or after the treatment [38]. They form a major source of heterogeneity and other causes of prostate cancer therapy failure and clinical recurrence, and are, therefore, an important intervention point. On tumor initiation, PCSCs have the special capability to form self-renewal and differentiation, which gives them the ability to create all the cellular diversity of prostate tumors [3]. This is particularly manifested in investigations during which even small amounts of 100–1000 PCSCs when xenografted in the immunocompromised mice may germinate into a complex multifaceted comprehensively developed tumor [39]. The way they can recolonize tumors after primary treatment points to their central importance in the creation and sustenance of prostate cancer.

PCSCs also play a big role in metastasis, they can cause secondary tumors in the metastatic sites because they have high motility, are more resistant to death during circulation, and can colonize other organ areas [40]. The epithelial-to-mesenchymal transition (EMT) process plays a pivotal part in this respect, imparting on the PCSCs the mesenchymal qualities of greater invasive capabilities and resistivity to anoikis [41]. In a secondary organ, PCSCs have the potential to go through mesenchymal-epithelial transition (MET) to reenter proliferative epithelial growth, resulting in the formation of metastatic tumor cells [42].

The problem, that is also extremely dangerous, when it comes to PCSCs is their resistance to therapy. In contrast to heterogeneous cancer cells that tend to be susceptible to both chemotherapy or ADT, PCSCs would survive as a result of a number of mechanisms. Such are their quiescent character, enabling them to avoid drugs that kill divide cells; increased Adenosine Triphosphate (ATP)-binding cassette (ABC) pumps that expel cytotoxic substances; more rapid DNA repair; and an increase in the levels of antioxidants, and can neutralize the drugs produced in response thereto, sequestering potentially dangerous reactive oxygen species [3]. Moreover, PCSCs are able to modify the tumor microenvironment to establish the niches leading to their survival and stemness, and it usually entails interactions with stromal cells, immune cells, and extracellular matrix elements [43]. The PCSCs resistance to

treatment is one of the principal causes of tumor recurrence and CRPC [44, 45]. Apparently, subsided PCSCs may persist in a dormant state and will finally reactivate, relapsing into an aggressive condition and producing a treatment-resistant condition [46]. Therefore, effective therapy of prostate cancer would require an approach that could not only decrease tumor load but one that also targets PCSC population.

2.4 Signaling pathways in PCSCs (Wnt/β-catenin, notch, hedgehog)

The multiple evolutionarily conserved signaling pathways which control the maintenance, self-renewal, and therapeutic resistance of PCSCs are the Wnt/transduction (β-catenin), Notch, as well as Hedgehog (Fig. 1) [47]. These pathways play key roles in embryonic formation and homeostasis of adult tissues and their misregulation in cancer, and results in uncontrolled growth and cancer stem cell (CSC) states of tissues [47].

Wnt/β-catenin regulation is the key pathway to the control of PCSC. In normal conditions, β-catenin is phosphorylated and degraded. However, in prostate cancer, aberrant Wnt signaling leads to β-catenin stabilization and nuclear translocation, where it binds to T-cell Factor (TCF)/Lymphoid Enhancer-Binding Factor (LEF) transcription factors to activate genes involved in proliferation and stemness, such as *c-Myc*, *Axin2*, and *Cyclin D1* [48, 49]. Activation of the Wnt pathway enhances the development of prostaspheres, induction of EMT, and develops therapeutic resistance [49]. Inhibiting this route by the use of Wnt inhibitors or β-catenin antagonists is currently being studied to annihilate PCSCs.

The second pathway involved in cell fate determination and the undifferentiated state is the Notch signaling. In prostate cancer, expression of both Notch ligands, *e.g.*, Jagged1, Delta-like ligand 1 and Notch receptor (Notch1–4) have been negatively correlated with patient survival and influence PCSCs proliferation [50]. After this ligand binding, the Notch receptor is cleaved proteolytically to release the Notch intracellular domain (NICD), which migrates to the nucleus where it induces target gene activation, such as of Hes1 and Hey1. Notch signaling can be inhibited by the use of γ-secretase inhibitors (GSIs) and decrease the PCSC survival and tumorigenicity [51].

The ligand-activated Hedgehog (Hh) pathway is when the Patched (PTCH) receptor is bound by ligands that include Sonic Hedgehog (Shh) then the suppression of Smoothened (SMO) is released and this causes the downstream Glioma-associated oncogene homologs (GLI-) mediated transcription [52]. Hedgehogs are over-expressed in CRPC and are linked with amplified construction of stemness standard genes. Blocking of this pathway with SMO antagonist, such as vismodegib or sonidegib, has demonstrated potential to decrease the frequency of PCSC and increase reversal of therapy resistance [53]. Also, Wnt, Notch, Hedgehog interacts with Phosphoinositide 3-Kinase (PI3K)/Protein Kinase B (AKT), Signal Transducer and Activator of Transcription 3 (STAT3), and Transforming Growth Factor Beta (TGF-β) to enhance the PCSC functions. Activation of PI3K/AKT cascade through depletion of Phosphatase and Tensin

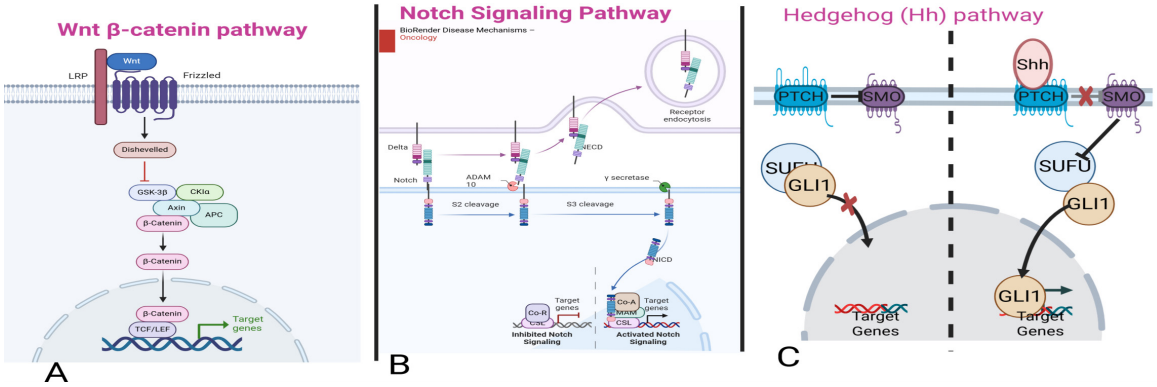

FIGURE 1. Key signaling pathways regulating prostate cancer stem cells (PCSCs) (created in https://BioRender.com). This figure illustrates the major signaling pathways: Wnt/β-catenin, Notch, and Hedgehog that regulate the maintenance, self-renewal, proliferation, and therapy resistance of prostate cancer stem cells (PCSCs). (A) The Wnt/β-catenin pathway stabilizes β-catenin, allowing its nuclear translocation and transcriptional activation of genes such as *c-Myc*, *Cyclin D1*, and *Axin2*, thereby promoting PCSC survival and epithelial-to-mesenchymal transition (EMT). (B) In the Notch pathway, ligand binding triggers proteolytic cleavage of the receptor, releasing the Notch intracellular domain (NICD), which translocates to the nucleus and activates downstream genes like *Hes1* and *Hey1*, maintaining the undifferentiated state of PCSCs. (C) Activation of the Hedgehog pathway involves binding of Sonic Hedgehog (Shh) to the Patched (PTCH) receptor, lifting inhibition of Smoothened (SMO) and enabling GLI-mediated transcription of stemness-associated genes. These core pathways are interconnected with additional signaling axes, such as PI3K/AKT, STAT3, and TGF-β, which further enhance PCSC survival and treatment resistance. TCF/LEF, T-cell factor/lymphoid enhancer factor; NICD, Notch intracellular domain; Shh, Sonic Hedgehog; PTCH, Patched receptor; SMO, Smoothened receptor; GLI, glioma-associated oncogene homolog; SUFU, Suppressor of Fused; ADAM, A Disintegrin and Metalloproteinase; NECD, Notch Extracellular Domain; Co-A, Co-Activator; Co-R, Co-Repressor; MAM, Mastermind-like Protein; CSL, CBF1/Su(H)/Lag-1; CKIα, Casein Kinase I Alpha; GSK, Glycogen Synthase Kinase (commonly GSK-3β in Wnt signaling); LRP, Low-Density Lipoprotein Receptor-Related Protein (commonly LRP5/6).

Homolog (PTEN) in prostate cancer vehicles promotes cell survival and induction of apoptotic resistance [54]. Activating of STAT3, by cytokines such as (Interleukin 6) IL-6, assists tumor growth and stemness. EMT and stemness in the advanced prostate cancer can be promoted by the TGF-β that is a tumor inhibitor at an early stage [55].

While critical pathways such as Wnt, Notch, Hedgehog, PI3K/AKT, STAT3, and TGF-β have been individually implicated in prostate cancer progression and stemness, their biological relevance lies not only in their independent functions but also in their extensive crosstalk and convergence on shared downstream targets [56]. For instance, Wnt and Notch signaling synergize to maintain prostate cancer stem cell self-renewal, while aberrant activation of Hedgehog can potentiate Wnt-driven transcriptional programs, amplifying tumorigenic potential. Similarly, the PI3K/AKT pathway interacts with STAT3 signaling to enhance survival and evade apoptosis, thereby reinforcing a microenvironment that favors therapy resistance [56]. TGF-β, though context-dependent, often cooperates with PI3K/AKT and STAT3 to promote EMT, thereby facilitating invasion, metastasis, and resistance to ADT and chemotherapy. The convergence of these pathways creates a highly redundant signaling network, such that inhibition of one axis may be compensated by activation of another, explaining the limited efficacy of monotherapies targeting single pathways [57]. Thus, a deeper understanding of the interconnectivity among Wnt, Notch, Hedgehog, PI3K/AKT, STAT3, and TGF-β underscores the need for combinatorial therapeutic strategies that disrupt these cooperative networks and overcome resistance mechanisms in prostate cancer management.

Besides the well-understood Wnt/β-catenin, Notch, and Hedgehog signaling pathways, there is currently a growing number of molecular pathways that are indispensible to the survival, self-renewal, plasticity, and resistance to treatment of PCSCs. These are the PI3K/AKT/mTOR, Janus Kinase (JAK)/STAT, Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), TGF-5, and Hippo pathway/Yes-Associated Protein (YAP) signaling axis, and other epigenetic regulators which form a complex regulatory network to maintain the biology of PCSC [58]. In prostate cancer, the PI3K/AKT/mTOR pathway is one of the most often activated pathways, particularly in prostate cancer with PTEN loss, a tumor suppressor regularly mutated in high-stage prostate cancer [59]. Stimulation of this pathway encourages cell survival, proliferation, metabolic adaptation, and resistance to apoptosis. PI3K/AKT signaling contributes to a maintenance of undifferentiated phenotype, provides resistance to ADT and/or chemotherapy. mTOR is a downstream effector that is important in controlling the protein synthesis and cell growth [60]. Dual targeting of PI3K and mTOR has demonstrated the ability to cooperate in lowering viability of PCSC, and rendering cancer treatment-susceptible [61].

Central to the immune evasive, stem cell like, and resistance functions of PCSCs is the JAK/STAT3 pathway that frequently becomes activated by inflammatory cytokines such as IL-6 [62, 63]. The stimulation of gene expression of self-renewal hNANOG (Homeobox protein NANOG), SOX2 (SRY-box 2), Oct4 (Octamer-binding transcription factor 4), proliferation, and anti-apoptotic signaling results in constitutive STAT3 activation [64, 65]. High concentrations of STAT3 activities correlate with aggressive prostate cancer and unfavourable treatment outcome. JAK kinase inhibitors, or direct STAT3 inhibition, can both block the formation of prostaspheres and tumor-initiating activity [66]. An additional inflammatory pathway relevant to PCSCs survival and immune evasion is the NF-κB signalling. NF-κB encourages the expression of anti-apoptotic genes (B-cell lymphoma-2 (Bcl-2), Survivin) and inflammation mediators, which favors the tumor promoting microenvironment [67]. Its crosslinking with the pathways of STAT3 and PI3K also enhance PCSC resistance. NF-κB blockers are being tried out with a view that it can interfere with this support system and decrease stemness [68].

TGF-β, though serving as a tumor suppressor at an early stage of prostate cancer, ironically activates metastasis, EMT and stem-like characteristics at an advanced stage. It causes transcriptional shifts which contribute to plasticity and resistance to therapy [69]. TGF-β boosts colonization and mesenchymal transition within PCSCs at the metastatic sites. One can attack TGF-β or downstream regulators such as Mothers Against Decapentaplegic Homolog 2/3 (SMAD2/3) and thereby decrease PCSC-caused metastasis [70].

Hippo/YAP signaling plays a critical role in regulating organ size, stem cell proliferation, and tissue homeostasis. When organ sizes are measured, Hippo/YAP signaling is commonly recognized as a key regulator of organ growth [71]. The transcriptional coactivator Yes-associated protein (YAP), when dysregulated, translocates to the nucleus where it drives stem-related gene expression, survival genes, and drug resistance genes [72]. The prostate cancer overexpression of YAP is associated with a malignant tumor and treatment resistance. Pharmacological YAP/TAZ inhibitors or the transcriptional partners of the YAP/TAZ, *e.g.*, TEADs (TEA Domain transcription factors) are being developed as PCSC targets [73]. Beside the traditional signaling cascades, PCSC gene expression is also controlled by epigenetic changes through DNA methylation, histone modifications, and chromatin restructuring. Enzymes, such as EZH2 (Polycomb Repressive Complex 2 component), DNMTs (DNA methyltransferases) and HDACs (histone deacetylates), are commonly upregulated in prostate cancer and contribute to the cancerous shutdown of tumour suppressor-genes and the maintenance of stemness programmes [74]. You can reprogram PCSCs through differentiation into epigenetic inhibitors (*e.g.*, EZH2 or HDAC inhibitors) and make them more susceptible to treatment. Lastly, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have become central regulators of the post-transcription network of signaling in PCSC [75]. An example is that miR-34a, miR-200c are tumor suppressors that inhibit genes related to stemness, whereas HOX Transcript Antisense Intergenic RNA (HOTAIR), lncRNA, and Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) encourage EMT and metastasizing [76].

Hence, the biology of PCSCs is dictated by complex interactions between signaling and epigenetic networks. Sabotaging only one cell signaling pathway may not be enough to destroy PCSCs since there is compensatory pathways. Hence, multiplexed signaling axis combinatorial targeting, in addition to standard treatment, holds potential in the elimination of PCSCs

and resistance to treatment in prostate cancer.

3. Natural products with anti-cancer stem cell activity in prostate cancer

Natural products have become prolific compounds in attacking PCSCs, special cells believed to be responsible for therapeutic resistance, metastasis, and recurrence of prostate cancer [12, 27, 77]. All of these compounds, both dietary and medicinal, or phytochemical in nature have multi-targeted effects, such as interference of signaling pathways, apoptosis, EMT inhibition, and self-renewal capacity suppression. Table 1 (Ref. [78–97]) showcases in detail a series of the selected natural compounds, their source and origin, mechanism of actions toward PCSCs in particular, preclinical evidence, *in vitro* models, significant findings, and shortcomings.

4. Nanotechnology-enabled delivery of natural products in prostate cancer therapy

Nanotechnology is revolutionary in cancer therapeutics and has introduced new methods for effective delivery of bioactive agents [23, 98]. Nanotechnology offers a potential platform to improve the efficacy of natural products in prostate cancer in which therapeutic resistance and tumor recurrence have always been a significant issue. The plants, marine or microbial origin of these natural compounds are potent anti-cancer agents but tend to be lowly bioavailable, unstable and non-specific in terms of their targets [20, 99]. These limitations can be overcome by using nanocarriers in their delivery system; this enhances solubility, prevents the exposure of compounds to degradants, their pharmacokinetics are improved, and there is a possibility to selectively deliver them to tumor tissues [77, 100].

Nanocarriers are nanometric-size construct nanomaterials that are design to confine, protect and move therapeutic agents [101]. Nanocarriers of various types in drug delivery have been developed, and each type of nanocarrier has dedicated structural and functional characteristics that suit a determined therapeutic purpose. Liposomes are containers made up of the phospholipid bilayers in spherical shapes which have the capability to transport hydrophilic chemicals and amphiphilic drugs [102]. They are biocompatible and have a structural similarity to biological membranes; hence they can be used in precision cancer treatment. Polymeric nanoparticles usually incorporate biodegradable polymers including, but not restricted to, those of Poly(lactic-co-glycolic) acid (PLGA) that have controlled release and increased stability. The same nanoparticles have the potential to be surface-functionalized to be able to target known tumor markers, enhancing targeted delivery to prostate cancer cells [103].

Solid lipid nanoparticle (SLN) is a combination between the strength of lipid-based systems and nanoparticles made of polymers [104]. SLNs are solidified lipids influenced by stabilizers, which are surfactants and may enclose the lipophilic natural products, which have low drug loading ability and perfect regulation of drug release [104]. Dendrimers are well defined three-dimensional tree-like macro-molecules with a clear architecture and surface functionalities [105]. Their multi-terminal groups can be used to conjugate natural products and targeting ligands which makes the Antibody-Drug Conjugates (ADCs) favorable in multivalent interactions with tumor cells. In aqueous solutions, the self-assembly (micelles) of block copolymers of amphiphilic nature can effectively solubilize the poorly water-soluble natural products. They increase the circulation time of the system and the concentration of therapeutic compounds in tumor tissues through the phenomenon of enhanced permeability and retention (EPR) [106].

The newest type of nanocarriers are exosomes and biomimetic carriers that take advantage of the communication system of the body to deliver drugs [107]. Exosomes refer to naturally occurring extracellular vesicles secreted by a cell and have an intercellular communication role [108]. Such vesicles would be suited to containing therapeutic natural products and presenting a targeting capability due to a natural targeting capability that cell type provides. Immune evasion and better biocompatibility, especially important in systemic administration during cancer therapy, are also provided by biomimetic carriers, *e.g.*, nanoparticles coated with cell membranes [109]. The enhanced bioavailability of nanoformulated natural products is one of the first benefits of such natural products. Numerous natural products, *e.g.*, curcumin and resveratrol, are poorly water-soluble and their bioavailability is undermined by fast metabolism, thus restricting their utility as therapeutics. Nanoformulations make them soluble, stable and resistant to enzymatic degradation and make them stay longer in the blood stream [110]. Also, nanocarriers can be altered to have targeting ligands, *e.g.*, antibodies or peptides, that recognise prostate cancer-specific markers (*e.g.*, prostate-specific membrane antigen (PSMA) and integrins), which would allow them to accumulate in prostate cancer tissue and minimise systemic toxicity [111].

Many research findings point that nanoformulated natural products are effective in prostate cancer models. In one example, curcumin-encapsulated liposomes exhibit cellular internalization and pro-apoptotic effect on prostate cancer cells, exhibiting higher cellular take up than free curcumin [112]. As well, encapsulation of resveratrol in polymeric nanoparticle has shown better anti-proliferative and anti-metastatic effect *in vitro* and *in vivo* [113]. A Green tea Polyphenol, Epigallocatechin gallate (EGCG), has also been effectively loaded into SLNs and dendrimers, enhancing its therapeutic index against prostate cancer xenografts. These nanoformulations are not only able to increase the pharmacological activities of natural products, but also could overcome the drug resistance processes through targeting cancer stem cells and regulating the important signaling processes [114] (Table 2, Ref. [115–131]).

The natural products delivery systems based on the use of nanotechnology has greatly improved the use of natural products in treating prostate cancer. Also, because of a combination of mitigation of pharmacokinetic constraints and targeted delivery, nanocarriers boost the efficacy and safety of bioactive compounds. The further study of the optimization of those nanocarriers, as well as their clinical implementation, has

great potential in making the therapy of prostate cancer more successful. Table 3 (Ref. [80, 132–150]) summarizes the key details on the progress in Nanotechnology-Enabled Delivery of Natural Products in Prostate Cancer Therapy.

5. Synergistic nanomedicine approaches for targeting prostate cancer stem cells

Reoccurrence and resistance to the conventional therapies of prostate cancer has been an ongoing problem, therefore, much scientific effort has been concentrated on PCSCs, a unique subpopulation of tumor-initiating cells with self-renewing, pluripotent, and extraordinary tumor propagating ability [151]. The cells that make up PCSCs are highly resistant to conventional chemotherapeutic drugs because of their quiescence, amplified DNA repair processes, and drug efflux transporters expression [27, 151]. This causes them to survive during the initial therapy, hence causing relapse and metastasis of the disease. To resolve this hurdle, scientists have created synergistic nanomedicine strategies that concentrate on comodulation of natural products and conventional chemotherapeutics. Natural compounds, like curcumin, resveratrol, quercetin, and epigallocatechin gallate, target multiple signaling pathways implicated in stemness, proliferation and chemoresistance, such as Wnt/β-catenin, Notch, Hedgehog, and PI3K/AKT [18, 152]. In a nanocarrier system in which traditional cytotoxic drugs like docetaxel or paclitaxel are co-delivered with natural compounds, these natural compounds have a sensitization effect upon PCSCs to chemotherapy, diminish drug resistance, and lead to an increase in therapeutic response. This bilateral approach has shown more apoptosis and tumor shrinkage in preclinical models, the added advantage being that the use of a controlled drug release and selective biodistribution greatly reduces systemic toxicity [153].

In this respect, another significant breakthrough in the field is the development of multifunctional and stimuli-responsive nanocarriers, which provide a much greater precision of drug delivery to PCSCs [154]. These nanocarriers are designed to have intelligent properties which enable them to respond to a select stimulus that is available in the tumor microenvironment, such as low pH, high glutathione level or overexpressed enzyme. As an example, redox-responsive or pH-sensitive liposomes or polymeric nanoprobes can resist the environment of the systemic circulation, but they should disintegrate or swell at the tumor location and hence discharge their drug content specifically in the cancerous tissue [154]. This specific release is less of a waste of the drugs and does not cause impact at the wrong place, ensuring that a maximum effect of the therapeutic agents is created at the right location. On the other hand, multifunctionality in the nanocarrier systems involves, besides using imaging agents to monitor the real-time activity, introduction of stealth coatings to avoid immune clearance, and also loading dual/triple-drugs to carry out combinatorial therapies [155]. A good example is a pH- and redox-responsive nanoplatform, which has a delivery of both a chemotherapeutic drug and phytochemical, which increases its intracellular uptake and induces synergistic killing of PCSCs. In addition, there are highly developed platforms that have photothermal or photodynamic therapy and the delivery of drugs, thus providing multi-modal therapy approach. These new generation nanocarriers mark a major leap to the development of a strategy in eliminating PCSCs and drug resistance in prostate cancer [156].

The ability to deliver nanomedicine to PCSCs via molecular ligands is a key factor of effective nanomedicine-based approach. Various surface markers, including CD44, CD133, ALDH1, and EpCAM, are strongly expressed in PCSCs and therefore useful targets in ligand-based delivery system [157]. Conjugation of ligands (such as monoclonal antibodies, aptamers, peptides or small-molecules) to the surface of nanocarriers have enabled researchers to selectively target and bind to PCSCs to increase drug accumulation and retention in the tumor stem cell niche [158]. An example is aptamer-coated nanoparticles with specificity to CD133 which have shown a high binding affinity, successful cellular internalization and enhanced apoptosis induction on PCSC populations [157, 159]. Compared to this, CD44-linked liposomes proved to be able to inhibit PCSCs proliferation, movement, and self-renewal potential. Such ligand-directed approaches do not only enhance the therapeutic index of nanomedicine constructs, but also enable the downstream of pluripotent-related pathways and metastasis inhibition [160]. Notably, such methods preserve normal cells and have minimal systemic side effects, which complies with precise oncology tenets. Taken together with the co-delivery of natural products and the smart characteristics of stimuli-responsive carriers, targeted nanomedicine platforms integrate a potent and wide-ranging approach to the clinical problem of PCSC-mediated resistance. A combination of such synergistic measures collectively heralds a paradigm shift in the treatment of prostate cancer, and provides cause of optimism that we will see more lasting responses, less likely recurrence, and an increase in patient survival.

Table 4 (Ref. [157, 161–176]) puts the spotlight on some typical examples of synergetic nanotherapeutic approaches that act to target PCSCs successfully. These strategies are based on the combination of the natural bioactive compounds with the common chemotherapeutic agents; they are co-encapsulated with the advanced carriers. The table serves to demonstrate the heterogeneity of nanocarrier platforms, such as liposomes, polymeric nanoparticles, dendrimers, and mesoporous silica nanoparticles, with a multi-functional, or stimuli responsive character to improve therapeutic specificity and precise drug release. In addition, such nanocarriers are conjugated to targeting agents (antibodies, aptamers, peptides) and/or bind to PCSC-surfaced markers (*e.g.*, CD44, CD133, ALDH1, EpCAM) on cells. The combination of co-delivery, responsive release, and molecular targeting demonstrates considerable enhancement of drug uptake, apoptosis programming, self-renewal detainment, and tumor recreating in the preclinical trials. This table provides an overall overview of the current developments and provides breakthroughs into how nanotechnology-based combinatorial treatments of prostate cancer will pan out translator-wise.

TABLE 1. Selected natural products with anti-PCSC activity in prostate cancer.

Serial number	Compound	Class of Compound	Source/Origin	Mechanism of Action	Preclinical Evidence	Experimental Model	Limitations	References
1	Curcumin	Polyphenol	*Curcuma longa* (Turmeric)	Inhibits Wnt/β-catenin, NF-κB, and PI3K/AKT	↓ sphere formation	PC3, DU145 cells, xenograft mice	Low bioavailability	[78]
2	Resveratrol	Stilbene	Grapes, berries	Suppresses STAT3, Notch, and EMT pathways	↓ CD44+ cell populations	DU145, LNCaP cells	Rapid metabolism	[79]
3	EGCG	Catechin (Flavonoid)	Green tea (*Camellia sinensis*)	Targets Hedgehog and Notch; induces apoptosis	↓ self-renewal	TRAMP model, PC3 cells	Requires high doses	[80]
4	Sulforaphane	Isothiocyanate	Broccoli, cruciferous vegetables	Inhibits ALDH1, Wnt/β-catenin	↓ tumor initiation	PC3, DU145 CSCs	Poor stability *in vivo*	[81]
5	Genistein	Isoflavone	Soybeans	Blocks AKT/NF-κB, reduces stemness markers	↓ prostasphere size	TRAMP mice, LNCaP, PC3	Estrogenic side effects	[82]
6	Withaferin A	Steroidal Lactone	*Withania somnifera*	Induces ROS, inhibits vimentin and EMT	↓ invasion & spheres	PC3, DU145	Cytotoxicity at high doses	[83]
7	Berberine	Isoquinoline Alkaloid	*Berberis vulgaris*	Inhibits AKT/mTOR, suppresses EMT	↓ ALDH+ CSCs	LNCaP, PC3, xenografts	Poor systemic absorption	[84]
8	Quercetin	Flavonol (Flavonoid)	Onions, apples	Inhibits YAP/TAZ, modulates cell cycle	↓ CD133+ cells	DU145, TRAMP mice	Moderate oral bioavailability	[85]
9	Parthenolide	Sesquiterpene Lactone	*Tanacetum parthenium*	Blocks NF-κB, induces CSC apoptosis	↓ tumorigenic cells	DU145 CSC-like cells	Limited clinical data	[86]
10	Honokiol	Biphenolic Lignan	Magnolia bark	Inhibits STAT3, reduces CSC frequency	↓ colony formation	PC3, DU145, mice	Rapid clearance	[87]
11	Apigenin	Flavone (Flavonoid)	Parsley, celery	Downregulates β-catenin and Oct4	↓ sphere size	PC3 CSCs, TRAMP mice	Weak *in vivo* effect	[88]
12	Luteolin	Flavone (Flavonoid)	Green pepper, celery	Modulates miR-21/PTEN, inhibits CSC migration	↓ migration/invasion	PC3 CSCs	Synergism with chemo not tested	[89]
13	Fisetin	Flavonol (Flavonoid)	Strawberries, apples	Inhibits PI3K/AKT and induces apoptosis	↓ PCSC survival	DU145 cells	Limited *in vivo* data	[90]
14	Baicalein	Flavone (Flavonoid)	*Scutellaria baicalensis*	Suppresses stemness-related transcription	↓ CD44+/CD133+ cells	PC3 spheres	Dose-dependent toxicity	[91]
15	Thymoquinone	Monoterpene Quinone	Black seed (*Nigella sativa*)	Suppresses STAT3 and c-Myc	↓ ALDH+ cell pool	DU145 CSC-like cells	Solubility issues	[92]
16	Nimbolide	Triterpenoid Lactone	*Azadirachta indica*	Inhibits Notch and NF-κB; induces apoptosis	↓ clonogenicity	PC3 CSCs	Incomplete pharmacokinetics	[93]

TABLE 1. Continued.

Serial number	Compound	Class of Compound	Source/Origin	Mechanism of Action	Preclinical Evidence	Experimental Model	Limitations	References
17	Garcinol	Polyisoprenylated Benzophenone	*Garcinia indica*	Inhibits Wnt/β-catenin; histone acetylation	↓ sphere-forming cells	PC3, TRAMP model	Requires formulation enhancement	[94]
18	Diosgenin	Steroidal Saponin	Fenugreek, yam	Disrupts Hedgehog signaling, ↓ ALDH activity	↓ tumorspheres	PC3 CSC-like cells	Variable potency	[95]
19	Silibinin	Flavonolignan	Milk thistle	Suppresses EMT and CD44 expression	↓ metastasis	DU145, LNCaP, mice	Low aqueous solubility	[96]
20	Betulinic acid	Pentacyclic Triterpenoid	Birch bark	Induces mitochondrial apoptosis in CSCs	↓ tumor initiation	PC3, DU145	Poor oral bioavailability	[97]

↓: *Decreased/reduced.*

PCa, Prostate Cancer; PCSCs, Prostate Cancer Stem Cells; CSC, Cancer Stem Cells; TRAMP, Transgenic Adenocarcinoma of Mouse Prostate (mouse model); ALDH, Aldehyde Dehydrogenase (stemness marker enzyme); STAT3, Signal Transducer and Activator of Transcription 3; EMT, Epithelial-to-Mesenchymal Transition; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; PI3K, Phosphoinositide 3-Kinase; AKT, Protein Kinase B; mTOR, Mechanistic Target of Rapamycin; ROS, Reactive Oxygen Species; YAP/TAZ, Yes-Associated Protein/Transcriptional co-Activator with PDZ-binding motif; Oct4, Octamer-binding Transcription Factor 4; miR, MicroRNA (e.g., miR-21); PTEN, Phosphatase and Tensin Homolog; c-Myc, Proto-oncogene Myc (transcription factor); CD, Cluster of Differentiation cell surface markers.

TABLE 2. Comparative overview of nanocarrier systems in prostate cancer: strengths, limitations, and translational evidence.

Serial number	Nanocarrier	Strengths	Weaknesses	Prostate-specific challenges/translational notes	Representative preclinical examples (natural + chemo)	Representative clinical/translational studies	References
1	Liposomes	Biocompatible; clinical precedent; load hydrophilic/amphiphilic drugs; PEGylation improves circulation	Limited payload for very hydrophobic drugs; heterogeneous tumour penetration; opsonization (unless stealth)	Good for systemic delivery but EPR in prostate tumours is variable; bone metastases require additional targeting	Curcumin-liposomes; honokiol-liposomes showing improved uptake and apoptosis in PCa models.	Liposomal platforms have entered clinical studies for various tumors; PSMA-targeted liposomal docetaxel (BIND-014) reached phase I/II in mCRPC (shows activity/tolerability).	[115, 116]
2	Polymeric nanoparticles (*e.g.*, PLGA)	Controlled/sustained release; robust surface functionalization; good for co-delivery	Potential biodegradation variability; scale-up and GMP complexity	Allow ligand targeting (PSMA, CD44), helpful to reach PCSC niches; careful design needed for bone tropism	Resveratrol-polymeric NPs + paclitaxel (preclinical co-delivery improved tumour control).	Several polymeric platforms evaluated in early translational studies and oncology trials; no widely adopted polymeric phytochemical product in PCa yet.	[117, 118]

TABLE 2. Continued.

Serial number	Nanocarrier	Strengths	Weaknesses	Prostate-specific challenges/translational notes	Representative preclinical examples (natural + chemo)	Representative clinical/translational studies	References
3	Solid lipid nanoparticles (SLN)	Good for lipophilic natural products; enhanced circulation; relatively simple formulation	Limited drug loading for some cargos; stability and burst release issues	Useful for EGCG/quercetin delivery in xenografts; heat/bone microenvironment may alter release	EGCG-SLNs, quercetin-SLNs showing improved efficacy in TRAMP/xenograft models.	Mostly preclinical; limited clinical translation to date in prostate cancer.	[119, 120]
4	Dendrimers	Precisely defined structure; multivalent surface for ligand conjugation; high payload density	Potential toxicity (cationic dendrimers); complex synthesis; regulatory hurdles	Multivalency supports PCSC marker targeting (CD44/CD133); toxicity needs addressing before clinical use	EGCG + cisplatin dendrimer (dual pH/ROS responsive) showed selective PCSC targeting *in vitro*.	Mostly preclinical; translational path requires toxicity mitigation.	[121]
5	Micelles	Excellent solubilization of hydrophobic phytochemicals; small size for tumour penetration	Less stable in circulation; premature drug release risk	Useful for small hydrophobic phytochemicals that need deep tumour penetration; circulation stability must be engineered	Berberine-docetaxel micelles showed enhanced antitumor effect in PCa models.	Preclinical examples dominate; engineered micelles in clinical oncology exist but limited PCa data.	[122, 123]
6	Exosomes/ biomimetic (cell-membrane coated)	Natural biodistribution; immune evasion; intrinsic targeting signals	Cargo loading control, batch variability, regulatory/manufacturing challenges	Potential to target metastatic niches and immune-suppressive microenvironment; promising for theranostics but translational complexity is high	Ursolic acid delivered via exosomes in orthotopic PCa models; engineered exosomes targeted NEPC in recent preclinical work.	Diagnostic exosome tests (ExoDx) are clinically used for PCa detection/triage; therapeutic exosomes are in early translational/first-in-human studies.	[124, 125]
7	Mesoporous silica nanoparticles (MSNs)	High surface area and loading; tunable pore release; easy surface modification	Potential long-term bioaccumulation; biocompatibility concerns	Good for co-delivery (curcumin + paclitaxel) with triggered glutathione release to target PCSCs in hypoxic niches	Curcumin + paclitaxel MSN (glutathione-responsive) depleted ALDH1+ cells in preclinical models.	Preclinical stage; translational concerns about silica clearance remain.	[126, 127]
8	Lipid-polymer hybrid NPs	Combine advantages of lipids + polymers (stability + biocompatibility); tunable release	More complex manufacture; regulatory pathway less established than simple liposomes	Suitable for co-delivery and surface targeting to PSMA/CD44; can be engineered for bone homing ligands	Resveratrol + temozolomide lipid-polymer NP (pH-sensitive) showed apoptosis and migration inhibition in PCSC models.	Mostly preclinical; strong potential for translation.	[128, 129]

TABLE 2. Continued.

Serial number	Nanocarrier	Strengths	Weaknesses	Prostate-specific challenges/translational notes	Representative preclinical examples (natural + chemo)	Representative clinical/translational studies	References
9	Magnetic/ theranostic NPs	Allow imaging + therapy (magnetothermal ablation); multimodal theranostics	Need external triggers; safety and off-target heating risk	Potential to ablate PCSC-rich lesions and track biodistribution; requires image guidance for bones/CNS	Quercetin + doxorubicin magnetic NP (magnetothermal + pH responsive) targeted CD44/CD133 in preclinical models.	A few early translational theranostic studies exist; not yet standard in PCa.	[130]
10	Nanogels/ hydrogel nanoparticles	High water content, excellent biocompatibility, allow enzyme/pH responsiveness	Potentially large size if not optimized; manufacturing complexity	Enzyme/pH dual responsive nanogels showed spheroid inhibition and improved drug sensitivity in PCSC models promising for intratumour/local delivery to bone lesions	EGCG + cisplatin nanogel inhibited spheroid formation and enhanced drug sensitivity (preclinical).	Preclinical; potential for loco-regional therapy strategies.	[124, 131]

SLN, Solid Lipid Nanoparticle; PLGA, Poly(lactic-co-glycolic) acid; PEG/PEGylation, Polyethylene Glycol/PEG-surface modification (improves stability & circulation time); EPR, Enhanced Permeability and Retention (passive tumor targeting effect); PSMA, Prostate-Specific Membrane Antigen; CD44/CD133, Cluster of Differentiation markers (prostate cancer stem cell markers); EpCAM, Epithelial Cell Adhesion Molecule; ALDH1, Aldehyde Dehydrogenase 1 (CSC marker enzyme); NEPC, Neuroendocrine Prostate Cancer; MSNs, Mesoporous Silica Nanoparticles; NPs, Nanoparticles; ROS, Reactive Oxygen Species; SPIONs, Superparamagnetic Iron Oxide Nanoparticles (used in imaging/theranostics); TEADs, TEA Domain transcription factors (partners of YAP/TAZ signaling); AR, Androgen Receptor; HIF-1α, Hypoxia-Inducible Factor 1-alpha (angiogenesis regulator); VEGF, Vascular Endothelial Growth Factor.

TABLE 3. Recent development in nanomedicine using natural products targeting PCSCs in prostate cancer models.

Serial number	Natural Product	Nanocarrier Type	Class of Compound	Target/Mechanism in PCa	Advantages of Nanoformulation	Preclinical Models	Preclinical Animal Models	Clinical Trials	References
1	Curcumin	Liposome	Polyphenol	Induces apoptosis; inhibits NF-κB	Improved stability and cellular uptake	PC-3, DU145 cells	Nude mouse xenografts	Multiple clinical trials in PCa prevention and therapy	[132]
2	Resveratrol	Polymeric Nanoparticles	Stilbene	Anti-proliferative; inhibits PI3K/AKT	Controlled release and enhanced bioavailability	LNCaP xenograft mice	Athymic mouse model	Clinical trials in PCa prevention and metabolic health	[132]

TABLE 3. Continued.

Serial number	Natural Product	Nanocarrier Type	Class of Compound	Target/Mechanism in PCa	Advantages of Nanoformulation	Preclinical Models	Preclinical Animal Models	Clinical Trials	References
3	EGCG	Solid Lipid Nanoparticles	Catechin	Downregulates androgen receptor signaling	Prolonged circulation and tumor targeting	TRAMP mouse model	TRAMP mice	Clinical trials in PCa chemoprevention	[80]
4	Quercetin	Dendrimers	Flavonoid	Suppresses PSA and AR signaling	Enhanced solubility and bio-distribution	PC-3 cells	Mouse xenografts	Limited human studies; not PCa-specific	[133]
5	Berberine	Micelles	Isoquinoline alkaloid	Inhibits telomerase and induces apoptosis	Improved water solubility and cellular uptake	DU145 cells	Rat xenografts	Clinical trials in metabolic disorders; not PCa	[134]
6	Honokiol	Liposome	Lignan	Targets cancer stem-like cells	Enhanced delivery across membranes	PC-3 xenografts	Nude mice	No clinical trial in PCa	[135]
7	Genistein	Polymeric Nanoparticles	Isoflavone	Inhibits cell cycle via AKT/mTOR	Controlled and sustained release	LNCaP and PC-3 cells	Mouse xenografts	Clinical trials in PCa prevention and therapy	[136]
8	Silibinin	Solid Lipid Nanoparticles	Flavonolignan	Inhibits migration, angiogenesis	Enhanced tumor accumulation via EPR effect	Orthotopic PCa model	TRAMP and xenografts	Clinical trials in PCa chemoprevention	[137]
9	Apigenin	Dendrimers	Flavone	Inhibits HIF-1α and VEGF pathways	Site-specific targeting with surface modification	DU145 and LNCaP cells	Nude mouse models	No PCa-specific trials	[138]
10	Thymoquino	Micelles	Quinone	Induces ROS-mediated apoptosis	Increased plasma half-life and tumor specificity	PC-3 cell line	Xenograft mice	Trials in metabolic and inflammatory disorders; not PCa	[139]
11	Luteolin	Liposome	Flavone	Suppresses Notch and AR pathways	Improves solubility and endocytosis	LNCaP cells	Nude mouse xenograft	No PCa-specific trials	[140]
12	Betulinic acid	Polymeric Nanoparticles	Triterpenoid	Triggers mitochondrial apoptosis	Enhanced permeability and retention	DU145 xenografts	Nude mice	Early cancer trials (non-PCa)	[141]
13	Diosgenin	Solid Lipid Nanoparticles	Steroidal saponin	Anti-proliferative, suppresses invasion	Stable and high drug-loading	TRAMP mouse model	TRAMP mice	No PCa-specific trials	[142]

TABLE 3. Continued.

Serial number	Natural Product	Nanocarrier Type	Class of Compound	Target/Mechanism in PCa	Advantages of Nanoformulation	Preclinical Models	Preclinical Animal Models	Clinical Trials	References
14	Ursolic acid	Exosomes	Pentacyclic triterpenoid	Targets PI3K/AKT and NF-κB	Natural targeting and immune evasion	PCa orthotopic model	Mouse orthotopic models	Phase I/II in solid tumors, not PCa	[143]
15	Baicalein	Biomimetic Carriers	Flavone	Inhibits EMT and CSCs	Improved bioavailability and biocompatibility	PC-3 and DU145	Mouse xenografts	No PCa-specific trials	[144]
16	Withaferin A	Polymeric Nanoparticles	Steroidal lactone	Suppresses vimentin and AKT/mTOR signaling	Enhanced cellular uptake and tumor suppression	PC-3 and LNCaP	Xenograft mice	No PCa trials; studied in other cancers	[145]
17	Ginsenoside Rg3	Liposome	Triterpenoid saponin	Induces apoptosis, anti-angiogenesis	Improved systemic delivery and tumor accumulation	LNCaP xenograft	Nude mice	Clinical trials in lung and gastric cancers; not PCa	[146]
18	Piperine	Solid Lipid Nanoparticles	Alkaloid	Enhances curcumin uptake and apoptosis	Increased synergism and bioavailability	PC-3 and DU145	Mouse xenograft	Human trials in drug metabolism enhancers; not PCa	[147, 148]
19	β-Caryophyllen	Micelles	Sesquiterpene	Inhibits cell growth via p53 activation	Increased solubility and drug retention	DU145 cells	Rat xenografts	No clinical trials	[149]
20	Gambogic acid	Dendrimers	Xanthonoid	Inhibits NF-κB and induces cell cycle arrest	Enhanced cytotoxicity and tumor targeting	Prostate cancer mouse model	BALB/c nude mice	Phase II trials in solid tumors (China); not PCa	[150]

NP, Nanoparticle; SLN, Solid Lipid Nanoparticle; EMT, Epithelial-to-Mesenchymal Transition; AR, Androgen Receptor; PSA, Prostate-Specific Antigen; PI3K, Phosphoinositide 3-Kinase; AKT, Protein Kinase B; mTOR, Mechanistic Target of Rapamycin; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; HIF-1α, Hypoxia-Inducible Factor 1-alpha; VEGF, Vascular Endothelial Growth Factor; CSC, Cancer Stem Cells; PCa, Prostate Cancer; TRAMP, Transgenic Adenocarcinoma of Mouse Prostate (mouse model); BALB/c nude mice, Immunodeficient laboratory mice (BALB/c strain) lacking T cells.

TABLE 4. Representative synergistic nanomedicine strategies for targeting prostate cancer stem cells (PCSCs).

Serial number	Nanocarrier Type	Co-Delivered Agents	Stimuli-Responsive Feature	Targeting Ligand	PCSC Marker Targeted	Therapeutic Outcome	References
1	Liposome	Curcumin + Docetaxel	pH-sensitive	Anti-CD44 antibody	CD44	Enhanced apoptosis and reduced PCSC self-renewal	[157]
2	Polymeric nanoparticle	Resveratrol + Paclitaxel	Redox-sensitive	CD133 aptamer	CD133	Improved drug uptake and stem cell inhibition	[161, 162]
3	Solid lipid nanoparticle	Quercetin + Doxorubicin	Enzyme-sensitive	EpCAM peptide	EpCAM	Synergistic cytotoxicity and tumor growth suppression	[163, 164]
4	Dendrimer	EGCG + Cisplatin	Dual pH/ROS-responsive	CD44 aptamer	CD44	Selective PCSC targeting and minimal systemic toxicity	[165, 166]
5	Mesoporous silica nanoparticle	Curcumin + Paclitaxel	Glutathione-sensitive	Anti-ALDH1 antibody	ALDH1	Depletion of PCSCs and sensitization to chemotherapy	[167, 168]
6	Micelle	Berberine + Docetaxel	Thermo-sensitive	CD133 antibody	CD133	Enhanced antitumor effect and reduced recurrence	[162, 169]
7	Lipid-polymer hybrid NP	Resveratrol + Temozolomide	pH-sensitive	Anti-CD44 antibody	CD44	Induced apoptosis and inhibited migration of PCSCs	[157, 170]
8	Magnetic nanoparticle	Quercetin + Doxorubicin	Magnetothermal + pH-responsive	CD44/CD133 dual aptamers	CD44 & CD133	Targeted ablation of PCSCs and bulk tumor reduction	[171, 172]
9	Nanogel	EGCG + Cisplatin	Enzyme/pH dual-responsive	CD133 aptamer	CD133	Inhibited spheroid formation and enhanced drug sensitivity	[173, 174]
10	Polymer-lipid nanoplatform	Silibinin + Paclitaxel	Acid-sensitive	Anti-EpCAM antibody	EpCAM	Reduced PCSC viability and metastatic potential	[175, 176]

NP, Nanoparticle; CD44, Cluster of Differentiation 44 (CSC surface glycoprotein); CD133, Cluster of Differentiation 133 (Prominin-1; CSC marker); ALDH1, Aldehyde Dehydrogenase 1 (enzyme; CSC marker); EpCAM, Epithelial Cell Adhesion Molecule; PCSCs, Prostate Cancer Stem Cells; CSC, Cancer Stem Cells.

6. Clinical translation and challenges

Although, natural product based nanomedicines have demonstrated good preclinical performance in targeting PCSCs, little clinical translation has been achieved [177]. Clinical trials have been conducted to establish the effectiveness of natural products, including resveratrol, curcumin, and granting, on prostate cancer, although their effectiveness has been impeded due to low bioavailability and high rate of metabolism, among a few [157, 178]. In order to resolve those shortcomings, nanocarrier-based delivery platforms have been proposed and tested in the early-stage clinical trials [179]. Chemotherapeutic agents (Liposomal versions of them) and compounds derived naturally in plants have enhanced the pharmacokinetics and limited the drug toxicities in patients, but trials were limited to examine nanomedicine and specifically attack PCSCs [180]. The investigations that are currently conducted regarding nanoparticle-based delivery into prostate cancer are at early phases, and there is no detailed information concerning their safety and efficiency in the long term. As a result, available studies on the combination of natural products with nanocarriers of clinical nature are still poorly developed [181, 182].

The most urgent questions that are faced by clinical translation, the safety, and biocompatibility of nanomedicine preparations deserve to be mentioned. Although natural products are believed to be non-hazardous, their interaction with synthetic carriers provides some concerns in the form of immunogenicity, off-target effects, and cumulative toxicities [183]. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) demand full toxicological profiling, biodistribution experiments, and pharmacodynamic testing, prior to approval. Moreover, there are no uniform procedures to assess the conduct of nanoparticles in biological systems, making the regulatory acceptance even more difficult [184]. The next level of complexity is associated with different cell compositions of PCSC populations, which could be heterogeneous in their responsiveness to any causal or therapeutic interventions, so stratification of the patient population and personalized treatment is essential [185]. The evaluation of the treatment response and the optimization of the dosing regimen are hard to do effectively without reliable PCSCs-related biomarkers in the clinical practice.

Scalability of manufacturing and knowledge gaps are two related challenges to clinical translation, in addition to safety and regulatory obstacles. Commercial-scale production of nanocarriers with homogeneous size, surface characteristics, and drug loading capacity is also technically challenging and expensive [186, 187]. Industrial-scale production is complicated by batch-to-batch variability, storage stability problems, and the demand of sterile production facilities [187]. Furthermore, biological complexity of PCSCs and tumor microenvironment is not fully elucidated, as it produces a gap in optimal target identification and delivery [188]. Improved knowledge of the interaction between nanocarriers and human physiology, more concrete regulatory systems, and additional clinical evidence will be necessary in closing the bench-to-bedside gap in the context of prostate cancer nanomedicine.

7. Future perspectives and conclusions

The development in nanotechnology has produced auspicious horizons towards the precision therapy of prostate cancer and especially the PCSCs, which are key in the therapeutic resistant, recurrence, and metastasis. Into the future, personalized nanomedicine holds out the prospect of a revolutionary approach to treatments that are more specific, with less toxicity that by-passes a target. Based on patient-specific biomarkers as well as genetic profiling and the tumor microenvironment signature, the next generation of nanomedicines may be tailored to the patient to showcase natural targeting of PCSCs with increased specificity in a more accurate manner. These individualized methods would allow specific ablation of PCSCs to spare unaffected tissues, which may lead to efficacious treatment and an overall minimization of side-effects. Further, personalization can also be improved by introducing the concept of omics-based tools and artificial intelligence (AI) in the design of nanoparticle systems, to provide adaptive changes in response to dynamic changes in tumors at real-time.

There is also another promising trend of diagnostic therapeutics integration in terms of creating theranostic nanoplatforms. These multi-purpose nanosystems are able to detect, monitor, and treat PCSCs in the tumor microenvironment simultaneously. Theranostic nanoparticles usually contain imaging elements, most commonly quantum dots, superparamagnetic iron oxide nanoparticles (SPIONs) or near infrared dyes, in conjunction with a therapeutic compound so that drug delivery and therapeutic success can be tracked in real-time. In addition, clinicians can use such platforms to determine PCSC burden and treatment response, thus helping to make the necessary changes in treatment in time. Combination of those systems with non-invasive imaging systems like Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), or optical imaging may be a revolution point in individual cancer management of prostate cancer patients. Moreover, on-target drug delivery that could be achieved using stimuli-responsive nanocarriers releasing therapeutic payloads upon exposure to tumor-specific stimuli, *e.g.*, pH, redox gradients, and enzyme activity, could additionally lower off-target toxicity.

Hence, the future of prostate cancer treatment is in the capacity to adequately eliminate PCSCs and block the recurrence and metastasis of the disease. With the current nanoplatforms, there is a chance that emerging nanomedicine approaches, especially those that utilize immunotherapy or gene-editing systems such as Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9 (CRISPR/Cas9), can break inherent and acquired PCSCs resistance. Considering that research on nanoparticle engineering, their scale-up manufacturing, and clinical translation is advancing, regulatory issues and safety information on the long-term should be studied to guarantee safety in use of nanoparticles on the patients. The oncologists, nanotechnologists, regulatory organizations, and industry stakeholders will also need to work across disciplines to move these innovations to bedside. The next-generation nanotherapeutics would have a critical role in enhancing survival and the quality of life of advanced prostate cancer

patients in case these problems are overcome.

8. Conclusions

The continuous struggle on the recurrence of prostate cancer, treatment resistance, and metastases highlights the importance of prostate cancer stem cells (PCSCs) in the progression of the cancer. The attack on PCSCs has come as a strategic way of neutralizing these barriers. Medicinal compounds found in plants are naturally produced, and have considerable promise in interfering with central pathways of the signaling related to PCSC persistence and survival. Nonetheless, they have not yet entered clinical use because of low solubility, poor bioavailability, and fast clearance of these compounds in the system. The nanotechnology field provides a new platform to get out of the challenge, and increases the delivery of these natural compounds to the tumor and stem cell niches, in addition to increasing their stability and specificity. These phytochemicals may then be accurately targeted to PCSCs via smart nanocarriers: liposomes, dendrimers, polymeric nanoparticles and biomimetic systems that reduce off-target effects and maximize therapeutic benefit. Combination approaches using synergistic nanomedicine strategies, that can lead to the co-delivery of natural products and traditional chemotherapeutics, have demonstrated synergy in preclinical models, sensitizing PCSCs and chemosensitizing drug-resistant cells.

Although encouraging, the successful use of the strategies in clinical practice is dependent on several issues surrounding the long-term safety, regulatory clearance, scale-up production, and patient stratification. It is also important that interdisciplinary cooperation, the development of personalized therapies, artificial intelligence, and theranostic nanoplatforms allow improving and accelerating the clinical practice of these therapies. Altogether, a combination of natural products and nanotechnology has the revolutionary potential to eliminate PCSCs, lower the recurrence of prostate cancer, and provide better survival rates in patients across the world.

AVAILABILITY OF DATA AND MATERIALS

All used data is fully presented in the manuscript.

AUTHOR CONTRIBUTIONS

DEU and EUA—conceived and designed the review. DEU, IB and SIE—conducted literature search. DEU, WAO and OPCU—performed figures generation. DEU and WAO—drafted the manuscript. All authors critically reviewed, edited, and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Adekiya TA, Owoseni O. Emerging frontiers in nanomedicine targeted therapy for prostate cancer. Cancer Treatment and Research Communications. 2023; 37: 100778.

[2] Andrew J, Ezra-Manicum AL, Witika BA. Developments in radionanotheranostic strategies for precision diagnosis and treatment of prostate cancer. EJNMMI Radiopharmacy and Chemistry. 2024; 9: 62.

[3] Semwal P, Painuli S, Abu-Izneid T, Rauf A, Sharma A, Daştan SD, *et al*. Diosgenin: an updated pharmacological review and therapeutic perspectives. Oxidative Medicine and Cellular Longevity. 2022; 2022: 1035441.

[4] Schafer EJ, Laversanne M, Sung H, Soerjomataram I, Briganti A, Dahut W, *et al*. Recent patterns and trends in global prostate cancer incidence and mortality: an update. European Urology. 2025; 87: 302–313.

[5] Acquah J, Bosson-Amedenu S, Eyiah-Bediako F, Buabeng A, Ouerfelli N. Modelling incidence and mortality cancer parameters with respect to GLOBOCAN 2020age standardized world estimates. Heliyon. 2024; 10: e36836.

[6] Giona S. The epidemiology of prostate cancer. 2021. Available at: https://doi.org/10.36255/exonpublications.prostatecancer.epidemiology.2021 (Accessed: 07 June 2025).

[7] Choi E, Buie J, Camacho J, Sharma P, de Riese WTW. Evolution of androgen deprivation therapy (ADT) and its new emerging modalities in prostate cancer: an update for practicing urologists, clinicians and medical providers. Research and Reports in Urology. 2022; 14: 87–108.

[8] He MX, Cuoco MS, Crowdis J, Bosma-Moody A, Zhang Z, Bi K, *et al*. Transcriptional mediators of treatment resistance in lethal prostate cancer. Nature Medicine. 2021; 27: 426–433.

[9] Liang H, Zhou B, Li P, Zhang X, Zhang S, Zhang Y, *et al*. Stemness regulation in prostate cancer: prostate cancer stem cells and targeted therapy. Annals of Medicine. 2025; 57: 2442067.

[10] Liu S, Zhang X, Wang W, Li X, Sun X, Zhao Y, *et al*. Metabolic reprogramming and therapeutic resistance in primary and metastatic breast cancer. Molecular Cancer. 2024; 23: 261.

[11] Lindell E, Zhong L, Zhang X. Quiescent cancer cells—a potential therapeutic target to overcome tumor resistance and relapse. International Journal of Molecular Sciences. 2023; 24: 3762.

[12] Zhu B, Qu S. The relationship between diabetes mellitus and cancers and its underlying mechanisms. Frontiers in Endocrinology. 2022; 13: 800995.

[13] Wang Z, Dai Z, Gao Y, Zhao Z, Li Z, Wang L, *et al*. Development of a machine learning-based predictive risk model combining fatty acid metabolism and ferroptosis for immunotherapy response and prognosis in prostate cancer. Discover Oncology. 2025; 16: 744.

[14] Jenča A, Mills DK, Ghasemi H, Saberian E, Jenča A, Karimi Forood AM, *et al*. Herbal therapies for cancer treatment: a review of phytotherapeutic efficacy. Biologics. 2024; 18: 229–255.

[15] Tuli HS, Garg VK, Bhushan S, Uttam V, Sharma U, Jain A, *et al*. Natural flavonoids exhibit potent anticancer activity by targeting microRNAs in cancer: a signature step hinting towards clinical perfection. Translational Oncology. 2023; 27: 101596.

[16] Alnasser SM, Alrobian AS, Alfayez MS, Almutairi OT, Almutairi SS, Alkeraidees TS. Pharmacological modulation of stem cells signaling pathway for therapeutic applications. Stem Cell Research & Therapy. 2025; 16: 327.

[17] Ali Abdalla YO, Subramaniam B, Nyamathulla S, Shamsuddin N, Arshad NM, Mun KS, *et al*. Natural products for cancer therapy: a review of their mechanism of actions and toxicity in the past decade. Journal of Tropical Medicine. 2022; 2022: 5794350.

[18] El-Saadony MT, Yang T, Korma SA, Sitohy M, Abd El-Mageed TA, Selim S, *et al.* Impacts of turmeric and its principal bioactive curcumin on human health: pharmaceutical, medicinal, and food applications: a comprehensive review. Frontiers in Nutrition. 2023; 9: 1040259.

[19] Bhange M, Telange D. Convergence of nanotechnology and artificial intelligence in the fight against liver cancer: a comprehensive review. Discover Oncology. 2025; 16: 77.

[20] Uti DE, Atangwho IJ, Alum EU, Ntaobeten E, Obeten UN, Bawa I, *et al*. Antioxidants in cancer therapy mitigating lipid peroxidation without compromising treatment through nanotechnology. Discover Nano. 2025; 20: 70.

[21] Martín-Contreras M, Navarro-Marchal SA, Peula-García JM, Jódar-Reyes AB. Progress and hurdles of therapeutic nanosystems against cancer. Pharmaceutics. 2022; 14: 388.

[22] Salehi S, Naghib SM, Garshasbi HR, Ghorbanzadeh S, Zhang W. Smart stimuli-responsive injectable gels and hydrogels for drug delivery and tissue engineering applications: a review. Frontiers in Bioengineering and Biotechnology. 2023; 11: 1104126.

[23] Maleki H, Aiyelabegan HT, Javadi P, Abdi F, Mirzavi F, Zarei Behjani Z, *et al*. Nanotechnology-mediated precision drug delivery strategies for breast cancer treatment. Biomedicine & Pharmacotherapy. 2025; 188: 118224.

[24] Rossi F, Noren H, Jove R, Beljanski V, Grinnemo KH. Differences and similarities between cancer and somatic stem cells: therapeutic implications. Stem Cell Research & Therapy. 2020; 11: 489.

[25] Ionescu F, Zhang J. How we treat metastatic castration-sensitive prostate cancer. Cancer Control. 2024; 31: 10732748241274190.

[26] Varaprasad GL, Gupta VK, Prasad K, Kim E, Tej MB, Mohanty P, *et al*. Recent advances and future perspectives in the therapeutics of prostate cancer. Experimental Hematology & Oncology. 2023; 12: 80.

[27] Obisi JN, Abimbola ANJ, Babaleye OA, Atidoglo PK, Usin SG, Nwanaforo EO, *et al*. Unveiling the future of cancer stem cell therapy: a narrative exploration of emerging innovations. Discover Oncology. 2025; 16: 373.

[28] Zhang P, Zhang C, Li J, Han J, Liu X, Yang H. The physical microenvironment of hematopoietic stem cells and its emerging roles in engineering applications. Stem Cell Research & Therapy. 2019; 10: 327.

[29] Lee SA, Cho GJ, Kim D, Kim DH. Biophysical interplay between extracellular matrix remodeling and hypoxia signaling in regulating cancer metastasis. Frontiers in Cell and Developmental Biology. 2024; 12: 1335636.

[30] Du G, Huang X, Su P, Yang Y, Chen S, Huang T, *et al*. The role of SOX transcription factors in prostate cancer: focusing on SOX2. Genes & Diseases. 2025; 12: 101692.

[31] Yehya A, Youssef J, Hachem S, Ismael J, Abou-Kheir W. Tissue-specific cancer stem/progenitor cells: therapeutic implications. World Journal of Stem Cells. 2023; 15: 323–341.

[32] Borsdorf S, Zeug A, Wu Y, Mitroshina E, Vedunova M, Gaitonde SA, *et al*. The cell adhesion molecule CD44 acts as a modulator of 5-HT7 receptor functions. Cell Communication and Signaling. 2024; 22: 563.

[33] Valentini V, Santi R, Silvestri V, Saieva C, Roviello G, Amorosi A, *et al*. CD44 methylation levels in androgen-deprived prostate cancer: a putative epigenetic modulator of tumor progression. International Journal of Molecular Sciences. 2025; 26: 2516.

[34] Pleskač P, Fargeas CA, Veselska R, Corbeil D, Skoda J. Emerging roles of prominin-1 (CD133) in the dynamics of plasma membrane architecture and cell signaling pathways in health and disease. Cellular & Molecular Biology Letters. 2024; 29: 41.

[35] Xu H, Niu M, Yuan X, Wu K, Liu A. CD44 as a tumor biomarker and therapeutic target. Experimental Hematology & Oncology. 2020; 9: 36.

[36] Li S, Sampson C, Liu C, Piao HL, Liu HX. Integrin signaling in cancer: bidirectional mechanisms and therapeutic opportunities. Cell Communication and Signaling. 2023; 21: 266.

[37] Gires O, Pan M, Schinke H, Canis M, Baeuerle PA. Expression and function of epithelial cell adhesion molecule EpCAM: where are we after 40 years? Cancer and Metastasis Reviews. 2020; 39: 969–987.

[38] Mei W, Lin X, Kapoor A, Gu Y, Zhao K, Tang D. The contributions of prostate cancer stem cells in prostate cancer initiation and metastasis. Cancers. 2019; 11: 434.

[39] Han S, Chen X, Li Z. Innate immune program in formation of tumor-initiating cells from cells-of-origin of breast, prostate, and ovarian cancers. Cancers. 2023; 15: 757.

[40] Liu M, Yang J, Xu B, Zhang X. Tumor metastasis: mechanistic insights and therapeutic interventions. MedComm. 2021; 2: 587–617.

[41] Leggett SE, Hruska AM, Guo M, Wong IY. The epithelial-mesenchymal transition and the cytoskeleton in bioengineered systems. Cell Communication and Signaling. 2021; 19: 32.

[42] Akhmetkaliyev A, Alibrahim N, Shafiee D, Tulchinsky E. EMT/MET plasticity in cancer and Go-or-Grow decisions in quiescence: the two sides of the same coin? Molecular Cancer. 2023; 22: 90.

[43] Zhong H, Zhou S, Yin S, Qiu Y, Liu B, Yu H. Tumor microenvironment as niche constructed by cancer stem cells: breaking the ecosystem to combat cancer. Journal of Advanced Research. 2025; 71: 279–296.

[44] Zhang S, Zhang T, Kinsella GK, Curtin JF. A review of the efficacy of prostate cancer therapies against castration-resistant prostate cancer. Drug Discovery Today. 2025; 30: 104384.

[45] Wahab A, Siddique H R. An update understanding of stemness and chemoresistance of prostate cancer. Expert Review of Anticancer Therapy. 2025; 25: 215–228.

[46] Cai M, Song XL, Li XA, Chen M, Guo J, Yang DH, *et al*. Current therapy and drug resistance in metastatic castration-resistant prostate cancer. Drug Resistance Updates. 2023; 68: 100962.

[47] Zhang Y, Wang X. Targeting the Wnt/β-catenin signaling pathway in cancer. Journal of Hematology & Oncology. 2020; 13: 165.

[48] Shah K, Kazi JU. Phosphorylation-dependent regulation of Wnt/beta-catenin signaling. Frontiers in Oncology. 2022; 12: 858782.

[49] Song P, Gao Z, Bao Y, Chen L, Huang Y, Liu Y, *et al*. Wnt/β-catenin signaling pathway in carcinogenesis and cancer therapy. Journal of Hematology & Oncology. 2024; 17: 46.

[50] Orzechowska M, Anusewicz D, Bednarek AK. Functional gene expression differentiation of the notch signaling pathway in female reproductive tract tissues—a comprehensive review with analysis. Frontiers in Cell and Developmental Biology. 2020; 8: 592616.

[51] Akil A, Gutiérrez-García AK, Guenter R, Rose JB, Beck AW, Chen H, *et al*. Notch signaling in vascular endothelial cells, angiogenesis, and tumor progression: an update and prospective. Frontiers in Cell and Developmental Biology. 2021; 9: 642352.

[52] Carballo GB, Honorato JR, de Lopes GPF, Spohr TCLSE. A highlight on sonic hedgehog pathway. Cell Communication and Signaling. 2018; 16: 11.

[53] Jing J, Wu Z, Wang J, Luo G, Lin H, Fan Y, *et al*. Hedgehog signaling in tissue homeostasis, cancers, and targeted therapies. Signal Transduction and Targeted Therapy. 2023; 8: 315.

[54] Goncharov AP, Dicusari Elissaiou C, Ben Aharon Farzalla E, Akhvlediani G, Vashakidze N, Kharaishvili G. Signalling pathways in a nutshell: from pathogenesis to therapeutical implications in prostate cancer. Annals of Medicine. 2025; 57: 2474175.

[55] Hashimoto S, Hashimoto A, Muromoto R, Kitai Y, Oritani K, Matsuda T. Central roles of STAT3-mediated signals in onset and development of cancers: tumorigenesis and immunosurveillance. Cells. 2022; 11: 2618.

[56] Manni W, Min W. Signaling pathways in the regulation of cancer stem cells and associated targeted therapy. MedComm. 2022; 3: e176.

[57] Xue C, Chu Q, Shi Q, Zeng Y, Lu J, Li L. Wnt signaling pathways in biology and disease: mechanisms and therapeutic advances. Signal Transduction and Targeted Therapy. 2025; 10: 106.

[58] Sher G, Masoodi T, Patil K, Akhtar S, Kuttikrishnan S, Ahmad A, *et al*. Dysregulated FOXM1 signaling in the regulation of cancer stem cells. Seminars in Cancer Biology. 2022; 86: 107–121.

[59] Shorning BY, Dass MS, Smalley MJ, Pearson HB. The PI3K-AKT-mTOR pathway and prostate cancer: at the crossroads of AR, MAPK, and WNT signaling. International Journal of Molecular Sciences. 2020; 21: 4507.

[60] Esfini Farahani M, Zhang Y, Akinyemi AO, Seilani F, Alam MR, Liu X. Unlocking the role of OCT4 in cancer lineage plasticity: a cross-cancer perspective with an emphasis on prostate cancer. Biomedicines. 2025; 13: 1642.

[61] Wu X, Xu Y, Liang Q, Yang X, Huang J, Wang J, *et al*. Recent advances in dual PI3K/mTOR inhibitors for tumour treatment. Frontiers in Pharmacology. 2022; 13: 875372.

[62] Huang B, Lang X, Li X. The role of IL-6/JAK2/STAT3 signaling pathway in cancers. Frontiers in Oncology. 2022; 12: 1023177.

[63] Veilleux C, Roy MÈ, Zgheib A, Desjarlais M, Annabi B. Evidence for a JAK2/STAT3 proinflammatory and vasculogenic mimicry interrelated molecular signature in adipocyte-derived mesenchymal stromal/stem cells. Cell Communication and Signaling. 2025; 23: 291.

[64] Zhang S, Xiong X, Sun Y. Functional characterization of SOX2 as an anticancer target. Signal Transduction and Targeted Therapy. 2020; 5: 135.

[65] DiNatale A, Castelli MS, Nash B, Meucci O, Fatatis A. Regulation of tumor and metastasis initiation by chemokine receptors. Journal of Cancer. 2022; 13: 3160–3176.

[66] Talukdar S, Das SK, Pradhan AK, Emdad L, Windle JJ, Sarkar D, *et al*. MDA-9/Syntenin (SDCBP) is a critical regulator of chemoresistance, survival and stemness in prostate cancer stem cells. Cancers. 2019; 12: 53.

[67] Cao Y, Yi Y, Han C, Shi B. NF-κB signaling pathway in tumor microenvironment. Frontiers in Immunology. 2024; 15: 1476030.

[68] Krajka-Kuźniak V, Belka M, Papierska K. Targeting STAT3 and NF-κB signaling pathways in cancer prevention and treatment: the role of chalcones. Cancers. 2024; 16: 1092.

[69] Chaves LP, Melo CM, Saggioro FP, Reis RBD, Squire JA. Epithelial-mesenchymal transition signaling and prostate cancer stem cells: emerging biomarkers and opportunities for precision therapeutics. Genes. 2021; 12: 1900.

[70] Sheikh KA, Amjad M, Irfan MT, Anjum S, Majeed T, Riaz MU, *et al*. Exploring TGF-β signaling in cancer progression: prospects and therapeutic strategies. OncoTargets and Therapy. 2025; 18: 233–262.

[71] Deng F, Wu Z, Zou F, Wang S, Wang X. The Hippo-YAP/TAZ signaling pathway in intestinal self-renewal and regeneration after injury. Frontiers in Cell and Developmental Biology. 2022; 10: 894737.

[72] Zhang Q, Han X, Chen J, Xie X, Xu J, Zhao Y, *et al*. Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) mediate cell density-dependent proinflammatory responses. Journal of Biological Chemistry. 2018; 293: 18071–18085.

[73] Li X, Zhuo S, Cho YS, Liu Y, Yang Y, Zhu J, *et al*. YAP antagonizes TEAD-mediated AR signaling and prostate cancer growth. The EMBO Journal. 2023; 42: e112184.

[74] Tresas T, Isaioglou I, Roussis A, Haralampidis K. A brief overview of the epigenetic regulatory mechanisms in plants. International Journal of Molecular Sciences. 2025; 26: 4700.

[75] Bae W, Ra EA, Lee MH. Epigenetic regulation of reprogramming and pluripotency: insights from histone modifications and their implications for cancer stem cell therapies. Frontiers in Cell and Developmental Biology. 2025; 13: 1559183.

[76] Singh A, Malvankar S, Ravi Kumar YS, Seervi M, Srivastava RK, Verma B. Role of various non-coding RNAs in EMT, cancer, and metastasis: recent trends and future perspective. Advances in Cancer Biology-Metastasis. 2022; 4: 100039.

[77] Alum EU, Nwuruku OA, Ugwu OPC, Uti DE, Alum BN, Edwin N. Harnessing nature: plant-derived nanocarriers for targeted drug delivery in cancer therapy. Phytomedicine Plus. 2025; 5: 100828.

[78] Wahnou H, El Kebbaj R, Liagre B, Sol V, Limami Y, Duval RE. Curcumin-based nanoparticles: advancements and challenges in tumor therapy. Pharmaceutics. 2025; 17: 114.

[79] Oršolić N, Jazvinšćak Jembrek M. Molecular and cellular mechanisms of propolis and its polyphenolic compounds against cancer. International Journal of Molecular Sciences. 2022; 23: 10479.

[80] Capasso L, De Masi L, Sirignano C, Maresca V, Basile A, Nebbioso A, *et al*. Epigallocatechin gallate (EGCG): pharmacological properties, biological activities and therapeutic potential. Molecules. 2025; 30: 654.

[81] Coutinho LL, Junior TCT, Rangel MC. Sulforaphane: an emergent anti-cancer stem cell agent. Frontiers in Oncology. 2023; 13: 1089115.

[82] Pejčić T, Zeković M, Bumbaširević U, Kalaba M, Vovk I, Bensa M, *et al*. The role of isoflavones in the prevention of breast cancer and prostate cancer. Antioxidants. 2023; 12: 368.

[83] Roy RV, Suman S, Das TP, Luevano JE, Damodaran C. Withaferin A, a steroidal lactone from Withania somnifera, induces mitotic catastrophe and growth arrest in prostate cancer cells. Journal of Natural Products. 2013; 76: 1909–1915.

[84] Murakami T, Bodor E, Bodor N. Approaching strategy to increase the oral bioavailability of berberine, a quaternary ammonium isoquinoline alkaloid: part 2. development of oral dosage formulations. Expert Opinion on Drug Metabolism & Toxicology. 2023; 19: 139–148.

[85] Azizi E, Fouladdel S, Komeili Movahhed T, Modaresi F, Barzegar E, Ghahremani MH, *et al*. Quercetin effects on cell cycle arrest and apoptosis and doxorubicin activity in T47D cancer stem cells. Asian Pacific Journal of Cancer Prevention. 2022; 23: 4145–4154.

[86] Hsu CY, Rajabi S, Hamzeloo-Moghadam M, Kumar A, Maresca M, Ghildiyal P. Sesquiterpene lactones as emerging biomolecules to cease cancer by targeting apoptosis. Frontiers in Pharmacology. 2024; 15: 1371002.

[87] Cao H, Feng Y, Sun P, Chen L, Wang D, Gao R. Zhoushi Qiling decoction inhibits proliferation of human prostate cancer cells through IL6/STAT3 pathway. Journal of Cancer. 2023; 14: 2246–2254.

[88] Sferrazza G, Corti M, Brusotti G, Pierimarchi P, Temporini C, Serafino A, *et al*. Nature-derived compounds modulating Wnt/β-catenin pathway: a preventive and therapeutic opportunity in neoplastic diseases. Acta Pharmaceutica Sinica B. 2020; 10: 1814–1834.

[89] Okpoghono J, Isoje EF, Igbuku UA, Ekayoda O, Omoike GO, Adonor TO, *et al*. Natural polyphenols: a protective approach to reduce colorectal cancer. Heliyon. 2024; 10: e32390.

[90] Zhou C, Huang Y, Nie S, Zhou S, Gao X, Chen G. Biological effects and mechanisms of fisetin in cancer: a promising anti-cancer agent. European Journal of Medical Research. 2023; 28: 297.

[91] Cai J, Hu Q, He Z, Chen X, Wang J, Yin X, *et al*. Scutellaria baicalensis Georgi and their natural flavonoid compounds in the treatment of ovarian cancer: a review. Molecules. 2023; 28: 5082.

[92] Pal RR, Rajpal V, Singh P, Saraf SA. Recent findings on thymoquinone and its applications as a nanocarrier for the treatment of cancer and rheumatoid arthritis. Pharmaceutics. 2021; 13: 775.

[93] Kashif M, Hwang Y, Kim WJ, Kim G. *In-vitro* morphological assessment of apoptosis induced by nimbolide; a limonoid from *Azadirachta indica* (*neem tree*). Iranian Journal of Pharmaceutical Research. 2019; 18: 846–859.

[94] Kopytko P, Piotrowska K, Janisiak J, Tarnowski M. Garcinol—a natural histone acetyltransferase inhibitor and new anti-cancer epigenetic drug. International Journal of Molecular Sciences. 2021; 22: 2828.

[95] Tak Y, Kaur M, Chitranashi A, Samota MK, Verma P, Bali M, *et al*. Fenugreek derived diosgenin as an emerging source for diabetic therapy. Frontiers in Nutrition. 2024; 11: 1280100.

[96] Ghosh R, Samanta P, Sarkar R, Biswas S, Saha P, Hajra S, *et al*. Targeting HIF-1α by natural and synthetic compounds: a promising approach for anti-cancer therapeutics development. Molecules. 2022; 27: 5192.

[97] Uti DE, Alum EU, Atangwho IJ, Ugwu OP, Egbung GE, Aja PM. Lipid-based nano-carriers for the delivery of anti-obesity natural compounds: advances in targeted delivery and precision therapeutics. Journal of Nanobiotechnology. 2025; 23: 336.

[98] Liu Y, Liang Y, Yuhong J, Xin P, Han JL, Du Y, *et al*. Advances in nanotechnology for enhancing the solubility and bioavailability of poorly soluble drugs. Drug Design, Development and Therapy. 2024; 18: 1469–1495.

[99] Alghamdi MA, Fallica AN, Virzì N, Kesharwani P, Pittalà V, Greish K. The promise of nanotechnology in personalized medicine. Journal of Personalized Medicine. 2022; 12: 673.

[100] Anwar DM, Hedeya HY, Ghozlan SH, Ewas BM, Khattab SN. Surface-modified lipid-based nanocarriers as a pivotal delivery approach for cancer therapy: application and recent advances in targeted cancer treatment. Beni-Suef University Journal of Basic and Applied Sciences. 2024; 13: 106.

[101] Teixeira MI, Lopes CM, Amaral MH, Costa PC. Surface-modified lipid nanocarriers for crossing the blood-brain barrier (BBB): a current overview of active targeting in brain diseases. Colloids and Surfaces B: Biointerfaces. 2023; 221: 112999.

[102] Taher M, Susanti D, Haris MS, Rushdan AA, Widodo RT, Syukri Y, *et al*. PEGylated liposomes enhance the effect of cytotoxic drug: a review. Heliyon. 2023; 9: e13823.

[103] Nair A, Chandrashekhar H R, Day CM, Garg S, Nayak Y, Shenoy PA, *et al*. Polymeric functionalization of mesoporous silica nanoparticles: biomedical insights. International Journal of Pharmaceutics. 2024; 660: 124314.

[104] Wang W, Zhou M, Xu Y, Peng W, Zhang S, Li R, *et al*. Resveratrol-

loaded TPGS-resveratrol-solid lipid nanoparticles for multidrug-resistant therapy of breast cancer: *in vivo* and *in vitro* study. Frontiers in Bioengineering and Biotechnology. 2021; 9: 762489.

[105] Pérez-Ferreiro M, M Abelairas A, Criado A, Gómez IJ, Mosquera J. Dendrimers: exploring their wide structural variety and applications. Polymers. 2023; 15: 4369.

[106] Abedi-Gaballu F, Dehghan G, Ghaffari M, Yekta R, Abbaspour-Ravasjani S, Baradaran B, *et al*. PAMAM dendrimers as efficient drug and gene delivery nanosystems for cancer therapy. Applied Materials Today. 2018; 12: 177–190.

[107] Araujo-Abad S, Berna JM, Lloret-Lopez E, López-Cortés A, Saceda M, de Juan Romero C. Exosomes: from basic research to clinical diagnostic and therapeutic applications in cancer. Cellular Oncology. 2025; 48: 269–293.

[108] Mukerjee N, Alharbi HM, Maitra S, Anand K, Thorat N, Gorai S. Exosomes in liquid biopsy and oncology: nanotechnological interplay and the quest to overcome cancer drug resistance. The Journal of Liquid Biopsy. 2023; 3: 100134.

[109] Lu J, Zhang Y, Yang X, Zhao H. Harnessing exosomes as cutting-edge drug delivery systems for revolutionary osteoarthritis therapy. Biomedicine & Pharmacotherapy. 2023; 165: 115135.

[110] Rugină D, Socaciu MA, Nistor M, Diaconeasa Z, Cenariu M, Tabaran FA, *et al*. Liposomal and nanostructured lipid nanoformulations of a pentacyclic triterpenoid birch bark extract: structural characterization and *in vitro* effects on melanoma B16-F10 and Walker 256 tumor cells apoptosis. Pharmaceuticals. 2024; 17: 1630.

[111] Kevadiya BD, Woldstad C, Ottemann BM, Dash P, Sajja BR, Lamberty B, *et al*. Multimodal theranostic nanoformulations permit magnetic resonance bioimaging of antiretroviral drug particle tissue-cell biodistribution. Theranostics. 2018; 8: 256–276.

[112] Yan Y, Kulsoom, Sun Y, Li Y, Wang Z, Xue L, *et al*. Advancing cancer therapy: nanomaterial-based encapsulation strategies for enhanced delivery and efficacy of curcumin. Materials Today Bio. 2025; 33: 101963.

[113] Cavalcante de Freitas PG, Rodrigues Arruda B, Araújo Mendes MG, Barroso de Freitas JV, da Silva ME, Sampaio TL, *et al*. Resveratrol-loaded polymeric nanoparticles: the effects of d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) on physicochemical and biological properties against breast cancer *in vitro* and *in vivo*. Cancers. 2023; 15: 2802.

[114] Tomar R, Das SS, Balaga VKR, Tambe S, Sahoo J, Rath SK, *et al*. Therapeutic implications of dietary polyphenols-loaded nanoemulsions in cancer therapy. ACS Applied Bio Materials. 2024; 7: 2036–2053.

[115] Nikolova MP, Kumar EM, Chavali MS. Updates on responsive drug delivery based on liposome vehicles for cancer treatment. Pharmaceutics. 2022; 14: 2195.

[116] Peter S, Khwaza V, Alven S, Naki T, Aderibigbe BA. PEGylated nanoliposomes encapsulated with anticancer drugs for breast and prostate cancer therapy: an update. Pharmaceutics. 2025; 17: 190.

[117] El-Hammadi MM, Arias JL. Recent advances in the surface functionalization of PLGA-based nanomedicines. Nanomaterials. 2022; 12: 354.

[118] Omidian H, Wilson RL. PLGA implants for controlled drug delivery and regenerative medicine: advances, challenges, and clinical potential. Pharmaceuticals. 2025; 18: 631.

[119] Pandey S, Shaikh F, Gupta A, Tripathi P, Yadav JS. A recent update: solid lipid nanoparticles for effective drug delivery. Advanced Pharmaceutical Bulletin. 2022; 12: 17–33.

[120] Borges A, Freitas V, Mateus N, Fernandes I, Oliveira J. Solid lipid nanoparticles as carriers of natural phenolic compounds. Antioxidants. 2020; 9: 998.

[121] Alamos-Musre S, Beltrán-Chacana D, Moyano J, Márquez-Miranda V, Duarte Y, Miranda-Rojas S, *et al*. From structure to function: the promise of PAMAM dendrimers in biomedical applications. Pharmaceutics. 2025; 17: 927.

[122] Guzmán Rodríguez A, Sablón Carrazana M, Rodríguez Tanty C, Malessy MJA, Fuentes G, Cruz LJ. Smart polymeric micelles for anticancer hydrophobic drugs. Cancers. 2022; 15: 4.

[123] Wang Q, Atluri K, Tiwari AK, Babu RJ. Exploring the application of micellar drug delivery systems in cancer nanomedicine. Pharmaceuticals. 2023; 16: 433.

[124] Quesada-Vázquez S, Eseberri I, Les F, Pérez-Matute P, Herranz-López M, Atgié C, *et al*. Polyphenols and metabolism: from present knowledge to future challenges. Journal of Physiology and Biochemistry. 2024; 80: 603–625.

[125] Alimohammadvand S, Kaveh Zenjanab M, Mashinchian M, Shayegh J, Jahanban-Esfahlan R. Recent advances in biomimetic cell membrane-camouflaged nanoparticles for cancer therapy. Biomedicine & Pharmacotherapy. 2024; 177: 116951.

[126] Frickenstein AN, Hagood JM, Britten CN, Abbott BS, McNally MW, Vopat CA, *et al*. Mesoporous silica nanoparticles: properties and strategies for enhancing clinical effect. Pharmaceutics. 2021; 13: 570.

[127] Dutta Gupta Y, Mackeyev Y, Krishnan S, Bhandary S. Mesoporous silica nanotechnology: promising advances in augmenting cancer theranostics. Cancer Nanotechnology. 2024; 15: 9.

[128] Gajbhiye KR, Salve R, Narwade M, Sheikh A, Kesharwani P, Gajbhiye V. Lipid polymer hybrid nanoparticles: a custom-tailored next-generation approach for cancer therapeutics. Molecular Cancer. 2023; 22: 160.

[129] Mohanty A, Uthaman S, Park IK. Utilization of polymer-lipid hybrid nanoparticles for targeted anti-cancer therapy. Molecules. 2020; 25: 4377.

[130] Chandrasekharan P, Tay ZW, Hensley D, Zhou XY, Fung BK, Colson C, *et al*. Using magnetic particle imaging systems to localize and guide magnetic hyperthermia treatment: tracers, hardware, and future medical applications. Theranostics. 2020; 10: 2965–2981.

[131] Radeva L, Yoncheva K. Nanogels-innovative drug carriers for overcoming biological membranes. Gels. 2025; 11: 124.

[132] Nocito MC, De Luca A, Prestia F, Avena P, La Padula D, Zavaglia L, *et al*. Antitumoral activities of curcumin and recent advances to improve its oral bioavailability. Biomedicines. 2021; 9: 1476.

[133] Wu J, Ji H, Li T, Guo H, Xu H, Zhu J, *et al*. Targeting the prostate tumor microenvironment by plant-derived natural products. Cellular Signalling. 2024; 115: 111011.

[134] Xiong RG, Huang SY, Wu SX, Zhou DD, Yang ZJ, Saimaiti A, *et al*. Anticancer effects and mechanisms of berberine from medicinal herbs: an update review. Molecules. 2022; 27: 4523.

[135] Jin X, Yang Q, Cai N, Zhang Z. A cocktail of betulinic acid, parthenolide, honokiol and ginsenoside Rh2 in liposome systems for lung cancer treatment. Nanomedicine. 2020; 15: 41–54.

[136] Nadile M, Kornel A, Sze NSK, Tsiani E. A comprehensive review of genistein's effects in preclinical models of cervical cancer. Cancers. 2023; 16: 35.

[137] Greco G, Agafonova A, Cosentino A, Cardullo N, Muccilli V, Puglia C, *et al*. Solid lipid nanoparticles encapsulating a benzoxanthene derivative in a model of the human blood-brain barrier: modulation of angiogenic parameters and inflammation in vascular endothelial growth factor-stimulated angiogenesis. Molecules. 2024; 29: 3103.

[138] Peanlikhit T, Aryal U, Welsh JS, Shroyer KR, Rithidech KN. Evaluation of the inhibitory potential of apigenin and related flavonoids on various proteins associated with human diseases using AutoDock. International Journal of Molecular Sciences. 2025; 26: 2548.

[139] Homayoonfal M, Asemi Z, Yousefi B. Potential anticancer properties and mechanisms of thymoquinone in osteosarcoma and bone metastasis. Cellular & Molecular Biology Letters. 2022; 27: 21.

[140] Almatroodi SA, Almatroudi A, Alharbi HOA, Khan AA, Rahmani AH. Effects and mechanisms of luteolin, a plant-based flavonoid, in the prevention of cancers via modulation of inflammation and cell signaling molecules. Molecules. 2024; 29: 1093.

[141] Iqbal Y, Asghar S, Hanif R, Amin F. PMA-coated gold nanoparticles functionalized with diamine-PEG conjugated with betulinic acid for *in vitro* mitochondrial-targeted anticancer and ROS detection study against MDA-MB-231 cell lines. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2025; 721: 137170.

[142] Aslam R, Tiwari V, Upadhyay P, Tiwari A. Revolutionizing therapeutic delivery: diosgenin-loaded solid lipid nanoparticles unleash advanced carriers. International Journal of Applied Pharmaceutics. 2024; 16: 124–133.

[143] Bakry SM, El-Shiekh RA, Hatem S, Mandour AA, El-Dessouki AM, Bishr A, *et al.* Therapeutic applications of ursolic acid: a comprehensive review and utilization of predictive tools. Future Journal of Pharmaceutical Sciences. 2025; 11: 48.

[144] Morshed AKMH, Paul S, Hossain A, Basak T, Hossain MS, Hasan MM,

et al. Baicalein as promising anticancer agent: a comprehensive analysis on molecular mechanisms and therapeutic perspectives. Cancers. 2023; 15: 2128.

[145] Kumar S, Mathew SO, Aharwal RP, Tulli HS, Mohan CD, Sethi G, *et al*. Withaferin A: a pleiotropic anticancer agent from the Indian medicinal plant withania somnifera (L.) Dunal. Pharmaceuticals. 2023; 16: 160.

[146] Zhu Y, Wang A, Zhang S, Kim J, Xia J, Zhang F, *et al*. Paclitaxel-loaded ginsenoside Rg3 liposomes for drug-resistant cancer therapy by dual targeting of the tumor microenvironment and cancer cells. Journal of Advanced Research. 2023; 49: 159–173.

[147] Ghasemi M, Nowroozzadeh MH, Ghorat F, Iraji A, Hashempur MH. Piperine and its nanoformulations: a mechanistic review of their anti-cancer activities. Biomedicine & Pharmacotherapy. 2025; 187: 118075.

[148] Yakubu J, Natsaridis E, du Toit T, Barata IS, Tagit O, Pandey AV. Nanoparticles with curcumin and piperine modulate steroid biosynthesis in prostate cancer. Scientific Reports. 2025; 15: 13613.

[149] Basheer I, Wang H, Li G, Jehan S, Raza A, Du C, *et al*. β-caryophyllene sensitizes hepatocellular carcinoma cells to chemotherapeutics and inhibits cell malignancy through targeting MAPK signaling pathway. Frontiers in Pharmacology. 2024; 15: 1492670.

[150] Fahmy SA, Elghanam R, Rashid G, Youness RA, Sedky NK. Emerging tendencies for the nano-delivery of gambogic acid: a promising approach in oncotherapy. RSC Advances. 2024; 14: 4666–4691.

[151] Gogola S, Rejzer M, Bahmad HF, Alloush F, Omarzai Y, Poppiti R. Anti-cancer stem-cell-targeted therapies in prostate cancer. Cancers. 2023; 15: 1621.

[152] Trofin AM, Scripcariu DV, Filipiuc SI, Neagu AN, Filipiuc LE, Tamba BI, *et al*. From nature to nanomedicine: enhancing the antitumor efficacy of rhein, curcumin, and resveratrol. Medicina. 2025; 61: 981.

[153] Teixeira PV, Fernandes E, Soares TB, Adega F, Lopes CM, Lúcio M. Natural compounds: co-delivery strategies with chemotherapeutic agents or nucleic acids using lipid-based nanocarriers. Pharmaceutics. 2023; 15: 1317.

[154] Majumder J, Minko T. Multifunctional and stimuli-responsive nanocarriers for targeted therapeutic delivery. Expert Opinion on Drug Delivery. 2021; 18: 205–227.

[155] Zhou Y, Wang X, Tian X, Zhang D, Cui H, Du W, *et al*. Stealth missiles with precision guidance: a novel multifunctional nano-drug delivery system based on biomimetic cell membrane coating technology. Materials Today Bio. 2025; 33: 101922.

[156] Aghajanzadeh M, Zamani M, Rajabi Kouchi F, Eixenberger J, Shirini D, Estrada D, *et al*. Synergic antitumor effect of photodynamic therapy and chemotherapy mediated by nano drug delivery systems. Pharmaceutics. 2022; 14: 322.

[157] Fu Z, Xiang J. Aptamer-functionalized nanoparticles in targeted delivery and cancer therapy. International Journal of Molecular Sciences. 2020; 21: 9123.

[158] Nsairat H, Khater D, Odeh F, Al-Adaileh F, Al-Taher S, Jaber AM, *et al*. Lipid nanostructures for targeting brain cancer. Heliyon. 2021; 7: e07994.

[159] Xia B, Zhu Q. Aptamer-ODN chimeras: enabling cell-specific ODN targeting therapy. Cells. 2025; 14: 697.

[160] Ragab EM, Gamal DME, El-Najjar FF, Elkomy HA, Ragab MA, Elantary MA, *et al*. New insights into Notch signaling as a crucial pathway of pancreatic cancer stem cell behavior by chrysin-polylactic acid-based nanocomposite. Discover Oncology. 2025; 16: 107.

[161] Gui K, Zhang X, Chen F, Ge Z, Zhang S, Qi X, *et al*. Lipid-polymer nanoparticles with CD133 aptamers for targeted delivery of all-trans retinoic acid to osteosarcoma initiating cells. Biomedicine & Pharmacotherapy. 2019; 111: 751–764.

[162] Ashrafizadeh M, Delfi M, Zarrabi A, Bigham A, Sharifi E, Rabiee N, *et al*. Stimuli-responsive liposomal nanoformulations in cancer therapy: pre-clinical & clinical approaches. Journal of Controlled Release. 2022; 351: 50–80.

[163] Gupta A, Jadhav SR, Colaco V, Saha M, Ghosh A, Sreedevi A, *et al*. Harnessing unique architecture and emerging strategies of solid lipid nanoparticles to combat colon cancer: a state-of-the-art review. International Journal of Pharmaceutics. 2025; 675: 125562.

[164] Kumar R, Dkhar DS, Kumari R, Divya, Mahapatra S, Srivastava A, *et al*. Ligand conjugated lipid-based nanocarriers for cancer theranostics. Biotechnology and Bioengineering. 2022; 119: 3022–3043.

[165] Jiang P, Xu C, Chen L, Chen A, Wu X, Zhou M, *et al*. EGCG inhibits CSC-like properties through targeting miR-485/CD44 axis in A549-cisplatin resistant cells. Molecular Carcinogenesis. 2018; 57: 1835–1844.

[166] Caliendo A, Camorani S, Ibarra LE, Pinto G, Agnello L, Albanese S, *et al*. A novel CD44-targeting aptamer recognizes chemoresistant mesenchymal stem-like TNBC cells and inhibits tumor growth. Bioactive Materials. 2025; 50: 443–460.

[167] Hegde M, Girisa S, BharathwajChetty B, Vishwa R, Kunnumakkara AB. Curcumin formulations for better bioavailability: what we learned from clinical trials thus far? ACS Omega. 2023; 8: 10713–10746.

[168] Liu Y, Shen Z, Zhu T, Lu W, Fu Y. Curcumin enhances the anti-cancer efficacy of paclitaxel in ovarian cancer by regulating the miR-9-5p/BRCA1 axis. Frontiers in Pharmacology. 2023; 13: 1014933.

[169] Duan H, Liu Y, Gao Z, Huang W. Recent advances in drug delivery systems for targeting cancer stem cells. Acta Pharmaceutica Sinica B. 2021; 11: 55–70.

[170] Arcella A, Palchetti S, Digiacomo L, Pozzi D, Capriotti AL, Frati L, *et al*. Brain targeting by liposome-biomolecular corona boosts anticancer efficacy of temozolomide in glioblastoma cells. ACS Chemical Neuroscience. 2018; 9: 3166–3174.

[171] Huang X, Wan J, Leng D, Zhang Y, Yang S. Dual-targeting nanomicelles with CD133 and CD44 aptamers for enhanced delivery of gefitinib to two populations of lung cancer-initiating cells. Experimental and Therapeutic Medicine. 2020; 19: 192–204.

[172] Fan R, Tao X, Zhai X, Zhu Y, Li Y, Chen Y, *et al*. Application of aptamer-drug delivery system in the therapy of breast cancer. Biomedicine & Pharmacotherapy. 2023; 161: 114444.

[173] Lu R, Zhao G, Yang Y, Jiang Z, Cai J, Hu H. Inhibition of CD133 overcomes cisplatin resistance through inhibiting PI3K/AKT/mTOR signaling pathway and autophagy in CD133-positive gastric cancer cells. Technol Cancer Res Treat. 2019; 18: 1533033819864311.

[174] Cao X, Geng X, Zhang C, Li L. Decoding the role of cancer stem cells in digestive tract tumors: mechanisms and therapeutic implications (Review). International Journal of Oncology. 2025; 67: 61.

[175] Mirzaei R, Shafiee S, Vafaei R, Salehi M, Jalili N, Nazerian Z, *et al*. Production of novel recombinant anti-EpCAM antibody as targeted therapy for breast cancer. International Immunopharmacology. 2023; 122: 110656.

[176] Liu Y, Wang Y, Sun S, Chen Z, Xiang S, Ding Z, *et al*. Understanding the versatile roles and applications of EpCAM in cancers: from bench to bedside. Experimental Hematology & Oncology. 2022; 11: 97.

[177] Thakur A. Nano therapeutic approaches to combat progression of metastatic prostate cancer. Advances in Cancer Biology Metastasis. 2021; 2: 100009.

[178] Nair B, Menon A, Rithwik Kalidas M, Nath LR, Calina D, Sharifi-Rad J. Modulating the JAK/STAT pathway with natural products: potential and challenges in cancer therapy. Discover Oncology. 2025; 16: 595.

[179] Alam K. Nanocarrier-based drug delivery systems using microfluidic-assisted techniques. Advanced NanoBiomed Research. 2023; 3: 2300041.

[180] Izadiyan Z, Misran M, Kalantari K, Webster TJ, Kia P, Basrowi NA, *et al*. Advancements in liposomal nanomedicines: innovative formulations, therapeutic applications, and future directions in precision medicine. International Journal of Nanomedicine. 2025; 20: 1213–1262.

[181] Zhao J, Zhang C, Wang W, Li C, Mu X, Hu K. Current progress of nanomedicine for prostate cancer diagnosis and treatment. Biomedicine & Pharmacotherapy. 2022; 155: 113714.

[182] Zhang H, Chen H, Guo G, Lin J, Chen X, Huang P, *et al*. Nanotechnology in prostate cancer: a bibliometric analysis from 2004 to 2023. Discover Oncology. 2025; 16: 451.

[183] Abbasi R, Shineh G, Mobaraki M, Doughty S, Tayebi L. Structural parameters of nanoparticles affecting their toxicity for biomedical applications: a review. Journal of Nanoparticle Research. 2023; 25: 43.

[184] Vervaeke P, Borgos SE, Sanders NN, Combes F. Regulatory guidelines and preclinical tools to study the biodistribution of RNA therapeutics. Advanced Drug Delivery Reviews. 2022; 184: 114236.

[185] Zuzčák M, Trnka J. Cellular metabolism in pancreatic cancer as a tool for prognosis and treatment (Review). International Journal of Oncology. 2022; 61: 93.

[186] Costa C, Padrela L. Progress on drug nanoparticle manufacturing:

exploring the adaptability of batch bottom-up approaches to continuous manufacturing. Journal of Drug Delivery Science and Technology. 2025; 111: 107120.

[187] Bi Y, Xie S, Li Z, Dong S, Teng L. Precise nanoscale fabrication technologies, the “last mile” of medicinal development. Acta Pharmaceutica Sinica B. 2025; 15: 2372–2401.

[188] Zhang J, Pan T, Lee J, Goldberg S, King SA, Tang E, *et al*. Enabling tumor-specific drug delivery by targeting the Warburg effect of cancer. Cell Reports Medicine. 2025; 6: 101920.

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