REVIEW ARTICLE

Drug delivery strategies for prostate targeting using nanotechnology: Comprehensive review with a focus on prostatitis

Kaarthegha Dhandapani, Poovi Ganesan *, Rajalakshmi Duraivel

Department of Pharmaceutics, College of Pharmacy, Mother Theresa Post Graduate and Research Institute of Health Sciences (A Government of Puducherry Institution), Affiliated to Pondicherry University, Indira Nagar, Gorimedu, Puducherry- 605 006, India

Prof. Dr. G. Poovi, Assistant Professor, Department of Pharmaceutics, College of Pharmacy, Mother Theresa Post Graduate and Research Institute of Health Sciences (A Government of Puducherry Institution), Affiliated to Pondicherry University, Gorimedu, Puducherry.

Abstract:

Prostatitis is the inflammation in prostate gland occurs commonly in adult males caused by presence or absence of bacteria in the region of pelvic region. It is third most occurred infection in urinary tract. Globally, 8-15% of men are affected. The condition is occurred in men aged between 30 to 50 years. The most commonly 90% of men are suffered from chronic prostatitis or chronic pelvic pain syndrome. Medication like antibiotics are used to treat prostatitis and some medications like Non-steroidal anti-inflammatory drugs, alpha blocker, antimuscarinic drugs etc., are used to manage symptoms of prostatitis. Treatment with those medication does not produce therapeutic effects effectively because of certain limitation. To overcome those limitation nanotechnology-based drug delivery system is adopted to treat prostatitis effectively. Information's regarding prostatitis, categories of prostatitis, factors responsible for prostatitis, symptoms of prostatitis, aetiology, epidemiology, pathophysiology, diagnosis, traditional treatment method, challenges in prostatitis in case of treatment and diagnosis, pharmacokinetic consideration, need of nanotechnology in prostate targeting, nanotechnology based strategies and applications are explained in this review. Finally, overall nanotechnology-driven prostate-targeted drug delivery represents a transformative approach for improving prostatitis treatment and patient quality of life.

Keywords: prostate-targeted drug delivery, traditional treatment, challenges, prostatitis, nanoparticles, recent advances in nanotechnology.

Abbreviation:

Benign Prostate Hyperplasia (BPH)

National Institutes of Health (NIH)

Transurethral needle resection (TUNA)

Non-steroidal anti-inflammatory drugs (NSAIDs)

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)

Calcitonin gene-related peptide (CGRP)

Substance P (SP)

Brain-derived neurotrophic factor (BDNF)

Nerve growth factor (NGF)

Granulocyte–macrophage colony-stimulating factor (GM-CSF)

Interleukin-1β (IL-1β)

Cyclooxygenase-2 (COX-2)

Prostaglandin E2 (PGE2)

Serotonin (5-HT),

Protease-activated receptor-2 (PAR2)

Transient receptor potential vanilloid-1 (TRPV1)

Tyrosine kinase receptor A (TrkA)

Acid-sensing ion channels (ASIC1a)

Purinergic receptors (P2X2, P2X3, and P2X4)

Chemokine receptors (CCR2, CXCR2, CXCR3, and CXCR4)

T-type potassium channels (TREK-1 and TREK-2)

N-methyl-D-aspartate receptors (NMDAR)

Quantum dots (QDs)

Single-walled carbon nanotubes (SWCNTs)

Double-walled carbon nanotubes (DWCNTs)

Triple-walled carbon nanotubes (TWCNTs)

Multi-walled carbon nanotubes (MWCNTs)

Carbon nanotubes (CNTs)

Interleukin-1 receptor antagonist (IL-1RA)

Folate receptors (FR-α and FR-β)

Prostate-specific membrane antigen (PSMA)

Superparamagnetic iron oxide nanoparticles (SPIONs)

Polylactic-co-glycolic acid (PLGA)

Polyethylene glycol (PEG)

Polyvinyl alcohol (PVA)

Polyhydroxyalkanoates (PHA)

Toll-like receptors (TLRs)

Blood–prostate barrier (BPB)

1. Introduction

Prostatitis is the inflammation in prostate gland which commonly occur in adult males caused by in presence or absence of bacteria in the region of pelvic (1,2). It is a common urinary tract condition that many doctors find problematic to treat effectively. It is estimated that nearly half of all men suffer from symptoms of prostatitis at some stage in their lives. Prostatitis is the third most commonly identified urinary tract infection found in men after Prostate cancer and Benign Prostate Hyperplasia (BPH) (3). Men age 50 years or older have a higher risk for prostatitis (4).Since, in case of inflammation present in the prostate gland plays a crucial role in promoting prostate cancer, by inducing damage to DNA and also cause mutagenesis in the prostate epithelium. Besides, 18% of prostatitis patient are developed with prostate cancer results in death in males (5). The prostate is present in the pelvic cavity, and thus a traditional methods of treatments result in poor therapeutic effects because of poor penetration. In recent years, nanotechnology is utilized in for diagnosis and treatment of prostatitis. Nanoparticle plays a great role in order to target a drug in prostate gland (2). In this review, prostatitis caused by bacterial organisms are detailed along with their respective treatment.

2. Categories of prostatitis

National Institutes of Health (NIH) categorized prostatitis into four categories are (Figure 1),

- Category I: Category I characterized critical signs of systemic infection and prostate infection which finally leads to result in acute bacterial urinary tract infection. Therefore, category I is considered as acute bacterial prostatitis (3,6). Men aged between 20 to 40 are majorly affected and also the incidence increases around at age of 60(7,8).
- Category II: Category II prostatitis is induced by chronic bacteria with or without serious signs. Therefore, category II is considered as chronic bacterial prostatitis (3,6,8)
- Category III: Category III is noted by persistent pelvic pain and probable voiding symptoms in the absence of urinary tract infection. This category is regarded as chronic prostatitis (3,6,8).
- Category IV: Category IV is called as asymptomatic inflammatory prostatitis is associated with inflammation of prostate in the absence of Urogenital tract symptoms (3,6,8).

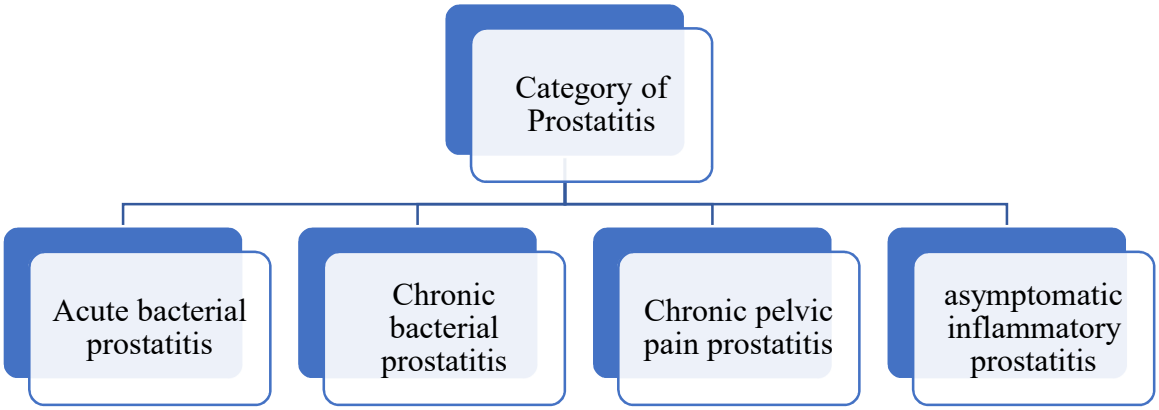

Figure 1: Categories of Prostatitis

3. Factors responsible for prostatitis

The factors responsible for prostatitis including infection due to pathogens, imbalance in sex hormone, urinary dysfunction, inflammation and abnormal activity of immune system(2).

3.1 Pathogen: Bacteria, fungi, viruses, and other infectious microorganisms result in prostatitis. Among them, bacteria plays a major pathogen causes prostatitis(3,9) and those pathogens are Escherichia coli, Klebsiella pneumonia, Enterobacter, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Enterococcus, Proteus, Salmonella, Staphylococcus aureus, Trichomonas vaginalis, Ureaplasma urealyticum, etc, (3).

3.2 Imbalance in sex hormone: Prostate is sex accessory reproductive organ. If any imbalance in sex hormone result in prostatitis(10).

3.3 Urinary dysfunction: In tissue, accumulation of urate crystal results in inflammation promote spasm and contraction of urethral sphincter leads of obstruction of urine(2).

3.4 Neuroregulatory Mechanisms: Prostate pain due to damage of spinal nerve segmental nerve. So, thereby nerve plays an important role in prostatitis(11).

3.4.1 Immune response: Scientist made a note that more than 90% T lymphocytes and other inflammatory cells are present in epithelial stromal region of prostate. Incase of infection prostate get stimulated to produce IFN-γ and IL-15 result in chronic inflammation. Prostate as well as contain cytokine receptor in epithelial cells and stromal cells of prostate release IL-1α,

IL-1β and IL-6. So, in case of prostatitis causes chronic inflammation. Therefore, prostatitis is called as autoimmune disease(2).

4. Symptoms of prostatitis

4.1 Chronic prostatitis/chronic pelvic pain syndrome: The signs of chronic prostatitis include pain in the following areas are the penis, scrotum, between scrotum & anus, lower back, lower abdomen, the pain occur during or after urination and also increases frequency of urination. It will be last for 3 or more than 3month (12).

4.1.1 Acute bacterial prostatitis: The signs of acute bacterial prostatitis occurs suddenly and severe. Men needs immediate medical care. Symptoms are frequent urination, fever, pain (groin, lower back, lower abdomen and genital area), nausea, vomiting, bodyache, urine urgency, etc, (12).

4.1.2 Chronic bacterial prostatitis. The signs of chronic bacterial prostatitis are similar to acute bacterial prostatitis. This type of prostatitis often occurs slowly and last for 3 or more months. The symptoms of chronic bacterial prostatitis are frequent urination, urgency in urination, buring feel or pain in urination, Pain (groin, lower back, lower abdomen and genital area) , painful ejaculation, etc, (12). The treatment utilized for CBP include the use of antibiotics and along with medicine which can lower the urinary tract symptoms to achieve best therapeutic effects (13).

5. Aetiology and Epidemiology

E. coli among the gram-negative organisms is the common cause result in urinary tract infections and bacterial prostatitis. The atypical organisms such as *Chlamydia*, other sexually transmitted infections and rare pathogens such as *M. tuberculosis* are also result in prostatitis (7).A prostatitis are diagnosed 13 times greater when patients visit urology than primary care. Around the world, approximately 8 million doctors are affected by chronic prostatitis, represent an overall global incidence of 8.2% in men. In US, prostatitis cases are reported as high as 16%. Occurrence of prostatitis is not based on racial preference (7).

6. Pathophysiology

In case of acute bacterial prostatitis, most commonly bacteria reaches prostate by entering through urethra and less commonly bacterial reaches prostate through direct

transmission or through lymphatic spread or may be due to hematogenous spread. Many bacterial organism causes prostatitis among which E.coli causes prostatitis. Sexually transmitted infections such as Chlamydia or Gonorrhoea are rare to cause prostatitis. Chronic bacterial prostatitis is persistent bacterial infection of the prostate with or without any signs (14).

7. Diagnosis (15,16)**:**

Prostatitis can be diagnosed by following methods,

7.1 Digital rectal examination: In this test, physician wear a gloves and insert his/her finger into rectum of patient to check whether patient feel any pain or swelling.

7.2 Urinalysis: Urine samples are analysed for any presence of bacteria.

7.3 Blood test: This test used to measure prostate-specific antigen level in prostate gland. High level of these protein indicates prostatitis.

7.4 Cystoscopy: It is a pencil sized lighted tube possess camera will be inserted by physician into rectum of patient to view any urinary tract problem.

7.5 Transrectal ultrasound: This test indicate presence of abnormalities of prostate gland by means of sound waves.

7.6 Urodynamic testing: This test utilized to measure the function of nerve and muscle, pressure within and outside of bladder and flow rates of urine.

8. Traditional treatment method:

Prostatitis can be treated by utilizing medication of antibiotic, over the counter relief (17), prostate massage, non-steroidal anti-inflammatory drugs, analgesics, phytotherapy, alpha-reductase inhibitors, muscle relaxants, thermotherapy, transurethral needle resection (TUNA), laser and surgery (18).Treatment by using antibiotics possess an ability to eliminate pathogenic bacteria and also improve the quality of semen in patient (13). Alpha-blockers are utilized to overcome the symptoms of prostatitis and benign prostatic hyperplasia (19).Carano et.al, reported that pain score are decreases if alpha blockers are utilized for greater than 3month

(20).Some of medication used in management of acute and chronic bacterial prostatitis (Figure 2 & 3) are,

8.1 Fluoroquinolones: These are first-line therapy for chronic bacterial prostatitis produce activity against typical urinary tract pathogens(21). It has a superior penetration property into prostatic tissue and possess excellent oral bioavailability(18,21). Fluoroquinolones act by inhibiting DNA topoisomerase and DNA gyrase to stop growth of bacteria. That enzymes are important in bacterial cell division. They are effective against gram negative bacteria. Fluoroquinolone-resistant members includes *E. coli*, *Klebsiella* and *Enterobacter*, have shown mutations in gyrA and DNA gyrase gene. If mutations in a gene affect permeability of cell membrane, marA are found in *E. coli*, which promote outflux and inhibit influx of antibiotics through the cell. *Pseudomonas* species gain resistance to fluoroquinolones because it naturally contain 12 different efflux pumps works to pump drug outside the cell and among which 2 pumps are overexpressed in case of resistance (22).More importantly Ciprofloxacin or Ofloxacin are used for treatment. Incase of chance of developing high risk of side effects can be overcomed by use of trimethoprim. The second chance of antibiotic are utilized for treatment are levo-floxacin or clotrimazole (23). Ciprofloxacin of dose of 125 or 250 mg once daily are effective in treatment (24).Ciprofloxacin are zwitterions can be accumulated in both alkaline and acidic medium of prostatic fluids possess broad antibacterial spectrum, and shows strong activity, particularly against Enterobacteriaceae (25).

8.2 Trimethoprim: It is also effective against gram negative bacteria (24). It have good penetration capacity into prostate. It can be administrated by means of oral route or parental route (18).Trimethoprim and sulfamethoxazole can be utilized for treatment over a period of 12 weeks of dose rage of 160 mg and 800 mg twice daily, cure prostatitis up to 40% of patient had reported. After this, treatment with fluroquinolone antibiotics such as ciprofloxacin of 500 mg twice daily for 2-4weeks cure 70% of prostatitis. 50 or 100 mg dose of trimethoprim once daily or 40 mg & 200 mg of Trimethoprim & sulfamethoxazole once daily is effective in treatment have been reported (24).

8.3 Erythromycin: Erythromycin is a macrolide antibiotic plays a important role in killing bacteria like Ureaplasma urealyticum and Chlamydia trachomatis(26).Hanus et al, reported that erythromycin of dose of 500 mg as stearate salt for 14days in which four a times daily (27). On oral administration, erythromycin is absorbed into blood and get distributed in the prostate gland. On reducing the bacterial load, erythromycin increases signs such as pain, discomfort,

and difficulty in urinating. Use of this medication used to treat prostatitis for a period of 4-6 weeks (28)

8.4 Doxycycline: It is effective against chlamydia or anyothers usual organisms that can cause chronic prostatitis. Treatment must be continued for two to three months (29).

8.5 Doxazosin: Evliyaoğlu et al., reported that doxazosin of dose of 4 mg given for period of 3 month have improved the quality of life of patient which have been proved by International Prostate Symptom Score (IPSS), pain score and quality of life scores. IPSS is considered as important tool used to find treatment outcome of chronic non-bacterial prostatitis (30).

8.6 Tamsulozin: Nickel et al, reported that tamsulosin are effective in prostatitis pelvic pain syndrome (31).

8.7 Oxybutynin: It is an antimuscarinic agent and urinary antispasmodic Agent. The drug antagonize M1,M2 and M3 receptor leads to get relive from muscle spasm of the bladder (32).It is used to treat bladder spasm and detrusor overactivity. It is used in management of symptoms of bladder overactivity (33) and prostatitis.

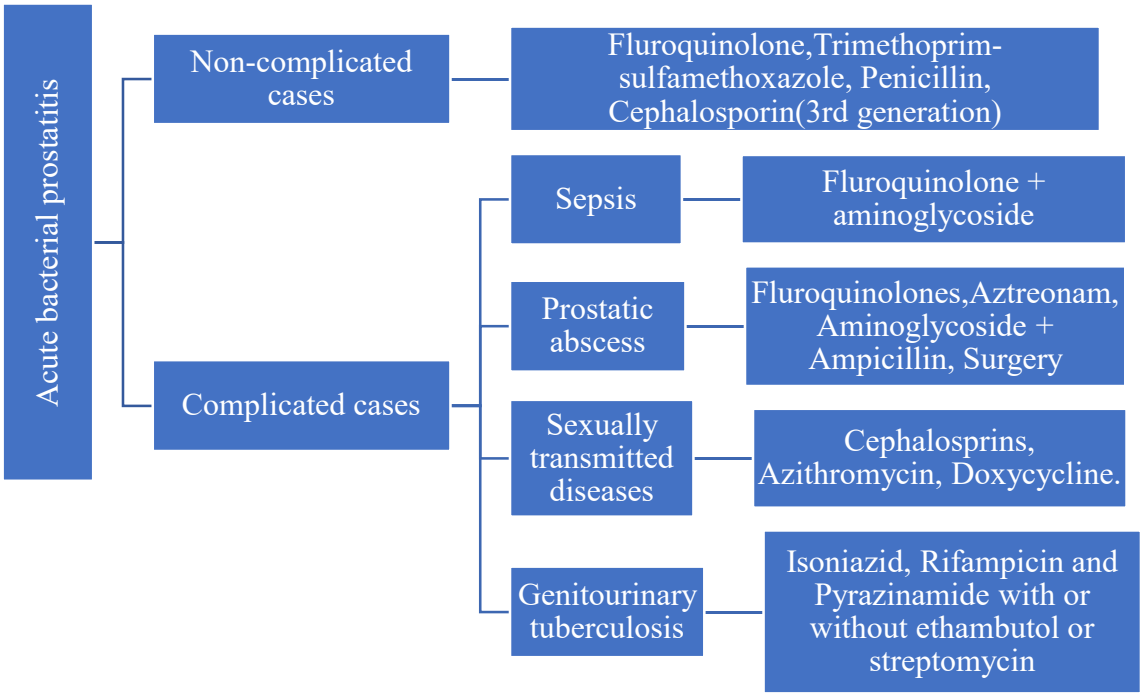

Figure 2: Treatment for Acute bacterial prostatitis (34)

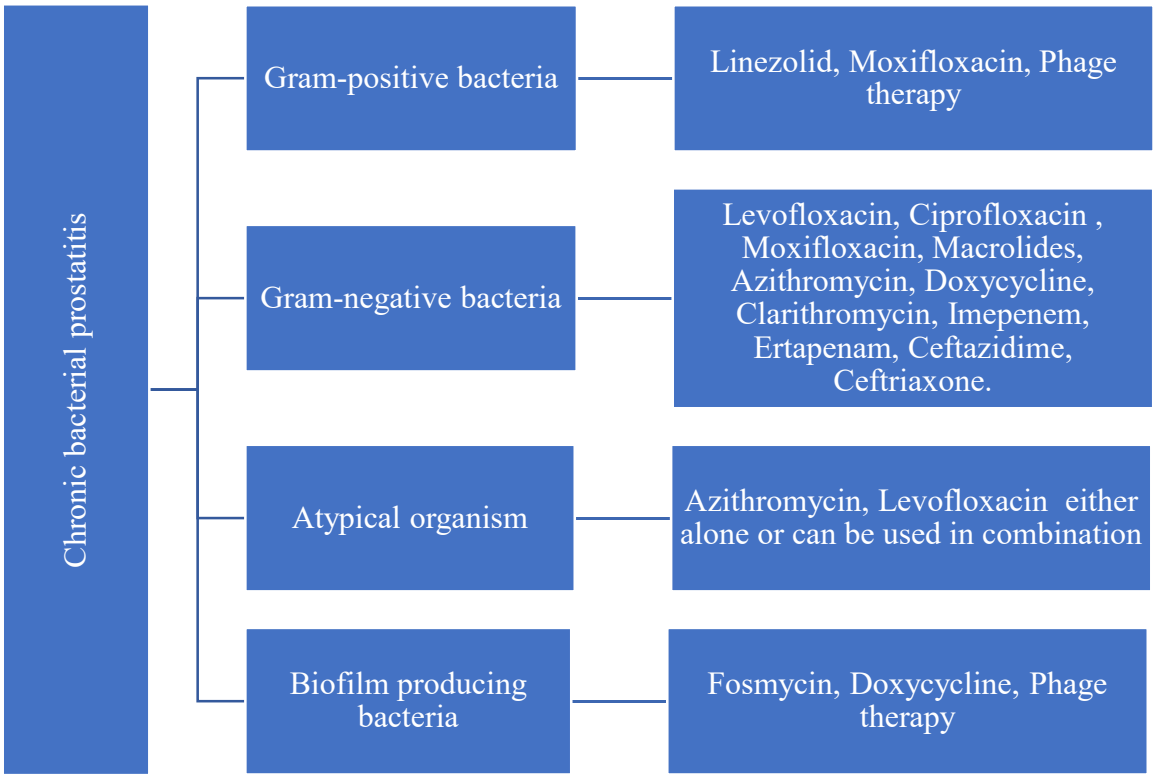

Figure 3: Treatment for Chronic bacterial prostatitis (34)

9. Challenges in treating prostatitis

Treatment and diagnostic procedure for prostatitis are still lacking, and so thereby, new drug delivery systems and diagnostic methods are needed.

9.1 Challenges in prostatitis treatment

Prostatitis presents with a wide range of clinical symptoms, and its etiology is often poorly defined (55), making effective treatment difficult. Conventional clinical management typically involves the use of antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and α-blockers (56). However, these therapies frequently demonstrate limited efficacy. The ineffectiveness of treatment is largely attributed to poor drug penetration into the prostate gland. This is due to several pathological factors, including inflammatory hyperplasia, increased intraprostatic pH, bacterial accumulation, reduced blood supply, limited drug penetration, and disruption of the blood–prostate barrier (27,57)

Inflammation of the prostate may lead to edema and prostatic hyperplasia. Increased intraglandular pressure can result in ductal stenosis or obstruction, thereby preventing adequate drug penetration. Additionally, elevated pressure exacerbates pelvic pain and urinary tract irritation (2).

An increase in prostatic pH further compromises drug penetration. Differences in pH across the prostatic membrane hinder the diffusion of drug molecules into prostatic fluid. Antimicrobial agents tend to accumulate in their unionized form; however, β-lactam antibiotics, which possess low pKa values and poor lipid solubility, exhibit limited penetration into prostatic tissue. Only certain cephalosporins can achieve inhibitory concentrations (59). In contrast, antimicrobial agents such as tetracyclines, macrolides, quinolones, sulfonamides, tobramycin, netilmicin, and nitrofurantoin demonstrate good to excellent penetration into prostatic fluid and tissue (59).

Bacterial colonization often occurs within or on calcified plaques inside the prostate. These calcifications may progress into prostatic stones, leading to ductal obstruction and recurrent infection. Consequently, calcified stones represent a major factor contributing to poor drug penetration and treatment failure (2).

9.2 Challenges in the Diagnosis of Prostatitis

The National Institutes of Health (NIH) has classified prostatitis into four categories. Notably, patients in the fourth category may remain asymptomatic, making diagnosis particularly challenging. The absence of clear clinical symptoms complicates accurate disease identification and delays appropriate treatment (9).

10. Pharmacokinetic Considerations

Drug penetration into the prostate is influenced by physicochemical properties such as lipid solubility, degree of ionization (pKa), protein binding, and molecular size. Drugs primarily enter the prostate via passive diffusion across lipid membranes, with optimal molecular sizes typically below 400 Å. The normal pH of prostatic fluid ranges between 6.5 and 6.7. In chronic prostatitis, prostatic pH increases, often ranging from 7.0 to 8.3 (59). This altered pH environment favors the accumulation of weakly basic drugs in their unionized form (2,59).

Effective prostatic penetration is associated with drugs that exhibit high lipid solubility, high pKa, weak ionization at physiological pH, low protein binding, and a favorable pH gradient between plasma and prostatic fluid (2,54,59). Conversely, β-lactam antibiotics exhibit poor penetration due to low lipid solubility and low pKa values, with the exception of some cephalosporins. Several antimicrobial agents, including tobramycin, netilmicin, tetracyclines, macrolides, quinolones, sulfonamides, and nitrofurantoin, demonstrate excellent penetration into prostatic tissue and fluid (59), making them more effective in the management of prostatitis

11. Need of Nanotechnology in Prostate Targeting

11.1 Barriers to Drug Delivery in Prostate Tissue

The anatomical and physiological barriers of the prostate gland significantly limit the effective delivery of therapeutic agents. The blood–prostate barrier (BPB) restricts drug transport into prostatic tissue, frequently resulting in treatment failure (60). Tight junctions present in prostate epithelial tissue consist of transmembrane proteins, cytosolic proteins, and cytoskeletal proteins. The major transmembrane components include occludin, claudins, and junctional adhesion molecules (JAM). Among these, occludin and claudins play a critical role in maintaining barrier integrity, with claudins being particularly important in regulating paracellular permeability (60). Nanotechnology-based drug delivery systems offer a promising approach to overcoming these biological barriers by enhancing drug penetration and enabling site-specific delivery to prostate tissue.

11.2 Limitations of Conventional Therapy

Conventional therapeutic strategies often fail to achieve adequate drug concentrations at the target site due to poor tissue penetration, rapid systemic clearance, and low bioavailability. Nanomedicine provides an advanced approach by enabling targeted drug delivery to the prostate, thereby enhancing therapeutic efficacy and prolonging drug action (61). In addition, nanocarriers can improve the solubility and bioavailability of poorly water-soluble drugs, which constitute a large proportion of currently available pharmaceutical compounds (62).

11.3 Receptor-Based Targeting Opportunities

Receptor-mediated targeting represents a key strategy in nanotechnology-assisted prostate therapy. Toll-like receptors (TLRs), which are transmembrane proteins involved in innate immune responses, play an important role in inflammatory signaling pathways. In humans, ten TLRs (TLR1–TLR10) have been identified (63). Studies conducted by Fan et.al., 2019 have demonstrated that TLR2 and TLR10 are involved in inflammatory processes within prostate epithelial cells. Besides, they reported that the activation of TLR2 induces inflammatory signaling cascades, whereas TLR10 exhibits anti-inflammatory effects. Therefore, modulation of these receptors through targeted nanotherapeutics may offer a novel strategy for managing prostate inflammation (64).

Sympathetic and parasympathetic nerve signaling also contributes significantly to the development of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Several inflammatory mediators and neurotransmitters—including calcitonin gene-related peptide (CGRP), substance P (SP), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin-1β (IL-1β), cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), serotonin (5-HT), and chemokines such as CCL3, CCL2, and CXCL1—are involved in pain generation and progression (65).

Multiple nociceptive receptors, including protease-activated receptor-2 (PAR2), transient receptor potential vanilloid-1 (TRPV1), tyrosine kinase receptor A (TrkA), acid-sensing ion channels (ASIC1a), purinergic receptors (P2X2, P2X3, and P2X4), chemokine receptors (CCR2, CXCR2, CXCR3, and CXCR4), T-type potassium channels (TREK-1 and TREK-2), and N-methyl-D-aspartate receptors (NMDAR), contribute to pain sensitization in prostatitis (65).

In addition, interleukin-1 receptor antagonist (IL-1RA) has been shown to inhibit androgen receptor signaling in basal prostate stem cells, promoting luminal differentiation and contributing to prostate hyperplasia (66). Folate receptors (FR-α and FR-β) and prostate-specific membrane antigen (PSMA) are overexpressed in prostate cancer and prostatitis, making them attractive targets for receptor-mediated nanotherapeutic delivery (67–69). Targeting these receptors using nanotechnology may significantly improve disease management in both prostatitis and prostate cancer.

11.4 Enhancement of Poorly Soluble Drugs

Approximately 70% of synthetic drugs exhibit poor aqueous solubility, leading to suboptimal pharmacokinetic profiles (61). Nanoparticles possess a large surface-area-to-volume ratio, which enhances drug dissolution, solubility, and bioavailability of poorly soluble compounds (62,70,71). This property makes nanotechnology particularly advantageous for improving therapeutic outcomes in prostate-related disorders.

11.5 Controlled and Sustained Drug Release

Nanoparticle-based drug delivery systems are capable of providing controlled and sustained drug release, thereby maintaining therapeutic drug levels over extended periods while minimizing systemic side effects (70). This controlled release profile is especially beneficial for chronic conditions such as prostatitis, where prolonged treatment is often required.

11.6 Nanotechnology-Based Strategies for Prostate Targeting

Nanoparticles are submicron-sized carriers ranging from 10 to 1,000 nm. Based on their structural characteristics, they include liposomes, dendrimers, nanospheres, hydrogels, and nanoemulsions (72). These systems offer multiple advantages, such as prolonged shelf life, enhanced drug-loading capacity, reduced dosing frequency, improved patient compliance, and decreased systemic toxicity.

Nanotechnology-based formulations have been successfully employed to deliver therapeutic agents including antibiotics, anti-inflammatory drugs, peptides, and genes to modulate the inflammatory microenvironment associated with prostatitis (27,70,73,74). Nanodrug delivery systems provide an effective approach to overcoming blood–prostate barrier limitations, particularly in chronic non-bacterial prostatitis (CNP/CPPS) (6).

The effectiveness of prostate-targeted nanocarriers depends on physicochemical properties such as particle size, surface charge, shape, and ligand-mediated surface modification (75). These characteristics influence cellular uptake, tissue penetration, and receptor specificity. Consequently, nanotechnology represents a promising and innovative strategy for improving therapeutic efficacy in prostatitis and prostate cancer management.

12. Nanotechnology-Based Drug Delivery Systems for Prostate Targeting

Nano-scale drug delivery systems have emerged as promising platforms for improving therapeutic efficacy in prostate-related disorders. Various nanocarriers have been developed to enhance drug solubility, bioavailability, tissue penetration, and targeted delivery while minimizing systemic toxicity.

12.1 Nanoemulsions

Nanoemulsions, also referred to as miniemulsions, are nanometric-sized emulsions with droplet sizes ranging from 20 to 200 nm. Owing to their small particle size, nanoemulsions can readily penetrate semipermeable biological membranes. They are commonly formulated as water-in-oil (w/o) or oil-in-water (o/w) systems. Nanoemulsions significantly enhance the solubility of poorly water-soluble drugs, improve formulation stability, and possess high drug-loading capacity, enabling the delivery of a wide range of therapeutic agents (76). Furthermore, nanoemulsions enhance drug bioavailability, making them suitable carriers for prostate-targeted therapy (77).

12.2 Nanosuspensions

Nanosuspensions are biphasic dispersions composed of submicron-sized drug particles (typically <1 μm) stabilized by polymers and surfactants. This system improves drug solubility, dissolution rate, and cellular membrane adhesion, particularly for hydrophobic drugs. Nanosuspensions represent an effective dosage form for poorly soluble compounds, and organic materials are commonly employed in their formulation (78). Their enhanced dissolution properties make them suitable for improving therapeutic outcomes in prostate disorders.

12.3 Polymeric Nanoparticles

Polymeric nanoparticles are solid colloidal particles composed of biodegradable or non-biodegradable polymers such as polycaprolactone, polylactic acid, polylactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyhydroxyalkanoates (PHA), cellulose, gelatin, and chitosan. Depending on formulation, the active pharmaceutical ingredient may be encapsulated within the polymer matrix or adsorbed onto the particle surface, forming nanospheres or nanocapsules (79,80). The physicochemical characteristics of polymeric nanoparticles—including particle size, surface charge, shape, hydrophobicity, and

surface coating—significantly influence tissue targeting and cellular uptake. Several biodegradable polymers, such as PLGA, gelatin, and chitosan, also exhibit intrinsic antibacterial properties, further enhancing their therapeutic potential (80).

12.4 Gelatin Nanoparticles

Gelatin nanoparticles are derived from gelatin, a naturally occurring biopolymer that behaves as a polyampholyte due to the presence of both acidic and basic functional groups. The degree of cross-linking in gelatin nanoparticles determines their mechanical strength, swelling behavior, and thermal stability. Common preparation methods include emulsification, dissolution, and coacervation techniques (81). Gelatin nanoparticles are particularly advantageous due to their ability to provide controlled and sustained drug release profiles (80).

12.5 Chitosan-Based Nanocarriers

Chitosan-based nanocarriers are synthesized from chitosan, a naturally occurring carbohydrate polymer obtained by partial N-deacetylation of chitin, which is abundant in crustacean shells. Chitosan exhibits excellent biocompatibility, low toxicity, and biodegradability, making it highly suitable for pharmaceutical and biomedical applications. Common formulation techniques include ionotropic gelation, microemulsion, emulsification–solvent diffusion, and polyelectrolyte complexation methods (82). Chitosan nanocarriers enable targeted and site-specific drug release, enhancing therapeutic efficiency (80).

12.6 Albumin-Based Nanocarriers

Albumin-based nanocarriers utilize albumin, the most abundant plasma protein, as a drug carrier. Albumin nanoparticles are biocompatible, non-toxic, biodegradable, and non-immunogenic. These carriers demonstrate high drug-binding capacity and are well tolerated without significant adverse effects (83). Albumin nanoparticles also facilitate targeted drug delivery and controlled release, making them suitable for prostate-targeted therapy (80).

12.7 Superparamagnetic Nanocarriers

Superparamagnetic iron oxide nanoparticles (SPIONs) are emerging as advanced drug delivery systems in prostate therapy. Typically ranging from 10 to 100 nm, SPIONs are composed of magnetic materials such as magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3). To

enhance stability and biocompatibility, SPIONs are often coated with polymers such as polyethylene glycol or dextran, which facilitate cellular adhesion and prolonged circulation time. Additionally, SPIONs induce hyperthermia under an external magnetic field, leading to selective destruction of cancer cells (84). Combination therapies using SPIONs loaded with anticancer drugs such as valrubicin have demonstrated significant activity against prostate cancer (85).

12.8 Metal Nanoparticles

Metal nanoparticles, particularly silver and gold nanoparticles, have gained significant attention in medical and industrial applications. These nanoparticles exhibit anticancer, anti-inflammatory, and antimicrobial properties and are widely used in drug delivery and medical imaging (86). Silver nanoparticles demonstrate strong antimicrobial activity against a broad spectrum of bacterial species, including Escherichia coli, and exhibit enhanced biological performance when compared to conventional silver formulations (87). Gold nanoparticles, with core sizes ranging from 1.5 to 10 nm, represent a versatile nanoplatform with applications in theranostics, photothermal therapy, and tissue imaging. They possess excellent conjugation capability with therapeutic agents and molecular targeting ligands, enabling active targeting of specific receptors involved in prostate disorders (88).

12.9 Carbon Nanotubes and Fullerenes

Carbon nanotubes (CNTs) are graphitic nanomaterials possessing at least one dimension below 100 nm and are composed of sp^2-hybridized carbon atoms arranged in tubular structures with a carbon–carbon bond length of approximately 1.4 Å. CNTs belong to the fullerene family, which represents the third allotrope of carbon alongside diamond and graphite. Owing to their unique physicochemical properties, CNTs have emerged as promising candidates for targeted drug delivery systems. However, their limited solubility and dispersion in biological environments pose significant challenges for biomedical applications. CNTs are classified into single-walled carbon nanotubes (SWCNTs), double-walled carbon nanotubes (DWCNTs), triple-walled carbon nanotubes (TWCNTs), and multi-walled carbon nanotubes (MWCNTs). CNT-based hybrid systems have been developed to enhance bioactive drug delivery, reduce toxicity, and improve safety and therapeutic efficacy (89). Notably, MWCNTs have been explored for detecting overexpressed prostate-specific antigen (PSA) and for the treatment of prostate cancer (90).

12.10 Quantum Dots

Quantum dots (QDs) are nanoscale semiconductor particles capable of confining electrons in zero-dimensional structures. They typically consist of a few hundred to several million atoms and contain fewer than one hundred free electrons. QDs are commonly synthesized from group II–VI elements (Zn, Cd, Hg with O, S, Se, or Te) or group III–V elements (B, Al, Ga, In with N, P, As, Sb, or Bi). Due to their tunable optical properties, QDs are extensively used in diverse biomedical applications (91). $AgInSe_2/ZnS$ quantum dots have demonstrated superior antibacterial activity against *Staphylococcus aureus* (Gram-positive bacteria) compared to *Escherichia coli* (Gram-negative bacteria), attributed to their negative surface charge. Additionally, QDs exhibit preferential uptake in prostate cancer cells compared to normal prostate cells, highlighting their potential in targeted prostate cancer therapy (92).

12.11 Nanosponges

Nanosponges are nanosized particles capable of encapsulating both hydrophilic and hydrophobic drug molecules within their porous structure. They enhance the solubility of poorly water-soluble drugs, facilitate controlled drug release at the target site, improve bioavailability, and minimize systemic side effects. These properties make nanosponges attractive carriers for prostate-targeted drug delivery systems (93).

12.12 Nanoshells

Nanoshells are a class of nanocomposites consisting of a thin outer shell coated around a core particle. The core can assume various geometries, including rods, rings, tubes, wires, or cubes, and is enveloped by a nanoscale shell composed of metals, semiconductors, or insulating materials. Nanoshells have demonstrated applications in optical imaging, biomedical diagnostics, targeted therapy, and gene delivery, and they also exhibit therapeutic potential in prostate-related diseases (94,95).

12.13 Dendrimers

Dendrimers are highly ordered, branched nanoscale macromolecules (1–100 nm) first discovered by Professor Donald Tomalia in 1985. They consist of three distinct components: a central core, internal repeating units known as dendrons, and terminal functional groups. Dendrimers are monodispersed and globular in structure, enabling efficient

encapsulation or conjugation of bioactive agents through covalent bonding, ionic interactions, or adsorption within internal cavities. Functionalization with polymers such as polyethylene glycol (PEG) and targeting ligands including antibodies, aptamers, folic acid, or carbohydrates further enhances their targeting efficiency (96). Dendrimers improve the solubility and bioavailability of poorly water-soluble drugs and exhibit broad therapeutic activity, including antibacterial, antiviral, antitubercular, and anticancer effects (97).

12.14 Liposomes

Liposomes were first discovered by British hematologist Dr. Alec D. Bangham in 1961. They are spherical vesicles composed of lipid bilayers capable of encapsulating both hydrophilic and hydrophobic drugs. Liposomes enhance drug solubility, improve bioavailability, promote controlled drug release, and facilitate targeted drug delivery. Their lipid bilayer structure closely resembles biological membranes, enabling efficient membrane penetration and drug transport to the target site (98,99).

13. Applications of Nanotechnology in Prostatitis Treatment

Nanotechnology-based drug delivery systems have demonstrated promising applications in the treatment of prostatitis. Nanoparticles combined with thermosensitive gels have been developed and evaluated in animal models. Specifically, emodin-loaded nanoparticles incorporated into thermosensitive gels have shown efficacy in the treatment of chronic nonbacterial prostatitis by enabling sustained drug release and prolonged retention of nanoparticles within prostate tissue (6). Furthermore, nanoparticles possess the ability to overcome the blood–prostate barrier, thereby enhancing the accumulation of therapeutic agents, such as antibiotics with poor penetration, at the target site. This targeted accumulation significantly improves treatment efficacy while reducing systemic exposure and adverse effects (75).

14. Recent Advances in Nanotechnology-Based Drug Delivery for Prostatitis and Prostate Disorders

Recent studies have demonstrated the growing potential of nanotechnology-based drug delivery systems for the treatment of prostatitis, chronic pelvic pain syndrome (CPPS), and prostate-related disorders. Yang et al. (2023) formulated dual-responsive nanoparticles

loaded with the glucocorticoid dexamethasone. The authors reported that dexamethasone nanoformulations were effective in the treatment of chronic pelvic pain syndrome and also contributed to the alleviation of depression-like symptoms in mice (74).

Hu et al. (2022) investigated folic acid–modified nanoparticles and reported that *in vivo* and *ex vivo* imaging studies confirmed optimal prostate targeting following tail-vein intravenous administration. The nanoparticles exhibited a particle size range of 180–190 nm, which facilitated enhanced accumulation within prostate tissues (75).

Zheng et al. (2022) developed reactive oxygen species–responsive nanoparticles loaded with cefpodoxime proxetil for the treatment of chronic bacterial prostatitis. These nanoparticles demonstrated the ability to bind to folate receptors, which are highly overexpressed in prostate cells during prostatitis, thereby improving drug targeting and overcoming the poor penetration associated with conventional antibiotic therapy (100).

Mohammad et al. (2024) designed antibody-coupled nanocarriers to enhance the delivery of ciprofloxacin to prostate tissue. This targeted delivery system inhibited cytokine receptors within the prostate, leading to a significant reduction in inflammation. The study highlighted the crucial role of nanocarriers in increasing drug concentration within the prostate gland while promoting site-specific drug delivery (27).

Gao et al. (2023) developed a nano-delivery system consisting of a curcumin–copper complex grafted with hyaluronic acid for the treatment of chronic prostatitis. The formulation exhibited antimicrobial activity due to the combined effects of curcumin and copper. Hyaluronic acid facilitated binding to CD44 receptors, promoting cellular uptake and drug accumulation, thereby enhancing therapeutic efficacy (101).

Almutairy et al. (2025) formulated a nanoemulsion loaded with silibinin (SIL) and cabazitaxel (CBX) for prostate cancer therapy. The nanoemulsion successfully overcame major limitations of these agents, including poor solubility, low bioavailability, and systemic toxicity, demonstrating the potential of nanotechnology in improving therapeutic outcomes (102).

Garcia et al. (2021) developed gold core–shell–based mesoporous silica nanoparticles combined with photothermal therapy for targeted drug release in prostate tissue. In this formulation, mesoporous silica nanoparticles encapsulated the antibiotic levofloxacin.

The authors reported that this nanotherapeutic approach significantly enhanced antimicrobial efficacy in the treatment of chronic prostatitis (103).

Liu et al. (2025) developed quercetin–copper nanoparticles grafted with chondroitin sulfate to improve aqueous solubility by approximately 30-fold. This formulation was applied in the treatment of bacterial prostatitis and demonstrated combined antimicrobial and antioxidant activities, highlighting its therapeutic potential (104).

Cheng et al. (2019) formulated nanoparticles carrying the autoantigen peptide T2, which significantly reduced disease symptoms in a mouse model of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), suggesting an immunomodulatory therapeutic approach (105).

Li et al. (2024) developed a luteolin–copper complex grafted with hyaluronic acid. Luteolin, a flavonoid with known antibacterial and anti-inflammatory properties, suffers from poor water solubility and low structural stability. These limitations were successfully addressed through nanoformulation, and the authors concluded that the developed system was effective for the treatment of bacterial prostatitis (106).

Chen et al. (2025) formulated poly(ferulic acid) nanoparticles loaded with celecoxib for the treatment of nonbacterial chronic prostatitis. Folic acid was incorporated as a targeting ligand due to the overexpression of folate receptors in prostatitis conditions. The formulation demonstrated 39% drug encapsulation efficiency, good stability, excellent biocompatibility, controlled drug release, and significant anti-inflammatory effects (107).

Yoon et al. (2011) conducted experimental studies on forty rats to evaluate the anti-inflammatory and antimicrobial effects of catechin and nanocatechin. The animals were randomly divided into four groups: control, ciprofloxacin, catechin, and nanocatechin. Catechin, a green tea extract, is known for its anti-inflammatory and antimicrobial properties. Through nanotechnology, catechin was coated with hydroxypropyl methylcellulose to produce nanocatechin, which reduced degradation during digestion and enhanced intestinal absorption. The study concluded that nanocatechin exhibited superior antimicrobial and anti-inflammatory activity against chronic bacterial prostatitis compared to conventional catechin due to its enhanced bioavailability (108).

Ncapayi et al. (2021) focused on the diagnostic applications of nanotechnology, particularly near-infrared (NIR) fluorescent quantum dots. These quantum dots demonstrated potential in the differentiation and detection of prostate cancer and prostatitis, highlighting their importance in early and accurate diagnosis of prostate-related disorders (92).

Peng et al. (2021) developed extracellular vesicles derived from mesenchymal stem cells obtained from human induced pluripotent stem cells. These vesicles exhibited significant therapeutic activity against chronic prostatitis, as confirmed through in vivo studies conducted in rat models, suggesting a promising regenerative and immunomodulatory treatment strategy (109).

Mahgoub et al. (2025) formulated a nanoemulsion containing beta-sitosterol and vitamin D3 designed to target the prostate gland effectively. The formulation demonstrated synergistic anticancer activity against prostate cancer cells along with antibacterial effects. This dual-action nanoemulsion offers a potential therapeutic approach for managing benign prostatic hyperplasia and prostate cancer while minimizing systemic side effects (110).

15. Conclusion

Prostatitis is the third most common and one of the most complex disorders affecting the prostate gland. A comprehensive understanding of its etiology, pathophysiology, and epidemiology is essential for effective disease management. However, conventional therapeutic approaches often fail to achieve optimal outcomes due to poor drug penetration, long treatment duration, repeated therapy, adverse effects, and inadequate patient compliance. Nanotechnology-based drug delivery systems present a promising alternative to overcome these limitations. Nanoformulations enhance drug solubility, stability, absorption, and targeted delivery to prostate tissue. Additionally, they improve drug penetration, enable sustained drug release, and reduce systemic side effects. Numerous experimental studies have demonstrated encouraging results, indicating that nanotechnology holds significant potential to improve therapeutic outcomes in prostatitis.

16. Conflict of interest:

The authors declare that there is no conflict of interest

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