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Light-controlled calcium signalling in prostate cancer and benign prostatic hyperplasia

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Abstract

Background: Identifying ways to reduce the burden of prostate cancer (Pca) or benign prostatic hyperplasia (BPH) is a top research priority. It is a typical entanglement seen in men which is portrayed by trouble in micturition. It stands as a significant problem in our society. Different molecular biomarker has high potential to treat Pca or BPH but also causes serious side effects during treatment.

Main text: The role of calcium signalling in the alteration of different biomarkers of Pca or BPH is important. Therefore, the photoswitch drugs may hold the potential to rebalance the altered calcium signaling cascade and the biomarker levels. Thereby play a significant role in the management of Pca and BPH. Online literature searches such as PubMed, Web of Science, Scopus, and Google Scholar were carried out. The search terms used for this review were photo-pharmacology, photo-switch drug, photodynamic therapy, calcium signalling, etc. Present treatment of Pca or BPH shows absence of selectivity and explicitness which may additionally result in side effects. The new condition of the calcium flagging may offer promising outcomes in restoring the present issues related with prostate malignancy and BPH treatment.

Conclusion: The light-switching calcium channel blockers aim to solve this issue by incorporating photo-switchable calcium channel blockers that may control the signalling pathway related to proliferation and metastasis in prostate cancer without any side effects.

Background

Chronic inflammatory conditions in benign prostatic hyperplasia (BPH) result in an altered prostatic immune system characterized by tissue damage caused by different inflammatory mediators through multiple molecular pathways [1, 2]. This condition is commonly associated with elderly patients [1]. Studies have also suggested that prostate cancer is influenced by the same factor. Multiple epidemiological and molecular studies have also concluded that patients with BPH live at a higher risk of developing prostate cancer at the later stages of their lives [3, 4]. So, there is a need of common therapeutic

approaches to their management [5]. Several prognostic markers are identified that can be further explored to halt the molecular pathways that are involved in the progression of chronic inflammation [6, 7]. Intracellular calcium signalling plays an important role in the regulation of gene expression [8, 9]. As a result, identification of calcium coupling receptors using molecular targets against Pca or BPH can be potentially useful in the management of these complications [7, 10]. So, it revealed that angiogenesis, metastasis, and tumor initiation and progression are regulated by intracellular Ca^{2+} homeostasis which is altered in cancer cells [11]. Application of chemotherapy to control these conditions comes with severe side effects affecting the cancer and normal cells simultaneously [12, 13]. So, the localized place is the promising way to treat cancer cells and prevent cell

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proliferation by targeting Ca^{2+} signalling [14, 15]. The mechanisms behind Ca^{2+} channels/transporters or Ca^{2+} ATPase pumps are still unclear [16, 17]. In this aspect, the current review is designed to study the role of cellular mechanisms underlying the regulation of Ca^{2+} signalling in proliferated cells in Pca or BPH. This review also focuses on the novel therapeutic evidence to control the proliferation through Ca^{2+} channels and intercellular communication in the tissue system [18–20]. Voltage-gated calcium channel $Ca_v3.2$ can be a potential differential biomarker for survival and treatment response in breast cancer subtypes [21]. Similarly, store-operated calcium entry (SOCE) plays a role in migration and proliferation [22]. Thus, we discuss about the role of different biomarkers linked with calcium signalling cascade and their use as a single therapeutic target and as a light switch in effective management of Pca or BPH.

Objective
The mechanism of a complex interplay of the inactivation and activation of extracellular and intracellular calcium oscillations on the molecular level in the context of BPH has not been fully elucidated and can be modified [23]. The experimental possibility of light-responsive biologically active materials in the therapy are a new domain, but it is difficult to give a rational therapeutic regimen. Most importantly, it requires precise manipulation of the area, dosage time, and concentration of the active form of drug molecules [24]. The caged compounds which are irreversibly activated with light can be modulated as light-sensitive compounds that can be switched between the active and inactive states [25, 26]. An attempt is made to address the fundamental use of photoswitches and their usefulness in pharmacological applications such as in Pca or BPH [27]. Researchers have studied the calcium oscillation in cells with the help of a photochromic molecule that switched between high and low affinity states. Ca^{2+} is the most diverse secondary messenger molecule in the cell [28, 29], and its levels are responsible for many physiological functions including muscle contraction and various signalling pathways [30, 31]. Similarly, several mechanisms are proposed that can regulate Ca^{2+} homeostasis [32, 33]. The uncontrolled cell proliferation cause disruptions in Ca^{2+} handling, and that can contribute to the pathogenesis of many diseases [34–36]. There are various inflammatory mediators such as CD19 or CD20, B lymphocytes (10–15%), macrophages (15%), and CD3$^+$ T lymphocytes (70–80%, mostly CD4 are implicated in cases of Pca or BPH). Chronic inflammation occurs in the prostate tissue due to the involvement of multiple factors including the autoimmune responses [4]. The present review briefly summarizes the latest advances in the development of photo-drug tools that are associated with Ca^{2+} signalling and their applications in remote cell modulation. Our goal is to provide a general approach to choose biomarkers linked with Pca or BPH for optical control of Ca^{2+} signalling, thereby resulting in better spatiotemporal control of drug action via advances in photoswitch technologies. Ultimately, we can expect an enhanced safety and efficacy profile of the photopharmaceutical agents that have lesser side effects compared to other conventional treatment options [37, 38].

Photodynamic therapy for benign prostatic hyperplasia
Boch et al. has used lemuteporfin as a photosensitizer to kill the cells after its activation at nanomolar concentration. This helped in transurethral photodynamic treatment and remedial consequences for lower urinary tract side effects [39, 40]. The outcome additionally indicates lemuteporfin photodynamic therapy is a novel treatment approach for men with lower urinary tract symptoms (LUTS) due to BPH [41]. In many cases, laser innovation has been utilized to treat BPH condition. However, this methodology plays an important role in minimizing the BPH side effect as transurethral resection of the prostate. Although the laser innovation offers the critical advantages to BPH patients, further chronic studies warranted to confirm the safety [42].

Promising targets of Pca (prostate cancer) and benign prostatic hyperplasia associated with Ca^{2+} signalling
Androgen receptor
In the cytoplasm, androgen receptor binds with active form dihydrotestosterone (DHT) and is responsible for the growth of prostate by encoded proteins. Androgen receptor is a major factor for prostate enlargement, due to the imbalance between cell death and proliferation; it is used to treat BPH/LUTS. In the current treatment approaches, the dynamic function of testosterone is hindered by utilizing 5α-reductase inhibitors, such as finasteride. Drugs like finasteride inhibit the conversion of testosterone to DHT [43–45]. The nuclear androgen receptor and its proliferation is influenced by androgen-induced calcium signalling pathways leading to disturbances in androgen receptor signalling via T-type Ca^{2+} channels. This promotes the prostate cell growth and significant morphological and biochemical changes [46–48]. Cifuentes et.al revealed that calmodulin (CaM) has a major role in proliferation in prostate cells so there is a need of CaM antagonist for blocking the AR activity in a wide variety of proliferated cells [49]. For using the photoswitch drug, it has been studied that AR has a role to increase cAMP which is potentiated by glucose-stimulated insulin secretion (GSIS) [50] via the mobilization of intracellular $Ca^{(2+)}$. However, the

objective of targeting allosteric sites is troublesome. In this way, they have utilized azobenzene determined prearranged positive allosteric modulators (PAMs) structured and tried against the glucagon-like peptide-1 receptor (GLP-1R) movement offering better management [51]. Simultaneously, there is a need for specific switches of calcium channels that are being regulated by androgen receptor which directly inhibits the proliferation of enlarged prostate cells as per the requirement.

Vitamin D receptor (VDR)

Increasing the expression of Ca^{2+} pumps is maintained by low Ca^{2+} levels to maintain vitamin D levels [52]. Calcium channels are regulated by VDR agonist which has immunomodulatory, anti-proliferative, antibacterial, and anti-inflammatory properties and could be an option to treat BPH. Vitamin D increases VDR protein level in all the tissues including prostate. Vitamin D metabolites inhibit the growth of normal and malignant prostate cells and probably act via ligand-dependent stabilization. Apoptosis, differentiation, and cell cycle are directly linked with VDR response elements [53, 54]. Cyclooxygenase-2 articulation and prostaglandin E2 generation in BPH stromal cells additionally produce an inhibitory impact on the RhoA/ROCK pathway. Vitamin D action at a dose of 6000 IU/day has shown to diminish the increased prostate volume in BPH patients [55–58]. 1,25-Dihydroxyvitamin D3 stimulation has also linked with calcium-associated TRPV6 in proliferation, apoptosis, and resistance providing synergistic effect [59–62]. Lehen'kyi et al. referenced in his article that TRPV6 is firmly controlled by intracellular Ca^{2+} fixations ($[Ca^{2+}]_i$) and leads highly calcium-selective currents in prostate cells [63–66]. This allows Ca^{2+} entry via TRPV6 and thereby promotes antiapoptotic pathways in cancer cells [66]. Considering this, all VDR can be a potential target in drug discovery of new photoswitch drugs.

Alpha (α)-1 receptors

Due to the rich source of α1 receptors in the prostate gland [67], presently, alpha-1 blocker is utilized for treating BPH conditions by bladder obstruction [68] and interrupts motor sympathetic nerve supply to prostate. Alpha-1 adrenoceptors in human prostatic muscle provide a rationale for using α-blockers [69]. Alpha adrenoceptor subtypes interact with G proteins of the Gq/11 family and activate phosphoinositide turnover and calcium signalling, although with different levels of effectiveness [70]. α1 blockers loosen up the prostate smooth muscle and decline urethral obstruction, at last prompting help in LUTS which is a noteworthy job in the pharmacotherapeutic management of BPH [69]. We talk about the prospects for the particular conveyance of light to these organs and the particular prerequisites for

light-active drugs [71]. Photoswitchable drugs are in the pipeline and identified with ionotropic glutamate receptors; kinate receptors; AMPA receptors; metabotropic glutamate receptors, adrenergic receptors, muscarinic acetylcholine receptors, dopamine, histamine, and serotonin receptors; calcium and potassium channels; and a number of transporters [72]. Thebault et al. revealed that alpha-1 adrenoceptors are directly regulating the activation of TRP-mediated Ca^{2+} entry, with all the members of the signalling cascade of α1-adrenoceptors that serve as targets for therapeutic interventions of cell proliferation which is ultimately responsible for the growth of prostate cancer cells [67, 73].

β-adrenoceptor agonists

Pharmacological apparatuses grew further endeavors to order prostatic β-adrenoceptors. Human stromal cells and epithelial cells appeared to raise adenylate cyclase by β-adrenoceptor [74]. Sharma et al. gave the information about coupling the beta-3 adrenoceptor to K_{ATP} and BK_{Ca} channels initiating the tocolytic impacts, which indicates the powerful trigger of β3-adrenoceptors in buffalo myometrium and intervening their impact through ascent in c-AMP [30]. Similarly, β3-adrenoceptor mRNA was recognized in human prostatic tissue. Haynes et al. studies show that activation on beta-3 and beta-1 adrenoceptor activation is decreasing the α1-adrenoceptor-mediated contractions [75, 76]. In some clinical studies, it is mentioned that the use of beta blockers by the patient increases the risk of BPH [77]. The beta-adrenoceptor is a G(s)-protein-coupled receptor which significantly increased cAMP in the smooth muscle cell [78]. In the case of a hypertensive patient who took beta blocker, there is more risk to develop BPH and also potentiate the response of alpha-adrenoceptor which activated the phospholipase C. This ultimately formed inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG), leading to the activation of myosin light-chain (MLC) kinase by calcium-dependent mechanisms and thereby contraction of the prostatic smooth muscle [75, 76, 79]. For treating the hypertensive patient, we have to be more focused on the development and/or use of beta blockers as photoswitches. This caution is important to avoid the activation of α1-adrenoceptor-mediated contractions in the prostate.

C-X-C motif chemokine ligand-5 (CXCL5)

Studies have demonstrated that the relocation and intrusion of prostate disease cells were significantly influenced by the CXC-type chemokines CXC-12 and CXC-5, in vitro and in vivo [80], *while the CXCL5 enacted comparative pathways related to prostate epithelial cell expansion or attack* [81, 82]. CXCL5 is involved in carcinogenesis and cancer progression has emerged, and it

could be used for future role in both diagnosis and cancer therapy [83, 84]. The fundamental development of CXCL is evoked by calcium signalling. P2X4 antagonist causes inhibition of CXCL5 secretion and is unable to find ways in the absence of extracellular Ca^{2+} [85]. Actuation of both calcium-activated potassium channels and chloride channels and tweak of L-type voltage-sensitive calcium channels is animated by CCR5. This investigation has been led in a focal sensory system so further examination is ought to be prompted in the Pca or BPH [86–88].

Histone deacetylase (HDAC)

Photoswitchable histone deacetylase (HDAC) inhibitors are potential antitumor specialists as reported [89]. The protein articulation levels are increased in HDAC1 and DNA methyltransferases (DNMTase) DNMT1 in prostate cancer [90]. Inhibition of HDAC assumes a noteworthy job in chemotherapy and chemoprevention in androgen-subordinate prostate malignant growth and androgen-autonomous prostate disease cells by utilizing 15 μM sulforaphane (SFN) in 40, 30, and 40% in BPH-1, LnCaP, and PC-3 cells, respectively, which propose a novel way to treat prostate malignancy [91]. Varga et.al contemplate and demonstrate that in the upregulation of HDAC inhibitors, protein articulation of Ca^{2+} pumps in an assortment of breast cancer cell lines uncovered low PMCA4b articulation in the ER-α-positive cells. So, we can say that Ca^{2+} pump levels shape the intracellular Ca^{2+} signals that influence a few downstream flagging pathways which might be valuable to treat BPH or prostate cancer [92]. Due to the depletion of ER calcium stores, the advancement of photoswitchable HDAC inhibitors is assumed to have a major role for HDAC inhibitor development with lesser side effects [93].

Transforming growth factor (TGFβ1)

Major inhibitory medications that are right now being grown basically to treat fibrotic malady are summarized [94]. Given the focal job of TGFβ1 in fibrosis, drugs focusing on TGFβ1 might be useful for the treatment of fibrosis [43]; however, along with the inflammatory cytokine inhibition of IL-10 and TGF-β, it shows significant cure rates after PDT [95]. TGF-beta1 induced intracellular Ca^{2+} signal [96], and it is generally a growth inhibitor of both benign prostatic epithelial cells [97, 98] and prostatic cancer cells [99]. TGF-beta1 treatment brought about abatement in ATP amalgamation and to a depolarization, prompting an arrival of Ca^{2+} from mitochondria and diminished action of the Ca^{2+} pumps. Zemfira et al.'s report demonstrates that TGF-b1 is expanded dimensions of calcium levels inside PC-3U cells. The effect was analyzed as being due to an inhibitory effect of TGF-b1 on the mitochondria of the cells [100].

So, we can say that light-delicate calcium channel blockers, calcium (CaV) channels, play pivotal jobs in the age of activity possibilities and in the synaptic transmission and are practical objectives for photopharmacology. Isomerization of the photoswitch with 380 nm/ 500 nm light abbreviated and stretched, unblocking and obstructing the pore [27, 101]. So, to control the TGFB-1 receptor, we can use the photoregulation procedure by diminishing the prostate growth and malignant growth, with decreasing impacts on another body.

Thromboxane A2

Jafari et al. [102] uncovered in his investigation on prostate malignant growth that NSAIDs give some level of defensive impact against prostate disease, yet further examination is required. Expanded articulation of thromboxane synthase was found in prostate tumors, and tumor cell motility was weakened by inhibitors of thromboxane synthase. This investigation was attempted to explain how tumor motility is directed by TxA_2. Here, we can say that human prostate malignant growth cells express useful receptors for TxA_2 (TP) [103, 104]. Moreover, thromboxane A_2 mediates smooth muscle contraction, and so, this inflammatory biomarker can be used to treat BPH [105]. TXA_2 pathway may be a potential target for PCa prevention/therapy, because it is upregulated in human prostate cancer [104]. The relation between the calcium and thromboxane A_2 is also well studied where cyclooxygenase products of AA, i.e., PGH2 and TXA_2, caused mobilization of intraplatelet calcium [106]. The studies show that the absence of $Ca^{(2+)}$-ATPase inhibitor-sensitive pool is responsible for the formation of TXA_2 in the presence of calcium [107]. Kiefmann demonstrated there is increase in cytosolic calcium in the TXA_2 receptor expression [108]. So, thromboxane A_2 evoked intracellular calcium in vascular smooth muscle cells [109], which indirectly related to prostate enlargement and muscle contraction.

N-methyl-D-aspartate receptor (NMDAr)

The memantine is a foe of NMDAr which hindered the in vitro development of cell lines, at 5 to 20 μg/ml (23 to 92 μM) memantine. Past studies demonstrate that *N*-methyl-D-aspartate (NMDA) receptor levels are utilized to balance for hippocampus-related learning and execution on specific memory undertakings in rodents by androgens. Furthermore, the information likewise gives proof to the articulation and action of NMDAr in prostate malignant growth [110, 111]. NMDA receptors are stimulated by direct depolarization and activated intracellular Ca^{2+} homeostasis and signalling [112]. Laprell et al. synthesized an azobenzene-triazole-glutamate (ATG) which is a diffusible photochromic glutamate analogue used as a photoswitchable agonist and used for

various neurological disorders and monitors the function of the synaptic neuron [113, 114]. Apart from that, it will also exacerbate NMDA-ΔCa^{2+} at the system [112]. So, there is a need for the development of antagonist drugs specific for NMDAR which ultimately controls the Ca^{2+} homeostasis at the site of prostate cells with lower side effects.

Transient receptor potential (TRPM2)

TRPM2 is a prominent role in prostate cancer by showing inhibitory activity while knocking down TRPM2 by small interfering RNA technique. It is a protein located in the nuclei in cancer cells [115]. The core cells containing TRPM2 proteins are situated in the malignancy cell. Oxidative stress is activated by Ca^{2+}-permeable channel. TRPM2 causes the survival and migration of SCC cancer cells. So, it could be a potential target for selective treatment [116], because inhibiting the nuclear ADP ribosylation of the prostate cancer cells affects the intracellular cell which is associated with the plasma lemma of benign prostate epithelial cells [6, 115]. While we know that due to deregulation of TRP channels, the NO availability is decreased in vascular smooth muscle [117]. The prostate cancer cells do not grow when there is a knockdown of the TRPM2 [115]. In the previous literature, novel azobenzene photoswitch were used for the optical control of TRPV1. So, there is a need to develop a strategy to make TRPM2 as one of these compounds which ultimately antagonizes and demonstrates a photoswitchable antagonist and applied in such a way that modulates ion channel activity [118].

TRPM2 testosterone-repressed prostate message-2

Miyake et al. distributed a movement in both in vitro and in vivo techniques which indicates improved chemosensitivity of TRPM2 in human androgen-autonomous prostate malignant growth of PC-3 cells. TRPM-2 concealment is not exacerbated by prostate development in portion subordinate antisense (AS) oligodeoxynucleotides (ODNs) AS ODN#2 in PC-3 cells. Thus, 60 to 80% tumor volumes have been diminished by in vivo organization of antisense (AS) ODN#2 in addition to either paclitaxel or mitoxantrone. These discoveries recommend that TRPM-2 has a potential to treat prostate disease with AS TRPM-2 ODN in addition to chemotherapeutics for patients [119]. TRPM-2 present in any sort of mammalian cells, so it might be valuable to recognize prostate amplification and utilized as a delicate molecular marker. This item was specifically in light of the fact that its union was not recognized in the typical rodent ventral prostate gland [120]. Typical investigations demonstrate that calcium channel antagonists in the initial 62 h of castration creating a dying effect on testosterone-repressed prostate message-2 (TRPM-2)

cells [121]. That ultimately improving the group of Sertoli cells [122]. Henceforth, clusterin (testosterone-repressed prostate message-2) (TRPM-2) has been utilized as a marker for apoptosis in the prostate, mammary organ, and other strong organs, and clusterin articulation in tissues, for example, the prostate and mammary organ, gives off an impression of being bound to the apoptotic pathway [123]. Kalka et al. demonstrate the involvement of clusterin in PDT-mediated cell death [124] which indicates overexpression of clusterin in the A431 cell line and no difference in clusterin was seen in the apoptosis-safe RIF-1 cells [125]. TRPM2 gene is positively regulated in the castration-induced and shows antiapoptotic property in LNcaP prostate cancer cells [126]; upregulation of TRPM2 is inhibited by calcium channel blocker due to activation of intracellular calcium which further activated endonuclease and support apoptotic pathways and delay progressions in Pca or BPH [127]. It is reasoned that TRPM2 has a noteworthy relationship with calcium flagging and could be driving a promising focus to treat Pca or BPH exactly.

Discussion

Here in the review, we discuss the role of calcium-associated biomarkers which could be further useful in the management of Pca or BPH and taken as potential target (Fig. 1) to be controlled by light. Thus, the molecules with anticancer potential with photo-induced calcium signalling and modulation is a new type of treatment to have lesser side effects for the cancer patient and targeted ion channel therapy [128, 129]. Development of light-sensitive Ca^{2+} channel blockers and proteins that are involved in Ca^{2+} signalling [130, 131] and its regulation in Ca^{2+} handling may lead to developing novel therapeutics for cancer [132–134]. All ligand-gated receptors such as acetylcholine, glutamate, and GABA receptors have been designed as photoswitchable regulators [135–137]. The photoswitches are also used to investigate neuronal circuit in all optical instruments. Thus, the review discusses the design and the properties and the application of these photoswitches, which can be useful for future perspectives [138–140]. In the previous study, diltiazem (DIL) (non-competitive) and verapamil (VRP) (competitive) inhibitor used as a calcium channel blocker. These drugs cause inhibitory effects of methotrexate (MTX) accumulation through VRP and DIL [141]. Therefore, calcium channel blockers (CCBs) would be used to stop the cancer progression by a complex mechanism in apoptosis [142] since the past examinations recommended that low Ca^{2+} levels forestall cation-mediated charge balance of DNA, subsequent in the incitement of apoptosis. It promotes apoptosis in both transformed and non-transformed cell models and produces effects of CCBs in Ca^{2+}-dependent and Ca^{2+}-
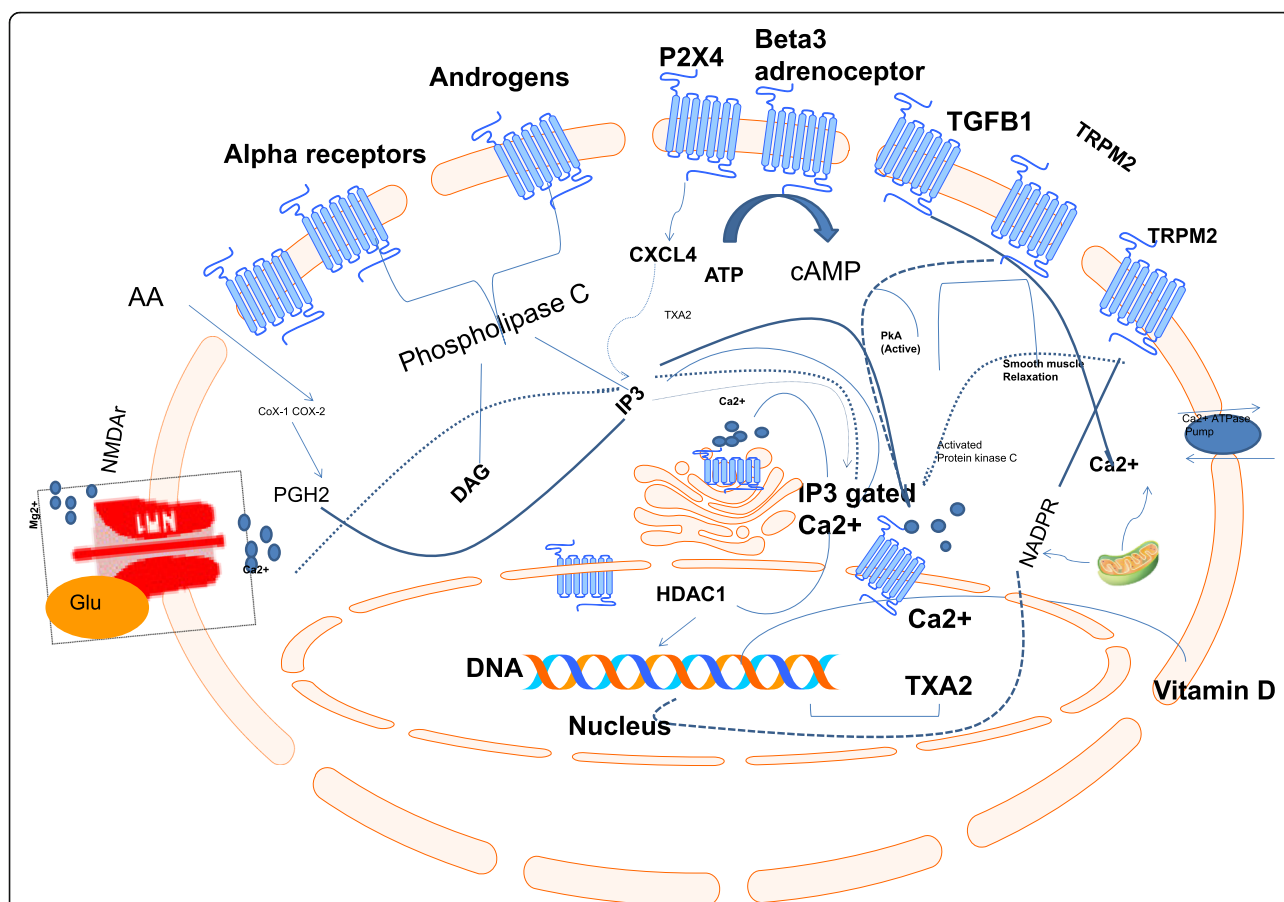
Fig. 1 Regulation of downstream signalling cascade of different biomarkers responsible for prostate cancer or benign prostatic hyperplasia. Ca^{2+} calcium channel; TRPM2 transient receptor potential cation channel, subfamily M, member 2; cAMP cyclin adenine monophosphate; TRP transient receptor potential; TRPV2 transient receptor potential cation channel, subfamily V, member 2; CXCL5 C-X-C motif chemokine ligand-5; HDAC histone deacetylase; DNMTase DNA methyltransferases; TGFβ1 transforming growth factor; CXCL5 C-X-C motif chemokine ligand-5; DAG diacylglycerol; IP_3 inositol-1,4,5-trisphosphate; VDR vitamin D receptor. Significant stimulation (blue arrow). Partial stimulation (dashed blue arrow)

independent [143–145], so it might be possible that androgen-dependent tissues will be treated by calcium channel agonists for using simultaneous treatment [121]. Mazo et al. clarified in his examinations in regard to the treatment of amiable prostatic hypertrophy (BPH), with helium-neon low-dimension laser treatment (LLLT) in a patient populace of 167. Twelve to 15 day by day sessions of 20 min was required, with dosages of 19.0~20.8 J per session. It would be discovered that every treated patient was demonstrated great reaction in prostatic issues. The creator recommends that the positive outcomes ought to energize such a twofold visually impaired preliminary to be set up and that helium-neon low-dimension laser treatment (LLLT) connected transrectally is a legitimate option or adjunctive treatment for the negligibly obtrusive and easy treatment of prostatic issues [146]. This result showed photodynamic therapy indirectly linked with photopharmacology in which we could say that photo-drug therapy consists in treating a patient with a light-sensitive prodrug that is inactivated

in the dark after the compound has distributed in the patient and the tumor; light irradiation on the tumor area insures that the light-induced toxicity of the compound is only released at the place of irradiation, i.e., in the tumor or prostate enlargement [95, 147]. So, the anticancer role with photo-induced calcium signalling and modulation is a new type of treatment to reach lower side effects for the BPH or prostate cancer [148] patient and targeted photo-modulate ion channel therapy [37]. The development of light-sensitive Ca^{2+} channel blockers and proteins that are involved in Ca^{2+} signalling and its deficiencies in Ca^{2+} handling may lead to the development of novel therapeutics for cancer [37, 149]. Azobenzene photo-responsive components can be introduced on yielding optical power over the cell capacity, and synapse discharge regulating the channel movement by photo-responsive elements weakens the development of diseased cells, both in vitro and in vivo, which opens another path for pharmaceutical research [135, 150]. When we design the photoswitch, there will be a

different scheme for different photoswitches, and it can be prepared by using proteins, drugs, and fatty acids [151]. To prepare the photo-switch using drug and light-responsive materials, we decided which drug (structure is important here) and photo-switch we have to take and then only we can derive its synthetic route [152]. In the articles, they have used different photo-switches for different proteins and fatty acids [153, 154]. In this case, we can modify the prostate cancer drugs or BPH drugs or fatty acids which act as a biomarker in the photo-switchable form, via targeting the biomarkers that associated with calcium channels, so that it effects in helping and making changes in the localized desired Ca^{2+} channels to inhibit the proliferation or the metastasis stage of cancer [155, 156]. Velema et al. delighted in the antimicrobial action of ciprofloxacin photoswitch conjugates and converted it into spirofloxacin, which fundamentally hindered the development rate of microorganisms within the sight of 365 nm, astoundingly, for one of them has a 50-overlap increment in movement contrasted with the first ciprofloxacin. Their antimicrobial action could be constrained by light [157]. Similarly, Hodson et al. showed in his study that light-sensitive drugs could be administered in the form of a pill or activated by irradiating a patch of skin with a blue LED (light-emitting diode). When the light is switched off, the drug flips back into the inactive form, because the active agent is released only where it is required and it gives us a controlled-release form which prevents from hypoglycemic activity [158]. It shows that with the use of light, we can limit the side effects when used to treat Pca or BPH disorder [151]. In other words, azobenzene-derived drugs which demand UV light to activate have cytotoxic properties. To overcome this situation, we have to investigate the concentration range of UV range, which helps to shift the wavelength of activation towards red light in the therapeutic window [159].

Conclusion

The photopharmacology focuses on the tumor or cell multiplication to prevent the metastasis in Pca or BPH. Now the inquiry is emerging why we have to focus on the calcium movement? In light of the fact that despite the side effects, there are biomarkers that cause the cell expansion with the help of calcium stores which eventually give the critical and synergistic advantages. So, there is a need to have focused and balanced medication identified as photoswitches, which can limit the symptoms and target just the abnormal proliferated cells.

Abbreviations
LED: Light emitting diode; VRP: Verapamil; GABA: Gamma-aminobutyric acid; MTX: Methotrexate; DIL: Diltiazem; CCBs: Calcium-channel blockers; LLLT: Low-level laser therapy; TRPM2: Transient receptor potential cation channel, subfamily M, member 2; TRP: Transient receptor potential; SCC: Squamous cell carcinoma; TRPV2: Transient receptor potential cation channel, subfamily V, member 2; ODNs: Oligodeoxynucleotides; AS: Antisense; CXCL5: C-X-C motif chemokine ligand-5; HDAC: Histone deacetylase; DNMTase: DNA methyltransferases; TGFβ1: Transforming growth factor; SFN: Sulforaphane; PDT: Photodynamic therapy; LUTS: Lower urinary tract symptoms; SOCE: Store-operated calcium entry; CXCL5: C-X-C motif chemokine ligand-5; DAG: Diacylglycerol; MLC: Myosin light chain; IP$_3$: Inositol-1,4,5-trisphosphate; AMPA: α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; VDR: Vitamin D receptor; DHT: Dihydrotestosterone; CaM: Calmodulin; cAMP: Cyclic adenosine monophosphate; GSIS: Glucose-stimulated insulin secretion; PAMs: Positive allosteric modulators; GLP-1R: Glucagon-like peptide-1 receptor; DHT: Dihydrotestosterone

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