REVIEW PAPER

Propranolol Hydrochloride as a Repurposed β-Blocker in Cancer Therapy: Mechanisms, Evidence, and Clinical Perspectives

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Abstract
Propranolol Hydrochloride, a non-selective β-adrenergic receptor antagonist originally developed for cardiovascular disorders, has attracted growing interest as a repurposed therapeutic candidate in oncology. Increasing experimental and translational evidence indicates that β-adrenergic signaling plays a pivotal role in tumor progression by linking chronic sympathetic nervous system activation to molecular pathways governing proliferation, angiogenesis, immune evasion, invasion, and metastatic spread. By competitively inhibiting β1- and β2-adrenergic receptors, propranolol interferes with catecholamine-mediated cAMP–PKA and EPAC signaling cascades, thereby modulating transcriptional programs associated with VEGF expression, matrix metalloproteinase activation, inflammatory cytokine production, epithelial–mesenchymal transition, and stress-induced immune suppression. Preclinical investigations across multiple tumor models demonstrate that propranolol can attenuate tumor growth, suppress angiogenesis, reduce metastatic colonization, and enhance anti-tumor immune responses. Importantly, its anti-cancer activity appears most pronounced in stress-responsive and highly vascular tumors, and in the perioperative setting where adrenergic surges may facilitate micrometastatic dissemination. Propranolol has also shown synergistic interactions with conventional chemotherapeutics, targeted agents, radiotherapy, and immune checkpoint blockade, supporting its development primarily as a co-adjuvant rather than a standalone cytotoxic therapy. The extensive clinical experience, affordability, and mechanistic plausibility of Propranolol Hydrochloride represents a compelling candidature for oncologic repurposing. Future directions should integrate biomarker-guided trial designs, combination regimens, advanced tumor-targeted delivery systems, and systems-biology or artificial intelligence-based repurposing pipelines to refine therapeutic positioning. Collectively, current mechanistic, preclinical, and emerging clinical data justify rigorous evaluation of Propranolol as a multi-pathway modulator in contemporary cancer therapy.

Key Words: Propranolol Hydrochloride, Cancer, Drug repurposing, β-Blocker
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1. Introduction

Cancer history begins with Paleopathological findings which suggest that cancer is not solely a modern disease; evidence of malignant tumors such as osteosarcoma has been identified in early hominin fossils from South Africa, indicating that neoplastic disorders have existed for nearly two million years[1]. Similarly, pathological examinations of Egyptian mummies dating to approximately 1500 BC have revealed lesions consistent with malignancy, underscoring the long-standing presence of this disease in human history[2]. The terminology associated with cancer also reflects its historical evolution. The word *"cancer,"* introduced by Hippocrates, originates from the Greek term *karkinos*, meaning crab, a reference to the crab-like extensions of malignant tumors infiltrating surrounding tissues. Later, Roman physicians adopted the term *"oncos,"* meaning swelling, which eventually gave rise to the modern discipline of oncology[3]. In earlier centuries, therapeutic interventions were rudimentary and largely empirical, often limited to herbal remedies or the application of topical preparations following minor incisions. A more systematic understanding of human anatomy and tumor biology began to emerge during the Renaissance, and the advent of anesthesia in the nineteenth century marked a turning point, enabling more extensive and deliberate surgical interventions[4].

Cancer is a complex and multifactorial disease characterized by uncontrolled cellular proliferation driven by cumulative genetic and epigenetic alterations. These alterations include mutations in oncogenes, inactivation of tumor suppressor genes, defects in DNA repair pathways, and dysregulation of key signaling

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networks that govern cell cycle progression, apoptosis, and differentiation [5, 6].

Despite substantial progress in biomedical science, cancer remains a leading cause of morbidity and mortality worldwide. The rising global burden of cancer, along with the toxicity and long-term adverse effects associated with many treatments, emphasizes the pressing need for safer and more personalized therapeutic strategies[8]. While innovative modalities such as immunotherapy and gene-based approaches have expanded the therapeutic landscape[9], conventional treatments—namely surgery, radiotherapy, chemotherapy, and hormonal therapy—continue to form the backbone of clinical oncology due to their established efficacy, accessibility, and comparatively lower cost[10].

Current management of cancer depends largely on surgery, chemotherapy, radiotherapy, or a combination of these modalities, tailored according to tumor type and stage[10]. For solid tumors, surgical resection remains the cornerstone of curative treatment[11], while chemotherapy and radiation therapy are widely used either as primary treatments or as adjuvant approaches[12]. As shown in this Radial timeline demonstration of the evolution of breast cancer therapy, the concentric rings represent chronological progression from early interventions at the center to modern targeted and combination strategies at the periphery. Four color-coded arms depict major therapeutic modalities: **Surgery (blue)** progressing from cauterization and primitive procedures to breast-conserving and robotic surgery; **Radiation therapy (purple)** advancing from early X-ray therapy to proton therapy, CBCT guidance, and IGRT/SBRT; **Chemotherapy (orange)** evolving from the mustine era to targeted therapy, immunotherapy, and CDK4/6 inhibitors; and **Hormonal therapy (green)** developing from oophorectomy and synthetic hormones to tamoxifen, aromatase inhibitors, LHRH agonists, and SERDs. This radial representation highlights the parallel and progressive refinement of multimodal breast cancer treatment strategies over time.

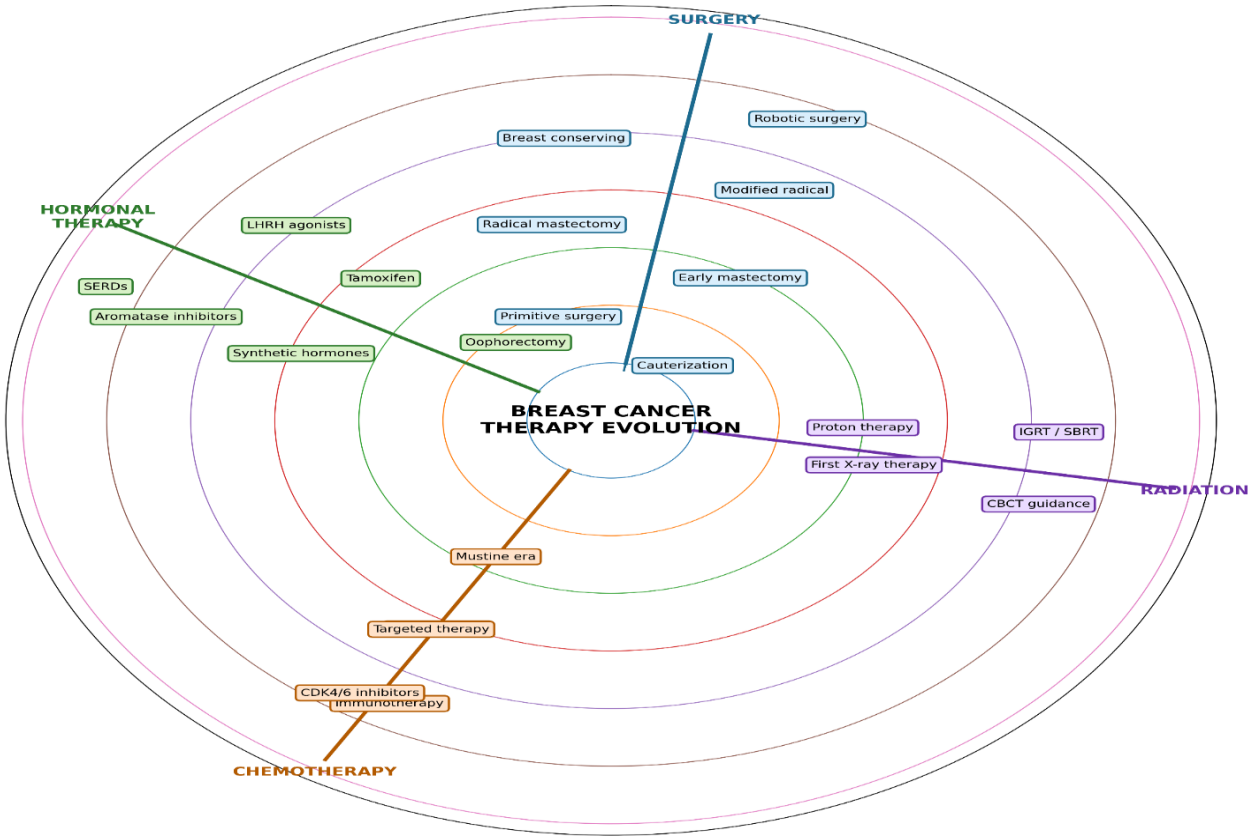

Figure 1: Radial timeline illustrating the evolution of breast cancer therapy.

Although these strategies have significantly improved survival outcomes, they are not without limitations. Radiotherapy, for instance, can induce collateral DNA damage in adjacent normal tissues, increasing the long-term risk of secondary malignancies[13]. Surgical success, on the other hand, depends heavily on early detection, tumor accessibility, institutional infrastructure, and surgical expertise[14]. Chemotherapy marked a major turning point in oncology; however, prolonged exposure to cytotoxic or targeted agents may inadvertently promote adaptive tumor responses, including metabolic reprogramming, enhanced metastatic potential, emergence of drug resistance, and enrichment of cancer stem cell populations[15–17]. Collectively, these concerns underscore the ongoing need for therapeutic strategies that are both biologically effective and clinically safer.

Conventional drug development is a lengthy and resource-intensive process. It typically begins with extensive preclinical evaluation in cell lines and animal models to assess efficacy, toxicity, pharmacokinetics, and pharmacodynamics[18]. Only after satisfactory preclinical results does a compound advance to phased clinical trials—Phase I to determine safety and dosage, Phase II to assess preliminary efficacy, and Phase III to confirm therapeutic benefit in larger populations[19]. This entire process often spans more than a decade and requires enormous financial investment, frequently exceeding billions of dollars[20]. Despite such efforts, only a small fraction of candidate molecules successfully progress to clinical approval[21]. The high attrition rate, combined with escalating costs, has prompted researchers to explore alternative and more efficient strategies for therapeutic innovation[22]. Drug repurposing—also referred to as drug repositioning—has emerged as one such strategy[23]. This approach involves identifying new therapeutic indications for drugs that are already approved or have well-characterized safety profiles[24]. Because these agents have undergone prior toxicological and pharmacokinetic evaluation, their clinical translation can be substantially accelerated compared with novel chemical entities[25]. In oncology, drug repurposing has gained considerable attention as a pragmatic and economically viable pathway to expand treatment options[26]. Several notable examples illustrate its potential. Alkylating agents originally derived from nitrogen mustard compounds evolved into chemotherapeutic agents for hematological malignancies[27]. Thalidomide, once associated with severe teratogenic effects, was later reintroduced under controlled conditions for the treatment of multiple myeloma and inflammatory disorders[27]. Similarly, arsenic trioxide and all-trans retinoic acid—compounds with distinct historical contexts—have been successfully integrated into the treatment of acute promyelocytic leukemia[28-30]. These cases demonstrate that, when guided by mechanistic insight and rigorous clinical evaluation, previously known compounds can acquire transformative therapeutic value.

In this review, we aim to provide a structured and critical overview of drug repurposing as a strategic avenue in cancer therapy. We first outline the conceptual framework and historical evolution of drug repurposing, followed by a discussion of the current cancer treatment landscape and the evolving understanding of tumor biology, including the expanded hallmarks of cancer that define key therapeutic targets. We then examine the molecular mechanisms by which repurposed agent; Beta Blocker Propranolol HCl exert antitumor effects, with particular attention to their interactions within the tumor microenvironment. Emerging strategies to enhance the efficacy of repurposed drugs, including nanotechnology-based delivery systems, are also discussed. Finally, we address the practical challenges associated with translating repurposed agents from bench to bedside and consider the regulatory, economic, and biological factors that influence their clinical adoption. Through this comprehensive analysis, we highlight the realistic and transformative potential of drug repurposing to deliver more accessible, cost-effective, and less toxic therapeutic options for patients with cancer.

2. Drug Repurposing and Tumor Biology

Drug repurposing represents a strategic paradigm in modern oncology that seeks to identify new anticancer indications for existing non-oncology drugs with established safety and pharmacological profiles[31]. Unlike conventional drug discovery, which is time-consuming, costly, and burdened by high attrition rates, drug repurposing follows a more efficient translational pathway[32]. It typically involves three key stages: hypothesis generation based on disease biology or clinical observation, validation of therapeutic efficacy using *in vitro* and *in vivo* models, and progression to phase II clinical trials once sufficient safety data are available[33]. Historically, repurposing efforts were often driven by serendipitous clinical observations or mechanistic overlap between disease pathways[34]. However, recent advances in cancer biology, systems medicine, and data science have transformed drug repurposing into a rational, hypothesis-driven discipline with strong translational relevance[35,36]. Contemporary drug repurposing strategies rely on an integrated combination of experimental and computational approaches[37]. Experimentally, advanced biological models such as patient-derived organoids and tumoroids have emerged as powerful platforms for screening repurposed drugs[38]. These three-dimensional systems faithfully recapitulate tumor architecture, genetic heterogeneity, histopathology, and therapeutic responses observed in patients, thereby offering superior predictive value compared to conventional cell lines[39]. In parallel, phenotypic screening approaches enable the identification of drugs based on functional outcomes—such as inhibition of proliferation, invasion, angiogenesis, or survival—without requiring prior knowledge of specific drug–target interactions[40]. This function-first strategy has proven particularly valuable in uncovering unexpected anticancer properties of approved drugs and in reducing early-stage clinical failure[41]. Computational methodologies further strengthen drug repurposing pipelines by enabling large-scale, data-driven candidate identification[42]. Advances in omics technologies, network biology, molecular docking, transcriptional signature matching, and machine learning have enabled researchers to systematically align drug-induced molecular signatures with cancer-specific disease profiles[43,44]. These approaches facilitate the identification of drugs capable of modulating oncogenic signaling pathways, tumor metabolism, immune evasion, angiogenesis, and DNA damage responses[45]. Importantly, computational predictions are increasingly validated through experimental models, creating a synergistic loop that accelerates discovery while reducing cost and risk[46]. Such integrative strategies are particularly well suited for targeting the complex and adaptive nature of cancer[47]. A defining strength of drug repurposing lies in its ability to target multiple hallmarks of cancer and

components of the tumor microenvironment (TME) simultaneously[48]. Repurposed drugs have been shown to interfere with proliferative signaling, induce regulated cell death, reprogram tumor metabolism, restore antitumor immunity, suppress angiogenesis, inhibit invasion and metastasis, modulate epigenetic regulation, reshape the microbiome, and influence tumor-associated neural signaling[49,50]. This central cluster sketch [Fig. 2] demonstrates the tumor microenvironment, with dashed radial connections linking to repurposed drugs positioned circumferentially. Each compound is associated with a specific cancer hallmark or microenvironmental process: metformin (phenotypic plasticity), oleanolic acid (immune evasion), celecoxib (tumor-promoting inflammation), genistein (genome instability and mutation), epigallocatechin-3-gallate (replicative immortality), triptolide/tanshinone IIA (resistance to cell death), mebendazole (invasion and metastasis), artemisinin (angiogenesis), statins (evasion of growth suppressors), leflunomide/disulfiram (cellular energetics), salidroside (proliferative signaling), baicalein (epigenetic regulation), piperine (microbiome modulation), and resveratrol (cellular senescence). This radial representation highlights how diverse repurposed agents modulate multiple tumor-promoting pathways within the cancer microenvironment.

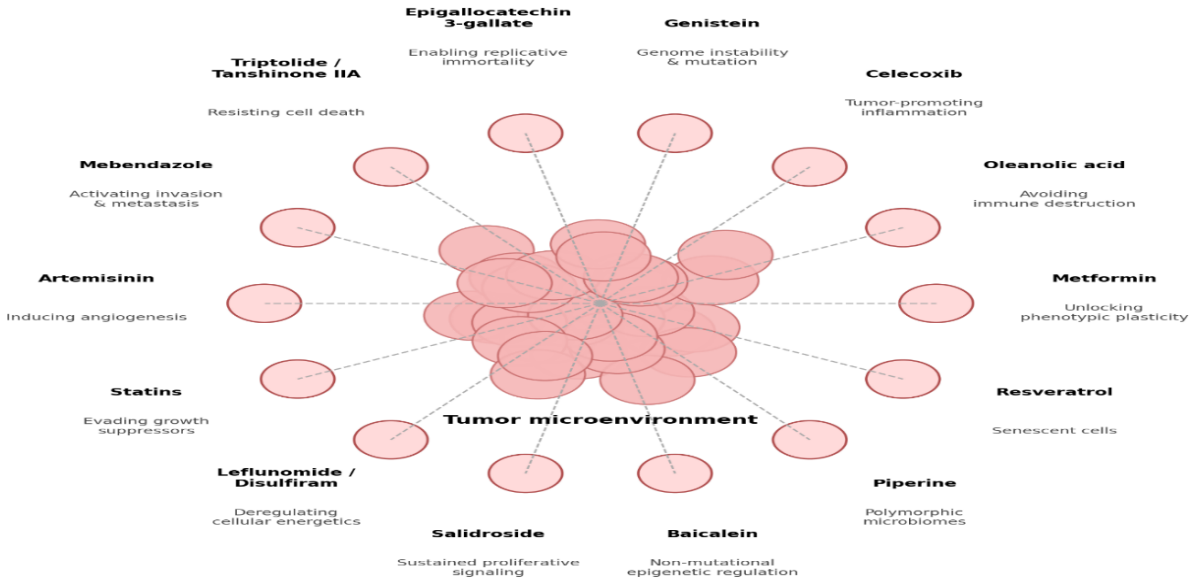

Figure 2: Radial schematic illustrating repurposed therapeutic agents targeting hallmarks of the tumor microenvironment.

Moreover, when combined with nanomaterial-based delivery systems, repurposed drugs can achieve improved bioavailability, enhanced tumor targeting, and reduced systemic toxicity[51,52]. Collectively, these features position drug repurposing as a transformative and pragmatic approach in oncology—one that complements existing therapies, enables combination regimens, and holds strong promise for delivering affordable, effective, and patient-centric cancer treatments[53].

The idea that psychological and behavioral factors influence cancer biology is no longer viewed as purely speculative[54]. Over the past two decades, increasing experimental evidence has linked chronic stress to molecular pathways that actively shape tumor progression[55]. While epidemiological data remain inconsistent regarding stress as a direct cause of cancer initiation, there is far stronger and mechanistically convincing evidence that stress-related neuroendocrine signaling can influence tumor growth, angiogenesis, immune surveillance, and metastatic spread[56,57]. Understanding these biological underpinnings requires careful examination of how the body's stress systems interact with the tumor microenvironment[58]. The stress response is primarily orchestrated by two major neuroendocrine systems: the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis[59]. Activation of these pathways leads to systemic and local release of catecholamines—epinephrine, norepinephrine, and dopamine—as well as glucocorticoids[60]. In acute settings, this response is adaptive and essential for survival, enabling the classical "fight-or-flight" physiological changes such as increased heart rate, blood pressure, and glucose mobilization. However, when stress becomes chronic, this tightly regulated system shifts into a sustained state of activation. Circulating norepinephrine and epinephrine remain persistently elevated, while dopamine levels may become depleted after an initial surge. Prolonged glucocorticoid exposure further alters

immune balance and circadian regulation. This chronic neuroendocrine imbalance can modify local tissue environments in ways that favor tumor-promoting processes[61]. Importantly, stress hormones are not confined to the bloodstream. Many tissues—including the ovary, bone marrow, and lymphoid organs—possess local sympathetic innervation and can accumulate catecholamines at concentrations higher than those observed in plasma[62]. Experimental models have demonstrated that enhanced sympathetic activity increases local catecholamine production, thereby reshaping organ-specific microenvironments[63]. In tumor settings, this neurochemical milieu may promote pro-angiogenic signaling, inflammatory cytokine production, and alterations in stromal and immune cell behavior[64]. Elevated interleukin-6 and other inflammatory mediators frequently accompany stress exposure, suggesting that neuroendocrine activation intersects closely with inflammatory pathways that are already known drivers of tumor progression[65].

Animal models have provided some of the clearest mechanistic insights into these interactions[66]. In orthotopic and transgenic tumor models, exposure to chronic stressors—such as restraint stress, social isolation, surgical stress, or hypothermia—consistently increases circulating catecholamines and glucocorticoids[67]. These changes are associated with enhanced tumor growth, increased angiogenesis, and greater metastatic burden across multiple cancer types[68]. Initially, these effects were attributed mainly to stress-induced suppression of antiviral and antitumor immunity. However, more recent work has revealed that catecholamines can directly stimulate tumor cells through β-adrenergic receptors, activating signaling pathways involved in proliferation, invasion, and survival—triggering effects that are independent of immune modulation[69]. Collectively, these findings support the concept that chronic stress is not merely a psychological burden but a biologically active state capable of reshaping tumor biology through sustained neuroendocrine signaling.

3. Repurposing of Propranolol HCl in Cancer therapy

Propranolol hydrochloride is a non-selective β-adrenergic receptor antagonist that has been widely used in clinical practice for more than five decades[70]. Initially introduced for the management of cardiovascular disorders such as hypertension, angina pectoris, arrhythmias, and myocardial infarction, propranolol marked a major milestone in the development of β-blocker therapy[71]. By competitively inhibiting both β_1- and β_2-adrenergic receptors, it reduces heart rate, myocardial contractility, and sympathetic nervous system activity[72]. Owing to its well-characterized pharmacological profile and long history of clinical use, propranolol remains one of the most extensively studied agents within the β-blocker class[73]. Chemically, propranolol hydrochloride is a lipophilic naphthyl derivative that readily crosses biological membranes, including the blood–brain barrier[74]. This property distinguishes it from several selective β_1-blockers and enables it to exert central as well as peripheral effects[75]. Beyond its cardiovascular indications, propranolol has been prescribed for migraine prophylaxis, essential tremor, hyperthyroidism, anxiety-related disorders, and portal hypertension[76]. Its broad therapeutic applicability reflects the widespread physiological influence of adrenergic signaling in the human body. Importantly, decades of clinical experience have established its safety profile, dosage ranges, and contraindications, which are critical considerations when exploring new therapeutic applications[77]. In recent years, propranolol has attracted attention outside the cardiovascular field due to emerging evidence linking β-adrenergic signaling to cancer progression[78]. Chronic activation of the sympathetic nervous system and sustained catecholamine release have been implicated in promoting angiogenesis, invasion, immune suppression, and metastatic dissemination[79]. As a non-selective β-adrenergic antagonist with central nervous system penetration, propranolol is uniquely positioned to counteract stress-mediated tumor-promoting pathways[80]. This repositioning of propranolol from a cardiovascular agent to a potential oncological co-adjuvant represents a compelling example of drug repurposing grounded in mechanistic understanding of tumor neurobiology[81]. Building upon the growing understanding of stress-mediated tumor biology and the role of β-adrenergic signaling in cancer progression, this review focuses on the emerging repositioning of Propranolol Hydrochloride as a rational therapeutic strategy in oncology. Rather than considering Propranolol solely as a cardiovascular agent, we examine its potential to disrupt stress-driven neuroendocrine pathways that influence tumor growth, angiogenesis, metastasis, immune escape, and therapeutic resistance[82]. By integrating insights from behavioral oncology, tumor biology, and pharmacology, this review establishes a mechanistic link between chronic sympathetic activation and targeted β-adrenergic blockade. In this context, propranolol is evaluated not as a primary anticancer cytotoxic drug, but as a co-adjuvant therapy capable of enhancing the effectiveness of conventional and modern oncologic treatments[83]. Particular emphasis is placed on its ability to modulate the tumor microenvironment, attenuate β-adrenergic receptor–mediated signaling cascades such as cAMP–PKA–CREB and NF-κB, and suppress key processes including VEGF-driven angiogenesis, epithelial–mesenchymal transition, inflammatory signaling, and stress-induced immunosuppression[84,85]. Preclinical evidence, retrospective clinical observations, and early-phase translational studies are critically examined to assess both the promise and the limitations of this approach across diverse cancer types[86]. By identifying current knowledge gaps—such as variability in β-adrenergic receptor expression among tumors, lack of standardized dosing strategies in oncology, limited prospective randomized trials, and challenges in patient stratification—this review aims to provide a structured scientific framework for future investigation[87]. We emphasize the need for biomarker-driven clinical trial

design, integration of stress-related biological indicators, and careful evaluation of combination strategies in multimodal therapy[88]. Ultimately, this review seeks to guide the rational incorporation of β-blockade into personalized cancer therapeutics, fostering a more precise and biologically informed application of propranolol in modern oncology[89].

4. Pharmacology of Propranolol Hydrochloride

4.1. Chemical Structure of Propranolol Hydrochloride

Propranolol ($C_{16}H_{21}NO_2$) possesses a well-defined molecular architecture in which a hydrophobic naphthalene ring system is linked to a propanolamine side chain, a structural arrangement that underpins its pharmacological activity[90]. The molecule contains two principal polar functional groups—a secondary alcohol (–OH) and a secondary amine (–NH–)—positioned on the side chain and connected to the aromatic moiety through an ether linkage[91]. This combination of aromatic rigidity and polar functionality gives propranolol a largely planar framework, a feature commonly observed in biologically active molecules[92]. Such planarity favors π-electron delocalization across the aromatic system and can stabilize conformations that are optimal for interaction with biological targets, thereby reducing the energetic cost of receptor binding[93].

The functional groups present in propranolol contribute distinctly to its chemical behavior and biological interactions. The secondary amine acts as both a hydrogen bond donor and a nucleophilic center, enabling strong electrostatic and hydrogen-bonding interactions with receptor sites[94]. The hydroxyl group further enhances hydrogen-bonding capacity and increases the molecule's hydrophilic character[95], while the ether linkage introduces polarity that supports dipole–dipole interactions[96]. Collectively, these features impart amphiphilic properties to propranolol, allowing it to partition efficiently between aqueous environments and lipid membranes[97]. This dual affinity is critical for effective membrane permeability and access to intracellular and central nervous system targets, as well as for stable binding to β-adrenergic receptors[98].

A notable structural feature of propranolol is the presence of a chiral center at the carbon atom bearing the hydroxyl group on the propanolamine side chain[99]. This stereogenic center gives rise to two enantiomers, (R)-propranolol and (S)-propranolol, which differ in their spatial arrangement and, consequently, in their biological behavior[100]. Commercially, propranolol is administered as a racemic mixture containing both enantiomers[101]. Chirality significantly influences physicochemical properties, receptor affinity, and metabolic pathways, and it has been shown that the enantiomers can differ in their pharmacodynamic potency and side-effect profiles[102,103].

From an electrostatic perspective, the chiral carbon plays a central role in shaping the local distribution of electron density within the molecule. Its proximity to the hydroxyl and amine groups creates regions of localized polarity that are essential for intermolecular interactions, including hydrogen bonding and electrostatic attraction at receptor binding sites[104]. This highlights that the chiral center is not merely a stereochemical feature but also a determinant of the molecule's interaction landscape[105]. Although clinical formulations typically do not separate the enantiomers, enantiomer-specific effects remain an important consideration in understanding propranolol's metabolism, efficacy, and safety profile[106].

4.2. Physicochemical Properties of Propranolol Hydrochloride

A defining physicochemical characteristic of propranolol is its marked lipophilicity, which arises from the presence of a bulky aromatic naphthalene ring coupled with an aliphatic side chain[107]. The balance between hydrophobic domains and polar, ionizable functional groups determines how a molecule distributes between aqueous and lipid phases[108]. In the case of propranolol, the reported logP value of approximately 3.5 reflects a strong tendency to partition into lipid environments rather than remaining in water[109]. This property has important pharmacological implications. Although drug absorption occurs in aqueous biological fluids, many pharmacological targets—particularly membrane proteins such as receptors and transporters—are embedded within hydrophobic lipid bilayers[110]. The lipophilic nature of propranolol therefore facilitates efficient interaction with these targets[111]. It also explains the drug's ability to readily cross the blood–brain barrier, which accounts for central nervous system effects such as sedation, vivid dreams, or fatigue observed in some patients[112]. Consistent with this behavior, propranolol exhibits a relatively large volume of distribution (approximately 4 L/kg), reflecting extensive tissue penetration[113].

From an acid–base perspective, propranolol behaves as a weak base due to its secondary amine group[114]. With a pKa of around 9.5, the molecule exists predominantly in its protonated (ionized) form at physiological pH[115]. The proportion of ionized versus non-ionized species varies with environmental pH and significantly influences membrane permeability[116]. The unprotonated form is more lipophilic and diffuses readily across biological membranes, whereas the protonated form is more water-soluble but less permeable[117]. In highly acidic conditions, such as in the stomach, propranolol is largely protonated and therefore crosses lipid membranes less efficiently[118]. As the pH increases in the small intestine and systemic circulation, a greater fraction becomes unprotonated, promoting more effective absorption and tissue distribution[119]. This pH-dependent partitioning influences oral bioavailability, onset of action, and tissue penetration[120]. Experimental studies using biomimetic membrane systems further suggest that both lipophilicity and ionization state govern membrane

interactions, and subtle stereochemical differences between enantiomers may also contribute to differences in membrane affinity and distribution[121,122].

In terms of solubility, propranolol is considered highly soluble under the Biopharmaceutics Drug Disposition Classification System (BDDCS Class 1), indicating both high solubility and high permeability[123]. In water, its solubility is sufficient to support oral and intravenous formulations, making it practical for routine clinical use[124]. Organic laboratory solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) dissolve propranolol readily and are commonly used in experimental settings, particularly for preparing concentrated stock solutions in cell-based assays[125]. Surfactant-based systems, including micellar or emulsion carriers, may enhance dispersion and improve bioavailability in biological environments[126]. In contrast, certain nonpolar organic solvents demonstrate limited solubility for propranolol and are therefore of limited pharmaceutical relevance[127]. Overall, the interplay between lipophilicity, ionization, and aqueous solubility underpins its favorable absorption profile[128].

4.3. β_1 and β_2 Receptor Blockade

Propranolol is a competitive, non-selective β-adrenergic receptor antagonist and serves as the prototype against which other β-blockers are often compared[129]. Originally developed by Sir James Black for the treatment of angina pectoris, propranolol represented a major advance in cardiovascular pharmacotherapy[130]. Over time, its clinical applications expanded well beyond angina to include hypertension, arrhythmias, heart failure, and coronary artery disease[131]. Its consistent ability to reduce morbidity and mortality in patients with ischemic heart disease and post–myocardial infarction states established it as a foundational drug in cardiovascular medicine[132].

At the molecular level, propranolol exerts its effects by competitively inhibiting both β_1- and β_2-adrenergic receptors, thereby preventing their activation by endogenous catecholamines such as epinephrine and norepinephrine[133]. β_1-receptors are predominantly expressed in cardiac tissue, including the sinoatrial (SA) node, atrioventricular (AV) node, and ventricular myocardium[134]. Under physiological conditions, stimulation of these receptors increases cyclic adenosine monophosphate (cAMP) production, leading to enhanced intracellular calcium influx and increased myocardial contractility and heart rate[135]. By blocking β_1-receptor activation, propranolol reduces heart rate, myocardial contractility, and conduction velocity, ultimately decreasing cardiac workload and myocardial oxygen demand[136]. This mechanism underlies its therapeutic benefit in angina, tachyarrhythmias, and prevention of ischemic episodes[137].

In contrast, β_2-receptors are widely distributed in bronchial smooth muscle, vascular smooth muscle, and metabolic tissues[138]. Activation of β_2-receptors also increases cAMP, which in smooth muscle cells promotes relaxation through protein kinase A–mediated pathways[139]. Consequently, β_2-receptor blockade by propranolol can result in mild vasoconstriction and bronchoconstriction[140]. This pharmacological property explains both some therapeutic effects and certain limitations of non-selective β-blockade[141]. For example, while β_2 inhibition may contribute to modulation of peripheral vascular tone, it can pose risks in individuals with reactive airway diseases, as it interferes with bronchodilatory responses to endogenous or exogenous catecholamines[142].

Because propranolol blocks both receptor subtypes without intrinsic agonist activity, it effectively dampens sympathetic over activity across multiple organ systems[143]. The drug is highly protein-bound and widely distributed throughout the body, reflecting its lipophilic nature and substantial volume of distribution[144]. This non-selective β-adrenergic antagonism is central not only to its cardiovascular indications but also to its broader therapeutic implications—including its emerging role in modulating stress-mediated neuroendocrine signaling in oncology[145].

4.4. CNS Penetration of Propranolol

One of the distinctive pharmacological features of propranolol is its ability to readily cross the blood–brain barrier (BBB)[146]. This property is primarily attributed to its high lipophilicity and moderate molecular weight, which favor passive diffusion across lipid-rich endothelial membranes of cerebral vasculature[147]. Unlike hydrophilic β-blockers, propranolol achieves measurable concentrations within the central nervous system (CNS), enabling it to directly modulate central adrenergic pathways[148]. This characteristic is particularly relevant in conditions, where sympathetic over activation contributes to pathology[149].

Chronic stress activates the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis, resulting in sustained elevations of catecholamines such as norepinephrine and epinephrine[150]. Central β-adrenergic signaling plays a critical role in regulating stress-related behavioral and physiological responses[151]. By penetrating the CNS, propranolol attenuates central β-adrenergic receptor activation, thereby reducing stress-induced sympathetic outflow[152]. This mechanism underlies its clinical utility in performance anxiety, migraine prophylaxis, and certain stress-associated disorders[153].

In the context of oncology, CNS penetration becomes particularly important. Neuroendocrine stress signaling has been implicated in tumor progression through β-adrenergic activation of pathways that promote angiogenesis, invasion, immune modulation, and resistance to therapy[154,155]. By blocking β-receptors both centrally and peripherally, propranolol may reduce systemic catecholamine signaling more effectively than peripherally restricted β-blockers[156]. This dual action positions propranolol as a compelling candidate in stress-modulating oncotherapy strategies[157].

Table 1: Comparison of Propranolol with Selective β-Blockers

Parameter	Propranolol	Atenolol	Metoprolol
β-Receptor Selectivity	Nonselective (β_1 + β_2)	Selective β_1	Selective β_1
Lipophilicity	High	Low (hydrophilic)	Moderate
CNS Penetration	High (readily crosses BBB)	Minimal	Moderate
Plasma Half-life	3–6 hours	6–7 hours	3–7 hours
First-Pass Metabolism	Extensive	Minimal	Moderate–Extensive
Bioavailability	25–35%	50%	40–50%
Volume of Distribution	High (~4 L/kg)	Low	Moderate
Stress Signaling Modulation	Central + Peripheral	Primarily Peripheral	Mainly Peripheral (limited central)
Risk of Bronchoconstriction	Present (β_2 blockade)	Low	Low–Moderate
Potential Role in Oncology (Investigational)	Strong preclinical and emerging clinical evidence	Limited evidence	Moderate but less consistent than propranolol

5. β-Adrenergic Signaling and Cancer Biology

The β-adrenergic signaling cascade represents a central molecular arm of the sympathetic nervous system (SNS) and is fundamentally responsible for coordinating the classical "fight-or-flight" response[158]. Sympathetic nerve fibers are widely distributed across nearly all major organs, and in response to physiological or psychological stressors, they release the catecholamine norepinephrine (NE) directly into local tissue microenvironments[159]. Acute stress also stimulates the adrenal medulla to secrete epinephrine (E) into the systemic circulation, producing a rapid and sometimes dramatic rise in circulating catecholamine levels[160]. These elevations can occur within seconds and may exceed basal concentrations many-fold[161]. Importantly, catecholamine levels are not uniform throughout the body. Local neural density, tissue metabolism, and degradation pathways create significant variation between blood and solid tissues, and even among different regions of the same organ[162]. This spatial heterogeneity becomes particularly relevant in tumor biology, where local NE concentrations within the tumor microenvironment may differ substantially from plasma levels[163].

The biological effects of NE and E are mediated through α- and β-adrenergic receptor families, each with distinct tissue distribution and intracellular signaling mechanisms[164]. Of particular relevance to cancer are the three β-adrenergic receptor subtypes—β_1, β_2, and β_3—which are expressed across numerous tissues that commonly serve as sites of tumor growth and metastasis, including the breast, prostate, lung, liver, brain, bone marrow, lymphoid organs, and vasculature[165]. β-Adrenergic receptors are present not only on tumor epithelial cells but also on stromal and immune components such as endothelial cells, fibroblasts, adipocytes, pericytes, and various myeloid and lymphoid populations[166]. Upon ligand binding, these receptors couple to the Gαs protein, leading to activation of adenylyl cyclase and subsequent synthesis of cyclic adenosine monophosphate (cAMP)[167]. This rise in intracellular cAMP acts as a second messenger that orchestrates a broad spectrum of downstream cellular responses[168].

One principal effector of cAMP is protein kinase A (PKA)[169]. Activation of PKA results in phosphorylation of serine and threonine residues on multiple target proteins, thereby modifying enzyme activity, cytoskeletal dynamics, and transcriptional regulation[170]. Through phosphorylation of transcription factors such as CREB and related ATF family members, PKA can influence the expression of a substantial fraction of the human genome[171]. These transcriptional changes often regulate metabolism, differentiation, stress adaptation, and survival pathways[172]. In cancer-relevant contexts, PKA signaling has been associated with altered cytokine production, enhanced angiogenic factor expression, and modulation of inflammatory mediators[173]. Additionally, PKA contributes to feedback regulation of β-receptors via activation of β-adrenergic receptor kinase (BARK), promoting receptor desensitization through β-arrestin recruitment[174]. Beyond desensitization, β-arrestin can initiate alternative signaling routes, including activation of the Src/Ras/MAPK pathway, thereby linking adrenergic stimulation to mitogenic and survival signaling networks[175].

A second major cAMP-dependent pathway operates through EPAC (Exchange Protein Activated by cAMP), a guanine nucleotide exchange factor distinct from PKA[176]. EPAC activates the small GTPase Rap1A, which subsequently engages the B-Raf/MEK/ERK cascade, a well-established regulator of proliferation and cell survival[177]. While there is some functional overlap between PKA and EPAC pathways, they often govern different aspects of cellular behavior[178]. EPAC signaling appears particularly important for modulating cell morphology, adhesion, motility, and secretory dynamics—processes directly relevant to tumor invasion and metastasis[179]. In contrast, PKA-driven transcriptional programs are more strongly linked to inflammatory and angiogenic gene expression[180]. Together, these complementary signaling arms translate

β-adrenergic receptor activation into coordinated changes in proliferation, immune regulation, angiogenesis, and metastatic potential, thereby providing a mechanistic bridge between chronic stress exposure and cancer progression[181].

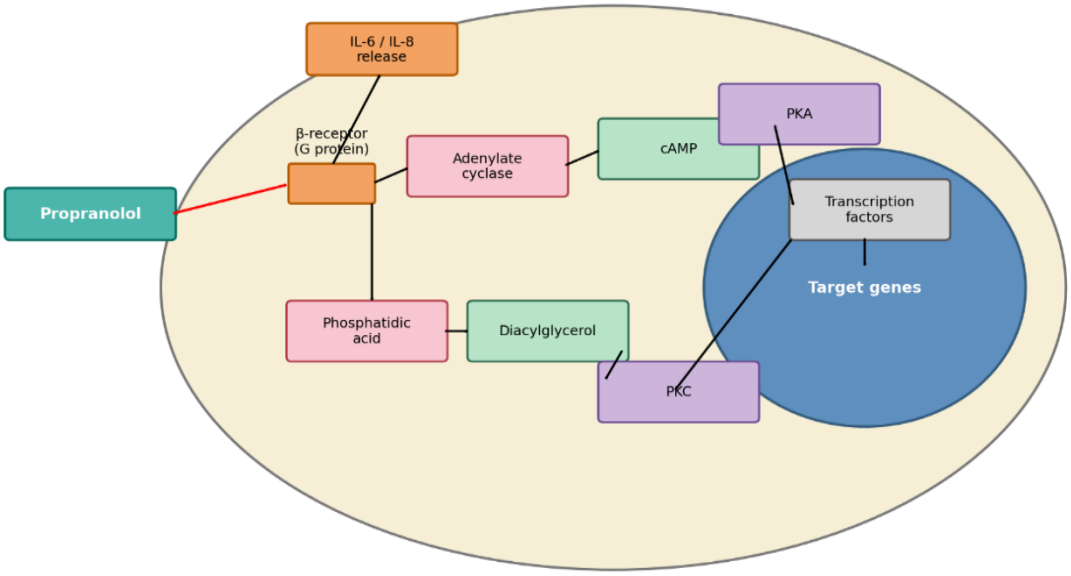

Figure 3. Propranolol-mediated modulation of β-adrenergic signaling pathways in cancer cells.

The schematic illustrates the β-receptor (G protein–coupled receptor) signaling cascade within a tumor cell and its inhibition by propranolol. Activation of the β-receptor stimulates adenylate cyclase, leading to increased cAMP production and subsequent activation of PKA, which promotes transcription factor activation and target gene expression. In parallel, receptor signaling influences phosphatidic acid and diacylglycerol generation, activating PKC and further regulating transcriptional activity. These pathways contribute to IL-6/IL-8 release and pro-tumorigenic gene expression. Propranolol blocks β-receptor activation, thereby attenuating downstream signaling and transcriptional responses associated with tumor progression.

5.1. β-adrenergic regulation of tumor biology

Interest in β-adrenergic regulation of tumor biology emerged from epidemiological observations showing that patients exposed to chronic psychological stress often experience faster progression of already diagnosed cancers[182]. In contrast, evidence linking stress to the initial development of cancer has remained limited and inconsistent[183]. Parallel clinical data have suggested that patients receiving β-adrenergic antagonists for cardiovascular indications sometimes demonstrate improved oncologic outcomes, prompting mechanistic investigation[184]. Experimental models have largely supported these observations. In xenograft and syngeneic tumor systems—where malignancy is already established—imposed stress reliably enhances metastatic spread, whereas effects on primary tumor initiation or early growth are comparatively modest[185]. In models of breast and prostate carcinoma, melanoma, and leukemia, β-blockers consistently inhibit stress-induced increases in metastasis without significantly altering primary tumor size or *in vitro* proliferation rates[186]. Conversely, administration of β-adrenergic agonists can accelerate tumor dissemination even in the absence of overt stress, reinforcing a direct mechanistic role for adrenergic signaling in tumor progression[187].

At the cellular level, β-adrenergic signaling influences several processes central to metastatic competence. Activation of β-receptors has been associated with increased recruitment of tumor-associated macrophages into the primary tumor microenvironment[188], enhanced expression of pro-inflammatory cytokines such as interleukin-6 and interleukin-8[189], and upregulation of vascular endothelial growth factor (VEGF), which collectively promote angiogenesis[190]. In parallel, β-adrenergic stimulation increases matrix metalloproteinase activity, facilitating extracellular matrix degradation and tissue invasion[191]. It also enhances tumor cell motility and mobilization[192], while conferring resistance to apoptosis through pathways involving focal adhesion kinase (FAK) and pro-survival regulators such as BAD[193]. Additional findings suggest that β-adrenergic activity may impair p53-mediated DNA repair[194], dampen cytotoxic T-cell and natural killer cell responses[195], suppress type I interferon signaling[196], and influence oncogenic pathways including HER2 activation and epithelial–mesenchymal transition (EMT)[197]. Although not every pathway has been definitively validated through inhibitor-based

mediation studies, the collective evidence indicates that sympathetic activation can modulate multiple molecular circuits relevant to tumor growth, immune evasion, angiogenesis, and metastatic spread[198].

Importantly, adrenergic influences on tumors appear to derive predominantly from local norepinephrine release rather than circulating catecholamines alone[199]. Analyses of human tumor specimens, particularly ovarian carcinomas, have demonstrated markedly higher norepinephrine concentrations within tumor tissue compared with peripheral blood, with minimal detectable epinephrine in the tumor microenvironment[200]. Moreover, intra-tumoral norepinephrine levels correlate with psychosocial stress indicators and tumor gene expression signatures, whereas circulating catecholamine levels do not show the same relationship[201]. Histological studies reveal dense peri-vascular sympathetic innervation in several solid tumors, including breast and ovarian cancers, providing a direct source of norepinephrine capable of acting on β-adrenergic receptors expressed by tumor and stromal cells[202]. This local neural input resembles patterns observed in other lymphoid and solid tissues, where sympathetic fibers regulate immune and vascular dynamics[203].

5.2. β-adrenergic regulation of systemic cancer biology

Beyond the primary tumor site, the sympathetic nervous system may influence cancer biology systemically. Adrenergic signaling regulates myelopoiesis within the bone marrow and shapes monocyte and macrophage trafficking[201]. Chronic stress can alter the density of sympathetic nerve fibers in hematopoietic niches and modulate gene expression profiles of circulating immune cells before they are recruited into tumors[202]. Such "preconditioning" may enhance the pro-tumorigenic behavior of infiltrating myeloid populations[203]. These systemic dynamics imply that β-adrenergic effects on tumor progression are not confined to receptor expression within the tumor itself but may involve remote sympathetic regulation of immune and hematopoietic compartments[204]. While this complexity presents challenges for precision targeting, it also supports the rationale for systemic β-blockade as an adjuvant strategy capable of interrupting both local and systemic sympathetic support of tumor progression.

6. Mechanisms of Action of Propranolol Relevant to Cancer Biology

Propranolol HCl (PRO) is a non-selective β-adrenergic receptor antagonist with comparable affinity for β_1 and β_2 receptors, and substantially lower affinity for β_3 receptors. Its selectivity profile is broadly similar to agents such as pindolol and carvedilol, which may also have repurposing potential. Many anticancer mechanisms proposed for Propranolol converge on β_2-adrenergic signaling, particularly in the context of metastatic progression[205,].

6.1. Effects on Proliferation

Interest in β-adrenergic control of proliferation dates back several decades. Chronic exposure to β-agonists such as isoproterenol has been shown to induce tissue overgrowth in rodent models through increased mitotic activity and DNA synthesis. Conversely, β-blockade—including Propranolol—has been associated with reduced growth rates in certain experimental systems. More recent studies demonstrate that PRO effectively blunts catecholamine- or isoproterenol-driven proliferation across multiple cancer types.

Comparative pharmacological analyses further support a predominant role for β_2-adrenergic signaling in these effects.

Notably, some discrepancies have been reported across experimental models. Certain breast cancer systems demonstrated β-agonist–induced growth suppression that was reversed by Propranolol, whereas other studies observed direct antiproliferative effects of Propranolol independent of prior agonist stimulation[206].

Interleukin-6 (IL-6) appears to be a key mechanistic mediator in specific tumor contexts. In oral squamous cell carcinoma (OSCC), β_2-adrenergic signaling increased IL-6 production, and Propranolol effectively inhibited IL-6–associated proliferative responses. Consistent with these findings, reduced circulating IL-6 levels accompanied by diminished metastatic burden have been reported in murine melanoma models treated with Propranolol[207].

6.2. Migration, Invasion, and Metastasis-Linked Remodeling

6.2.1. Apoptosis and Cell-Cycle Control

In pancreatic cancer models, Propranolol reduced expansion of PC-1 cells through increased apoptosis, with evidence pointing to β_2 rather than β_1 blockade, as supported by comparative analyses using the β_2-selective antagonist butaxamine versus the β_1-selective blocker metoprolol [208, 209]. In gastric cancer cell lines, PRO treatment was associated with G_1-phase cell-cycle arrest and induction of apoptosis. In gastric cancer models, exposure to high in vitro concentrations of PRO (approximately 200 μM) resulted in cell-cycle arrest and apoptosis and was accompanied by reduced expression of NF-κB, vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2), and matrix metalloproteinases MMP-2 and MMP-9 [185, 209- 212].

In head and neck squamous cell carcinoma (HNSCC) cell lines, Propranolol induced apoptosis across different p53 genetic backgrounds, indicating p53-independent mechanisms. Mechanistic investigations implicated members of the p53 family, particularly p63 and p73, with Propranolol exposure leading to downregulation of the anti-apoptotic ΔNp63α isoform and induction of the pro-apoptotic TAp73β isoform. Consistent with these observations, related studies reported increased expression of p53 and p73 following Propranolol treatment in neuroblastoma models[204].

6.2.2. Angiogenesis and Vascular Signaling

Adrenergic control of angiogenesis was initially described in non-cancerous tissues, where norepinephrine was shown to increase vascular endothelial growth factor (VEGF) expression[190,191]. Translating these findings into oncology, β-agonists

were found to increase VEGF expression in ovarian cancer cell lines such as EC and SKOV3, an effect that was effectively blocked by Propranolol at concentrations as low as 1 μM[192]. This observation provided a plausible mechanistic link between behavioral stress and angiogenesis-driven tumor support. In vivo, chronic stress increased tumor growth, vascular density, and expression of VEGF, MMP-2, and MMP-9 in ovarian cancer models, with cAMP–PKA signaling identified as a central driver of these effects[193]. Surgical stress has similarly been shown to enhance β-adrenergic signaling, tumor angiogenesis, and growth; notably, peri-operative administration of Propranolol inhibited VEGF induction and angiogenic expansion[194].

Anti-angiogenic effects associated with Propranolol—most commonly mediated through suppression of VEGF—have been reported across multiple malignancies, including nasopharyngeal carcinoma[195], melanoma[196], pancreatic cancer[208], leukemia[198], oral squamous cell carcinoma (OSCC), and infantile hemangiomas[213]. In neuroblastoma models, combinations of β-blockers (including Propranolol) with vincristine significantly reduced angiogenesis and improved survival outcomes[202].

Additional signaling pathways may also contribute to the anti-angiogenic effects of β-blockade. In glioblastoma-related studies using patient biopsy material and endothelial cell systems, Propranolol downregulated endothelial MMP-9 expression and reduced tubulogenesis of brain microvascular endothelial cells, consistent with diminished angiogenic potential[191]. Hypoxia-associated signaling intersects strongly with adrenergic biology: norepinephrine has been shown to upregulate hypoxia-inducible factor-1α (HIF-1α) via cAMP/PKA/Akt/p70S6K signaling, resulting in increased VEGF expression and capillary formation; Propranolol effectively blocked these effects, and similar findings have been reported using β_2-selective antagonists in pancreatic cancer models [208, 209].

Inflammation-linked mediators further connect adrenergic signaling to angiogenesis. In gastric cancer models, isoproterenol increased cyclooxygenase-2 (COX-2) expression, whereas Propranolol significantly reduced COX-2 levels ($P < 0.05$). Given that the COX-2/prostaglandin E_2 (PGE_2) axis is a well-established promoter of tumor angiogenesis, this pathway may represent an additional mechanism through which β-blockade alters vascular biology, potentially involving NF-κB regulation. Consistent with this concept, genetic deletion of β_2-adrenergic receptors has been associated with impaired angiogenesis in murine models, and isoproterenol has been shown to promote IκBα degradation and NF-κB transcriptional activation.

6.2.3 Treatment Sensitization: Chemo- and Radio-Response

Early studies suggested that Propranolol could partially reverse drug-resistance phenotypes in several experimental systems, including doxorubicin-resistant P388 leukemia and multidrug-resistant (MDR) CEM leukemia. However, these effects were highly dependent on both the chemotherapeutic agent and the tumor model, with limited impact observed on cisplatin sensitivity in certain non-small cell lung cancer (NSCLC) settings[192].

With respect to radiotherapy, PRO pre-treatment has been shown to increase radiosensitivity and apoptosis in gastric cancer models following exposure to 50 μM PRO for 24 h[214]. Similar radiosensitizing effects were reported in head and neck squamous cell carcinoma (HNSCC) cell lines, with additional evidence of synergy when Propranolol was combined with cisplatin[194]. Supporting clinical relevance, case reports in angiosarcoma have described the concurrent use of Propranolol alongside chemoradiotherapy[215]. A unifying mechanistic explanation for these observations involves inhibition of the NF-κB/COX-2/PGE_2 signaling axis, which has been repeatedly implicated in radioresistance across multiple cancer types [196, 197, 198, 216].

Examples of therapeutic sensitization include potentiation of rapamycin in PC3 prostate cancer cells, reversal of trastuzumab resistance in HER2-positive breast cancer, inhibition of stress-associated attenuation of sunitinib efficacy in colorectal cancer models, and enhanced sensitivity of thyroid cancer cells harboring BRAF-V600E mutations to vemurafenib[204].

Combination chemotherapy studies have yielded particularly compelling results. PRO demonstrated dose- and context-dependent interactions with paclitaxel and 5-fluorouracil (5-FU) in vitro and improved therapeutic outcomes in vivo in an orthotopic triple-negative breast cancer (TNBC) model. In this xenograft system (MDA-MB-231), PRO administered at 10 mg/kg (5 days/week) in combination with paclitaxel significantly increased median survival compared with paclitaxel monotherapy, with a comparable survival benefit observed when Propranolol was combined with 5-FU. The authors attributed this synergy primarily to enhancement of anti-angiogenic activity at relatively low Propranolol concentrations (~10 μM). Subsequent studies extended these findings by demonstrating synergistic effects between PRO and vincristine in neuroblastoma models[216].

7. Conclusion

The accumulated evidence surrounding propranolol in oncology presents a compelling, though still evolving, narrative. Originally introduced as a non-selective β-adrenergic receptor antagonist for cardiovascular indications, Propranolol has emerged as a biologically plausible modulator of tumor progression through its ability to interrupt stress-mediated adrenergic signaling. By blocking β1 and β2 receptors, it influences multiple cancer-relevant pathways including angiogenesis, inflammation, invasion, immune suppression, and metastatic dissemination. These effects are not confined to tumor cells alone but extend to the tumor microenvironment, immune compartments, and even distant pre-metastatic niches.

Preclinical models across diverse malignancies—such as breast cancer, melanoma, angiosarcoma, pancreatic cancer, colorectal cancer, and glioma—consistently

demonstrate that β-adrenergic blockade can attenuate stress-enhanced tumor growth and metastasis. Importantly, Propranolol appears to exert its greatest value not as a direct cytotoxic agent, but as a biological modifier that enhances the efficacy of chemotherapy, radiotherapy, and immunotherapy. Its anti-angiogenic properties, suppression of pro-inflammatory cytokines, modulation of immune cell dynamics, and ability to sensitize tumors to conventional treatments collectively support its positioning as a co-adjuvant strategy rather than monotherapy.

Clinical data, while still limited, are encouraging. Early-phase trials and observational studies suggest potential benefits in breast cancer, melanoma, ovarian cancer, colorectal cancer, and vascular tumors. The perioperative setting is particularly intriguing, as transient stress-related sympathetic activation during surgery may facilitate micrometastatic spread—an effect that β-blockade may counteract. Nevertheless, robust randomized controlled trials remain essential to confirm survival benefits, define optimal dosing schedules, identify responsive subgroups, and clarify long-term safety in oncology populations.

Looking ahead, the integration of Propranolol into modern cancer therapy will likely depend on precision strategies—biomarker-guided selection, rational combination regimens, tumor-targeted delivery systems, and advanced computational modeling to identify responsive tumor profiles. Given its well-characterized pharmacology, affordability, and extensive clinical experience in other fields, Propranolol represents one of the most practical and biologically grounded examples of drug repurposing in oncology. With carefully designed translational and clinical studies, β-adrenergic blockade may evolve into a meaningful adjunct in comprehensive cancer management.

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