REVIEW ARTICLE

# The *PRKC* Gene Family: Structural Organization, Signaling Mechanisms, and Therapeutic Implications

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**Abstract**

Protein kinase C enzyme/isoforms (PKC) represents a family of serine/threonine kinases encoded by the *PRKC* gene family that plays a central role in intracellular signal transduction. PKC isoforms act as molecular switches that translate extracellular signals into coordinated cellular responses regulating proliferation, differentiation, apoptosis, metabolism, immune activation, and neuronal signaling. Molecular studies have established that PKC comprises multiple isoenzymes with distinct regulatory domains, cofactor requirements, tissue distribution, and functional specificity. Dysregulation of PKC signaling is implicated in a wide range of pathological conditions, including cancer, metabolic disorders, cardiovascular disease, immune-mediated disorders, and neurodegenerative diseases. From a green pharmacy perspective, increasing attention has focused on plant-derived and naturally occurring compounds capable of modulating PKC activity with improved safety and sustainability profiles. This review provides a comprehensive and plagiarism-safe overview of the *PRKC* gene family, detailing the structural organization, activation mechanisms, signaling pathways, and physiological roles of PKC isoforms. Furthermore, it highlights the involvement of PKC dysregulation in human diseases and discusses emerging therapeutic strategies, with particular emphasis on natural and phytochemical PKC modulators relevant to green pharmacy research. Understanding PRKC biology at the molecular and systems levels is essential for the rational development of sustainable, isoform-selective therapeutic interventions.

**Key words:** Green pharmacy, phytochemicals, *PRKC* genes, protein kinase C, signal transduction, therapeutic targeting

## INTRODUCTION

Protein kinase C (PKC) was first described as a calcium-dependent, phospholipid-activated protein kinase, a discovery that significantly advanced the understanding of lipid-mediated intracellular signaling. This seminal finding established diacylglycerol (DAG) as a second messenger and positioned PKC as a critical regulator of cellular responses to extracellular stimuli.[1-5] Subsequent molecular cloning and biochemical characterization demonstrated that PKC is not a single enzyme but a multigene family encoded by distinct *PRKC* genes, giving rise to multiple isoenzymes with unique regulatory properties.

PKC isoforms function as key signaling intermediates integrating signals from hormones, growth factors, cytokines, neurotransmitters, and environmental cues. Through phosphorylation of a diverse array of substrates, PKCs regulate essential biological processes including cell proliferation, differentiation, apoptosis, metabolism, immune activation, cytoskeletal remodeling, and synaptic plasticity. Given this central role in cellular homeostasis, it is not surprising that dysregulation of PKC signaling contributes to numerous pathological conditions such as cancer, diabetes mellitus, cardiovascular disease, immune dysfunction, and neurodegenerative disorders.[4,7,8]

In recent years, the concept of green pharmacy has gained prominence, emphasizing the discovery and development of therapeutics derived from natural sources with improved safety, biodegradability, and environmental sustainability. Several

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plant-derived compounds, including flavonoids, alkaloids, terpenoids, and polyphenols, have been shown to modulate.

Several plant-derived compounds, including flavonoids, alkaloids, terpenoids, and polyphenols, have been reported to modulate PKC Signalling either directly through enzyme interaction or indirectly via upstream regulatory pathways. These observations highlight the relevance of PRKC signaling as a promising target within green pharmacy frameworks. This review aims to provide an integrated and updated overview of the *PRKC* gene family, with particular emphasis on structural features, signaling mechanisms, physiological functions, disease associations, and the potential of natural PKC modulators for sustainable drug development.

## *PRKC* GENE FAMILY AND CLASSIFICATION

### *PRKC* Gene Organization

The *PRKC* gene family consists of multiple genes, including *PRKCA, PRKCB, PRKCG, PRKCD, PRKCE, PRKCH, PRKCQ, PRKCZ*, and *PRKCI*. These genes encode PKC isoenzymes that share a conserved C-terminal catalytic kinase domain while differing significantly in their N-terminal regulatory regions. This modular organization underlies isoform-specific differences in activation mechanisms, subcellular localization, and substrate recognition.[2,5]

Alternative splicing further expands PKC functional diversity. A well-characterized example is PRKCB, which generates PKCβI and PKCβII isoforms that differ in their C-terminal sequences and phosphorylation dynamics, resulting in distinct signaling behavior. Such molecular diversity enables fine-tuned regulation of PKC signaling across tissues, developmental stages, and physiological contexts.

### Functional Classification of PKC Isoforms

Based on structural features and cofactor requirements, PKC isoenzymes are classified into three major subfamilies [Figure 1]: conventional, novel, and atypical PKCs. Conventional PKCs require calcium, DAG, and phosphatidylserine for activation. Novel PKCs are activated by DAG but are independent of calcium, whereas atypical PKCs do not require either calcium or DAG. This classification reflects differences in regulatory domain composition and provides a functional framework for understanding isoform-specific signaling.

Schematic classification of PKC isoforms encoded by *PRKC* genes into conventional, novel, and atypical subfamilies based on cofactor requirements and regulatory domain composition is summarized in Tables 1 and 2.

## STRUCTURAL ORGANIZATION AND ACTIVATION MECHANISMS

PKC isoenzymes exhibit a conserved modular architecture composed of an N-terminal regulatory domain and a C-terminal catalytic kinase domain [Figure 2] connected by a flexible hinge region. The regulatory domain contains an autoinhibitory pseudosubstrate sequence that occupies the substrate-binding cleft of the catalytic domain, thereby maintaining the enzyme in an inactive conformation under basal conditions. In addition, the regulatory region includes one or two C1 domains that bind DAG or phorbol esters, as well as a C2 domain that mediates calcium-dependent phospholipid binding in conventional PKCs.

The catalytic domain is highly conserved and contains the ATP-binding site, substrate recognition motifs, and three critical phosphorylation sites: the activation loop, turn motif, and hydrophobic motif. Phosphorylation at these sites is required for PKC maturation, stability, and catalytic competence. Activation of PKC is typically initiated by receptor-mediated stimulation of phospholipase C, leading to hydrolysis of phosphatidylinositol 4,5-bisphosphate and generation of DAG and inositol 1,4,5-trisphosphate. DAG recruits PKC to cellular membranes, while inositol 1,4,5-trisphosphate induces calcium release from intracellular stores, facilitating activation of conventional PKC isoforms. These events trigger conformational changes that displace the pseudosubstrate sequence and permit substrate phosphorylation [Figure 3].[3,6]

Domain architecture of PKC isoforms showing the N-terminal regulatory region (pseudosubstrate, C1 and C2 domains) and the C-terminal catalytic kinase domain.

## PRKC-MEDIATED SIGNAL TRANSDUCTION

Activated PKC isoforms phosphorylate a broad spectrum of downstream substrates and regulate multiple intracellular signaling pathways. Prominent among these are the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, the phosphatidylinositol 3-kinase/Akt pathway, and the nuclear factor kappa B pathway. Through these cascades, PKC isoforms influence gene expression programs governing cell proliferation, differentiation, survival, metabolism, and inflammatory responses.[2,7]

Beyond transcriptional regulation, PKCs play important roles in cytoskeletal dynamics, vesicular trafficking, and membrane organization. PKC-mediated phosphorylation of cytoskeletal and adaptor proteins regulates actin remodeling, focal adhesion turnover, and endocytosis, thereby influencing cell migration, adhesion, and polarity. Signaling specificity is achieved through isoform-selective localization, interaction

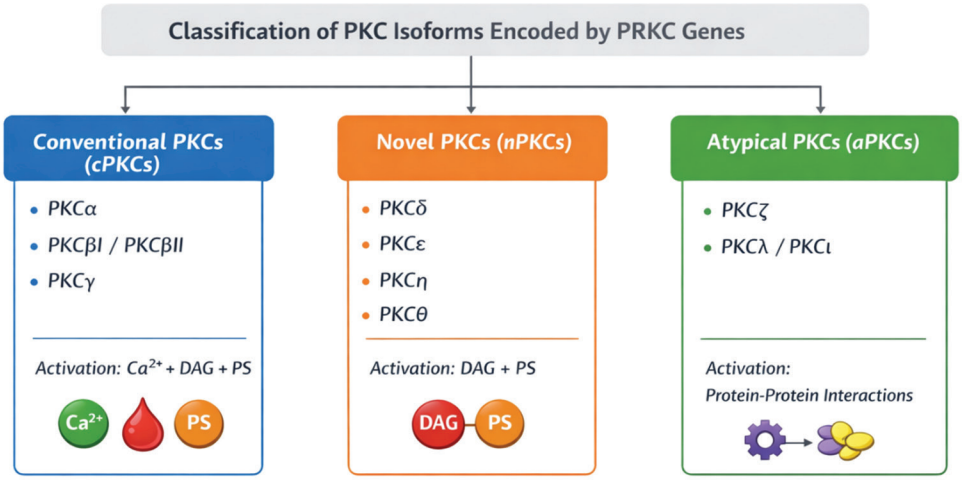


**Figure 1:** Classification of the *PRKC* gene family

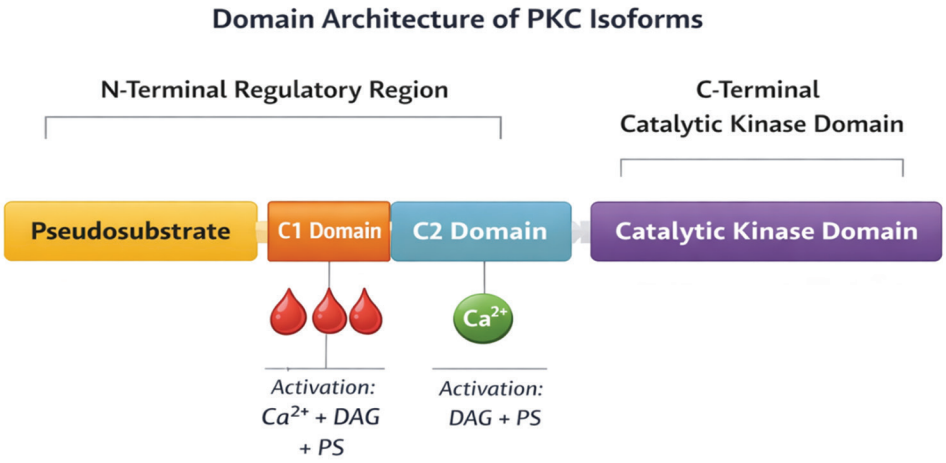


**Figure 2:** Structural organization of PKC isoenzymes

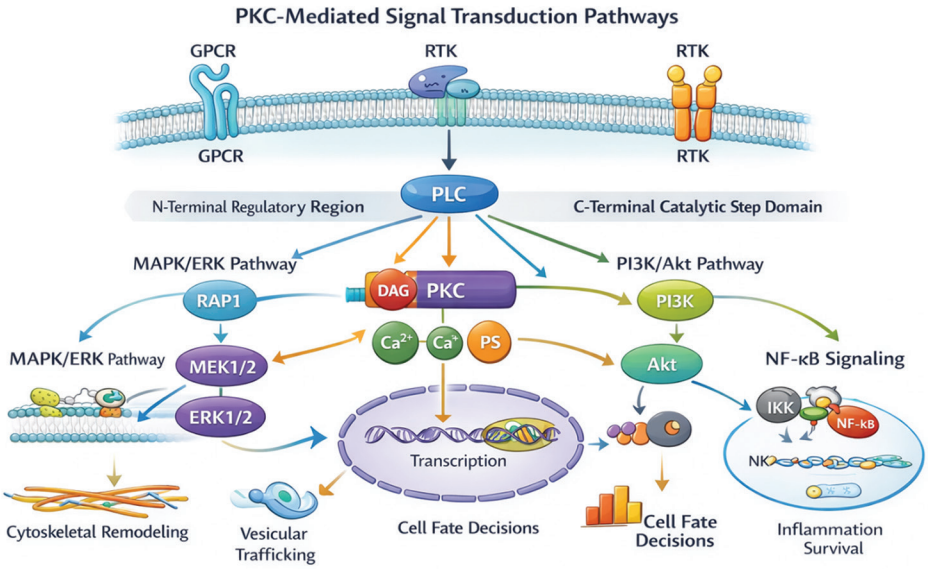


**Figure 3:** Mechanism of PKC activation and signaling

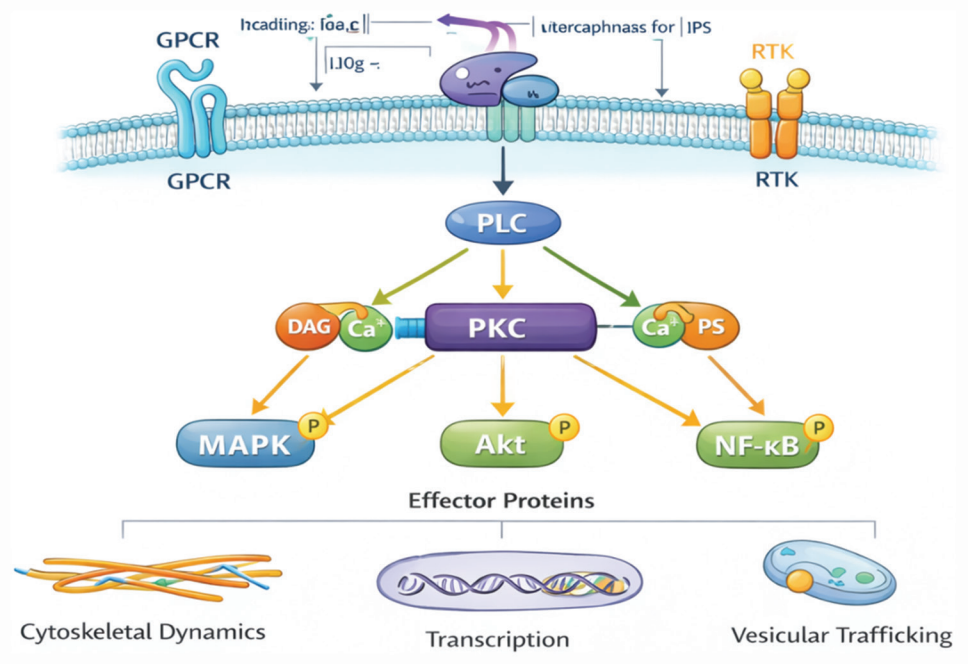


**Figure 4:** Mechanism of PKC activation and signaling

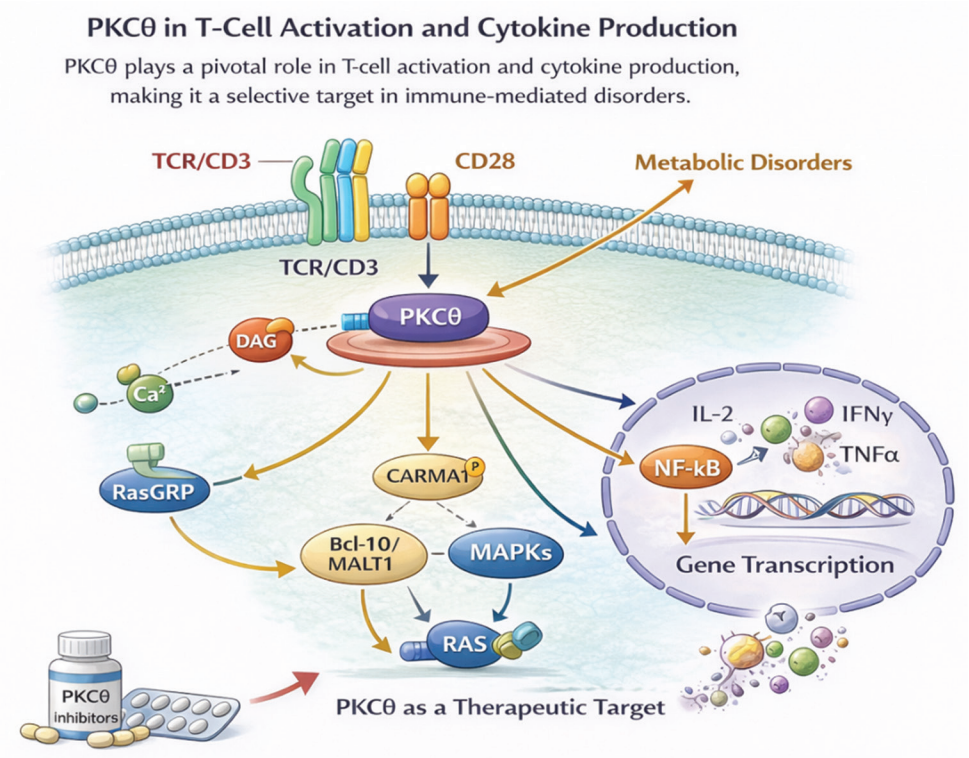


**Figure 5:** Immune function PKC activation, and signaling

with anchoring proteins, and spatially restricted availability of lipid cofactors.

Once localized to the membrane, PKC undergoes conformational changes that relieve autoinhibition by its pseudosubstrate domain, thereby exposing the catalytic site for substrate interaction.[1,3,6] Activated PKC subsequently phosphorylates a broad range of downstream effector proteins, modulating diverse cellular processes including gene transcription, cytoskeletal organization, vesicular trafficking, and signal integration governing cell survival, proliferation, or apoptosis.[2,4,7] The specificity of PKC-mediated responses is determined by the isoform involved, its precise subcellular localization, and the local

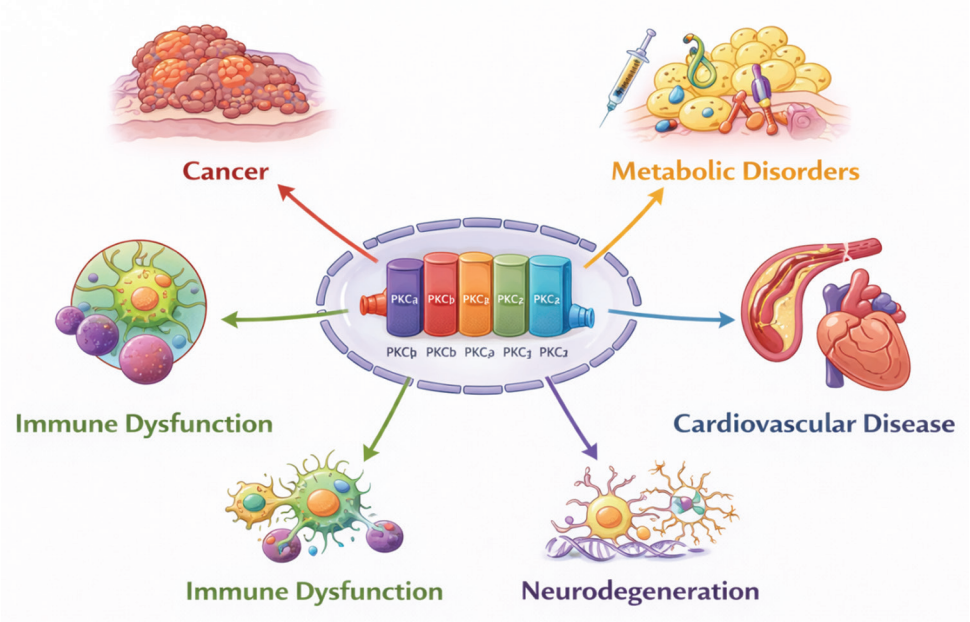


**Figure 6:** PRKC dysregulation in human diseases

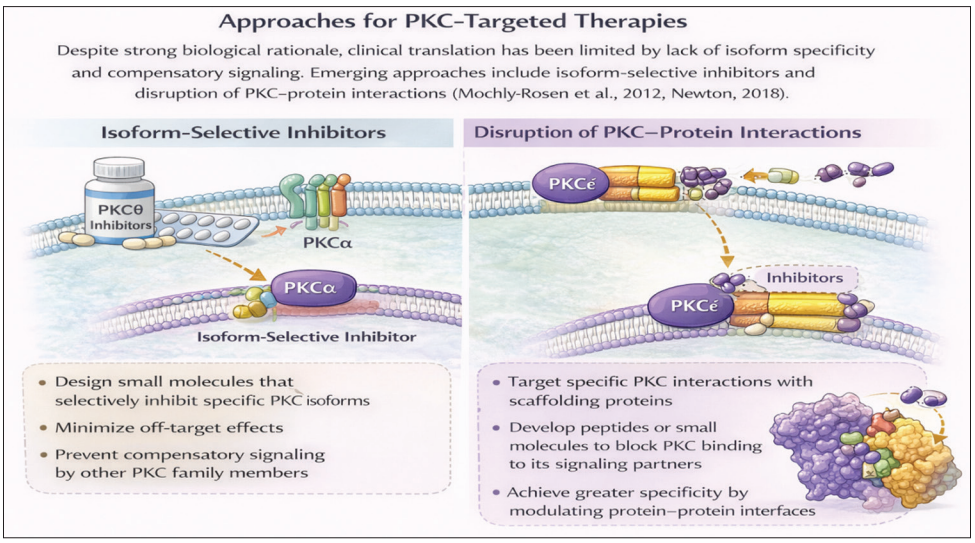


**Figure 7:** Therapeutic targeting of PRKC isoforms

**Table 1:** *PRKC* genes and corresponding PKC isoforms

| ***PRKC* gene** | **PKC isoform** | **Subfamily** | **Major tissue expression** | **Key functions** |
|---|---|---|---|---|
| *PRKCA* | PKCα | Conventional | Ubiquitous | Cell growth, survival |
| *PRKCB* | PKCβI/βII | Conventional | Immune, adipose | Insulin signaling |
| *PRKCG* | PKCγ | Conventional | Brain | Synaptic plasticity |
| *PRKCD* | PKCδ | Novel | Ubiquitous | Apoptosis |
| *PRKCE* | PKCε | Novel | Heart, liver | Metabolism |
| *PRKCQ* | PKCθ | Novel | T lymphocytes | Immune activation |
| *PRKCZ* | PKCζ | Atypical | Ubiquitous | Cell polarity |
| *PRKCI* | PKCλ/ι | Atypical | Epithelial tissues | Cell survival |

**Table 2:** Cofactor requirements of PKC subfamilies

| PKC subfamily | Calcium | Diacylglycerol | Phosphatidylserine |
|---|---|---|---|
| Conventional | Required | Required | Required |
| Novel | Not required | Required | Required |
| Atypical | Not required | Not required | Required |

**Table 3:** PRKC isoforms as therapeutic targets

| PKC isoform | Disease association | Disease association | Challenge |
|---|---|---|---|
| PKCβ | Diabetes | Diabetes | Limited specificity |
| PKCθ | Autoimmune disease | Autoimmune disease | Immune balance |
| PKCε | Metabolic disorders | Metabolic disorders | Redundancy |
| PKCδ | Cancer | Pro-apoptotic targeting | Context dependence |

availability of cofactors, ensuring accurate and context-dependent regulation of intracellular signaling pathways in response to extracellular stimuli.[3,6,11] This lipid-mediated activation mechanism underscores PKC's central role as a critical signaling hub that translates extracellular cues into coordinated functional cellular outcomes [Figure 4].[1,4,6]

## PHYSIOLOGICAL FUNCTIONS OF PRKC ISOFORMS

### Cell Proliferation and Apoptosis

Distinct PKC isoforms exert opposing effects on cell survival and programmed cell death. PKCα and PKCε are generally associated with pro-survival and proliferative signaling through activation of the mitogen-activated protein kinase/extracellular signal-regulated kinases and PI3K/Akt pathways. These isoforms enhance transcriptional programs that support cell cycle progression and protect cells from apoptotic stimuli. In contrast, PKCδ frequently functions as a pro-apoptotic kinase. In response to cellular stress, such as DNA damage or oxidative insult, PKCδ translocates to the nucleus and mitochondria, where it phosphorylates substrates involved in apoptotic execution. This functional divergence highlights the isoform-specific roles of PKCs in determining cell fate and maintaining tissue homeostasis.[5,7]

### Metabolic Regulation

PKCβ and PKCε are key regulators of insulin signaling and metabolic homeostasis. Elevated intracellular levels of DAG in insulin-sensitive tissues activate these isoforms, leading to inhibitory phosphorylation of insulin receptor substrates and attenuation of downstream PI3K/Akt signaling. As a consequence, glucose uptake and glycogen synthesis are reduced. Chronic activation of PKCβ and PKCε in conditions of nutrient excess contributes to insulin resistance, hyperglycemia, and the development of metabolic disorders such as type 2 diabetes mellitus and non-alcoholic fatty liver disease.[8,10]

### Immune Function

Protein kinase C theta, encoded by PRKCQ, plays a central role in T-cell activation and immune responses [Figure 5]. Upon engagement of the T-cell receptor and co-stimulatory receptors, PKCθ is recruited to the immunological synapse, where it orchestrates activation of nuclear factor kappa B, mitogen-activated protein kinases, and activator protein-1. These signaling pathways drive transcription of cytokines essential for T-cell proliferation, differentiation, and effector function. Dysregulated PKCθ signaling has been implicated in autoimmune diseases and chronic inflammatory conditions, making this isoform an attractive target for selective immunomodulation are summarized in Table 3.[9]

## PRKC DYSREGULATION IN HUMAN DISEASES

Aberrant PKC signaling contributes to the pathogenesis of numerous human diseases. In cancer, PKC isoforms display context-dependent roles, acting as oncogenic drivers or tumor suppressors depending on tissue type and molecular environment. In metabolic disorders, sustained PKC activation promotes insulin resistance, endothelial dysfunction, and vascular inflammation. PKC dysregulation is also implicated in immune-mediated diseases, cardiovascular complications, and neurodegenerative disorders, underscoring the broad pathological relevance of PRKC signaling networks.

Association of PKC isoforms with major disease categories, including cancer, metabolic disorders, immune dysfunction, cardiovascular disease, and neurodegeneration are shown in Figure 6.

## GREEN PHARMACY PERSPECTIVE: NATURAL MODULATORS OF PKC

From a green pharmacy standpoint, naturally derived compounds that modulate PKC activity represent promising alternatives to synthetic inhibitors. Several flavonoids, including quercetin, apigenin, and genistein, have been shown to influence PKC activation and downstream signaling. Curcumin, resveratrol, and epigallocatechin gallate have also

been reported to modulate PKC-mediated pathways involved in inflammation, cancer, and metabolic regulation. These phytochemicals often exhibit multitarget activity, lower toxicity, and improved environmental sustainability, aligning with green pharmacy principles.[4,7,8] Continued exploration of natural PKC modulators may facilitate the development of safer and more sustainable therapeutic agents.

## THERAPEUTIC TARGETING OF PRKC ISOFORMS

Despite a strong biological rationale, therapeutic targeting of PKC has proven challenging. Early clinical approaches using non-selective PKC inhibitors were limited by poor specificity and adverse effects. Current strategies focus on isoform-selective inhibitors, peptide-based modulators, and disruption of PKC-protein interactions rather than direct catalytic inhibition [Figure 7]. These approaches aim to achieve precise modulation of disease-relevant signaling pathways while preserving essential physiological functions of PKC isoforms.[12-15]

## CONCLUSION

The *PRKC* gene family encodes a diverse group of serine/threonine kinases that play a central role in regulating intracellular signaling and maintaining cellular homeostasis. Isoform-specific differences in regulation, localization, and function allow precise control over critical biological processes, including cell proliferation, apoptosis, metabolic regulation, and immune responses. However, this functional complexity also complicates therapeutic intervention, as individual PKC isoforms can exert distinct or even opposing effects depending on cellular context and disease state. These challenges highlight the need for refined strategies that move beyond non-selective kinase inhibition toward isoform and pathway-specific modulation.

Integrating molecular insights into PRKC biology offers a promising direction for future therapeutic development. Natural and plant-derived compounds provide structurally diverse, biologically compatible, and environmentally sustainable options for selectively modulating PKC signaling. By emphasizing isoform selectivity, reduced toxicity, and ecological responsibility, such approaches have the potential to overcome longstanding limitations in PKC-targeted drug discovery. Continued interdisciplinary research bridging molecular pharmacology, natural product chemistry, and systems biology will be essential for translating these advances into clinically effective and environmentally responsible therapies.

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