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Polyphenol Compounds and PKC Signaling

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Abstract

Background—Naturally occurring polyphenols found in food sources provide huge health benefits. Several polyphenolic compounds are implicated in the prevention of disease states, such as cancer. One of the mechanisms by which polyphenols exert their biological actions is by interfering in the protein kinase C (PKC) signaling pathways. PKC belongs to a superfamily of serine-threonine kinase and are primarily involved in phosphorylation of target proteins controlling activation and inhibition of many cellular processes directly or indirectly.

Scope of review—Despite the availability of substantial literature data on polyphenols' regulation of PKC, no comprehensive review article is currently available on this subject. This article reviews PKC-polyphenol interactions and its relevance to various disease states. In particular, salient features of polyphenols, PKC, interactions of naturally occurring polyphenols with PKC, and future perspective of research on this subject are discussed.

Major conclusions—Some polyphenols exert their antioxidant properties by regulating the transcription of the antioxidant enzyme genes through PKC signaling. Regulation of PKC by polyphenols is isoform dependent. The activation or inhibition of PKC by polyphenols has been found to be dependent on the presence of membrane, Ca^{2+} ion, cofactors, cell and tissue types etc. Two polyphenols, curcumin and resveratrol are in clinical trials for the treatment of colon cancer.

General significance—The fact that 74% of the cancer drugs are derived from natural sources, naturally occurring polyphenols or its simple analogs with improved bioavailability may have the potential to be cancer drugs in the future.

Keywords

polyphenol; protein kinase C; signal transduction; cancer; antioxidant

1. Introduction

Understanding the action mechanisms of naturally occurring chemo-preventive agents is an important step in designing therapeutics for cancer and related diseases. These agents are known to exert a plethora of actions on multiple targets eliciting an either known or

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unknown hierarchy of biological responses. This review focuses on one such chemo-preventive class of agents, polyphenols, which are popularly known as antioxidants and are mostly found in dietary supplies. One of the mechanisms by which polyphenols exert their actions is by regulation of the protein kinase C (PKC), a central kinase in intracellular signal transduction. Discovered in the late 1970s, PKCs have been implicated in many disease states. This article focuses on the PKC-polyphenol interactions and its biological consequences. Despite the availability of substantial literature data on polyphenols' regulation of PKC and highlighting its therapeutic potential for disease states, no comprehensive review article is currently available on this important subject. Here we present important features of polyphenols, PKC, and interactions of naturally occurring polyphenols with PKC, and future perspective of research on this subject.

2. Polyphenols

Polyphenols are a vast family of molecules characterized by more than one connected hydroxylated/multi-hydroxylated benzene rings-phenols. As a consequence of their enormous structural diversity in nature, they are often divided into four different classes-phenolic acid, stilbenes, lignans and flavonoids based on their structural properties alone [1]. These classes are consequently divided into an array of subclasses such as monohydroxybenzoic acids, dihydroxybenzoic acids, flavones, flavonols, flavanones, isoflavones, monomeric stilbene, oligomeric stilbene, diarylbutane derivatives, 2,3-dibenzylbutyrolactone derivatives, tetrahydrofuran derivatives, 4-aryltetrahydronaphthalene derivatives and a few others (Figure 1) [1–4]. Some natural sources are known to contain copious amounts of polyphenols including apples, cranberries, red grapes, blueberries black tea, pomegranate juice, red wine, and red onions, green tea, strawberry, bananas, corn, watermelon, plums, kiwi, potato, lemon juice, soy beans, cherries etc.[5].

Polyphenols have been implicated as potential preventive and curative therapeutic agents for a host of diseases like Alzheimer's [6, 7], Huntington[8], Parkinson's [9, 10], hypercholesterolemia [11], chronic fatigue syndrome [12, 13], diabetes[14], stroke [15, 16], various forms of cancer [17, 18], cardiovascular diseases [19, 20], autism [21, 22], vitiligo [23], etc. They have also been linked in curbing some of the phenotypes associated with senescence [24, 25]. In most of these instances, the antioxidant property of polyphenols is suggested as being responsible for their observed beneficial effects. Despite the predominant focus on the antioxidant activities, polyphenols have also been implicated in other roles independent of their antioxidant property like antibacterial [26, 27], anti-inflammatory [28] and modulation of ion transport [29].

2.1. Mechanisms of polyphenols' antioxidant properties

Currently, within the scientific community there is an ongoing debate on the primary mechanisms through which polyphenols exert their antioxidant property. Among the several possible mechanisms (Figure 2), the radical scavenging hypothesis postulates that polyphenols specifically `hunt' for free radicals and bind to them[30, 31]. Reactive Oxygen Species (ROS) is a class of molecules generated from metabolic reactions within aerobic organisms. ROS includes superoxide ($O_2^{-\cdot}$), hydroxyl radical ($^{\cdot}OH$) and hydrogen peroxides

(H_2O_2). Radical scavenging mechanism has been described as overly simplistic and also unsound in the case of radicals like ˙OH, which are highly reactive and react with almost all organic compounds within the cell [32]. The observation of direct scavenging of ROS by the higher concentrations of polyphenols in the *in vitro* cell culture seems unlikely to happen in the *in vivo* system where the concentrations of the consumed polyphenol concentrations are relatively low.

On the other hand, the transition metal chelating hypothesis contends that polyphenols bind free metals (especially iron) within the cells thus preventing the progression of the Fenton reaction (Figure 3)[5]. The Fenton reaction is a reaction pathway through which free iron (Fe^{2+}) reacts with hydrogen peroxide to yield hydroxyl radical. This hypothesis has been questioned based on the fact that under normal human physiological condition iron concentration is nearly negligible due to its strict regulation by intracellular enzymes [33]. Nevertheless, in some disease states like Alzheimer and beta thalassemia, iron concentration is not negligible and is a primary contributor to oxidative stress [33]. Although, the radical scavenging hypothesis and the transition metal (primarily iron) chelation hypothesis are the most commonly cited and observed mechanisms of action in *vitro* and *in vivo*, evidence of stimulation of ROS-terminating enzymes and inhibition of ROS-producing enzymes by some polyphenols has also been reported. ROS are physiologically important as they are essential players in some cell signaling pathways [32, 34]. Nevertheless, beyond a certain threshold (not known *in vivo* or *in vitro*) they can have a particularly damaging physiological effect, for instance, both superoxide and hydroxyl radicals have been shown to cause damage to DNA [33]. Beyond this threshold, the cell is considered to be under oxidative stress. Oxidative stress caused by ROS has been correlated with the occurrence of some forms of cancers [35], cardiovascular diseases [36] and with neurodegenerative diseases like Alzheimer's [37] and Parkinson's [38]. Given the beneficial effects of ROS in the right amounts and the potentially harmful effects that may result from an excess, the formation and destruction processes of ROS is tightly controlled for maintaining proper balance. NADPH oxidase and xanthine oxidase are a few examples of enzymes that are known to regulate the production of some ROS. Conversely, superoxide dismutase, peroxidase and catalase are known to catalyze the destruction of ROS. Some polyphenols exert their antioxidant influence by inhibiting free radical generating enzymes like NADPH and xanthine oxidase [39] or *via* increasing expression levels/activities of radical terminating enzymes like superoxide dismutase and catalase [40, 41].

An elegant mechanism by which the polyphenols regulate the expression of antioxidant enzymes is through the activation of Keap1/Nrf2/ARE pathway (Figure 4). Kelch-like ECH-associated protein 1 (Keap 1) remains bound to transcription regulator nuclear factor E2-related factor 2 (Nrf2), and prevents its signaling. Polyphenols directly or indirectly cause dissociation of Keap1 from the Nrf2-Keap1 complex. Phosphorylation of Nrf2 and its dissociation from the complex allows it to translocate to the nucleus where it binds to the antioxidant response element (ARE) in the regulatory region of the target genes, and induce transcription of antioxidant/detoxification enzymes (Figure 4). Several upstream kinases such as, extracellular signal-regulated kinase (ERK), protein kinase B (Akt) and PKC regulate this translocation and transcriptional activation. Several polyphenols regulate the activity of these kinases thereby exerting their antioxidant properties.

Despite existing evidence for the mechanisms mentioned above, most studies have not ruled out the possibility that polyphenols exert their antioxidant effects *via* a signal transduction cascade perhaps *via* interactions with cellular receptors. It has also been posited that polyphenols undergo further processing upon ingestion and lose their antioxidant property before reaching the cells hence their beneficial properties could be largely independent of their antioxidant properties [42]. Some studies have even proposed the antioxidant properties are exhibited in the gastrointestinal tract before absorption [43].

3. Protein Kinase C (PKC)

PKC belongs to a superfamily of serine-threonine kinase [44], primarily involved in phosphorylation of target proteins controlling activation and inhibition of many cellular processes directly or indirectly. Discovered by Yasutomi Nishizuka in the late seventies [45, 46], the PKC family plays a key role in many biological functions such as, apoptosis, cell proliferation [47], transcription regulation, immune responses, cell signaling [48], learning and memory [49], etc.

PKC family consists of 11 isozymes which are classified into three groups based on their N-terminal regulatory domain structure and activators bound to it (second messenger role) [50]. Conventional PKCs (α, βI, βII and γ) are activated by Ca^{2+}, diacylglycerol (DAG)/phorbol ester (Figure 5), and phosphatidylserine (PS) whereas, novel PKCs (δ, ε, θ and η) are activated by DAG/phorbol ester but not by Ca^{2+}. Atypical PKCs (ζ and ι / λ isoforms) are not activated by either DAG or Ca^{2+}, but usually can be activated by phosphatidylinositol (3, 4,5)-trisphosphate (PIP_3) and PDK1 [51]. A recent study showed that PKCζ_can be activated independent of PIP_3 [52].

PKC isozymes are expressed ubiquitously in tissues. PKCα is expressed in the adult liver, heart, epithelium and brain. PKCθ is expressed in T lymphocytes and relatively high levels in platelets [53]. PKCγ, PKCδ and PKCε are present in the heart [54]. PKCδ is expressed in vascular smooth muscle cells. PKCε was detected in the adult brain, heart, and liver, but not the adult kidney and lung. PKCζ was more abundant in the fetal/neonatal than in the adult brain, lung, kidney, and heart. PKCβ immunoreactivity was prominent in brain tissue [55].

Abnormalities in PKC signaling play a major role in cancer. Because phorbol esters are tumor promoters and also high affinity PKC ligands, there exists a correlation between PKC and cancer. Most of the changes occur in expression and activation of PKC α, β, δ during cancer progression [56]. Role of different PKC isoforms in various types of cancer has been reviewed by Griner and Kazanietz [57]. PKCs are also implicated in cardiovascular diseases like ischemic heart disease [58, 59], acute and chronic heart disease [60], heart failure [61], stroke [62], lung [63] and kidney complications [64], diabetes [65], various dermatological conditions including psoriasis [66], neurological disease states like bipolar disorders [67], Parkinson's disease [68, 69] dementia [70], Alzheimer's disease [71, 72], and pain [73]. One of the major goals of studying PKC isozymes is to develop potent and selective ligands to regulate PKC signaling in these disease states and the significance of PKC as a therapeutic target has been elegantly reviewed by Mochley-Rosen et al [74].

3.1. PKC domains and structure

Structurally, PKC consists of four conserved (C1–C4) and five variable (V1–V5) regions (Figure 6A). The conserved region is divided into sub regions. Regulatory region is at the N–terminal, where several different second messengers bind and the highly conserved catalytic region is at the C-terminal. The regulatory region has C1 and C2 domains. The C1 domain of conventional and novel PKCs are composed of the C1A and C1B subdomains, each having approximately 50 amino acids [75]. These subdomains contain two zinc ions, each of which is coordinated by three cysteines and one histidine [76]. The C1A and C1B bind to DAG/phorbol ester. While DAG is an endogenous second messenger, phorbol ester is a tumor-promoter isolated from plant, and mimic the functions, but more potent than DAG [77–79]. The C2 domain binds to Ca^{2+} and phosphatidylserine in conventional PKCs, but in some cases novel PKCs bind to negatively charged phospholipids in a Ca^{2+}-independent manner [76, 80]. PKC regulatory domain region contains a pseudosubstrate domain which helps in maintaining the enzyme in active or inactive conformation. The catalytic domain contains C3 and C4 domains having 12 highly conserved subdomains which fold into one catalytic core [81]. The C3 domain binds to ATP and C4 domain binds to substrate.

The three-dimensional structure of each truncated domains of PKC has been determined. The structure of PKCδC1B complexed with phorbol 13-O-acetate[82] (Figure 6B) revealed that there are two sets of three cysteines and one histidine that form two Zn^{2+} ion coordination sites at the end of the β sheets. In order to allow for ligand binding, the two β sheets are pulled apart and an “unzipped” groove is created. PKCδC1B possesses two long beta sheets (20% β-sheet) forming a V-shaped activator (DAG/phorbol ester) binding groove and a short alpha helix (4% α-helix) at the C-terminal end. Phorbol-13-O-acetate forms five hydrogen bonds in the activator binding groove.

The C2 domain of PKCα is composed of 8 β-sheets and calcium binds to CBR1 and CBR3 formed by the N- and C-terminal loops of the C2-key motif [83]. The crystal structure of the kinase domain of PKCβII revealed that this domain is composed of a classical bilobal fold. The N-terminal lobe formed of a five stranded β-sheets and two α-helices whereas the C-terminal lobe consists of eight α-helices. The N- and C-terminal lobes are connected by a linker region and the binding site for ATP lies between these lobes [84].

Crystal structure of full-length PKCβII was determined at 4Å resolution by Leonard et al in 2011(Figure 6C) [85]. The C1B domain is located close to the kinase domain rather than the C2 domain and interacts with the residues 619–633 of the C-terminal tail. The kinase active site has an open conformation for substrate. Still, the conformation of the active site has a low-activity state, because the ATP-binding side chain of Phe-629 of the conserved NFD motif is displaced. The C1B domain forms a clamped conformation and the NFD helix is kept in a low-activity conformation, which is reversed upon membrane binding [85]. The C1A domain is undefined in this structure.

3.2.PKC activation

PKC activation, extensively studied for conventional isotypes, occurs in multiple steps [86, 87]. In the inactive state of the enzyme the pseudosubstrate domain at the N-terminus

occupies the substrate binding site at the catalytic domain. This shielding the substrate binding domain prevents phosphorylation of the substrate. After assuming an active conformation by phosphorylation of the catalytic domain and calcium ion binding to the C2 domain, PKC then binds to the membrane anchoring through the C2 domain and phosphatidylserine (PS). In the next step endogenous DAG binds to the C1 domain. Membrane penetration and DAG binding pull the pseudosubstrate region from the active site in the kinase domain, resulting in enzyme activation and subsequent phosphorylation of the target proteins, thereby regulating apoptotic or anti-apoptotic pathways [88–90] (Figure 7). Phosphorylation of Nrf2 at its Ser-40 by PKC and subsequent regulation of the antioxidant enzymes is one of the mechanisms by which PKC participate in the antioxidant defense mechanism in the cell [91–93].

3.3. PKC and small molecules

Several classes of natural and synthetic compounds are known to modulate PKC activity [87]. These include phorbol esters, prostratin, bryostatins, indo- and benzolactams, ingenol esters, aplysiatoxin, mezerein, resiniferatoxin, daphnoretin, iridals, anthracyclin derivatives, retinoids etc. The prominent synthetic class of molecule that modulate PKC activity are diacylglycerol lactone, isophthalic acid derivatives etc. While these molecules bind to the C1 domain with nanomolar affinity and activate different PKC isoforms, natural compounds such as, staurosporin are PKC inhibitors that compete with the ATP-binding site. In 2012, FDA and EMA approved PKC-targeting ingenol-3-angelate (Picato or PEP005) for treating actinic keratosis and several other PKC-based drugs are under clinical trials [74].

4. PKC modulation by polyphenols

PKCs are regulators of many intracellular signaling pathways. Their balanced activity is essential for a healthy cell [57, 94]. Hyperactivity and hypo-activity of different isoforms of PKCs have been linked with pathogenesis (e.g. carcinogenesis), hence, there is an immense focus and body of work on how they can be of therapeutic value. Since they contain redox susceptive residues, it is speculated that their activity could be controlled in a redox pathway [95, 96]. Polyphenols demonstrate for the most part antioxidant properties in vitro and influence cellular redox processes and could influence PKC activity.

Below is a list of polyphenols, their sources, biological importance and what is known about their effects on different PKC isoforms.

4.1. Curcumin

Curcumin (Figure 1) is a β-diketone constituent of turmeric obtained from the powdered root of *Curcuma* L [97, 98]. Not only is it used as a spice to give a specific flavor and yellow color to curry, which is consumed in trace quantities daily by millions of people, curcumin has also been used as traditional medicine for liver disease (jaundice), indigestion, urinary tract diseases, rheumatoid arthritis, and insect bites [97–99]. Curcumin is a promising therapeutic agent for diseases such as cancer, diabetes, multiple sclerosis, Alzheimer's, HIV and cardiovascular disease [100–102].

Modulation of PKC activity by curcumin can affect transcription up-regulation or down-regulation, thereby affecting many disease states [103, 104]. For example, inhibition of PKC can produce downstream effects in NFκB, activator protein-1 (AP-1), epidermal growth factor (EGFR), UGT1A1. In human colon cancer cells (HCT1) curcumin induces apoptosis indicating that curcumin could be a therapeutic intervention for colon cancer. In fact, curcumin is under clinical trial for colorectal cancer [104]. In colon cancer, several signaling molecules are affected by curcumin (Figure 8). It suppresses the activity of PKC, subsequently affecting MAPK and C-jun. The down-stream effects of PKC include inhibition of UGT, ERK pathway and EGFR affecting the transcription factors and regulators, AP-1, NF-kB and ERG-1. Studies indicate that curcumin also attenuates diabetic nephropathy [105]and diabetic cardiomyopathy [106] through PKC signaling pathways. In human monocyte, curcumin exerts its antioxidant property by activating the PKCδ/Nrf2/ARE system [107].

There are well documented studies on the modulation of PKC activity by curcumin [108–115]. However, the mechanism by which curcumin modulates PKC activity is poorly understood. In studies involving purified proteins, curcumin (<20 μM) was shown to activate PKCα in the presence of membrane [115]. At higher curcumin concentration (>20 μM), a decrease in activity was observed. In another study using purified protein, it was also shown that curcumin (6–48 μM) activated calcium sensitive PKC (e.g. PKCα) in the presence of membrane and inhibited it in the absence of membrane [114]. Similarly, another study also showed that in a membrane-free system, curcumin (100 μM) inhibited PKC [109]. All these results indicated that membrane, Ca^{2+} and curcumin concentration are important determinants for curcumin to behave as an activator or inhibitor. Studies using cultured NIH3T3 fibroblasts found that curcumin (15–20 μM) alone did not affect basal PKC activity, but it inhibited the TPA-induced PKC activity [108]. In a study involving mouse skin, curcumin (10 μmol) inhibited TPA-induced membrane translocation of both PKCα and PKCε [112]. However, in CHO-K1 cells curcumin and its derivatives show high selectivity for PKCα over PKCε. While curcumin (5–10 μM) inhibited TPA-induced translocation of PKCα, but not PKCε from cytosol to plasma membrane, the modification of its hydroxyl group with an unsaturated aliphatic chain completely abolished this PKCα inhibition[116].

These differences could be due to the differences in the membrane translocation machinery present in different cellular systems.

In studying the effect of curcumin on purified PKC, Mahmmoud proposed that curcumin may bind to the Ca^{2+} binding site in the regulatory domain and also at a site at the kinase domain [114]. However, the observed inhibition of membrane translocation of calcium insensitive PKCs (PKCε, PKCη) by curcumin in mouse skin [112] indicated that Ca^{2+} may not be the only factor that regulated this membrane translocation process by curcumin. From the recent binding and modeling studies [117, 118] it was proposed that curcumin could bind to the C1 domains of PKCs.

4.2.Resveratrol

Resveratrol (Figure 1) is a naturally occurring phytoalexin found in grapes, red wine, peanuts, olive oil, cranberries, and other food [119, 120]. Numerous studies highlighted the

effects of resveratrol in a variety of human disease models, including cardio- and neuroprotection, immune regulation, and cancer chemoprevention [121–126].

Resveratrol's direct and indirect effects on PKC and related signaling molecules have been implicated in several medical conditions [127]. Resveratrol (15 μM) inhibited TPA-induced PKC expression in human mammary and oral epithelial cells [128], inhibited TPA-induced expression of PKCδ and reduced the metastatic potential of human cervical cancer at 50 μM [129], and affects protein kinase C activity and promotes apoptosis in human colon carcinoma cells at a concentration as high as 200 μM [130]. Resveratrol suppresses the activity of kinases such as protein kinase C (PKC), mitogen-activated protein kinases (MAPK) and IκB kinase (IKK) and transcription factors such as hypoxia-inducible factor-1α (HIF-1α), signal transducer and activator of transcription 3 (STAT3), nuclear factor κB (NF-κB) and activator protein-1 (AP-1) leading to various conditions in response to oncogenic stimuli (Figure 9) [127]. Resveratrol is also currently in clinical phase II trials as an anti-cancer drug for treatment of human colon cancer [131, 132]. Recent studies show that resveratrol's neuroprotective effects are mediated by the activation of PKCγ at 3 μM [133] and anti-neutrophil activity by inhibiting PKC activity at 10 and 100 μM [134]. Resveratrol regulates cellular PKCα and PKCδ to inhibit growth and induce apoptosis in gastric cancer cells [135], antagonizes EGFR-dependent Erk1/2 activation in human androgen-independent prostate cancer cells associated with isozyme-selective PKCα inhibition [136], inhibits PKC-catalyzed phosphorylation of a cofactor-independent, arginine-rich protein substrate [137], and inhibits a PKCδ splice variant in 3T3L1 adipocytes indicating its role in controlling obesity [138].

Effect of resveratrol on the activities of purified recombinant PKC isozymes in association with model lipid membranes was investigated using an *in vitro* assay system in which the cofactor and activator concentrations were systematically varied [139]. It inhibited PKCα with an IC_{50} of ~2 μM, PKCβ1 with an IC_{50} of ~105 μM, whereas PKCε and PKCζ remained unaffected. The authors proposed that resveratrol binds to the C1 domain of PKCα [139]. Recent studies showed that chemical modification of resveratrol moiety could attenuate activity of PKCα and PKCε [140, 141].

4.3.Epigallocatechin 3-gallate (EGCG)

Epigallocatechin 3-gallate (EGCG) (Figure 1) is present in green tea [142]. It has antiviral, antitumor, antihypertensive, antimalarial and hepatoprotective properties [143]. Some studies have further identified it as a potential therapeutic agent for diseases like Alzheimer's [144] and arthritis [145].

(−)-Epigallocatechin 3-gallate and its dehydroxy analog (−)-epicatechin gallate inhibit PKCα with IC_{50} values of 4.8 μM and 5.9 μM respectively [146]. EGCG competitively inhibited both ATP and phorbol ester binding to PKC [146, 147]. In human prostate cancer cells, EGCG down-regulated the expression of PKCα at 12 μM, while the expression of PKCβ, PKCδ, PKCε, PKCμ, PKCη and PKCζ were unaffected [148]. There are multiple studies showing EGCG's involvement in neuroprotection by attenuating PKC signaling pathways. Its neuroprotective effect was linked with the up-regulation of PKCα and PKCε [149]. Using rat hippocampal neuronal cells it was found that PKCγ plays a critical role in

the neuro-protective action of EGCG and resveratrol [133]. Neuroprotective mechanism of EGCG can also involve a rapid PKC-mediated degradation of bcl-Associated Death Protein (Bad) by the proteasome [150]. The neuroprotective mechanism of EGCG against oxidative stress-induced cell death includes stimulation of PKC and modulation of cell survival/cell cycle genes [151]. Besides, EGCG (100 μM) down-regulated glucose-induced phosphorylation of PKCα and PKCβII in glomerular epithelial cells thereby providing nephroprotection [152]. EGCG's promotion of keratinocyte differentiation at 5–40 μM was found to be PKCδ-dependent, but neither PKCα nor PKCε-dependent [153]. It also exerts its inhibitory action of dopamine transporter internalization through PKC activation at the concentration range 1-100 μM [154]. EGCG effects a facilitation of glutamate release from glutamatergic terminals by positively modulating N- and P/Q-type Ca2+ channel activation through a signaling cascade involving PKC at 0.5 μM [155]. It attenuates high glucose-induced endothelial cell inflammation by suppression of PKC and NF-kappaB signaling in human umbilical vein endothelial cells at 10–50 μM, suggesting its therapeutic value in the treatment of diabetic vascular complications [156, 157].

Some actions of EGCG are mediated through its binding to cellular receptors. High affinity EGCG-binding proteins were identified by using affinity chromatography [158]. Tachibana et al. have shown that EGCG can bind with high affinity to 67-kDa laminin receptor and through which it can induce some anticancer effects [159]. Others have shown the importance of this receptor in neuroprotection occurring with submicromolar concentrations of EGCG [160]. Nevertheless, PKC may still play an important role in mediating the actions of EGCG as the downstream signaling of 67LR involves generation of reactive oxygen species and subsequent oxidative regulation of PKC isoenzymes [160, 161].

4.4. Quercetin

Quercetin (Figure 1) is a flavonol that can be obtained from curly kale, *Ginkgo biloba*, broccoli, apples, red wine, red onion, and lettuce [1, 162–164]. Quercetin has been shown to be radioprotective (protects cells/tissues against damage caused by radiation), antidiabetic, hepatoprotective, antitumor, and antihypertensive [165].

Quercetin inhibits PKC [166, 167]. In a study with rat brain and pig thyroid PKC, quercetin exhibited biphasic effect on PKC activity. At lower concentrations (10^{-7} M) it stimulated, whereas, at higher concentrations it inhibited calcium and phospholipid dependent PKCs [168]. Another study using breast cancer cell line (MCF-7) linked the observed inhibition of PKCδ translocation to the membrane fraction with its antitumor property [169]. Studies using human leukemia (HL 60) [170], mouse melanoma (B16-BL6) [171], and HepG2 [172, 173] cell lines linked the anti-metastatic properties of quercetin to its PKC regulation. Furthermore, a docking study showed quercetin as being able to directly bind to the catalytic domain of PKC [174]. Quercetin was also found to initiate apoptotic sensitivity in the human lymphocyte (HPB-all) cell line via activation of PKCα at a concentration of 50 μM [175]. It inhibits PKCθ phosphorylation indirectly in human mast cells at 1-100 μM, suggesting its therapeutic uses in inflammatory conditions [176]. Quercetin and its structural analog, catechin synergistically act in reducing platelet recruitment via inhibition of PKC-

dependent NADPH oxidase activation, indicating their roles in cardiovascular diseases [177].

4.5. Ellagic acid

Ellagic acid (Figure 1) can be found in raspberry, strawberry, pomegranate, and red wine [162]. For the most part, in nature, they exist as complexes called ellagitannins, which usually undergo hydrolysis in the gastrointestinal tract to form ellagic acid [178]. *In vitro* and *in vivo* studies have shown ellagic acid to exert antidiarrheal [179], anti-diabetic [180], anti-carcinogenic [181, 182], anti-inflammatory [183] properties.

Ellagic acid (50 or 80 μM) has been shown to inhibit overall PKC activity in a pathway that prevents platelet aggregation [184]. It was suggested that ellagic acid initially inhibited the PLCγ2-PKC cascade and/or hydroxyl radical formation, followed by decreased phosphorylation of MAPKs and Akt, ultimately leading to the inhibition of platelet aggregation. This study also pointed out that ellagic acid did not play a direct role in PKC activation. Using Dalton lymphoma (DL) mice, however, another group observed that ellagic acid, at 40–80 mg/Kg doses, altered activity and expression of several PKC isoforms [95, 185–187] and affected apoptosis and antioxidant defense system.

4.6. Caffeic acid

Caffeic acid (Figure 1) belongs to the hydrocinnamic class of polyphenols. It can be found in coffee, blueberry, pear, apple and spinach [162]. It has been shown to have anti-inflammatory [188], antitumor, analgesic [189] properties in *in vivo* studies.

Caffeic acid is reported to be a noncompetitive inhibitor of overall PKC activity in partially purified human monocytes (U937 cell line) and in purified PKC containing PKCα, PKCβ and PKCγ at 100 μM [190].

4.7. Protocatechuic acid

Protocatechuic acid (Figure 1) can be found in raspberry, *Cardiospermum halicacabum*, and *Harrisonia perforate* [1, 191, 192]. It is one of the major metabolites of dietary anthocyanins [193] and has been implicated as having lifespan lengthening [194] cognitive improving [195] diabetic ameliorating and anti-inflammatory [196] functions.

Its extensive interactions with PKCs were identified in a study of Swiss mouse epidermis in which 16 μmol protocatechuic acid affected translocation of PKCα and reduced its activity by 59% [197]. In this study, PKCζ, PKCγ and PKCα translocation to membrane fractions was inhibited, however, PKCβI and βII were not affected. These effects were identified as a possible link to its antitumor properties. It has been observed that expression of PKCα and PKCβ was inhibited by protocatechuic acid (2 and 4%) which was associated with amelioration diabetic symptoms [198].

4.8.Tannic acid

Tannin can be isolated from black tea, *A. japonica* and *Pongamia pinnata* [199–201]. Historically, tannic acid (Figure 1) has been used primarily to treat burns. More recently, it

has been identified as suitable for treatment of abrasions. It has been linked as having antitumor, antihypertensive, antibacterial, antiviral, antibiofilm, and neuroprotective properties [202]. However, tannic acid has also been shown to be hepatotoxic [203] and cytotoxic to mouse fibroblasts at a concentration higher than 100 μM.

Tannic acid (16 μmol) decreases PKCα, PKCβI and PKCβII activities in mouse epidermal cell line, which is linked with its antitumor properties [197]. It also increased the levels of PKCα, PKCβI, PKCβII in the cytosolic fraction of mouse epidermis between 127% to 492% as compared with phorbol ester-treated group and decreased their activity by 94% in the membrane fraction [197]. Tannic acid inhibits PKC autophosphorylation without interfering with PKC translocation to membrane and consequently inhibits DNA synthesis in mouse fibroblast at 12–100 μM [204]. In human carcinoma cell line, tannic acid inhibited PKC activity at very high concentrations (IC_{50}=350μM) [205]. It was also found that tannin inhibited chloride secretion in airway epithelial cells, in part, by inhibiting PKC [206]. Testing 56 different tannins on the inhibition of PKC, Kashiwada et al showed that some of them competed with phorbol ester with IC_{50} values ranging 2–20 μM, indicating the binding of tannins in the regulatory domain of PKC [207].

4.9.Chlorogenic acid

Chlorogenic acid (Figure 1) is an ester of caffeic acid and quinic acid [208]. It is present in large amounts in green coffee extract and also can be found in bamboo, peach and Chinese hawthorn [209]. Chlorogenic acid is considered to inhibit fat accumulation, helps lose weight [210] and has anti-hypertensive properties [211].

It affects TPA-stimulated activities of conventional PKCs, PKCζ and their distribution in mouse epidermis, and alters the tumor promotion. At 16 μmol, chlorogenic acid affected translocation of PKCα and reduced its activity by 43% [197].

4.10. Apigenin

Apigenin (Figure 1) belongs to the flavone polyphenol subclass [162]. It can be found in celery, hot pepper, oregano, thyme and olives [162]. In addition to its anti-proliferative effects, it has been implicated as a potential therapeutic agent for many forms of allergies, such as, cedar pollinosis and asthma [212].

In leukemia cells, apigenin (50 μM) increased PKCδ activity causing apoptosis [213]. A study using mouse embryonic fibroblasts also observed apigenin to be a competitive inhibitor of ATP binding to PKC [214]. In human epidermal keratinocytes, however, apigenin (20 μM) inhibited PKCδ activation and apoptosis of keratinocytes was not observed [215].

4.11. Theaflavin-3, 3'-digallate

Theaflavin-3, 3'-digallate (TF-3) (Figure 1) is found in black tea [216]. TF-3 is considered to have many health benefits, such as, it reduces risk of coronary heart disease, viral infection and prevention of cancer [217, 218].

TF-3 is known to repress the activities of xanthine oxidase, cyclooxygenase, EGF-receptor tyrosine kinase along with PKC. Inhibition of these proteins is thought to be by blocking the mitogenic and differentiating signals through modulating EGFR function, MAPK cascades, NF-κB activation, as well as c-myc, c-jun and c-fos expression, which leads to the suppression of tumor promotion. At 20 μM, TF-3 blocks PKCα translocation from cytosol to membrane in TPA-treated NIH3T3 cells [219].

4.12. Verbascoside

Verbascoside (Figure 1) is obtained from plant species such as, *Ansbidaea pulchra*, *Buddleja brasiliensis*, *Verbasom phlomoides*, *Penstemon barbatus* and *Retzia capensis* [220–224]. It is recognized for its anti-inflammatory [225], anti-tumor [226], analgesic [227], neuroprotective [228] and antihypertensive [229] properties as demonstrated in several *in vitro* and *in vivo* studies. It is a hetero-trimer made up of caffeic acid, glucose and a catechol unit.

Verbascoside competitively and non-competitively inhibits rat brain PKC for ATP (Ki= 22 μM) and histone IIIs respectively [230]. The authors further suggested that the antitumor activity of verbascoside could be in part through its binding to PKC.

4.13. Viniferin

Viniferin (Figure 1) is present in plant species such as, *Paeonia suffruricosa*, *Paconia lactifora*, *Rheum lhasaense*, *Smilax scolanicaulis*, *Vitis amurensis*, *Vitis vinifera* and *Hopea chinensis* [231–236]. It has been identified as a potential antifungal [237], antitumor [238], antibacterial [239], antidiabetic [240], neuroprotective [241] and cardioprotective [242] agent. Viniferin exists in nature in different isoforms such as α-viniferin, β-viniferin, γ-viniferin, δ-viniferin and ε-viniferin [243].

α-Viniferin inhibits PKCα, PKCβII, PKCγ, PKCδ and PKCε in a non-competitive manner at lower micromolar concentrations[244].The assay was performed with partially purified PKC isoforms expressed and purified from Sf9 cells.

4.14. Rosmarinic acid

Rosmarinic acid (Figure 1) is an ester of caffeic acid which is present in copious amounts in Salvia fruticosa tea, *Prunella vulgaris*, Sweet basil, *Perrilla frutescens*, and *Melissia offinalis* [245–248]. It shows anti-diabetic, melanogenic, tumor degenerative, antidepressive, and analgesic properties [248]. At 15 μM rosmarinic acid showed less than 20% inhibition rat brain PKC [146].

4.15. Miyabenol C

Miyabenol C (Figure 1) is present in plant species such as, *Vitis vinifera*, *Vitis amurensis*, *Murabilis rotondifolia*, *Caragana sinica*, and *Sophora davidii* [235, 249–251]. It also shows potent antifungal [252] and tumor inhibitory [253] properties in *in vitro* studies. Miyabenol C inhibits activity of partially purified rat brain PKC non-competitively with an IC_{50} of 27.5 μM [254]. Another study reported that inhibition of PKCα, PKCβII, PKCγ, PKCδ and PKCε by miyabenol C can occur at low micromolar concentrations[244].

4.16. Rottlerin

Rottlerin (Figure 1) is isolated from *Mallotus philippenis* (Kamala) found in Southeast Asia. It is used as laxatives. Rottlerin has many other functions, such as it acts on potassium (BK Ca^{2+}) channel and improves cardiac performance after cardioplegia arrest through improved cardiomyocyte contraction and coronary perfusion [255]. This phenolic compound has antioxidant and anti-carcinogenic properties, and increases cardioplegia-induced phosphorylation of protein kinase B (Akt). Initially, rottlerin was known to inhibit calcium-unresponsive PKCδ but recent studies report that rottlerin also inhibits CAM kinase III and other protein kinases [256]. Liao et al. showed that rottlerin inhibited cell proliferation and activated cell apoptosis in different cell lines, which is possibly through the PKCδ pathway [257]. For many years rottlerin has been marketed as PKCδ inhibitor, but a recent study by Stephen P. Soltoff disapproves and reports that it inhibits other kinases and non-kinases, but not PKCδ [258].

4.17. Miscellaneous

Polyphenolic extracts from several plants and fruits were tested for their PKC activity. Apple polyphenol extract inhibited PKC in a cell-free system [259]. Other polyphenols such as vanicoside A1 and B2 (Figure 1) isolated from Polygonum pensylranicum are also reported to inhibit PKC [260]. A study involving the screening of 43 natural compounds from different sources for their inhibition against PKCα activity and competitive binding identified several flavonoid compounds such as isorhametin, kaempferol, luteolin, myricetin, rhamnetin, gallate such as, dodecyl gallate, and suggested that these compounds may bind to the catalytic domain of PKCα [146]. Ginseng is a Chinese herb that contains a polyphenol mixture. Its lipophilic fraction induced neurite extension and promoted survival of rat cortical neurons. These effects were blocked by PKC inhibitors, suggesting that the lipophilic fraction of ginseng exerts its neurotrophic effects via PKC-dependent pathways [261]. Flavonoids such as fisetin, luteolin, morin and rutin have been reported to inhibit PKC [166, 167]. Hydroxytyrosol, the major polyphenol in olive oil reduces metalloproteinase (MMP)-9 and COX-2 induction in activated human monocyte via PKCα and PKCβI inhibition, explaining its vascular protective (anti-inflammatory) effects [262]. Polymeric black tea polyphenols inhibit TPA-induced PKC phosphorylation to exert their anti-tumor promoting activity [263]. It has been also suggested that green tea polyphenols may act as potential neuroprotective agents against blood brain barrier damage through regulation of PKCα signaling pathway [264].

The effect of different polyphenols on PKC is summarized in Table 1.

5. Summary and future perspectives

PKC and polyphenols are involved in the regulation of numerous diseases states. Whereas PKC can be regulated by several classes of natural and synthetic compounds, polyphenols have multiple biological targets. From the extensive literature data compiled on PKC-polyphenol interactions in this article, the following highlights emerge: (1) Polyphenols attenuate PKC signaling pathways directly or indirectly regulating many disease states. (2) Some polyphenols exert their antioxidant properties by regulating the transcription of

antioxidant enzymes through PKC. (3) Regulation of PKC by polyphenols is isoform-dependent. (4) For a particular polyphenol, the activation or inhibition of PKC depends on the presence of membrane, Ca^{2+} ion, cofactors, cell and tissue types etc. (5) Polyphenols are low affinity PKC ligands as compared to phorbol ester/DAG. (6) The site of action of polyphenols on PKC is not unequivocally determined. (7) Two polyphenols, curcumin and resveratrol are in clinical trials for the treatment of colon cancer.

The facts that both PKC and polyphenols play important roles an anticancer mechanisms and that 74% of cancer drugs are derived from natural sources [265], naturally occurring polyphenols such as curcumin, resveratrol or EGCG or its simple analogs may have the potential to be cancer drugs in future. Several critical issues however should be addressed toward this end. First, the contribution of PKC-polyphenol interactions in a particular disease state should be dissected. For example, the anticancer activities of curcumin [266], resveratrol [267, 268] and EGCG [269] are exerted through multiple mechanisms with multiple targets including PKC. It is important to understand how significant PKC-polyphenol interaction is in the pathophysiology of this disease state. Second, the bioavailability of polyphenols after oral intake should be improved. While several polyphenols show promising therapeutic effect in the in vitro system, the effects could reduce to none in the in vivo system or in the clinical trials, indicating bioavailability as a major determinant of the therapeutic potency. Bioavailability of a polyphenol depends on its first pass metabolism, lipophilicity, phase II metabolism, stability in plasma etc. For example, poor bioavailability of curcumin (1%) [270], resveratrol (1%) [271, 272] and EGCG (0.1%) [273] has been a major obstacle in the in drug development relating to these agents. This will also have a significant bearing on the concentration of these agents in the brain after transporting through the blood brain barrier (BBB) [274, 275]. Improvement bioavailability of polyphenols using different delivery systems is a major area of current research [276].

Future research on PKC-polyphenol interactions is expected to evolve around identifying new biological targets of polyphenols in the PKC signaling pathways, systematic study of isoform-selective PKC for each polyphenol, determining the sites of action of polyphenols on PKC so that new molecules could be developed based on these sites. Because most of the high affinity PKC ligands are complex in structure and show poor isoform selectivity, use of simple polyphenol templates, such as curcumin and resveratrol could be used for structure/activity studies for developing isoform-selective PKC modulators for therapeutic purposes. A recent study of curcumin derivative in CHO-K1 cells provides a proof of principle toward this strategy [116]. Furthermore, polyphenol analogs should be designed focusing on the improved bioavailability and PK/PD properties. All these research should be directed toward the goal of developing new anticancer agents and/or identifying a dietary food combination that would be beneficial for a particular type of cancer.

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Abbreviations

AP-1	Activated protein-1
ARE	antioxidant response element
BBB	Blood brain barrier
CAT	catalase
CHO	Chinese Hamster Ovary
DAG	Diacylglycerol
EGFR	Epidermal growth factor receptor
EGR	Early growth response
ERK	Extracellular signal-regulated kinase
GCL	γ-glutamylcysteine synthatase
GPx	Glutathione peroxidase
GST	glutathione S-transferase
HIF-1α	Hypoxia-inducible factor-1α
HO-1	Heme oxygenase-1
IKK	IκB kinase
Keap 1	Kelch-like ECH-associated protein 1
MAPK	Mitogen activated protein kinase
NF-κB	Nuclear factor κB
NFD	Asparagine Phenylalanine Aspartic acid
Nrf2	Nuclear factor E2-related factor 2
PDB	Protein data Bank
PKC	protein kinase C
PK/PD	Pharmacokinetic/Pharmacodynamic
PRX	peroxiredoxin
ROS	Reactive oxygen species
STAT3	Signal transducer and activator of transcription 3
SOD	superoxide dismutase
TPA	phorbol 12-myristate 13- acetate

Trx	thioredoxin
UGT	UDP-glucuronosyltransferase

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Highlights

- Polyphenols attenuate PKC signaling pathways regulating many disease states
- PKC regulation is dependent on membrane, Ca^{2+} ion, cofactors, cell and tissue types
- Polyphenols are low affinity PKC ligands
- Bioavailability is a major concern for polyphenol based drug development
- Curcumin and resveratrol are in clinical trials for the treatment of colon cancer

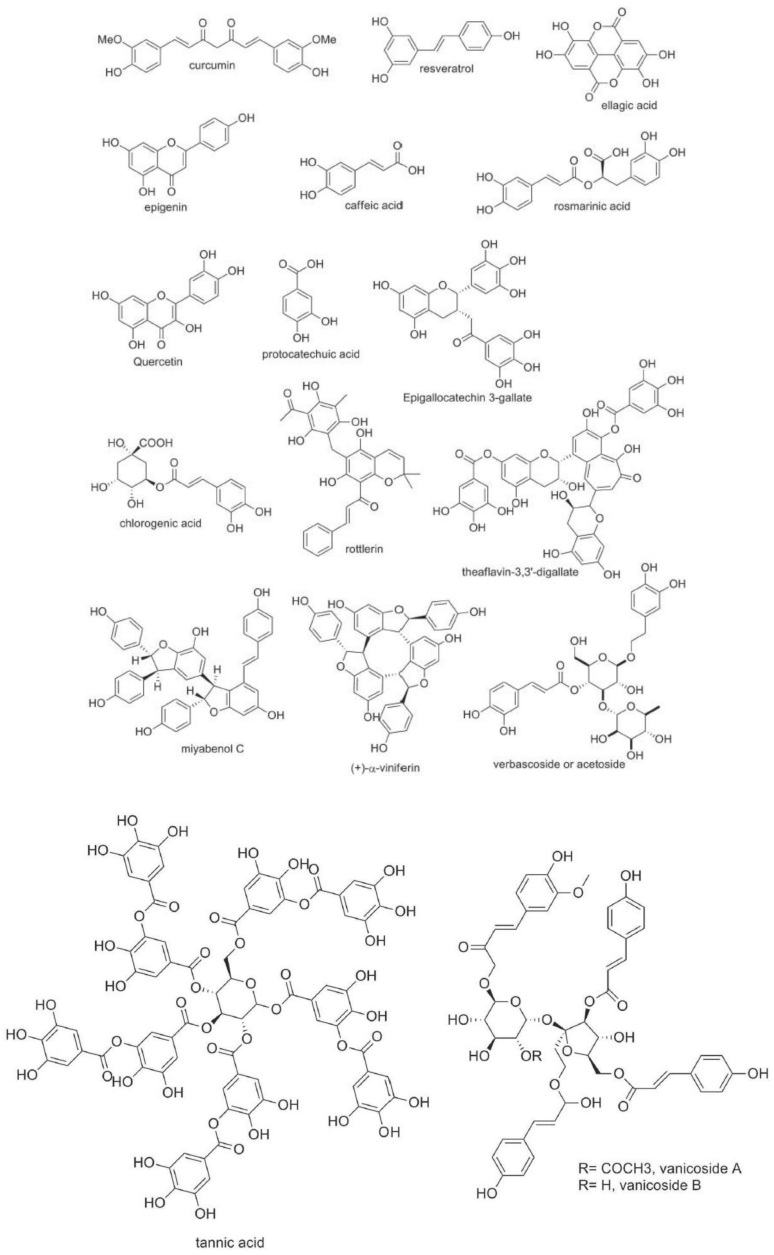

Fig.1.
Chemical structure of the polyphenols.

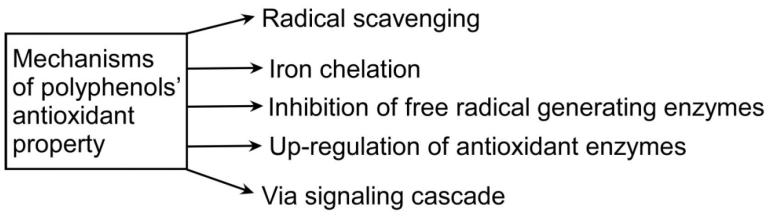

Fig.2.
Different mechanisms for polyphenols' antioxidant properties.

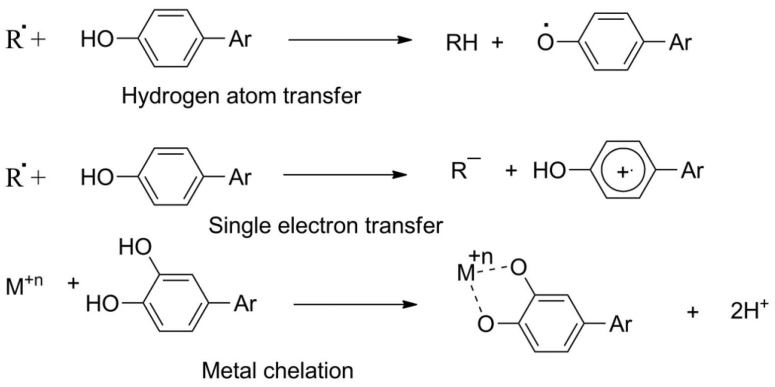

Fig.3.

Types of reaction mechanisms for polyphenols' antioxidant properties.

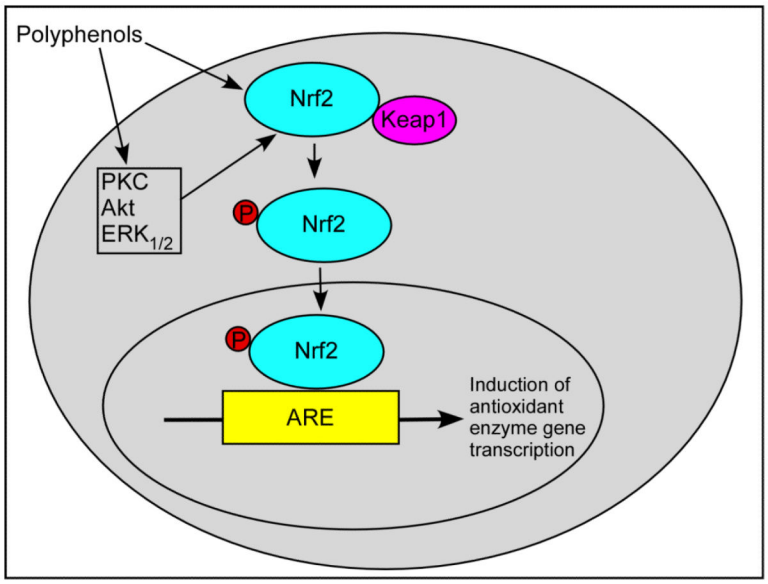

Fig.4.

Mechanism of polyphenols' antioxidant properties. Polyphenols activate Keap1/Nrf2/ARE pathway and induce the expression of antioxidant/detoxification enzymes. Keap 1 protein always bound to Nrf2 transcription regulator and prevents its signaling. Polyphenols directly or indirectly cause dissociation of Keap1 from the Nrf2-Keap1 complex and subsequent translocation of Nrf2 to the nucleus where it binds to the ARE in the regulatory region of the target genes and induce transcription of antioxidant/detoxification enzymes. ARE, antioxidant response element; CAT, catalase; ERK, extracellular signal-regulated kinase; GCL, g-glutamylcysteine synthatase; GPx, glutathione peroxidase; GST, glutathione S-transferase; HO-1, heme oxygenase-1; Keap 1, Kelch-like ECH-associated protein 1; Nrf2, Nuclear factor E2-related factor 2; PRX, peroxiredoxin; SOD, superoxide dismutase; Trx, thioredoxin.

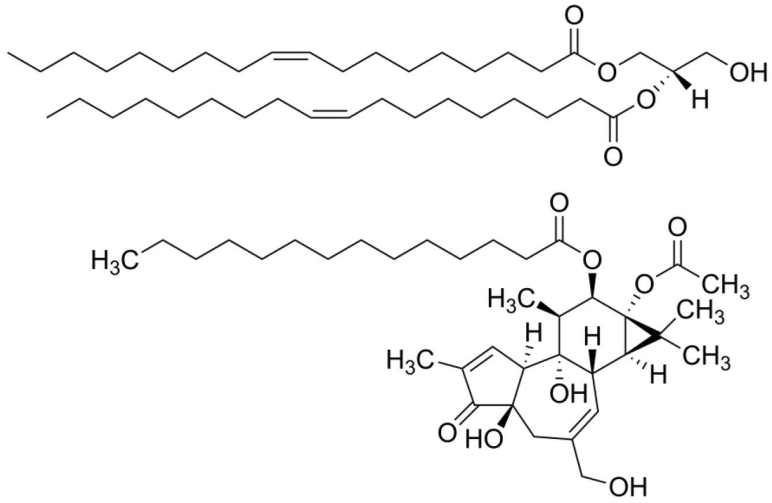

Fig.5.

DAG, *sn*-1, 2-dioleoylglycerol (top) and phorbol ester, phorbol 12-myristate 13- acetate (TPA) (bottom).

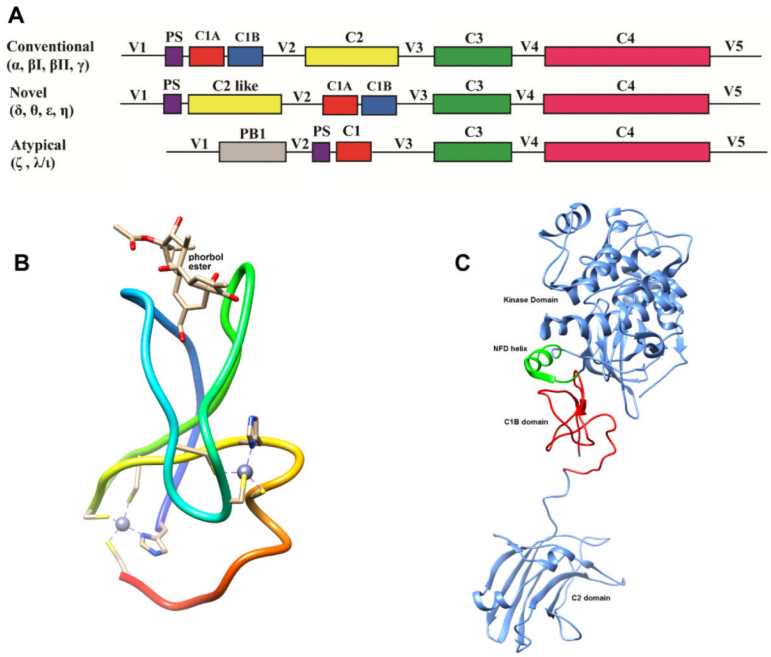

Fig.6.

A. Schematic representation of the PKC domains. For conventional and novel PKCs, four distinct domains are C1, C2, C3 and C4 and five variable regions are V1, V2, V3, V4 and V5. PS is the pseudosubstrate domain. B, Structure of the phorbol ester-bound PKCδC1B (PDB ID: 1PTR). C, Ribbon representation of the structure of the full-length PKCβII (PDB ID: 3PFQ), comprising the C1B domain (red), C2 domain (cornflower blue), kinase domain (cornflower blue) and NFD helix (green).

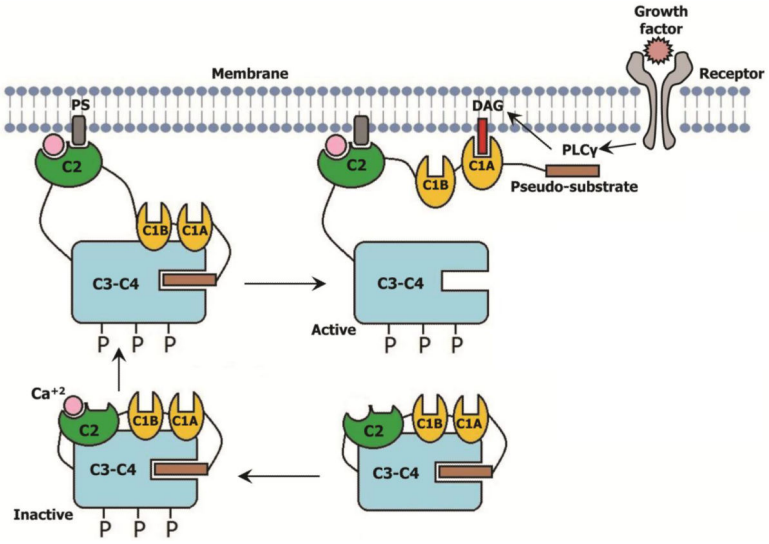

Fig.7.

Simplified scheme showing the activation process of Ca^{+2}-sensitive PKCs. Embedded C2 domain in C3–C4 domain of inactive conventional PKC first binds to cytosolic calcium. In the next step the calcium bound C2 domain anchored to the PS of the membrane, which pulls out the C1 domains away from the catalytic domain. Then the C1A domain first binds to the DAG which eventually pulls out the pseudosubstrate motif from the substrate binding pocket and thereby activating the PKC.

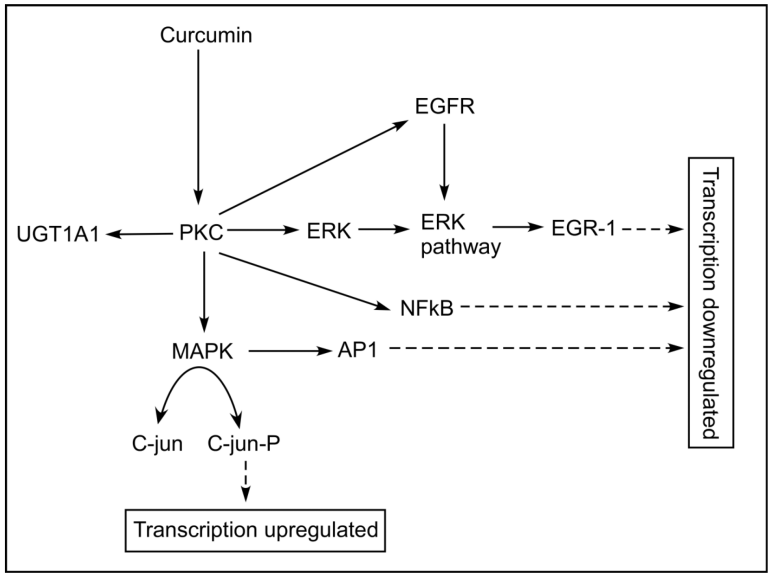

Fig.8.

Curcumin and PKC signaling pathway in colon cancer. Curcumin suppresses the activity of PKC subsequently affecting MAPK and C-jun. The down-stream effects of PKC include inhibition of UGT, ERK pathway and EGFR affecting the transcription factors and regulators AP-1, NF-kB and ERG-1. UGT, UDP-glucuronosyltransferase; ERK, Extracellular signal-regulated kinase; EGFR, Epidermal growth factor receptor; MAPK, Mitogen activated protein kinase; AP-1, Activated protein-1; EGR, Early growth response.

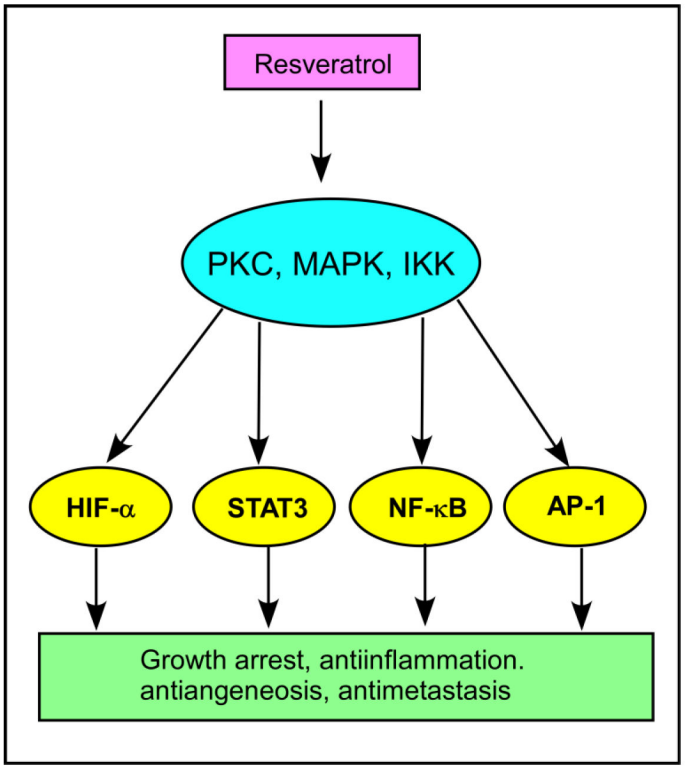

Fig.9.

Effect of resveratrol on various PKC-mediated biological responses. Resveratrol suppresses the activity of kinases such as protein kinase C (PKC), mitogen-activated protein kinases (MAPK) and IκB kinase (IKK) and transcription factors such as hypoxia-inducible factor-1α (HIF-1α), signal transducer and activator of transcription 3 (STAT3), nuclear factor κB (NF-κB) and activator protein-1 (AP-1) leading to various conditions in response to oncogenic stimuli.

Table 1

Mode of regulation of PKC by dietary polyphenols

Polyphenol	Mode of PKC regulation	References
Curcumin	Activation of PKCα in the presence of lipid	[115]
	Inhibition of PKCα in the absence of lipid	[115]
	Activation of Ca^{++}-sensitive PKC in the presence of lipid	[114]
	Inhibition of Ca^{++}-sensitive PKC in the absence of lipid	[114]
	Inhibition of PKC in NIH 3T3 fibroblasts	[108]
	Inhibition of PKCα, PKCε, PKCη in mouse skm	[112]
	Inhibition of PKCα in CHO-K1 cells	[116]
	Inhibition of purified PKC	[109]
Resveratrol	Activation of PKCγ	[133]
	Inhibition of PKCα in prostate cancer cells	[136]
	Inhibition of PKC in neutrophil	[134]
	Inhibition of PKCδ splice variant in 3T3L1 adipocytes	[138]
	Inhibition of purified PKCα and PKCβI	[139]
	Inhibition of PKCα in CHO-K1 cells	[141]
	Downregulation of PKC expression in mammary and epithelial cells	[128]
	Downregulation of PKCδ expression	[129]
Epigallocatechin 3-gallate	Inhibition of PKCα	[146]
	Activation of PKC	[154]
	Inhibition of PKC	[156], [157]
	Downregulation of PKCα expression	[148]
	Upregulation of PKCα and PKCε	[149]
	Downregulation glucose-induced phosphorylation of PKCα and PKCβII in glomerular epithelial cells	[152]
Quercetin	Inhibition of PKC	[166], [167]
	Activation of Ca^{++}-sensitive PKC at low concentration	[168]
	Inhibition of Ca^{++}-sensitive PKC at higher concentration	[168]
	Inhibition of PKCδ in MCF-7 cell	[169]
	Activation of PKCα in human lymphocyte cell	[175]
	Inhibition of PKCθ in mast cell	[176]
Ellagic acid	Inhibition of PKC in platelet	[184]
	Upregulation of PKCδ activity in in DL mice	[187]
	Upregulation of expression of PKCδ, PKCε, PKCη and PKCθ in DL mice	[187]
Caffeic acid	Inhibition of PKCα, PKCβ and PKCγ in monocyte and in partially purified protein	[190]
Protocatechuic acid	Inhibition of PKCα, PKCγ and PKCζ in Swiss mouse epidermis	[197]
Tannic acid	Inhibition of PKCα, PKCβI, PKCβII in mouse epidermis	[197]

Polyphenol	Mode of PKC regulation	References
	Inhibition of PKC autophosphorylation in mouse fibroblasts	[204]
	Inhibition of PKC activity in human carcinoma cells	[205]
	Inhibition of PKC activity in airway epithelial cells	[206]
	Inhibition of PKC activity in purified protein	[207]
Chlorogenic acid	Inhibition of PKCα and PKCζ in mouse epidermis	[197]
Apigenin	Activation of PKCδ in leukemia cell	[213]
	Inhibition of PKCδ in keratinocyte	[214]
	Inhibition of PKC in embryonic fibroblasts	[215]
Theaflavin 3,3-digallate	Inhibition of PKCα in NIH 3T3 cells	[219]
Verbacoside	Inhibition of rat brain PKC	[230]
Viniferin	Inhibition of PKCα, PKCβII, PKCγ, PKCδ, PKCε in partially purified protein	[244]
Rosmarinic acid	Inhibition of rat brain PKC	[146]
Miyabenol C	Inhibition of rat brain PKC	[254]
	Inhibition of PKCα, PKCβII, PKCγ, PKCδ, PKCε in partially purified protein	[244]
Vanicoside A1 and B2	Inhibition of PKC	[260]
Hydroxytyrosol	Inhibition of PKCα and PKCβI	[262]
Isorhametin, kaempferol, luteolin, myricetin, rhmnetin, dodecyl gallate	Inhibition of PKCα	[146]
Fisetin, luteolin, morin, rutin	Inhibition of PKC	[166], [167]