



# Anticancer potential of delphinidin and its derivatives: therapeutic and mechanistic insights

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## Abstract

Anthocyanins are water-soluble naturally occurring flavonoids present in fruits, flowers, leaves, and roots of fruit plants and vegetables. One of the important anthocyanidin components of red wine and berries is delphinidin (DP). This review provides an update on the potential of DP in cancer therapy, with a further understanding of the mechanisms involved. Delphinidin has been shown to elicit inhibitory effects on catabolizing enzymes of human granulocytes and parasites, TNF-induced COX-2 expression in mouse epidermal cells, and reduce oxidative stress. It also inhibited anchorage-independent growth and caused cell death in breast cancer cell lines. Delphinidin increased Nrf2 expression, increased HO-1 production, and promoted mRNA expression of mitochondrial biogenesis-related factors. Further, DP has anti-proliferative and pro-apoptotic effects in various cancer cell lines such as lung, breast, and ovarian cancer cells. The mTOR-related pathway is the most important signaling pathway in the activation of autophagy, and DP has been shown to exert its cytotoxic effects on cancer cell lines via activating protein kinases. Among DP derivatives, delphinidin-3-O-glucoside has the best anticancer activity because it is easily absorbed. However, the metabolism of DP and its bioavailability in biological systems need to be explored to fully understand its benefits.

**Keywords** Pro-inflammatory genes · Target sites · Antiproliferative effect · Anthocyanins

## Introduction

In ancient times, medicines were primarily derived from natural sources due to their perceived safety, availability and affordability. Today, most drugs are synthetic, and are derived from scaffolds or plant-based molecules with known health benefits such as sterols, carotenoids, polyphenols, and anthocyanins [1]. The pharmacological

activities of phytoconstituents have been extensively studied. In this context, flavonoids (flavones, flavanones, isoflavonoids, flavonols, flavans, and anthocyanins) feature as one of the well-known phytochemical groups which differs structurally at the heterocyclic oxygen ring. One of the most important flavonoids is the anthocyanin, delphinidin (Fig. 1).

Delphinidin (3,3,4,5,5,7-hexahydroxyflavylium) is abundant in colored fruits and vegetables, especially blueberries, pomegranates, grapes, beets and eggplants [2, 3]. Several derivatives of delphinidin (DP) have been reported in plants (Table 1; Fig. 2), and some have displayed interesting anti-mutagenic, anti-angiogenic, anti-oxidant, and anti-inflammatory activities [4]. Delphinidin is light-sensitive and remains stable only at pH 3. It is quickly degraded in physiological settings, poorly absorbed and thus its bioavailability is low [5]. Although DP and its derivatives have a vast array of therapeutic effects, the underlying molecular mechanisms are not yet clearly understood [6]. In this review, we delve into the anticancer potential of DP and its derivatives, giving the mechanistic insights into its mode of action.

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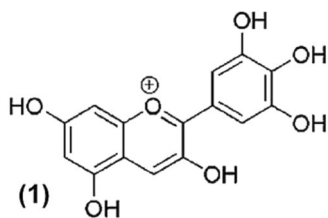


Fig. 1 Chemical structure of delphinidin

## Structural characteristics of delphinidin and its derivatives, and their relationships with anticancer activities

Delphinidin is a polyphenolic compound with its basic structure based on the flavylium cation, which consists of a three-ring system ( $C_6-C_3-C_6$ ), otherwise called the anthocyanidin skeleton. This structure has two aromatic rings: A (resorcinol) and B (catechol), and C (3-O-substituted-pyrylium), a heterocyclic ring [4]. Delphinidin has hydroxyl groups (-OH) at the 3, 5, 7, 3', 4', and 5' positions of the anthocyanidin skeleton. Oxygen in the first position is linked to the sugar moiety at the 3-O- $\beta$ - position of the C ring. In the three rings, DP has 6 hydrogen bond donor and 6 hydrogen bond acceptor atoms. Because of the presence of numerous electron donor atoms, DP acts as a potent antioxidant by scavenging reactive oxygen species (ROS). The presence of a 3-hydroxyl group in ring B of DP distinguishes it from other anthocyanins. It also possesses two hydroxy groups in ring A. Because these -OH groups interact potently with a wide range of proteins, they are accountable for several important biological processes [7].

Although DP is more active in its aglycone form, its bioavailability depends on a sugar moiety being present in the third position of the C ring [8]. Due to the presence of several hydroxyl groups, DP is extremely polar in comparison to other anthocyanins and is hence readily soluble in methanol and water [9]. In the C-3 position, DP is connected to a range of sugar moieties, including glucoside and arabinoside. These glycosides (DP derivatives; Fig. 2) have improved solubility and stability compared to the aglycone form. The type, quantity, and location of sugars in the DP molecule, the degree of hydroxyl group methylation, and the number of aliphatic or aromatic acids attached to sugars in a DP derivative are the features that distinguish DP derivatives from one another [10]. Acylation (addition of acyl groups, for example, p-coumaric and caffeic acids) of the glycosyl moieties are typical modifications that can enhance the stability and bioavailability of DP derivatives. Such acylated DP derivatives tend to elicit enhanced anticancer activities owing to increased lipophilicity and improved interaction with cellular membranes [11]. Another important

structural feature of DP derivatives is methylation at hydroxyl positions, which can lead to increased stability and altered bioactivity. For instance, the methylation of hydroxyl groups can affect the antioxidant properties and interaction with cellular targets as in malvidin, a DP derivative [12].

Regarding the relationship of the structural features of DP and its derivatives to their anticancer properties, several aspects can be highlighted. Firstly, the hydroxyl groups of DP and its derivatives are largely responsible for their scavenging free radicals and ROS, which are implicated in cancer development and progression. By reducing oxidative stress, DP and its derivatives can inhibit the initiation and promotion stages of carcinogenesis [13]. Secondly, pro-apoptotic effects (induction of apoptosis and cell cycle arrest) of DP are mediated through various pathways (discussed in later sections) in cancer cells, including the mitochondrial pathway and the activation of caspases. The presence of hydroxyl groups enhances its ability to interact with and modulate apoptotic proteins. Specifically, DP can cause cell cycle arrest, particularly in the G2/M phase, by modulating the expression of cell cycle regulatory proteins such as cyclins and cyclin-dependent kinases (CDKs) [14]. Thirdly, the anti-inflammatory properties of DP is achieved through inhibition of inflammatory pathways (key inflammatory mediators such as NF- $\kappa$ B and COX-2) which are often upregulated in cancer cells. This anti-inflammatory action contributes to its anticancer effects. Further, DP can exert an effect on signaling pathways, and by modulating signaling pathways involved in inflammation and cell proliferation, it can suppress tumor growth and metastasis [14]. Fourthly, DP can inhibit angiogenesis (the process of new blood vessel formation) which is essential for tumor growth and metastasis. This is partly achieved by downregulating pro-angiogenic factors like VEGF. The antioxidant and anti-inflammatory properties of DP contribute to its anti-angiogenic effects, thereby reducing the nutrient and oxygen supply to tumor cells [13] (Sharma et al. [13]). Lastly, the epigenetic modulatory effect of DP and its derivatives are reportedly crucial in inhibiting tumor progression. The molecules modulate the expression of genes involved in cancer progression through epigenetic mechanisms, such as histone modification and DNA methylation. Such epigenetic modulations can lead to the reactivation of tumor suppressor genes and the silencing of oncogenes, contributing to the anticancer effects of DP [15].

Taken together, the structural characteristics of DP and its derivatives, particularly the presence of hydroxyl groups and potential modifications like glycosylation, acylation, and methylation are crucial for their anticancer

**Table 1** Occurrence of delphinidin and its derivatives in plants based on published literature

Plant part/common name	Scientific name	Delphinidin and its derivatives	References
<b>1. Fruits</b>			
Bilberry	<i>Vaccinium myrtillus</i> L.	Delphinidin-3-glucoside (2)	[91]
Mulberry	<i>Malus pumila</i> L.	Delphinidin-3-rutinoside (3)	[92, 93]
Blueberry	<i>Vaccinium corymbosum</i> L.	Delphinidin-3-galactoside (4) Delphinidin-3-arabinoside (5)	[91]
Currant	<i>Ribes rubrum</i> L. <i>Ribes nigrum</i> L.	Delphinidin-3-glucoside (2), Delphinidin-3-rutinoside (3) Delphinidin-3-glucoside (2), Delphinidin-3-rutinoside (3)	[91, 94] [91, 94]
Grape	<i>Vitis vinifera</i> L.	Mono-glucoside (6), Di-glucoside (7)	[91, 95]
Orange	<i>Citrus sinensis</i> L.	Delphinidin glycosides (8)	[96]
Pomegranate	<i>Punica granatum</i> L.	Delphinidin-3-glucoside (2), Delphinidin-3,5-diglucoside (9)	[97, 98]
Saskatoon Berry	<i>Amelanchier alnifolia</i> Nutt.	Delphinidin-3-glucoside (2)	[99]
<b>2. Leguminous plants</b>			
Beans	<i>Phaseolus</i> species	Delphinidin-3,5-diglucoside (9)	[100, 101]
Eggplant	<i>Solanum melongena</i> L.	Delphinidin-3-glucoside (2), Delphinidin-3-rutinoside (3), Delphinidin-3- <i>p</i> -coumarylrutinoside-5-glucoside (10), Delphinidin-3-glucosylrhamnoside (11)	[102, 103]
Lentil	<i>Lens culinaris</i> Medic	Delphinidin-3,5-diglucoside (9), Delphinidin-3-glucosylarabinoside (12)	[104, 105]
Pea	<i>Pisum sativum</i> L.	Delphinidin-3-xylosylgalactoside-5-acetylglucoside (13), Delphinidin-3-xylosylgalactoside-5-glucoside (14)	[106]
Pepper	<i>Capsicum annuum</i> L.	Delphinidin-3- <i>trans</i> -coumaroylrutinoside-5-glucoside (15)	[107]
Rhubarb	<i>Rheum</i> species	Delphinidin-3-rutinoside (3)	[108]
Soybean	<i>Glycine max</i> L.	Delphinidin-3-glucoside (2), Delphinidin-3-galactoside (4)	[109, 110]
Barley	<i>Hordeum vulgare</i> L.	Delphinidin-3-glucoside (2), Delphinidin-3-rutinoside (3)	[111–113]
Rice	<i>Oryza sativa</i> L.	Delphinidin-3-galactoside (4), Delphinidin-3-arabinoside (5)	[114, 115]
Rye	<i>Secale cereale</i> L.	Delphinidin-3-glucoside (2), Delphinidin-3-rutinoside (3)	[116]
Wheat	<i>Triticum</i> species	Delphinidin-3-glucoside (2), Delphinidin-3-rutinoside (3)	[117, 118]
Da Zao	<i>Ziziphus jujube</i> Mill.	Delphinidin-3-glucoside (2), Delphinidin-3,5-diglucoside (9)	[119]
Juju (Chicory)	<i>Cichorium glandulosum</i> Bioss.	Delphinidin-3-malonylglucoside-5-glucoside (16)	[120]
Sha Ji (Common Sea Buckthorn)	<i>Hippophae rhamnoides</i> L.	Delphinidin-3-glucoside (2), Delphinidin-3-rutinoside (3)	[99]
Zi Hua Di Ding	<i>Viola yedoensis</i>	Delphinidin-3- <i>cis-p</i> -coumaroylrutinoside-5-glucoside (17) Delphinidin-3-acetylrutinoside-5-glucoside (18)	[121]
Kamala	<i>Nelumbo nucifera</i>	Delphinidin-3-glucoside (2)	[122, 123]
Ceylon Gooseberry	<i>Dovyalis hebecarpa</i>	Delphinidin-3-glucoside (2), Delphinidin-3-rutinoside (3), Delphinidin-3-(6''-acetyl)-glucoside (19)	[124]
Jaboticaba (or Jabuticaba)	<i>Myrciaria cauliflora</i>	Delphinidin-3-glucoside (2)	[125]
Jamelão	<i>Syzygium cumini</i>	Delphinidin-3,5-diglucoside (9)	[2]
Maqui Berry (also known as Maqui or Chilean Blackberry)	<i>Aristotelia chilensis</i>	Delphinidin-3-glucoside (2), Delphinidin-3,5-diglucoside (9), Delphinidin-3-sambubioside (20), Delphinidin-3-sambubioside-5-glucoside (21)	[126–129]
Roselle	<i>Hibiscus sabdariffa</i> L.	Delphinidin-3-glucoside (2)	[130]

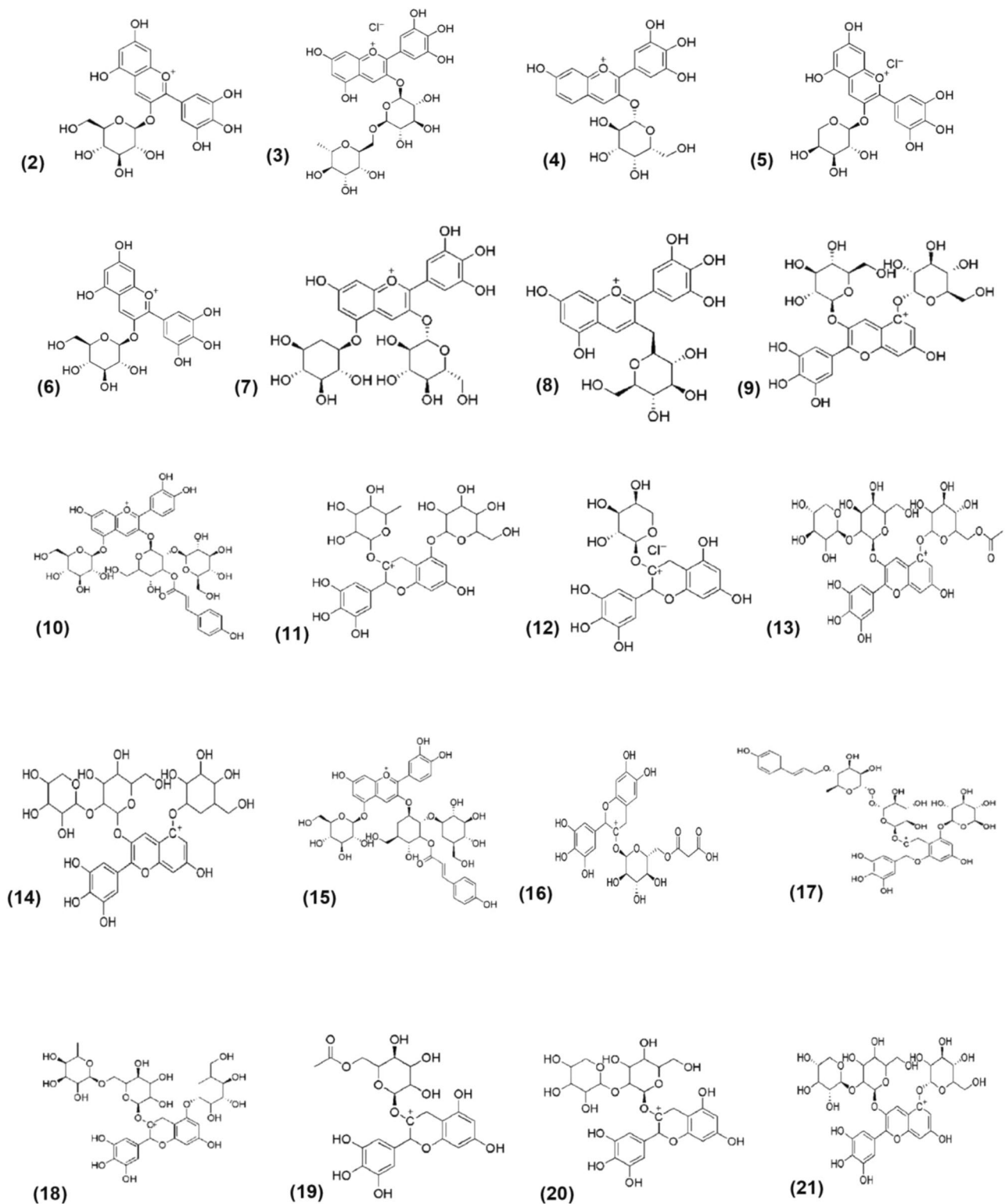
properties. These features enable DP to exert antioxidant, pro-apoptotic, anti-inflammatory, anti-angiogenic, and epigenetic effects, making it a promising candidate for cancer prevention and therapy. However, further research is evidently required to fully understand and optimize these properties for clinical applications.

## Biosynthesis of delphinidin

Naturally, DP is biosynthesised from coumaroyl-CoA and malonyl-CoA, with 3',5'-hydroxylase serving as the primary enzyme (Fig. 3). The de novo assembly approach for anthocyanin biosynthesis involves the use of uni-genes, the genes for chalcone synthase (CHS) and

cinnamoyl-4-hydroxylase (C4H) [16, 17]. The enzymes proanthocyanidins and flavonoid 3-O-glucosyltransferase (UFGT) compete to produce anthocyanins and reductase, respectively. Enzymatic reduction of DP and leucodelphinidin results in the formation of galocatechin and epigallocatechin. Prodelphinidin is created by polymerization of both epigallocatechin and galocatechin (catechin) [18].

The flavonoid route, which follows a similar upstream pathway with pro-anthocyanidins until anthocyanins are formed by the catalysis of anthocyanidin synthase (leucoanthocyanidin dioxygenase) is responsible for the synthesis of free anthocyanins in grapes [19]. Examining the pre- and post-harvest mechanisms, blueberry anthocyanin production was found to be significantly boosted

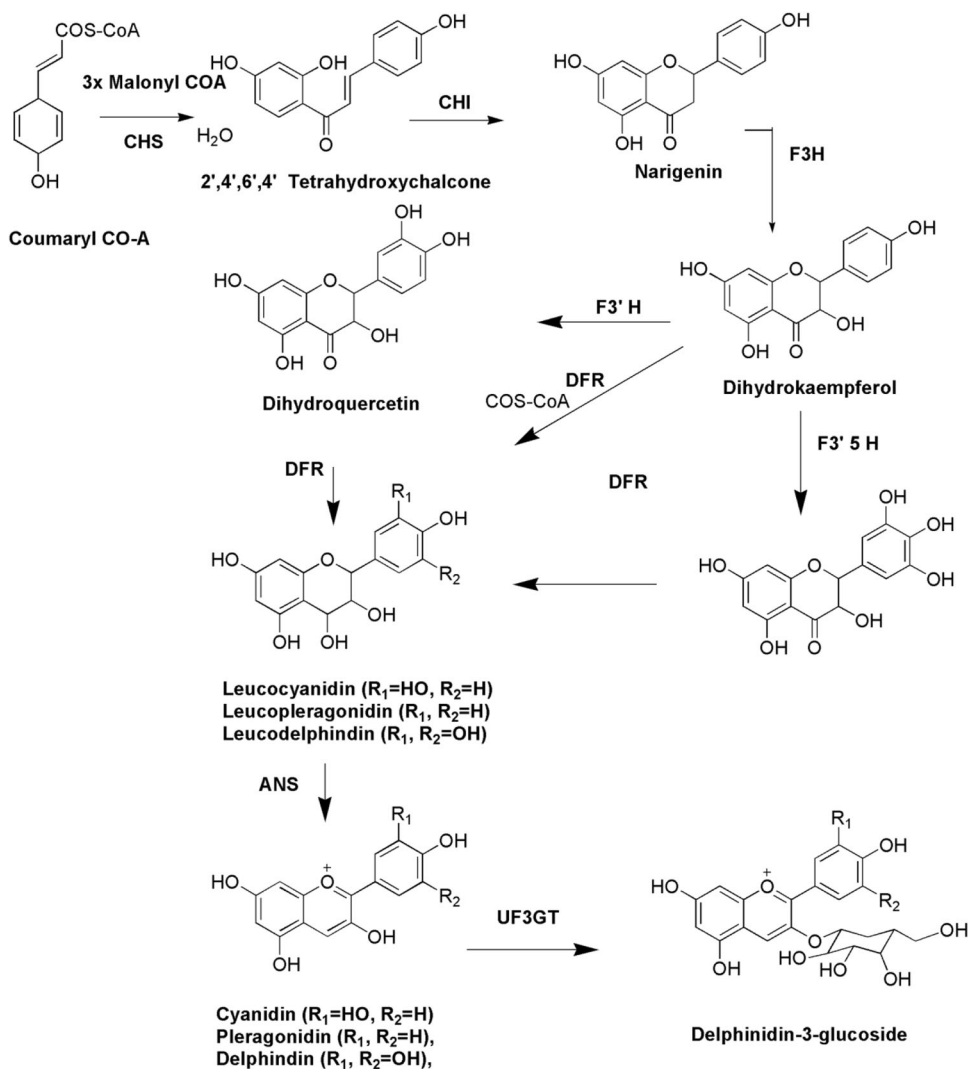


**Fig. 2** Structure of delphinidin derivatives identified in various plants and herbal products. The numbers (1 to 20) refer to the molecules mentioned in Table 1

by pre-harvest UV-B, C, and post-harvest UV-A, B, and C irradiation [20]. Anthocyanin production was enhanced in purple-colored leaves, according to a variety of

metabolites detected by HPLC-MS, with the highest concentrations of anthocyanidins, pro-anthocyanidins, and kaempferol glycoside [21].

**Fig. 3** Delphinidin biosynthetic pathway. F3'H flavanone-3/5'-hydroxylase, CHI chalcone isomerase, CHS chalcone synthase, F3H flavanone 3-hydroxylase, UF3GT UDP-Glc flavanoid 3-O-glucosyl transferase, DFR dihydroflavonol-4-reductase, F3'5'H flavanoid-3',5'-hydroxylase, ANS anthocyanidin synthase. Adapted from [4]



## Anticancer potential of delphinidin

Anthocyanins are widely promoted due to the vast array of their perceived health benefits. Both DP and its derivatives has anticancer efficacy against various molecular subtypes of well-established cancer cell lines (Table 2). DP inhibited anchorage-independent growth and caused apoptosis in HER2-overexpressing, ER-positive breast cancer cell lines. The upregulation of mitogenic kinases in breast cancer cells pretreated with DP was found to have been blocked [22]. DP was shown to reduce the risk of cancer by inducing apoptosis in endothelial cells [23, 24]. The mechanism of cytotoxicity involved DNA damage of the treated cells that were unable to produce tyrosyl-DNA-phosphodiesterase 1, suggesting that topoisomerase was not the primary cause of DNA strand breakage. In another study, DP prevented menadione-induced DNA damage in HT29 cells and exerted an antioxidative effect in the presence of catalase when hydrogen peroxide formation was reduced in cells [25].

Similarly, DP inhibited COX-2 expression and tumor progression in mouse skin epidermal cells by targeting mitogen protein kinase [26]. In human colon cancer cells, DP treatments upregulated caspases 3–8 and 9 while Bcl-2 protein decreased and the cellular division was arrested at the G2/M phase [27]. A mechanistic study found that DP exhibited anticancer effects in treating ovarian cancer with poor prognosis and resistance to treatment via inhibition of ERK1/2 MAPK and PI3K/AKT signal transduction cascades in ES2 cells from ovarian clear cell carcinoma [28]. This was in agreement with earlier studies which concluded that DP downregulated ERK-MAPK and PI3K/AKT signaling cascades in SKOV3 cells and inhibited cancer cell progression, suggesting that these signaling pathways are the main targets of DP for the prevention of epithelial ovarian cancer that is resistant to paclitaxel [29]. Brain-derived neurotrophic factor (BDNF) induced increased cell migration and invasion of SKOV3 ovarian cancer cells but DP treatments reinstated cell invasion and migration by

**Table 2** Protective effect of delphinidin against different cancer cell progressions

Cancer	Experimental model	IC <sub>50</sub>	Test concentrations	Results	References
Ovarian	ES2	ND	0.1, 1, 10, 50, and 100 $\mu$ M	PI3K/Akt $\downarrow$ , ERK1/2/JNK $\downarrow$	[28]
Ovarian	SKOV3	ND	50 and 75 $\mu$ M	MMP-2, -9 $\downarrow$ , p-Akt $\downarrow$ , NF-kB $\downarrow$	[30]
Ovarian	SKOV3	ND	0.1, 1, 10 $\mu$ M	pS6 $\downarrow$ , p-Akt $\downarrow$ , pP70S6K $\downarrow$ , p-ERK1/2 $\downarrow$ , p-P38 $\downarrow$ , MAPK $\downarrow$	[29]
Colorectal	HCT-116, CRC, HT29, PBMCs	D3G; 395.8 $\mu$ g/mL C3G; ND	100 to 600 $\mu$ g/mL	PD-L1 $\downarrow$	[31]
Colorectal	SW620 DLD-1, SW480	ND	20, 40, 60, 80, 100 $\mu$ M	EMT $\downarrow$ , $\beta$ -catenin $\downarrow$ , MMP-2 $\downarrow$ , E-cadherin $\downarrow$	[32]
Colorectal	Mice	ND	100 $\mu$ M	FAK $\downarrow$ , Src $\downarrow$	[32]
Colorectal	HT-29	ND	25 $\mu$ g/mL	PGK1 $\downarrow$	[33]
Colorectal	HCT-116	DP; 106 $\mu$ M	80, 100, 120 $\mu$ M	BAX $\uparrow$ , caspase-3, -8, -9 $\uparrow$ , p-ERK1/2 $\downarrow$ , p-STAT-3 $\downarrow$ , Cytochrome C $\downarrow$ , p-p38 $\downarrow$ ,	[34]
Colorectal	HCT-116	ND	30, 60, 120, 180, 240 $\mu$ M	p53 $\uparrow$ , Bcl-2 $\downarrow$ , NF-kB $\downarrow$	[27]
Lung	A549	ND	10, 20, 40 $\mu$ M	HIF-1 $\alpha$ $\downarrow$ , Angiogenesis $\downarrow$ , PI3K/Akt/mTOR $\downarrow$ , VEGF $\downarrow$	[35]
Lung	NSCLC	DP; 30.1 $\mu$ M	1, 5, 10, 20 $\mu$ M	ATG12 $\uparrow$ , JNK/MAPK $\uparrow$ , LC3-II $\uparrow$	[36]
Lung	Mice	ND	1, 2 mg	PCNA $\downarrow$ , CD31 $\downarrow$ , VEG $\downarrow$ , Ki67 $\downarrow$	[37]
Lung	NSCLC	ND	5, 10, 20, 40, 60 $\mu$ M	VEGFR2 $\uparrow$ , BAX $\uparrow$ , EGFR $\downarrow$	[37]
Prostate	PC-3	DP; 90 $\mu$ mol/L	30, 60, 90, 20, 180 $\mu$ mol/L	Caspase-3, -9 $\uparrow$ , Cyclin D1 $\downarrow$ , Cyclin A $\downarrow$ , cdk1 $\downarrow$ , cdk2 $\downarrow$	[38]
Prostate	LNCaP	ND	30, 60, 90 $\mu$ M	BAX $\downarrow$ , XIAP $\downarrow$ , caspase-7, -8, -9 $\uparrow$ , DR5 $\uparrow$ , Bcl-2 $\downarrow$	[39]
Prostate	Mice	ND	2 mg	Bcl-2 $\downarrow$ , BAX $\uparrow$ , NF-kB $\downarrow$ , cyclin D1 $\downarrow$	[38]
Prostate	LNCaP	ND	50, 100, 150 $\mu$ M	BAX $\uparrow$ , HDAC3 $\uparrow$ , PARP-1 $\downarrow$ , PUMA $\uparrow$	[40]
Prostate	PC-3	ND	15, 30, 60, 120, 180, 240 $\mu$ M	Catenin $\downarrow$ , E-cadherin $\uparrow$	[41]
Skin	HaCaT	ND	1.5, 10, 15, 20 $\mu$ M	Cleaved PARP $\downarrow$ , Lipid peroxidation $\downarrow$	[42]
Skin cancer	JB6 P+	ND	5, 10, 20, 40 $\mu$ M	PGE2 $\downarrow$ , NF-kB $\downarrow$ , COX-2 $\downarrow$ , p-MSK $\downarrow$ , AP-1 $\downarrow$ , p-ERK $\downarrow$ p-90RSK $\downarrow$	[26]
Skin	SKH-1	ND	1 mg	8-OHd $\downarrow$ , CPDs $\downarrow$	[42]
Skin	JB6 P+	DP; <20 $\mu$ M	10, 20, 40, 60, 80, 100 $\mu$ M	DNMTs $\downarrow$ , Nrf2 $\uparrow$ , Hmox1 $\uparrow$ , Nqo1 $\uparrow$ , SOD1 $\downarrow$ , HDACs $\downarrow$	[15]
Skin	HaCaT	DP; 20 $\mu$ M	510 $\mu$ M	Elastic modulus $\uparrow$	[43]
Liver	HepG2	DP; 10.8 $\mu$ M Cyanidin; 18.4 $\mu$ M Malvidin; 50.4 $\mu$ M	50, 100, 150, 200 $\mu$ M	Bcl-2 $\uparrow$ , c-Jun $\uparrow$ , p-JNK $\uparrow$	[44]
Liver	SMMC7721	ND	100, 150 $\mu$ M	EGFR $\downarrow$ , EMT $\downarrow$ , MMP2 $\downarrow$ , ERK $\downarrow$ , AKT $\downarrow$	[45]
Leukemia	HL-60	ND	100 $\mu$ M	Caspase-3 $\uparrow$ , p-JNK $\uparrow$ , c-Jun $\uparrow$	[46]
Leukemia	HL-60	<i>Hibiscus</i> extracts; 3 mg/mL	0, 0.1, 0.3, 0.5, 0.7 mg/mL	Cell arrest at phase G2/M	[47]
Leukemia	HL-60	<i>Hibiscus</i> extracts; 2.49 mg/ml	3 mg/mL	p-p38 $\uparrow$ , p-c-jun $\uparrow$ , caspase-3, -8 $\uparrow$ , Cytochrome C $\uparrow$	[48]
Leukemia	HL-60	DP; 1.9 $\mu$ M Cyanidin; 11.7 $\mu$ M Pelargonid; 16.4 $\mu$ M	10, 30, 100 $\mu$ M	Apoptosis $\uparrow$	[49]
Leukemia	HL-60	Dp3-Sam; 75 $\mu$ M	25, 50, 75, 100, 125 $\mu$ M	Caspase-9, -8, -3 $\uparrow$ , Cytochrome C $\downarrow$	[50]
Leukemia	Jurkat	ND	100 $\mu$ M	ROS $\downarrow$ , p-Bad $\downarrow$ , p-Akt, $\downarrow$ , UHRF $\downarrow$	[51]

**Table 2** (continued)

Cancer	Experimental model	IC <sub>50</sub>	Test concentrations	Results	References
Bladder	T24	DP; 34 µg/ml	10, 20, 30, 40, 50, 60 µg/mL	ROS ↓	[52]
Osteosarcoma	U2OS	ND	10, 50, 100, 200 µM	Cell viability ↑, ROS ↓, LC3-II ↓, p62 ↓	[131]
Osteosarcoma	U2OS, HOS	ND	10, 25, 50, 75, 100 µM	E-cadherin ↓, Slug ↓, Snail ↓, EMT ↓, ERK ↓	[132]
Glioma	U-87 MG	ND	35, 50 µM	TGF/Smad2 ↓, TGF/ERK ↓, Snail ↓	[53]
Glioma	LN18, U87MG	ND	10, 25, 50 µM	p-Akt ↓, NF-κB ↓, VEGF ↓, MMP-2, -9 ↓	[54]
Breast	MCF-10A	ND	5, 10, 20, 40 µM	p-JNK ↓, p-Crk ↓, p-FAK ↓, p-src ↓	[133]
Breast	Mice	ND	Del 10 mg/kg	Apoptosis ↑	[134]
Breast	MCF-7	ND	12.5, 25, 50, 100 µM	Antiproliferative effect	[55]
Breast	MDA468, MDA453, MCF7, HCC1806, MDA231	DP; 50 µg/mL	12.5, 50, 25, 100 µg/mL	p-HER2 ↓, p-ERK1/2 ↓, p-Akt ↓	[22]
Breast	MDA-MB-231	ND	50, 25, 12.5 µM	p-GSK3 ↓, Bcl-2 ↓, p53 ↓	[134]
Breast	MCF-7	ND	15, 30, 60, 90 µM	p-JNK ↓, MMP-9 ↓, p-p38 ↓	[56]

↓ means Downregulated, ↑ means Upregulated, ND means Not determined

downregulating the expression of MMP-2 and MMP-9, Akt and NF-κB [30]. In another investigation where HCT-116 and HT-29 human colorectal cancer cells were treated with pure phenolics such as delphinidin-3-O-glucoside (D3G), and cyanidin-3-O-glucoside (C3G) either alone or in combination (100–600 µg/mL), programmed death ligand 1 (PD-L1) fluorescence intensity was found to be 39% reduced by C3G. In peripheral blood mononuclear cells, anthocyanins reduced programmed death protein-1 (PD-1) expression by 41 and 55% in monoculture, 39 and 26% (for C3G), 50 and 51% (D3G) in co-culture with HCT-116 and HT-29 cells, respectively [31]. Huang et al. also inferred that DP (<100 µM) encumbered the progression of colorectal cell lines (DLD-1, SW480 and SW620) via inhibition of focal adhesion kinase (FAK)/Src/paxillin, integrin αV/β3, and interfered with cytoskeletal assembly as well as lowered the migratory capacity and invasiveness in the treated CRC cell lines [32].

Jang et al. performed proteomic analysis and western blotting and demonstrated that phosphoglycerate kinase 1 (PGK1) was increased by hydrogen peroxide in a dose-dependent manner and that its expression was inhibited by co-treatment with the recognized antioxidant DP [33]. According to Zhang et al. [34], DP treatments induced changes in mitochondrial membrane potential which triggered Bax, Caspase-3, 8, and 9, cytochrome C, and suppressed anti-apoptotic protein expression, phosphorylation of the activities of STAT-3 and MAPKinase signaling in colon cancer cells (HCT116). Yu and colleagues examined the antiproliferative and proapoptotic characteristics of DP in human colon cancer (HCT116) cells and unraveled that subjecting the cells to DP (30–240 µM; 48 h) led to: (i) a reduction in cell viability; (ii) apoptosis; (iii) PARP

cleavage; (iv) upregulation of caspases-3, -8, and -9; (v) upregulation of Bax and downregulation of Bcl-2 protein; (vi) G2/M phase cell cycle arrest [27]. In A549 cells, DP decreased the activity of hypoxia response element (HRE) promoter triggered by cobalt chloride and epidermal growth factor (EGF) by inhibiting VEGF, ERK, PI3K/Akt/mTOR/p70S6K signaling pathways, reduced HIF-1 binding to the HRE promoter, and greatly prevented the development of new blood vessels caused by EGF in animal models [35].

According to another research group, DP upregulated the expression of autophagy-induced cell death-related protein and downregulated the phosphorylation of PI3K, AKT, and mTOR in non-small cell lung cancer (NSCLC) cells exposed to radiations [36]. Athymic nude mice treatment with DP caused (i) tumor growth inhibition, (ii) reduced proliferation of PCNA and Ki67 and (iii) increased programmed cell death [37]. Similarly, PC3 cells treated with DP elicited a dose-dependent reduction of (a) phosphorylation of IκB kinase γ (NEMO), (b) phosphorylation of the inhibitory protein IκBα of nuclear factor-κB (NF-κB), (c) phosphorylation of NF-κB/p65 at Ser536 and NF-κB/p50 at Ser529, (d) nuclear translocation of NF-κB/p65, and (e) NF-κB DNA binding activity [38]. PC3 cells were treated with DP and outcomes showed inhibition of the cell progression by intrinsic and extrinsic apoptotic pathways via death receptor 5 and cleavage of histone deacetylase 3 [39]. Jeong [40] also found that DP treatments of LNCaP cells—a human prostate cancer cell line with p53 wild-type—increased the activity of caspase-3, -7, and -8 and decreased histone deacetylase and HDAC3, one of the class I HDACs activities. In addition, DP (15–180 µM, 72 h) triggered the formation of Axin and glycogen synthase kinase 3β

phosphorylation, blocked translocation of  $\beta$ -catenin and downregulated target  $\beta$ -catenin [41].

Based on the work of Afqaa and others, pretreating keratinocyte HaCaT cells with DP (1–20  $\mu$ M for 24 h) shielded cells from UVB (15–30  $\text{mJ}/\text{cm}^2$ )-mediated (i) apoptosis induction; (ii) reduction in cell viability; (iii) lipid peroxidation, (iv) reduced 8-hydroxy-2'-deoxyguanosine (8-OHdG), (v) expression of the nuclear antigen; (vi) lowered poly(ADP-ribose) polymerase cleavage; (vii) caspase activation; (viii) downregulation of Bcl-2; (ix) upregulation of Bax; (x) increase in the expressions of Bid and Bak [42]. Actually, DP was found to directly target and inhibit Raf and mitogen-activated protein kinase (MEK), and COX2 to repress 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced transformation production in JB6 promotion-sensitive mouse skin epidermal (JB6 P+) cells [26]. Other findings indicate that DP triggered Nrf2 promoter to modulate Nrf2-ARE pathway in JB6 P+ cells (skin cancer cells) and thereby could be a potent chemopreventive agent to treat skin cancer [15]. Evidently, UVB-exposed human keratinocyte cells (HaCaT) characterized by diminished metabolic activity, actin cytoskeleton rearrangement and elimination of 53BP1 cell repair marker had their normal activity restored by treatment with DP at 5 or (10  $\mu$ M) [43]. Along with cyanidin and malvidin, DP exerted growth inhibitory effects against human hepatoma (HepG2) cells via activation of caspase-3 in a time-dependent manner and activated poly (ADP-ribose) polymerase (PARP) cleavage. In addition, DP upregulated the expression of JNK and c-Jun according to RT-PCR and Western blot studies [44].

Another study indicated that DP triggered LC3 lipidation, a hallmark of macroautophagy in hepatocellular carcinoma (HCC) cells as inhibited with 3-methyladenine treatments, and resulted in extensive necrosis. Consequently, anthocyanins may cause distinct forms of cell death in various malignancies. Moreover, a combination of anthocyanins and a macroautophagy inhibitor may be utilized to treat malignancies like HCC [45]. In human promyelocytic leukemia cells (HL-60), the effective induction of apoptosis by DP was recorded at a concentration of 100  $\mu$ M in 6 h. In the study, DP promoted the activation of the JNK pathway, which included JNK phosphorylation, c-jun gene expression, and caspase-3 activation, concurrently with apoptosis in the HL-60 cells [46]. Tsai et al. was examined the impact of *Hibiscus* anthocyanins (HAs) that contain DP, in the human leukemia cell line HL-60 and the results of flow cytometry analysis were observed cell cycle arrest at the G2/M phase [47]. A previous study revealed that HAs in HL-60 cells, may induce apoptosis in cancer cells. In HL-60 cells, HAs administration (0–4 mg/ml) significantly and time- and dose-dependently promoted apoptosis and elevated phosphorylation in p38 and c-Jun, cytochrome c release, tBid, Fas, and FasL [48]. Takasawa

et al. also probed into the inhibitory properties of anthocyanidins (including pelargonidin, cyanidin, and DP) but only DP caused dose- and time-dependent apoptosis in HL-60 cells [49]. According to molecular evidence, delphinidin 3-sambubioside (Dp3-Sam) treatment of HL-60 cells caused the release of cytochrome c from mitochondria into the cytosol, the truncation of Bid, and a decrease of mitochondrial membrane potential in a time- and dose-dependent manner [50]. In Jurkat cells treated with blackcurrant extract that were rich in cyanidin-3-O-rutinoside, delphinidin-3-O-rutinoside, delphinidin-3-O-glucoside and cyanidin-3-O-glucoside, apoptosis was induced along with G2/M phase cell cycle arrest, upregulation of p73 and caspase 3 but downregulation of Bad, Akt and Bcl-2 [51].

Other than the foregoing, DP (10–60  $\mu$ g/mL) showed a noteworthy cytotoxic impact on T24 cells with a considerable proportion of dead cells observed [52]. Further, Ouanouki et al. explored the effects of anthocyanidins on TGF- $\beta$ -induced epithelial-mesenchymal transition (EMT) and their underlying mechanism(s), including cyanidin (Cy), DP, malvidin (Mv), pelargonidin (Pg), and petunidin (Pt). Anthocyanidins were added to human U-87 glioblastoma (U-87 MG) cells either before, concurrently with, or after the addition of TGF- $\beta$ . The results showed that depending on the treatment circumstances, anthocyanidins had varying effects on TGF- $\beta$ -induced EMT. Due to its ability to block both the TGF- $\beta$  Smad and non-Smad signaling pathways, DP was shown to be the most powerful EMT inhibitor [53]. Previous research was elucidated that the combination of DP treatment and the transfection of miR-137 mimics resulted in the reduction of cell invasion and the growth factor receptor (EGFR), angiogenic factors (VEGF and b-FGF), invasive factors (MMP-9 and MMP-2), and survival factors (p-Akt and NF- $\kappa$ B) [54]. MCF-10A cell treatments with DP was consequently inhibited hepatocyte growth factor (HGF) induced the expression of Met receptors, phosphorylated downstream regulators such as Src and FAK, and blocked mediated tyrosyl-phosphorylation [42]. Every anthocyanin pigment under investigation suppressed the growth of the MCF-7 in a dose-dependent manner. MCF-7 cell treatments with Dp-3-gluc was increased the cytotoxicity as compared to the corresponding portosin. The data suggested that the moiety in the phenolic ring (ortho-trihydroxylated) is a crucial structural component to exert cytotoxic activity in breast cancer (MCF-7) cells than dihydroxylated compounds [55]. DP treatments resulted in a partial reduction of MAPK signaling in ER-negative chemically altered MCF10A cells and triple-negative cells (Table 2).

In HER2-overexpressing cells, DP significantly increased the rate of apoptosis along with HER2 and MAPK signaling reductions [22]. In MCF-7 (human breast) cancer cells, DP dramatically reduced the expression of the MMP-



9 protein generated by phorbol 12-myristate 13-acetate (PMA). It blocked the activation of NF $\kappa$ B (NF- $\kappa$ B) through MAPK signaling pathways, hence inhibiting the transcriptional activity of the MMP-9 gene. Furthermore, DP inhibited PMA-induced cancer cell invasion. According to these findings, DP may be an effective antimetastatic molecule that inhibits PMA-induced cancer cell invasion by selectively blocking the expression of the MMP-9 gene, which is dependent on NF- $\kappa$ B [56]. It is important to mention that among the DP derivatives, delphinidin-3-O-glucoside has the best anticancer activity because it is easily absorbed and appears in the blood plasma within 15 min of oral administration. Catechol-O-methyl transferase metabolizes delphinidin-3-O-glucoside by methylating the 4' OH group in the B-ring and the metabolite shows a better distribution profile [57].

## Insights into the mechanisms of anticancer activity of DP and its derivatives

### Anticancer activity by differentiation induction

The phenomenon known as differentiation induction occurs as a result of differentiation inducers, malignant cells differentiate into mature, normal cells. Many cancerous cells go through cell division and generate less differentiated cells [58, 59]. Anthocyanins can impede tumorigenesis and cause cancer cells to differentiate terminally. Cyanidin-3-O- $\beta$ -glucopyranoside (Cy-g), for example, triggered PI3K and PKC in a dose-dependent manner to induce the differentiation of the human acute promyelocytic leukemia cell line (HL-60). This was understood by identifying indicators and kinase inhibitors during cell differentiation. Moreover, Cy-g (200 mg/mL) administration caused HL-60 cells to prevent the oncogene (c-Myc) and exhibit differentiation features such as improved adhesion and greater esterase activity. However, after being treated with PI3K and PKC inhibitors, marked decrement in the differentiation activity of Cy-g against HL-60 was observed [60]. Lastly, Cy-g upregulated the expression of cAMP, tyrosinase, and MART-1 which induced the differentiation in the melanoma cell line (TVM-A12) [61]. Thus, DP and its derivatives can hinder cancer at early stages by inducing differentiation, which in turn affects the final size of the tumor and malignancy. Such extents of differentiation influence the malignancy to some degree.

### Anticancer effect via inhibition of cellular transformations

One of the processes which favor tumorigenesis are cellular changes. Certain carcinogens, including 12-O-

tetradecanoylphorbol-13-acetate (TPA) and EGF, trigger transcription factors AP-1 and NF- $\kappa$ B in different cancer cell lines via PI3K-Akt and MEK-ERK pathways [62]. Interestingly, DP has been shown to suppress TPA-induced AP-1, NF- $\kappa$ B, COX-2, PGE2 expression in JB6P+ cells [26]. DP also mitigated TPA-cellular transformation brought via inhibiting the phosphorylation of ERK, MEK, ribosomal protein S6 kinase, and mitogen stress activator protein kinase in JB6P mouse epidermal cells [63]. Cyanidin can directly interact with PI3K in an ATP-competitive manner to block AP-1 and NF- $\kappa$ B production via the PI3K/Akt/p70S6 pathway. It can also prevent JB6P+ cells from undergoing cellular transformation when treated with EGF [64]. These studies indicate that DP and its derivatives (in part) elicit their anticancer effect through prevention of cellular transformation.

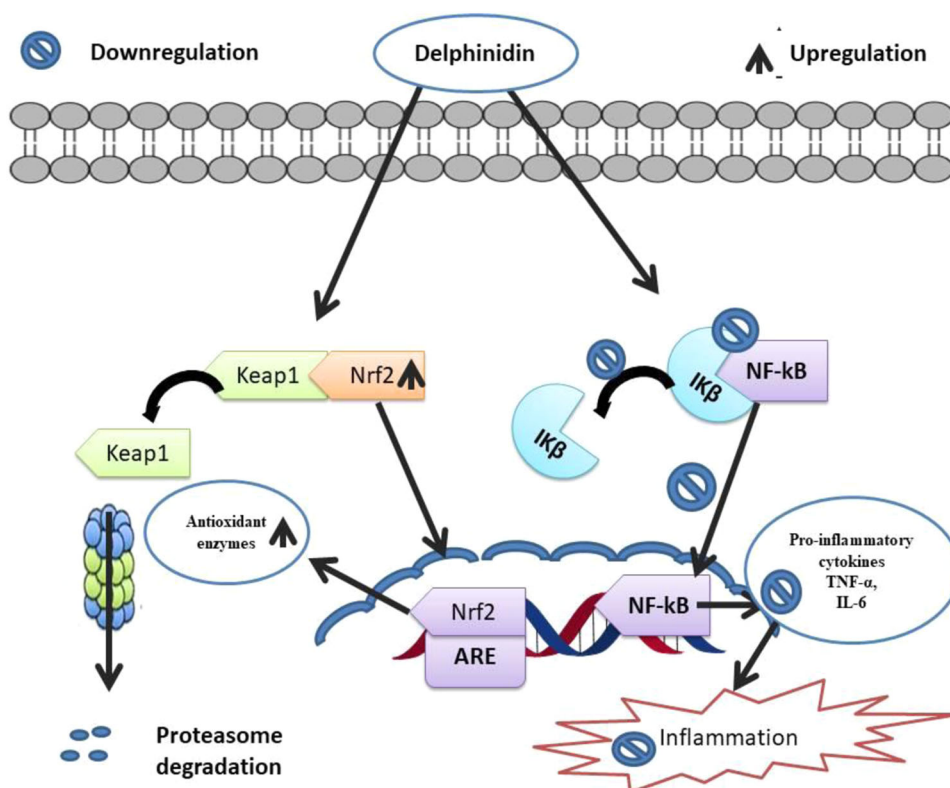
### Modulation of anti-oncogene and relative protein expression

Ha et al. elucidated that anthocyanins was triggered the transcription of p21 and p27 in colon and prostate cancer cells as well as upregulated p53 to activate the DNA repair system. Cancer cells underwent cell cycle arrest on the coupling of p21 and CDKs [65]. Anwar et al. discovered that Caco-2 cell growth was suppressed by berry anthocyanin-rich extract. This was achieved by upregulating the expression of p21Waf/Cif1, arresting the cell cycle, and further causing death by activating caspase-3 [66]. According to Chen et al. [67], anthocyanins (peonidin 3-Glucoside and cyanidin 3-Glucoside) was induced cell cycle arrest at G0/G1 and G2/M, downregulated the expressions of CDK-1 and CDK-2, cyclin-E, cyclin-B, cyclin-A in breast cancer cells. Consequently, anthocyanins was inhibited the progression of breast cancer cells by arresting the cell cycle at various stages of division by up-regulating the expression of anti-oncogenes and down-regulating the expression of oncogenes, along with the expression of various cyclins and their partners, CDKs and/or CDKIs [67].

### Chemoprotective effect via modulation of the Nrf2 pathway

The epidermal growth factor receptor (EGFR) inhibitor is the potential inhibitor of tumor development and metastasis. In one of the earlier attempts, DP suppressed vascular endothelial growth factor receptor 2 (VEGFR2), receptor tyrosine kinase 2 (ErbB2), VEGF receptor-3 (VEGFR3), and insulin-like growth factor 1 receptor (IGF1R), indicating that the molecule has a wide range of receptor tyrosine kinases inhibitory activity [68]. In another study, DP

**Fig. 4** Anticancer effect of delphinidin through mechanisms linked to Nrf2-dependent signaling



reduced VEGF-induced angiogenesis and enhanced antioxidative activities [69]. It was also shown to considerably improve tetradecanoylphorbol acetate -induced in mouse epidermal cells, increase the activity of ARE-driven luciferase, and upregulated Nrf2-related genes. Demethylation at CpG positions of the Nrf2 promoter was associated with activation of the Nrf2-ARE pathway in the mouse. Other researchers identified that DNA methyltransferase and histone deacetylase protein expression decreased in tandem after reduction of CpG methylation in the Nrf2 promoter area [15]. The findings of Xu et al. indicated that hydrogen peroxide reduced liver cancer cell line viability via ROS generation, but DP pretreatment promoted cell survival. DP pretreatment increased Nrf2 expression by facilitating the uncoupling of Nrf2 and Keap1 and Nrf2 was modulated its expression via an ARE-like element located in the proximal region of NFE2L2 gene promoter and DP-assisted to inhibit NF-Kb pathway that results in inhibition of translation of genes related to pro-inflammatory cytokines [70] (Fig. 4).

### Inhibition of cancer via modulation of ERK1/2 and PI3K/AKT signaling pathways

The signaling pathway of protein kinases is inhibited due to autophagy [50]. More research is required to understand how it regulates redox equilibrium. For example, through antioxidative activity, and the possible mechanisms. An investigation involving endothelial cells revealed the

antiproliferative and antiangiogenic effects of DP, which could have been mediated through the deactivation of PDE2 in VEGF-induced upregulation of extracellular kinases MEK/ERK, PI3K, and activating transcription factors (CREB/ATF1). Hypoxia-inducible factor-1 (HIF-1), VEGF, and epidermal growth factor (EGF) expression was reduced after the exposure of DP in cobalt chloride-induced lung cancer due to inhibition of PI3K/Akt/mTOR and ERK signaling [71]. Human lung cancer cell (A549) treatments with DP reduced cell proliferation by inducing overexpression of PI3K/Akt and EGFR/VEGFR2 signaling [35]. Another report indicated that DP exerted anti-proliferative activity against colon and rat breast cancer cells, where endothelial cells after exposure to DP mitigated mitochondrial respiration by activating Akt [72].

Usually, the tumor growth factor (TGF)- $\beta$  triggers the EMT which facilitates tumor cell invasion and advancement. It has since been shown that DP is an effective EMT inhibitor in human glioblastoma cell line by downregulating the TGF/ERK, TGF/Smad2, and EMT-related proteins i.e., snail and fibronectin [40]. In agreement with the foregoing results, EMT induction was prevented in hepatocellular carcinoma cells after treatments with DP. This was achieved via modulation of the expressions of matrix metalloproteinase-2 (MMP2), EGFR, AKT, and ERK. In ovarian cancer cell lines, DP inhibited cell proliferation and promoted apoptosis via modulating PI3K/Akt and ERK1/2/JN phosphorylation [73].

This is further supported by the anti-proliferative and pro-apoptotic effects of DP in ovarian cancer cells that are resistant to paclitaxel via downregulating the expressions of PI3K/AKT and ERK1/2 signaling [74]. It is expected that autophagy-mediated vacuolization and growth inhibition is another possible mechanism of DP anticancer activity in HCC cell lines. One such probe found that DP reduced cell proliferation, promoted apoptosis, and induced protective autophagy against breast cancer cells by downregulating AKT/mTOR and upregulating AMPK/FOXO3a [75]. Ozbay and Nahta were elucidated that DP has a significant degree of cytotoxicity for breast cancer cells and has strong interaction with the Her2 receptor and in vitro experiment was detected downregulation of ERK1/2 signaling pathway by treatments of DP (12.5 to 100 µg/mL) in DHER2 and ER-positive breast cancer cells in a dose-dependent manner [22].

### Inhibition of cancer progression via regulation of mTOR-related pathway

The mTOR-related pathway is involved in autophagy and is the most important in the activation of autophagy. In breast cancer cell types bearing the MCF-7 phenotype, several phytochemical substances influence autophagy via the mTOR pathway [76]. The link between DP, autophagy, and the mTOR pathway was investigated. The eukaryotic translation initiation factor 4E (eIF4e) and 70 kDa ribosomal S6 kinase (p70s6k) were shown to be adversely affected following DP treatment, which showed that delphinidin had an influence on mTOR activity. Treatment with delphinidin particularly inhibits the Akt branch upstream of mTOR [77, 78]. According to Steelman et al. breast cancer is typically caused by a malfunction in the mTOR pathway in mammary tissue rather than uterine tissue [78]. Delphinidin reduced the proliferation of positive breast cancer cells (HER-2) through the mTOR pathway, which suggests that DP reduces proliferation and autophagy produced via modulating the mTOR pathway. Under situations of oxidative stress and energy shortage in eukaryotic cells, 5' AMP-activated protein kinase (AMPK), an energy sensor in cells, activates autophagy. According to Aryal et al., autophagy was triggered in pancreatic cells by AMPK and directly activates the downstream Unc-51 Like Autophagy Activating Kinase 1 (ULK1) via inhibiting mTOR phosphorylation [79]. The study found that AMPK phosphorylated ULK1 at ser317 and reduced the activation of mTOR, which showed a link between ULK1 and mTOR in delphinidin-induced autophagy. So, it was concluded that delphinidin was inhibited the proliferation of breast cancer cell lines (BT474 and MDA-MB-453) via activating liver kinase B1 (LKB1) and AMPK [80] Forkhead box O (FoxO) transcription factor

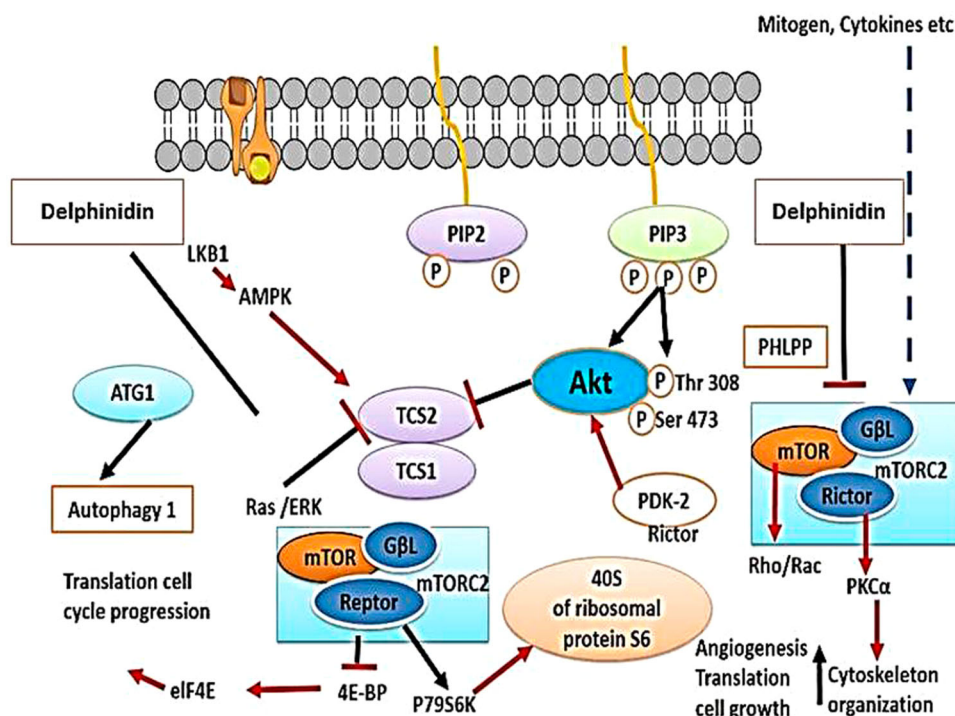
FOXO3a was shown to promote the expression of genes involved in autophagy. When AMPK was activated, FOXO3a was increased, which led to the activation of autophagy. It was indicated that FOXO3a triggers autophagy-related genes. Autophagy-related genes are regulated by the AMPK-FOXO3a axis in a variety of cell types, according to several studies [81]. The PI3K/Akt/mTOR pathway is a desirable target for anticancer drugs and DP targets these pathways to exert its anticancer activity. The mTOR, protein kinase B (Akt), and phosphoinositol-3 kinase (PI3K) signal transduction pathways are crucially involved in the control of numerous vital physiological processes, including growth, angiogenesis, apoptosis, survival, and metabolism [82, 83]. These signaling pathways are typically downregulated in a variety of malignancies and other inflammatory diseases like psoriasis [84]. DP-regulated PI3K/Akt/mTOR pathway by feedback loops, partly through the upregulation of mTOR. Two functionally different protein complexes contain mTOR: mTORC1 and mTORC2. Protein translation results from phosphorylated mTORC1 of p70S6 kinase (p70S6K), which phosphorylates 4E-BP1 and the S6 ribosomal protein [85]. As part of the feedback loop, mTORC2 phosphorylates serine 473 to activate Akt, which then phosphorylates TSC2 and PRAS40 to activate mTORC1 and promote keratinocyte hyperproliferation while suppressing differentiation [86, 87] (Fig. 5).

### Clinical evidence on the anticancer potential of delphinidin and its derivatives

While preclinical studies provide strong evidence for the anticancer potential of DP and its derivatives, clinical evidence supporting the same is still limited and requires further validation through rigorous trials. Most of the evidence supporting DP's anticancer effects comes from in vitro studies and animal models. Some observational studies have shown that diets rich in anthocyanins, including delphinidin, are associated with a reduced risk of certain cancers [88, 89]. For example, Zhang et al. [90] found that dietary intake of total anthocyanidins and of all six subclasses including cyanidin, DP and its derivatives (malvidin and petunidin), peonidin, and pelargonidin was related to a reduced risk of lung cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening cohort.

In general, there is still limited clinical trial data to validate the efficacy and safety of DP and its derivatives in humans. Such studies when conducted in the future could also consider employing combination therapies by investigating the potential synergistic effects of DP with other anticancer agents which could provide new therapeutic strategies and improve the stability of DP to exploit its anticancer benefits.

**Fig. 5** Delphinidin modulates PI3K/Akt/mTOR signaling by inhibiting both upstream and downstream signals in the system, PI3K/Akt and mTOR can be targeted at the same time to reduce cell and tissue development, promote angiogenesis, and restore normal tissue architecture. Delphinidin inhibits cell survival and proliferation by blocking the PI3K/Akt pathway as well as the mTOR pathway



### Limitations of delphinidin and its derivatives as sources of anticancer drugs

Delphinidin has shown promise as an anticancer agent due to its antioxidant, anti-inflammatory, and antiproliferative properties. However, several limitations must be addressed before it can be considered a viable anticancer drug. These include:

- Poor solubility of DP in water poses challenges for formulation and delivery. Such low solubilities lead to poor absorption in the gastrointestinal tract, which can limit its bioavailability and efficacy when administered orally. Moreover, DP undergoes rapid metabolism and degradation in the body, which further reduces its effective concentration at the target site.
- The pharmacokinetics of DP is another striking medical limitation of its use in anticancer therapy. For example, DP is a molecule with a short biological half-life, emphasizing that it can be rapidly eliminated from the body. This would necessitate frequent dosing to maintain its therapeutic concentrations at any given time. It is to date not very clear how the distribution of DP to cancerous tissues occurs, and its ability to reach and penetrate tumors in effective concentrations is under debate.
- There are stability issues around DP and its derivatives. DP is in principle a chemically unstable molecule, especially under physiological conditions, which can lead to rapid degradation and loss of

activity. Thus, specific storage conditions and facilities are inevitably required to keep it stable, and this ultimately complicates its use in clinical settings.

- As with most phytochemicals, there are probable toxicity and side effects associated with DP. The molecule is generally considered to be safe but its cytotoxicity on normal (healthy non-cancerous) cells at higher concentrations raise concerns about potential side effects. Thus, long-term safety data and potential toxicological effects of DP in humans will need to be explored further in future.
- The exact mechanisms through which DP exerts its anticancer effects are yet to be fully elucidated. This complexity can make it difficult to predict its behavior in different cancer types and stages. It should also be expected that the effectiveness of DP and its derivatives will vary significantly depending on the type of cancer, the stage of the disease, and individual patient factors.
- Delivering of DP is another challenge in its utilization for cancer therapy, and at the moment, effective delivery systems that can specifically target cancer cells while sparing normal cells are still under development.

Overall, DP and its derivatives hold a great promise as source of anticancer molecules. However, the aforementioned limitations have to be addressed through advanced research and development efforts, including improved

delivery systems, comprehensive clinical trials, and detailed studies on its mechanisms of action and long-term safety.

## Conclusions

Delphinidin and its derivatives have been shown to exert anticancer properties against various cell lines, including breast cancer, endothelial cells, and human colon cancer cells. DP and derivatives promote apoptosis in cancer cells and have potential health benefits. The anticancer mechanism of action involved targeting cyclooxygenase-2-Prostaglandin E2 pathway, mitogen-activated protein kinases/extracellular signal-regulated kinase signaling pathway, induction of epithelial-to-mesenchymal transition, intrinsic apoptotic pathway, and inhibition of Poly ADP-ribose polymerase, PI3K/AKT pathways, and modulate mTOR, and Nrf2 signaling. The review highlighted important signaling pathways that showed DP and its derivatives influence a broad range of signaling mediators. The review has narrated preclinical trials to report the anticancer effect of DP and mentioned the occurrence of DP derivatives in different plants that can be isolated and investigated for their anticancer effects and possible development into anticancer drugs.

**Author contributions:** SI conceptualized and performed literature search. SI and TO drafted the initial version of the manuscript. Visualization of collected data were done by IK and UMK. All the authors read and approved the manuscript.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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## Abbreviations

ATG-12	Autophagy-related gene 12
ATG-5	Autophagy-related gene 5
b-FGF	Basic fibroblast growth factor
CDK1/2	Cyclin-dependent kinase 1/2,
CD31	Cluster of differentiation 31
CPD	Cyclobutane pyrimidine dimer
DHT	Dihydrotestosterone
DNMT	DNA methyltransferase
EGFR	Epidermal growth factor receptor
DR5	Death receptor 5
HDACs	Histone deacetylases
HDAC3	Histone deacetylase 3
HIF- $\alpha$	Hypoxia-inducible factor alpha, Hmox1: heme oxygenase 1

LC3-II	Microtubule-associated protein light chain 3-II
MCL-1	Myeloid cell leukemia 1
MMP-2	Matrix metalloproteinases 2
MMP-9	Matrix metalloproteinase-9
mTOR	Mammalian target of rapamycin
NQO1	Nad(p)h/quinone oxidoreductase 1
PARP	Poly(adp-ribose) polymerase
p-Akt	Phosphorylated akt
p-BAD	Phosphorylated bcl-2-associated death promoter
p-ERK	Phosphorylated extracellular signal-regulated protein kinase
p-FAK	Phosphorylated focal adhesion kinase
PGE2	Prostaglandin E2
PGK1	Phosphoglycerate kinase 1
p-GSK3 $\beta$	Phosphorylated glycogen synthase kinase-3 $\beta$
PI3K	Phosphatidylinositol-3-kinase
p-MSK	Phosphorylated mitogen and stress-activated protein kinase,
p-p90RSK	Phosphorylated p90 ribosomal S6 kinase,
PSA	Prostate-specific antigen
p-SHP-2	Phosphorylated SH2 domain-containing protein tyrosine phosphatase-2
pS6	Phosphorylated S6,
PUMA	p53 upregulated modulator of apoptosis
p70S6K	Phosphorylated 70S6 kinase,
SRD5A1	Steroid 5 $\alpha$ -reductase type I
TGF $\beta$	Transforming growth factor $\beta$
UHRF1	Ubiquitin-like PHD ring finger 1
XIAP	X-linked inhibitor of apoptosis protein
8-OHdG	8-hydroxy-20-deoxyguanosine.

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