Pharmacological Research 153 (2020) 104635

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Piceatannol: A natural stilbene for the prevention and treatment of cancer

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ARTICLE INFO

Keywords:
Piceatannol
Stilbene
Cancer
Natural product
Chemoprevention
Molecular targets

ABSTRACT

The World Health Organization (WHO) has documented that cancer is the second foremost reason for death worldwide. Various factors are responsible for cancer, for instance, exposure to different physical, chemical and biological carcinogens, infections, hereditary, poor dietary habits and lifestyle *etc.* Cancer is a preventable disease if detected at an early stage; however, most of the cases of cancer are diagnosed at an incurable advanced or metastatic stage. According to WHO about 70 % of deaths due to cancer occur in countries with low- or middle-income. The major problems associated with the conventional therapies are cancer recurrence, development of chemoresistance, affordability, late-stage diagnosis, adverse side effects and inaccessible treatment. Thus, there is an urgent need to find alternative treatment modalities, which have easy accessibility and are affordable with minimum side effects. In this article, we reviewed the natural stilbene known as "Piceatannol" for its anticancer properties. Numerous preclinical studies have reported the potential of Piceatannol to prevent or impede the growth of various cancers originating from different organs such as brain, breast, cervical, colon, liver, lung, prostate, skin, *etc.* The current review primarily emphasises on the insights of Piceatannol source, chemistry, and the molecular mechanisms involved in the regression of the tumor. This review supports Piceatannol as a potential anticancer and chemopreventive agent and suggests that it can be effectively employed as a capable anti-cancer drug.

1. Introduction

Cancer is one of the most devastating disease causing a massive loss of life worldwide [1–8]. Cancer is mainly caused due to multiple mutations in the genome, which leads to deregulation of molecular signalling cascades [9–19]. Sustained growth signal, insensitive to anti-growth, resistance to apoptosis, enhanced angiogenesis, tissue invasion and metastasis, increased replicative potential, and genome instabilities are the essential hallmarks of cancer [20,21]. The conventional treatment modalities include radiotherapy, chemotherapy, and surgery and their combinations; however, disease relapse due to chemoresistance and the adverse side effect are the major problems associated with these treatment procedures. Commercially available FDA approved drug mostly target single gene product or pathway only [9,22–31]. Therefore, there is a need to identify such novel medicines which can target multiple gene products and have a negligible amount of side effects. Significant risk factor includes improper diet, pollution, obesity, consumption of carcinogenic substances, lifestyle and lack of physical activity [32–35].

Mother Nature is a repository of a large number of plant-based natural products; however, it is requisite to unravel this vast reserve for further identification of various novel phytochemicals and chemotherapeutic agents for the better management of this deadly disease [1,36–45]. Many plant-based compounds have proved to be a potent anticancer agent, act as a chemosensitizer and to overcome chemoresistance in different cancers. Moreover, 40 % of the FDA approved drugs in the market are based on plant products, and 74 % of which are the anticancer drugs [46–53]. Plant-based products are more health-

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https://doi.org/10.1016/j.phrs.2020.104635
Received 16 October 2019; Received in revised form 19 December 2019; Accepted 6 January 2020
Available online 08 January 2020
1043-6618/

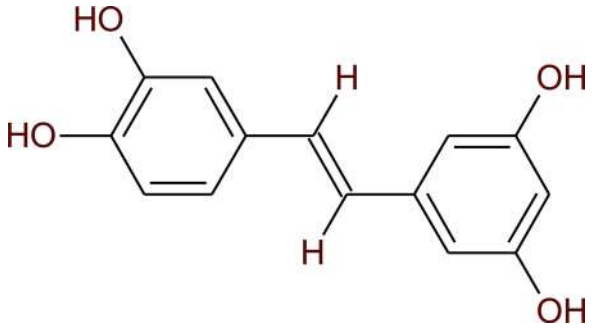

Fig. 1. Structure of Piceatannol.

friendly and are less toxic to normal cells. Nowadays, researchers are emphasising on the unexplored reserves of phytochemicals such as alkaloids, glycosides, flavonoids, terpenoids, phenolics, and saponins to prevent the adverse side effects of the chemotherapeutic drugs, prolong the survival time and improve the quality of life in cancer patients [40,54–56].

Piceatannol (PIC) (trans-2,3′,4′, 5-tetrahydroxystilbene) is a phenolic compound (stilbenoid) and a hydroxylated analogue of resveratrol [57] (Fig. 1). Grapes, passion fruit, white tea, Japanese knotweed, Asian legume, and Korean rhubarb are some crucial sources of PIC [58]. Because the level of PIC in grapes and wines are lower than that of resveratrol [59], it has received very less research attention compared to resveratrol. Scientists have reported that the seeds of passion fruit (*Passiflora edulis*) have a high content of PIC [60] and it displays various biological activities such as protection of the skin from ultraviolet B (UVB) irradiation [61]; inhibition of melanogenesis; promotion of collagen synthesis [60]; a vasorelaxant effect [62] and Sirt1 induction activity [63]. PIC possesses potent antioxidant activity and has chemopreventive and anticancer properties. Due to its antioxidant, antitumor, and anti-inflammatory activities, and lack of toxicity in humans, it has slowly been able to grab the attention of many scientists across the globe [58]. The plausible molecular mechanisms responsible for the therapeutic potential of PIC are decreased cell survival or proliferation, increased cell cytotoxicity; reduced reactive oxygen species (ROS) level; induction of autophagy, regulation of cell cycle proteins and modulation of the various cellular signaling pathway [58,64]. Numerous *in vitro* studies have led to a handful of *in vivo* studies on various animal models which showed the potential of PIC in tumor regression, induction of apoptosis and suppression of angiogenesis, invasion, migration and metastasis. This review summarises the essential molecular mechanisms liable for the anticancer activity that untangles the prospective of PIC as a competent candidate that can be designed and established into an accomplished anticancer drug.

2. Source and chemistry of PIC

PIC (phenolic compound) is a naturally occurring plant stilbenoid [65]. It is an active plant ingredient mainly found in different plant sources, for example, *Aiphanes aculeata* (coyure palm), *Ampelopsis brevipedunculata* (amur peppervine), *Arachis hypogaea* (peanut), *Caragana tibetica, Cassia garretiana* (Asian legume), *Cassia marginata* (red shower Tree), *Euphorbia lagascae* (spurge), *Melaleuca leucadendron* (white tea tree), *Mezoneuron cucullatum* (brasiletto climber), *Parthenocissus tricuspidata I* (Japanese creeper), *Passiflora edulis* (passion fruit), *Rheum rhaponticum* (rhubarb), *Rheum undulatum* (Korean rhubarb), [66–73], *Rhodomyrtus tomentosa* (sim fruit) [74], *Vaccinium berries* [75], *Vitis amurensis* (amur grape), *Vitis thunbergii* (Taiwan wild grape), and *Vitis vinifera* (wine grapes) [73].

PIC appears as a white powder with chemical formula $C_{14}H_{12}O_4$ and molecular weight 244.24 g/mol. PIC is nonpolar, it is soluble in organic solvents such as DMSO and ethanol and has a melting point of 226–223 °C [76]. The IUPAC name of PIC is 4-[(E)-2-(3,5-dihydroxyphenyl) ethenyl] benzene-1,2-diol and also called by astringinin and analogue of resveratrol. PIC exists in both stereoisomeric form, but the trans form is more stable sterically and well studied [75]. Unlike stilbene, in the structure of PIC, one of the phenyl group is replaced by a hydroxyl group at position 3, 4 and other is replaced at position 3, 5. It consists of hydroxystilbene (phenolic group) joined on either side of central ethylene group [77]. PIC shows maximum absorbance spectra at 322 nm and shows structural similarity with some other plant stilbene such as pterostilbene, astringin, and resveratrol [76] (Fig. 2). Synthesis of PIC takes place by conventional stilbene synthesis phenylpropanoid pathway [78]. PIC can be synthesized chemically, benzylhalides is a precursor molecule for synthesis, on Michaelis–Arbuzov rearrangement with triethyl phosphite at 130 °C form benzylphosphonates, which further on Horner–Wadsworth–Emmons reaction yield desired methoxystilbene. Finally, demethylation is carried out at room temperature with borontribromide [75].

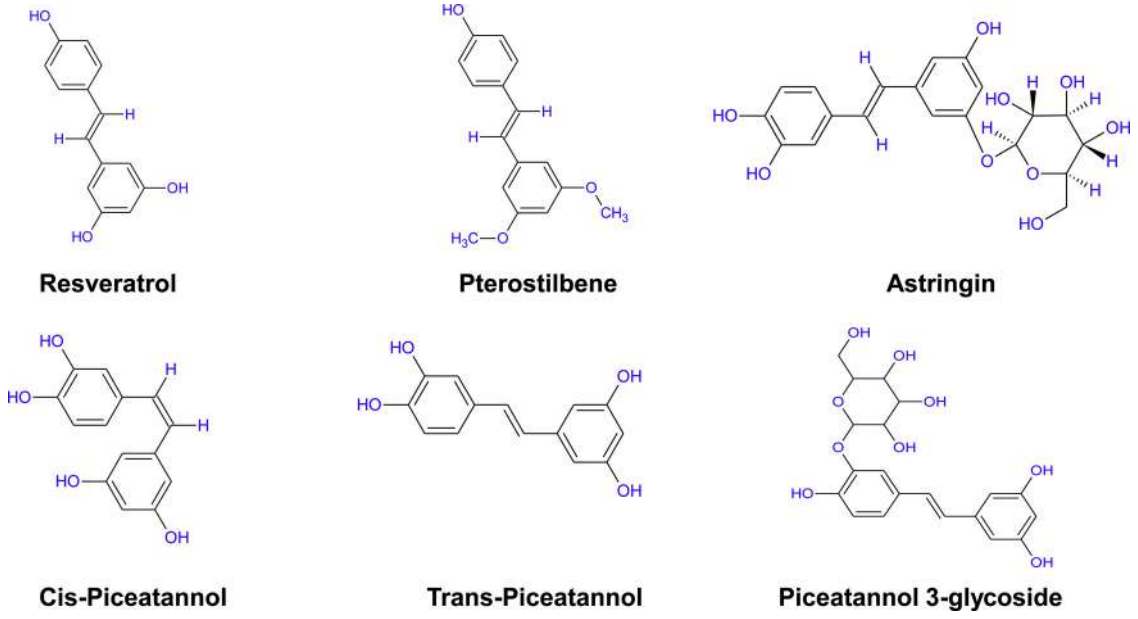

Fig. 2. Structural analogues of Piceatannol.

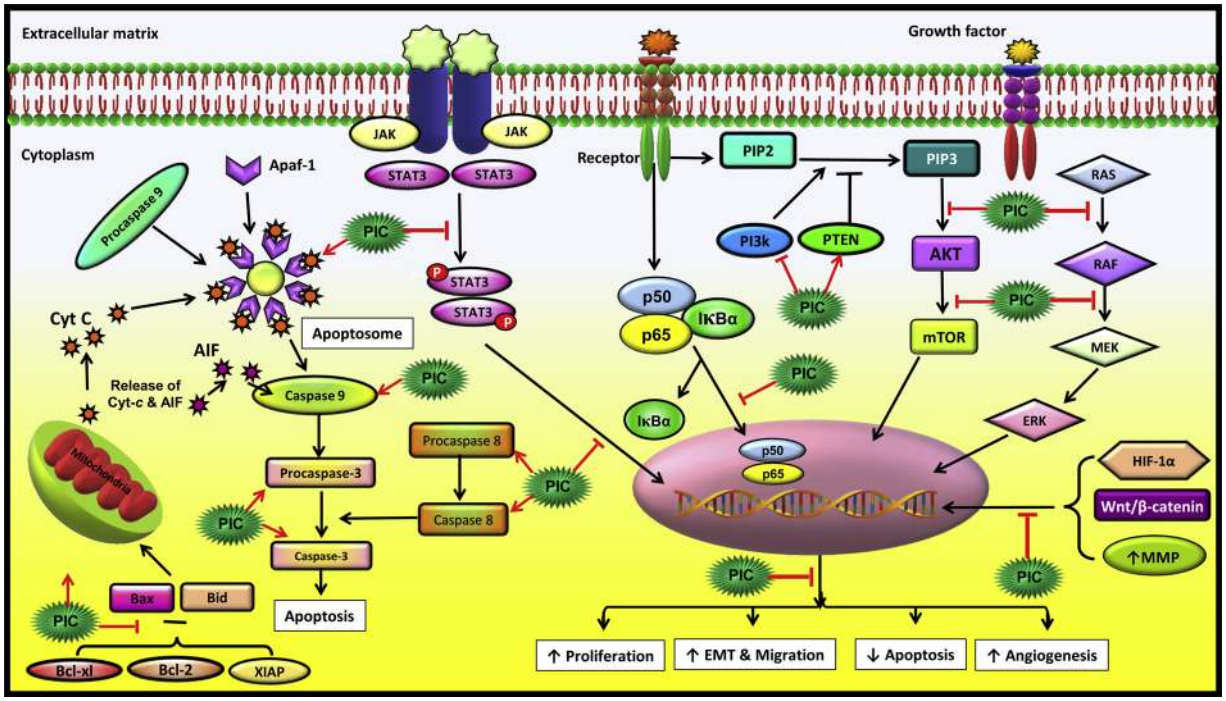

Fig. 3. Piceatannol regulates various signaling pathways involved in cancer progression. Piceatannol: PIC; T: Inhibition/Downregulation; ⊤: Inhibition/Downregulation by PIC; ↑: Upregulation/Activation; ↑: Upregulation/Activation by PIC.

3. Molecular targets of PIC

Investigations into the anticancer activity of this compound have revealed its ability to modulate several cell signalling pathways, majorly targeting factors, such as phosphoinositide 3-kinase (PI3K), cyclooxygenase-2 (COX2), spleen tyrosine kinase (Syk), and ATPase (Fig. 3). As low as 10 − 20 μM PIC has been reported to suppress PI3K signalling in human aortic smooth muscle cells (HASMCs) [79]. Besides, PIC has been found to regulate PI3K-dependent proliferation and migration in breast cancer cells [80]. The inhibitory effect of PIC upon PI3K signalling is reportedly higher than LY294002, the potential small-molecule inhibitor of PI3K. In another study, PIC has been reported to target the downstream AKT/mTOR pathway, thereby inhibiting the proliferation of prostate cancer cells [81]. Moreover, PIC has also been found to suppress COX-2 activity [82–85]. COX-2 is an essential marker of proliferation and inflammation in cancer cells. The inhibitory effect of PIC upon COX-2 has been found nearly equivalent to the commercial COX-2 inhibitor, celecoxib. In addition, PIC also selectively inhibits Spleen Tyrosine Kinase (Syk) protein, which is involved in the regulation of the immune and the inflammatory responses of hematopoietic cells and maintenance of vascular integrity [86–89]. Furthermore, PIC has been reported to be a mixed-type inhibitor of ATPase, specifically, the mitochondrial F0F1-ATPase/ATP synthase, which is essential for cell growth and survival [90].

The antiproliferative activity of PIC is further facilitated by its ability to inhibit DNA synthesis by attenuating the activity of ribonucleotide reductases [91–93]. Moreover, studies have suggested that PIC induced an intrinsic mode of apoptosis in cells and it induced Fas and FasL expression as well as mitogen-activated protein kinase (MAPK)-mediated activation of the c-Jun and activating transcription factor 2 (ATF-2) pathways in human leukemia cells [94]. In addition, PIC has also been found to induce apoptosis in human leukemic U937 cells *via* activation of caspases and down-regulation of the anti-apoptotic protein, B-cell lymphoma (Bcl)-2 [95]. Studies have also evidenced that PIC regulates the activation of the transcription factor, nuclear factor-kappa B (NF-κB) which is involved in inflammatory and other signalling pathways in cancer cells [96–98]. In another study, the role of PIC as a signal transducer and activator of transcription 3 (STAT3) inhibitor was evident in 2F7, an AIDS-related non-Hodgkin's lymphoma (NHL) cell line, which requires interleukin (IL)-10 for survival. In this *in vitro* model, PIC was also found to reverse resistance of 2F7 cells to chemotherapeutic drugs such as cisplatin, adriamycin, fludarabine, and vinblastine through the inhibition of janus kinase (JAK)1/STAT3 pathway [99]. Further, studies suggested that PIC exerted potent anti-inflammatory activity *via* regulation of molecular targets such as iNOS and AP-1 and inhibition of production of cytokines including tumor necrosis factor (TNF)-α, IL-1β, Il-6, IL-8, IL-18, *etc.* and inhibition of synthesis of inflammatory mediators such as PGE2 and NO [85,97,98,100–108]. Not only this, but studies have also revealed that PIC induced modulation of several other targets which involve kinases such as serine/threonine kinases such as ERK, JNK, *etc.;* and proteins such as matrix metalloproteinases (MMP)-9, heme oxygenase-1 (HO-1), Nrf2, p65 *etc.* [84,85,97,100,102,108,109]. Another study involving rat models with renal damage reported that PIC reduced nitric oxide (NO) and malondialdehyde (MDA) production and induced glutathione peroxidase activity thereby mitigating this damage [110]. Thus, PIC is a multitargeted compound.

4. Bioavailability of PIC

Most of the biological compounds have poor absorption, distribution, rapid metabolism and excretion, which curtails its bioavailability [111]. For a compound to exert its activity, its minimal physiologically relevant concentration is required. Though no clinical studies have been conducted till date to understand the bioavailability of PIC, reports from *in vitro* and *in vivo* studies suggest poor bioavailability of PIC. In 2014, Setoguchi et al., reported that upon oral administration of 360 μmol/kg PIC, the maximum concentration found in rat plasma was 8.1 μM only and after 24 h, PIC was not detected in plasma for a range of doses [112]. Therefore, studies have been undertaken to enhance the pharmacokinetics and bioavailability of PIC by modifying the structure or synthesizing nanoparticles and lipid complexes. For instance, the prenylated form of the PIC (trans-arachidin-1 [tA1]) demonstrated slower glucuronidation and higher affinity for cannabinoid receptors,

thereby suggesting higher biological activity of the prenylated form than its parent compound [113]. Also, the oral bioavailability of PIC analog trans-3,5,3′,4′-tetramethoxystilbene (M-PIC), upon oral administration using 2-hydroxypropyl-β-cyclodextrin as a carrier vehicle, was found to be 50.7 ± 15.0 % which was higher than that of PIC alone [114]. The improved bioavailability of M-PIC over PIC can be attributed to the stability of the methylated structure conferred due to the presence of the methoxy group rather than the hydroxyl group. This replacement has also been found to increase the antiproliferative and antiangiogenic properties of PIC [115–117]. The same study showed higher absorption and retention of M-PIC in plasma of rats after 12 h when taken through the oral route in comparison to the intravenous route [114]. In 2016, Inagaki et al., reported the beneficial effects of the intake of PIC complexed with α-Cyclodextrin (αCD) in rats. This αCD complex was found to improve intestinal absorption. Further, the solubility of the compound in both neutral and acidic solutions was elevated in αCD concentration-dependent manner and the maximum plasma concentration of intact PIC and the time-to-maximum plasma concentration of the PIC metabolites were increased upon PIC administration in the form of αCD complex [118]. Similarly, b-cyclodextrin was found to increase the solubility of PIC dose-dependently [119]. Recently, in 2018, Dhanapal and Balaraman Ravindrran synthesized chitosan/poly (lactic acid) nanoparticles loaded with PIC (CS/PLA-PIC NPs). These particles demonstrated remarkable antioxidant activity and higher cytotoxic and apoptotic effects compared to PIC and CS-PLA NPs *in vitro* [120]. Overall, these studies conclude that structural modification of PIC and encapsulating PIC in the form of nanoparticles or cyclodextrin complexes have increased the bioavailability of PIC leading to its increased biological activity. Further, clinical studies are warranted to determine PIC levels in blood and serum in humans. These studies would help in designing proper dosage and treatment of various diseases including cancer with PIC.

5. Effect of PIC in different cancers

Aforementioned, PIC plays a crucial therapeutic role in the prevention and treatment of cancer. The anticancer effect of this compound is mediated by modulation of several proteins in the tumor microenvironment, that regulate various processes involved in carcinogenesis, such as proliferation, survival, invasion, metastasis, angiogenesis, *etc.* Studies have evinced the chemopreventive activity of PIC against various cancers such as bladder cancer, prostate cancer, colorectal cancer, breast cancer, lung cancer, melanoma, leukemia, lymphoma, *etc.* (Table 1) [80,95,121–126]. The regulatory mechanisms of PIC in different malignancies are briefly discussed below.

5.1. Bladder cancer

Urinary tract cancer is also known as bladder cancer, and it can affect both the genders, however, the frequency of bladder cancer in males is four times higher than females [127]. *In vitro* study on the effect of PIC on bladder cancer cells revealed that PIC mediated its effects by significantly inhibiting benzidine-induced mutagenicity and lipid peroxidation [128]. Another study conducted by Sáez et al., in the year 2018 showed that PIC possesses immense antiproliferative activity against bladder cancer cell line J82 [129]. PIC augmented the cell cycle arrest at G0/G1 phase and induced apoptosis in T24 and HT1376 human bladder cancer cells. In addition, it also upregulated the expression of p21/WAF1 and Fas ligand resulting in increased apoptosis and antiproliferative effect [125].

5.2. Breast cancer

It is one of the widely studied malignancy all around the world, and approximately 1.7 million women were diagnosed with this deadly disease in the year 2012 [130]. Several preclinical studies have proven the efficacy of PIC against breast cancer. PIC in combination with resveratrol decreased tumor cell existence by cell cycle arrest and increased DNA damage, enhanced γH2AX, and the cleavage of caspase -3 and downregulation of survival markers, p38, MAPK, c-Myc [131]. Ferraz da Costa et al., in the year 2018, displayed that breast cancer cells upon treatment with PIC inhibited mutant p53C aggregation [132]. In another study, chitosan-coated PIC nanoparticle showed immense antioxidant and cytotoxic activity against MCF7 cells due to increased DNA fragmentation and induction of apoptosis [120]. MDA-MB-231 human breast cancer cells upon treatment with PIC showed activation of the apoptotic pathway by the increased intracellular level of calcium. This calcium release is mediated by G protein-coupled IP3 pathway. Increase in the level of calcium further activates p53 and upregulates the proapoptotic proteins like PIG8, CD95, PIDD, TP53INP, RRM2B, Noxa, p21 and PUMA which in turn prevent the tumor growth [133]. Another animal study on syngeneic female BALB/c mice showed that oral administration of PIC leads to regression of tumor growth and metastasis. Further analysis showed that PIC downregulated the transcription factors like p-NF-κB, p65, p-STAT3 and HIF-1α; different proteins involved in cell cycle regulation, for example, Ki67, cyclin D1, cyclin A, CDK2 and CDK4; proteins involved in angiogenesis, lymphangiogenesis, and metastasis like VEGF-A, VEGFR-2, VE-cadherin, CD31, VEGF-C, LYVE-1 and MMP-9; the antiapoptotic protein Bcl-2. PIC also induced the expression of pro-apoptotic protein Bax and increased cleaved caspase-3. In addition, PIC decreased the tissue levels of M-CSF and MCP-1. The same study also reported that PIC inhibited the secretion of MCP-1 and M-CSF by 4T1 cells and migration of 4T1 cells and monocytes [134].

Treatment of PIC against MCF10A cells showed that it inhibited the H-ras-induced phosphorylation of AKT, the activity of MMP-2, and PI3K and also downregulated the phosphatidylinositol (3,4,5)-trisphosphate (PIP3) expression, which ultimately leads to the inhibition of metastatic and invasive property of MCF10A cells [135]. Another study revealed that PIC mediates its cytotoxic and antimetastatic effect against MDA-MB-231 cells *via* inhibition of expression of PI3K/AKT and NF-κB and suppression of MMP-9 [80]. PIC potentially blocked the TPA-induced activation of NF-κB and expression of COX-2 in MCF-10A cells which ultimately inhibited anchorage-independent growth of human mammary epithelial cells and migration of the cancer cells. It was speculated that PIC mediated its action by direct modification of IKKbeta presumably at the cysteine 179 residue [96]. A study revealed the potential link of inflammation and carcinogenesis. Compared to resveratrol and oxyresveratrol, PIC markedly inhibited TPA-induced NF-κB DNA binding to a greater extent and abrogated the phosphorylation and degradation of IkBa as well as nuclear translocation of the phosphorylated form of p65 [84].

5.3. Cervical cancer

Cervical cancer accounts for approximately 4 % of all the cancer cases and is the fourth most common malignancy in the females [136,137]. Chen et al., in their study reported that PIC displays potent antiproliferative effect against HeLa cells by suppressing the expression of phosphorylated STAT3 [138].

5.4. Colon cancer

According to the global cancer statistics 2012, colorectal cancer is the third most common cancer occurring globally [139]. *In vitro* study conducted by Wolter et al., demonstrated that human colon carcinoma cell line Caco-2 and HCT-116 cells upon treatment with PIC reduced cell proliferation and causes cell cycle arrest at the S phase by regulating the expression of CDK 2,6 and cdc2 levels and inhibiting the expression of cyclin D1, B1and CDK 4 level [122]. Another study carried out by Lucas et al., in the year 2018 proved that the combination of PIC and resveratrol could enhance the expression of programmed cell

Table 1
Piceatannol and its mechanism of action against different cancers

Cancer	*In vitro*/ *In vivo*	Model / Cell line	IC_{50} Value	Mechanism of action	Reference
Bladder cancer	*In vitro*	J82	6.7 ± 0.3 μg mL−1 or (27.7 ± 1.4) μM	↑Antiproliferative	[129]
	In vitro	T24, HT1376	3.9 μM &4.6 μM	↑p21/WAF1, Fas ligand cell cycle arrest at G0/G1 phase apoptosis	[125]
	In vitro	–	–	↓Lipid peroxidation	[128]
Brain cancer	*In vitro*	–	8–9 μM	↓F0-F1-ATPase activity	[90]
Breast cancer	*In vitro*	BT549, SKBR3	–	↑Cell cycle arrest, DNA damage γH2AX, cleavage of caspase-3; ↓p38, MAPK, c Myc	[131]
	In vitro	MDA-MB-231, HCC-70, MCF-7	–	↓Mutant p53C aggregation	[132]
	In vitro	MCF7	–	↑Antioxidant capacity, cytotoxic, DNA fragmentation, Apoptosis	[120]
	In vitro	MDA-MB-231	–	↑Calcium, Apoptosis, p53, PIG8, CD95, PIDD, TP53INP, RRM2B, Noxa, p21	[133]
	In vivo			↓Tumor growth	
	In vivo	BALB/c mice	–	↓Tumor growth, metastasis P-NF-κB, p65, P-STAT3, HIF-1α, Ki67, cyclin D1, cyclin A, CDK2, CDK4, VEGF-A, VEGFR-2, VE-cadherin, CD31, VEGF-C, LYVE-1, MMP-9, Bcl-2 CSF, MCP-1; ↑Bax, cleaved caspase-3	[134]
	In vitro	MCF10A	–	↓MMP-2, phosphatidylinositol 3-kinase phosphatidylinositol (3,4,5)-trisphosphate	[135]
	In vitro	MDA-MB-231	–	↓PI3K/AKT and NF-κB, MMP-9	[80]
	In vitro	MCF10A	–	↓NF-κB, COX-2	[96]
	In vitro	MCF10A	–	↓NF-κB, COX-2	[84]
Cervical cancer	*In vitro*	HeLa	–	↓p-STAT3	[138]
Colon Cancer	*In vitro*	Caco-2, HCT-116	–	↑Cyclin E & A, cell cycle arrest at S phase; ↓Cell proliferation, cyclin D1, B1 CDK4	[122]
	In vitro	SW480	–	↑PD L1, DNA damage, G1-to-S cell cycle arrest, γH2AX, cleavage of caspase-3; ↓p38-MAPK/c Myc;	[131]
	In vivo	–	–	↓Tumor growth	
	In vitro	HCT116, HT29	–	↑Hypoxia-inducible factor	[140]
	In vivo	–	–	↑iNOS, NF-κB, STAT3, ERK	[106]
Fibrosarcoma	*In vitro*	HT1080	–	↑Cytotoxicity	[150]
	In vitro	HT1080	–	↓MMP-9, HIF-1α	[141]
Glioblastoma	*In vitro*	U251MG, U87MG	–	↓SYK	[143]
Gastric cancer	*In vitro*	SGC-7901	–	↓MMP-11	[147]
	In vitro	AGS	10.8 ± 0.7 μg mL−1 44.4 ± 3.2μM	↑Antiproliferative	[129]
Leukemia	*In vitro*	THP-1, HL-60, U937, L1210	–	↑DNA damage, cell cycle arrest, ↓XIAP, ROS	[148]
	In vitro	K562	–	↑ER stress, promote autophagy	[151]
	In vitro	AMO-1,U266, RPMI8226	–	↓SYK; ↑PARP-1 cleavage, release of cytochrome c, Apoptosis	[152]
	In vitro	U937	–	↓miR-183, Akt/Foxp3	[154]
	In vitro	HL-60	50 μM	↑Apoptosis	[153]
	In vitro	THP-1, U937,HL-60	–	↑Apoptosis, TRAIL3, DNA fragmentation, PARP cleavage, Sp1, ERK	[155]
	In vitro	U937	5 μM	↑Apoptosis, Fas and FasL, Ca(2+), t-Bid	[94]
	In vitro	HL-60	14 μM	↑Apoptosis, cell cycle arrest at G2-M phase	[92]
	In vitro	U937	–	↑Apoptosis, caspase-3, PARP cleavage, DNA fragmentation, cell cycle arrest; ↓Bcl-2 and cIAP-2	[95]
	In vitro	FL cells	–	↑Antiproliferative, ↓Syk, mTOR activity	[156]
	In vitro	L1210, K562,HL-60	–	↑Antioxidant, DNA protection	[149]
	In vitro	HL-60	–	↑Apoptosis, DNA fragmentation, caspases -3, -8, -9	[150]
	In vitro	BJAB	25 μM	↑Apoptosis, caspases -3, -8, -9	[121]
Liver cancer	*In vitro*	HepG2	–	↑Apoptosis, DNA fragmentation	[120]
	In vitro	AH109A	–	↑Apoptosis, cell cycle arrest	[166]
	In vivo	–	–	↓Tumor growth, metastasis	
	In vitro	HepG2	–	↓protein S	[167]
	In vitro		–	↓Mutagenicity	[128]
	In vitro	F1	4 μM	↓F0-F1-ATPase activity	[90]
Lung cancer	*In vitro*	SK-MES-1	7.64 ± 0.5 μg mL−1 31.3 ± 2.1μM	↑Antiproliferative	[129]
	In vitro	A549	–	↑Apoptosis, DNA fragmentation	[120]
	In vitro	NCI-H522	53, 23 &17 μM	↓Human glyoxalase I	[174]
	In vitro	NSCLC A459	–	↑Cytotoxicity, Bak	[175]
	In vivo	–	–	↓Tumor growth, Metastasis, P-NF-κB, p65, P-STAT3, HIF-1α, Ki67, cyclin D1, A, CDK2, CDK4, Bcl-2 VEGF-A, VEGFR-2, VE-cadherin, CD31, VEGF-C, LYVE-1, MMP-9, ↑ Apoptosis, Bax, cleaved caspase-3	
	In vitro	–	–	↓Cell migration, CSF, MCP-1	
	In vivo	–	–	↓Tumor growth, Metastasis	[123]
Oral cancer	*In vivo*	–	–	↓Tumor growth, SYK	[180]
Ovarian cancer	*In vivo*	–	–	↓Tumor growth	[182]
	In vitro	OVCA	29.1 μM	↑Apoptosis	
Skin	*In vitro*	A2058, WM266-4	15.6 μM, 29.4 μM respectively	↑Apoptosis, miR-181a	[184]
	In vitro	–	–	↓Melanogenesis	[185]

(*continued on next page*)

Table 1 (*continued*)

Cancer	*In vitro*/ *In vivo*	Model / Cell line	IC_{50} Value	Mechanism of action	Reference
	In vitro	B16F10	1.53 μM	↓Melanogenesis, ROS	[186]
	In vitro	SK-Mel-28	–	↑Apoptosis, Cell cycle arrest, ↓cyclins A, E and B1	[124]
Prostate cancer	*In vitro*	LNCaP	–	↓Dihydrotestosterone synthesis, androgen sensitivity	[192]
	In vivo	–	–	↓Tumor growth, androgen sensitivity	[191]
	In vitro	H295R	–	↓CYP17A1 Enzyme	[193]
	In vitro	CWR22Rv1	–	↓Quinone reductase 2	[194]
	In vivo	–	–	↓Tumor growth	[197]
	In vitro	LNCaP, Du145, PC3M cells	12.7 μM, 42.3 μM, 31.5μM respectively	↓Cell colonization	[197]
	In vitro	DU145	–	↓MMP-9, Akt phosphorylation	[109]
	In vitro	LNCaP, PC-3	–	↑Cell cycle arrest in G1/S, DNA damage, Apoptosis, Cyt c, DNA damage, phosphorylated histone H2AX; ↓PARP,	[81]
	In vitro	DU145, PC3, MAT-Ly-Lu (MLL), TRAMP-C2	–	↑STAT3, IL-6; ↓ MMP-9, uPA, VEGF	[196]
	In vitro	DU145	–	↑Cyt c, Bid, Bax, Bik, Bok, Fas, ↓Mcl-1, rBcl-xL	[195]
	In vitro	DU145	–	↑Cell cycle arrest at G1 phase; ↓Cyclin A, D1, CDK2, CDK4	[126]

Abbreviations: AIF: apoptosis inducing factor; AMPK: AMP-activated protein kinase; Bax :Bcl-2-associated X protein; Bcl-2 :B-cell lymphoma 2; BID :BH3 interacting-domain death agonist; Ca(2+): calcium; CDC25A: cell division cycle 25 homolog A CDK: cyclin-dependent kinase; Cip1: CDK-interacting protein 1; COX-2: Cyclooxygenase-2; Cyt.C :cytochrome-c; DNA: Deoxyribo Nucleic Acid; DR5: Death receptor 5 EGFR :epidermal growth factor receptor; ERK: extracellular phosphorylated signal-regulated kinase; FoXO3:Forkhead box O3; GAS5: growth arrest-specific 5 HIF-1α:hypoxia-inducible factors-1α; IGF-1:Insulin-like growth factor 1; IGF-1:Insulin-like growth factor-1; IGFBP-5:Insulin-like growth factor binding Protein-5; iNOS :inducible nitric oxide synthase; Kip1: Kinase inhibitory protein; 5-LO: 5-lipoxygenase; LOX: Lysyl oxidase; LT: leukotriene; MDR: Multidrug resistance; MMP: Matrix metalloproteinases ; MRP: Multidrug resistance protein; mTOR: mammalian target of rapamycin; NF-κB: Nuclear factor kappa B; NSCLC :Non-small cell lung cancer cell lines; PARP: Poly ADP ribose polymerase; PCNA: Proliferating cell nuclear antigen; P-gp: Phosphorylated-glycoprotein. PI3K:Phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC: protein kinase C; PLA2:phospholipase A2; PLC :phospholipase C; PTEN: phosphatase and tensin homolog; SOC: Store-operated Ca2+ channels; TNF-α: Tumor necrosis factor-alpha; TRAIL: TNF-related apoptosis-inducing ligand; uPA: urokinase plasminogen activator; VEGF: Vascular endothelial growth factor; Mcl-1: Induced myeloid leukemia cell differentiation protein; STAT3: Signal transducer and activator of transcription 3; IL-6: Interleukin 6; ROS: reactive oxygen species; SYK: Spleen tyrosine kinase; MCP-1:Monocyte chemotactic protein 1; LYVE-1: Lymphatic Vessel Endothelial Hyaluronan Receptor 1; cIAP2: cellular inhibitor of apoptosis 2; Sp1: specificity protein 1; CD95: cluster of differentiation 95.

death ligand 1 (PD-L1) along with more significant DNA damage, G1-to-S phase cell cycle arrest, diminished proliferation and growth of tumor cells. Additionally, it also upregulated the expression level of γH2AX, cleavage of caspase-3 and suppressed the survival markers, p38-MAPK/c-Myc [131]. PIC possesses potent anti-colitic effect as a result of increased expression of HIF-1 expression [140]. PIC and resveratrol upon oral administration in mouse inhibited dextran sulfate sodium (DSS) induced inflammatory damage to colon mucosa cells through upregulation of iNOS expression, and activation of NF-κB, STAT3, and ERK [106].

5.5. Fibrosarcoma

Fibrosarcoma or very rare soft tissue sarcoma is a malignant neoplasm composed of fibroblasts with variable collagen production. PIC-3-O-β-D-glucopyranoside (PG) showed potent anti-metastatic and anti-angiogenic activities. Treatment of PG against human fibrosarcoma (HT1080cells) showed downregulation of MMP-9 expression, which is induced by phorbol 12-myristate 13-acetate (PMA) exposure, and HIF-1α pathway [141].

5.6. Glioblastoma

Glioblastoma is one of the most aggressive primary tumor in adults and accounts for 2 % of all cancer cases in the world [142]. Different studies reported that PIC exhibited potent anticancer potential against glioblastoma cells in both *in vitro* and the *in vivo* settings. An analysis of the effect of PIC on glioblastoma revealed that it downregulated the phosphorylation of β-catenin at position Tyrosine 142 *via* inhibition of regulatory enzyme Spleen Tyrosine Kinase (Syk). Additionally, it also decreased the concentration of phosphorylated β-catenin levels at centrosomes [143]. *In vivo* study carried out by Zheng et al., showed treatment of PIC with rat brain solubilised and submitochondrial preparations inhibited the F0-F1-ATPase activity by targeting the F1 sector located at the inner membrane of mitochondria and plasma membrane of the cancer cells [90].

5.7. Gastric cancer

Gastric cancer is one of the most common malignant tumors in the digestive system, and it is the third most leading cause of deaths due to cancer in the world [144–146]. *In vitro* SGC-7901 cells upon PIC, treatment inhibited the expression of MMP-11 induced by IGF-1 [147].

5.8. Leukemia

In vitro studies carried out on multiple cell lines of leukemia such as THP-1, HL-60, U937, L1210, and K562 upon treatment with PIC, displayed enhanced antioxidant properties and induced apoptosis along with initiation of DNA damage, increase in number of cells arrested in the sub-G_1 phase, upregulation of caspases -3, -8 and -9, inhibition of ROS generation and inhibition of XIAP expression [92,148–150]. In another study, Papandreou et al., showed PIC treatment with acute lymphoblastic leukemia cells could potentially induce ER stress and promote autophagy in cells [151].

An analysis on the effect of PIC on multiple myeloma cell lines, for example, AMO-1, U266 and RPMI8226 showed that PIC inhibited spleen tyrosine kinase which triggered apoptosis through regulation of pro-caspase-3 expression and increased poly(ADP-ribose) polymerase (PARP)-1 cleavage and release of Cyt c [152]. Furthermore, Morales et al., claimed PIC treatment induced apoptosis in HL-60 cells, which is independent of ROS cell death pathway [153]. Human leukemia U937 cells upon treatment with PIC promoted the inhibition of TNFα-mediated NF-κB activation and downregulation of miR-183 expression by augmenting inactivation of Akt/Foxp3 expression in the treated cells [154]. *In vitro* analysis of THP-1 cells upon treatment with PIC enhanced the TRAIL-induced apoptosis *via* increased DNA fragmentation and PARP cleavage along with upregulation of a TRAIL death receptor protein DR5 *via* activation Sp1 and ERK [155]. PIC was also found to induce apoptosis against U937 cells *via* upregulation of Fas and FasL

protein expression along with increased intracellular Ca(2+) concentration, ERK inactivation, p38 MPAK dependent activation of c-Jun and ATF-2, degradation of procaspase-8 and upregulation of t-Bid expression [94]. PIC induced apoptosis in human leukemia cell line U937, which was linked with the proteolytic activation of caspase-3, and cleavage of PARP protein. In addition, PIC potentially promoted cell cycle arrest, DNA fragmentation in the treated cells along with the reduced expression of anti-apoptotic protein Bcl-2 and cIAP-2 [95]. Follicular lymphoma cells upon treatment with PIC inhibited Syk-dependent mTOR expression [156]. Treatment with PIC induced apoptosis in BJAB Burkitt-like lymphoma cells *via* activation of caspase-3 and change in mitochondrial permeability [121].

5.9. Liver cancer

In men, liver cancer is the fifth most commonly occurring cancer, whereas in females, it is the seventh most common cause of cancer [157–165]. Many *in vitro* and *in vivo* studies have proven the efficacy of PIC against liver cancer. Chitosan coated PIC nanoparticle upon treatment with HepG2 cells showed antioxidant capacity and showed potent cytotoxic effect due to increased DNA fragmentation and induction of apoptosis [120]. Another study carried out by Kita et al., evinced that in the *in vitro* setting treatment of PIC on AH109A hepatoma cells promoted cell cycle arrest, induced apoptosis and increased antioxidative potential through improved ROS scavenging capacity. Furthermore, in the *in vivo* settings treatment of PIC showed regression in tumor growth and diminished metastasis [166]. HepG2 cells upon treatment with PIC downregulated the expression of protein S which plays a critical role as an anticoagulant factor in Protein C [167]. A study conducted by Makena et al., revealed that PIC inhibited benzidine induced mutagenicity through ameliorating the effect of Cyt. p450 and peroxidase enzymes [128].

5.10. Lung cancer

It is one of the foremost cause of deaths due to cancer in males and is the most frequently diagnosed cancer accounting for 13 % of total cancer diagnoses [139,168–173]. An *in vitro* study on the efficacy of PIC against human lung cancer SK-MES-1 cells showed that PIC possesses an inhibitory effect on the proliferation of these cell [129]. In another study, chitosan-coated PIC nanoparticle treated A549 cells showed increased antioxidant effect and potent cytotoxic activity due to increased DNA fragmentation and induction of apoptosis [120]. Takasara et al., in their study, reported that PIC mediated its activity against NCI-H522 cells by inhibiting Human glyoxalase I (GLO I) enzyme [174].

Moreover, another *in vitro* study revealed that combination of PIC in combination with gemcitabine enhanced anticancer efficacy of PIC and increased cytotoxicity in the treated NSCLC cells by enhancing the expression of apoptotic protein Bak [175]. Furthermore, an *in vivo* study carried out by Song et al., demonstrated that upon treatment with PIC, it resulted in reduced tumor growth and decreased metastasis. This action was mediated through the regulation of various proteins, for example, the expression of p-NF-κB, p65, p-STAT3, HIF-1α, Ki67, cyclin D1, cyclin A, CDK2, CDK4, VEGF-A, VEGFR-2, VE-cadherin, CD31, VEGF-C, LYVE-1, MMP-9, and Bcl-2 was suppressed however, the expression of Bax and cleaved caspase-3 was upregulated. In addition, the *in vitro* study studies revealed that treatment with PIC reduced the secretion of CSF, MCP-1 and inhibited migration of monocytes and 4T1 cells [134]. PIC and its derivative PIC acetate significantly inhibited tumor growth and the metastasis to the lung in a dose-dependent manner in carcinectomized mice. In addition, it also prolonged the survival time and inhibited the formation of capillary-like networks of HUVECs [123].

5.11. Oral cancer

Oral cancer is one of the leading causes of global morbidity and mortality, affecting a substantial population of the world [139,176–179]. *In vivo* studies conducted by Gao et al., in the year 2017, revealed that PIC attenuated tumor growth in oral squamous cell carcinoma (OSCC) by inhibiting the Spleen tyrosine kinase (SYK) enzyme [180]. PIC treatment with squamous cell carcinoma HSC-2, HSC-3 cells showed potent cytotoxicity against the treated cell lines [150].

5.12. Ovarian cancer

The five-year survival rate of ovarian cancer is below 45 %, and it is the seventh most common cancer in woman globally [181]. Farrand et al., reported that ovarian cancer cells upon treatment with PIC increased cisplatin sensitisation and promoted apoptosis by upregulation of factors including, p53-facilitated expression of the pro-apoptotic proteins NOXA, XIAP degradation, caspase-3 activation and Drp1-dependent mitochondrial fission. Furthermore, *in vivo* study on the combination of PIC along with cisplatin against ovarian cancer mouse model displayed regression in tumor growth [182].

5.13. Skin (Melanoma)

Melanoma or skin cancer is a global health concern as it is highly susceptible in the white population of the world [183]. Preclinical studies have manifested the potential of PIC against melanoma. WM266-4 and A2058 cells upon treatment with PIC reduced cell viability and augmented apoptosis *via* upregulation of miR-181a expression [184]. Besides, PIC potentially inhibited melanogenesis in the treated human melanoma cells by inhibiting a viral protein-tyrosine kinase LMP2A [185]. Moreover, another analysis carried out by Yokozawa et al., showed PIC treatment with B16F10 melanoma cell inhibited melanogenesis by the antioxidative mechanism through the inhibition of ROS generation [186]. *In vitro* study carried out by Larrosa et al., showed that SK-Mel-28 melanoma cells upon treatment with PIC augmented apoptosis and cell cycle arrest at G2 phase *via* downregulation of cyclins-A, -E and -B1 [124].

5.14. Prostate cancer

According to GLOBOCAN 2012, approximately 1.1 million new cases of prostate cancer have been reported all across the globe [139,187–190]. The activation of the androgen receptor (AR) is a key process in the development of prostate cancer and the attenuation of this therapeutic target is vital for the treatment of prostate cancer. *In silico* studies have suggested the anti-androgenic potential of PIC against prostate tumors [191]. *In vitro* studies have also supported this finding. For instance, in 2017, Lundqvist et al., showed that PIC inhibited androgen synthesis and androgen receptor activation in the T877A mutant human prostate cancer cell line, LNCaP [192]. In 2014, PIC was also reported to inhibit CYP17A1, a key enzyme involved in androgen biosynthesis [193]. Furthermore, Hsieh and group reported the quinone reductase 2 (NQO2) mediated anticancer activity of PIC in CWR22Rv1 cells. *In silico* investigation confirmed the interaction of PIC with NQO2 [194]. Another study by the same group had earlier shown that the anti-proliferative effect of PIC was plausibly mediated through the inhibition of AKT/mTOR pathway in the androgen-dependent prostate cancer cell line, LNCaP, and androgen-independent prostate cancer cells, DU145 and PC-3.

In this study, PIC was found to induce cell cycle arrest at G(1)/S and S phases of cell cycle in LNCaP and PC-3 cells while it was found to induce apoptosis in DU145 cells *via* the downregulation of PARP, cleavage of caspase-3 and apoptosis-inducing factor (AIF), and activation of cytochrome c (Cyt c). PIC also induced increased phosphorylation of histone H2AX which contributed to DNA damage and

subsequently, apoptosis [81]. In another study, PIC was reported to induce apoptosis in DU145 cells *via* activation of both intrinsic and extrinsic pathways [195]. Besides, PIC has also been found to exert anti-invasive and anti-metastatic effect by decreasing the expression of MMP-9 through inhibition of NF-κB activation and Akt phosphorylation in TNF-α-treated DU145 prostate cancer cells [109]. In 2012, Kwon et al., also demonstrated PIC–mediated inhibition of invasion and migration in DU145 cells. In this study, PIC treatment was found to inhibit EGF-induced interleukin (IL)-6 secretion and phosphorylation of STAT3, besides downregulation of mRNA expression and secretion of MMP-9, urokinase-type plasminogen activator (uPA) and vascular endothelial growth factor (VEGF) [196]. The anticancer potential of PIC was also evidenced from another study that demonstrated PIC mediated G1 phase arrest in DU145 prostate cancer cells through modulation of cyclin A, cyclin D1, CDK2 and CDK4 [126]. Further, preclinical studies also evinced PIC induced attenuation of tumor growth and tumor volume in prostate cancer xenografts [197]. Overall, these studies indicate the chemopreventive role of PIC against prostate cancer.

6. Conclusion

PIC is a natural polyphenol that displays enormous chemopreventive and therapeutic potential against various cancers in both *in vitro* and *in vivo* settings. It has been widely studied for its disease-preventing and health-promoting functions, for example, antidiabetic, cardioprotective, neuroprotective, anti-obese, anti-ageing, and anti-allergic properties. This review highlights the chemistry, source, putative mechanism of action of PIC against different cancers through induction of both mitochondrial-dependent and independent pathway of apoptosis by elevating the levels of pro-apoptotic proteins, lowering the levels of anti-apoptotic proteins; and regulation of the Akt/mTOR, NF-κB, and JAK-STAT3 pathway. It also demonstrates potent anti-metastatic effects *via* suppression of MMPs, Wnt signalling pathways and PI3K/Akt/mTOR, epithelial to mesenchymal transition. PIC also displays its anticancer potential by the modulation of EGFR signalling pathway *via* suppression of either EGFR phosphorylation or EGFR expression. However, human trials are required to confirm these possible mechanisms of action of PIC and its anticancer effects. A major drawback of PIC, as observed through a number of *in vitro* and *in vivo* studies, is its poor bioavailability. Recent studies have shown that this limitation can be met by modifying the structure or PIC or forming nanoparticles with PIC or PIC complexes with αCD, βCD, *etc.* These strategies have shown improved bioavailability and biological activity of PIC and demand clinical trials for further validation. Additionally, the safety and toxicity profile of PIC and PIC formulations should also be evaluated in clinical settings. Not only this, the dosage and mode of administration should also be determined before using it as medication. Thus, more preclinical and clinical studies are essential to establish the use of this small bioactive compound for the treatment and prevention of cancer. Furthermore, as PIC is obtained from Mother Nature, it is expected to reduce the expenses involved in the treatment of cancer significantly.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by BT/556/NE/U-Excel/2016 grant awarded to AK by Department of Biotechnology (DBT), Government of India. The authors Abhishek Manoj Ranaware and Kishore Banik acknowledge UGC, New Delhi, India, for providing their fellowship.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.104635.

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