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A REVIEW ON ANTICANCER ACTIVITY OF *PUNICA GRANATUM* LINN

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ABSTRACT
Medicinal plants have been used in traditional health care system and are considered as a source of healthy human life. *Punica granatum* Linn is one of the potential medicinal plants which find its use in treatment of number of diseases apart from being consumed as fruit. The plant part which is used for activity is root bark, flower bud, fruit and fruit rind. Number of phytoconstituents viz., punicalin, punicaligin, ellagic acid, granatin B, gallagyldilactone, casuarinin, pedunculagin, grantin A, tellimagrandin I, gallicacid, corilagin, pentunidin are isolated from the plant. The pharmacological activities reported so far are antioxidant, anticarcinogenic, anti-inflammatory, cardiovascular diseases, diabetes, dental conditions, anthemintic, antifertility, gastro protective, antifungal, analgesic, hypoglycemic activity, atherosclerosis etc properties. The aim of present study is to give a review of *Punica granatum* in relation to anticancer activity reported so far.

KEYWORDS: Anti cancer activity; *Punica granatum;* review; phytoconstituents.

INTRODUCTION

Cancer continues to be one of the major causes of death worldwide and only modest progress has been made in reducing the morbidity and mortality of this disease. Cancers may be caused in one of three ways, namely incorrect diet, genetic predisposition, and via the environment. As many as 95% of all cancers are caused by life style and may take as long as 20–30 years to develop.

Current estimates from the American Cancer Society and from the International Union Against Cancer indicate that 12 million cases of cancer were diagnosed last year, with 7 million deaths worldwide; these numbers are expected to double by 2030 (27 million cases with 17 million deaths).

According to a report of World Health Organization, more than 80% of world's populations depend on traditional medicine for their primary health care needs. Naturally occurring drugs that are part of the war against cancer include vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine), taxanes (paclitaxel, docetaxel), podophyllotoxin and its derivative (etoposide, teniposide), camptothecin and its derivatives (topothecan, irinothecan), anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin) and others.

Extensive research is being carried out for the cure of cancer and many of the research has been successful in the treatment of patients. The side effects and drug resistance are the major threat for health care professionals to manage the cancer therapy. There is tremendous need for search of newer anticancer drug to alleviate the pain and suffering of patients. This review is focused on exploring the detailed anti-cancer property of *Punica granatum* in addition to its traditional uses and phytoconstituents isolated so far in brief.

Punica granatum Linn (Punicaceae) commonly known as pomegranate is large deciduous shrub or a small tree up to 5-10 m in height, wild and cultivated throughout India up to an altitude of 2000 m in the hills.[1]

In Traditional System of Medicine, root and stem bark are used as astringent, cooling, anthelmintic,good for tapeworm, strengthening gums and diarrohoea; flowers are used for styptic to gums, ophthalmic pain, haematuria, intrinsic hemorrhage, hemorrhoids, diarrhea, dysentery, ulcer, pharnyngitis and epistaxis; fruits are sweet, sour, astringent, cooling, tonic, aphrodisiac, laxative, diuretic, anaemia, hyperdipsia, dyspepsia, pharyngitis, ophthalmic pain, pectoral disease, splenic disorder, bronchitis, earache and diarrhea; fruit rind is used for dysentery, gastric disorder, bleeding piles, freckles and gonorrhea; seeds are used as astringent, stomachic, diuretic, cardio tonic, vomiting, excessive thirst, hepatic and splenic disorder.[1,2]

P.granatum contains a number of chemical constituents

that interact in a complex way to elicit their pharmacological activities. A number of active constituents responsible for the medicinal properties have been isolated and characterized.

Active constituents isolated from different parts of *Punica granatum*

Fruits: It is composed of a rich variety of flavonoids, which comprise approximately 0.2% to 1.0% of the fruit. Around 30% of all the anthocyanidins found in pomegranate is within the peel. Nicotinic acid, pectin, protein, riboflavin, thiamine, Vitamin C, delphinidin, aspartic acid, citric acid, ellagic acid, gallic acid, malic acid, glutamine and isoquercetin.

Seeds: Isoflavones like genistein, diadzin, diadzein, genistin and the metabolic derivative of estradiol – estron and punicic acid.

Stems and roots: Alkaloids like isopelletierine, pseudopelletierine, and N-methylisopelletierine, anthocyanidins-Pelargonidin, ellagotannins, gallicacid, ellagic acid.

Flower: Asiatic acid, masliic acid, pelargonidin-3,5diglucoside, sitosterol and its β-D-glycoside.

Bark: Betulic acid, granatan-3-one, isopelletierine, pseudopelletierine, methylisopelletierine, pelletierine and friedelin.

Leaves: Granatin A and B and punicatolin.

Fruit rind: Punicalin, punicaligin, ellagic acid, granatin B, gallagyldilactone, casuarinin, pedunculagin, grantin A, tellimagrandin I, gallicacid, corilagin and pentunidin.[3-6]

Several systematic scientific studies are also being conducted regarding the efficacy of whole plant or its parts in different extract forms for the treatment of different diseases. This plant has been reported to have antibacterial, antifungal, hypoglycemic, anti-oxidative, hypolipidemic, analgesic, immunomodulatory, anticonvulsant, anthelmintic, antifertility, antidiabetic, anti-inflammatory, gastro protective, uterine stimulant cytotoxic, carcinogenesis, angiogenesis, atherosclerosis, hypertension, carotid artery stenosis, myocardial perfusion, dental conditions, ultraviolet radiation, erectile dysfunction, male fertility, neonatal hypoxia ischemic brain injury, Alzheimer disease, obesityand anticancer activities.[7-9] A review giving the different methods of green synthesis of nanoparticles using plant extract of *Punica granatum* and *Murraya koenigii* and their application also described the use of the plant.[10]

Detailed review of anticancer activity of *Punica granatum*

Many modern anti-cancer drugs are analogues of natural compounds.[11] The right combination of drug and the natural component could improve the overall effectiveness of the treatment. It is believed that phytomedicines which are rich in polyphenols and flavonoids molecules might be helping to protect normal cells from the harmful effects of anti-cancer drugs.[12]

In vitro assays utilizing three prostate cancer cell lines (DU-145, LNCaP, and PC-3) demonstrated various pomegranate extracts (juice, seed oil, peel) potently inhibit prostate cancer cell invasiveness and proliferation, cause cell cycle disruption, induce apoptosis, and inhibit tumor growth. These studies also demonstrated combinations of pomegranate extracts from different parts of the fruit were more effective than any single extract.[13, 14]

Pomegranate [Pg] polyphenols, ellagitannin-rich extract and whole juice extract inhibited gene expression of HSD3B2 (3β-hydroxysteroid dehydrogenase type 2), AKR1C3 (aldo-ketoreductase family 1 member C3) and SRD5A1 (steroid 5α reductase type 1), which are key androgen-synthesizing enzymes in LNCaP, LNCaP-AR, and DU-145 human prostate cancer cells. Because Pg inhibits CYP activity/expression which is necessary for activation of procarcinogens, it may have anti-carcinogenesis effects.[15]

Treatment with (50-150 μg/mL) pomegranate fruit extract (PFE) for 72 h was found to result in a significant inhibition of lung cancer, with dose-dependent arrest of cells in G0/G1 phase of the cell cycle, induction of WAF1/p21 and KIP1/p27, decrease in the protein expressions of cyclins D1, D2, and E, decrease in cyclin-dependent kinase (cdk) 2, cdk4 and cdk6 expression, phosphorylation of MAPK proteins, inhibition of PI3K, phosphorylation of Akt at Thr308, NF-kB and IKK (inhibitor of kappa kinase) alpha, degradation and phosphorylation of IκB, Ki-67 and PCNA.[15]

Several animal studies have elucidated pomegranate's potential anticancer mechanisms. Two studies in mice implanted with the prostate cancer PC-3 cell line demonstrated pomegranate fruit extract (PFE; edible parts of the fruit, excluding the peel) inhibits cell growth and induces apoptosis via modulation of proteins regulating apoptosis.[16]

In vitro studies show several PFEs inhibit prostate cancer cell growth, induce apoptosis of several prostate cancer cell lines (including highly aggressive PC-3 prostate carcinoma cells), suppress invasive potential of PC-3 cells, and decrease proliferation of DU-145 prostate cancer cells.[13,14,15]

It was found that combining equal amounts of fermented pomegranate juice (FPJ), pomegranate peel extract(PPE) and cold pressed seed oil (CPSO) extracts resulted in a 99-percent suppression of DU-145 prostate cancer cell invasion across a Matrigel matrix. CPSO extract or FPJ extract alone resulted in 60-percent suppression of

invasion, and combining any two extracts induced 90-percent suppression. Studies in mice have also demonstrated PFE inhibits prostate tumor growth and decreases PSA levels.[15, 16]

In an open-label, phase II clinical trial in 46 men with recurrent prostate cancer, 16 patients (35%) showed a significant decrease in serum prostate specific antigen (PSA) levels (average=27%) during treatment with eight ounces of pomegranate juice. Corresponding *in vitro* assays using patient plasma and serum demonstrated significant decreases in prostate cancer cell line proliferation and increased apoptosis. Nitric oxide preservation via ingestion of pomegranate polyphenols significantly correlated with lower PSA values. These results indicate pomegranate may affect prostate cancer because of antiproliferative, apoptotic, antioxidants and possibly anti-inflammatory effects.[17]

The promising results lead to conduct a two-stage phase II clinical trial in men with recurrent prostate cancer and rising PSA levels. All eligible patients had previous surgery or radiation therapy for prostate cancer, Gleason scores (a grading system for predicting the behavior of prostate cancer) ≤7, rising PSA value of 0.2-5.0 ng/mL, no prior hormonal therapy, and no evidence of metastases. Baseline PSA doubling times were established for 22 participants who were then started on eight ounces PJ (570 mg total polyphenol gallic acid equivalents) daily until meeting disease progression endpoints. Endpoints measured were effect on PSA levels, serum lipid peroxidation and nitric oxide levels, *in vitro* induction of proliferation and apoptosis of LNCaP cells in patient serum containing pomegranate constituents and overall safety of extract administration.[17]

Based on preliminary results achieved in phase I, 24 additional patients were enrolled and 46 patients were evaluated over 13 months in both stages of the trial. Of these, 35 percent (n=16) demonstrated decreased PSA levels, the primary trial endpoint – average decrease=27%; median decrease=18%; range 5-85%. Four of 46 patients (8.7%) met objective response criteria and exhibited >50-percent reduction in PSA values, meeting criteria for a phase III trial. In addition, an average 40-percent reduction in serum oxidative state was observed in patients accompanied by a significant reduction in serum lipid peroxidation compared to baseline. Nitric oxide serum metabolites measured at nine months after study initiation revealed an average 23-percent increase, which significantly correlated with baseline PSA levels.[17]

An *in vitro* trial using patient serum investigated whether pomegranate juice [PJ] consumption had any effect on growth rates or apoptosis of LNCaP prostate cancer cells in culture. Serum collected at nine months after study initiation and incubated with LNCaP decreased cell growth by an average of 12 percent in 84 percent of patients compared to baseline. An average 17.5-percent increase in apoptosis in 75 percent of patients was also noted. This study indicates PJ or PJ constituents may have promise as a therapy for prostate cancer, particularly recurrent type with rising PSA levels.[17]

Pomegranate constituents inhibit angiogenesis via down regulation of vascular endothelial growth factor in MCF-7 breast cancer and human umbilical vein endothelial cell lines were investigated.[18]

The anti-angiogenic potential of Pg was evaluated by measuring vascular endothelial growth factor (VEGF), IL-4, and migration inhibitory factor (MIF) in the conditioned media of estrogen sensitive (MCF-7) or estrogen resistant (MDA-MB-231) human breast cancer cells, and immortalized normal human breast epithelial cells (MCF-10A). VEGF was strongly decreased in MCF-10A and MCF-7; however, MIF was increased in MDA-MB-231, showing significant potential for inhibitory effects of angiogenesis by Pg fractions on human umbilical vein endothelial cells (HUVEC).[18]

In HT-29 colon cancer cells, cyclooxygenase-2 (COX-2) expression is increased via activation of nuclear factor kappa-B (NFκB) by tumor necrosis factor-alpha (TNF-α), an inflammatory cell signaling process that may be a cause of cancer initiation and progression. Treatment of HT-29 colon cancer cells with PJ, total pomegranate tannins, or concentrated pomegranate punicalagin induced a significant decrease in COX-2 expression. PJ treatment resulted in the highest level of COX-2 suppression (79%) compared to treatment with single constituents. The effects were attributed to synergistic activity of the bioactive constituents thought to be necessary for pomegranate's anti-inflammatory and anticarcinogenic activity.[19]

Another *in vitro* study investigated the effects of punicalagin, ellagic acid, total pomegranate tannins, and PJ on several cell lines. Although all preparations decreased viable cell numbers in KB and CAL-27 oral cancer cell lines, as well as in HT-29 and HCT-116 colon cancer cell lines, a higher degree of suppression was obtained with pure PJ, an affect attributed to the synergy of its bioactive constituents.[20] Research utilizing breast cancer cell lines MCF-7 and MB-MDA-231 demonstrates pomegranate constituents effectively inhibit angiogenesis[18], tumor growth, proliferation[21], invasiveness[22] and induce apoptosis.[23]

To examine the effect of FPJ and CPSO extracts, and an HPLC-isolated peak B (from the fruit extract), mouse mammary organ culture, an animal model of breast cancer having ≥75-percent accuracy of predicting *in vivo* carcinogenesis was investigated. They found cancerous glands treated with each pomegranate compound exhibited decreased lesion incidence – 37 percent for FPJ, and 75-90 percent for both peak B and CPSO. Seed oil is comprised mainly of punicic acid, a trienoic acid

with anticarcinogenic properties and effective at very low doses (1 mg/mL in organ culture). Peak B is believed to be a phenolic compound with potent chemopreventative properties.[18]

Some metabolites of pomegranates chemical components such as 3, 8-dihydroxy-6H-dibenzo [b, d] pyran-6-one (urolithin A, UA) which is produced from Ellagitannins (ETs) may also possess anti-cancer effects.[20]

Research in mice has shown PFE inhibits tumorigenesis in lung cancer and skin cancer models. In the lung cancer study, mice given daily oral dosages of PFE comparable to what humans could reasonably consume (exact dosages were not available) exhibited significantly less lung tumor growth than mice not receiving PFE.[24]

In mice treated with skin-cancer-inducing 12-O-tetradecanoylphorbol-13-acetate (TPA), animals treated topically with PFE had significantly reduced incidence of skin tumors. In the PFE-treated group, only 30 percent of mice exhibited tumors compared to 100 percent of mice treated with TPA and no PFE. This result was attributed to suppression of inflammation (COX-2, MAPKs, NFκB) and the tumor proliferation marker ornithine decarboxylase.[25]

It was investigated the effect of flavonoid-rich PJ and FPJ and pomegranate pericarp extracts on HL-60 human leukemia cell differentiation (the ability of cancer cells to revert to normal cells) and proliferation. Because of the structural similarity between plant flavonoids and retinoid (the latter being established pro-differentiating agents), it was hypothesized that flavonoid-rich pomegranate extracts might have a similar effect on differentiation. *In vitro* assays confirmed both the FPJ and pericarp extracts strongly promoted cellular differentiation and inhibited proliferation in HL-60 cell cultures; the effect of PJ on cellular differentiation was less significant. This study suggests another mechanism by which pomegranate constituents impart an anticarcinogenic effect.[26]

Pomegranate fruit, pomegranate juice, seed and seed oil are effective in prostate, breast, skin, colon, lung, oral and leukemia cancers, due to its antioxidant and antiproliferation (growth inhibition, cell cycle disruption and apoptosis) action.[27,28]

Pomegranate seed oil incorporated in the diet, markedly reduced the incidence and multiplicity of colonic carcinoma (measured as number of tumors/rat) induced by azoxymethane. In this experiment, pomegranate seed oil was added to AIN-76A diet. Increasing concentration of 0.01%, 0.1% and 1% (w/w), of pomegranate seed oil did not exhibit a dose response effect but anti-carcinogenic effects were observed at all the doses used in the study.[29]

Pomegranate seed oil and fermented juice polyphenols tend to inhibit breast cancer cell proliferation, invasion, and promotes apoptosis of breast cancer cells.[18] Fermented pomegranate juice polyphenols consistently showed twice higher anti-proliferative effect as compared to fresh pomegranate juice polyphenols.[30] Research on lung cancer revealed that PFE (Pomegranate fruit extract) is effective treatment of lung cancer. The results suggested that PFE can be used as a chemo preventative agent against lung cancer.[31]

The effects of pomegranate oil, seed oil, fermented juice polyphenols, and pericarp polyphenols on human prostate cancer cell growth *in vivo* and found that it demonstrated significant antitumor activity against human prostate cancer.[14]

Pomegranate fruit extract showed that cell growth was inhibited and followed by apoptosis of extremely aggressive human prostate carcinoma PC-3 cells. The fermented pomegranate juice polyphenols were also tested in combination with pericarp polyphenols on the proliferation of DU 145 human prostate cancer cell lines *in vitro*. Supra-additive and synergistic effects were experimentally proven.[13] These studies provide evidence, suggesting that consuming pomegranate may delay prostate cancer progression.[15]

Pomegranate possesses inhibitory effects on different type of cancers such as prostate[32, 33], breast[34], colon[35, 36] and lung cancers.[37]

Caffeic acid phenethyl ester (CAPE), a compound of Pg which is also derived from honey bee propolis has shown dose-dependent decreases in MMP and TIMP-2 mRNA levels in HT1080 human fibro sarcoma cells, as detected by reverse transcriptase-polymerase chain reaction (RT-PCR). Gelatin zymography analysis confirmed this when compared to controls. This study shows the role of CAPE as a potent anti-metastatic agent, which can significantly inhibit the metastatic and invasive capacity of malignant cells.[38]

Pg has shown dose-dependent inhibition effect on NF-kB-dependent reporter gene expression which is associated to proliferation, invasion, and motility in aggressive breast cancer phenotypes. This effect is behind to decrease RhoC and RhoA protein expression, suggests a role for these extracts in lowering the metastatic potential of aggressive breast cancer species.[39]

Four pure chemicals, ellagic acid, caffeic acid, luteolin, and punicic acid, obtain from the Pg fruit were presented as potential inhibitors of *in-vitro* invasion of human PC-3 prostate cancer cells in an assay employing Matrigel artificial membranes.[40]

Punica granatum extract (PE) inhibited the proliferation of mouse mammary cancer cell line (WA4), derived

from mouse MMTV-Wnt-1 mammary tumors in a time and concentration-dependent manner through an arrest of cell cycle progression in the G0/G1 phase.[41]

Ellagitannins, derived from Pg juice, and their metabolites, urolithins exhibit dose and time-dependent decreases in cell proliferation and clonogenic efficiency of HT-29 cells through cell cycle arrest in the G0/G1 and G2/M stages of the cell cycle followed by induction of apoptosis. Moreover, Pg treatment induced a dose-dependent arrest in the G0/G1 phase of the cell cycle which was assessed by DNA cell cycle analysis in the lung cancer cell line (A549).[31]

Pg pretreatment of normal human epidermal keratinocytes (NHEK) has been found to increase the cell cycle arrest induced by UVA in the G1 phase of the cell cycle.[42] Furthermore, Androgen-independent cell line, DU 145 has shown a significant increase from 11% to 22% in G2/M cells ($p < 0.05$) by treatment with (35 µg/mL) Pg cold-pressed oil.[14]

Ellagic acid is a phenolic compound, which may belong to Pg, and induces cell cycle arrest and apoptosis in T24 human bladder cancer cells *in-vitro* through induced G0/G1 phase arrest, increased p53 and p21 and decreased cyclin-dependent kinase (Cdk2) gene expression.[14] Cdks as the mainly one Cdk4 is a key molecule in the regulation of cell cycle progression at the G1-S phase restriction point is inhibited by p16 (INK4a), a tumor suppressor. It has been reported that the N-terminal of different truncated p16 (INK4a) molecules is not crucial for the interaction with Cdk4.[43] However, it have previously shown that the C-terminal domain of p16 (INK4a) is adequate in inducing cell cycle arrest, growth inhibition, and CDK4/6 interaction.[44]

Pg extracts and punic acid, an omega-5 long chain poly unsaturated fatty acid derived from Pg, have been shown to induce apoptosis in both an estrogen in sensitive breast cancer cell line (MDA-MB-231) and an estrogen sensitive cell line developed from MDA-MB-231 cells (MDA-ERalpha7) through lipid peroxidation and the PKC (Protein kinase C) signaling pathway. They also cause disruption to the cellular mitochondrial membrane.[45]

The relationship between pg-induced apoptosis in human prostate cancer cells (LAPC4) and the IGF/IGFBP system have been investigated. POMx (a highly potent Pg extract prepared from skin and arils, minus the seeds) and IGFBP-3 have been shown to synergistically stimulate apoptosis. Inhibition of cell growth resulted in increased JNK phosphorylation and decreased Akt and mTOR activation.[32]

Pg treatment of normal human epidermal keratinocytes (NHEK) inhibited UVB-mediated activation of MAPK and NF-kB pathways, as well as other signal transducers and activators of the apoptosis pathway including transcription 3 (STAT3), PKB/AKT, ERK1/2, mTOR, PI3K, Bcl-X(L) (antiapoptotic protein), Bax and Bad (proapoptotic proteins).[42]

The role of MAPK signaling pathways and effects of PI3K/AKT, ERK1/2, P38, and JNK on epidermal growth factor (EGF) signaling in proliferation of human mesenchymal stem cells (hMSCs) have been shown *in-vitro*.[46] The cell growth is controlled by the interaction of survival and cell growth arrest pathways and the activity of survival pathways such as Akt and ERK1/2 with regard to XIAP (inhibitor of apoptosis) in serum starvation has been investigated and the survival role for ERK in serum starvation has been reported.[47] Recently, the Pg inhibition of cell growth, followed by apoptosis of highly aggressive human prostate carcinoma PC3 cells through modulations in the cyclin kinase inhibitor-cyclin-dependent kinase machinery has been shown. These events were associated to alterations in the levels of Bax and Bcl-2, shifting the Bax: Bcl-2 ratio in favor of apoptosis.[15] Ellagitannins (ETs) and hydrolysable tannins, which are found in Pg and their hydrolyzed product, as well as ellagic acid (EA), have been reported to induce apoptosis in human colon cancer Caco-2 cells through down-regulation of cyclins A and B1, upregulation of cyclin E, cell-cycle arrest in the S phase, induction of apoptosis via intrinsic pathways (FAS-independent, caspase-8 independent) through bcl-XL down-regulation with mitochondrial release of cytochrome c into the cytosol as well as activation of initiator caspase-9 and effector caspase-3.[48]

Induction of Bax and Bak (proapoptotic), down-regulation of Bcl-X(L) and Bcl-2 (anti-apoptotic), induction of WAF1/p21 and KIP1/p27, a decrease in cyclins D1, D2, and E, and a decrease in cdk2, cdk4, and cdk6 expression have been shown to occur in prostate cancer PC3 cells, following Pg treatment.[16]

Studies have shown that Pg inhibits prostate cancer cell growth, induces apoptosis in PC-3 cells (highly aggressive prostate carcinoma cells), suppresses invasion of PC-3 cells and decreases proliferation of DU-145 prostate cancer cells *in vitro*. Treatment of HT-29 colon cancer cells has been indicated by Pg juice through decreasing COX-2 expression and inhibiting inflammatory cell signaling processes which may cause cancer initiation and progression.[19] Furthermore, COX-2 is involved in the proliferative response of human periodontal fibroblast (HPLF) cells to Emdogain (EMD).[50] There has been a correlation between inducible nitric oxide (iNOS) synthase and COX-2 expression in human colorectal adenocarcinoma. In fact, a possible link between advanced stages of this disease and higher expression of iNOS and COX-2 has been shown.[51]

CONCLUSION

The quantum of research happening in the field of anti-cancer therapy is high and includes huge investments.

Crossing the line of clinical studies has stuttered many a researchers. That is when much of the research stays at lab scale or pharmacological levels. The medicinal benefits of *Punica granatum* plant was utilized well for centuries by our ancestors. This gives an added advantage to the bioactive molecules in this plant. The bioactive components of *Punica granatum* should be analyzed further to interpret and discover the possibilities of this species emerging as a reliable cure for cancer.

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Ethical Issues

There is none to be applied.

Conflict of Interest

None to be declared.

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