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Phytochemical, hematologic and anti-tumor activity evaluations of *Carica papaya* leaf extract

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Abstract

Carica Papaya has been used for its homeostatic and health-promoting properties in several non-Western medicinal practices (*e.g.,* Ayurveda, Traditional Chinese and Vietnamese, Unani) for centuries. More recently, anecdotal reports have emerged suggesting regular consumption of tea made from C. Papaya leaf extract has been associated with remission of certain cancers including some advanced solid-tumor cancers. We aimed, therefore, to use scientific methodologies to investigate *C. Papaya* leaf extract and its *in vitro* effects on human cancer cells and *in vivo* effects in human patients with cancer. Liquid chromatography-mass spectroscopy (LC-MS) was used to determine the phytochemical composition of *C. Papaya* leaf extract, immune-modulatory and ant-cancer properties were studies in peripheral blood mononuclear cells and various solid-tumor cell lines, and clinical laboratory measurements (hematologic and organ-specific and non-specific parameters) were examined in 116 cancer patients receiving capsules of *C. Papaya* leaf extract. Our results indicate that *C. Papaya* may have substantial potential as an adjuvant therapy for certain cancers, and additional investigation is warranted.

Introduction

Plants provide a healthful source of nutrition, and the use of plants for medicinal purposes dates to ancient history [1]. Contemporary consensus holds that diets high in fruits and vegetables promote good health and overall wellbeing [2]. Therapeutic properties of various plants and plant components have been demonstrated using modern clinical sciences techniques (*e.g.,* randomized controlled trials) [3-5]. Reports of findings from studies of *Carica Papaya* have suggested that phytochemicals (carotenoids and polyphenols) in the leaf extract have healthful properties, promoting both anti-tumor and homeostatic activity [6-9]. Native to Central and South America and parts of southern Mexico, *C. Papaya* is cultivated in most tropical countries. Its leaves, fruits, latex, and roots are routinely used as a natural remedy against a variety of ailments. The constituents of the various parts of the *C. Papaya* plant (Table 1) have been determined and reported previously [6]. Here in we report our *in vitro* and *in vivo* investigations of *C. Papaya* leaf extract.

Materials and methods

Collection and Processing of *C. Papaya*

C. Papaya was purchased from a market region in Gainesville, Florida (USA) and deposited at the lab of the Department of Pharmaceutical Outcomes and Policy at the College of Pharmacy of the University of Florida (USA). *C. Papaya* leaf specimens were authenticated by visual inspection, rinsed thoroughly with purified water, size-reduced, and triturated to a fine powder. A uniform mortar paste was formed by combining the fine powder with minimal amounts of purified water. Gravity filtration of the paste resulted in purified *C. Papaya* leaf extract.

Phytochemical Analysis of *C. Papaya* Leaf Extract

Laser-coupled mass spectrometry (LCMS) methodology was utilized to conduct the phytochemical analysis of the purified extract of *C. Papaya* leaf. The extract was subjected to chromatographic separation on Phenomonex Phase C-18 Columns (water:acetonitrile

Table 1. Primary constituents of *C. Papaya*

Part	Constituents
Fruits	Fat, carbohydrates, phosphorous, iron, Vitamin C, thiamine, riboflavin, niacin, and carotene, amino acids, citric and malic acids (green fruits), volatile compounds: linalool, benzylisothiacyanate, protein, fat and fiber
Latex	Peptidase A and B and lysozymes, proteolytic enzymes, papain and chemopapain, glutamine cyclotransferase, chymopapains A, B and C
Leaves	Vitamin C and E, Alkaloids carpain, pseudocarpain and dehydracarpaine I and II, choline, carposide
Root	Enzyme myrosin and carposide

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ratio 80:20, 24 degrees Celsius, flow rate 1.4ml/min, electronic spray ionization mode, m/z range 50-1000) [10,11]. Spectra analysis in both positive and negative mode were performed to determine the phytochemical constituents of the purified extract of *C. Papaya* leaf.

In vitro Studies of *C. Papaya* Leaf Extract

To assess potential anti-cancer properties of *C. Papaya*, measurements of 3H-thymidine (^{3}[H]- TdR) incorporation in various solid-tumor cell lines (Hela, MCF-7, HepG2, PC-14, Panc-1 and H2452) and large-cell lymphoma cell lines (Jurkat, ARH77, Raji and Karpas-299) after 24-hour exposure to various concentrations of *C. Papaya* leaf extract were performed [12]. Annexin V measurements in controls and after exposure to *C. Papaya* leaf extract at various concentrations were also compared, and measurements of luminescence after 0, 18 and 24-hour exposure to etoposide or *C. Papaya* leaf extract were compared. To investigate the effect of *C. Papaya* leaf extract on cytokine production, peripheral blood mononuclear cells (PBMCs) were stimulated with immobilized anti-CD3 and soluble CD28 in the presence or absence of *C. Papaya* (24-hour exposure) [13]. Supernatants from triplicate cultures were collected and quantification of IL-2, IL-4, IL-10, IL-12p40, IFN-γ, and TNF-α was performed by enzyme-linked immunosorbent assay (ELISA). The cytotoxicity of *C. Papaya* leaf extract was evaluated by measuring ^{3}[H]- TdR incorporation and percent lysis in PBMC controls and in PBMCs after 24-hour exposure to *C. Papaya* leaf extract at various effector-target (E/T) ratios [14]. To investigate the effect of *C. Papaya* leaf extract on genetic expression and regulation, mRNA concentrations were measured in PBMCs without exposure and with 24-hour exposure to various doses of *C. Papaya* leaf extract. Quantification of mRNA was performed by real-time polymerase chain reaction (PCR) standard methodology.

Clinical Investigation of Capsules of *C. Papaya* Leaf Extract

Purified leaf extract of *C. Papaya* was dried for 20 hours to obtain low moisture and encapsulated, producing capsules of uniform *C. Papaya* leaf extract content suitable for human consumption. Preparation and encapsulation were performed at the pharmaceutical lab of the Department of Pharmaceutical Outcomes and Policy at the College of Pharmacy of the University of Florida under the auspices of the Florida Department of Health Internal Review Board. During the period of January 2014 to October 2016, *C. Papaya* capsules were administered to oncology patients to determine the effects on hematology and biochemical parameters. *C. Papaya* capsules were administered to 11 pediatric patients (males and females, 3-8 years of age, of various racial and ethnic backgrounds, and of various body composition) at the Loyola University Medical Center in Chicago Illinois (USA). *C. Papaya* capsules were administered to 95 adult patients (males and females, 18-72 years of age, of various racial and ethnic backgrounds, and of various body composition) with solid-tumor cancers (lung, breast) at the Loyola University Medical Center in Chicago Illinois (USA) or the Saint Bernard Hospital in Chicago Illinois (USA). *C. Papaya* capsules were administered to 10 adult Vietnamese patients (males and females, 18-72 years of age, and of various body composition) with solid-tumor cancer (tonsillar) at the International Medical Center in Ho Chi Minh City (Vietnam). Human consumption of *C. Papaya* capsules was supervised by licensed medical doctors and was under the auspices of the respective hospital's Internal Review Boards. Hematologic and biochemical parameters were measured in the respective hospital's clinical pathology laboratories using standard clinical methodologies.

Table 2. Phytochemical analysis of extract of leaf of *C. Papaya*

Number	Compound	Molecular Mass
1.	Tocopherol	420.67
2.	Ascorbic acid	173.05
3.	Carpaine	455.76
4.	Deoxykaempfe	267.41
5.	Kaempferol	278.67
6.	Deoxyquercetin	280.34
7.	Quercetin	300.45
8.	Dicoumarol	340.42
9.	Coumaroylquin	344.57
10.	Coumarin	147.67
11.	Folic acid	440.65
12.	Cystine	120.32
13.	Homocysteine	133.59
14.	Cysteine	176.33
15.	L Glutamic	143.33
16.	p- C. Alcohol	152.44
17.	dime- phenol	153.67
18.	umbelliferone	160.11
19.	phenylalanine	164.59
20.	Caff-Alcohol	165.02
21.	Methyl- ketone	169.79

Results and discussion

LC-MS analysis of *C. Papaya* leaf extract was used to detect the spectra (Figure 1), and 21 phyto-chemical constituents (Table 2) were identified. The presence of various pharmacologic phyto-compounds (alkaloids, phenolics, flavonoids, amino acids) was consistent with previously reported analyses of parts of *C. Papaya* specimens.

The *in vitro* results shown in Figure 2 strongly suggest that *C. Papaya* leaf extract may inhibit tumor cell growth and proliferation and may promote apoptotic activity in tumor cells. Decreased ^{3}[H]- TdR incorporation, resulting from exposure to increased concentrations of *C. Papaya* leaf extract, suggests a dose-dependent inhibition of tumor cell growth and proliferation in solid-tumor cells lines (Hela, MCF-7, HepG2, PC-14, Panc-1 and H2452) and large-cell lymphoma cell lines (Jurkat, ARH77, Raji and Karpas-299). Increased 7-Aminoactinomycin D (7-AAD) fluorescent marker and decreased Annexin V^- cell detection after exposure to increased concentration of *C. Papaya* leaf extract suggest a dose-dependent promotion of apoptotic activity. The increased detection of luminescence after 0, 18 and 24-hour exposure to *C. Papaya* leaf extract or etoposide (positive control) demonstrates a dose-dependant promotion of apoptotic activity in these cancer cells.

The *in vitro* results shown in Figure 3 strongly suggest that *C. Papaya* leaf extract may have important immune-modulatory effects. Decreased levels of inflammatory markers (IL-2, IL-4, IL-12 p40, IL-12 p70, INF-γ, and TNF-α) in human PBMCs following 24-hour exposure to increased concentrations of *C. Papaya* leaf extract demonstrate a dose-dependent attenuation of immune-oncologic activity.

The *in vitro* results shown in Figure 4 strongly suggest that *C. Papaya* leaf extract may have important cytotoxic effects. The decreased ^{3}[H]- TdR detected and the increased percent lysis detected in human PBMCs after 24-hour exposure to *C. Papaya* leaf extract at increased effector-target ratios (E/T) demonstrate a dose-dependent cytotoxic effect in these cancer cells.

The *in vitro* results shown in Figure 5 strongly suggest that *C. Papaya* leaf extract may have important effects on genetic expression and regulation. Real-time PCR analysis revealed that increased mRNA expression in several cancer-related and/or immuno-regulatory genes (*CCL2*, *CCL7*, *CCL8* and *SERPINB2*) resulted from exposure to *C. Papaya* leaf extract, and the results suggest that this effect on

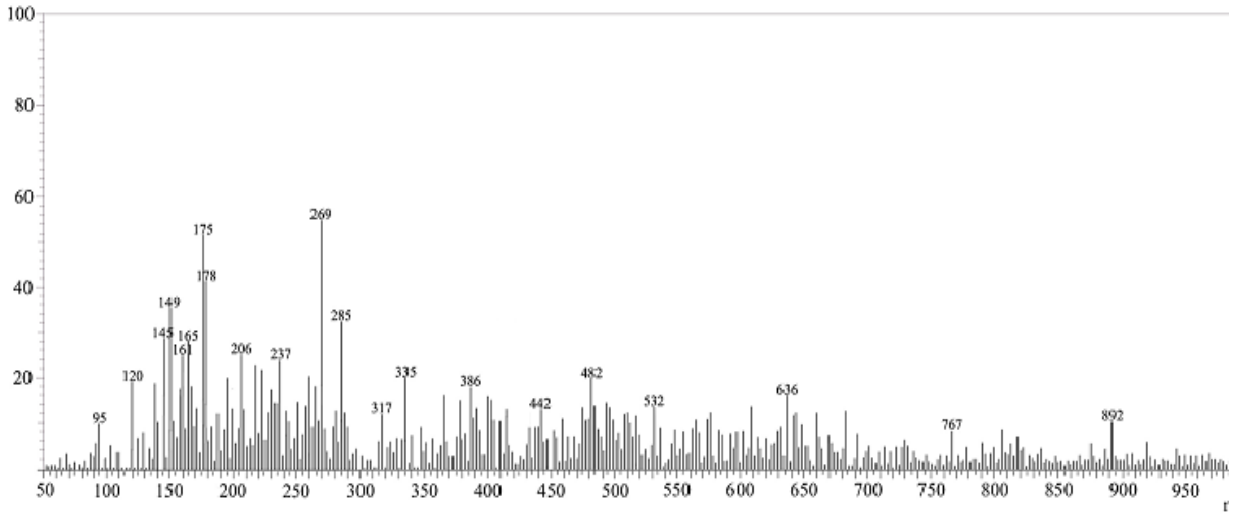

Figure 1a. LCMS spectrum (positive mode) analysis of extract of leaf of *C. Papaya*

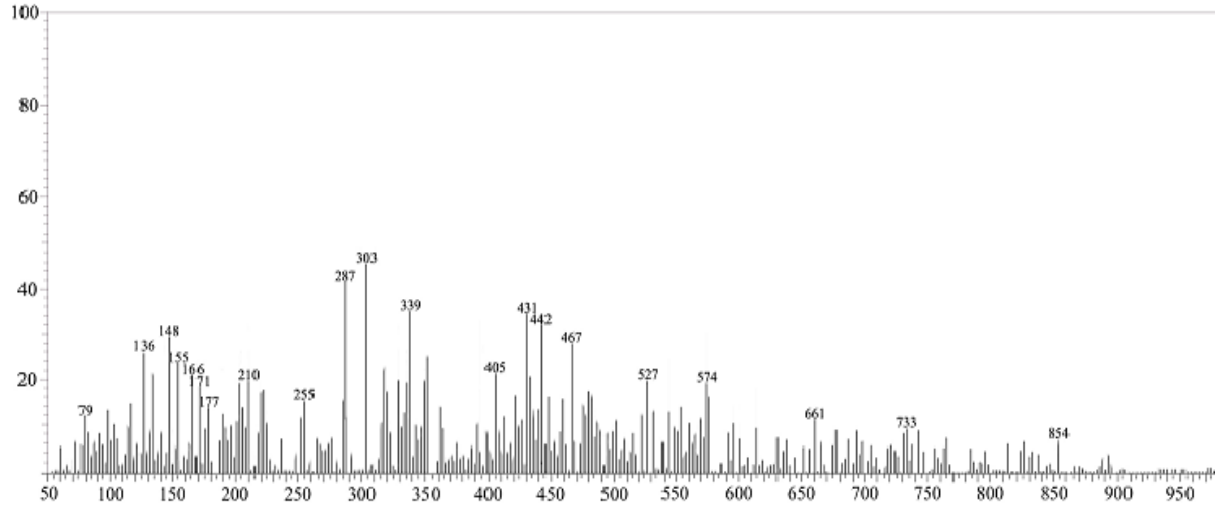

Figure 1b. LMCS spectrum (negative mode) analysis of extract of leaf of *C. Papaya*

Table 3. Hematologic parameters in male and female patients consuming various amounts of *C. Papaya* leaf extract. Values are expressed as mean+/-standard deviation. WBC: White Blood Cells; RBC: Red Blood Cells; HBG: Hemoglobin; MCV: Mean Corpuscular volume; MCHC: mean corpuscular hemoglobin concentration. * indicates a statistically significant ($p<0.05$) difference for control.

Gender	Hematologic Parameter	Control	***C. Papaya*** Leaf Extract 0.01g/kg BW	0 ***C. Papaya*** Leaf Extract 0.16g/kg BW	***C. Papaya*** Leaf Extract 2.0 g/kg BW
Male	WBC (10K/mcL)	3.4+/-3.5	7.0+/-2.1	3.7+/-3.2	7.5+/-1.8
	RBC (1000KxmcL)	6.5+/-0.3	6.8+/-0.3	7.2+/-0.2	7.0+/-0.2
	Hb(g/dL)	13.0+/-0.5	14.4+/-0.7	14.0+/-0.3	14.6+/-0.6
	MCV (fL)	63.8+/-0.8	63.4+/-0.4	*60.9+/-1.0	63.2+/-2.6
	Lymphocyte (%)	83.4+/-6.5	86.8+/-2.0	83.0+/-3.0	83.5+/-6.0
	Platelet (10K/mcL)	1012+/-221	1022+/-140	998+/-236	1022+/-130
	MCHC (g/dL)	33.3+/-0.7	34.5+/-0.6	32.1+/-0.5	33.0+/-0.2
Female	WBC (10K/mcL)	6.8+/-2.0	5.9+/-0.8	4.2+/-3.4	6.5+/-1.7
	RBC (1000KxmcL)	6.6+/-0.5	6.3+/-0.1	6.4+/-0.2	6.5+/-0.6
	Hb(g/dL)	13.9+/-0.7	13.3+/-0.3	13.6+/-0.6	13.7+/-0.7
	MCV (fL)	62.3+/-2.4	63.5+/-1.3	62.3+/-1.0	61.8+/-1.7
	Lymphocyte (%)	81.6+/-10.1	84.6+/-1.7	83.2+/-4.9	82.0+/-5.3
	Platelet (10K/mcL)	1030+/-434	1075+/-103	1153+/-300	1085+/-285
	MCHC (g/dL)	34.0+/-0.8	34.5+/-0.2	22.0+/-0.3	20.2+/-0.6

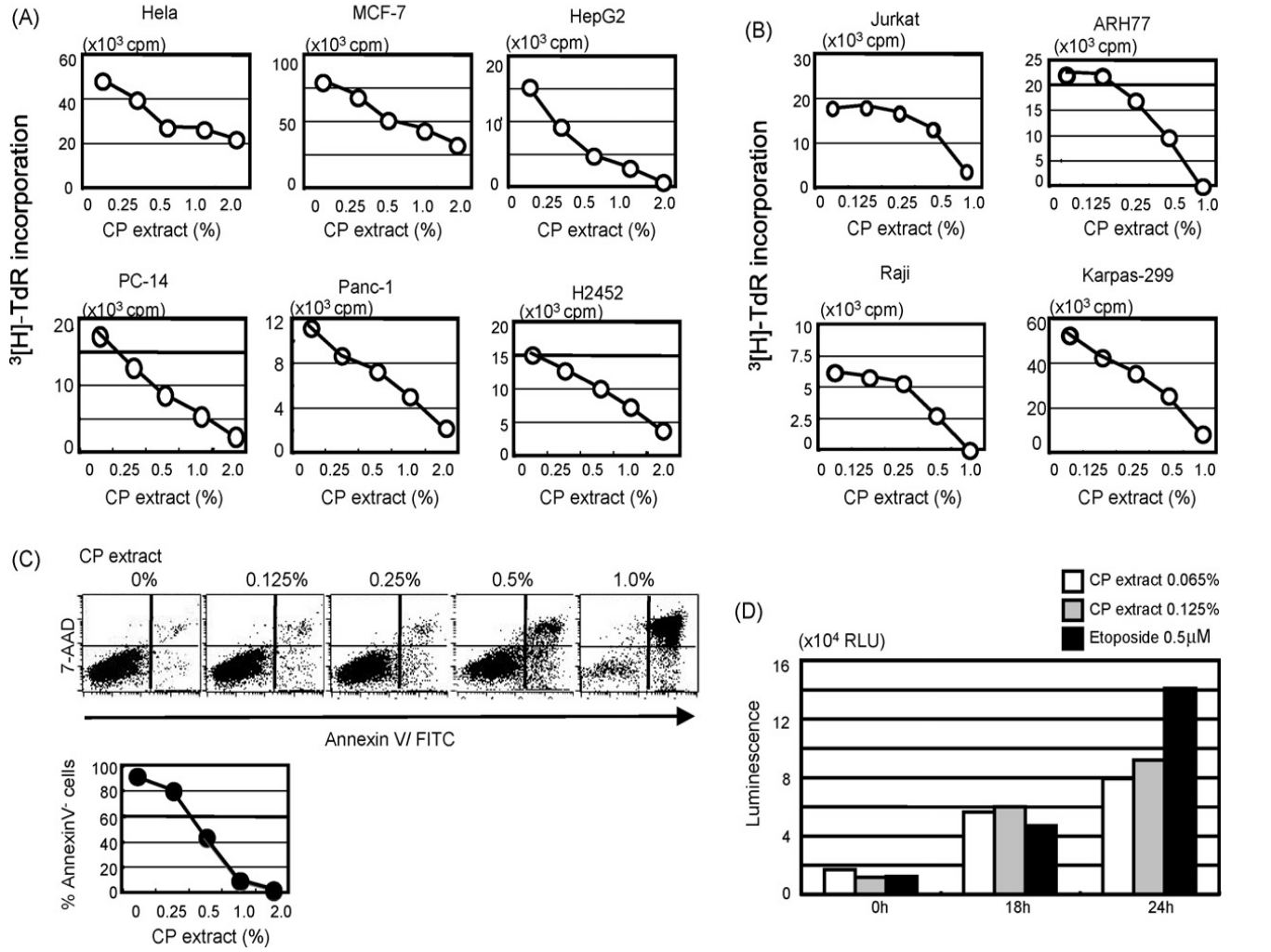

Figure 2. Effects of *C. Papaya* leaf extract on tumor cell growth, proliferation and induction of apoptotic activity. (A) Fractional incorporation of 3H-thymidine (^{3}[H]- TdR) in solid-tumor cell lines Hela, MCF-7, HepG2, PC-14, Panc-1 and H2452 at various concentrations of extract of *C. Papaya* leaf extract. Decreased ^{3}[H]- TdR incorporation at higher extract concentrations demonstrates dose-dependent inhibition of tumor cell proliferation. (B) Fractional incorporation of 3H-thymidine (^{3}[H]- TdR)TdR incorporation in large-cell lymphoma cell lines Jurkat, ARH77, Raji and Karpas-299 cells at various concentrations of extract of *C. Papaya* leaf extract. Decreased ^{3}[H]- TdR incorporation at higher extract concentrations demonstrates dose-dependent inhibition of tumor cell proliferation. (C) 7-Aminoactinomycin D (7-AAD) fluorescent marker for detection of DNA from dead cells and labeled Annexin V- cells were used to measure apoptotic activity after exposure to *C. Papaya* leaf extract at various concentrations. (D) Luminescence after 0, 18 and 24-hour exposure to etoposide or *C. Papaya* leaf extract. Increased luminescence indicates increased apoptotic activity.

Table 4. Clinical laboratory values in male and female patients consuming various amounts of *C. Papaya* leaf extract. Values are expressed as mean+/-standard deviation. AST: aspartate transaminase; ALT: Alanine Aminotransferase; CK: Creatinine Kinase; LDH: Lactate dehydrogenase. * indicates a statistically significant ($p<0.05$) difference for control.

Gender	Organ Profile	Parameter	Control	***C. Papaya*** Leaf Extract 0.01g/kg BW	***C. Papaya*** Leaf Extract 0.16g/kg BW	***C. Papaya*** Leaf Extract 2.0 g/kg BW
Male	Metabolic	Glucose (mmol/L)	6.3+/-1.5	10.0+/-4.4	11.5+/-9.0	8.1+/-5.0
	Liver	AST (U/L)	199+/-42	225+/-20	250+/-75	232+/-25
		ALT (U/L)	58.2+/-12	*82.0+/-16.0	*83.5+/-2.6	66.0+/-3.5
	Renal	Creatinine (mcmol/L)	49.4+/-10.7	54.52+/-7.9	56.8+/-16.5	50.8+/-5.7
	Cardiac	CK (U/L)	1021+/-190	1002+/-231	1189+/-675	740+/-196
		LDH (U/L)	2505+/-340	2530+/-380	2070+/-560	2328+/-302
	Lipid	Total Cholesterol (mmol/L)	1.3+/-0.2	1.3+/-0.2	1.5+/-0.1	1.4+/-0.3
Female	Metabolic	Glucose (mmol/L)	11.1+/-4.5	12.5+/-4.2	12.9+/-4.0	11.6+/-4.7
	Liver	AST (U/L)	43.2+/-33	39.4+/-42	316+/-74	265+/-117
		ALT (U/L)	52.5+/-22	61.4+/-4.8	89.0+/-7.0	73.5+/-40
	Renal	Creatinine (mcmol/L)	64.2+/-4.2	70.4+/-10.3	65.4+/-3.5	50.0+/-5.9
	Cardiac	CK (U/L)	1223+/-521	1209+/-423	1506+/-733	1223+/-570
		LDH (U/L)	1768+/-820	1700+/-849	2169+/-805	2850+/-190
	Lipid	Total Cholesterol (mmol/L)	1.7+/-0.3	1.8+/-0.3	*2.1+/-0.1	1.3+/-0.3

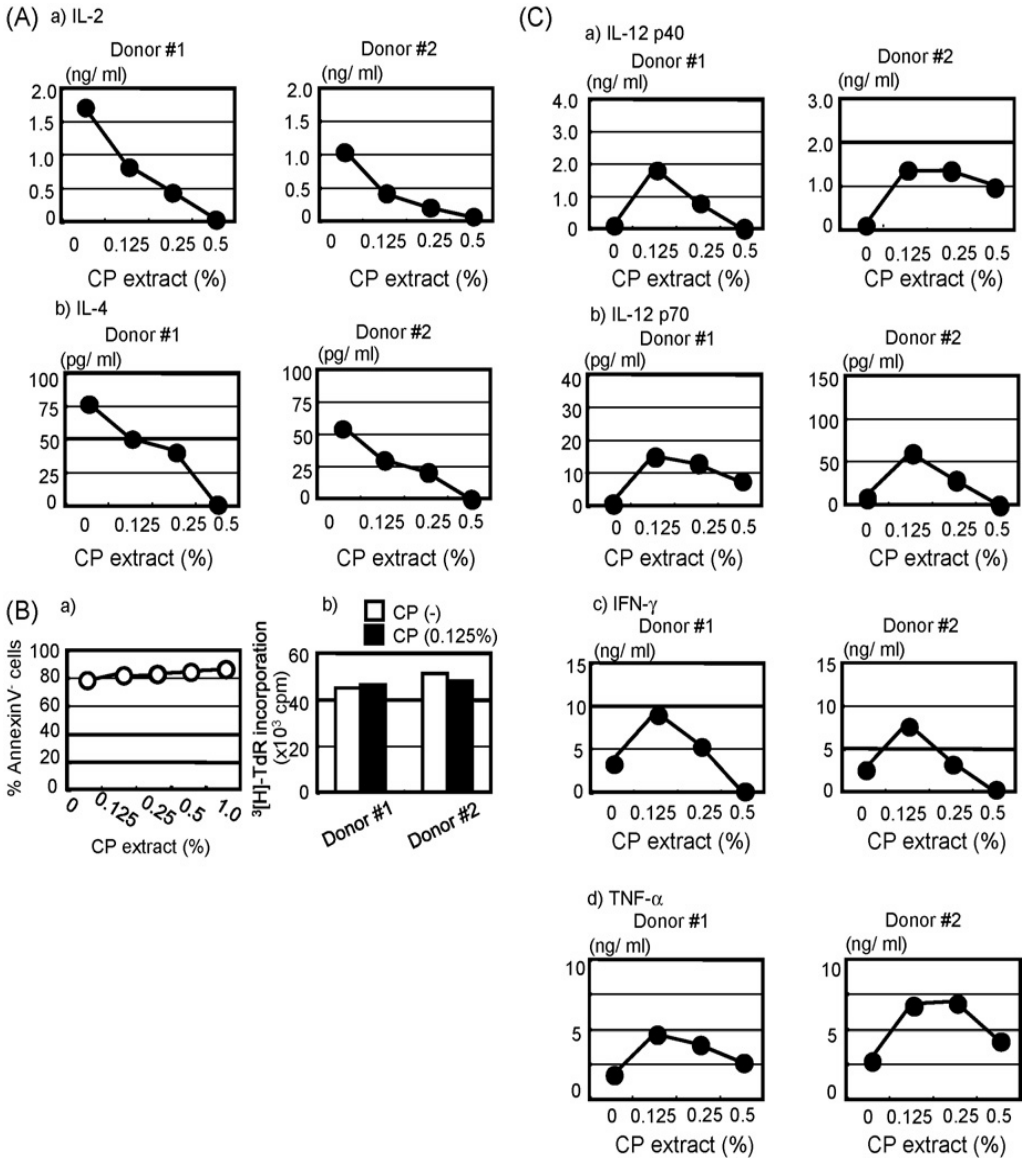

Figure 3. Immuno-modulatory activity secondary to *in vitro* exposure to *C. Papaya* leaf extract. (A) Measured concentrations of a) IL-2 and b) IL-4 in human peripheral blood mononuclear cells (PBMCs) following 24-hour exposure to various concentrations of *C. Papaya* leaf extract. (B) a) Percent of annexin V-negative cells in human PBMCs following 24-hour exposure to *C. Papaya* leaf extract and b) fractional incorporation of 3H-thymidine (^{3}[H]- TdR) in human PBMCs without and with 72-hour exposure to *C. Papaya* leaf extract. C) Measured concentrations of a) IL-12 p40, (b) IL-12 p70, (c) INF-γ, and (d) TNF- α in human PBMCs following 24-hour exposure to various concentrations of *C. Papaya* leaf extract.

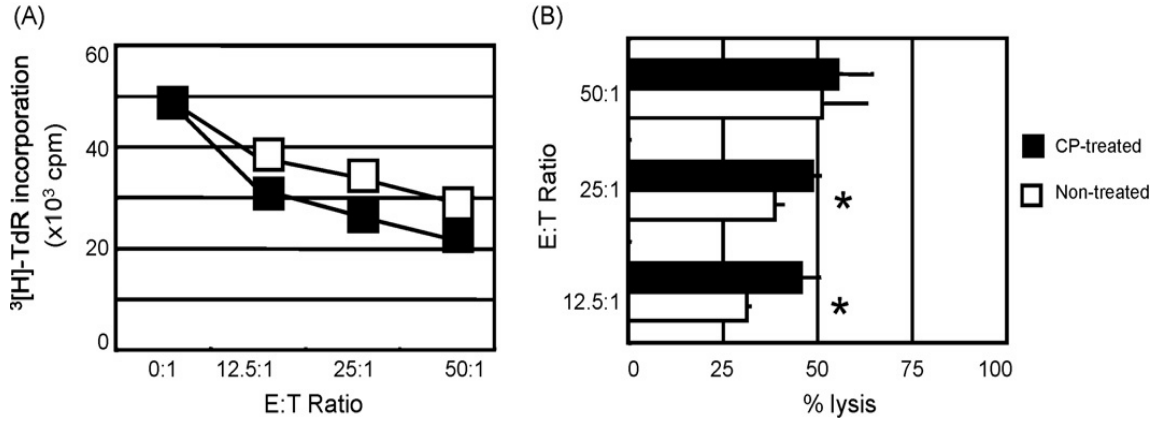

Figure 4. Cytotoxic effects of *C. Papaya* leaf extract. (A) fractional incorporation of 3H-thymidine (^{3}[H]- TdR) in human peripheral blood mononuclear cells after 24-hour exposure to *C. Papaya* leaf extract at various effector-target ratios (E/T ratio)**.** (B) Percent lysis of PBMCs at various E/T ratios. * denotes statistical significance ($p < 0.05$).

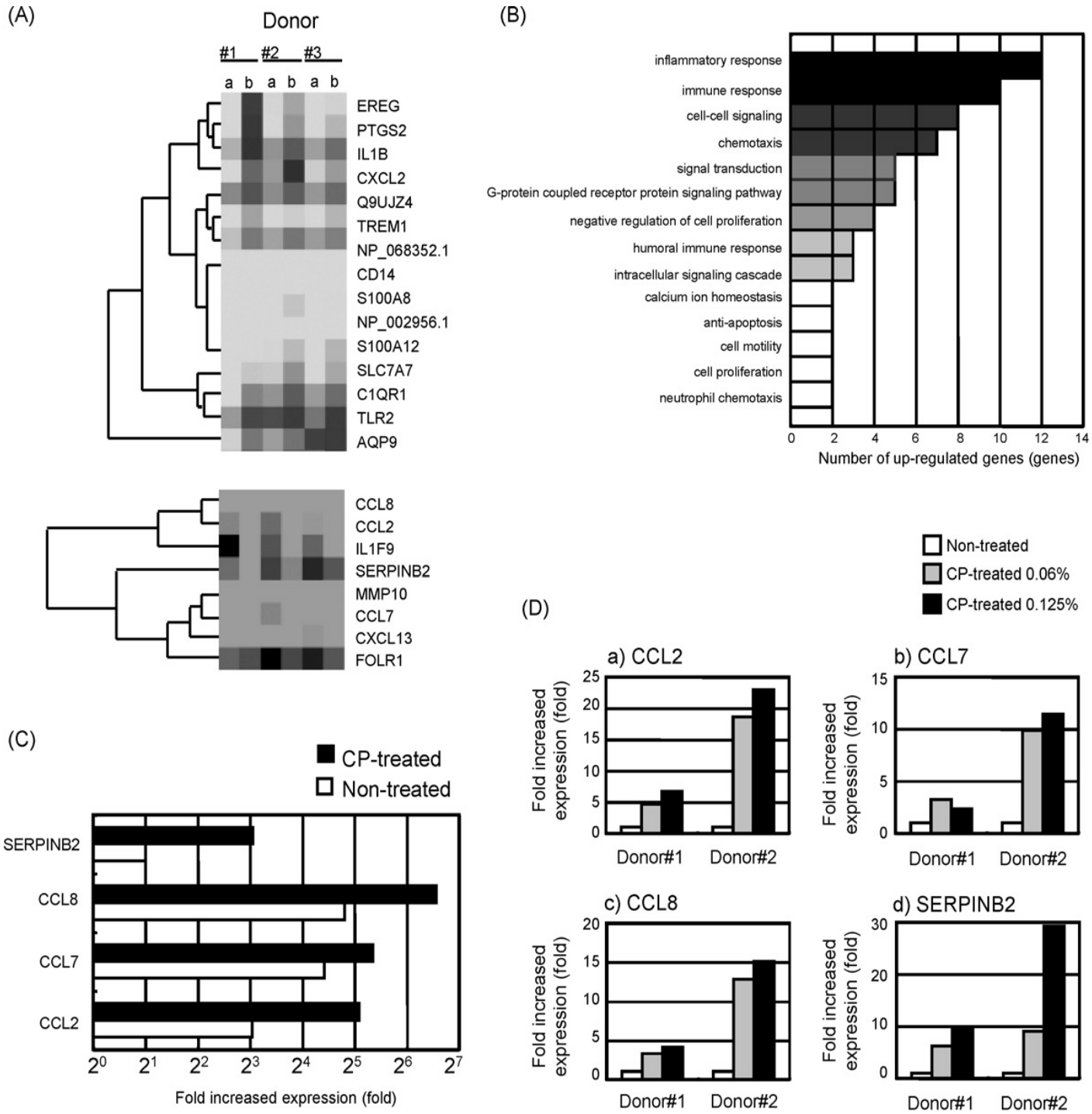

Figure 5. Genetic expression and regulatory effects secondary to *in vitro* exposure to *C. Papaya* leaf extract. A) Real-time PCR analysis performed on peripheral blood mononuclear cells (PBMCs) without exposure (lane a) and with 24-hour exposure (lane b) to *C. Papaya* leaf extract. B) Genetic up-regulation of select genes in PBMCs after 24-hour exposure to *C. Papaya* leaf extract. C) Increased mRNA expression of select cancer biology related genes measured in PBMCs with and without 24-hour exposure to *C. Papaya* leaf extract. D) Dose-dependent increased mRNA expression of select cancer biology related genes measured in PBMCs without and with 24-hour exposure to *C. Papaya* leaf extract at low (0.06%) and high (0.125%) doses.

mRNA was dose-dependant. The clinical implications of the results are uncertain, and additional investigation is warranted.

Human hematology laboratory measurements in cancer patients that received oral doses of encapsulated *C. Papaya* leaf extract are presented in Table 3. A decrease in MCV was observed in male patients treated with medium dose of *C. Papaya* leaf extract (p=0.043). The clinical importance of this finding is uncertain. Human clinical laboratory measurements (metabolic and organ system parameters) in cancer patients that received oral doses of *C. Papaya* leaf extract are presented in Table 4. Increased ALT levels were observed in male patients that received low and medium doses (p=0.032 and 0.029, respectively) of *C. Papaya* leaf extract. Increased Total Cholesterol was

observed in female patient treated with medium doses (p=0.01).The clinical importance of these finding is uncertain. Oral consumption of *C. Papaya* leaf extract (capsules) was well tolerated: no adverse effects were observed and no patient complaints were reported.

Conclusions

Anecdotal reports along with the *in vivo* and *in vitro* studies presented in this report suggest that the leaf extract of *C. Papaya* has substantial potential as an adjuvant treatment for solid tumors (*e.g.,* lung, breast, tonsil). Some significant effects on certain hematologic and organ chemistry parameters were also observed. Additional investigation of *C. Papaya* leaf extract is warranted.

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