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Crucial Role of Curcumin, Piperine and Taurine on Immunological Criteria in Hepatocellular Carcinoma Patients

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Abstract

Introduction: Hepatocellular carcinoma is the fifth most common cancer worldwide. The majority of HCC patients are diagnosed at advanced stage, and curative therapeutic options for HCC are very limited. Therefore, searching for additional therapy is strongly recommended. It has been shown that, curcumin and taurine revealed therapeutic role against hepatocarcinoma cells propagated *ex-vivo* and *in vivo* using experimental animal model in addition to piperine was found to increase the absorption and the bioavailability of curcumin.

Patients and methods: Mononuclear leukocytes (MNLs) and serum were obtained from HCC patients (N=15) before and after treatment with 4 g curcumin mixed with 0.02 gm piperine and 0.5 gm taurine taken daily for three weeks, and six weeks compared to untreated healthy control (N=30). Sera Cytokines levels and immunophenotypic characterization of MNL were determined. Clinical data for the patients were also performed.

Results: Regarding, cytokine evaluation in sera of the patient's post-treatment did show that, IL-10 was significant decrease, on contrary there was significant increase in IFN-γ level. On contrast, levels of IL-6, IL-8, TNF-α, and TGF-α did not show significant difference compared to baseline (before treatment). As for immunophentyping of MNL of the patients under investigation; there were highly significant differences in CD4+%, CD8+%, CD4+CD25+%, and CD8+CD25+% after treatment compared to baseline (untreated patients).

Conclusion: Curcumin, piperine and taurine open novel avenue as promising therapeutic natural derived agents in treatment of patients suffering from hepatocellular Carcinoma.

Keywords: HCC; Curcumin; Piperine; Taurine; Cytokines; Immunophentyping

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Introduction

Hepatocellular carcinoma (HCC) is considered to have a high mortality rate among malignancies [1]. Therapeutic options for HCC patients are limited. Conventional therapies as resection, liver transplantation, and loco- regional treatment are utilized to treat patients at early stages. So additional therapies are needed for HCC patients. Therefore, immunotherapy could be effective additional therapy for different types of malignancies such as HCC patients particularly those do not respond to Conventional therapy [2]. HCC has an immunological characteristic and has

several immunologic mechanisms as evasion of immune response, immunosuppressive environment, and T cell exhaustion which plays a role to promote HCC development and progression [3]. The previous studies focused on the role of immune system in HCC [1].

Curcumin [1, 7-bis-(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene 3, 5dione] is a natural polyphenolic yellow colored compound isolated from the rhizome of Curcuma longa [4]. Curcumin has various activities such as ant- inflammatory, anti-mutagenic, anti-diabetic, wound healing, radio-protective, antioxidant, immunomodulation and anticarcinogenic [5]. Curcumin has also anticancer effect in various types of cancers including HCC. It inhibits the proliferation of HCC cells and enhances antitumor effect of certain traditional chemotherapeutic and molecular target drugs [6].

On the other hand, piperine is a major component of piper species. It is enhancing the serum concentration and bioavailability of curcumin [7]. Piperine listed by FDA as a safe agent to be used without side effect [8]. It has a chemopreventive, antioxidant, anticarcinogenic, immunomodulatory and hepatoprotective effect [9].

In addition, taurine (2-aminoethylsulphonic acid) is a semi-essential amino acid derivative with high concentration in mammalian cells and plasma. It is presented in neutrophilic granulocytes, lymphocytes and monocytes [10]. Taurine is also involved in cytoprotection and maintaining homeostasis of cells involved in acute and chronic inflammatory and oxidative stress [11,12]. It inhibits tumor proliferation by inhibiting tumor markers, enhancement the antioxidant effect, inducing tumor cell apoptosis [13].

Patients and Methods

Fifteen patients with HCC (12male, and 3 females, age (58.66 ± 5.53)), and thirty healthy control (23 male, and 7 female age (52.5 ± 9.35)) were enrolled in this study. The patients admitted to HCC unit of National Hepatology and Tropical Medicine Research Institute (NHTMRI) in the period from 2013 to 2014. This study was approved by ethical committee 2013- NHTMRI- Cairo-Egypt. The patients were treated orally with 4 gram of curcumin containing 0.020 g piperine every day. The products (curcumin and piperine) were produced by (Phytochem science- China) and 0.5 gram of taurine once a day. The latter was produced by (Puritan" pride, INC. Holbrook, NY. 11741 USA). The patients were treated for six weeks. Blood were collected in plane tube for serum separation and EDTA tube for mononuclear leukocytes cells (MNLs) for patients before treatment, as well as after three and six weeks of treatment compared to untreated healthy control. IL- 10 (Boster, USA, and Catalog Number: EK0416), IL-6 (Boster, USA, and Catalog Number: EK0410), IL- 8 (assay pro, Catalog No. EI1008-1), TNF- α (Boster, USA, and Catalog Number: EK0525), IFN- γ (Boster, USA, and Catalog Number: EK0373), and TGF- α (Boster, USA, and Catalog Number: EK0511) were measured according to manufacture instruction.

Cell isolation and flow cytometry

Peripheral blood mononuclear cells were isolated by Ficoll histopaque 1.077(Biowest, South America) density gradient centrifugation. Flow cytometry were performed by anti-human CD4 and CD8 PE cocktail reagent (eBioscience, Inc), and anti-human CD25 (Beckman coulter, Inc) were performed.

Data analysis

The data were presented as Mean ± SD, the student t test or X2 tests were performed using the Graph pad prism software version 5.00 (Graph pad software) to compare two groups, and kruskalwallis (Mann- Whitney U test) if more than two groups. p-value<0.05 was set as significant criteria.

Results

Characteristic of Patients

The HCC patients enrolled in the study had ages range from (35-65) with mean ± SD equal to (58.66 ± 5.53), the male to female ratio was 4: 1, 80% were male (n=12), while 20% were female (3). About 100% of patients were found to be HCV- positive, 93% of patients no ascites found, and 100% no encephalopathy. Also about 100% of patients were child B as shown in **Table 1.**

Immunological profile of HCC patients before treatment compared to healthy control

The sera levels of IL- 10, IL- 6, IL-8, and TGF- α in HCC patients before treatment (base line) were highly significant elevated compared to untreated healthy control ($p<0.0001$) as shown in **Table 2.** Also, TNF- α level showed a significant elevation ($p<0.05$) as shown in **Table 2**. On contrary, IFN- γ level was a highly significant decrease in base line of HCC patient compared to healthy control persons ($p<0.0001$) **Table 2.**

Table 1 Baseline characteristics of HCC patients.

Age (Years) (mean ± SD)	(35- 65) 58.66 ± 5.53
Sex, No. (%) male/female	12 (80%)/3 (20%)
Etiology, No. (%)	
HCV[a]	15 (100%)
HBV[b]	0 (0%)
other	0 (0%)
Ascites, No. (%)	
None	14 (93%)
Mild moderate	1 (7%)
Sever	--
Hepatic encephalopathy	
None	15 (100%)
AFP[c]	
>200	8 (53%)
<200	7 (47%)
Barcelona Clinic Liver Cancer (BCLC) staging system	
Child B	15 (100%)

a: Hepatitis C virus, b: Hepatitis B virus, c: Alpha fetoprotein

Effect of curcumin (C), piperine (P) and taurine (T) on immunological profile of HCC patients

A highly significant decrease of IL- 10 ($p<0.001$) in HCC patients after treatment with CPT for six weeks was shown in **Table 3.** While there were non-significant differences in IL- 6, IL- 8, TNF- α, and TGF-α levels ($p>0.05$) due to treatments with the previous mentioned agents compared to pre- treatment patients as base line as shown in **Table 3.** On contrary, IFN- γ level was highly elevated after 3 and 6 weeks of the treatments compared to untreated (base line) patients as shown in **Table 3**.

Immunophentyping profile of mononuclear leukocytes (MNLs) in HCC patients compared to healthy control

CD4+ % and CD8+ % of MNLs in HCC patients before treatments with CPT (Base Line) showed highly significant decrease ($p<0.0001$) compared to healthy control as shown in **Table 4.** On contrary, CD4+ CD25+ % and CD8+ CD25+ % in previous mention patients showed highly significant increase ($p<0.0001$) as shown in **Table 4.** Flow cytometric analysis of CD4+, CD8+ and their sub-populations in base line HCC patients in comparison with healthy control were clearly shown in **Figure 1.**

Effect of Curcumin (C), piperine (P) and taurine (T) on immunophentyping profile

CD4+ % and CD8+ % were highly significant increase ($p<0.0001$, and $p<0.001$ in HCC patients' post- treatment for three and six weeks with CPT respectively compared to untreated patients as shown in **Table 5.** While, CD4+ CD25+ % was significantly decrease ($p<0.01$) in the previous mentioned patients as shown in **Table 5**. In case of CD8+ CD25+ %, there was a highly significant decrease ($p<0.0001$) in HCC treated patients for the previous mentioned periods as shown in **Table 5.** Flow cytometric analysis of CD4+, CD8+ and their subpopulations in patients with HCC treated with CPT for 3 and 6 weeks in comparison with untreated HCC patients were shown in **Figure 2**.

Discussion

HCC is most common malignant disease worldwide with limited therapeutic option [14]. The therapeutic strategy for HCC is limited to liver surgery and transplantation but recurrence is common, therefore it is necessary to search for novel therapeutic model and additional therapy against HCC [15].

Our results; regarding the immunological criteria in HCC patient before treatment (base line) showed high significant elevation of cytokines such as IL- 10, IL- 6, IL- 8, and TGF- α, and TNF- α. While IFN- γ level was highly significant decrease, which is consistent with results of the previous studies which showed that IL- 10 is highly expressed in HCC tumors compared to healthy control and that increase was correlated with progression and a worse of disease [16], Also, It has been shown that IL- 6 is essential for HCC cells growing and gain the ability to release in HCC patients serum [17].

Table 2 Immunological criteria levels in HCC patients before treatment compared to healthy control.

Parameters	Healthy control (n=30)	HCC patients Before treatment (n=15)	p-value
IL- 10	19.11 ± 3.48	34.77 ± 10.92	<0.0001***
IL- 6	1.96 ± 0.87	12.96 ± 6.37	<0.0001***
IL- 8	16.36 ± 4.82	75.0 ± 44.0	<0.0001***
TNF- α	77.32 ± 18.1	189.40 ± 161.63	<0.05*
IFN- γ	88.43 ± 16.1	63.31 ± 23.07	<0.0001**
TGF- α	34.39 ± 15.76	49.31 ± 15.99	<0.0001***

Results represented as mean ± SD, *: p-value<0.05, **: p-value<0.001, ***: p-value<0.0001.

Table 3 Immunological criteria levels in HCC patients before and after three and six weeks of treatment.

HCC patients (n= 15)				
Parameters	**Before treatment (base line)**	**After three weeks**	**After six weeks**	**p-value**
IL- 10	34.77 ± 10.92	32.03 ± 6.2	24.06 ± 5.9^{b*}	<0.001*
IL- 6	12.96 ± 6.37	13.29 ± 7.69	15.94 ± 9.13	NS
IL- 8	75.0 ± 44.0	73.8 ± 48.16	82.2 ± 57.1	NS
TNF- α	189.40 ± 161.63	117.0 ± 49.94	121.5 ± 36.39	NS
IFN- γ	63.31 ± 23.07	96.85 ± 33.91^{a**}	98.71 ± 29.44^{b***}	<0.001*
TGF- α	49.31 ± 15.99	48.53 ± 12.57	39.84 ± 12.58^{c*}	NS

Results represented as mean ± SD, *: p-value<0.05, **: p-value<0.001, ***: p-value<0.0001, a: comparison between before and after treatment with CPT for three weeks, b: comparison between before and after treatment for six weeks, C: comparison between three and six weeks of treatment with CPT.

Table 4 Immunophenotyping profile in HCC patients before treatment compared to healthy control.

Percentage of lymphocyte subpopulation	Healthy control (n=30)	HCC patients Before treatment (n=15)	p-value
CD4+ %	50.33 ± 5.10	42.4 ± 2.69	<0.0001***
CD8+ %	30.1 ± 2.48	24.5 ± 3.66	<0.0001***
CD4+ CD25+ %	5.18 ± 2.43	10.74 ± 5.50	<0.0001***
CD8+ CD25+ %	1.24 ± 0.56	8.99 ± 4.81	<0.0001***

Results represented as mean ± SD, *: p-value < 0.05, **: p-value<0.001, ***: p-value<0.0001.

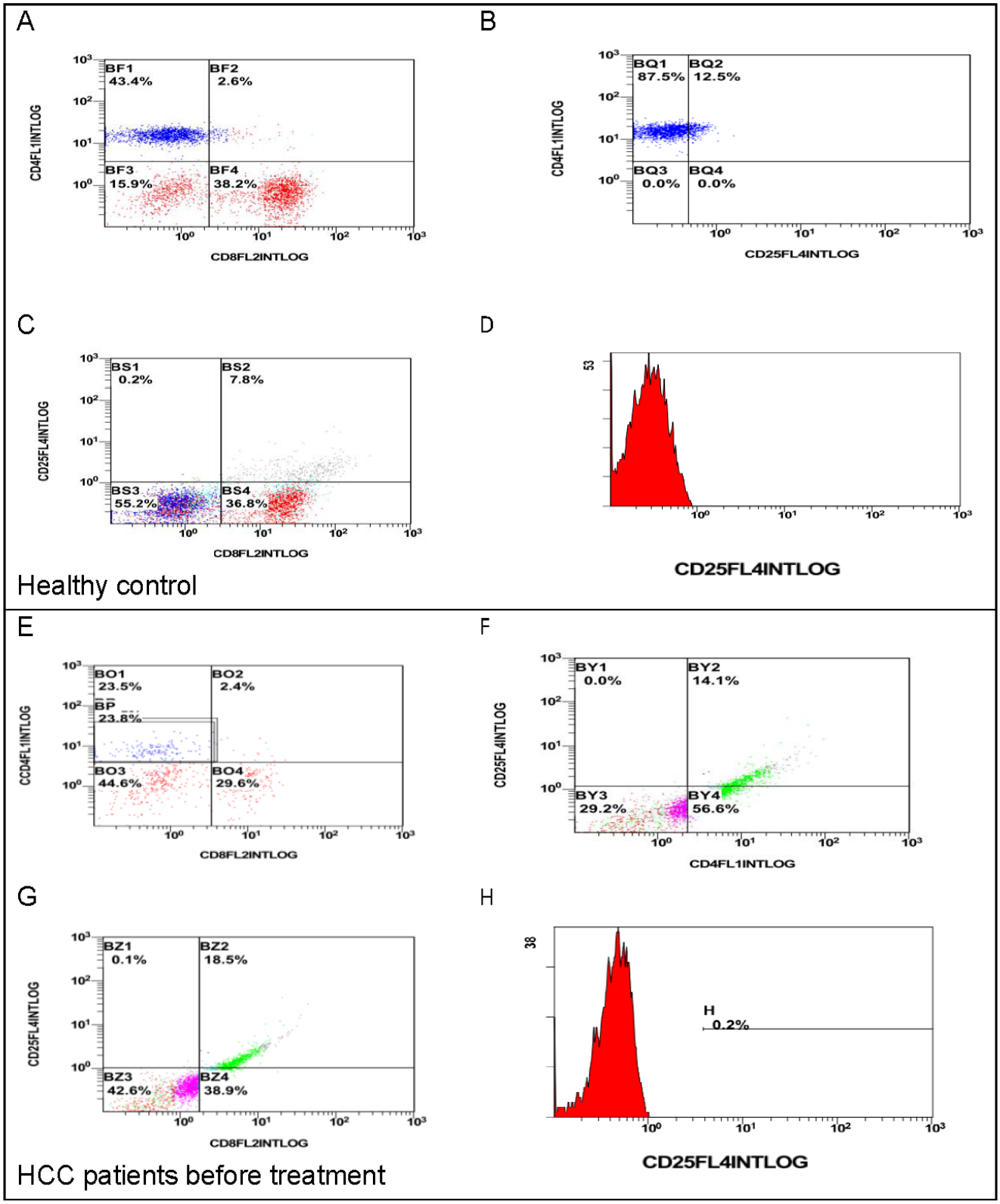

Figure 1 Flow cytometry analysis for phenotypic characterization of healthy control (A, B, C and D) compared to HCC patients before treatment (E, F, G and H).

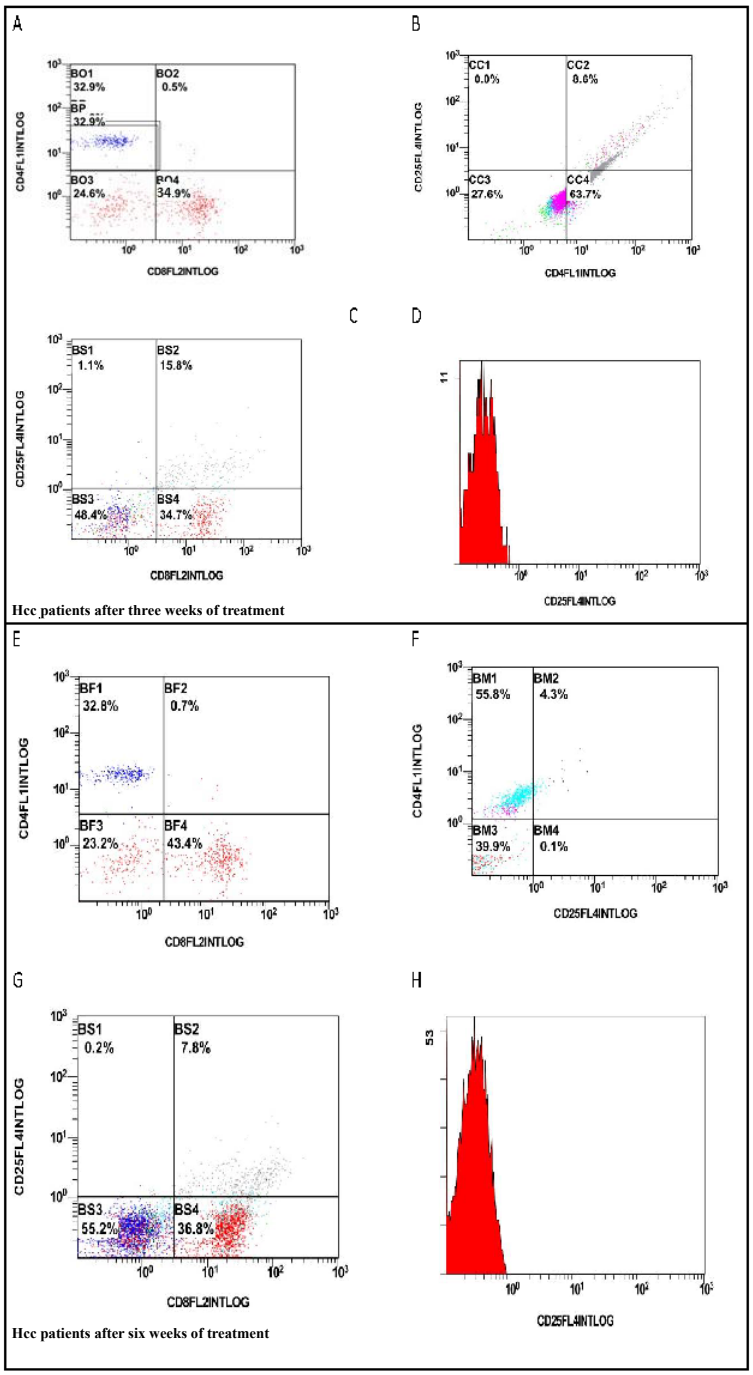

Figure 2 Flow cytometry analysis for phenotypic characterization of HCC patients after three weeks of treatment (A, B, C and D) and HCC patients after six weeks of treatment (E, F, G and H).

Moreover, our results supported also with the previous studies revealing increase in IL- 8 expression associated with tumor growth and survival, tumor cell migration, and increased angiogenesis [18].

It was demonstrated that TNF-α is involved in promoting invasion, angiogenesis, and metastasis [19], The previous study showed also that, the over expression of TGF-α was closely correlated to the development and progression of HCC patients [20].

Regarding the immunophenotyping profile; our results showed that; CD4+ % and CD8+ % were significant decrease in untreated HCC patients (Base Line). In comparison with normal healthy persons. Meanwhile a highly significant elevation of CD4+ and CD8+ was achieved after treatment. On contrary, CD4+ CD25+ % and CD8+ CD25+ % were highly significant decrease. The previous studies agreed with our study reporting that; in HCC patients CD4+ and CD8+T cells increase in early stages of the disease and exhausted as disease progressed [21], also our results was supported by what has been shown that, regulatory T cells (CD4+CD25+) inhibit the stimulated CD8+Tcells their

Table 5 Immunophenotyping profile in HCC patients before and post- treatment (three and six weeks).

HCC patients (n= 15)				
Percentage of lymphocyte subpopulation	Before treatment (Base Line)	After three weeks of Treatment	after six weeks of Treatment	p-value
CD4+ %	42.4 ± 2.69	49.6 ± 4.27^{a**}	50.9 ± 4.99^{b***}	<0.0001***
CD8+ %	24.5 ± 3.66	33.3 ± 5.1^{a*}	30.1 ± 5.25^{b*}	<0.001**
CD4+ CD25+ %	10.74 ± 5.50	8.30 ± 4.72	5.38 ± 2.40$^{b***, c*}$	<0.01*
CD8+ CD25+ %	8.99 ± 4.81	5.48 ± 2.84^{a***}	2.44 ± 0.82 $^{b***, c**}$	<0.0001***
Results represented as mean ± SD, *: p-value<0.05, **: p-value<0.001, ***: p-value<0.0001.				

proliferation, activation, and production of granzyme and perforin resulting an inhibition of tumor specific T cells response in HCC patients [22]. Therefore the inability of immune system to recognize liver cancer cell is due to an increase in Treg and impairment of CD4+ T cells function [23].

Moreover, the increased number of T-reg in peripheral blood and tissue of HCC patient could lead to impairment of CD8+ T cells function in HCC patients [15].

Also, the present study revealed that; the treatment with curcumin, piperine and taurine (CPT) caused high significant decrease in IL- 10 level and in contrary, high significant elevation in IFN- γ. while, the treatment led to decrease in TNF-α and TGF- α but not significant. In case of IL- 6 and IL- 8, there were no significant differences due to the previous mentioned treatment. Our finding in the present study is in consistent with previous studies which showed that curcumin reduced Treg cells population as well as IL- 10 and TGF- α in tumor that led to improve the ability of effector T cells to kill tumor cells [24]. In contrary, increase in IL- 10 level by curcumin in rats with hepatoxicity which induced by CCL4 resulting in reduction of liver fibrosis and inflammation [25,26].

Regarding IFN-γ, our results agreed with what have been shown that, Curcumin has ability to up-regulate IFN- γ level leading to an enhanced antitumor immunity [27]. Also, curcumin down-regulates pro-inflammatory cytokines such as IL- 1, IL- 2, IL- 6, and IL- 8 [26].

Moreover, our results agreed with what was reported that taurine combined with curcumin inhibited experimental hepatocarcinogenesis in rat. The same study showed also that; the levels of IL- 2 and IFN- γ in sera of the animals were highly elevated after treatment with curcumin and taurine [28].

Furthermore, our present study showed also that; highly significant increase of CD4+ % and CD8+ % in HCC patients treated with CPT for 3 and 6 weeks compared to untreated (base line) patients. On contrary, CD4+ CD25+ and CD8+ CD25+ % T cells did show significant decrease. These results were in consistent with previous studies showing that, curcumin is an effective agent in restoring population of CD4+ and CD8+ T cells in the tumor microenvironment driving the cytokines toward Th1 (CD4+) type response again [29]. Also, our results agreed with what revealed that curcumin can effectively reduce Treg population (CD4+ CD25+) and level of TGF- β and IL-10 [27,30].

Conclusion

Moreover, our results regarding Immunophenotyping profile of Mononuclear leukocytes of HCC patients after treatment with curcumin, piperine and taurine can be supported by other study showing that taurine treated normal persons could enhance immune function, increased population of naïve B and T cells in secondary lymphoid tissues and these have a protective effect on immune response.

A combination of curcumin, piperine and taurine could be potential promising therapy for those patients suffering from HCC through the modulation of the immune system.

Conflict of Interest

The authors declare that there is no conflict of interest.

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