CHAPTER V

CONCLUSION

The conclusions can be summarized from the results obtained in this study and they are outlined as below:

(A) Pure curcumin from turmeric distinctly showed the anti-leukemia activity. It downregulated *WT1* gene expression in dose and time dependant manners in K562 cell line. It also showed anti-proliferative activity in WT1 isoforms transfected K562 cells.

(B) This study suggests that WT1 protein activity is involved in leukemic cell proliferation and may be implicated leukemogenesis. Interestingly, the activity of pure curcumin was absolutely reversed by the overexpression of WT1 isoforms.

(C) Pure curcumin could downregulate the exogenous WT1 +/+ protein in the transfected U937 cells. Suppression of the exogenous WT1 +/+ level in the transfected U937 cells after pure curcumin treatment was related to destabilizing of WT1 +/+ protein. The exogenous WT1 +/+ was presented in an unstable form because it was blocked the phosphorylation process by the PKC was blocked. The result related to the previous reports that curcumin inhibited the phosphorylation capacity of PKC (274, 277, 282).

(D) These results indicated that the effect of pure curcumin on *WT1* gene expression in the leukemic K562 cell line was mediated through PKCα signaling upstream of the WT1 transcription factor auto-regulatory function. Importantly,

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this study also suggested that the signaling cascade which was involved the downregulation of *WT1* gene expression by pure curcumin was PI3K, PKCα, JNK in the upstream of WT1 transcription factor. The result from both ChIP and reporter gene assay demonstrated that pure curcumin affected the interaction between transcription factor and *WT1* gene promoter.

These results can be concluded that the inhibitory mechanisms of pure curcumin on both endogenous and exogenous WT1 proteins in K562 cells were regulated by PKCα. This novel mechanistic knowledge of how pure curcumin affects WT1 transcriptional function in leukemic cells may be useful for the alternative therapeutic treatment of leukemia patients in the future. Therefore this research should be further studied in the clinical trials.

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