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Letter to the Editor:

Emerging role of berbamine as an anti-cancer agent in systemic malignancies besides chronic myeloid leukemia

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The recent article by Liang *et al*. (2011), published in *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*, is highly interesting. Interestingly, the past few years have seen the increasing application of berbamine as an anti-cancer agent in other systemic malignancies besides chronic myeloid leukemia.

For instance, berbamine administration alters the Bcl-2/Bax ratio and mitigates cell migration and thereby augments the anti-proliferative ability of trichostatin A in non-small cell lung cancers (Duan *et al*., 2010). Similarly, berbamine inhibits p65 translocation, up-regulates A20 and increases the activation of the GADD45/c-Jun N-terminal kinase (JNK) pathway, thereby enhancing cellular apoptosis in multiple myelomas (Liang *et al*., 2009a; 2009b). Similarly, alteration of the nuclear factor-kappa B (NF-κB) pathway results in enhanced apoptosis in lymphomas (Du *et al*., 2010).

Similarly, the apoptotic ability of chemotherapeutic agents such as doxorubicin and carmofur is markedly enhanced by co-administration of berbamine, as a result of attenuated expression of cdc2/p34 and vascular endothelial growth factor (VEGF) in affected cells (Cheng *et al*., 2006; Wang S. *et al*., 2009; Liu *et al*., 2010). This results in accentuated G_2/M cell cycle arrest and reversal of multidrug resistance in MCF-7/ADR breast cancer tissue (Liu *et al*., 2010). Similarly apoptosis in hepatocellular carcinomas is augmented by berbamine-mediated induction of the Fas apoptotic pathway and loss in mitochondrial trans-membrane potential (Wang G.Y. *et al*., 2007; 2009).

The above examples clearly illustrate the significant anti-proliferative activity of berbamine and the need for further studies to fully elaborate its anti-cancer properties.

References

Cheng, Y.H., Qi, J., Xiong, D.S., Liu, J.W., Qi, S.L., Pan, B., Yang, C.Z., Zhu, H.F., 2006. Reversal of multidrug resistance in drug-resistant human breast cancer cell line MCF-7/ADR by calmodulin antagonist *O*-(4-ethoxylbutyl)-berbamine. *Acta Acad. Med. Sin.*, **28**(2):164-168 (in Chinese).

Du, H.P., Shen, J.K., Yang, M., Wang, Y.Q., Yuan, X.Q., Ma, Q.L., Jin, J., 2010. 4-Chlorobenzoyl berbamine induces apoptosis and G_2/M cell cycle arrest through the PI3K/Akt and NF-kappaB signal pathway in lymphoma cells. *Oncol. Rep.*, **23**(3):709-716.

Duan, H., Luan, J., Liu, Q., Yagasaki, K., Zhang, G., 2010. Suppression of human lung cancer cell growth and migration by berbamine. *Cytotechnology*, **62**(4):341-348. [doi:10.1007/s10616-009-9240-x]

Liang, Y., Xu, R.Z., Zhang, L., Zhao, X.Y., 2009a. Berbamine, a novel nuclear factor kappaB inhibitor, inhibits growth and induces apoptosis in human myeloma cells. *Acta Pharmacol. Sin.*, **30**(12):1659-1665. [doi:10.1038/aps.2009.167]

Liang, Y., Zhao, X.Y., Wei, Y.L., Xu, R.Z., 2009b. Berbamine induces apoptosis of multiple myeloma RPMI 8226 cells by activating GADD45/JNK pathway. *J. Zhejiang Univ. (Med. Sci.)*, **38**(5):439-444 (in Chinese).

Liang, Y., Qiu, X., Xu, R.Z., Zhao, X.Y., 2011. Berbamine inhibits proliferation and induces apoptosis of KU812 cells by increasing Smad3 activity. *J. Zhejiang Univ.-Sci. B (Biomed. & Biotechnol.)*, **12**(7):568-574. [doi:10.1631/jzus.B1000230]

Liu, R., Zhang, Y., Chen, Y., Qi, J., Ren, S.M., Xushi, M.Y., Yang, C.Z., Zhu, H., Xiong, D.S., 2010. A novel calmodulin antagonist *O*-(4-ethoxyl-butyl)-berbamine overcomes multidrug resistance in drug-resistant MCF-7/ADR breast carcinoma cells. *J. Pharm. Sci.*, **99**(7):3266-3275. [doi:10.1002/jps.22082]

Wang, G.Y., Zhang, J.W., Lu, Q.H., Xu, R.Z., Dong, Q.H., 2007. Berbamine induces apoptosis in human hepatoma cell line SMMC7721 by loss in mitochondrial transmembrane potential and caspase activation. *J. Zhejiang Univ.-Sci. B*, **8**(4):248-555. [doi:10.1631/jzus.2007.B0248]

Wang, G.Y., Lv, Q.H., Dong, Q., Xu, R.Z., Dong, Q.H., 2009. Berbamine induces Fas-mediated apoptosis in human hepatocellular carcinoma HepG2 cells and inhibits its tumor growth in nude mice. *J. Asian Nat. Prod. Res.*, **11**(3):219-228. [doi:10.1080/10286020802675076]

Wang, S., Liu, Q., Zhang, Y., Liu, K., Yu, P.F., Liu, K., Luan, J.L., Duan, H.Y., Lu, Z.Q., Wang, F.F., *et al*., 2009. Suppression of growth, migration and invasion of highly-metastatic human breast cancer cells by berbamine and its molecular mechanisms of action. *Mol. Cancer*, **8**(1):81. [doi:10.1186/1476-4598-8-81]

Authors' response

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For the Letter to the Editor "Emerging role of berbamine as an anti-cancer agent in systemic malignancies besides chronic myeloid leukemia", we are pleased with the interest in our article (Liang *et al*., 2011), and appreciate the insightful comments made by Dr. Kapoor (2012). He systemically reviewed application of berbamine as an anti-cancer agent during the past few years and found that berbamine also shows anti-cancer activity for other systemic malignancies besides chronic myeloid leukemia. Extensive scrutiny of its molecular targets and mechanism of action in the past few decades has provided important insights. At the cellular level, berbamine exhibits significantly antiproliferative activity, inhibiting the proliferations of leukemia, lymphoma (Du *et al*., 2010), breast cancer (Liu *et al*., 2010), and hepatocellular carcinoma (Wang *et al*., 2009). At the molecular level, berbamine-mediated anti-tumor activity was shown to be involved in PI3K/Akt, nuclear factor-kappaB (NF-κB) (Du *et al*., 2010), Fas-mediated apoptosis (Wang *et al*., 2009), and P-glycoprotein (Liu *et al*., 2010). However, its targets and molecular mechanism of action are still largely elusive. We feel that identification of the direct molecular target of berbamine will account for the diverse biological activities.

References

Du, H.P., Shen, J.K., Yang, M., Wang, Y.Q., Yuan, X.Q., Ma, Q.L., Jin, J., 2010. 4-Chlorobenzoyl berbamine induces apoptosis and G_2/M cell cycle arrest through the PI3K/Akt and NF-kappaB signal pathway in lymphoma cells. *Oncol. Rep.*, **23**(3):709-716.

Kapoor, S., 2012. Emerging role of berbamine as an anti-cancer agent in systemic malignancies besides chronic myeloid leukemia. *J. Zhejiang Univ.-Sci. B (Biomed. & Biotechnol.)*, **13**(9):761-762. [doi:10.1631/jzus.B1200110]

Liang, Y., Qiu, X., Xu, R.Z., Zhao, X.Y., 2011. Berbamine inhibits proliferation and induces apoptosis of KU812 cells by increasing Smad3 activity. *J. Zhejiang Univ.-Sci. B (Biomed. & Biotechnol.)*, **12**(7):568-574. [doi:10.1631/jzus.B1000230]

Liu, R., Zhang, Y., Chen, Y., Qi, J., Ren, S.M., Xushi, M.Y., Yang, C.Z., Zhu, H., Xiong, D.S., 2010. A novel calmodulin antagonist *O*-(4-ethoxyl-butyl)-berbamine overcomes multidrug resistance in drug-resistant MCF-7/ADR breast carcinoma cells. *J. Pharm. Sci.*, **99**(7):3266-3275. [doi:10.1002/jps.22082]

Wang, G.Y., Lv, Q.H., Dong, Q., Xu, R.Z., Dong, Q.H., 2009. Berbamine induces Fas-mediated apoptosis in human hepatocellular carcinoma HepG2 cells and inhibits its tumor growth in nude mice. *J. Asian Nat. Prod. Res.*, **11**(3):219-228. [doi:10.1080/10286020802675076]