



**UNIVERSITI PUTRA MALAYSIA**

***EFFECTS OF *Curcuma longa* L. RHIZOMES IN PREVENTING THE PROGRESSION OF CARCINOGENESIS IN LEUKAEMIA-LYMPHOMA RATS***

**YUSNAINI BT MD YUSOFF**

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PROGRESSION OF CARCINOGENESIS IN LEUKAEMIA-LYMPHOMA  
RATS**

**By**

**YUSNAINI BT MD YUSOFF**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,  
in Fulfillment of the Requirements for the Degree of Master of Science**

**July 2013**

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UPM

*This thesis is dedicated with love and gratitude especially  
to my parents, Md Yusoff Ahmad and Maimunah Samuri;  
my siblings, Yusnita Md Yusoff, Yusliza Md Yusoff, Md Yusri Md Yusoff, Md Yaziz  
Azam Md Yusoff, Md Yusfahizal Md Yusoff and Nur Nilam Sari Md Yusoff*

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment  
of the requirement for the degree of Master of Science

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**YUSNAINI MD YUSOFF**

**July 2013**

**Chairman : Hazilawati Hamzah, PhD**

**Faculty : Veterinary Medicine**

Blood diseases including leukaemia and lymphoma are among the top ten cancers around the world. The link of anti apoptotic gene and pro apoptotic gene expression in regulating the apoptosis machinery was extensively discussed in previous studies. Curcumin the active compound in *Curcuma longa* L. (*C. longa* L.) has been proven to act as an anti cancer by inhibit the expression of Bcl-2 (anti apoptotic gene) and trigger the expression of Bax (pro apoptotic gene) in cancer researches. However, the effects of turmeric itself on the expression of those genes have not been determined in lymphoma and leukaemia research. Therefore the study present objectives were 1) to evaluate the effects of crude *C. longa* L. rhizomes in Sprague Dawley rats with leukaemia-lymphoma via evaluation of Bcl-2 to Bax transcription ratios in the blood and spleen using quantitative real time reverse transcription polymerase chain reaction (qRT-PCR) assay, blood analyses, urinalysis and histopathology, and 2) to examine the reliability of using *N*-methyl-*N*-nitrosourea (MNU) in inducing leukaemia-lymphoma in Sprague Dawley rats for a duration of 20 weeks. A total of 64 rats were used in this study. Rats in group A were treated as controls which were fed with a standard pellet diet. Each rat in groups B and D received daily supplementation of crude *C. longa* L. rhizomes at 5000 mg/kg for 20 weeks. Rats in groups C and D were injected with MNU intraperitoneally (i.p.) with a total dose of 240 mg/kg of body weight (60 mg/kg of body weight per injection for four injections in two week) to induce leukaemia-lymphoma. Blood samples were collected at weeks 0, 10 and 20 (experiment end) for haematological and serum biochemical analyses. The presence of leukaemic cells was further examined through blood smear. For molecular analysis, blood samples at weeks 0 and 20 were run for RNA extraction and qRT-PCR assay to determine the transcription ratio of Bcl-2 and Bax. Urine samples were collected once using metabolic cages before the rats were euthanised for determination of urine protein to creatinine ratio (UPC) and creatinine clearance values. Organ samples include liver, lungs, kidneys, heart, spleen and lymph nodes were taken for histopathological analysis. Spleen of each rat was also

run for qRT-PCR assay. Results of blood smear showed that 64% and 100% of rats in group C had leukaemia without lymphocytosis at week 10 and week 20, respectively. The qRT-PCR assay showed the transcription ratios of Bcl-2 to Bax of the leukaemic rats were significantly higher, 3.3 fold ( $10.50 \pm 1.26$ ) in blood and 10 fold ( $30.0 \pm 1.16$ ) in spleen, as compared to the control rats, which indicate that MNU apparently disturbed the apoptosis pathway. High transcription ratio of Bcl-2 to Bax in the spleen was related to the splenic lesion scoring results of rats that had splenic lymphoma. Histopathology results were evidenced for the presence of metastatic malignant lymphocytes in the heart (23%), liver (23%), lungs (31%) and kidneys (15%) which encompass approximately 30% metastatic lesions observed in the rats, and malignant lymphocytes in the spleen (86%), mesenteric lymph nodes (86%) and other lymph nodes (57%) in group C rats. Serum biochemical results of the rats revealed significant elevation in the ALP, total bilirubin and uric acid levels compared to other groups, although the values were within the normal ranges. The rats had also shown significant elevation in the UPC level and decrease in the creatinine clearance value compared to control, which consistent with lymphoma-induced renal injury. Interestingly, significant reduction of Bcl-2 to Bax transcription ratios in the blood and spleen of group D was observed when compared to group C. However, the transcription levels of Bcl-2 to Bax in the blood and spleen were not correlated with the lesion scoring results in the organs. The lymphoma lesion scoring results constituted in the heart, liver, lungs, kidneys, spleen, mesenteric lymph nodes and other lymph nodes of these rats were 27%, 27%, 20%, 13%, 80%, 80% and 53%, respectively, which were not significantly different form group C. Haemogram result, however, supported results of the qRT-PCR, where significant reduction in the percentages of leukaemic rats at week 10 and week 20 (19% and 88%, respectively) in group D were observed when compared to group C (64% and 100%, respectively). The UPC ratio and creatinine clearance of group D also showed a similar trend of reduction as compared to group C. In conclusion, the administration of MNU with a total dosage of 240 mg/kg successfully induced 100% leukaemia and 86% nodal and splenic lymphoma in male Sprague Dawley rats within 20 weeks period, however less than 30% of the rats had metastatic lesions in the vital organs. Urinalysis results of the rats were in accordance to the lymphoma lesions observed in the kidneys. The transcription ratios of Bcl-2 and Bax in the blood and spleen were also significantly increased and correlated to the lesion scoring results in the organs. Meanwhile, the effectiveness of crude *C. longa* L. rhizomes was demonstrated by the reduction in number of leukaemic rats and transcription ratio of Bcl-2 and Bax in the blood. Low transcription ratio of Bcl-2 to Bax in the spleen and urinalysis results further elucidate the effectiveness of the herb in preventing progression of carcinogenesis via inhibiting the proliferation of lymphoma cells in the spleen and minimising renal injury induced by the lymphoma cells in the rats, respectively.

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**KESAN AKAR KUNYIT DALAM MENCEGAH PERKEMBANGAN  
KARSINOGENIK PADA TIKUS LEUKEMIA-LYMPHOMA**

Oleh

**YUSNAINI MD YUSOFF**

**Julai 2013**

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**Fakulti : Perubatan Veterinar**

Penyakit darah termasuk leukemia dan limfoma adalah antara sepuluh kanser tertinggi di dunia. Kajian terdahulu telah membuktikan hubungan antara gen penghalang apoptosis dan gen pencetus apoptosis dalam kitaran kematian sel. Curcumin iaitu bahan aktif di dalam kunyit memainkan peranan sebagai penghalang kanser dimana Bcl-2 berperanan sebagai gen penghalang apoptosis dan Bax sebagai gen pencetus apoptosis melalui penyelidikan kanser. Walau bagaimanapun, kesan kunyit itu sendiri terhadap gen-gen tersebut belum ditentukan dalam penyelidikan limfoma dan leukemia. Oleh itu, objektif kajian ini adalah 1) untuk menentukan kesan kunyit terhadap tikus Sprague Dawley yang menghidap leukemia dan limfoma melalui pengesanan gen Bcl-2 dan Bax dalam cDNA menggunakan kaedah pengesanan kuantitatif tindak balas transkripsi rantai polimeras berbalik pada masa sebenar (qRT-PCR), analisis darah, ujian air kencing dan histopatologi dan 2) untuk menilai keberkesanan menggunakan *N*-methylnitrosourea (MNU) bagi mencetuskan leukemia dan limfoma dalam tikus Sprague Dawley bagi tempoh 20 minggu. Sejumlah 64 ekor tikus digunakan dalam kajian ini. Tikus dalam kumpulan A mewakili tikus kawalan yang diberikan diet makanan biasa. Setiap tikus kumpulan B dan D menerima makanan sampingan kunyit kasar pada dos 5000 mg/kg bagi tempoh 20 minggu. Tikus kumpulan C dan D diberikan suntikan MNU intraperitoneali pada dos 240 mg/kg (60 mg/kg setiap suntikan untuk empat kali suntikan) to induce leukaemia-lymphoma. Sampel darah diambil pada minggu 0, 10 dan 20 untuk analisis serum biokimia dan hematologi. Kehadiran sel-sel leukemia pada calitan darah diperiksa. Bagi analisis molekul, sampel darah pada minggu 0 dan 20 diekstrak untuk mendapatkan RNA dan qRT-PCR untuk menentukan nisbah Bcl-2 kepada Bax. Bagi ujian air kencing, sampel air kencing dikumpulkan menggunakan sangkar metabolik sebaik sebelum tikus dimatikan untuk menentukan nisbah protein air kencing kepada nilai kreatinin (UPC). Sementara itu, organ-organ termasuk hati, paru-paru, buah pinggang, jantung, limpa dan nodus limfa diambil untuk pemeriksaan histopatologi. Sebahagian sampel limpa juga digunakan untuk analisis qRT-PCR. Keputusan menunjukkan kehadiran sel-sel leukemia tanpa limfositosis



masing-masing memberi 64% dan 100% tikus leukemia dalam kumpulan C pada minggu 10 dan 20. Berdasarkan data pengasaan qRT-PCR, nisbah Bcl-2 kepada Bax untuk tikus leukemia adalah lebih tinggi iaitu 3.3 kali ganda ( $10.50 \pm 1.26$ ) dalam sampel darah dan 10 kali ganda ( $30.0 \pm 1.16$ ) dalam limpa berbanding tikus kawalan, dimana ianya menunjukkan bahawa MNU telah mengganggu mekanisme apoptosis dalam tikus leukemia. Nisbah transkripsi Bcl-2 dan Bax yang tinggi dalam limpa adalah berhubung kait dengan kecederaan limpa pada tikus yang mempunyai limfoma limpa. Keputusan histopatologi menunjukkan bahawa terdapat metastasis limfosit neoplastik dalam jantung (23%), hati (23%), paru-paru (31%), buah pinggang (15%), limpa (86%), mesentrik nodus limfa (86%) dan lain-lain nodus limfa (57%) bagi tikus kumpulan C. Sementara itu, keputusan serum biokimia bagi nilai ALP, bilirubin, dan asid uric dalam tikus kumpulan C menunjukkan peningkatan yang ketara berbanding kumpulan lain, dimana nilai purata tersebut adalah dalam lingkungan normal. Tikus leukemia juga menunjukkan peningkatan nisbah protein kepada kreatinin yang ketara dan juga penurunan yang ketara bagi nilai pelepasan kreatinin berbanding kumpulan kawalan, dimana berkadaran dengan kecederaan buah pinggang. Menariknya, terdapat penurunan yang ketara bagi nisbah Bcl-2 kepada Bax dalam tikus kumpulan D berbanding kumpulan C dalam sampel darah dan limpa. Walaubagaimanapun, pengekspresan nisbah Bcl-2 dan Bax di dalam darah dan limpa tidak berkait dengan hasil kecederaan yang diperolehi daripada histopatologi organ. Kecederaan limfoma terdapat dalam jantung, hati, paru-paru, buah pinggang, limpa, nodus limfa mesentrik dan lain-lain nodus limfa bagi tikus dalam kumpulan D masing-masing adalah (27%, 27%, 20%, 13%, 80%, 80% and 53%) dan menyerupai penemuan bagi kumpulan C. Penemuan analisis hematologi adalah serupa dengan penemuan daripada qRT-PCR, dimana terdapat penurunan yang ketara dalam peratusan tikus leukemia pada minggu ke 10 dan 20, masing-masing (19% dan 88%) bagi tikus kumpulan D berbanding kumpulan C masing-masing (64% dan 100%). Nilai nisbah protein kepada kreatinin dan nilai pelepasan kreatinin di dalam kumpulan D juga menunjukkan corak penurunan yang sama jika dibandingkan dengan kumpulan C. Kesimpulannya, penggunaan MNU bagi jumlah dos 240 mg/kg telah berjaya menyebabkan 100% leukemia dan 86% kelenjar dan limfa limfoma pada tikus Spague Dawley dalam tempoh 20 minggu, bagaimanapun hanya menyebabkan kurang dari 30% metastasis dalam organ-organ lain. Analisis air kencing adalah berkadarangan langsung dengan kehadiran kecederaan limfoma pada buah pinggang. Nisbah transkripsi Bcl-2 dan Bax di dalam darah dan limpa menunjukkan perbezaan yang ketara dan berkait dengan kecederaan pada organ-organ. Di samping itu, keberkesanan kunyit dapat dilihat pada penyusupan peratusan tikus leukemia dan nisbah transkripsi Bcl-2 dan Bax dalam darah. Nisbah transkripsi Bcl-2 dan Bax yang rendah di dalam limpa dan analisis air kencing seterusnya menjelaskan keberkesanan herba ini dalam mencegah perkembangan karsinogenik melalui perkembangan sel limfoma yang dihalang di dalam limfa dan pengurangan kecederaan buah pinggang yang dicetuskan oleh sel limfoma di dalam tikus.



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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of Supervisory Committee were as follows:

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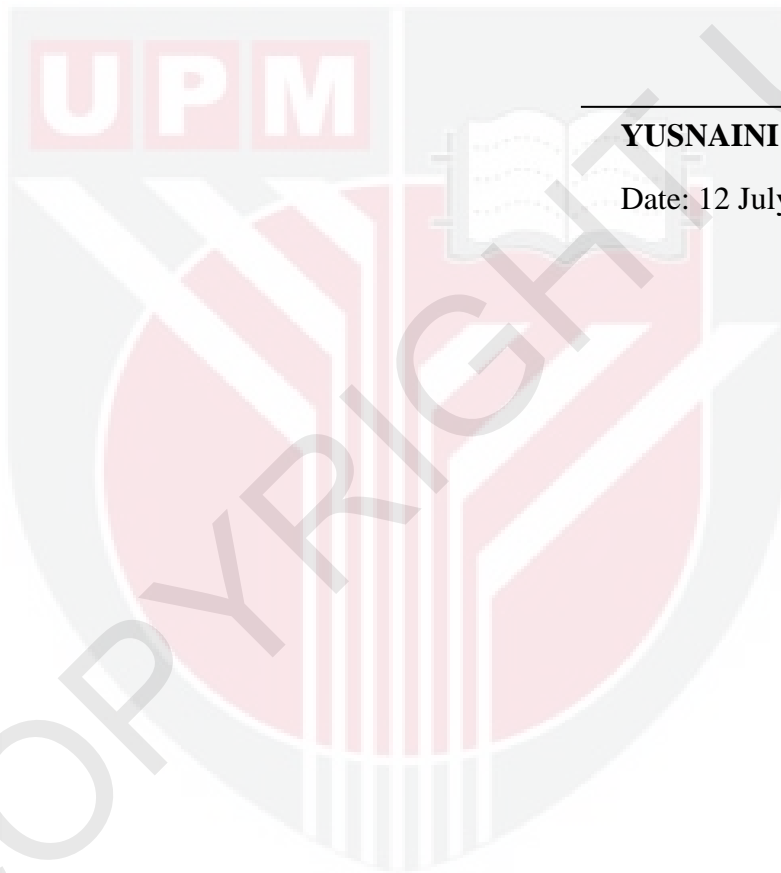
**BUJANG BIN KIM HUAT, PhD**

Professor and Dean  
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Date:

## DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.



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**YUSNAINI MD YUSOFF**

Date: 12 July 2013

## REFERENCES

- Abdul Rahman Md. Derus (1996). Pengenalan dan Penggunaan Herba Ubatan. Orient Press Sdn. Bhd. Kuala Lumpur.
- Abbott, B.L. (2006). Chronic lymphocytic leukemia : Recent advanced in diagnosis and treatment. *The Oncologist*, 11(1), 21 – 30.
- Acehan, D., Jiang, X., Morgan, D.G., Heuser, J.E., Wang, X. and Akey, C.W. (2002). Three-dimensional structure of the apoptosome: implications for assembly, procaspase-9 binding and activation. *Molecular Cell*, 9(2), 423 – 32.
- Adams, B.K., Cai, J., Armstrong, J. Herold, M., Lu, Y.J., Sun, A., Snyder, J.P. Liotta, D.C., Jones, D.P. and Shoji, M. (2005). EF24, a novel synthetic curcumin analog, induces apoptosis in cancer cells via a redox-dependent mechanism. *Anticancer Drugs*, 16, 263 – 275.
- Agarwal, R., Goel, S. K. and Behari, J. R. (2010). Detoxification and antioxidant effects of curcumin in rats experimentally exposed to mercury. *The Journal of Applied Toxicology*, 30, 457 – 468.
- Aggarwal, B.B., Kumar, A. Aggarwal, M.S. and Shishodia, S. (2005). Curcumin derived from turmeric (*Curcuma longa*): a spice for all seasons. *CRC Press New York*, 349 – 387.
- Aggarwal, B.B., Kumar, A. and Bharti. A.C. (2003). Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Research*, 23, 363 – 398.
- Alizadeh, A.A., Eisen, M.B., Davis, R.E., Ma, C., Lossos, I.S., Rosenwald, A., Boldrick, J.C., Sabet, H., Tran, T., Yu, X., Powell, J.I., Yang, L., Marti, G.E., Moore, T., Hudson, J.Jr., Lu, L., Lewis, D.B., Tibshirani, R., Sherlock, G., Chan, W.C., Greiner, T.C., Weisenburger, D.D., Armitage, J.O., Warnke, R., Levy, R., Wilson, W., Grever, M.R., Byrd, J.C., Botstein, D., Brown, P.O. and Staudt, L.M. (2000). Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*, 403, 503 – 511.
- Ammon, H.P.T. and Wahl, M.A. (1991). Pharmacology of *Curcuma longa*. *Plantation Medicine*, 57, 1 – 7.
- Anderson, N.S., Bermudez, Y., Badqwell, D., Chen, R., Nicosia, S.V., Bast, R.C.Jr. and Kruk, P.A. (2009). Urinary levels of Bcl-2 are elevated in ovarian cancer patients. *Gynecology Oncology*, 112(1), 60 – 7.
- Annapurna, A., Suhasin, G., Akondi, R.B., Jaya, P.G. and Siva, R.C. (2011). Anti-cancer activity of *Curcuma longa* linn. (Turmeric). *Journal of Pharmacy Research*, 4(4), 1274 – 1276.
- Antonsson, B., Montessuit, S., Lauper, S., Eskes, R. and Martinou, J.C. (2000). Bax oligomerization is required for channel-forming activity in liposomes and to trigger cytochrome c release from mitochondria. *Biochemistry Journal*, 345, 271 – 8.
- Aratanechemuge, Y., Komiya, T., Moteki, H., Katsuzaki, H., Imai, K. and Hibasami, H. (2002). Selective induction of apoptosis by ar-turmerone isolated from turmeric (*Curcuma longa* L) in two human leukemia cell lines, but not in human stomach cancer cell line. *International Journal of Molecular Medicine*, 9(5), 481 – 4.
- Asawalam, E.F. and Dioka, U.J. (2012). Evaluation of toxicity of *Dennitia tripetala baker* F. and *Curcuma longa* L. rhizomes against cowpea seed *Bruchid, callosobruchus maculatus* (F.) coleoptera: bruchidae. *Agricultural Science Research Journal*, 2(6), 308 – 311.

- Ashkenazi, A. (2002). Targeting death and decoy receptors of the tumour necrosis factor superfamily. *Nature Reviews Cancer*, 2, 420 – 430.
- Bain, B.J. (2005). Diagnosis from the blood smear. *The New England Journal of Medicine*, 353, 498 – 507.
- Baldrick, P. (2005). Carcinogenicity evaluation comparison of tumour data from dual control groups in the Sprague Dawley rat. *Toxicology and Pathology*, 33(2), 283 – 291.
- Beane Freeman, L.E., Blair, A., Lubin, J.H., Stewart, P.A., Hayes, R.B., Hoover, R.N. and Hauptmann, M. (2009). Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. *Journal of National Cancer Institute*, 101(10), 751 – 761.
- Bedossa, P., Poitou, C., Veyrie, N., Bouillot, J.L., Basdevant, A., Paradis, V., Tordjman, J. and Clement, K. (2012). Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. *Hepatology*, unpublished.
- Belaud-Rotureau, M.A., Durrieu, F., Labroille, G., Lacombe, F., Fitoussi, O., Agape, P., Marit, G., Reiffers, J. and Belloc, F. (2000). Study of apoptosis-related response of leukemic blast cells to in vitro anthracycline treatment. *Leukemia*, 14(7), 1266 – 75.
- Bernard, P.S. and Wittwer, C.T. (2002). Real-time PCR technology for cancer diagnostic. *The American Association for Clinical Chemistry*, 48(4), 1178 – 1185.
- Bernardi, P., Scorrano, L., Colonna, R., Petronilli, V. and Di Lisa, F. (1999). Mitochondria and cell death: mechanistic aspects and methodological issues. *Europe Journal of Biochemistry*, 264(3), 687 – 701.
- Betancourt, A.P., Lema, C. and Thordarson, G. (2011). Gene expression profiles of N-methyl-N-nitrosourea (MNU)-induced mammary cancers from intact and ovariectomized rats. *Endocrine Reviews*, 32, P1 – 80.
- Bolliger, A.P., Everds, N.E., Zimmerman, K.L., Moore, D.M., Smith, S.A. and Barnhart, K.F. Hematology of Laboratory Animals. In Weiss, D.J. and Wardrop, K.J. (Eds.), *Schalm's Veterinary Hematology 6<sup>th</sup> ed.* (2010), (p. 852 – 854). Blackwell Publishing Ltd.
- Borgmann, A., Zinn, C., Hartmann, R., Herold, R., Kaatsch, P., Escherich, G., Moricke, A., Henze, G., von Stackelberg, A. and ALL-REZ BFM Study Group. (2008). Secondary malignant neoplasms after intensive treatment of relapsed acute lymphoblastic leukaemia in childhood. *Europe Journal Cancer*, 44, 257 – 68.
- Brambrink, M.A., Schneider, A., Noga, H., Astheimer, A., Gotz, B., Korner, I., Heimann, A., Welschof, M. and Kempfski, O. (2000). Tolerance-inducing dose of 3-nitropropionic acid modulates bcl-2 and bax balance in the rat brain: A potential mechanism of chemical preconditioning. *Journal of Cerebral Blood Flow and Metabolism*, 20, 1425 – 1436.
- Brune, B. (2003). Nitric oxide: NO apoptosis or turning it ON? *Cell Death and Differentiation*, 10, 864 – 9.
- Bustin, S.A., Benes, V., Nolan, T. and Pfaffl, M.W. (2005). Quantitative real-time RT-PCR – a perspective. *Journal of Molecular Endocrinology*, 34, 597 – 601.
- Bustin, S.A., Benes, V., Garson, J.A., Hellemans, J., Hugget, J., Kubista, M., Mueller, R., Nolan, T., Pfaffl, M.W., Shipley, G.L., Vandesompele, J. and Wittwer, C.T. (2009). The MIQE guidelines; minimum information for publication of quantitative real-time PCR experiments. *Clinical Chemistry*, 55, 4.

- Caspas, C., Cosialls, A.M., Barraqan, M., Iglesias-Serret, D., Santidrian, A.F., Coll-Mulet, L., de Frias, M., Domingo, A., Pon, G. and Gil, J. (2006). Bcl-2 inhibitors induce apoptosis in chronic lymphocytic leukaemia cells. *Experimental Hematology*, 34(12), 1663 – 9.
- Chang, Y.C., Hsu, J.D., Lin, W.L., Lee, Y.J. and Wang, C.J. (2011). High incidence of acute promyelocytic leukemia specifically induced by N-nitro-N-methylurea (NMU) in Sprague Dawley rats. *Archieve of Toxicology*, 86(2), 315-27.
- Chen, G. and Goeddel, D.V. (2002). TNF-R1 signaling: a beautiful pathway. *Science*, 296(5573), 1634 – 5.
- Chen, J., Rider, D.A. and Ruan, R. (2006). Identification of valid housekeeping genes and antioxidant enzyme gene expression change in the aging rat liver. *Journal of Gerontology: Biological Sciences*, 21A, 20 – 27.
- Chendil, D., Ranga, R.S., Meigooni, D., Sathishkumar, S. and Ahmaed, M.M. (2004). Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3. *Oncogen*, 23(8), 1599 – 607.
- Cheng, A.C., Hsu, C.H., Lin, J.K., Hsu, M.M., Ho, Y.F., Shen, T.S., Ko, J.Y., Lin, J.T., Lin, B.R., Ming-Shiang, W., Yu, H.S., Jee, S.H., Chen, G.S., Chen, T.M., Chen, C.A., Lai, M.K., Pu, Y.S., Pan, M.H., Wang, Y.J., Tsai, C.C. and Hsieh, C.Y. (2001). Phase 1 clinical trial of curcumin, a chemopreventive agent in patients with high risk or pre-malignant lesions. *Anticancer Research*, 21(4B), 2895 – 900.
- Cheson, B.D., Bennett, J.M., Grever, M., Kay, N., Kreating, M.J., O'Brien, S. and Rai, K.R. (1996). National Cancer Institute – Sponsored working group guidelines for chronic lymphocytic leukemia : Revised guidelines for diagnosis and treatment. *Blood*, 87(12), 4990 – 4997.
- Close, B., Banister, K., Baumans, V., Bernoth, E-M., Bromage, N., Bunyan, J., Erhardt, W., Flecknell, P., Gregory, N., Hackbarth, H., Morton, D. and Warwick, C. (1997). Recommendations for euthanasia of experimental animals: Part 1, working party report. *Laboratory Animals*, 30, 293 – 316.
- Cohen, S.M., Petryk, M., Varma, M., Kozuch, P.S., Ames, E.D. and Grossbard, M.C. (2006). Non-hodgkin's lymphoma of mucosa-associated lymphoid tissue. *The Oncologist*, 11(10), 1100 – 1117.
- Cory, S. and Adams, J.M. (2002). The Bcl2 family: regulators of the cellular life or death switch. *Nature Reviews Cancer*, 2(9), 647 – 56.
- Da Silva Franchi, C.A., Bacchi, M.M., Padovani, C.R. and de Camargo, J.L. (2003). Thymic lymphomas in Wistar rats exposed to N-methyl-N-nitrosourea (MNU). *Cancer Sciences*, 94(3), 240 – 3.
- Da Silva, M.G., Castro, A.A., Ramos, E.A.G., Peixoto, E., Miranda Jr, F., de Benjamin-Brandao-Pitta, G., de Farita-Bittencourt-Costa, R. and Juliano, Y. (2005). Histological and biochemical serum effects of alpha-tocopherol on ischemia/reperfusion-related injuries induced in the pelvic limb of rats. *Journal of Acta Cirurgica Brasileira*, 20(5), 1678 – 2674.
- David, F. and Lad, V. (1993). The Yoga of Herbs: An ayurvedic guide to herbal medicine. *Lotus Light Publications*.
- Del Poeta, G., Venditti, A., Del Principe, M.I., Maurillo, L., Buccisano, F., Tamburini, A., Cox, M.C., Franchi, A., Bruno, A., Mazzone, L., Panetta, P., Suppo, G., Masi, M. and Amadori, S. (2002). Amount of spontaneous apoptosis detected by Bax/Bcl-2 ratio predict outcome in AML. *Blood*, 101(6), 2125 – 2131.



- Dexter, T.M., Schofield, R., Lajtha, L.G. and Moore, M. (1974). Studies on the mechanisms of chemical leukaemogenesis. *British Journal of Cancer*, 30(4), 325-331.
- Dhillon, N., Aggarwal, B.B., Newman, R.A., Wolff, R.A., Kunnumakkara, A.B., Abbruzzese, J.L., Ng, L.S., Badmaev, V. and Kurzrock, R. (2008). Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clinical Cancer Research*, 14(14), 4491 – 9.
- Domrongkitchaiporn, S., Sritara, P., Kitiyakara, C., Stitchantrakul, W., Krittaphol, V., Lolekha, P., Cheepudomwit, S. and Yipintsoi, T. (2005). Risk factors for development of decreased kidney function in a southeast Asian population: a 12-year cohort study. *Journal American Society of Nephrology*, 16, 791 – 799.
- Drake, M., Kettle, P., Lynch, T., Morris, C., Page, W., Shiels, A. and Venkatramen, L. (2007). The role of PET/CT in lymphoma part I. *Imaging*, 1, 16 – 19.
- Dreyling, M. (2009). Newly diagnosed and relapsed follicular lymphoma: EMSO clinical recommendation for diagnosis, treatment and follow-up. *Annals of Oncology*, 20(4), iv119 – iv120.
- Edelstein, R.A., Zietman, A.L., de las Morenas, A., Krane, R.J., Babayan, R.K. and Dallow, K.C. (1996). Implications of prostate micrometastases in pelvic lymph nodes: an archival tissue study. *Journal of Urology*, 47, 370 – 5.
- Egan, M.E., Pearson, M., Weiner, S.A., Rajendran, V., Rubin, D., Glockner-Pagel, J., Canny, S., Du, K., Lukacs, G.L. and Caplan, M.J. (2004). Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects. *Science*, 304, 600 – 602.
- Eigner, D. and Scholz, D. (1999). *Ferula asa-foetida* and *Curcuma longa* in traditional medical treatment and diet in Nepal. *Journal of Ethnopharmacology*, 67, 1 – 6.
- El Hindy, N., Bachmann, H.S., Lambertz, N., Adamzik, M., Nuckel, H., Worm, K., Zhu, Y., Sure, U., Siffert, W. and Sandalcioglu, I.E. (2011). Association of the CC genotype of the regulatory BCL2 promoter polymorphism (-938C>A) with better 2-year survival in patients with glioblastoma multiforme. *Journal of Neurosurgical*, 114, 1631 - 1639.
- Elaziz, E.A., Ibrahim Z.S. and Elkattawy. A.M. (2010). Protective effect of *Curcuma longa* against CCL4-induced oxidative stress and cellular degeneration in rats. *Global Veterinaria*, 5(5), 272 – 281.
- Elmore, S. (2007). Apoptosis: A review of programmed cell death. *Toxicology Pathology*, 35(4), 495 – 516.
- Esposti, M.D. (2010). Bcl-2 antagonists and cancer: from the clinic, back to the bench. *Cell Death and Disease*, 1, e37.
- Farah Dina, P., Hazilawati, H., Rosly, S.M., Shanmugavelu, S. and Noordin, M.M. (2011). Expression of circulating CD146 associated with endorascular dysfunction in adenine-induced chronic renal failure in rats using an EvaGreen real time RT-PCR assay. *Pertanika Journal of Tropical Agriculture Science*, 34(2), 381 – 391.
- Favaloro, B., Allocati, N., Graziano, V., Di Llio, C., De Laurenzi, V. (2012). Role of apoptosis in disease. *Aging*, 4(5), 330 – 49.
- Ferrari, A.C., Stone, N.N., Eyler, J.N., Gao, M., Mandeli, J. and Unger, P. (1997). Prospective analysis of prostate-specific markers in pelvic lymph nodes of patients with high-risk prostate cancer. *Journal National Cancer Institute*, 89, 1498 – 1504.



- Garber, M.E., Troyanskaya, O.G., Schluens, K., Petersen, S., Thaesler, Z., Pacyna-Gengelbach, M., Van de Rijn, M., Rosen, G.D., Perou, C.M., Whyte, R.I., Altman, R.B., Brown, P.O., Botstein, D. and Petersen, I. (2001). Diversity of gene expression in adenocarcinoma of the lung. *Proceeding of National Academy Sciences USA*, **98**, 13784 – 13789.
- Garg, S.N., Bansal, R.P., Gupta, M.M. and Kumar, S. (1999). Variation in the rhizome essential oil and curcumin contents and oil quality in the land races of turmeric *Curcuma longa* of North Indian plains. *Journal of Flavour and Fragrance*, **14**, 315 – 318.
- Gascoyne, R.D., Adomat, S.A., Krajewski, S., Krajewska, M., Horsman, D.E., Tolcher, A.W., O'Reilly, S.E., Hoskins, P., Coldman, A.J., Reed, J.C. and Connors, J.M. (1997). Prognostic significance of Bcl-2 protein expression and Bcl-2 gene rearrangement in diffuse aggressive non-Hodgkin's lymphoma. *Blood*, **90**, 244 - 251.
- Gavathiotis, E., Reyna, D.E., Bellairs, J.A., Leshchiner, E.S. and Walensky, L.D. (2012). Direct and selective small-molecule activation of proapoptotic BAX. *Nature Chemical Biology*, **8**, 639 – 645.
- George, T.I., Etzell, J.E., Bradley, K.T., Clarke, M.R., Crossey, M.J., Davis, B.H., Keren, D.F., Perkins, S.L., Piscitelli, J.B., Rizzo, K.A., Shier, L.R., Werner, A.L., Wong, A.K., Zwick, D.L., Eberle, C., Girgis, G.M. and Salansky, S. (2006). Hematology, clinical microscopy and body fluid glossary. *Hematology*, 1 – 63.
- Geurts, J.J.G., Bo, L., Pouwels, P.J.W., Castelijns, J.A., Polman, C.H. and Barkhof, F. (2005). Cortical Lesions in Multiple Sclerosis: Combined Postmortem MR Imaging and Histopathology. *American Journal of Neuroradiology*, **26**, 572 – 577.
- Ghatak, N. and Basu, N. (1972). Sodium curcumin as an effective anti-inflammatory agent, *Indian Journal of Experimental Biology*, **10**(3), 235 – 6.
- Gobe, G., Rubin, M., Williams, G., Sawczuk, I. and Buttyan, R. (2002). Apoptosis and expression of Bcl-2, Bcl-XL, and Bax in renal cell carcinomas. *Cancer Investigation*, **20**, 324 - 332.
- Gordon, G.J., Coleman, W.B. and Grisham, J.W. (2000). Bax-mediated apoptosis in the livers of rats after partial hepatectomy in the retrorsine model of hepatocellular injury. *Hepatology*, **32**(2), 312 – 20.
- Hallek, M., Cheson, B.D., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., Dohner, H., Hillmen, P., Keating, M.J., Montserrat, E., Rai, K.R. and Thomas, J. (2008). Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. *Blood*, **111**, 5446 – 5456.
- Hamblin, S. and Terry, J. (2001). Achieving Optimal Outcomes in Chronic Lymphocytic Leukaemia. *Drugs*, **61**(5), 593 – 611.
- Han, H., Landreneau, R.J., Santucci, T.S., Tung, M.Y., Macherey, R.S., Shackney, S.E., Sturgis, C.D., Raab, S.S. and Silverman, J.F. (2002). Prognostic value of immunohistochemical expressions of p53, HER-2/neu, and bcl-2 in stage I non-small-cell lung cancer. *Human Pathology*, **33**, 105 - 110.
- Hanahan, D. and Weinberg, R.A. (2011). Hallmarks of cancer: the next generation. *Cell*, **144**, 646 – 674.
- Hauptmann, M., Stewart, P.A., Lubin, J.H., Beane Freeman, L.E., Hornung, R.W., Herrick, R.F., Hoover, R.N., Fraumeni Jr, J.F., Blair, A. and Hayes, R. B. (2009). Mortality from lymphohematopoietic malignancies and brain cancer among

- embalmers exposed to formaldehyde. *Journal of National Cancer Institute*, 101(24), 1696 – 1708.
- Hauptrock, B. and Hess, G. (2008). Rituximab in the treatment of non-Hodgkin's lymphoma. *Biologics*, 2(4), 619 – 633.
- Hazilawati, H., Farah Dina, P., Rosly, S.M., Shanmugavelu, S. and Noordin, M.M. (2010a). Phyllanthus niruri reduces renal azotaemia in rats induced with chronic renal failure. *The Medical Journal of Malaysia*, 65, 132 – 134.
- Hazilawati, H., Hutheyfa, A.H., Rosly, S.M., Jasni, S., Noordin, M.M., & Shanmugavelu, S. (2010b). Haematological parameters of leukaemic rats supplemented with *Morinda citrifolia*. *The Medical Journal of Malaysia*, 65, 125-126.
- Hazilawati, H., Nursyuhada, H., Rosly, S.M., Shanmugavelu, S. and Noordin, M.M. (2010c). Effects of *Morinda citrifolia* on Early Stage of Leukaemia in Rats. *The Medical Journal of Malaysia*, 65, 135-136.
- Heng, M.C., Song, M.K., Harker, J. and Heng, M.K. (2000). Drug-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. *British Journal of Dermatology*, 143, 937 – 949.
- Holy, J.M. (2002). Curcumin disrupts mitotic spindle structure and induces micronucleation in MCF-7 breast cancer cells. *Mutation Research*, 518(1), 71 – 84.
- Horner, M.J., Ries, L.A.G., Krapcho, M., Neyman, N., Aminou, R., Howlander, N., Altekruse, S.F., Feuer, E.J., Huang, L., Mariotto, A., Miller, B.A., Lewis, D.R., Eisner, M.P., Stinchcomb, D.G., Edwards, B.K. (2009). SEER Cancer Statistics Review, 1975-2006, *National Cancer Institute*.
- Houwen, B. (2000). Blood Film Preparation and Staining Procedures. *Laboratory Hematology*, 6, 1 – 7.
- Hsu, C. H. and Cheng, A. L. (2007). Clinical studies with curcumin, *Advances in Experimental Medicine Biology*, 595, 471 – 480.
- Huang, M.T. (1991). Inhibitory effects of curcumin on in vitro lipoxygenase and cyclooxygenase activities in mouse epidermis. *Cancer Research*, 51, 813.
- Huang, M.T., Wang, Z.Y., Georgiadis, C.A., Laskin, J.D. and Conney, A.H. (1992). Inhibitory effects of curcumin on tumour initiation by benzo [a] pyrene and 7,12 dimethylbenz[a]anthracene. *Carcinogenesis*, 13(11), 2183 – 2186.
- Huang, M.T., Lou, Y.R., Ma, W., Newmark, H.L., Reuhl, K.R. and Conney, A.H. (1994). Inhibitory effects of dietary curcumin on fore stomach, duodenal, and colon carcinogenesis in mice. *Cancer Research*, 54(22), 5841 – 5847.
- Huang, M.T., Lou, Y.R., Xie, J.G., Ma, W., Lu, Y.P., Yen, P., Zhu, B.T., Newmark, H. and Ho, C.T. (1998). Effect of dietary curcumin and dibenzoylmethane on formation of 7,12 dimethyl benz[a] anthracene induced mammary tumours and lymphoma/leukemias in Sencar mice. *Carcinogenesis*, 19(9), 1697 – 1700.
- Huggett, J., Dheda, K., Bustin, S. and ZumLa, A. (2005). Real-time RT-PCR normalisation; strategies and considerations. *Genes and Immunity*, 6, 279 – 284.
- Hutheyfa, A.H., Hazilawati, H., Rosly, S.M., Jasni, S., Noordin, M.M. and Shanmugavelu, S. (2011). Histopathological Features of Peripheral T-cell Lymphoma in Sprague Dawley Rats Induced with *N*-methyl-*N*-nitrosourea. *Pertanika Journal of Tropical Agriculture in Science*, 34 (2), 351 – 361.
- Hutheyfa. (2011). Master Thesis, Universiti Putra Malaysia.

- IARC. 1974. Benzene. In Some Anti-Thyroid And Related Substances, Nitrofurans And Industrial Chemicals.
- IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 7. Lyon, France: International Agency for Research on Cancer. pp. 203-221.
- IARC. 1982. Benzene. In Some Industrial Chemicals and Dyestuffs. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 29. Lyon, France: International Agency for Research on Cancer. pp. 93-148.
- IARC. 1987. Benzene. In Overall Evaluations of Carcinogenicity. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl 7. Lyon, France: International Agency for Research on Cancer. pp. 120-122.
- IARC. 1989. Occupational exposures in petroleum refining. In Occupational Exposures in Petroleum Refining; Crude Oil and Major Petroleum Fuels. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 45. Lyon, France: International Agency for Research on Cancer. pp. 39-118.
- IPCS. 1993. Environmental Health Criteria No. 150. Benzene. International Programme on Chemical Safety.
- Iseki, K., Ikemiya, Y., Inoue, T., Iseki, C., Kinjo, K. and Takashita, S. (2004). Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *American Journal of Kidney*, 44, 642 – 650.
- Jassal, M.S., Nedeltchev, G.G., Osborne, J. and Bishai, W.R. (2011). A modified scoring system to describe gross pathology in the rabbit model of tuberculosis. *BMC Microbiology*, 11, 49.
- Johnson, J. J. and Mukhtar, H. (2007). Curcumin for chemoprevention of colon cancer, *Cancer Letters*, 255, 170 – 181.
- Joshi, V.V. and Frei, J.V. (1970). Gross and microscopic changes in the lymphoreticular system during genesis of malignant lymphoma induced by single injection of methylnitrosourea in adult mice. *Journal of National Research Institute*, 44, 379-389.
- Kagawa, S., Gu, J., Swisher, S.G., Ji, L., Roth, J.A., Lai, D., Stephens, L.C. and Fang, B. (2000). Antitumour Effect of Adenovirus-mediated Bax Gene Transfer on p53-sensitive and p53-resistant Cancer Lines. *Cancer Research*, 60(5), 1157 – 61.
- Kalantari, H., Khorsandi, L.S. and Taherimobarakeh, M. (2007). The protective effects of the Curcuma longa extract on acetaminophen-induced hepatotoxicity in mice. *Jundishapur Journal of Natural Pharmaceutical Products*, 2(1), 7 – 12.
- Kalos, M., Levine, B.L., Porter, D.L., Katz, S., Grupp, S.A., Bagg, A. and June, C.H. (2011). T cells with chimeric antigen receptors have potent antitumour effects and can establish memory in patients with advanced leukemia. *Science Translation Medicine*, 3(95), 95 – 73.
- Kaneko, J.J., Harvey, J.W. and Bruss, M.L. *Clinical Biochemistry of Domestic Animals 6<sup>th</sup> ed.* (2008), (p. 889 – 895). Elsevier: Academic Press Inc.
- Kang, M.Y., Cho, S.H., Lim, Y.H., Seo, J.C. and Hong, Y.C. (2013). Effects of environmental cadmium exposure on liver function in adults. *Occupational and Environmental Medicine*, 70(4), 268 – 73.
- Kasetsart, J., Surojanametakul, V., Satmalee, P., Saengprakai, J., Siliwan, D. and Wattanasiritham, L. (2010). Preparation of curcuminoid powder from turmeric root (*Curcuma longa* Linn) for food ingredient use. *Journal of National Science*, 44, 123 – 130.

- Kaufmann, S.H. and Earnshaw, W.C. (2000). Induction of apoptosis by cancer chemotherapy. *Experimental Cell Research*, 256(1), 42 – 9.
- Kelly, P.N. and Strasser, A. (2011). The role of Bcl-2 and its pro-survival relatives in tumorigenesis and cancer therapy. *Cell Death and Differentiation*, 18, 1414 – 1424.
- Kim, M.S., Kang, H.J. and Moon, A. (2001). Inhibition of invasion and induction of apoptosis by curcumin in H-ras-transformed MCF10A human breast epithelial cells. *Archives of Pharmacal Research*, 24(4), 349 – 354.
- Kipps, T.J. (2010). Chronic lymphocyte leukemia and related disease. In: Lichtman M.A et al William Hematology. 8<sup>th</sup> ed New York. McGraw-Hill Companies, 1431 – 1481.
- Kotoh, K., Enjoji, M., Kato, M., Kohjima, M., Nakamuta, M. and Takayanagi, R. (2008). A new parameter using serum LDH and ALT level is useful for predicting the prognosis of patients at an early stage of acute liver injury: A retrospective study. *Comparative Hepatology*, 7:6, 1 – 8.
- Kroemer, G. and Reed, J.C. (2000). Mitochondrial control of cell death. *Nature Medicine*, 6(5), 513 – 9.
- Kumbhare, D., Parkinson, W. and Dunlop, B. (2008). Validity of serum creatine kinase as a measure of muscle injury produced by lumbar surgery. *Journal of Spinal Disorder and Techniques*, 21(1), 49 – 54.
- Kuo, C. P., Lu, C. H., Wen, L. L., Cheng, C. H., Wong, C. S., Borel, C. O., Ju, D. T., Chen, C. M. and Wu, C. T. (2011). Neuroprotective effect of curcumin in an experimental rat model of subarachnoid hemorrhage. *Anesthesiology*, 115, 1229 – 1238.
- Lailier, L., Cartron, P.F., Juin, P., Nedelkina, S., Manon, S., Bechinger, B. and Vallette, F.M. (2007). Bax activation and mitochondrial insertion during apoptosis. *Apoptosis*, 12(5), 887 – 96.
- Lao, C.D., Ruffin, M.T., Normolle, D., heath, D.D., Murray, S.I., Bailey, J.M., Boggs, M.E., Crowell, J., Rock, C.L. and Brenner, D.E. (2006). Dose escalation of a curcuminoid formulation. *BMC Complementary Alternative Medicine*, 17, 6:10.
- Lekanne Deprez, R.H., Fijnvandraat, A.C., Ruijter, J.M. and Moorman, A.F. (2002). Sensitivity and accuracy of quantitative real time polymerase chain reaction using SYBR green 1 depends on cDNA synthesis conditions. *Analytical Biochemistry*, 307, 63 – 67.
- Lessene, G., Czabotar, P.E. and Colman, P.M. (2008). Bcl-2 family antagonists for cancer therapy. *National Reviews Drug Discovery*, 7, 989 – 1000.
- Letai, A., Sarcinelli, M.D., Beard, C. and Korsmeyer, S.J. (2004). Antiapoptotic Bcl-2 is required for maintenance of a model leukemia. *Cancer Cell*, 6, 241 – 249.
- Li, C.J., Zhang, L.J., Dezube, B.J., Crumpacker, C.S. and Pardee, A.B. (1993). Three inhibitors of human type 1 immunodeficiency virus long terminal repeat directed gene expression and virus replication. *Proceeding of National Academy Science (USA)*, 90, 1839 – 42.
- Li, Y., Chen, J. and Shu, W. (2011). A Cross-Sectional Investigation of Chronic Exposure to Microcystin in Relationship to Childhood Liver Damage in the Three Gorges Reservoir Region, China. *Environmental Health Perspectives*, 119(10), 1483 – 1488.



- Liesveld, J.L., Raubertas, R.F. and Bennett, J.M. (1991). Treatment patterns in low-grade non-Hodgkin's lymphomas: A single institution study. *Medical and Pediatric Oncology*, 19(1), 1 – 7.
- Lim, G.C.C., Rampal, Y. and Halimah, Y. (2008). Cancer incidence in peninsular Malaysia, 2003 – 2005. National Cancer Registry, Kuala Lumpur.
- Liska, J., Macejoca, D., Ondkova, S. and Brtko, J. (2012). Morphology of 1-methyl-1-nitrosourea induced rat mammary tumours after treatment with precursor of phytanic acid or its combination with vitamin D analogue. *Endocrine Regulations*, 46(1), 21 – 6.
- Lisowska-Myjak, B. (2010). Serum and urinary biomarkers of acute kidney injury. *Blood Purification*, 29, 357 – 365.
- Liu, J.J., Huang, R.W., Lin, D.J., Peng, J., Wu, X.Y., Lin, Q., Pan, X.L., Song, Y.Q., Zhang, M.H., Hou, M. and Chen, F. (2005). Expression of surviving and Bax/Bcl-2 in peroxisome proliferator activated receptor- $\gamma$  ligands induces apoptosis on human myeloid leukemia cells in vitro. *Annals of Oncology*, 16(3), 455 – 459.
- Livak, K.J. and Schmittgen, T.D. (2001). Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta CT) method. *Methods*, 25, 402 – 408.
- Luo, X., Budihardjo, I., Zou, H., Slaughter, C. and Wang, X. (1998). Bid, a Bcl-2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. *Cell*, 94(4), 481 – 90.
- Macejova, D. and Brtko, J. (2001). Chemically induced carcinogenesis: a comparison of 1-methyl-1-nitrosourea, 7,12-dimethylbenzanthracene, diethylnitroso-amine and azoxymethan models (minireview). *Endocrine Regulation*, 35, 53 – 59.
- Mackay, I.M., Arden, K.E. and Nitsche, A. (2002). Real-time PCR in virology. *Nucleic Acids Research*, 30, 1292 – 1305.
- Martin, R.C., Aiyer, H.S., Malik, D. and Li, Y. (2011). Effect on pro-inflammatory and antioxidant genes and bioavailable distribution of whole turmeric vs curcumin: Similar root but different effects. *Food and Chemical Toxicology*, 50, 227-231.
- McCarthy, B.A., Boyle, E., Wang, X.P., Guzowski, D., Paul, S., Catera, R., Trott, J., Yan, X., Croce, C.M., DamLe, R., Yancopoulos, S., Messmer, B.T., Lesser, M., Allen, S.L., Rai, K.R. and Chiorazzi, N. (2008). Surface Expression of Bcl-2 in Chronic Lymphocytic Leukemia and Other B-Cell Leukemias and Lymphomas Without a Breakpoint t(14;18). *Molecular Medicine*, 14, 618 – 627.
- McLeay, Y., Barnes, M.J., Mundel, T., Hurst, S.M., Hurst, R.D. and Stannard, S.R. (2012). Effect of New Zealand blueberry consumption on recovery from eccentric exercise-induced muscle damage. *Journal of the International Society of Sports Nutrition*, 9, 19.
- Meier, P., Finch, A. and Evan, G. (2000). Apoptosis in development. *Nature*, 407(6805), 796 – 801.
- Melo, J.V., Catovsky, D. and Galton, D.A.G. (1986). The relationship between chronic lymphocytic leukaemia and prolymphocytic leukaemia: IV. Analysis of survival and prognostic features. *British Journal of Haematology*, 63, 377 – 387.
- Milionis, H.J., Bourantas, C.L., Siamopoulos, K.C. and Elisaf, M.S. (1999). Acid-Base and Electrolyte Abnormalities in Patients With Acute Leukemia. *American Journal of Hematology* 62:201–207.

- Minka, N.S. and Ayo, O.J. (2010). Serum biochemical activities and muscular soreness in transported goats administered with ascorbic acid during the hot-dry season. *European Journal Translational Myology - Basic Applied Myology*, 1(4), 193 – 203.
- Miquel, J. A., Bernd, J., Sempere, M., Diaz-Alperi, J. and Ramirez, A. (2002). The Curcuma antioxidants pharmacological effects and prospects for future clinical use. *A Review, Archives of Gerontology and Geriatrics*, 34, 37-46.
- Mirmomeni, M.H., Suzangar, M., Wise, A., Messripour, M. and Emami, H. (2006). Biochemical studies during aflatoxin B<sub>1</sub>-induced liver damage in rats fed different levels of dietary protein. *International Journal of Cancer*, 24, 471-476.
- Mital, A. (2012). *Curcuma longa L., Zingiberaceae. Medicinal plant monographs publications*, 183 – 195.
- Mitsumori, K., Takegawa, K., Shimo, T., Onodera, H., Yasuhara, K. and Takahashi, M. (1996). Morphometric and immunohistochemical studies on atrophic changes in lympho-hematopoietic organs of rats treated with piperonyl butoxide or subjected to dietary restriction. *Achieve of toxicology*, 70(12), 809 – 14.
- Mizoguchi, M., Naito, H., Kurata, Y., Shibata, M.A., Tsuda, H., Wild, C.P., Montesano, R. and Fukushima, S. (1993). Influence of aging on multi-organ carcinogenesis in rats induced by N-Methyl-N-Nitrosourea. *Japanese Journal of Cancer Research*, 4, 139 – 146.
- Moley, J.F., Morrison, S.D., Gorschboth, C.M. and Norton, J.A. (1988). Body Composition Changes in Rats with Experimental Cancer Cachexia:Improvement with Exogenous Insulin. *Cancer Research*, 48, 2784 – 2787.
- Morton, D., Bailey, K.L., Stout, C.L., Weaver, R.J., White, K.A., Lorenzen, M.J. and Ball, D.J. (2008). N-Methyl-N-Nitrosourea (MNU): A positive control chemical for p53 <sup>-/-</sup> mouse carcinogenicity studies. *Toxicologic Pathology*, 36, 926 – 931.
- Mughal, T.I., Goldman, J.M. and Mughal, S.T. (2006). *Understanding leukaemias, lymphoma and myelomas*. London: Taylor & Francis.
- Muhammed, M., Badmaev, V., Shivakumar, U. and Rajendran, R. (1995). *Curcuminoids: antioxidant phytonutrients*. NutriScience Publishers Inc.
- Nagabhushan, M. and Bhide, S.V. (1987). Antimutagenicity and anticarcinogenicity of turmeric. *Journal of Nutrition, Growth and Cancer*, 4(2), 83.
- Nagakawa, T., Mazzali, M., Kang, D.H., Kanellis, J., Watanabe, S., Sanchez-Lozada, L.G., Rodriguez-Iturbe, B., Herrera-Costa, J. and Johnson, R.J. (2003). Hyperuricemia causes glomerular hypertrophy in the rat. *American Journal of Nephrology*, 23, 2 – 7.
- Nishimura, A. (1999). Changes in Bcl-2 and Bax expression in rat tongue during 4-nitroquinoline 1-oxide-induced carcinogenesis. *Journal of Dental Research*, 78(6), 1264 – 9.
- Nolan, T., Hands, R.E. and Bustin, S.A. (2006). Quantification of mRNA using real-time RT-PCR. *Nature Protocols*, 1, 1559 – 1582.
- Nursyuhada, H., Haziawati, H., Rosly, S.M., Hutheyfa, A.H., Shanmugavelu, S., Noordin, M.M. and Jasni, S. (2011). Detection of Bcl-2 Gene in Leukaemic Rats Using an EvaGreen Real-time RT-PCR Assay. *Pertanika Journal of Tropical Agricultural Science*, 34(2), 373-380.
- Nursyuhada Haron. (2012). Master Thesis, Universiti Putra Malaysia.

- Obermayr, R.P., Temml, C. and Klauster-Braun, R. (2008). Elevated Uric Acid Increases the Risk for Kidney Disease. *Journal of The American Society of Nephrology*, 19(12), 2407 – 2413.
- O'Brien, S., Moore, J.O., Boyd, T.E., Larratt, L.M., Skotnicki, A., Koziner, B., Chanan-Khan, A.A., Seymour, J.F., Bociek, R.G., Pavletic, S. and Rai, K.R. (2007). Randomized Phase III Trial of Fludarabine Plus Cyclophosphamide With or Without Oblimersen Sodium (Bcl-2 antisense) in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia. *Journal of Clinical Oncology*, 25(9), 1114 – 1120.
- Oeffinger, K.C. and Bhatia, S.C. (2009). Second primary cancers in survivors of childhood cancer. *The Lancet*, 374, 1484 – 1485.
- Omar, Z.A. and Tamin, S.I. (2007). National cancer registry report: Malaysia cancer statistics. Ministry of Health Malaysia, 1 – 81.
- Park, E., Jeon, C. H., Ko, G., Kim, J. and Sohn, D. H. (2000). Protective Effect of Curcumin in Rat Liver Injury Induced by Carbon Tetrachloride. *Journal of Pharmacy and Pharmacology*, 52, 437 – 440.
- Passmore, S.J., Draper, G. and Brownbill, P. (1998). Case-control studies of relation between childhood cancer and neonatal vitamin K administration. *British Medicinal Journal*, 316, 178 – 84.
- Pearson, A.S., Spitz, F.R., Swisher, S.G., Kataoka, M., Sarkiss, M.G., Meyn, R.E., McDonnell, T.J., Cristiano, R.J. and Roth, J.A. (2000). Up-Regulation of the Proapoptotic Mediators Bax and Bak after Adenovirus-mediated *p53* Gene Transfer in Lung Cancer Cells. *Clinical Cancer Research*, 6, 887 – 890.
- Peres, W., Tunon, M.J., Collado, P.S., Herrmann, S., Marroni, N. and Gonzalez-Gallego, J. (2000). The flavonoid quercetin ameliorates liver damage in rats with biliary obstruction. *Journal of Hepatology*, 33, 742 – 750.
- Perline, I.R. (1971). An inexpensive mouse urine collection system. *Physiology and Behaviour*, 6, 597.
- Pervin, S., Singh, R. and Chaudhuri. (2003). Nitric-oxide-induced Bax integration into the mitochondrial membrane commits MDA-MB-468 cells to apoptosis: essential role of Akt. *Cancer Research*, 63(17), 5470 – 9.
- Peters, J.M., Preston-Martin, S. and London, S.J. (1994). Processed meats and risk of childhood leukemia (California, USA). *Cancer Causes Control*, 5, 195 – 202.
- Pfaffl, M.W. (2001). A new mathematical model for relative quantification in real-time RT-PCR. *Nucleic Acids Research*, 29, 2002 – 2007.
- Pine, S.R., Yin, C., Matloub, Y.H., Sabaawy, H.E., Sandoval, C., Levendoglu-Tugal, O., Ozkaynak, M.F. and Jayabose, S. (2005). Detection of central nervous system leukemia in children with acute lymphoblastic leukemia by real-time polymerase chain reaction. *Journal of Molecular Diagnosis*, 7(1), 127 – 132.
- Pinkerton, L.E., Hein, M.J. and Stayner, L.T. (2004). Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occupational Environment Medicine*, 61(3), 193 – 200.
- Placzek, W.J., Wei, J., Kitada, S., Zhai, D., Reed, J.C. and Pellicchia, M. (2010). A survey of the anti-apoptotic Bcl-2 subfamily expression in cancer types provides a platform to predict the efficacy of Bcl-2 antagonists in cancer therapy. *Cell Death and Disease*, 1, e40.
- Polasa, K., Raghuram, T.C., Krishna, T.P. and Krishnaswamy, K. (1992). Effect of turmeric on urinary mutagens in smokers. *Mutagenesis*. 7(2), 107 – 9.



- Pozharitskaya, O.N., Ivanova, S.A., Shikov, A.N. and Makarov, V.G. (2008). Separation and Free Radicals scavenging activity of major Curcuminoids of *Curcuma longa* using HPTLC-DPPH method. *Phytochemical Analysis*, 19, 236 – 243.
- Quiles, J. C., Mesa, M. D., Ramirez-Totosa, C.L., Aguilera, C.M., Battino, M., Gil, A. and Ramirez-Tortosa, M. C. (2002). *Curcuma longa* extract supplementation reduces oxidative stress and attenuates aortic fatty streak development in rabbits. *Arteriosclerosis, Thrombosis and Vascular Biology*, 22, 1225-1231.
- Rai, K.R., Sawitsky, A., Cronkite, E.P., Chanana, A.D., Levy, R.N and Pasternack, B.S. (1975). Clinical staging of chronic lymphocytic leukemia. *Journal of Blood*, 46, 219 – 234.
- Rai, P.K., Jaiswal, D., Mehta, S., Rai, D.K., Sharma, B. and Watal, G. (2010). Effect of *Curcuma longa* freeze dried rhizome powder with milk in STZ-induced diabetic rats. *Indian Journal of Clinical Biochemistry*, 25(2), 175 – 181.
- Raisova, M., Hossini, A.M., Eberle, J., Riebeling, C., Wieder, T., Sturm, I., Daniel, P.T., Orfanos, C.E. and Geilen, C.C. (2001). The Bax/Bcl-2 ratio determines the susceptibility of human melanoma cells to CD95/Fas-mediated apoptosis. *Journal Investigative Dermatology*, 117(2), 333 – 40.
- Rampino, N., Yamamoto, H., Ionov, Y., Li, Y., Sawai, H., Reed, J.C. and Perucho, M. (1997). Somatic frameshift mutations in the BAX gene in colon cancers of the microsatellite mutator phenotype. *Science*, 275, 967 – 969.
- Ranger, A.M., Zha, J., Harada, H., Datta, S.R., Danial, N.N., Gilmore, A.P., Kutok, J.L., Le Beau, M.M., Greenberg, M.E. and Korsmeyer, S.J. (2003). *Bad*-deficient mice develop diffuse large B cell lymphoma. *Proceeding of the National Academy of Sciences of the United State of America*, 100(16), 9324 – 9329.
- Rao, S. D., Sekhara, C. N., Satyanarayana, M. N. and Srinivasanj, M. (1970). Effect of Curcumin on Serum and Liver Cholesterol Levels in the Rat. *Nutrition*, 100, 1307 – 1316.
- Rao, C.V. (1993). Antioxidant activity of curcumin and related compounds. Lipid peroxide formation in experimental inflammation. *Cancer Research*, 55, 259.
- Rao, C.V., Rivenson, A., Simi, B. and Reddy, B.S. (1995). Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. *Cancer Research*, 55(2), 259 – 66.
- Ravindran, P.N. and Silvaram, K.N.B.K. (2007). *Turmeric: the genus Curcuma* Taylor and Francis Group.
- Raymakers, K. (2010). Diagnosing leukemia. *Leukemia and Lymphoma Guide*, updated 22, September 2010.
- Robison, L. and Ross, J. (1995). Epidemiology of leukaemias and lymphomas in childhood. In Bailliere's Clinical Paediatrics (Chessells J, Hann I, eds). London: WB Saunders Company, 639 - 657.
- Rodriguez-Burford, C., Lubet, R.A., Eto, I., Juliana, M.M., Kelloff, G.J., Grubbs, C.J. and Steele, V.E. (1999). Effect of reduced body weight gain on the evaluation of chemopreventive agents in the methylnitrosourea-induced mammary cancer model. *Carcinogenesis*, 20(1), 71 – 76.
- Rosenwald, A., Alizadeh, A.A., Widhopf, G., Simon, R., Davis, R.E., Yu, X., Yang, L., Pickeral, O.K., Rassenti, L.Z., Powell, J., Botstein, D., Byrd, J.C., Grever, M.R., Cheson, B.D., Chiorazzi, N., Wilson, W.H., Kipps, T.J., Brown, P.O. and Staudt, L.M. (2001). Relation of gene expression phenotype to immunoglobulin mutation genotype in B cell chronic lymphocytic leukemia. *Journal of Experimental Medicine*, 194, 1639 – 1647.

- Ross, J.A., Davies, S.M. and Potter, J.D. (1994). Epidemiology of childhood leukemia, with a focus on infants. *Epidemiology Review*, 16, 243-72.
- Ross, J., Potter, J. and Robison, L. (1994). Infant leukemia, topoisomerase II inhibitors, and the MLL gene. *Journal National Cancer Institute*, 86, 1678-1680.
- Ross, D.D., Karp, J.E., Chen, T.T. and Doyle, L.A. (2000). Expression of breast cancer resistance protein in blast cells from patients with acute leukaemia. *Blood*, 96(1), 365 – 368.
- Rosly S.M., Shamugavelu, S., Murugaiyah, M., Hadijah, H., Ahmad Tarmizi, S., Noridayusni, Y. and Subramaniam, K. (2011). Subchronic oral toxicity study of *Morinda citrifolia* (mengkudu) in Sprague Dawley rats. *Pertanika Journal Tropical Agriculture Science*, 34(2), 341 – 349.
- Rozenberg, G. (2011). Microscopic haematology: A practical guide for the laboratory. *Elsevier Australia*, pp. 106 – 107.
- Ruwanpura, S.J. and Shi, Y. (2004). Molecular mechanisms of caspase regulation during apoptosis. *Nature Reviews Molecular Cell Biology*, 5, 897 – 907.
- Saeed, M.K., and Deng, Y. and Dai, R. (2008). Attenuation of biochemical parameters in streptozotocin-induced diabetic rats by oral administration of extracts and fractions of cephalotaxus sinensis. *Journal of Clinical Biochemical Nutritional*, 42, 21 – 28.
- Saif, M.W., Alexander, D. and Wicox, C.M. (2005). Serum Alkaline Phosphatase Level as a Prognostic Tool in Colorectal Cancer: A Study of 105 patients. *Journal of Applied Research*, 5(1), 88 – 95.
- Sait, Şen. and Banu, Sarsık. (2010). A Proposed Histopathologic Classification, Scoring, and Grading System for Renal Amyloidosis: Standardization of Renal Amyloid Biopsy Report. *Archives of Pathology and Laboratory Medicine*, 134(4), 532 – 544.
- Saladin, K.S. (2004). Anatomy and physiology-the unity of form and function. 3<sup>rd</sup>. New York: McGraw-Hill.
- Salakou, S., Kardamakis, D., Tsamandas, A.C., Zolota, V., Apostolakis, E., Tzelepi, V., Papatheanasopoulos, P., Bonikos, D.S., Papapetropoulos, T., Petsas, T. and Dougenis, D. (2007). Increased Bax/Bcl-2 ratio up regulates caspase-3 and increases apoptosis in the thymus of patients with myasthenia gravis. *In Vivo*, 21(1), 123 – 32.
- Sandler, D.P. and Ross, J.A. (1997). Epidemiology of acute leukemia in children and adults. *Seminar Oncology*, 24, 3 – 16.
- Sarasua, S. and Savitz, D.A. (1994). Cured and broiled meat consumption in relation to childhood cancer: Denver Colorado (United States). *Cancer Causes Control*, 5, 141 – 8.
- Sathiya, M. and Muthuchelian, K. (2009). Significance of immunologic markers in the diagnosis of lymphoma. *Academic Journal of Cancer Research*, 2, 40 – 50.
- Savitz, D.A., Wachtel, H. and Barnes, F.A. (1988). Casecontrol study of childhood cancer and exposure to 60-Hz magnetic fields. *Journal of Epidemiology*, 128, 21 – 38.
- Savitz, D.A. and Andrews, K.W. (1997). Review of epidemiology evidence on benzene and lymphatic and hematopoietic cancer. *American Journal of Industrial Medicine*, 31(3), 287 – 295.
- Schuyer, M., van der Burg, M.E.L., Henzen-Logmans, S.C., Fieret, J.H., Klijn, J.G.M., Look, M.P., Foekens, J.A., Stoter, G. and Berns, E.M.J.J. (2001). Reduced expression of BAX is associated with poor prognosis in patients with

- epithelial ovarian cancer: a multifactorial analysis of TP53, p21, BAX and BCL-2. *British Journal of Cancer*, 85(9), 1359 – 1367.
- Scopa, C.D., Vagianos, C., Kardamakis, D., Kourelis, T.G., Kalofonos, H.P. and Tsamandas, A.C. (2001). Bcl2/Bax ratio as a predictive marker for therapeutic response to radiotherapy in patients with rectal cancer. *Applied Immunohistochemistry and Molecular Morphology*, 9(4), 329 – 34.
- Sehn, L.H., Donaldson, J., Filewich, A., Fitzgerald, C., Gill, K.K., Runzer, N., Searle, B., Souliere, S., Spinelli, J.J., Sutherland, J. and Connors, J.M. (2007). Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely delivered in the community setting. *Blood*, 109(10), 4171 – 4173.
- Sharma, O.P. (1976). Antioxidant activity of curcumin and related compounds. *Biochemical Pharmacology*, 25, 1811 – 1812.
- Sharma, R.A., McLelland, H.R., Hill, K.A., Ireson, L.R., Euden, S.A., Manson, M.M., Pirmohamed, M., Marnett, L.J., Gescher, A.J. and Steward, W.P. (2001). Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clinical Cancer Research*, 7(7), 1894 – 900.
- Sharma, R. A., Euden, S. A., Platton, S. L., Cooke, D. N., Shafayat, A., Hewitt, H.R., Marczylo, T.H., Morgan, B., Hemingway, D., Plummer, S.M., Pirmohamed, M., Gescher, A.J. and Steward, W.P. (2004). Phase I clinical trial of oral curcumin: Biomarkers of systemic activity and compliance. *Clinical Cancer Research*, 10, 6847 – 6854.
- Sharma, R.A., Gescher, A.J. and Steward, W.P. (2005). Curcumin: the story so far. *European Journal of Cancer*, 41(13), 1955 – 1968.
- Shibata, M.A., Liu, M.L., Knudson, M.L., Shibata, E., Yoshidome, K., Bandey, T., Korsmeyer, S.J. and Green, J.E. (1999). Haploid loss of Bax leads to accelerated mammary tumour development in C3(1)/SV40-Tag transgenic mice: reduction in protective apoptotic response at the preneoplastic stage. *EMBO Journal*, 18, 2692 – 2701.
- Shishodia, S., Sethi, G. and Aggarwal, B.B. (2005). Curcumin: Getting back to the roots. *Annual New York Academic Sciences*, 1056, 206 – 217.
- Shu, X.O., Ross, J.A. and Pendergrass, T.W. (1996). Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study. *Journal National Cancer Institute*, 88, 24 – 31.
- Shukla, P. K., Khanna, V. K., Khan, M. Y. and Srimal, R.C. (2003). Protective effect of curcumin against lead neurotoxicity in rat. *Human Experimental Toxicology*, 22, 653 – 658.
- Siegel, R., Naishadham, D. and Jemal, A. (2012). Cancer statistic 2012. *CA: A Cancer Journal for Clinicians*, 62, 10 – 29.
- Siu, Y.P., Leung, K.T., Tong, M.K. and Kwan, T.H. (2006). Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *American Journal of Kidney*, 47, 51 – 59.
- Slee, E.A., Harte, M.T., Kluck, R.M., Wolf, B.B., Casiano, C.A., Newmeyer, D.D., Wang, H.G., Reed, J.C., Nicholson, D.W., Alnemri, E.S., Green, D.R. and Martin, S.J. (1999). Ordering the cytochrome c-initiated caspase cascade: hierarchical activation of caspases-2, -3, -6, -7, -8, and -10 in a caspase-9-dependent manner. *Journal of Cell Biology*, 144(2), 281 – 92.

- Snyder, G.K. and Sheafor, B.A. (1999). Red Blood Cells: Centerpiece in the Evolution of the Vertebrate Circulatory System. *American Journal of Intergrative and Comparative Biology*, 39(2), 189 – 198.
- Soffritti, M., Belpoggi, F., Esposti, D.D., Lambertini, L., Tibaldi, E. and Rigano, A. (2006). First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague Dawley rats. *Environmental Health Perspectives*, 114(3), 379 – 385.
- Soni, K.B., Rajan, A. and Kuttan, R. (1992). Reversal of aflatoxin induced liver damage by turmeric and curcumin. *Cancer Letters*, 66, 115 – 21.
- Speakman, J.R. (2005). Body size, energy metabolism and lifespan. *The Journal of Experimental Biology*, 208, 1717 – 1730.
- Srimal, R.C. and Dhawan, N. (1973). Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent, *Journal of Pharmacology*, 25, 447.
- Srivastava, R., Dikshit, M., Srimal, R.C. and Dhawan, B.N. (1985). Antithrombotic effect of curcumin. *Thrombosis Research*, 40, 413 – 417.
- Stephen, W.G.T. and Douglas, R.G. (2010). Mitochondria and cell death outer membrane permeabilization and beyond. *Molecular Biology*, 11, 621 – 632.
- Sung, H.J., Kim, S.J., Lee, J.H., Lee, G., Lee, K.A., Choi, C.W., Kim, B.S., and Kim, J.S. (2007). Persistent anemia in a patient with diffuse large B cell lymphoma: Pure red cell aplasia associated with latent Epstein-Barr virus infection in bone marrow. *Journal of Korean Medical Science*, 22, 167 – 170.
- Susin, S.A., Lorenzo, H.K., Zamzami, N., Marzo, I., Snow, B.E., Brothers, G.M., Mangion, J., Jacotot, E., Costantini, P., Loeffler, M., Larochette, N., Goodlett, D.R., Aebersold, R., Siderovski, D.P., Penninger, J.M. and Kroemer, G. (1999). Molecular characterization of mitochondrial apoptosis-inducing factor. *Nature*, 397(6718), 441 – 6.
- Syukla, S. H., Kytai, T., Nguyen, S. N., Kajal, P., Robert C. E. and Liping, Tang. (2004) Molecular responses of vascular smooth muscle cells and phagocytes to curcumin-eluting bioresorbable stent materials. *Biomaterials*, 5, 5333-5346.
- Szegezdi, E., Logue, S.E., Gorman, A.M. Samali, A. (2006). Mediators of endoplasmic reticulum stress-induced apoptosis. *EMBO Reports*, 7(9), 880 – 885.
- Tanaka, T., Makita, H. and Ohnishi, M. (1994). Chemoprevention of 4-nitroquinoline 1-oxide-induced oral carcinogenesis by dietary curcumin and hesperidin: comparison with the protective effect of betacarotene. *Cancer Research*, 54(17), 4653 - 4659.
- Tawfik, K., KimLer, B.F., Davis, M.K., Fan, F. and Tawfik, O. (2012). Prognostic significance of Bcl-2 in invasive mammary carcinomas: a comparative clinicopathologic study between "triple-negative" and non-"triple-negative" tumours. *Human Pathology*, 43(1), 23 – 30.
- Tayyem, R.F., Heath, D.D., Al-Delaimy, W.K. and Rock, C.L. (2006). Curcumin content of turmeric and curry powders. *Nutrition and Cancer*, 55(2), 126 – 31.
- Thomas, A., Pepper, C. Hoy, T. and Bentley, P. (2000). Bcl-2 and Bax expression and chlorambucil-induced apoptosis in the T-cells and leukemic B-cells of untreated B-cell CLL patients. *Leukemia Research*, 24(10), 813 – 21.
- Tsukamoto, T., Mizoshita, T. and Tatematsu, M. (2007). Animal models of stomach carcinogenesis. *Toxicologic Pathology*, 35(5), 636 – 648.
- Tsujimoto, Y. and Shimizu, S. (2000). Bcl-2 regulation by the Bcl-2 family of proteins. *Cell Death and Differentiation*, 7(12), 1174 – 81.



- Twomey, C. and McCarthy, J.V. (2005). Pathways of apoptosis and importance in development. *Journal of Cellular and Molecular Medicine*, 9(2), 345 – 359.
- Ukil, A., Maity, S., Karmakar, S. Datta, N., Vedasiromoni, J.R. and Das, P.K. (2003). Curcumin, the major component of food flavour turmeric, reduces mucosal injury in trinitrobenzene sulphonic acid-induced colitis. *British Journal of Pharmacology*, 139, 209 – 218.
- Usha, K. (1994). The possible mode of action of cancer chemopreventive spice, turmeric. *Journal of American College of Nutrition*, 13, 519.
- Van Cruchten, S. and Van Den Broeck, W. (2002). Morphological and biochemical aspects of apoptosis, oncosis and necrosis. *Anatomia Histologia Embryologia*, 31(4), 214 – 23.
- Van der Meer, W. (2006). Blood cell morphology: Controversies and alternatives. Radboud University Nijmegen The Netherlands. Thesis.
- Van Hove, L., Schisano, T. and Brace, L. (2000). Anemia diagnosis, classification and monitoring using cell-dyn technology reviewed for the new millennium. *Laboratory Hematology*, 6, 93 – 108.
- Van't Veer, L.J., Dai, H., van de Vijver, M.J., He, Y.D., Hart, A.A., Mao, M., Peterse, H.L., Kooy, K., Marton, M.J., Witteveen, A.T., Schreiber, G.J., Kerkhoven, R.M., Roberts, C., Linsley, P.S., Bernards, R. and Friend, S.H. (2002). Gene expression profiling predicts clinical outcome of breast cancer. *Nature*, 415, 530 – 536.
- Varley, J.M. (2003). GermLine TP53 mutations and Li-Fraumeni syndrome. *Human Mutation*, 21, 313 – 320.
- Vaux, D.L., Cory, S. and Adams, J.M. (1988). Bcl-2 gene promotes haemopoietic cell survival and cooperates with c-myc to immortalize pre-B cells. *Nature*, 335, 440 – 442.
- Vento, P.S., Swartz, M.E., Martin, L.B. and Daniels, D. (2008). Food intake in laboratory rats provided standard and fenbendazole-supplemented diets. *Journal of American Association for Laboratory Animal Science*, 47(6), 46 – 50.
- Verhagen, A.M., Ekert, P.G., Pakusch, M., Silke, J., Connolly, L.M., Reid, G.E., Moritz, R.L., Simpson, R.J. and Vaux, D.L. (2000). Identification of DIABLO, a mammalian protein that promotes apoptosis by binding to and antagonizing IAP proteins. *Cell*, 102(1), 43 – 53.
- Wajant, H. (2002). The Fas signaling pathway: more than a paradigm. *Science*, 296(5573), 1635 – 6.
- Wang, X. (2001). The expanding role of mitochondria in apoptosis. *Genes and Development*, 15(22), 2922 – 33.
- Welch, H.M. (2012). The polymerase chain reaction. *Metastasis Research Protocol*, 878, 71 – 88.
- Wheeler, G., Thompson, K., Samers, J. and Seymour, J.F. (2009). Challengers facing survivors of childhood and adolescent cancer. *Cancer Forum*, 33(3), 188 – 195.
- William, L. (2004). Comprehensive review of hematopoiesis and immunology: implications for hematopoietic stem cell transplant recipients in ezzone's. *Hematopoietic Stem Cell Transplantation: A Manual for Nursing Practice Oncology Nursing Society: Pittsburgh, P.A.* pp. 1 – 12.
- William, B.M., Goodrich, A., Peng, C., Li, S. (2008). Curcumin inhibits proliferation and induces apoptosis of leukemic cells expressing wild-type or T315I-BCR-ABL and prolongs survival of mice with acute lymphoblastic leukemia. *Hematology*, 13, 333-343.

- Wiwanitkit, V. (2001). High serum alkaline phosphatase levels, a study in 181 Thai adult hospitalized patients. *BioMed Central Family Practice*, 2(2), 1471 – 2296.
- Wong, M.L. and Medrano, J.F. (2005). Real-time PCR for mRNA quantification. *Biotechniques*, 39, 75 – 85.
- Wright, L.E., Frye, J.B., Timmermann, B.N. and Funk, J.L. (2010). Protection of Trabecular Bone in Ovariectomized Rats by Turmeric (*Curcuma longa* L.) is Dependent on Extract Composition. *Journal of Agriculture Food Chemistry*, 58(17), 9498 – 9504.
- Xuejiang, W., Ying, Q. and Ping, F. (2000). A study of the effects of Huqi powder on isoenzyme in the serum of hepatic precancerous rats. *Journal of Beijing University of Traditional Chinese Medicine*, 2000-S1.
- Yang, F., Lim, G.P., Begum, A.N., Ubeda, O.J., Simmons, M.R., Ambegaokar, S.S., Chen, P.P., Kayed, R., Glabe, C.G., Frautschy, S.A. and Cole, G.M. (2005). Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. *The Journal of Biological Chemistry*, 280, 5892 – 5901.
- Yin, C., Knudson, C.M., Korsmeyer, S.J. and Van Dyke, T. (1997). Bax suppresses tumorigenesis and stimulates apoptosis in vivo. *Nature*, 385, 637 – 640.
- Zinkel, S.S., Hurov, K.E., Ong, C., Abtahi, F.M., Gross, A. and Korsmeyer, S.J. (2005). A role for proapoptotic BID in the DNA-damage response. *Cell*, 122, 579 - 591.
- Zipursky, A., Brown, E. and Christensen, H. (1997). Leukemia and/or myeloproliferative syndrome in neonates with Down syndrome. *Seminar Perinatology*, 21, 97 – 101.