REFERENCES

- Adams, M.R., Kinlay, S., Blake, G.J., Orford, J.L., Ganz, P. and Selwyn A.P. Pathophysiology of atherosclerosis: development, regression, restenosis. <u>Curr Atheroscler Rep</u> 2 (2000): 251-8.
- Alkhouri, N., Tamimi, T.A., Yerian, L., Lopez, R., Zein, N.N. and Feldstein, A.E. The Inflamed Liver and Atherosclerosis: A Link Between Histologic Severity of Nonalcoholic Fatty Liver Disease and Increased Cardiovascular Risk. <u>Dig Dis</u> <u>Sci</u>. 2009. DOI 10.1007/s10620-009-1075-y.
- Almuti, K., Rimawi, R., Spevack, D. and Ostfeld, R.J. Effects of statins beyond lipid lowering: potential for clinical benefits. <u>Int J Cardiol</u> 109 (2006): 7-15.
- Alsheikh-Ali, A.A., Maddukuri, P.V., Han, H. and Karas, R.H. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials. <u>J Am Coll Cardiol</u> 50 (2007): 409-18.
- Amacher, D.E. Serum transaminase elevations as indicators of hepatic injury following the administration of drugs. <u>Regul Toxicol Pharmacol</u> 27 (1998): 119-30.
- American Heart Association. Heart Disease and Stroke Statistics 2009 update. Am Heart Assoc 2009.
- Armitage, J. The safety of statins in clinical practice. Lancet 370 (2007): 1781-90
- Attie, A.D. ABCA1: at the nexus of cholesterol, HDL and atherosclerosis. <u>Trends</u>
 <u>Biochem Sci</u> 32 (2007): 172-9.
- Ballantyne, C.M., Corsini, A., Davidson, M.H., et al. Risk for myopathy with statin therapy in high-risk patients. Arch Intern Med 163 (2003): 553-64.
- Balkwill, F.R. and Burke, F. The cytokine network. <u>Immunol Today</u> 10 (1989): 299-304.
- Barath, P., Fishbein, M.C., Cao, J., Berenson, J., Helfant, R.H. and Forrester, J.S. Tumor necrosis factor gene expression in human vascular intimal smooth muscle cells detected by in situ hybridization. <u>Am J Pathol</u> 137 (1990): 503-9.
- Barter, P.J., Nicholls, S., Rye, K.A., Anantharamaiah, G.M., Navab, M. and Fogelman, A.M. Antiinflammatory properties of HDL. <u>Circ Res</u> 95 (2004): 764-72.

- Bays, H. Statin safety: an overview and assessment of the data—2005. Am J Cardiol 97 (2006): 6C-26C.
- Blake, G.J., and Ridker, P.M. Are statins anti-inflammatory? <u>Curr Control Trials</u>

 <u>Cardiovasc Med</u> 1 (2000): 161-165.
- Blasi, C. The autoimmune origin of atherosclerosis. <u>Atherosclerosis</u> 201 (2008): 17-32.
- Bocan, T.M., Mueller, S.B., Mazur, M.J., Uhlendorf, P.D., Brown, E.Q. and Kieft, K.A. The relationship between the degree of dietary-induced hypercholesterolemia in the rabbit and atherosclerotic lesion formation. Atherosclerosis 102 (1993): 9-22.
- Bradham, C.A., Plümpe, J., Manns, M.P., Brenner, D.A. and Trautwein, C. Mechanisms of hepatic toxicity. I. TNF-induced liver injury. <u>Am J Physiol</u> 275 (1998): G387-92.
- Brånén, L., Hovgaard, L., Nitulescu, M., Bengtsson, E., Nilsson, J. and Jovinge, S. Inhibition of tumor necrosis factor-alpha reduces atherosclerosis in apolipoprotein E knockout mice. <u>Arterioscler Thromb Vasc Biol</u> 24 (2004): 2137-42.
- Cai, B. and Xie, M. Simvastatin inhibits plaque rupture and subsequent thrombus formation in atherosclerotic rabbits with hyperlipidemia. <u>JCCM</u> 1 (2006): 6-11.
- Cavender, D., Saegusa, Y. and Ziff, M. Stimulation of endothelial cell binding of lymphocytes by tumor necrosis factor. J Immunol 139 (1987): 1855-60.
- Chamberlain, J., Francis, S., Brookes, Z., et al. Interleukin-1 regulates multiple atherogenic mechanisms in response to fat feeding. <u>PLoS One</u> 4 (2009): e5073.
- Chivapat, S., Hirunsaree, A., Junsuwanitch, N., et al. Subchronic toxicity of Wan Chak Motluk (*Curcuma comosa* Roxb.) extract. Proceeding of the 3rd Symposium on the Family Zingiberaceae, Khon Kaen, Thailand, 2003.
- Cipollone, F., Fazia, M., Mincione, G., et al. Increased expression of transforming growth factor-beta1 as a stabilizing factor in human atherosclerotic plaques.

 <u>Stroke</u> 35 (2004): 2253-7.
- Clark, D.P. Molecular Biology. 1st edition. London: Academic Press, 2005.

- Cohen, D.E., Anania, F.A. and Chalasani, N. An assessment of statin safety by hepatologists. Am J Cardiol 97 (2006): 77C-81C.
- Cushing, S.D., Berliner, J.A., Valente, A.J., et al. Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. Proc Natl Acad Sci U S A 87 (1990): 5134-8.
- Davidson, M.H. Rosuvastatin: a highly efficacious statin for the treatment of dyslipidaemia. Expert Opin Investig Drugs 11 (2002): 125-41.
- de Lemos, J.A., Blazing, M.A., Wiviott, S.D., et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. <u>JAMA</u> 292 (2004): 1307-16.
- de Waal Malefyt, R., Abrams, J., Bennett, B., Figdor, C.G. and de Vries, J.E. Interleukin 10(IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. <u>J Exp Med</u> 174 (1991): 1209-20.
- Decker, K. Biologically active products of stimulated liver macrophages (Kupffer cells). <u>Eur J Biochem</u> 192 (1990): 245-61.
- Denger, S., Jahn, L., Wende, P., Watson, L., Gerber, S.H., Kübler, W., Kreuzer, J. Expression of monocyte chemoattractant protein-1 cDNA in vascular smooth muscle cells: induction of the synthetic phenotype: a possible clue to SMC differentiation in the process of atherogenesis. <u>Atherosclerosis</u> 144 (1999): 15-23.
- Derynck, R. and Zhang, Y.E. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature 425 (2003): 577-84.
- DiChiara, M.R., Kiely, J.M., Gimbrone, M.A. Jr, Lee, M.E., Perrella, M.A. and Topper, J.N. Inhibition of E-selectin gene expression by transforming growth factor beta in endothelial cells involves coactivator integration of Smad and nuclear factor kappaB-mediated signals. <u>J Exp Med</u> 192 (2000): 695-704.
- Diehl, A.M. Cytokine regulation of liver injury and repair. <u>Immunol Rev</u> 174 (2000): 160-71.
- Di Febbo, C., Baccante, G., Reale, M., Castellani, M.L., Angelini, A., Cuccurullo, F. and Porreca, E. Transforming growth factor beta1 induces IL-1 receptor antagonist production and gene expression in rat vascular smooth muscle cells.

 <u>Atherosclerosis</u> 136 (1998): 377-82.

- Draude, G. and Lorenz, R.L. TGF-beta1 downregulates CD36 and scavenger receptor

 A but upregulates LOX-1 in human macrophages. Am J Physiol Heart Circ

 Physiol 278 (2000): H1042-8.
- Endo, A. The origin of the statins. 2004. Atheroscler Suppl 5 (2004): 125-30.
- Esper, R.J., Nordaby, R.A., Vilariño, J.O., Paragano, A., Cacharrón, J.L. and Machado, R.A. Endothelial dysfunction: a comprehensive appraisal. Cardiovasc Diabetol 5 (2006): 4.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III).

 JAMA 285 (2001): 2486-97.
- Ferro, D., Parrotto, S., Basili, S., Alessandri, C. and Violi, F. Simvastatin inhibits the monocyte expression of proinflammatory cytokines in patients with hypercholesterolemia. <u>J Am Coll Cardiol</u> 36 (2000): 427-31.
- Fiorentino, D.F., Bond, M.W. and Mosmann, T.R. Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. <u>J Exp Med</u> 170 (1989): 2081-95.
- Frutkin, A.D., Otsuka, G., Stempien-Otero, A., et al. TGF-[beta]1 limits plaque growth, stabilizes plaque structure, and prevents aortic dilation in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol 29 (2009): 1251-7.
- Galis, Z.S., Muszynski, M., Sukhova, G.K., Simon-Morrissey, E. and Libby, P. Enhanced expression of vascular matrix metalloproteinases induced in vitro by cytokines and in regions of human atherosclerotic lesions. <u>Ann N Y Acad Sci</u> 748 (1995): 501-7.
- Garg, A.K. and Aggarwal, B.B. Reactive oxygen intermediates in TNF signaling. Mol Immunol 39 (2002): 509-17.
- Geng, Y., Wu, Q.W., Muszynski, M., Hansson, G.K. and Libby, P. Apoptosis of vascular smooth muscle cells induced by in vitro stimulation with interferon-γ, tumor necrosis factor-α, and interleukin-1β. <u>Arterioscler Thromb Vasc Biol</u> 16 (1996): 19-27.

- Gosling, J., Slaymaker, S., Gu, L., et al. MCP-1 deficiency reduces susceptibility to atherosclerosis in mice that overexpress human apolipoprotein B. <u>J Clin Invest</u> 103 (1999): 773-8.
- Grainger, D.J., Kemp, P.R., Metcalfe, J.C., et al. The serum concentration of active transforming growth factor-beta is severely depressed in advanced atherosclerosis. <u>Nat Med</u> 1 (1995): 74-9.
- Grainger, D.J., Kemp, P.R., Witchell, C.M., Weissberg, P.L. and Metcalfe, J.C. Transforming growth factor beta decreases the rate of proliferation of rat vascular smooth muscle cells by extending the G2 phase of the cell cycle and delays the rise in cyclic AMP before entry into M phase. Biochem J 299 (1994): 227-35.
- Grundy, S.M., Cleeman, J.I., Merz, C.N., et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. <u>Circulation</u> 110 (2004): 227-39.
- Gu, L., Okada, Y., Clinton, SK., Gerard, C., Sukhova, G.K., Libby, P., Rollins, B.J. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice. <u>Mol Cell</u> 2 (1998): 275-81.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 360 (2002): 7-22.
- Hoebe, K.H., Witkamp, R.F., Fink-Gremmels, J., Van Miert, A.S. and Monshouwer, M. Direct cell-to-cell contact between Kupffer cells and hepatocytes augments endotoxin-induced hepatic injury. <u>Am J Physiol Gastrointest Liver Physiol</u> 280 (2001): G720-8.
- Howard-Alpe, G., Foëx, P. and Biccard, B. Cardiovascular protection by antiinflammatory statin therapy. <u>Best Pract Res Clin Anaesthesiol</u> 22 (2008): 111-33.
- Ioannou, G.N., Weiss, N.S., Boyko, E.J., Mozaffarian, D. and Lee, S.P. Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. <u>Hepatology</u> 43 (2006): 1145-51.
- Jantaratnotai, N., Utaisincharoen, P., Piyachaturawat, P., Chongthammakun, S., Sanvarinda, Y. Inhibitory effect of *Curcuma comosa* on NO production and cytokine expression in LPS-activated microglia. <u>Life Sci</u> 78 (2006): 571-7.

- Jerome, W.G. Advanced atherosclerotic foam cell formation has features of an acquired lysosomal storage disorder. Rejuvenation Res 9 (2006): 245-55.
- Keaney, J.F. Jr. Atherosclerosis: from lesion formation to plaque activation and endothelial dysfunction. Mol Aspects Med 21 (2000): 99-166.
- Kirii, H., Niwa, T., Yamada, Y., et al. Lack of interleukin-1beta decreases the severity of atherosclerosis in ApoE-deficient mice. <u>Arterioscler Thromb Vasc Biol</u> 23 (2003): 656-60.
- Kleemann, R., Zadelaar, S. and Kooistra, T. Cytokines and atherosclerosis: a comprehensive review of studies in mice. Cardiovasc Res 79 (2008): 360-76.
- Kiortsis, D.N., Filippatos, T.D., Mikhailidis, D.P. and Elisaf, M.S, Liberopoulos EN. Statin-associated adverse effects beyond muscle and liver toxicity. Atherosclerosis 195 (2007): 7-16.
- Kolodgie, F.G., Katocs A.S., Largis, E.E., et al. Hypercholesterolemia in the rabbit induced by feeding graded amounts of low level cholesterol. <u>Arterioscler</u> Thromb Vasc Biol 16 (1996): 1454-64
- Kromer, A. and Moosmann, B. Statin-induced liver injury involves cross-talk between cholesterol and selenoprotein biosynthetic pathways. <u>Mol Pharmacol</u> 75 (2009): 1421-9.
- Lacour, S., Gautier, J.C., Pallardy, M. and Roberts, R. Cytokines as potential biomarkers of liver toxicity. Cancer Biomark 1 (2005): 29-39.
- Laws, P.E., Spark, J.I., Cowled, P.A. and Fitridge, R.A. The role of statins in vascular disease. <u>Eur J Vasc Endovasc Surg</u> 27 (2004): 6-16.
- Li, J.J. and Chen, X.J. Simvastatin inhibits interleukin-6 release in human monocytes stimulated by C-reactive protein and lipopolysaccharide. <u>Coron Artery Dis</u> 14 (2003): 329-34.
- Li, J.J., Li YS, Fang, C.H., Hui, R.T., Yang, Y.J., Cheng, J.L. and Gao, R.L. Effects of simvastatin within two weeks on anti-inflammatory cytokine interleukin 10 in patients with unstable angina. <u>Heart</u> 92 (2006): 529-30.
- Liebler, J.M., Kunkel, S.L., Allen, R.M., Burdick, M.D. and Strieter, R.M. Interferongamma Stimulates Monocyte Chemotactic Protein-1 Expression by Monocytes. <u>Mediators Inflamm</u> 3 (1994): 27-31.
- Lohmann, C., Schäfer, N., von Lukowicz, T., et al. Atherosclerotic mice exhibit systemic inflammation in periadventitial and visceral adipose tissue, liver, and

- pancreatic islets. <u>Atherosclerosis</u> 2009, doi:10.1016/j.atherosclerosis. 2009.05.004.
- Loppnow, H., Zhang, L., Buerke, M., et al. Statins potently reduce the cytokine-mediated IL-6 release in SMC / MNC cocultures. <u>J Cell Mol Med</u> 2010, doi: 10.1111/j.1582-4934.2010.01036.x.
- Lu, B., Rutledge, B.J., Gu, L., et al. Abnormalities in monocyte recruitment and cytokine expression in monocyte chemoattractant protein 1-deficient mice. <u>J</u>

 <u>Exp Med</u> 187 (1998): 601-8.
- Luheshi, N.M., Rothwell, N.J. and Brough, D. Dual functionality of interleukin-1 family cytokines: implications for anti-interleukin-1 therapy. <u>Br J Pharmacol</u> 157 (2009): 1318-29.
- Luscinskas, F.W., Gerszten, R.E., Garcia-Zepeda, E.A., et al. C-C and C-X-C chemokines trigger firm adhesion of monocytes to vascular endothelium under flow conditions. <u>Ann N Y Acad Sci</u> 902 (2000): 288-93.
- Maeda, H., Kuwahara, H., Ichimura, Y., Ohtsuki, M., Kurakata, S. and Shiraishi, A. TGF-beta enhances macrophage ability to produce IL-10 in normal and tumor-bearing mice. <u>J Immunol</u> 155 (1995): 4926-32.
- Marra, F. Selective inhibition of NF-kappaB in Kupffer cells: good, but not for everything. <u>Gut</u> 58 (2009): 1581-2.
- Massaro, M., Zampolli, A., Scoditti, E., Carluccio, M.A., Storelli, C., Distante, A. and Statins inhibit cyclooxygenase-2 Caterina. R. and matrix metalloproteinase-9 in human endothelial cells: anti-angiogenic actions contributing plaque stability. Cardiovasc Res 2009 possibly to doi:10.1093/cvr/cvp375.
- Mallat, Z., Besnard, S., Duriez, M., et al. Protective role of interleukin-10 in atherosclerosis. Circ Res 85 (1999): e17-24.
- Manzoni, M. and Rollini, M. Biosynthesis and biotechnological production of statins by filamentous fungi and application of these cholesterol-lowering drugs. <u>Appl Microbiol Biotechnol</u> 58 (2002): 555-64.
- McGill, H.C. Jr, McMahan, C.A., Herderick, E.E., Malcom, G.T., Tracy, R.E. and Strong, J.P. Origin of atherosclerosis in childhood and adolescence. <u>Am J Clin Nutr</u> 72 (2000): 1307S-1315S.

- McPherson, M.J. and Møller, S.G. <u>PCR</u> 2nd edition. New York: Taylor & Francis, 2006.
- Meindl-Beinker, N.M. and Dooley, S. Transforming growth factor-beta and hepatocyte transdifferentiation in liver fibrogenesis. <u>J Gastroenterol Hepatol</u> 23 (2008): S122-7.
- Merck Sharp & Dohme Corp. Zocor®-9876254 Prescribing information 2010.
- Michalopoulos, G.K. Liver regeneration: molecular mechanisms of growth control. FASEB J 4 (1990): 176-87.
- Miller, S.J. Emerging mechanisms for secondary cardioprotective effects of statins.

 Cardiovasc Res 52 (2001): 5-7.
- Ming, W.J., Bersani, L. and Mantovani, A. Tumor necrosis factor is chemotactic for monocytes and polymorphonuclear leukocytes. <u>J Immunol</u> 138 (1987): 1469-74.
- Montecucco, F., Burger, F., Pelli, G., Poku, N.K., Berlier, C., Steffens, S. and Mach, F. Statins inhibit C-reactive protein-induced chemokine secretion, ICAM-1 upregulation and chemotaxis in adherent human monocytes. Rheumatology (Oxford) 48 (2009): 233-42.
- Nakamura, K., Sasaki, T., Cheng, X.W., Iguchi, A., Sato, K. and Kuzuya, M. Statin prevents plaque disruption in apoE-knockout mouse model through pleiotropic effect on acute inflammation. <u>Atherosclerosis</u> 206 (2009): 355-61.
- Namiki, M., Kawashima, S., Yamashita, T., et al. Local overexpression of monocyte chemoattractant protein-1 at vessel wall induces infiltration of macrophages and formation of atherosclerotic lesion: synergism with hypercholesterolemia.

 <u>Arterioscler Thromb Vasc Biol</u> 22 (2002): 115-20.
- Navab, M., Yu, R., Gharavi, N., et al. High-density lipoprotein: antioxidant and anti-inflammatory properties. <u>Curr Atheroscler Rep</u> 9 (2007): 244-8.
- Neuschwander-Tetri, B.A. and Caldwell, S.H. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. <u>Hepatology</u> 37 (2003): 1202-19.
- Nicholls, S.J., Tuzcu, E.M., Sipahi, I., et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. <u>JAMA</u> 297 (2007): 499-508.
- Niumsakul, S., Hirunsaree, A., Wattanapitayakul, S., Junsuwanitch, N. and Prapanupun, K. An antioxidative and cytotoxic substance extracted from

- Curcuma comosa Roxb. J of Thai Traditional & Alternative Medicine 5 (2007): 24-9.
- Nold, M., Goede, A., Eberhardt, W., Pfeilschifter, J. and Mühl, H. IL-18 initiates release of matrix metalloproteinase-9 from peripheral blood mononuclear cells without affecting tissue inhibitor of matrix metalloproteinases-1: suppression by TNF alpha blockage and modulation by IL-10. Naunyn Schmiedebergs

 Arch Pharmacol 367 (2003): 68-75.
- Ohta, H., Wada, H., Niwa, T., et al. Disruption of tumor necrosis factor-alpha gene diminishes the development of atherosclerosis in ApoE-deficient mice.

 Atherosclerosis 180 (2005): 11-7.
- Otsubo, R., Higuchi Mde, L., Gutierrez, P.S., Benvenuti, L.A., Massarollo, P.C., Costa, A.L., and Ramires, J.A. Influence of chronic liver disease on coronary atherosclerosis vulnerability features. Int J Cardiol 109 (2006): 387-91.
- Ozer, J., Ratner, M., Shaw, M., Bailey, W. and Schomaker, S. The current state of serum biomarkers of hepatotoxicity. <u>Toxicology</u> 245 (2008): 194-205.
- Ozeren, A., Aydin, M., Tokac, M., Demircan, N., Unalacak, M., Gurel, A. and Yazici, M. Levels of serum IL-1beta, IL-2, IL-8 and tumor necrosis factor-alpha in patients with unstable angina pectoris. <u>Mediators Inflamm</u> 12 (2003): 361-5.
- Panousis, C.G., Evans, G. and Zuckerman, S.H. TGF-beta increases cholesterol efflux and ABC-1 expression in macrophage-derived foam cells: opposing the effects of IFN-gamma. J Lipid Res 42 (2001): 856-63.
- Pestka, S., Krause, C.D., Sarkar, D., Walter, M.R., Shi, Y. and Fisher, P.B. Interleukin-10 and related cytokines and receptors. <u>Annu Rev Immunol</u> 22 (2004): 929-79.
- Piyachaturawat, P., Chai-ngam, N., Chuncharunee, A., Komaratat, P., and Suksamrarn, A. Choleretic activity of phloracetophenone in rats: structure-function studies using acetophenone analogues. <u>Eur J Pharmacol</u> 387 (2000): 221-7.
- Piyachaturawat, P., Charoenpiboonsin, J., Toskulkao, C., et al. Reduction of plasma cholesterol by *Curcuma comosa* extract in hypercholesteroamic hamsters. <u>J</u>

 <u>Ethnopharmacol</u> 66 (1999): 199-204.
- Piyachaturawat, P., Gansar, R. and Suksamrarn, A. Choleretic effect of *Curcuma comosa* rhizome extracts in rats. <u>Int J pharmacog</u> 34 (1996): 174-178.

- Piyachaturawat, P., Srivoraphan, P., Komaratat, P., Chuncharunee, A. and Suksamrarn, A. Cholesterol lowering effects of a choleretic phloracetophenone in hypercholesterolemic hamsters. <u>Eur J Pharmacol</u> 439 (2002a): 141-7.
- Piyachaturawat, P., Suwanampai, P., Komaratat, P., et al. Effect of phoracetophenone on bile flow and biliary lipids in rat. <u>Hepatology Research</u> 12 (1998): 198-206.
- Piyachaturawat, P., Tubtim, C., Chuncharunee, A., Komaratat, P. and Suksamram, A. Evaluation of the acute and subacute toxicity of a choleretic phloracetophenone in experimental animals. <u>Toxicol Lett</u> 129 (2002b): 123-32.
- Potteaux, S., Ait-Oufella, H. and Mallat, Z. Mouse models of atherosclerosis. <u>Drug</u>
 Discov Today Dis Models 4 (2007): 165-70.
- Qian, H., Neplioueva, V., Shetty, G.A., Channon, K.M. and George, S.E. Nitric oxide synthase gene therapy rapidly reduces adhesion molecule expression and inflammatory cell infiltration in carotid arteries of cholesterol-fed rabbits. Circulation 99 (1999): 2979-82.
- Rajavashisth, T.B., Xu, X.P., Jovinge, S., et al. Membrane type 1 matrix metalloproteinase expression in human atherosclerotic plaques: evidence for activation by proinflammatory mediators. <u>Circulation</u> 99 (1999): 3103-9.
- Ramadori, G. and Armbrust, T. Cytokines in the liver. <u>Eur J Gastroenterol Hepatol</u> 13 (2001): 777-84.
- Rallidis, L.S., Hamodraka, E.S., Fountoulaki, K., Moustogiannis, G., Zolindaki, M.G. and Kremastinos, D.T. Simvastatin exerts its anti-inflammatory effect in hypercholesterolaemic patients by decreasing the serum levels of monocyte chemoattractant protein-1. <u>Int J Cardiol</u> 124 (2008): 271-2.
- Ramji, D.P., Singh, N.N., Foka, P., Irvine, S.A. and Arnaoutakis, K. Transforming growth factor-beta-regulated expression of genes in macrophages implicated in the control of cholesterol homoeostasis. <u>Biochem Soc Trans</u> 34 (2006): 1141-4.
- Rattanachamnong, P. <u>Prevention of atherosclerosis in hypercholesterolemic rabbits by hexane extracts of *Curcuma comosa* Roxb. Master Thesis, Graduated school, Srinakharinwirot University, 2008.</u>

- Reape, T.J. and Groot, P.H. Chemokines and atherosclerosis. <u>Atherosclerosis</u> 147 (1999): 213-25.
- Rej, R. Aminotransferases in disease. Clin Lab Med 9 (1989): 667-87.
- Rezaie-Majd, A., Maca, T., Bucek, R.A., et al. Simvastatin reduces expression of cytokines interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients. <u>Arterioscler</u> Thromb Vasc Biol 22 (2002): 1194-9.
- Robertson, A.K., Rudling, M., Zhou, X., Gorelik, L., Flavell, R.A. and Hansson, G.K. Disruption of TGF-beta signaling in T cells accelerates atherosclerosis. <u>J Clin Invest</u> 112 (2003): 1342-50.
- Rosenson, R.S. Statins in atherosclerosis: lipid-lowering agents with antioxidant capabilities. Atherosclerosis 173 (2004): 1-12.
- Rudd, J.H. and Fayad, Z.A. Imaging atherosclerotic plaque inflammation. <u>Nat Clin Pract Cardiovasc Med</u> 5 (2008): S11-7.
- Russo, M.W., Scobey, M. and Bonkovsky, H.L. Drug-induced liver injury associated with statins. <u>Semin Liver Dis</u> 29 (2009): 412-22.
- Saleh, H.A. and Abu-Rashed, A.H. Liver biopsy remains the gold standard for evaluation of chronic hepatitis and fibrosis. <u>J Gastrointestin Liver Dis</u> 16 (2007): 425-6.
- Sambrook, J. and Russell, D. Molecular cloning: A laboratory manual, 3rd edition. New York: Cold Spring Harbor Laboratory Press, 2001.
- Sanvarinda, Y., Phivthong-ngam, L., Ratacachamnong, P. and Piyachaturawat P. Hypolipidemic and antiatherosclerotic effects of *Curcuma comosa* on high cholesterol-fed rabbits. Thai J Pharmacol 29 (2007): 56-9.
- Sanz, J. and Fayad, Z.A. Imaging of atherosclerotic cardiovascular disease. <u>Nature</u> 451 (2008): 953-7.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). <u>Lancet</u> 344 (1994): 1383-1389.
- Schachter, M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. <u>Fundam Clin Pharmacol</u> 19 (2005): 117-25.

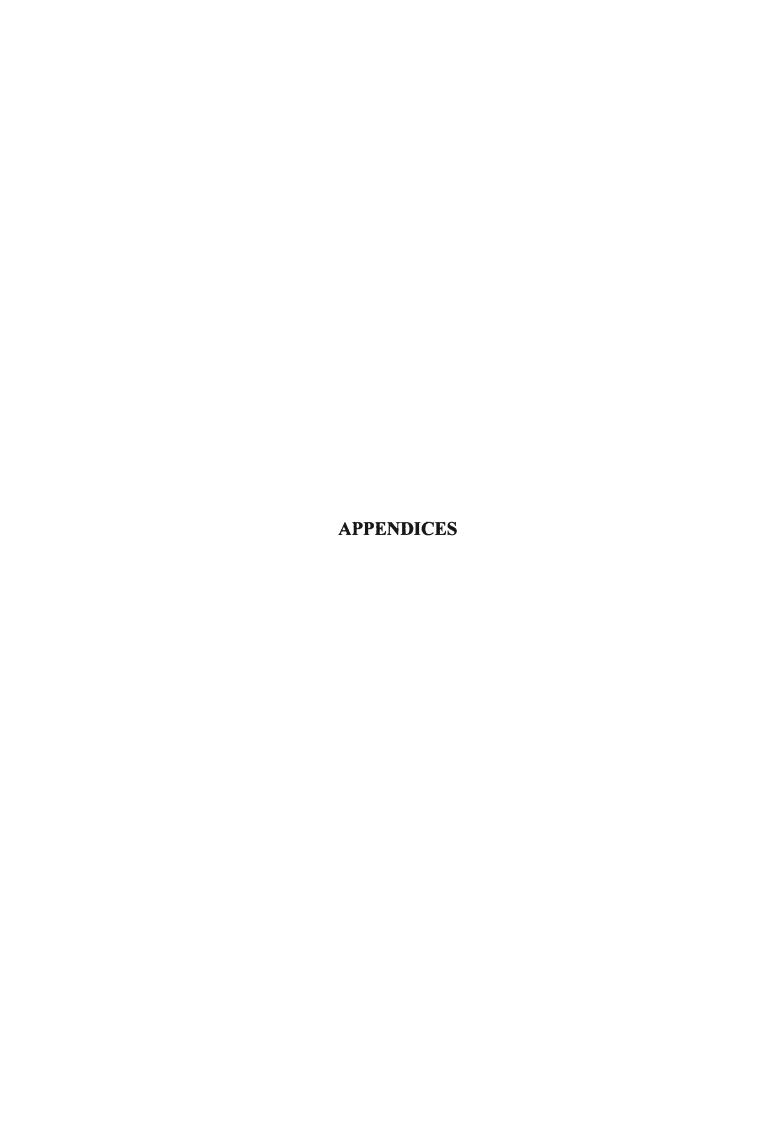
- Seino, Y., Ikeda, U., Takahashi, M., Hojo, Y., Irokawa, M., Kasahara, T. and Shimada, K. Expression of monocyte chemoattractant protein-1 in vascular tissue. <u>Cvtokine</u> 7 (1995): 575-9.
- Shetty, S., Lalor, P.F. and Adams, D.H. Lymphocyte recruitment to the liver: molecular insights into the pathogenesis of liver injury and hepatitis.

 <u>Toxicology</u> 254 (2008): 136-46.
- Silverstein, R.L. Inflammation, atherosclerosis, and arterial thrombosis: role of the scavenger receptor CD36. <u>Cleve Clin J Med</u> 76 (2009): S27-30.
- Singh, R.B., Mengi, S.A., Xu, Y.J., Arneja, A.S. and Dhalla, N.S. Pathogenesis of atherosclerosis: A multifactorial process. Exp Clin Cardiol 7 (2002): 40-53.
- Smitinand, T. <u>Thai plant names</u>. (Revised edition). Bangkok: Prachachon Co., Ldt., 2001.
- Sprague, A.H. and Khalil, R.A. Inflammatory cytokines in vascular dysfunction and vascular disease. <u>Biochem Pharmacol</u> 78 (2009): 539-52.
- Sodsai, A., Piyachaturawat, P., Sophasan, S., Suksamrarn, A. and Vongsakul, M. Suppression by *Curcuma comosa* Roxb. of pro-inflammatory cytokine secretion in phorbol-12-myristate-13-acetate stimulated human mononuclear cells. <u>International Immunopharmacology</u> 7 (2007): 524-31.
- Steffens, S. and Mach, F. Inflammation and atherosclerosis. Herz 29 (2004): 741-8.
- Stocker, R. and Keaney, J.F. Role of oxidative modifications in atherosclerosis. Physiol Rev 84 (2004): 1381-478.
- Suksamrarn, A., Eiamong, S., Piyachaturawat, P. and Byrne, L.T. A phloracetophenone glucoside with choleretic activity from *Curcuma comosa*.

 Phytochemistry 45 (1997): 103-5.
- Suksamrarn, A., Eiamong, S., Piyachaturawat, P. and Charoenpipoonsin, J. Phenolic Diaryheptanoids from *Curcuma xantho*rrhiza. <u>Phytochemistry</u> 36 (1994): 1505-1508.
- Tacke, F., Luedde, T. and Trautwein, C. Inflammatory pathways in liver homeostasis and liver injury. <u>Clin Rev Allergy Immunol</u> 36 (2009): 4-12.
- Tahara, N., Kai, H., Ishibashi, M., et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. <u>J Am Coll</u> Cardiol 48 (2006): 1825-31.

- Tandon, V., Bano, G., Khajuria, V., Parihar, A. and Gupta, S. Pleiotropic effects of statins. <u>Indian J Pharmacol</u> 37 (2005): 77-85.
- Taub, D.D., Ortaldo, J.R., Turcovski-Corrales, S.M., Key, M.L., Longo, D.L. and Murphy, W.J. Beta chemokines costimulate lymphocyte cytolysis, proliferation, and lymphokine production. <u>J Leukoc Biol</u> 59 (1996): 81-9.
- Tedgui, A. and Mallat, Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. Physiol Rev 86 (2006): 515-81.
- Terkeltaub, R.A. IL-10: An "immunologic scalpel" for atherosclerosis? <u>Arterioscler</u>
 Thromb Vasc Biol 19 (1999): 2823-5.
- Tipping, P.G. and Hancock, W.W. Production of tumor necrosis factor and interleukin-1 by macrophages from human atheromatous plaques. <u>Am J Pathol</u> 142 (1993): 1721-8.
- Tolman, K.G. Defining patient risks from expanded preventive therapies. <u>Am J Cardiol</u> 85 (2000):15E-9E.
- Uyemura, K., Demer, L.L., Castle, S.C., et al. Cross-regulatory roles of interleukin (IL)-12 and IL-10 in atherosclerosis. <u>J Clin Invest</u> 97 (1996): 2130-8.
- Vinereanu, D. Risk factors for atherosclerotic disease: present and future. <u>Herz</u> 31 (2006): 5-24.
- Wang, P., Wu, P., Siegel, M.I., Egan, R.W. and Billah, M.M. Interleukin (IL)-10 inhibits nuclear factor kappa B (NF kappa B) activation in human monocytes. IL-10 and IL-4 suppress cytokine synthesis by different mechanisms. <u>J Biol</u> Chem 270 (1995): 9558-63.
- Wang, X., Feuerstein, G.Z., Gu, J., Lysko, P.G. and Yue, T. Interleukin-1β induces expression of adhesion molecules in human vascular smooth muscle cells and enhances adhesion of leukocytes to smooth muscle cells. <u>Atherosclerosis</u> 115 (1995):89-98.
- Wong, V.W., Wong, G.L., Tsang, S.W., et al. Metabolic and histological features of non-alcoholic fatty liver disease patients with different serum alanine aminotransferase levels. <u>Aliment Pharmacol Ther</u> 29 (2009): 387-96.
- Woo, C.H., You, H.J., Cho, S.H., Eom, Y.W., Chun, J.S., Yoo, Y.J. and Kim, J.H. Leukotriene B(4) stimulates Rac-ERK cascade to generate reactive oxygen species that mediates chemotaxis. <u>J Biol Chem</u> 277 (2002): 8572-8.

- World Health Organization. World health statistics 2009 [online]. Available from: http://www.who.int/entity/whosis/whostat/EN_WHS09_Full.pdf [2009, September 27].
- Yanni, A.E. The laboratory rabbit: an animal model of atherosclerosis research. <u>Lab</u> Anim 38 (2004): 246-56.
- Yin, M., Zhang, L., Sun, X.M., Mao, L.F. and Pan, J. Lack of apoE causes alteration of cytokines expression in young mice liver. Mol Biol Rep 2009, doi: 10.1007/s11033-009-9660-x.
- Ylä-Herttuala, S., Lipton, B.A., Rosenfeld, M.E., et al. Expression of monocyte chemoattractant protein 1 in macrophage-rich areas of human and rabbit atherosclerotic lesions. <u>Proc Natl Acad Sci U S A</u> 88 (1991): 5252-6.
- Yomchot, C. Effects of *Curcuma comosa* rhizome on paraoxonase activity and oxidative stress in rabbits fed with high-cholesterol diet. Master Thesis, Department of Pharmacology, Faculty of Pharmaceutical Sciences, Chulalongkorn University, 2007.
- Yomchot, C., Lawanprasert, S., Phivthong-ngam, L., Sanvarinda, Y. and Porntadavity, S. Effect of *Curcuma comosa* powder on serum paraoxonase activities in cholesterol-diet fed rabbits. <u>Thai J Pharmacol</u> 29 (2008): 83-87
- Yu, C., Wu, H., Chen, T., Yeh, R. and Chen, K. The valuation of blood and tisse enzymes for clinical diagnosis in New Zealand White and Rex rabbits. <u>Taiwan</u> <u>Vet J</u> 35 (2009): 1-8.
- Yu, X., Dluz, S., Graves, D.T., et al. Elevated expression of monocyte chemoattractant protein 1 by vascular smooth muscle cells in hypercholesterolemic primates. Proc Natl Acad Sci U S A 89 (1992): 6953-7.
- Zubelewicz-Szkodzińska, B., Szkodziński, J., Danikiewicz, A., et al. Effects of simvastatin on pro-inflammatory cytokines in patients with hypercholesterolemia. <u>Kardiol Pol</u> 59 (2003): 465-74.



Appendix A

Preparation of *C. comosa* rhizome, chemical identification, and preparation of *C. comosa* suspension

Preparation of Curcuma comosa rhizome

C. comosa rhizome was kindly provided by Professor Dr. Apichart Suksamrarn, Faculty of Sciences, Ramkamhaeng University, Thailand. In brief, dried rhizome of C. comosa was collected from Nakornpathom province. A voucher specimen (BKF No. 97298) was deposited at the Forest Herbarium, Royal Forest Department, Ministry of Agriculture and Cooperatives, Bangkok. C. comosa rhizomes were sliced and dried at 50 – 60 °C. The dried rhizomes were pulverized before giving to the animals.

Chemical identification

C. comosa was characterized by Apichart Suksamrarn et al. (unpublished data). The major constituent in C. comosa powder were two diarylheptanoids: 1,7-diphenyl-(6E)-6-hepten-3-ol and 1,7-diphenyl-(4E,6E)-4,6-heptadien-3-ol.

Preparation of C. comosa suspension

C. comosa suspension for animal administration were prepared daily by dissolving 400 mg of C. comosa powder with 1 ml of deionized water to make a concentration of 400 mg/ml of C. comosa suspension and mixed before feeding to experimental animals.

Appendix B

Preparation of simvastatin

Preparation of simvastatin

Vascor® (containing 10 mg simvastatin per tablet manufactured by Biolab Co., Ltd., Samutrprakarn, Thailand) was purchased from an accredited drugstore, Bangkok, Thailand. The expired date of drug was checked. Each tablet of simvastatin was divided in half before giving to the animals.

Appendix C

Experimental diets

Food

1. Standard food for rabbits was purchased from Charoen Pokphand Foods Public Company Limited, Thailand. The composition of the standard food was as following:

Raw protein	17.00%
Raw fiber	17.00%
Raw ash	7.00%
Raw fat	2.5%
Methionine	0.35%
Lysine	0.95%
Calcium	0.85%
Phosphate	0.55%
Sodium	0.30%
Magnesium	0.25%
Vitamin A	30.00 IU/kg
Vitamin D3	1.00 IU/kg
Vitamin E	100.00 IU/kg

2. High-cholesterol diet was the standard food combined with 1.0% cholesterol or 0.5% cholesterol by Charoen Pokphand Foods Public Company Limited, Bangkok, Thailand.

Appendix D

Experimental animals treatment and samples collection

Experimental animals

Twelve male New Zealand White (NZW) rabbits of body weigh between $1.5-2.0\,\mathrm{kg}$ were obtained from the National Laboratory Animal Center, Mahidol University, Salaya, Nakornpathom, Thailand. The animals were housed one per cage at the Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand and acclimatized for two weeks before being entered into an experiment. All animals were kept in a controlled humidify room at a constant temperature of 25 ± 2 °C and maintained on 12-hour alternate light-dark cycle. They were allowed to freely access to food and drinking water.

Animal treatment

Twelve NZW rabbits were randomly divided into three treatment groups of 4 rabbits each as following:

- 1. Group 1: NZW rabbits were given orally with 1.0% cholesterol diet for 1 month. After 1 month, the animals were continually given 0.5% cholesterol diet for 3 months
- 2. Group 2: NZW rabbits were given orally with 1.0% cholesterol diet for 1 month. After 1 month, the animals were continually given 0.5% cholesterol diet and simvastatin at the dosage of 5 mg/day for 3 months
- 3. Group 3: NZW rabbits were given orally with 1.0% cholesterol diet for 1 month. After 1 month, the animals were continually given 0.5% cholesterol diet and *C. comosa* at the dosage of 400 mg/kg/day for 3 months

Samples collection

At the end of the treatment, animals were fasted for 12 hours before anesthesized with sodium pentobarbital by intravenous at the dosage of 100 mg/kg before collecting blood. Tissue samples were immediately removed from the body of rabbits, rinsed with PBS buffer pH 7.4 for 3 times, and then stored at -80 °C until analysis of cytokine expression.

Appendix E

- Study Protocol Approval by Ethic Committee of the Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand
- Study Protocol Approval by Ethic Committee of the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand, 2008



62 หมู่ 7 จำเภอจงครักษ์ จังหวัดนครบาชก 26120 โทร.0-3739-5085 ต่อ 10513

ใบอนุญาตให้ใช้สัตว์ ในงานวิจัย งานทดสอบ งานผลิตชีววัตถุ และงานสอน

เลขที่หนังสือรับรอง 10/2550

ชื่อใครงการวิจัย	การศึกษาผลของสารสกัดว่านจักมดลูกต่อการอับยั้งใรคหลอดเลือดแข็งตัวใน	
	ানচানত of atherosclerosis development in rabbits by crude extracts of	
	Curcuma Comosa Roxb.	
ชื่อพัวหน้าโครงการ /	ผศ คร.ลัศดาวัลย์ ผิวทองงาม / ภาควิชาเภสัชวิทยา	
หน่วยงานที่สังกัด	คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ	
รพั นใครงการ	10/2550	
สถานที่ทำการวิจัย	คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ	
เลกสารรับรอง	- แบบเสนอโครงการวิจัยเพื่อขอรับการพิจารณา	
	- แบบพ่อร์มรออนุญาคไร้สัดวั	
รับรองโดย	คณะกรรมการรับผิดชอบและดูแลการใช้สัตว์พคลอง	
วันที่รับรอง	8 พฤศจิกาชน 2550	
วับหมดชายุ	7 พฤศจิกายน 2551	

ใบอนุญาตนี้ให้ไว้เพื่อแรงงาคณะกรรมการรับผิดรอบและดูแลการใช้ลัดวัทคลอง คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรณ ซึ่งมีหน้าที่กำกับดูแลการใช้ลัดว์ ในงานวิจัย งานทดสอบ งานผลิตรี ววัตถุ และ งานสอนให้เป็นไปตามจรรยาบรรณการใช้สัตว์ของสภาวิจัยแห่งชาติ

un huda

(ผู้ร่วยศาสตราจารย์ ดร.ปัทมา ลิ้วนิช)

ประธานคณะกรรมการ ฯ

.....

(ศาสตราจารย์ นายแพทย์สมเกียรติ วัฒนศิริรัยกุล)

คณบดีคณะแพทยศาสตร์

Chulalongkorn University Animal Care and Use Committee

Certificate of Project Approval	☑ Original □ Renew	
Animal Use Protocol No. 08-33-002	Approval No. 08-33-002	
Protocol Title		
Trotocol Time		
Effects of Curcuma comosa rhizome on paraoxona	se activity and oxidative stress in rabbits fed with	
high-cholesterol diet		
Principal Investigator		
Somsong Lawanprasert, Ph.D.		
Certification of Institutional Animal Care and U	se Committee (IACUC)	
This project has been reviewed and approved by the IACUC in accordance with university regulations and		
policies governing the care and use of laboratory animals. The review has followed guidelines documented in		
Ethical Principles and Guidelines for the Use of Animals for Scientific Purposes edited by the National		
Research Council of Thailand.		
Date of Approval	Date of Expiration	
March 24, 2008	March 24, 2009	
Applicant Faculty/Institution		
Faculty of Pharmaceutical Sciences, Chulalongkorn University, Phyathai Rd.,		
Pathumwan BKK-THAILAND. 10330 Signature of Chairperson	Signature of Authorized Official	
	Signature of Authorized Official	
Withous Familiaga +	'cky &e	
Name and Title	Name and Title	
WITHAYA JANTHASOOT	RUNGPETCH SAKULBUMRUNGSIL, Ph.D.	
Chairman	Associate Dean (Research and Academic Service)	
The official signing above certifies that the in	formation provided on this form is correct. The institution	
assumes that investigators will take responsibility and follow university regulations and policies for the care		

sumes that investigators will take responsibility, and follow university regulations and policies for the care and use of animals.

This approval is subjected to assurance given in the animal use protocol and may be required for future investigations and reviews.

VITAE

Mr. Puttavee Charoenwanthanang was born on November 30, 1985 in Bangkok, Thailand. He graduated with a Bachelor of Science in Pharmacy (First Class Honours) in 2008 from Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand.

