

Curriculum Vitae

JIRAPORN TOCHARUS, Ph.D.

Office Address: Department of Physiology, Faculty of Medicine
Chiang Mai University
110 Intrawaroros Road
Sriphum, Muang District, Chiang Mai 50200
Thailand
Phone : 053-945362
Fax : 053-945365
E-mail : jtocharus@gmail.com

Marital Status married

EDUCATION

2001-2004 Ph.D. (Biological Sciences), Laboratory of Gene Function in Animals,
Division of Biomedical Science, Graduate School of Biological Sciences,
Nara Institute of Science and Technology, Nara, Japan

PROFESSIONAL APPOINTMENT

2011-Present Instructor, Department of Physiology, Faculty of Medicine,
Chiang Mai University, Chiang Mai, Thailand
2011-2017 Assistant Professor, Department of Physiology, Faculty of Medicine,
Chiang Mai University, Chiang Mai, Thailand
2018-present Associated Professor, Department of Physiology, Faculty of Medicine,
Chiang Mai University, Chiang Mai, Thailand

PRESENTATIONS AT INTERNATIONAL MEETINGS

September 2013 5th BBBB International Conference: From Drug Discovery and
Formulation Strategies To Pharmacokinetics-Pharmacodynamics,
Athens, Greece
May 2015 12th Asian Congress of Nutrition, Yokohama, Japan
July 2017 Natural Products in Health, Agro-Food and Cosmetics, Lille, France
April 2019 9th Federation of the Asian and Oceanian Physiological Societies
(FAOPS) Congress, Kobe, Japan

Special Academic Appointments

20011-Present Graduate School Faculty, Chiang Mai University, Chiang Mai,
Thailand

RESEARCH GRANT SUPPORT

2011-2014 The Thailand Research Fund and Commission on Higher Education (PI)
2013-2014 Faculty of Medicine Research Fund (PI)
2012-2013 Research Fund from the National Research Council, Thailand (PI)
2014-2015 Research Fund from the National Research Council, Thailand (PI)
2014-2015 Faculty of Medicine Research Fund (PI)
2014-2015 Chiang Mai University (PI)
2015-2016 Research Fund from the National Research Council, Thailand (PI)
2015-2016 Faculty of Medicine Research Fund (PI)
2017-2020 The Thailand Research Fund (PI)

PREVIOUS GRANT SUPPORT

2005-2007 The Thailand Research Fund and Commission on Higher Education (PI)
2006-2007 The National Research Council of Thailand (PI)
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2008-2010 The Thailand Research Fund and Commission on Higher Education (PI)
2008-2009 The National Research Council of Thailand (PI)
2009-2010 The National Research Council of Thailand (PI)
2009-2011 Agricultural Research Development Agency
2011-2014 The Thailand Research Fund and Commission on Higher Education (PI)
2012-2013 The National Research Council of Thailand (PI)
2012-2013 Agricultural Research Development Agency (Co)

PEER REVIEWED ARTICLES

1. Yawoot N., Chumboatong W., Sengking J., Wicha P., Tocharus C., **Tocharus J.** Chronic high-fat diet consumption exacerbates pyroptosis- and necroptosis-mediated HMGB1 signaling in the brain after ischemia and reperfusion injury. *J Physiol Biochem.* 2022; 78(4):833-844.

2. Thangwong P, Jearjaroen P, Govitrapong P, Tocharus C, **Tocharus J.** Melatonin improves cognitive function by suppressing endoplasmic reticulum stress and promoting synaptic plasticity during chronic cerebral hypoperfusion in rats. *Biochem Pharmacol* 2022, 198:114980.
3. Wongpun J, Chanmanee T, Tocharus C, Chokchaisiri R, Chantorn S, Pabuprapap W, Suksamrarn A, **Tocharus J.** The effects of festidinol treatment on the D-galactose and aluminium chloride-induced Alzheimer-like pathology in mouse brain. *Phytomedicine* 2022, 98:153925.
4. Khamchai S, Chumboatong W, Hata J, Tocharus C, Suksamrarn A, **Tocharus J.** Morin attenuated cerebral ischemia/reperfusion injury through promoting angiogenesis mediated by angiopoietin-1-Tie2 axis and Wnt/ β -catenin pathway. *Neurotox Res* 2022, 40:14-25.
5. Nazir Y, Linsaenkart P, Khantham C, Chaitep T, Jantrawut P, Chittasupho C, Rachtanapun P, Jantanasakulwong K, Phimolsiripol Y, Sommano SR, **Tocharus J,** Mingmalairak S, Wongs A, Arjin C, Sringarm K, Berrada H, Barba FJ, Ruksiriwanich W. *J Fungi* 2021, 7:1100.
6. Panthiya L, Tocharus J, Onsa-Ard A, Chaichompoo W, Suksamrarn A, Tocharus C. Hexahydrocurcumin ameliorates hypertensive and vascular remodeling in L-NAME-induced rats. *Biochim Biophys Acta Mol Basis Dis* 2022, 1868:166317.
7. Chumboatong W, Khamchai S, Tocharus C, Govitrapong P, Tocharus J. Agomelatine exerts an anti-inflammatory effect by inhibiting microglial activation through TLR4/NLRP3 pathway in pMCAO rats. *Neurotox Res* 2022, 40:259-266.
8. Yawoot N, Sengking J, Wicha P, Govitrapong P, Tocharus C, Tocharus J. Melatonin attenuates reactive astrogliosis and glial scar formation following cerebral ischemia and reperfusion injury mediated by GSK-3 β and RIP1K. *J Cell Physiol* 2021,
9. Chanmanee T, Wongpun J, Tocharus C, Govitrapong P, Tocharus J. The effects of agomelatine on endoplasmic reticulum stress related to mitochondrial dysfunction in hippocampus of aging rat model. *Chem Biol Interact* 2022, 351: 109703.
10. Sengking J, Oka C, Wicha P, Yawoot N, Tocharus J, Chaichompoo W, Suksamrarn A, Tocharus C. Neferine protects against brain damage in permanent cerebral ischemia rat associated with autophagy suppression and AMPK/mTOR regulation. *Mol Neurobiol* 2021, 58:6304-6315.
11. Jittiwat J, Suksamrarn A, Tocharus C, Tocharus J. Dihydrocapsaicin effectively mitigates cerebral ischemia-induced pathological changes in vivo, partly via antioxidant and anti-apoptotic pathways. *Life Sci* 2021, 283: 119842.
12. Chokchaisiri R, Chaichompoo W, Pabuprapap W, Sukcharoen O, Tocharus J, Ganranoo L, Bureekaew S, Sangvichien E, Suksamrarn A. Biotransformation of 1, 11 α -dihydroxyisopimara-8(14),15-diene by *Cunninghamia echinulate* NRRL 1386 and their neuroprotective activity. *Bioorg Chem* 2021, 110:104799.
13. Jumnonpraknon P, Chokchaisiri R, Thummayot S, Suksamrarn A, Tocharus C, **Tocharus J.** 5,6,7,4'-Tetramethoxyflavanone attenuates NADPH oxidase $\frac{1}{4}$ and promotes sirtuin-1 to inhibit cell stress, msenescence and apoptosis in Ab25-35-mediated SK-N-SH dysfunction. *EXCLI J* 2021, 20: 1346-1362.
14. Sivasinprasasn S, Wikan N, **Tocharus J,** Chaichompoo W, Suksamrarn A, Tocharus C. Pelargonic acid vanillylamide and rosuvastatin protect against oxidized low-density lipoprotein-induced endothelial dysfunction by inhibiting the NF- κ B/NLRP3 pathway and improving cell-cell junctions. *Chem Biol Interact* 2021; 345:109572.
15. Pakdeepak K, Chokchaisiri R, Govitrapong P, Tocharus C, Suksamrarn A, **Tocharus J.** 5,6,7,4'-Tetramethoxyflavanone alleviates neurodegeneration in a dexamethasone-

- induced neurodegenerative mouse model through promotion of neurogenesis via the Raf/REK1/2 pathway. *Phytotherapy Res* 2021;35(5):2536-2544..
16. Jearjaroen P, Pakdeepak K, Tocharus C, Chaichompoo W, Suksamrarn A, **Tocharus J**. Inhibitory Effect of Hexahydrocurcumin on Memory Impairment and Amyloidogenesis in Dexamethasone-Treated Mice. *Neurotox Res* 2021;39(2):266-276.
 17. Yawoot N, Govitrapong P, Tocharus C, **Tocharus J**. Ischemic stroke, obesity, and the anti-inflammatory role of melatonin. *Biofactors* 2021;47: 41-58.
 18. Wicha P, **Tocharus J**, Janyou A, Jittiwat J, Chaichompoo W, Suksamrarn A, Tocharus C. Hexahydrocurcumin alleviated blood-brain barrier dysfunction in cerebral ischemia/reperfusion rats. *Pharmacol Rep* 2020;72: 659-671.
 19. Chumboatong W, Khamchai S, Tocharus C, Govitrapong P, **Tocharus J**. Agomelatine protects against permanent cerebral ischaemia via the Nrf2-HO-1 pathway. *Eur J Pharmacol* 2020;874: 173028.
 20. Janyou A, Wicha P, Seechamnaturakit V, Bumroongkit K, Tocharus C, Suksamrarn A, **Tocharus J**. Dihydrocapsaicin-induced angiogenesis and improved functional recovery after cerebral ischemia and reperfusion in a rat model. *J Pharmacol Sci* 2020;143: 9-16.
 21. Khamchai S, Chumboatong W, Hata J, Tocharus C, Suksamrarn A, **Tocharus J**. Morin protects the blood-brain barrier integrity against cerebral ischemia reperfusion through anti-inflammatory actions in rats. *Sci Rep* 2020;10: 13379.
 22. Wikan N, **Tocharus J**, Sivasinprasasn S, Kongkaew A, Chaichompoo W, Suksamrarn A, Tocharus C. Capsaicinoid nonivamide improves nonalcoholic fatty liver disease in rats fed a high-fat diet. *J Pharmacol Sci* 2020;143: 188-198.
 23. Pakdeepak K, Chokchaisiri R, **Tocharus J**, Jearjaroen P, Tocharus C, Suksamrarn A. 5,6,7,4'-Tetramethoxyflavanone protects against neuronal degeneration induced by dexamethasone by attenuating amyloidogenesis in mice. *EXCLI J* 2020;19:16-32.
 24. Namyen J, Permpoonputtana K, Nopparat C, **Tocharus J**, Tocharus C, Govitrapong P. Protective effects of melatonin on methamphetamine-induced blood brain barrier dysfunction in rat model. *Neurotox Res* 2020;37: 640-660.
 25. Pantan R, **Tocharus J**, Nakaew A, Suksamrarn A, Tocharus C. Ethyl Rosmarinate Prevents the Impairment of Vascular Function and Morphological Changes in L-NAME-Induced Hypertensive Rats. *Medicina* 2019;55(12):777.
 26. Sivasinprasasn S, Wikan N, **Tocharus J**, Pantan R, Chaichompoo W, Suksamrarn A, Tocharus C. Synergistic effects of the capsaicinoid nonivamide and rosuvastatin on obesity-related endothelial dysfunction in rat fed a high-fat diet. *Phytother Res* 2019;33: 1815-1826.
 27. Panthiya L, Pantan R, **Tocharus J**, Nakaew A, Suksamrarn A, Tocharus C. Endothelium-dependent and endothelium-independent vasorelaxant effects of titiacorinine 12-O-acetate and mechanisms on isolated rat aorta. *Biomed Pharmacother* 2019;109:2090-2099.
 28. Singhrang N, Tocharus C, Thummayot S, Sutheerawattananonda M, Tocharus J. Protective effects of silk lutein extract from *Bombyx* cocoons on β -amyloid peptide-induced apoptosis in PC12 cells. *Biomed Pharmacother* 2018;103:582-587.

29. Thummayot S, Tocharus C, Jumnonpraknon P, Suksamrarn A, **Tocharus J**. Cyanidin attenuates A β ₂₅₋₃₅-induced neuroinflammation by suppressing NF-kB activity downstream of TLR4/NOX4 in human neuroblastoma cells. *Acta Pharmacol Sin* 2018;39(9):1439-1452.
30. Wicha P, **Tocharus J**, Janyou A, Jittiwat J, Changtam C, Suksamrarn A, Tocharus C. Hexahydrocurcumin protects against cerebral ischemia/reperfusion injury, attenuates inflammation and improves antioxidant defense in a rat stroke model. *PLoS One* 2017;12:e0189211.
31. Janyou A, Wicha P, Jittiwat J, Suksamrarn A, Tocharus C, **Tocharus J**. Dihydrocapsaicin attenuates blood brain barrier and cerebral damage in focal cerebral ischemia/reperfusion via oxidative stress and inflammatory. *Sci Rep* 2017;7(1): 10556.
32. Jenwitheesuk A, Park S, Wongchitrat P, **Tocharus J**, Mukda S, Shimokawa I, Govitrapong P. Comparing the effects of melatonin with caloric restriction in the hippocampus of aging mice: involvement of sirtuin1 and FOXOs pathway. *Neurochem Res* 2018;43:144-152.
33. Jenwitheesuk A, Boontem P, Wongchitrat P, **Tocharus J**, Mukda S, Govitrapong P. Melatonin regulates the aging mouse hippocampal homeostasis via the sirtuin1-FOXO1 pathway. *EXCLI J* 2017;16:340-353.
34. Jumnonpraknon P, Sivasinprasasn S, Govitrapong P, Tocharus C, **Tocharus J**. Activation of melatonin receptor (MT1/2) promotes P-gp transporter in methamphetamine-induced toxicity on primary rat brain microvascular endothelial cells. *Toxicol In Vitro* 2017;41: 42-48.
35. Tungkum W, Jumnonpraknon P, Tocharus C, Govitrapong P, **Tocharus J**. Melatonin suppresses methamphetamine-triggered endoplasmic reticulum stress in C6 cells glioma cell lines. *J Toxicol Sci* 2017;42: 63-71.
36. Chumboatong W, Thummayot S, Govitrapong P, Tocharus C, Jittiwat J, **Tocharus J**. Neuroprotection of agomelatine against cerebral ischemia/reperfusion injury through an antiapoptotic pathway in rat. *Neurochem Int* 2017;102:114-122.
37. Sivasinprasasn S, Pantan R, Thummayot S, **Tocharus J**, Suksamrarn A, Tocharus C. Cyanidin-3-glucoside attenuates angiotensin II-induced oxidative stress and inflammation in vascular endothelial cells. *Chem Biol Interact* 2016;260:67-74.
38. Thummayot S, Tocharus C, Suksamrarn A, **Tocharus J**. Neuroprotective effects of cyanidin against Ab-induced oxidative and ER stress in SK-N-SH cells. *Neurochem Int* 2016;101:15-21.
39. Pantan R, **Tocharus J**, Phatsara M, Suksamrarn A, Tocharus C. Synergistic effect of atorvastatin and cyanidin-3-glucoside against angiotensin II-mediated vascular smooth

- muscle cell proliferation and migration through MAPK and PI3K/Akt pathways. *Arch Pharm Res* 2016;
40. Jumnonprakhon P, Govitrapong P, Tocharus C, **Tocharus J**. Inhibitory effect of melatonin on cerebral endothelial cells dysfunction induced by methamphetamine via NADPH oxidase-2. *Brain Res* 2016;1650:84-92.
 41. Jumnonprakhon P, Govitrapong P, Tocharus C, **Tocharus J**. Melatonin promotes blood-brain barrier integrity in methamphetamine-induced inflammation in primary rat brain microvascular endothelial cells. *Brain Res* 2016;1646:182-192.
 42. Pantan R, **Tocharus J**, Suksamrarn A, Tocharus C. Synergistic effect of atorvastatin and cyanidin-3-glucoside on angiotensin II-induced inflammation in vascular smooth muscle cells. *Exp Cell Res* 2016;342: 104-112.
 43. Wicha P, **Tocharus J**, Nakaew A, Pantan R, Suksamrarn A, Tocharus C. Ethyl rosmarinate relaxes rat aorta by an endothelium-independent pathway. *Eur J Pharmacol* 2015;766: 9-15.
 44. Moohammadaree A, Changtam C, Wicha P, Suksamrarn A, **Tocharus J**, Tocharus C. Mechanisms of vasorelaxation induced by hexahydrocurcumin in isolated rat thoracic aorta. *Phytother Res* 2015;29: 1806-1813.
 45. Pinkaew D, Changtam C, Tocharus C, Govitrapong P, Jumnonprakhon P, Suksamrarn A, **Tocharus J**. Association of neuroprotective effect of Di-O-demethylcurcumin on A β _{25.35}-induced neurotoxicity with suppression of NF-kb and activation of Nrf2. *Neurotox Res* 2016;29: 80-91.
 46. Janyou A, Changtam C, Suksamrarn A, Tocharus C, **Tocharus J**. Suppression effects of O-demethylmethoxycurcumin on thapsigargin triggered on endoplasmic reticulum stress in SK-N-SH cells. *Neurotoxicology* 2015;50:92-100.
 47. Jumnonprakhon P, Govitrapong P, Tocharus C, Pinkaew D, **Tocharus J**. Melatonin protect methamphetamine-induced neuroinflammation through NF-kB and Nrf2 pathways in glioma cell line. *Neurochem Res* 2015;40:1448-1456.
 48. Hasan MZ, Ikawati M, **Tocharus J**, Kawaichi M, Oka C. Abnormal development of placenta in HtrA1-deficient mice. *Dev Biol* 2015;397:89-102.
 49. Pinkaew D, Changtam C, Tocharus C, Thummayot S, Suksamrarn A, **Tocharus J**. Di-O-demethylcurcumin protects SK-N-SH cells against mitochondrial and endoplasmic reticulum-mediated apoptotic cell death induced by A β _{25.35}. *Neurochem Int* 2015;80:110-119.
 50. Thummayot S, Tocharus C, Pinkaew D, Viwatpinyo K., Sringarm K, **Tocharus J**. Neuroprotective effect of purple rice extract and its constituent against amyloid beta-induced neuronal cell death in SK-N-SH cells. *Neurotoxicology*. 2014;45:149-158.

51. Pantan R, Onsa-Ard A, **Tocharus J**, Wonganan O, Suksamrarn A, Tocharus C. Endothelium-independent vasorelaxation effects of 16-O-acetyldihydroisosteviol on isolated rat thoracic aorta. *Life Sci* 2014;116(1):31-36.
52. Tocharus C, Puriboriboon Y, Junmanee T, **Tocharus J**, Ekthuwapranee K, Govitrapong P. Melatonin enhances adult rat hippocampal progenitor cell proliferation via ERK signaling pathway through melatonin receptor. *Neuroscience* 2014;275:314-21.
53. Onsa-Ard A, Shimbhu D, **Tocharus J**, Sutheerawattananonda M, Pantan R, Tocharus C. Hypotensive and vasorelaxant effects of sericin-derived oligopeptides in rats. *ISRN Pharmacol* 2013;717529.
54. Jumnonprakon P, Govitrapong P, Tocharus C, Tungkum W, **Tocharus J**. Protective effect of melatonin on Methamphetamine-induced apoptosis in glioma cell line. *Neurotox Res* 2014;25:286-294.
55. Srimuangwong K, Tocharus C, **Tocharus J**, Suksamrarn A, Chintana PY. Effects of hexahydrocurcumin in combination with 5-fluorouracil on dimethylhydrazine-induced colon cancer in rats. *World J Gastroenterol* 2012;18(47):6951-6959.
56. Srimuangwong K, Tocharus C, Yousungnoen Chintana P, Suksamrarn A, **Tocharus J**. Hexahydrocurcumin enhances inhibitory effect of 5-fluorouracil on HT-29 human colon cancer cells. *World J Gastroenterol* 2012;18(19):2383-2389.
57. **Tocharus J**, Jamsuwan S, Tocharus C, Changtam C, Suksamrarn A. Curcumin analogs inhibit nitric oxide production from LPS activated microglial cells. *J Nat Med* 2011;66(2):400-5.
58. Tocharus C, Sooksaen P, Shimbhu D, **Tocharus J**. *Butea superba* (Roxb.) improves penile erection in diabetic rats. *Andrologia* 2011;44:728-733.
59. **Tocharus J**, Khonthun C, Chongthammakun S, Govitrapong P. Melatonin attenuates methamphetamine-induced overexpression of pro-inflammatory cytokines in microglial cell lines. *J Pineal Res* 2010;48(4):347-352.
60. **Tocharus J**, Chongthammakun S, Govitrapong P. Melatonin inhibits amphetamine-induced nitric oxide synthase mRNA overexpression in microglial cell lines. *Neurosci Lett* 2008;439(2):134-137.
61. Tsuchiya A, Yano M, **Tocharus J**, Kojima H, Fukumoto M, Kawaichi M, Oka C. Expression of mouse HtrA1 serine protease in normal bone and cartilage and its upregulation in joint cartilage damaged by experimental arthritis. *Bone* 2005;37(3):323-336.
62. **Tocharus J**, Tsuchiya A, Kajikawa M, Ueta Y, Oka C, Kawaichi M. Developmentally regulated expression of mouse HtrA3 and its role as an inhibitor of TGF- β signaling. *Develop. Growth Differ* 2004;43:257-274.

CONFERENCE SHORT PAPERS AND ABSTRACTS

1. Teera Chanmanee, Piyarat Govitrapong, **Jiraporn Tocharus**, Ranida Quiggins, Kanokkan Bumroongkit, Chainarong Tocharus. Effect of Melatonin on adult rat hippocampal neurogenesis *in vitro*. The 34th Anatomy association of Thailand. 27-29 April 2011, Krabi, Thailand.
2. Atcharobon Thanyacharoen, Piyarat Govitrapong, Chainarong Tocharus, **Jiraporn Tocharus**. The effect of Transforming growth factor-beta1 (TGF- β 1) on viability of amphetamine treated microglial cell. The 2nd Science Research Conference. 9-10th March 2009, Naresuan University, Phitsanulok, Thailand.
3. Nongnuch Singhrang, Chainarong Tocharus, Apichart Suksamrarn, and **Jiraporn Tocharus**. Protective effects of curcuminoid analogs on β -amyloid peptide-induced neuronal cells death. The 5th Naresuan Research Conference. 28-29th July 2009. Naresuan University, Phitsanulok, Thailand.
4. Sataporn Jamsuwan, Chainarong Tocharus, Apichart Suksamrarn, Sukumal Chongthumakun, **Jiraporn Tocharus**. Curcumin analogs inhibit NO production from LPS activated HAPI microglial cells. The 9th National Grad Research Conference. 14-15th March 2008, Burapha University, Chonburi, Thailand.
5. Chankkapong Konthum, Chainarong Tocharus, Piyarat Govitrapong, **Jiraporn Tocharus**. The effect of methamphetamine on cytotoxic factor gene expression in microglial cells. The 9th National Grad Research Conference. 14-15th March 2008, Burapha University, Chonburi, Thailand.
6. Atcharobon Thanyacharoen, Piyarat Govitrapong, Chainarong Tocharus, **Jiraporn Tocharus**. The effect of Transforming growth factor-beta1 (TGF- β 1) on viability of amphetamine treated microglial cell. The 9th National Grad Research Conference. 14-15th March 2008, Burapha University, Chonburi, Thailand.
7. Nawaphat Jungphattananont, **Jiraporn Tocharus**, Apichart Suksamrarn, Watcharee Tiangyou. Effects of curcuminoid analogs on cadmium induced-apoptosis in human embryonic kidney cells (HEK 293). The 34th Anatomy association of Thailand. 27-29 April 2011, Krabi, Thailand. The 34th Anatomy association of Thailand. 27-29 April 2011, Krabi, Thailand.
8. Chontida Puedsing, **Jiraporn Tocharus**, Sukanya Horpaopan, Arampa Ruchiratantiangkoor, Chainarong Tocharus. The effect of kaempferia parviflora on penile erection in rats.

9. Pornchai Sooksaen, **Jiraporn Tocharus** and Chainarong Tocharus. Protective effects of *Butea superba* (Roxb.) on cavernosal smooth muscle of streptozotocin-induced diabetic rats. The 3rd International Conference on Forensic Science and Medical Science. Naresuan University. 28-29 July, 2008.
10. Chakkraphong Khonthun, Piyarat Govitrapong, Chainarong Tocharus, **Jiraporn Tocharus**. Inhibitory effect of melatonin on the expression of cytotoxic factor genes in methamphetamine-induced HAPI microglia. The 3rd International Conference on Forensic Science and Medical Science. Naresuan University. 28-29 July, 2008.
11. Nongnuch Singhrang, Chainarong Tocharus, Apichart Suksamrarn, Sukumal Chongthammakun and **Jiraporn Tocharus**. The 3rd International Conference on Forensic Science and Medical Science. Naresuan University. 28-29 July, 2008
12. Sataporn Chamsuwan, Chainarong Tocharus, Apichart Suksamrarn, Sukumal Chongthammakun and **Jiraporn Tocharus**. Protective effect of curcumin and its analogs on amyloid peptide₂₅₋₃₅ mediated microglial cells death. The 3rd International Conference on Forensic Science and Medical Science. Naresuan University. 28-29 July, 2008.
13. Khanitta Sriramaungwong , Chainarong Tocharus, Pornphorm Chintana, **Jiraporn Tocharus**. Anti-colon carcinogenesis of curcumin analogs *in vitro*. 4th Naresuan Research Conference. 28-29 July, 2008.

RESEARCH FIELDS OF INTEREST

1. Neurodegenerative diseases