

## 研究開発部門

Department of Research and Development

## 国際共同研究分野

Division of International Cooperative Research

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## ◆研究目的及び概要

目覚ましい発展を遂げた現代西洋医学においても治療に難渋する疾患が多く、天然物を活用した伝統医学に関する研究成果や臨床効果に期待が寄せられている。伝統医学に関わる研究を高い水準で維持・発展させるためには、最新の研究方法論や天然物に関する情報交換が必要である。和漢医薬学総合研究所は天然物の研究を発展させるために、3カ国・4機関との間に国際協力拠点（ICC）を形成するとともに、8カ国・15機関と部局間協定を締結している。

国際共同研究分野は、各国の大学及び研究機関の研究者と連携して、伝統医学と現代医学を融合した国際共同研究を促進することを目的に、(1) タイ・チュラロンコン大学薬学部や中国・北京大学医学部薬学院との国際協力拠点を通じた国際共同研究の推進、(2) 大学間や部局間協定締結機関とのジョイントシンポジウム、学生交流を通じた国際共同研究の維持・発展を図っている。

## ◆原著論文

- 1) Duan KF, Zang XY, Shang MY, Zhang W, Xie BB, Wang L, Xu F, Cai SQ. Non-ephedrine constituents from the herbaceous stems of *Ephedra sinica*. *Fitoterapia*. 2021 Sep;153:104998. doi: 10.1016/j.fitote.2021.104998.
- 2) Wang CQ, Yi LW, Zhao L, Zhou YZ, Guo F, Huo YS, Zhao DQ, Xu F, Wang X, Cai SQ. 177 Saponins, Including 11 New Compounds in Wild Ginseng Tentatively Identified via HPLC-IT-TOF-MS<sup>n</sup>, and Differences among Wild Ginseng, Ginseng under Forest, and Cultivated Ginseng. *Molecules*. 2021 Jun 2;26(11):3371. doi: 10.3390/molecules26113371.
- 3) Patikorn C, Taychakhoonavudh S, Sakulbumrungsil R, Ross-Degnan D, Anantachoti P. Financing Strategies to Facilitate Access to High-Cost Anticancer Drugs: A Systematic Review of the Literature. *Int J Health Policy Manag*. 2021 Sep 22. doi: 10.34172/ijhpm.2021.138.
- 4) Fahmy SA, Issa MY, Saleh BM, Meselhy MR, Azzazy HME. *Peganum harmala* Alkaloids Self-Assembled Supramolecular Nanocapsules with Enhanced Antioxidant and Cytotoxic Activities. *ACS Omega*. 2021 Apr 27;6(18):11954-11963. doi:10.1021/acsomega.1c00455.
- 5) Azzazy HME, Fahmy SA, Mahdy NK, Meselhy MR, Bakowsky U. Chitosan-Coated PLGA Nanoparticles Loaded with *Peganum harmala* Alkaloids with Promising Antibacterial and Wound Healing Activities. *Nanomaterials (Basel)*. 2021 Sep 18;11(9):2438. doi: 10.3390/nano11092438.
- 6) Abdellatif AA, Zhou Y, Yamada A, Elmekawy SA, Kohyama A, Yokoyama S, Meselhy MR, Matsuya Y, Sakurai H, Hayakawa Y. Synthetic E-guggulsterone derivative GSD-1 inhibits NF- $\kappa$ B signaling and suppresses the metastatic potential of breast cancer cells. *Biomed Pharmacother*. 2021 Aug;140:111737. doi:10.1016/j.biopha.2021.111737.
- 7) Rasheed DM, Emad AM, Ali SF, Ali SS, Farag MA, Meselhy MR, Sattar EA. UPLC-PDA-ESI/MS

- metabolic profiling of dill shoots bioactive fraction; evidence of its antioxidant and hepatoprotective effects in vitro and in vivo. *J Food Biochem.* 2021 Jun;45(6):e13741. doi: 10.1111/jfbc.13741.
- 8) Madi YF, Choucry MA, Meselhy MR, El-Kashoury EA. Essential oil of *Cymbopogon citratus* cultivated in Egypt: seasonal variation in chemical composition and anticholinesterase activity. *Nat Prod Res.* 2021 Nov;35(21):4063-4067. doi: 10.1080/14786419.2020.1713125.
  - 9) El-Mekkawy S, Hassan AZ, Abdelhafez MA, Mahmoud K, Mahrous KF, Meselhy MR, Sendker J, Abdel-Sattar E. Cytotoxicity, genotoxicity, and gene expression changes induced by methanolic extract of *Moringa stenopetala* leaf with LC-qTOF-MS metabolic profile. *Toxicon.* 2021 Nov;203:40-50. doi:10.1016/j.toxicon.2021.09.025.
  - 10) Kohyama A, Kim MJ, Yokoyama R, Sun S, Omar AM, Phan ND, Meselhy MR, Tsuge K, Awale S, Matsuya Y. Structure-activity relationship and mechanistic study on guggulsterone derivatives; Discovery of new anti-pancreatic cancer candidate. *Bioorg Med Chem.* 2021 Dec 11;54:116563. doi: 10.1016/j.bmc.2021.116563.
  - 11) Hirasawa Y, Tanaka T, Hirasawa S, Wong CP, Uchiyama N, Kaneda T, Goda Y, Morita H. Cliniatines A-C, new Amaryllidaceae alkaloids from *Clivia miniata*, inhibiting Acetylcholinesterase. *J Nat Med.* 2022 Jan;76(1):171-177. doi:10.1007/s11418-021-01570-6.
  - 12) Yoshioka T, Itagaki Y, Abe Y, Kawahara N, Goda Y, Ozeki Y, Yamada A. NaCl dependent production of coniferin in *Alluaudiopsis marnieriana* suspension cultured cells. *Plant Biotechnol (Tokyo).* 2021 Mar 25;38(1):183-186. doi:10.5511/plantbiotechnology.21.0102a.
  - 13) Uchiyama N, Hosoe J, Sugimoto N, Ishizuki K, Koide T, Murabayashi M, Miyashita N, Kobayashi K, Fujimine Y, Yokose T, Ofuji K, Shimizu H, Hasebe T, Asai Y, Ena E, Kikuchi J, Kiyota K, Fujita K, Makino Y, Yasobu N, Iwamoto Y, Miura T, Mizui K, Asakura K, Suematsu T, Muto H, Kohama A, Goto T, Yasuda M, Ueda T, Goda Y. Purity Determination of Cyclophosphamide Hydrate by Quantitative <sup>31</sup>P-NMR and Method Validation. *Chem Pharm Bull (Tokyo).* 2021 Jul 1;69(7):630-638. doi: 10.1248/cpb.c21-00109.
  - 14) Maniwa A, Tsuji G, Ito T, Uchiyama N, Hosoe J, Ohtsuki T, Matsufuji H, Demizu Y, Goda Y. [Changes in Test Methods for Internationalization in the Japanese Pharmacopoeia (Part 1): Establishment of a Quantitative Test Method for Clonidine Hydrochloride Using HPLC Analysis]. *Yakugaku Zasshi.* 2021;141(4):591-598. Japanese. doi: 10.1248/yakushi.20-00237.
  - 15) Maniwa A, Tsuji G, Ito T, Uchiyama N, Hosoe J, Ohtsuki T, Matsufuji H, Demizu Y, Goda Y. [Changes in Test Methods for Internationalization in the Japanese Pharmacopoeia (Part 2): Establishment of a Quantitative Method for Lorazepam Using HPLC Analysis]. *Yakugaku Zasshi.* 2021;141(7):961-970. Japanese. doi:10.1248/yakushi.21-00010.
  - 16) Tanaka S, Uchiyama N, Goda T, Iida T, Horie S, Masada S, Arai R, Yamamoto E, Hakamatsuka T, Okuda H, Goda Y. A simple and rapid method to simultaneously analyze ciclesonide and its impurities in a ciclesonide metered-dose inhaler using on-line supercritical fluid extraction/supercritical fluid chromatography/quadrupole time-of-flight mass spectrometry. *J Pharm Biomed Anal.* 2021 Sep 10;204:114253. doi: 10.1016/j.jpba.2021.114253.
  - 17) Zhou T, Hirayama Y, Tsunematsu Y, Suzuki N, Tanaka S, Uchiyama N, Goda Y, Yoshikawa Y, Iwashita Y, Sato M, Miyoshi N, Mutoh M, Ishikawa H, Sugimura H, Wakabayashi K, Watanabe K. Isolation of New Colibactin Metabolites from Wild-Type *Escherichia coli* and *In Situ* Trapping of a Mature Colibactin Derivative. *J Am Chem Soc.* 2021 Apr 14;143(14):5526-5533. doi:10.1021/jacs.1c01495.
  - 18) Yamamoto E, Takeda Y, Ando D, Koide T, Amano Y, Miyazaki S, Miyazaki T, Izutsu KI, Kanazawa H, Goda Y. Discrimination of ranitidine hydrochloride crystals using X-ray micro-computed tomography for the evaluation of three-dimensional spatial distribution in solid dosage forms. *Int J Pharm.* 2021 Aug 10;605:120834. doi: 10.1016/j.ijpharm.2021.120834.
  - 19) Yokoo H, Yamamoto E, Masada S, Uchiyama N, Tsuji G, Hakamatsuka T, Demizu Y, Izutsu KI,

- Goda Y. N-Nitrosodimethylamine (NDMA) Formation from Ranitidine Impurities: Possible Root Causes of the Presence of NDMA in Ranitidine Hydrochloride. *Chem Pharm Bull (Tokyo)*. 2021;69(9):872-876. doi:10.1248/cpb.c21-00289.
- 20) Masada S, Hosoe J, Arai R, Demizu Y, Hakamatsuka T, Goda Y, Uchiyama N. Miroestrol Quantification in *Pueraria mirifica* Crude Drugs and Products by Single-Reference UPLC/PDA/MS Using Relative Molar Sensitivities to Kwakhurin. *Chem Pharm Bull (Tokyo)*. 2021 Jun 1;69(6):573-580. doi: 10.1248/cpb.c21-00160.
  - 21) Miyazaki T, Aso Y, Goda Y. [Detection and Analysis of Drug Crystals in Medical Transdermal Patches by Using X-ray Diffraction Measurement]. *Yakugaku Zasshi*. 2022 Jan 1;142(1):65-74. Japanese. doi: 10.1248/yakushi.21-00160.
  - 22) Tsuji G, Uchiyama N, Goda Y, Demizu Y. Study on the elimination of harmful reagents on the testing methods in the Japanese Pharmacopoeia III. *Pharmaceutical and Medical Device Regulatory Science*. 2021; 52: 496-510.
  - 23) Takahashi H, Yang J, Yamamoto H, Fukuda S, Arakawa K. Complete Genome Sequence of *Adlercreutzia equolifaciens* subsp. *celatus* DSM 18785. *Microbiol Resour Announc*. 2021 May 13;10(19):e00354-21. doi:10.1128/MRA.00354-21.
  - 24) Watanabe Y, Takeuchi N, Yang J, Obana N, Morinaga K, Kusada H, Tamaki H, Fukuda S, Arakawa K. Complete Genome Sequence of *Atopobiaceae* Bacterium Strain P1, Isolated from Mouse Feces. *Microbiol Resour Announc*. 2021 Jul 15;10(28):e0062721. doi: 10.1128/MRA.00627-21.
  - 25) Sato S, Shimizu E, He J, Ogawa M, Asai K, Yazu H, Rusch R, Yamane M, Yang F, Fukuda S, Kawakami Y, Tsubota K, Ogawa Y. Positive Effects of Oral Antibiotic Administration in Murine Chronic Graft-Versus-Host Disease. *Int J Mol Sci*. 2021 Apr 3;22(7):3745. doi: 10.3390/ijms22073745.
  - 26) Nakamura A, Kurihara S, Takahashi D, Ohashi W, Nakamura Y, Kimura S, Onuki M, Kume A, Sasazawa Y, Furusawa Y, Obata Y, Fukuda S, Saiki S, Matsumoto M, Hase K. Symbiotic polyamine metabolism regulates epithelial proliferation and macrophage differentiation in the colon. *Nat Commun*. 2021 Apr 8;12(1):2105. doi:10.1038/s41467-021-22212-1.
  - 27) Kurokawa S, Tomizawa Y, Miyaho K, Ishii D, Takamiya A, Ishii C, Sanada K, Fukuda S, Mimura M, Kishimoto T. Fecal Microbial and Metabolomic Change during treatment course for depression: An Observational Study. *J Psychiatr Res*. 2021 Aug;140:45-52. doi: 10.1016/j.jpsychires.2021.05.009.
  - 28) Nishimoto Y, Nomaguchi T, Mori Y, Ito M, Nakamura Y, Fujishima M, Murakami S, Yamada T, Fukuda S. The Nutritional Efficacy of *Chlorella* Supplementation Depends on the Individual Gut Environment: A Randomised Control Study. *Front Nutr*. 2021 May 31;8:648073. doi: 10.3389/fnut.2021.648073.
  - 29) Ejima R, Akiyama M, Sato H, Tomioka S, Yakabe K, Kimizuka T, Seki N, Fujimura Y, Hirayama A, Fukuda S, Hase K, Kim YG. Seaweed Dietary Fiber Sodium Alginate Suppresses the Migration of Colonic Inflammatory Monocytes and Diet-Induced Metabolic Syndrome via the Gut Microbiota. *Nutrients*. 2021 Aug 16;13(8):2812. doi: 10.3390/nu13082812.
  - 30) Takahashi H, Yang J, Yamamoto H, Fukuda S, Arakawa K. Correction for Takahashi et al., "Complete Genome Sequence of *Adlercreutzia equolifaciens* subsp. *celatus* JCM 14811<sup>T</sup>". *Microbiol Resour Announc*. 2021 Jun 3;10(22):e0050721. doi: 10.1128/MRA.00507-21.
  - 31) Furusawa C, Tanabe K, Ishii C, Kagata N, Tomita M, Fukuda S. Decoding gut microbiota by imaging analysis of fecal samples. *iScience*. 2021 Nov 22;24(12):103481. doi: 10.1016/j.isci.2021.103481.
  - 32) Yokoyama Y, Shinohara K, Kitamura N, Nakamura A, Onoue A, Tanaka K, Hirayama A, Aw W, Nakamura S, Ogawa Y, Fukuda S, Tsubota K, Watanabe M. Metabolic Effects of Bee Larva-

- Derived Protein in Mice: Assessment of an Alternative Protein Source. *Foods*. 2021 Nov 1;10(11):2642. doi: 10.3390/foods10112642.
- 33) Connell S, Kawashima M, Nakamura S, Imada T, Yamamoto H, Tsubota K, Fukuda S. Lactoferrin Ameliorates Dry Eye Disease Potentially through Enhancement of Short-Chain Fatty Acid Production by Gut Microbiota in Mice. *Int J Mol Sci*. 2021 Nov 17;22(22):12384. doi: 10.3390/ijms222212384.
- 34) Yang Y, Kumrungsee T, Kato N, Fukuda S, Kuroda M, Yamaguchi S. Supplemental *Aspergillus* lipase and protease preparations display powerful bifidogenic effects and modulate the gut microbiota community of rats. *Fermentation*. 2021; 7(4), 294. doi:<https://doi.org/10.3390/fermentation7040294>.
- 35) Suzuki K, Nakaoka S, Fukuda S, Masuya H. Energy landscape analysis elucidates the multistability of ecological communities across environmental gradients *Ecol. Monogr*. 2021;91, e01469. doi:<https://doi.org/10.1002/ecm.1469>.
- 36) Maruyama Y, Nishimoto Y, Umezawa K, Kawamata R, Ichiba Y, Tsutsumi K, Kimura M, Murakami S, Kakizawa Y, Kumagai T, Yamada T, Fukuda S. Comparison of oral metabolome profiles of stimulated saliva, unstimulated saliva, and mouth-rinsed water. *Sci Rep*. 2022 Jan 13;12(1):689. doi: 10.1038/s41598-021-04612-x.
- 37) Nihei KI, Peigneur S, Tytgat J, Lange AB, Konno K. Isolation and characterization of FMRFamide-like peptides in the venoms of solitary sphecid wasps. *Peptides*. 2021 Aug;142:170575. doi: 10.1016/j.peptides.2021.170575.
- 38) Kanehara R, Tonouchi A, Konno K, Hashimoto M. Cyclohumulanoid Sesquiterpenes from the Culture Broth of the Basidiomycetous Fungus *Daedaleopsis tricolor*. *Molecules*. 2021 Jul 19;26(14):4364. doi:10.3390/molecules26144364.
- 39) Alberto-Silva C, Portaro FCV, Kodama RT, Pantaleão HQ, Rangel M, Nihei KI, Konno K. Novel neuroprotective peptides in the venom of the solitary scoliid wasp *Scolia decorata ventralis*. *J Venom Anim Toxins Incl Trop Dis*. 2021 Jun 11;27:e20200171. doi: 10.1590/1678-9199-JVATITD-2020-0171.
- 40) Alberto-Silva C, Vieira Portaro FC, Kodama RT, Pantaleão HQ, Inagaki H, Nihei KI, Konno K. Comprehensive Analysis and Biological Characterization of Venom Components from Solitary Scoliid Wasp *Campsomeriella annulata annulata*. *Toxins (Basel)*. 2021 Dec 10;13(12):885. doi: 10.3390/toxins13120885.