化学応用部門

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本部門では，化学的手法を応用する和漢薬の基礎研究として，天然薬物を中心とする生理活性分子の医薬化学的及び生物有機化学的研究を行っている。即ち，天然薬物の成分単離，構造解析，合成等の，和漢薬成分に関する化学的研究を行う。さらに，その過程で構造が明らかとなる天然薬物成分について，その構造・活性相関，構造・機能相関の化学的解明に取り組んでいる。

本年度の主な研究課題は下記の通りである。

Ⅰ．天然薬物成分の単離，構造解析，合成，作用

1）升麻，人参，丹参等の和漢生薬
2）インドネシア，スリランカ，ネパール等の薬用植物
3）麝香から単離した新規成分ムスクライド類の合成及び誘導体化
4）肝臓病や骨粗鬆症に有効な天然薬物成分の開発研究

Ⅱ．薬物・生体高分子相互作用系の生物有機化学

1）構造・機能相関解析に有用な独自の化学的手法の開発
2）イオンチャンネル，レセプター，酵素等の機能性生体高分子の構造生物学

上記の研究課題によって得られた本年度の成果（原著及び学会報告）は下記の通りである。

◇　原　　著

Ⅰ．天然薬物成分の単離，構造解析，合成，作用

1）和漢生薬の化学的解明

1）Study on the Baths with Crude Drug. III. The Effect of Ligustici Chuanxiong Rhizoma Extract on the Percutaneous Absorption of Some Natural Compounds

Sekiya K., Kadota S., Katayama K., Koizumi T., Namba T., *Biol. Pharm. Bull.*, 20, 983–987 (1997).

To investigate the permeability of natural compounds through hairless mouse skin, compounds having a range of lipophilicity, *i.e.*, ginsenoside-Re (**1**), baicalin (**2**), glycyrrhizin (**3**), baicalein (**4**), wogonin (**5**), honokiol (**6**), magnolol (**7**), bergapten (**8**), shikonin (**9**) and sinomenine (**10**) were used. These compounds permeated through the skin a little, however, they were generally accumulated into the skin. The uptake amount into the skin of each compound related to their lipophilicities in the *in vitro* experiment. Furthermore, Ligustici Chuanxiong Rhizoma (Senkyu) ether extract (SEE) enhanced their permeability into the skin; especially, it exhibited an effect on the skin permeability of moderately lipophilic compounds such as **4**, **8**. The effect of SEE *in vivo* was similar to that obtained in the *in vitro* experiment. From these results, it was clarified that natural compounds having high lipophilicity sufficiently permeated into the hairless mouse skin owing to their accumulative property, and SEE enhanced the permeability of the moderately lipophilic compounds into the skin.

2) **Aldose Reductase Inhibitory Constituents of the Root of *Salvia miltiorhiza* BUNGE**
Tezuka Y., Kasimu R., Basnet P., Namba T., Kadota S., *Chem. Pharm. Bull.*, 45, 1306-1311 (1997).

The constituents of the MeOH extract of *Salvia miltiorhiza* BUNGE, which showed strong aldose reductase (AR) inhibitory activity, were examined, and two new abietane-type diterpenoids, danshenol A (**1**) and danshenol B (**2**), were isolated together with six known ones: dihydrotanshinone I (**3**), cryptotanshinone (**4**), tanshinone I (**5**), tanshinone IIA (**6**), (-)-danshexinkun A (**7**), and sugiol (**8**). Among them, **4**, **5**, and 8 were weak AR inhibitors with IC_{50} from 4.80 to >10.0 μM, while **1**, **2**, **3**, **6**, and **7** were strong inhibitors (IC_{50} from 0.10 to 1.75 μM). Danshenol A (**1**), the strongest inhibitor, had IC_{50} of 0.10 μM which is comparable to that of epalrestat in clinical use. Moreóver, from a consideration of IC_{50} and yield of each compound, it was concluded that tanshinone IIA (**6**) is the major active constituent of the MeOH extract and danshenol A (**1**) and (-)-danshexinkun A (**7**) are the minor ones.

3) **Six Novel Diarylheptanoids Bearing Chalcone or Flavanone Moiety from the Seeds of *Alpinia blepharocalyx***
Prasain J.K., Tezuka Y., Li J.-X., Tanaka K., Basnet P., Dong H., Namba T., Kadota S., *Tetrahedron*, 53, 7833-7842 (1997).

Six novel diarylheptanoids bearing chalcone or flavanone moiety (**1-6**) were isolated from the seeds of *Alpinia blepharocalyx* K. Schum. Their structures were determined by spectroscopic analysis. Stereo-chemical assignment of diarylheptanoid part of these compounds was done by NMR spectral analysis of their MTPA esters. These compounds inhibited nitric oxide (NO) production in endotoxin-activated murine macrophages, J774.1.

4) **Danshenols A and B, New Aldose Reductase Inhibitors from the Root of *Salvia miltiorhiza* BUNGE**
Kasimu R., Basnet P., Tezuka Y., Kadota S., Namba T., *Chem. Pharm. Bull.*, 45, 564-566 (1997).

Two new abietane-type diterpenoids, danshenols A (**1**) and B (**2**), were isolated from an MeOH extract of *Salvia miltiorhiza* BUNGE, and their structures determined by chemical and spectroscopic methods including the 2D NMR technique. Danshenol A (**1**) showed strong inhibitory activity against aldose reductase isolated from the eye lens of rats.

5) **15-Hydroxyacorenone: New Acorane-Type Sesquiterpene from the Culture Broth of the Mycoparasitic Fungus *Trichoderma harzianum***
Tezuka Y., Tasaki M., Huang Q., Hatanaka Y., Kikuchi T., *Liebigs Ann.*, 2579-2580 (1997).

A new acorane-type sesquiterpene, 15-hydroxyacorenone, has been isolated from the culture broth of *Trichoderma harzianum*, which in turn was isolated from the fruiting body of a medicinal mushroom, *Ganoderma lucidum* (FR.) Karst. (the oriental crude drug "Lin-Chi"). The structure of 15-hydroxyacorenone was determined by spectroscopic methods to be (1*S*,4*S*,5*S*)-8-hydroxymethyl-1-isopropyl-4-methylspiro[4.5]dec-8-en-7-one (**1**).

2) インドネシア，スリランカ，ネパール等の薬用植物

1) **A comparative Study on Swertiae Herba from Japan, Nepal, and China and Their Hypoglycemic Activities in Streptozotocin (STZ)-Induced Diabetic Rats**
Komatsu K., Basnet B., Yamaji S., Kadota S., Namba T., *Natural Medicines*, 51, 265-268 (1997).

Four commercial ethno-medicines, "Senburi" from Japan, "Chirayta" from Nepal, and "Zanyinchen" (two samples) from China were identified morphologically to be the whole plants in flowering season of *Swertia japonica, S. chirayta* mixed up with small amounts of *S. alata,* and *S. mussotii* (one sample contained a trace amount of *S. cincta*), respectively. These crude drugs were extracted with 70 % ethanol and these extracts were studied for the comparative hypoglycemic activities in the streptozotocin (STZ)-induced diabetic rats. "Semburi" and "Chirayta" significantly decreased the blood glucose level of STZ-induced diabetic rats, "Semburi" being the more active of the two.

3) 麝香から単離した新規成分ムスクライド類の合成及び誘導体化

1) Synthesis and Structure Revision of Musclides-A2 and -B

Tezuka Y., Kudoh M., Hatanaka Y., Kadota S., Kikuchi T., *Nat. Prod. Lett.*, 9, 297-304 (1997).

(4*R*)-Musclide-A2 and (2*R*,5*R*)- and (2*S*,5*R*)-musclide-B were synthesized from L-leucine and their enantiomers from D-leucine. Comparisons of spectral and $[\alpha]_D$ data of synthetic and natural musclides indicated that the absolute configuration at C-4 of natural musclide-A2 and that at C-5 of natural musclide-B should be 4S. Thus, the structures of natural musclides-A2 and -B are revised to (4*S*)-1-hydroxy-6-methylhept-4-yl hydrogen sulfate and (2*R*,5*S*)-2-hydroxy-7-methyloct-5-yl hydrogen sulfate, respectively.

4) 肝臓病や骨粗鬆症に有効な天然薬物成分の開発研究

1) Hepatoprotective Effect of *Hovenia dulcis* THUNB. on Experimental Liver Injuries Induced by Carbon Terachloride or D-Galactosamine/Lipopolysaccharide

Hase K., Ohsugi M., Xiong Q., Basnet P., Kadota S., Namba T., *Biol. Pharm. Bull.*, 20, 381-385 (1997).

The hepatoprotective effects of the fruits of *Hovenia dulcis* THUNB. on chemically or immunologically induced experimental liver injury models were examined. The methanol extract showed significant hepatoprotective activity against CCl_4-toxicity in rats and D-galactosamine (D-GalN)/lipopolysaccharide-induced liver injury in mice. The methanol extract also significantly protected against CCl_4-toxicity in primary cultured rat hepatocytes. Hepatoprotective activity-guided fractionation and chemical analysis led to the isolation of an active constituent, (+)-ampelopsin (**1**) from the methanol extract.

2) Effect of *Hovenia dulcis* on lipopolysaccharide-induced liver injury in chronic alcohol-fed rats

Hase K., Basnet P., Kadota S., Namba T., *J. Trad. Med.*, 14, 28-33 (1997).

The hepatoprotective effect of the H_2O and MeOH extracts from the fruits of *Hovenia dulcis* THUNB. was examined on endotoxin (lipopolysaccharide; LPS)-induced hepatotoxicity in chronic ethanol-fed rat. Rats were injected with LPS after feeding ethanol (36 % of total calories) diet for 4 weeks. The H_2O extract of *H. dulcis* significantly inhibited the elevation of serum ALT and AST levels by LPS challenge after chronic ethanol consumption. In addition, the H_2O extract suppressed the accumulation of triglyceride (TG), total cholesterol (t-CHOL) and malondialdehyde (MDA) in rat liver.

3) Effects of Cimicifugae rhizoma on serum calcium and phosphate levels in low calcium dietary rats and on bone mineral density in ovariectomized rats

Li J.-X., Kadota S., Li H.-Y., Miyahara T., Wu Y.-W., Seto H., Namba T., *Phytomedicine*, 3, 379-385 (1997).

We studied the effects of ethyl acetate-(EtOAc) soluble fractions from methanol (MeOH) extracts of Cimicifugae rhizoma derived from two species— *Cimicifuga heracleifolia* Komarov and *C. foetida* L. — and four triterpenoids (**1**-**4**) isolated from them on the serum calcium (Ca) and phosphate (P) levels in low-Ca dietary rats. The EtOAc-soluble fraction from *C. heracleifolia* Komarov (HE) significantly decreased Ca levels when administered. Similarly, the EtOAc-soluble fraction from *C. foetida* L. (FE) significantly lowered serum Ca levels at doses of 100 and 200 mg/kg/day, while the four triterpenoids (**1**-**4**) did the same at a dose of 25 mg/kg/day. Interestingly only 7,8-didehydro-24-*O*-acetylhydroshengmanol-3-*O*-β-xyloside (**4**) showed a significant influence on serum P levels. The effects of HE and FE on the bone mineral density (BMD) of the lumbar spine (L 2-4) in ovariectomized rats were measured by dual energy X-ray absorptiometry (DXA). Rats treated with HE and FE showed a significant increase in BMD compared to untreated ovariectomized rats. BMD was lower in the latter than in sham-operated rats.

4) Immunostimulating Activity of Celosian, an Antiheptatoxic Polysaccharide Isolated from *Celosia argentea*

Hase K., Basnet P., Kadota S., Namba T., *Planta Med.*, 63, 216-219 (1997).

Celosian, an acidic polysaccharide from the seeds of *Celosia argentea* (Amaranthaceae) was found to be a potent antihepatotoxic agent for chemical and immunological liver injury models in animals. The immunomodulating action of celosian was studied to clarify the preventive mechanism of celosian on liver injuries. Celosian induced tumor necrosis factor-α (TNF-α) production in mice. Celosian also induced the production of interleukin-1β (IL-1β) and nitric oxide (NO) in macrophage cell line J774.1 in a concentration-dependent manner (1 to 1000 μg/ml). Moreover, celosian induced IL-1β secretion in human mononuclear cells. In addition, celosian enhanced gamma interferon (IFN-γ) production activity of concanavalin A (Con A) in mice spleen cells, though celosian alone did not significantly influence IFN-γ production. These results indicate that celosian is an immunostimulating agent in addition to antihepatotoxic effects.

5) **Hepatoprotective Principles of *Swertia japonica* MAKINO on D-Galactosamine/Lipopolysaccharide-Induced Liver Injury in Mice**
Hase K., Li J., Basnet P., Xiong Q., Takamura S., Namba T., Kadota S., *Chem. Pharm. Bull.*, 45, 1823-1827 (1997).

The *n*-BuOH extract of *Swertia japonica* showed a significant hepatoprotective effect on D-galactosamine (D-GalN)/lipopolysaccharide (LPS)-induced liver injury in mice. The activity-guided fractionation led to the isolation of a new tetrahydroxanthone derivative, tetrahydroswertianolin (**1**), as well as two known iridoids, gentiopicroside (**2**) and sweroside (**3**). Their structures were elucidated by spectroscopic methods and chemical reactions. Of the three compounds, **2** and **3** possesed mild hepatoprotective activity at a dose range of 25-50 mg/kg, whereas, **1** exhibited potent activity in a dose-dependent manner. The hepatoprotective effect of tetrahydroswertianolin (**1**) was stronger than that of glycyrrhizin which was used as a positive control.

II. 薬物・生体高分子相互作用系の生物有機化学

1) 構造・機能相関解析に有用な独自の化学的手法の開発

1) **A Versatile Approach for Functionalization of 3-Aryl-3-trifluoromethyldiazirine Photophor**
Hashimoto M., Kanaoka Y., Hatanaka Y., *Heterocycles*, 46, 119-122 (1997).

We introduce here a novel and simple method for the carbonylation of (alkoxyphenyl)diazirine. 3-(3-Methoxyphenyl)-3-trifluoromethyldiazirine was found to be stable under a typical Friedel-Crafts reaction producing carboxaldehyde derivatives of methoxyphenyldiazirine. The formyl group was easily converted to carboxylic acid, olefin, alcohol, or benzyl bromide providing new derivatives of diazirine photophor in the field of photoaffinity labeling.

2) イオンチャンネル，レセプター，酵素等の機能性生体高分子の構造生物学

1) **Novel Photoreactive Carbohydrate Probes for Photoaffinity Biotinylation**
Hatanaka Y., *Glycoconjugate J.*, 14, S122 (1997).

Photochemical biotinylation with a photoreactive carbene-generating *N*-acetylglucosamine derivative BDGA was investigated for the analysis of acceptor binding-site of β1,4-galactsyltransferase (GalT). Combined use of the photoprobe BDGA with an immobilized avidin was found to be effective for the purification of photolabeled GalT from a mixture containing a large amount of unlabeled GalT protein. An efficient approach combining with the selective retrieval of labeled GalT and chemiluminescent detection based on avidin-biotin complex led us to the identification of photolabeled GalT fragments. The results clearly demonstrate that the biotinylation using BDGA could provide efficient methods for the structural analysis of GalT acceptor binding-site.

2) **Photocrosslinking as an Approach to Structural Biology : Structural Analysis of β1,4-Galactosyltransferase**
Hatanaka Y., Hashimoto M., Kanaoka Y., *Photomedicine and Photobiology*, 19, 83-84 (1997).

A novel photochemical crosslinking reagent, *N*-

[2-[2-[2-(2-biotinylaminoethoxy)ethoxy]ethoxy]-4-[3-(trifluoromethyl)-3*H*-diazirin-3-yl]-benzoyl]-*N*4-[2-(acetylamino)-2-deoxy-β-D-glucopyranosyl]-L-aspartamide (BDGA), was applied for the analysis of acceptor binding-site within β1,4-galactosyltransferase (GalT). Using this carbene-generating *N*-acetylglucosamine derivative, a biotin tag was specifically introduced at the acceptor substrate binding-site of GalT. The biotin tag photochemically attached on GalT protein harness the power of avidin-biotin technology for the high-sensitive detection and one-step purification of photolabeled GalT protein. Thus, we have examined an efficient strategy for the localization of photolabeled site by using a chemiluminescent technique for the radioisotope free detection trace amount of labeled products and an immobilized avidin for the selective retrieval of biotinylated components. Our approach successfully identified photolabeled fragments corresponding to the GalT acceptor substrate region where is no predictable sequence from the homology search. The results clearly demonstrate that the biotinylation using BDGA could provide efficient methods for the structural biology of glycosyltransferases which shares no significant sequential homology or is difficult to crystallize.

Ⅲ. その他の原著論文

1) **Effect of Japanese Angelica Roots Extract on Pentobarbital-Induced Sleep in Group-Housed and Socially Isolated Mice: Evidence for the Central Action**
Matsumoto K., Kohono S., Tezuka Y., Kadota S., Watanabe H., *Jpn. J. Pharmacol.*, 73, 353-356 (1997).

2) **Studies on the Constituents of *Scutellaria* Species. XVIII. Structures of Neoclerodane-Type Diterpenoids from the Whole Herb of *Scutellaria rivularis* WALL.**
Kizu H., Imoto Y., Tomimori T., Kikuchi T., Kadota S., Tsubono K., *Chem. Pharm. Bull.*, 45, 152-160 (1997).

3) **Antibacterial Activity of Trichorabdal A from *Rabdosia trichocarpa* Against *Helicobacter pylori***
Kadota S., Basnet P., Ishii E., Tamura T., Namba T., *Zbl. Bakt.*, 286, 63-67 (1997).

4) **Antibacterial Activity of Lupulone from Hop (Female Inflorescence of *Humulus lupulus* L.) against *Helicobacter pylori***
Namba T., Kadota S., Ohsugi M., Ishii E., Tamura T., *臨床消化器内科*, 12, 1189-1194 (1997).

5) ***In Vitro* and *In Vivo* Studies on Anti-Lipid Peroxidation Effect of Extract from Luobuma Leaves**
Yokozawa T., Dong D., Kashiwagi H., Kim D. W., Hattori M., Kadota S., Namba T., *Natural Medicines*, 51, 325-330 (1997).

6) **Pharmacognostical Studies on the Sino-Japanese Crude Drugs "Huajiao" and "Sansho" (Part 5) On Essential Oils and Pungent Principles of Pericarps of Subgen. Zanthoxylum Plants and Commercial Samples**
Ito C., Katagiri H., Sato A., Shi D.W., Kadota S., Komatsu K., Namba T., *Natural Medicines*, 51, 249-258 (1997).

◇ 学会報告

Ⅰ. 天然薬物成分の単離，構造解析，合成，作用

1) カシム熱娜, Basnet Purusotam, 手塚康弘, 門田重利, 難波恒雄：新疆丹参（*Salvia deserta* SCHARG の根）の生理活性成分の研究. 日本薬学会第117年会, 1997, 3, 東京.

2) 河野慎一, 松本欣三, 生島一真, 渡辺裕司, 手塚康弘, 門田重利：隔離飼育マウスの pentobarbital 睡眠に対する当帰分画成分の作用. 日本薬学会第117年会, 1997, 3, 東京.

3) 黒川昌彦, 中野道夫, 白木公康, 穂積豊治, 門田重利, 難波恒雄, 川名　尚：伝統医薬エキスによるヘルペスウイルス（HSV）自然回帰発症予防効果と抗 HSV 作用機序. 日本薬学会第117年会, 1997, 3, 東京.

4) 熊　泉波, 長谷耕二, 門田重利, 難波恒雄：肉蓯蓉（*Cistanche deserticola* の茎）の生理活性成分の研究(2) Phenylethanoid 配糖体の肝障害抑制作用について. 日本薬学会第117年会, 1997, 3, 東京.

5) 金　東郁, 横澤隆子, 服部征雄, 門田重利, 難波恒雄：LDL の酸化における羅布麻葉（*Apocynum venetum* L.）の関与. 日本薬学会第117年会, 1997, 3, 東京.

6）李　慧英，李　建新，手塚康弘，宮原龍郎，利波修一，瀬戸　光，多田貴広，門田重利，難波恒雄：伝統薬物による抗骨粗鬆活性成分の研究（III）接骨木 *Sambucus sieboldiana* BLUME ex GRAEBN.（茎）と漢方方剤について．第14回和漢医薬学会大会，1997，8，大阪．

7）李　建新，李　慧英，手塚康弘，宮原龍郎，門田重利，利波修一，瀬戸　光，難波恒雄：牛膝の抗骨粗鬆活性に関する研究．第14回和漢医薬学会大会，1997，8，大阪．

8）入川志保，長谷耕二，熊　泉波，李　建新，手塚康弘，門田重利，難波恒雄：マクロファージからのＮＯ産生を抑制する生薬の探索．第14回和漢医薬学会大会，1997，8，大阪．

9）関谷幸治，門田重利，片山和憲，小泉　保，難波恒雄：生薬を用いた浴湯剤に関する研究（III）生薬成分の皮膚透過に対する中国産川芎の吸収促進効果．第14回和漢医薬学会大会，1997，8，大阪．

10）金　東郁，横澤隆子，服部征雄，門田重利，難波恒雄：羅布麻（*Apocynum venetum*）エキスの血圧に及ぼす影響．第14回和漢医薬学会大会，1997，8，大阪．

11）川芳弘，藤猪英樹，大西康晴，作川理恵子，済木育夫，難波恒雄，長谷耕二，門田重利：マウス結腸癌実験的肝転移モデルにおける青葙子の転移抑制効果について．第14回和漢医薬学会大会，1997，8，大阪．

12）黒川昌彦，白木公康，Purusotam Basnet，難波恒雄，門田重利，穂積豊治：ヘルペスウイルス（ＨＳＶ）感染症に有効な大根草エキスの抗ＨＳＶ活性成分の同定とその作用機序の解析．第14回和漢医薬学会大会，1997，8，大阪．

13）渡辺千恵，奥　亨，済木育夫，長谷耕二，門田重利，難波恒雄，永井博弐：ススキ花穂による実験的アトピー性皮膚炎に及ぼす効果．第14回和漢医薬学会大会，1997，8，大阪．

14）白木公康，黒川昌彦，中野道夫，湯川倫代，門田重利，難波恒雄，穂積豊治：伝統医薬から抗ウイルス剤の開発．第14回和漢医薬学会大会，1997，8，大阪．

15）Kasimu R., Tezuka Y., Li J. X., Tanaka K., Basnet P., Namba T., and Kadota S.: Constituents of Roots of *Salvia miltiorhiza* BUNGE and *Salvia deserta* SHANG. 日本生薬学会第44回年会，1997, 10, 京都．

16）Prasain J. K., Tezuka Y., Li J. X., Tanaka K., Basnet P., Dong H., Namba T., and Kadota S.: Novel Diarylheptanoids from the Seeds of *Alpinia blepharocalyx*. 日本生薬学会第44回年会，1997, 10, 京都．

17）Xiong Q., Hase K., Ohsugi M., Tezuka Y., Namba T., and Kadota S.: Bioactive Constituents of *Cistanche deserticola*: Inhibition of Acteoside on D-Galactosamine/lipopolysaccharide-induced Hepatic Apoptosis in Mice. 日本生薬学会第44回年会，1997, 10, 京都．

18）Hase K., Li J., Basnet P., Xiong Q., Takamura S., Namba T., and Kadota S.: Hepatoprotective Principles of *Swertia japonica* on Immunological Liver Injury in Mice. 日本生薬学会第44回年会，1997, 10, 京都．

19）田中愛子，半明敬子，斉藤智裕，大杉瑞恵，門田重利，小松かつ子，川西千恵美，田澤賢次：ミネラルウォーターの活性酸素消去能．Japanese Society for Food Factor 第2回学術集会，1997, 12.

II．薬物・生体高分子相互作用系の生物有機化学

1）橋本　誠，畑中保丸，金岡祐一：光アフィニティービオチン化（VI）β-1,4-ガラクトース転移酵素のアクセプター結合部位解析．日本薬学会第117年会，1997, 3, 東京．

2）我妻卓司，中村憲夫，手塚康弘，畑中保丸：光アフィニティービオチン化（VII）光反応性ナルトレキサミンによるマウスδ-オピオイド受容体の光ラベル．日本薬学会第117年会，1997, 3, 東京．3．

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