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◇研究目的

和漢薬や天然薬物（特にアジアの伝統薬物）から，膵臓癌，糖尿病，抗マラリア，骨粗鬆症，痛風などに有用な医薬シーズを探索すること，ならびに，和漢薬や天然薬物が薬物代謝酵素に及ぼす影響を解明することを目的とする

◇研究概要

Ⅰ)　伝統薬物から栄養飢餓状態で殺細胞作用を有する物質の探索

国立がんセンターとの共同研究で，膵臓癌 PANC-1 細胞株を用い，低栄養状態(IMEM)で PANC-1 に対する殺細胞活性を示し，通常培地（DMEM）では細胞の成育に活性を示さないような薬物を天然資源より探索している。これまでに，伝統薬物 600 種のエキス中，36 エキスに PANC-1 細胞株に対する選択的な細胞毒性があることを見いだした。現在，牛蒡子，独活の活性成分について研究を進めている。

Ⅱ)　天然薬物から酵母 Ca^{2+} シグナル伝達阻害物質の探索と医薬への応用

広島大学で開発したポジティブスクリーニング法を用いて，新規医薬シーズ開発を目的に研究を行っている。中国及び東南アジア産生薬によるスクリーニングを行い，これまで約 1000 サンプルの試験を終え，25 検体に阻害活性を見い出している。この中で，*Combretum quadrangulare* の活性物質について詳しい作用機序を検討中である。

Ⅲ)　東南アジア産薬用植物から抗マラリア活性物質の探索

現代のマラリア流行地は，ほぼ熱帯・亜熱帯に限定され，それら地域では多剤耐性マラリアに有効な新しい抗マラリア薬が必要とされている。我々は東南アジア等で抗マラリア薬として用いられている薬用植物エキスについて多剤耐性マラリアに対する活性のスクリーニングを行い，活性を示した薬用植物中の活性物質を単離・構造解析を行っている。現在，インドネシアおよびミャンマー産薬用植物 *Caesalpinia crista* について抗マラリア作用を検討し，その活性物質を構造解析した。

Ⅳ)　天然薬物の薬物代謝酵素阻害に関する研究

通常，和漢薬を始めとする天然薬物は合成医薬品と併用されている。このような現状では，天然薬物が“薬物代謝酵素（シトクローム P450，CYP）”に及ぼす影響（薬物間相互作用）を系統的に検証しておく事が，天然薬物の有効利用の上で必要とされている。我々は，漢方生薬 78 種及びインドネシアのジャムウ生薬 30 種について CYP3A4 及び CYP2D6 阻害活性を検索した。次いで，阻害活性を示した漢方生薬“呉茱萸”およびジャムウ生薬 "*Piper cubeba*", "*Catharanthus roseus*" の活性成分を明らかにした。更に，得られた活性成分について，代謝依存的阻害（metabolism-dependent inhibition）を示す可能性について検討した。

V)　骨粗鬆症に有効な天然薬物成分の開発研究

中医学において骨粗鬆症に類似の疾患（骨痿や骨痺）の治療に補腎剤や強筋骨剤が使用されている事に注目し，使用されている漢薬 30 種について抗骨粗鬆症活性をスクリーニングした。その結果，強い活性を示した漢薬“メンヒセン（*Dioscorea spongiosa* の根茎）”の成分の解明を行い，得られた成分の pQCT 装置による抗骨粗鬆症活性と合わせて，活性本体がステロイド配糖体である事を明らかにした。また，紅豆杉の活性成分のリグナンが，抗骨粗鬆症活性がある事も判明した。現在，中国で骨粗鬆症の治療に繁用されている 19 種の方剤について科学的評価を行っている。

VI)　ベトナム産生薬の Xanthine Oxidase 阻害活性物質の研究

痛風治療薬の開発を目的に，ベトナム産生薬（98 種）について Xanthine Oxidase 阻害作用を指標にスクリーニングした。阻害作用の強かった *Caesalpinia sappan* から活性物質の構造を決定した。

VII)　NO 産生阻害活性成分の検索

東南アジア各地で採集した *Orthosiphon stamineus* について，地理的な成分比較ならびに NO 阻害活性物質の構造を解析した。また，ネパール産プロポリスから，非常に強い NO 阻害活性物質を見い出し構造解析を行った。

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。

◇原著論文

1) **Usia T., Watabe T., Kadota S., and Tezuka Y.: Potent CYP3A4 Inhibitory Constituents of *Piper cubeba*. *J. Nat. Prod.*, 68: 64–68, 2005.**

Abstract: The EtOAc-soluble fraction of the water extract of *Piper cubeba*, having shown potent inhibitory activity on the metabolism mediated by CYP3A4, was subjected to activity-guided isolation to yield two new lignans, (8*R*,8'*R*)-4-hydroxycubebinone (**1**) and (8*R*,8'*R*,9'*S*)-5-methoxyclusin (**2**), and two new sesquiterpenes, (5α,8α)-2-oxo-1(10),3,7(11)-guaiatrien-12,8-olide (**3**) and (1α,2β,5α,8α,10α)-1,10-epoxy-2-hydroxy-3,7(11)-guaiadien-12,8-olide (**4**), along with 16 known compounds (**5**–**20**). The structures of the isolated compounds were elucidated on the basis of spectroscopic and chemical analyses. The isolated compounds were tested for their inhibitory activity on the metabolism mediated by CYP3A4 or CYP2D6 using [*N*-methyl-^{14}C]erythromycin or [*O*-methyl-^{14}C]dextromethorphan as a substrate, respectively. The compounds, (8*R*,8'*R*,9'*S*)-5-methoxyclusin (**2**), (–)-clusin (**10**), (–)-yatein (**13**), ethoxyclusin (**15**), and (–)-dihydroclusin (**17**), having one methylenedioxyphenyl moiety in their structures, showed very potent and selective inhibitory activity against CYP3A4 with IC_{50} values (0.44–1.0 μM) identical to that of the positive control, ketoconazole (IC_{50}, 0.72 μM).

2) **Yin J., Tezuka Y., Subehan, Shi L., Ueda J., Matsushige K., and Kadota S.: Combination of Soft-shell Turtle and Essential Oil of Unicellular Chorophyte Prevented Bone Loss and Decrease of Bone Strength in OVX Rats. *Biol. Pharm. Bull.*, 28: 275–279, 2005.**

Abstract: The effects of soft-shell turtle (*Trionyx sinensis*) powder (SST) on the proximal tibiae of ovariectomized (OVX) rats were investigated using peripheral quantitative computed tomography (pQCT) and examination of serum biochemical markers. Considering the relationship between the antioxidative property and antiosteoporotic activity, the synergistic effects of a mixture of SST and essential oil of the microalgae *Haematococcus pluvialis* (OHP) with strong antioxidant activity were also examined. Oral administration of SST (100, 200 mg/kg) or a mixture of SST (100, 200 mg/kg) and OHP (13, 26 mg/kg) three times weekly prevented the decrease in bone mineral content (BMC) in total bone, BMC and bone mineral density (BMD) in cortical bone, and bone strength indices induced by

ovariectomy in a dose-dependent manner without uterine side effects. However, OHP alone showed no significant effects.

3) **Kalauni S.K., Awale S., Tezuka Y., Banskota A.H., Linn T.Z., and Kadota S.: New Cassane-type Diterpenes of *Caesalpinia crista* from Myanmar. *Chem. Pharm. Bull.*, 53: 214–218, 2005.**

Abstract: Seven new cassane-type diterpenes, caesalpinin MF–ML (**1**–**7**), and a new norcassane-type diterpene, norcaesalpinin MD (**8**), have been isolated from the CH_2Cl_2 extract of seed kernels of *Caesalpinia crista* from Myanmar, together with 16 known cassane-type diterpenes, 7-acetoxybonducellpin C, caesaldekarin e, caesalmin C, caesalmin G, 2-acetoxycaesaldekarin e, ζ-caesalpin, caesalpinin D, caesalpinin E, caesalpinin F, caesalpinin H, caesalpinin I, caesalpinin J, caesalpinin K, caesalpinin M, caesalpinin N, and caesalpinin O. The structures of the isolated compounds were elucidated by the use of spectroscopic techniques.

4) **Usia T., Watabe T., Kadota S., and Tezuka Y.: Mechanism-Based Inhibition of CYP3A4 by Constituents of *Zingiber aromaticum*. *Biol. Pharm. Bull.*, *28*: 495–499, 2005.**

Abstract: Sixteen compounds isolated from *Zingiber aromaticum* and showing concentration-dependent inhibition with IC_{50} values less than 100 μM, were analyzed for their possibility of time-, concentration-, and NADPH-dependent inhibition of CYP3A4 and four were analyzed for CYP2D6. All seven kaempferol glycosides and two kaempferol derivatives (**4**, **5**, **8**–**14**) appear to be the mechanism-based inhibitors of CYP3A4 enzyme in which the inhibition is irreversible and driven by the catalytic process. The other compounds showed no NADPH-dependent inhibition or reversible inhibition, and thus do not appear to be mechanism-based inhibitors. K_I values for compounds **4**, **5**, **8**–**14** were in the range of 2.21–27.01 μM, whereas the k_{inact} values were 0.23–0.65 min^{-1}. Kaempferol-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside) (**5**) was found to be the most potent CYP3A4 inactivator with K_I and k_{inact} values of 2.21 μM and 0.45 min^{-1}, respectively.

5) **Subehan, Usia T., Kadota S., and Tezuka Y.: Constituents of *Zingiber aromaticum* and Their CYP3A4 and CYP2D6 Inhibitory Activity. *Chem. Pharm. Bull.*, 53: 333–335, 2005.**

Abstract: A new sesquiterpene 2,9-humuladien-6-ol-8-one (**1**) was isolated from methanol extract of *Zingiber aromaticum*, along with 15 known compounds. The structures of the isolated compounds were elucidated on the basis of spectroscopic analyses. The isolated compounds were tested for their inhibitory activity on the metabolism mediated by cytochrome P450 3A4 (CYP3A4) and CYP2D6.

6) **Usia T., Watabe T., Kadota S., and Tezuka Y.: Metabolite–cytochrome P450 complex formation by methylenedioxyphenyl lignans of *Piper cubeba*; mechanism-based inhibition. *Life Sci.*, 76: 2381–2391, 2005.**

Abstract: Five methylenedioxyphenyl lignans, (–)-clusin (**1**), (–)-dihydroclusin (**2**), (–)-yatein (**3**), (–)-hinokinin (**4**), and (–)-dihydrocubebin (**5**), were isolated from *Piper cubeba* as potent and selective inhibitors against cytochrome P450 3A4 (CYP3A4). In this study, we investigated the mechanism of inhibition of CYP3A4 by these lignans and the possibility of their mechanism-based inhibition. Using [*N*-methyl-^{14}C]erythromycin as a substrate, all lignans appear to be shown mixed-type of inhibition with apparent K_i of 1.96–4.07 μM. Furthermore, all lignans (**1**–**5**) inhibited CYP3A4 in a time-, concentration-, and NADPH-dependent manners and thus appear to be the mechanism-based inhibitors of CYP3A4. The apparent inactivation parameter, K_I for these compounds were in the range of 0.054–0.373 μM, whereas the k_{inact} values were 0.225–0.320 min^{-1}. Among them, (–)-clusin (**1**) and (–)-dihydroclusin (**2**) were found to be the most potent CYP3A4 inactivator with apparent K_I and k_{inact} values of 0.082, 0.054 μM and 0.253, 0.310 min^{-1}, respectively. Spectral scanning of microsomes with these lignans yielded an absorbance at 455 nm, suggesting that all of them appear to inactivate the cytochrome P450 via the

formation of a metabolite intermediate complex. This pattern is consistent with the metabolism of the methylenedioxyphenyl compounds. These results indicate that (–)-clusin (**1**), (–)-dihydroclusin (**2**), (–)-yatein (**3**), (–)-hinokinin (**4**), and (–)-dihydrocubebin (**5**) are effective mechanism-based inhibitors of CYP3A4.

7) **Iwata H., Tezuka Y., Kadota S., Hiratsuka A., and Watabe T.: Mechanism-Based Inactivation of Human Liver Microsomal CYP3A4 by Rutaecarpine and Limonin from Evodia Fruit Extract. *Drug. Metab. Pharmakokin.*, 20: 34–45, 2005.**

Abstract: Evodia fruit (Evodiae Fructus) is used as a herbal medicine prepared from the matured fruit of the *Evodia rutaecarpa* Benth or *Evodia officinalis* Dode, of the Rutaceae plant family. An extract of Evodia fruit in the presence of NADPH was shown to inhibit human liver microsomal erythromycin *N*-demethylation activity, mediated by cytochrome P450 3A4 (CYP3A4), in a preincubation-time dependent manner. The present study was conducted to identify components of Evodia fruit extract having preincubation-time dependent inhibitory effects on CYP3A4 by analyzing human liver microsomal erythromycin *N*-demethylation activity. Rutaecarpine, a major component of Evodia fruit, and limonin caused the most dramatic decrease in residual CYP3A4 activity (IC_{50} before and after 20 min preincubation with: rutaecarpine, >100 μM and 1.4 μM; limonin; 23.5 μM and 1.8 μM, respectively). Furthermore, rutaecarpine and limonin were identified as mechanism-based inhibitors of CYP3A4 from the following observations: 1) The inhibitory effects of rutaecarpine and limonin on CYP3A4 activity were dependent on the preincubation time, 2) The inhibition required NADPH, 3) The inhibition was depressed in the presence of the competitive CYP3A4 inhibitor, ketoconazole, 4) Dialysis resulted in no recovery of CYP3A4 activity. The kinetic parameters for inactivation k_{inact} and K_I were: 0.387 min^{-1} and 107.7 μM for rutaecarpine, 0.266 min^{-1} and 23.2 μM for limonin, respectively. These results indicate that rutaecarpine and limonin are mechanism-based inhibitors of CYP3A4.

8) **Zhang Y., Li J.X., Zhao J., Wang S.Z., Pan Y., Tanaka K., and Kadota S.: Synthesis and activity of oleanolic acid derivatives, a novel class of inhibitors of osteoclast formation. *Bioorg. Med. Chem. Lett.*, 15: 1629–1632, 2005.**

9) **Linn T. Z., Awale S., Tezuka Y., Banskota A. H., Kalauni S. K., Attamimi F., Ueda J., Asih P. B. S., Syafruddin D., Tanaka K., and Kadota S.: Cassane- and Norcassane-type Diterpenes from *Caesalpinia crista* of Indonesia and Their Antimalarial Activity against the Growth of *Plasmodium falciparum*. *J. Nat. Prod.*, 68: 706–710, 2005.**

Abstract: The CH_2Cl_2 extract of the seed kernels of *Caesalpinia crista*, which exhibited promising antimalarial activity against *Plasmodium berghei*-infected mice in vivo, was examined and resulted in the isolation of seven new furanocassane-type diterpenes [caesalpinins C–G (**1**–**5**) and norcaesalpinins D and E (**6**, **7**)] together with norcaesalpinins A–C (**8**–**10**) and 11 known compounds (norcaesalpinins A–C, 2-acetoxy-3-deacetoxycaesaldekarin e, caesalmin B, caesaldekarin e, caesalpin F, 14(17)-dehydrocaesalpin F, 2-acetoxycaesaldekarin e, 7-acetoxybonducellpin C, and caesalmin G). Their structures were determined on the basis of spectroscopic analysis. The isolated diterpenes showed significant dose-dependent inhibitory effects on *Plasmodium falciparum* FCR-3/A2 growth in vitro. Their IC_{50} values ranged from 90 nM to 6.5 μM, and norcaesalpinin E (**7**) showed the most potent inhibitory activity (IC_{50}, 90 nM).

10) **Usia T., Watabe T., Kadota S., and Tezuka Y.: Cytochrome P450 2D6 (CYP2D6) Inhibitory Constituents of *Catharanthus roseus*. *Biol. Pharm. Bull.*, 28: 1021–1024, 2005.**

Abstract: The MeOH-soluble fraction of the water extract of *Catharanthus roseus* from Indonesia, having shown potent inhibitory activity on the metabolism mediated by CYP2D6, was subjected to activity-guided isolation to yield two triterpenes, ursolic acid (**1**) and oleanolic acid (**2**), and three alkaloids, vindoline (**3**), ajmalicine (**4**), and serpentine (**5**). The isolated compounds were tested for their

inhibitory activity on the metabolism mediated by CYP3A4 or CYP2D6 using [*N*-methyl-^{14}C]-erythromycin or [*O*-methyl-^{14}C]dextromethorphan as a substrate, respectively. Ajmalicine (**4**) and serpentine (**5**) showed very potent inhibitory activity against CYP2D6 with IC_{50} values of 0.0023 and 3.51 μM, respectively. All isolated compounds showed weak or no inhibition against CYP3A4. On time-, concentration-, and NADPH-dependent assay, serpentine (**5**) appear to be the mechanism-based inhibitor for CYP2D6 enzyme in which the inhibition was irreversible and driven by catalytic process. K_I and k_{inact} values for serpentine (**5**) were 0.148 μM and 0.090 min^{-1}, respectively. On the other hand, ajmalicine (**4**) showed no time-dependent inhibition or reversible inhibition, and thus appears to be not a mechanism-based inhibitor.

11) Awale S., Kawakami T., Tezuka Y., Ueda J., Tanaka K., and Kadota S.: Nitric Oxide (NO) Production Inhibitory Constituents of *Tabebuia avellanedae* from Brazil. *Chem. Pharm. Bull.*, 53: 710–713, 2005.

Abstract: From the water extract of Brazilian *Tabebuia avellanedae*, two new iridoids (**1**, **2**) and a new phenylethanoid glycoside (**3**) have been isolated together with twelve known compounds (**4**–**15**). Their structures were determined based on the spectroscopic data. The isolated compounds inhibited nitric oxide (NO) production in lipopolysaccharide (LPS)-activated macrophage-like J774.1 cells. Compounds **1**, **3**, **10**, **11**, and **12** showed inhibitory activities more potent (IC_{50}, 13.8–26.1 μg/ml) than a positive control N^G-monomethyl-L-arginine (L-NMMA; IC_{50}, 27.4 μg/ml).

12) Awale S., Shrestha S.P., Tezuka Y., Ueda J., Matsushige K., and Kadota S.: Neoflavonoids and Related Constituents from Nepalese Propolis and Their Nitric Oxide Production Inhibitory Activity. *J. Nat. Prod.*, 68: 858–864, 2005.

Abstract: A methanolic extract of Nepalese propolis yielded 10 new open-chain neoflavonoids (**1**–**10**), a new chalcone (**11**), and eight previously reported compounds (**12**–**19**). Their structures were determined based on the spectroscopic data and chemical conversion. The isolated compounds other than **5**, **8**, and **16**, showed dose–dependent inhibitory activities on nitric oxide (NO) production in lipopolysaccharide (LPS)-activated macrophage-like J774.1 cells, and were more active than a positive control, N^G-monomethyl-L-arginine (L-NMMA; IC_{50}, 27.1 μM). The most potent activities, of **6** and **7** (IC_{50}, 0.5 μM), were greater than another positive control, caffeic acid phenethyl ester (CAPE; IC_{50}, 4.8 μM).

13) Nguyen M.T.T., Awale S., Tezuka Y., Tran Q.L., and Kadota S.: Xanthine Oxidase Inhibitos from the Hartwood of Vietnamese *Caesalpinia sappan*. *Chem. Pharm. Bull.*, 53: 984–988, 2005.

Abstract: From the MeOH extract of Vietnamese *Caesalpinia sappan*, a novel biogenetically exclusive benzindenopyran, with a new carbon framework, neoprotosappanin (**1**), and a new compound, protosappanin A dimethyl acetal (**3**), were isolated together with protosappanin E-2 (**2**), neosappanone A (**4**), and 13 previously reported phenolic compounds (**5**–**17**). Their structures were elucidated on the basis of spectroscopic data. Compounds **1**–**4**, **7**, **13**, and **15**–**17** showed significant xanthine oxidase inhibitory activity in a concentration-dependent manner, and sappanchalcone (**17**) showed the most potent activity with an IC_{50} value of 3.9 μM, comparable to that of positive control allopurinol (IC_{50}, 2.5 μM). The kinetic study of these inhibitors indicated that they are competitive inhibitors, the same as allopurinol, except for **1** and **16** which are noncompetitive inhibitors.

14) Li J.-X., Hareyama T., Tezuka Y., Zhang Y., Miyahara T., and Kadota S.: Five New Oleanolic Acid Glycosides from *Achyranthes bidentata* with Inhibitory Activity of Osteoclast Formation. *Planta Med.*, 71: 673–679, 2005.

Abstract: Bioassay-directed fractionation of a butanol-soluble fraction of methanol extract of the root of *Achyranthes bidentata* resulted in the isolation of 5 new oleanolic acid glycosides **1**–**5**, namely,

18-(β-D-glucopyranosyloxy)-28-oxoolean-12-en-3β-yl-3-*O*-(β-D-glucopyranosyl)-β-D-glucopyranosid uronic acid methyl ester (**1**), achyranthoside C dimethyl ester (**2**), achyranthoside C butyl dimethyl ester (**3**), achyranthoside E dimethyl ester (**4**), and achyranthoside E butyl methyl ester (**5**), together with 10 known compounds. Their structures were established on the basis of spectroscopic interpretation and chemical methods. All the oleanolic acid glycosides inhibited the formation of osteoclast-like multinucleated cells (OCLs) induced by $1\alpha,25(OH)_2D_3$ in a co-culture assay system.

15) **Kalauni S.K., Awale S., Tezuka Y., Banskota A.H., Linn T.Z., and Kadota S.: Methyl Migrated Cassane-type Furanoditerpenes of *Caesalpinia crista* from Myanmar. *Chem. Pharm. Bull.*, 53: 1300–1304, 2005.**

Abstract: From the CH_2Cl_2 extract of seed kernels of *Caesalpinia crista* from Myanmar, two rare and biogenetically interesting methyl migrated cassane-type furanoditerpenes [caesalpinins MM1and MN (**2**)] and two normal cassane-type furanoditerpenes [caesalpinins MQ3and MP (**4**)] have been isolated, together with eight known cassane-type diterpenes, 1-deacetoxy-1-oxocaesalmin C (**5**), 1-deacetylcaesalmin C (**6**), caesalmin C (**7**), bonducellpin C (**8**) caesaldekarin e (**9**), 2-acetoxycaesaldekarin e (**10**), 2-acetoxy-3-deacetoxycaesaldekarin e (**11**), and norcaesalpinin E (**12**). Among the known compounds, compounds **5** and **6** were for the first time isolated from a natural source. The structures of these compounds were elucidated by the use of spectroscopic techniques.

16) **Nguyen M.T.T., Awale S., Tezuka Y., Shi L., Zaidi S.F.H., Ueda J., Tran Q.L., Murakami Y., Matsumoto K., and Kadota S.: Hypouricemic Effects of Acacetin and 4,5-*O*-Dicaffeoylquinic Acid Methyl Ester on Serum Uric Acid Levels in Pottasium Oxonate-Pretreated Rats. *Biol. Pharm. Bull.*, 28: 2231–2234, 2005.**

Abstract: The effects of acacetin (**1**) and 4,5-*O*-dicaffeoylquinic acid methyl ester (**2**), compounds contained in the flowers of *Chrysanthemum sinense* Sabine, on the serum uric acid level were investigated using the rats pretreated with the uricase inhibitor potassium oxonate as an animal model for hyperuricemia. When administered per orally at doses of 20 and 50 mg/kg, **1** reduced the serum uric acid level by 49.9 and 63.9%, respectively and **2** reduced the level by 31.2 and 44.4 %, respectively. On the other hand, when the same doses were given intraperitoneally, both of compounds also exhibited a dose-dependent and more marked reduction of the serum uric acid level (% reduction at 20 and 50 mg/kg were 63.0 and 95.1% in **1**, respectively and 66.9 and 86.5% in **2**, respectively). Furthermore, the compounds **1** and **2** inhibited the rat liver xanthine oxidase activity with IC_{50} values of 2.22 μM and 5.27 μM, respectively. These results demonstrated the hypouricemic action of **1** and **2**, which may be attributable to their xanthine oxidase inhibitory activity.

17) **Subehan, Ueda J., Fujino H., Attamimi F., and Kadota S.: A field survey of agarwood in Indonesia. *J. Trad. Med.*, 22: 244–251, 2005.**

Abstract: Agarwood is one of the most valuable non-timber forest products harvested from the tropical forest in Southeast Asia. We have surveyed agarwood in Indonesia which is performed through interviewed collectors, businessmen, and government officers (Ministry of Forestry, East Kalimantan, Indonesia) and also surveyed the wild agarwood and its cultivation in South Sulawesi and East Kalimantan Provinces. High economic value is one of the reason for collecting agarwood to increase family income of the peoples living near by the forest. Each surveyed area has a different classification and price of each grade, according to their experience by observing the darkness, smell, oily, and density of agarwood. Over exploitation of natural resource of agarwood makes the stock becoming exhausted. It has been an an initiative for conservating the plant of source agarwood by cultivation. Fungi, the known stimulators in formation of agarwood, are used in the cultivation of agarwood. *Fusarium laseritum* is the faster fungus infected of *Aquilaris* sp. tree, and can be isolated and inoculated easily into medium. Thus, this fungus is used by inoculate into the holes on the trunk. One year after inoculation obtained agarwood

with the lowest grade. This cultivation program was supported by Indonesian government through research and training to the collector who cultivate agarwood.

18) Nakashima E.M.N., Nguyen M.T.T., Tran Q.L., and Kadota S.: Field survey of agarwood cultivation at Phu Quoc Island in Vietnam. *J. Trad. Med.*, 22: 296–300, 2005.

Abstract: Agarwood is one of most valuable minor forest products of tropical Southeast Asia forests. In Vietnam, considered as rich source of high quality product, agarwood is collected from heartwood of *Aqilaria cassna* (Thymelaeaceae). Continuing the survey of agarwood in Vietnam, it was carried out on plantations at Phu Quoc Island, and information about cultivation of agarwood was gathered from interview with local people. The results showed that cultivation of agarwood by islanders is increasing every year. Local plantations are based on seeds, seedlings and young *Aquilaria* trees, which grows together with other crops, for a future profit. The promotion and development of agarwood plantations would be an initiative to preserve natural *Aqilaria* trees, as well as supply the high demand for agarwood in world market.

19) Li X., Matsumoto K., Murakami Y., Tezuka Y., Wu Y., and Kadota S.: Neuroprotecive effects of *Polygonum multiflorum* on nigrostriatal dopaminergic degradation induced by paraquat and maneb in mice. *Pharmacol. Biochem. Behav.*, 82: 345–352, 2005.

20) Toyooka N., Kawasaki M., Nemoto H., Awale S., Tezuka Y., and Kadota S.: Synthetic Studies on Poison-Frog Alkaloid 261C. *Synlett*, 3109–3110, 2005.

◇総　説

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