

未病解析応用部門

Department of Presymptomatic Health Promotion

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◇研究目的

本部門は、和漢医薬学など東洋の知を始め世界中の伝統医学を調査研究し、伝統医学が持つ「未病（未だ病まざる状態：病気の前段階）」で対処し、健康増進をする「テーラーメイドの予防医学的体系（養生法）」を創生し、安全性と有用性を科学的に解明することで、古くて新しい未病予防システムを構築することを目的とする。

未病を治す養生法は、内治と外治、さらに、いずれにも属さない気功や太極拳などの不内外治に分類される。内治とは、漢方薬の内服や薬膳などの経口的な治療法であり、外治とは、温浴・薬浴や鍼灸・マッサージ、薬用オイルの滴油療法など、皮膚や体外から行う方法である。本部門では、未病のマーカーを使って、内治と外治など養生法の有効性と安全性、作用機序の科学的解明を行い、その研究成果をもとに、実用的で有用性の高い、テーラーメイドの養生法や Peri-surgical care などを創生することを目指す。

◇研究概要

I) 内治の研究

- 1) 未病のマーカーを利用した薬膳の有効性と安全性の検証
- 2) 環境問題も考慮した新たな薬膳処方 (Mottainai Yakuzen Foods) や特定保健用食品などの開発

II) 外治の研究

- 1) 外治の、未病への有効性と安全性、作用機序の科学的解明とプログラム化
- 2) 外治を、病院での Peri-surgical care や家庭での養生法として普及する

III) 未病の診断と経過のマーカー、個体差マーカーの探索

- 1) 未病の診断や経過観察のための未病マーカーを測定する機器や評価プログラムの開発
- 2) プロテオームやゲノム解析などと伝統医学的な体質との関連を調査し、体質判定用のプロテインチップや DNA チップを開発する

◇著書

- 1) 上馬場和夫監修：ラルフ・クインラン・フォード著・チベット医学の真髄，ガイブックス，東京，2008年。

◇原著論文

- 1) Uebaba K., Xu FH., Ogawa H., Tatsuse T., Wang B., Hisajima T., Venkatraman S.: Psychoneuroimmunological Effects of Ayurvedic Oil-dripping Treatment. *J Alter. Complem. Med.* 14(10):1189-1198,2008.

Abstract: This study assessed the psychoneuroimmunological changes achieved by *Shirodhara*, an Ayurvedic treatment, characterized by dripping oil on the forehead, in a randomized, controlled protocol involving a novel approach using a robotic system. In the first experiment for the determination of the

most appropriate conditions of *Shirodhara*, sixteen healthy females (33 +/-9 years old) underwent a 30-minute treatment. In the second study, another sixteen healthy females (39 +/-9 years old) were assigned to either the *Shirodhara* treatment or control position for 30 minutes, with monitoring of physiological, biochemical, immunological, and psychometric parameters including anxiety and altered states of consciousness (ASC).

The subjects receiving *Shirodhara* treatment showed lowered levels of state anxiety and higher levels of ASC than those in the control position. Plasma noradrenalin and urinary serotonin excretion decreased significantly more after *Shirodhara* treatment than in the control. Plasma level of TRH, dopamine and Natural killer (NK) cell activity were different between control and *Shirodhara* treatment. The correlation between anxiolysis and the depth of ASC was significant in the *Shirodhara* treatment group ($r=0.52$, $p<0.05$, $N=16$), while, in the control no correlation was obtained ($r=0.13$, $p=0.64$, $N=16$). The increase in foot skin temperature after *Shirodhara* showed a significant correlation with anxiolysis and the depth of Trance of ASC ($r=0.58$, $p<0.01$, $r=0.43$, $p<0.01$ respectively). NK cell activity after *Shirodhara* treatment showed a significant correlation with anxiolysis and the depth of Trance of ASC ($r=0.33$, $p<0.05$, $r=0.56$, $p<0.01$ respectively). These results indicate that *Shirodhara* has anxiolytic and ASC-inducing effects, and it promotes a decrease of noradrenalin and exhibits a sympatholytic effect, resulting in the activation of peripheral foot skin circulation and immunopotentiality.

2) **Xu FH., Uebaba K., Ogawa H., Tatsuse T., Wang B., Hisajima T., Venkatraman S.: Pharmacophysio-psychological Effect of Ayurvedic Oil-dripping Treatment Using an Essential Oil From *Lavendula angustifolia*. J Alter. Complem.Med. 14(8):947-956,2008.**

Abstract: Ayurvedic oil-dripping treatment, *Shirodhara*, involves the use of medicated herbal sesame oils. In our previous reports, we found that *Shirodhara* with plain sesame oil induced anxiolysis and an altered state of consciousness (ASC) in healthy subjects. We studied the pharmacophysio-psychological effect of *Shirodhara* with medicated sesame oil including an essential oil from *Lavendula angustifolia* (lavender) in the present study. Sixteen healthy females (38 +/-8 years old) were assigned at random to three treatments applied by a robotic oil-dripping system: plain sesame oil (plain *Shirodhara*), medicated sesame oil with a 0.3 volume % of lavender essential oil (lavender *Shirodhara*), or the control supine position. Psycho-physiological parameters including the heart rate, skin temperature of the dorsum of hands and feet, as well as anxiety and ASC were monitored, and the rates of change of these items were calculated to assess the psycho-physiological changes brought about by *Shirodhara*.

Lavender *Shirodhara* showed potent anxiolytic and ASC-inducing or promoting effects, and induced the largest increase in foot skin temperature. The correlation between anxiolysis and ASC, as well as the correlation between these psychological effects and the elevated foot skin temperature were larger in the lavender *Shirodhara* than in the other two conditions. It was speculated that the psycho-physiological effects of lavender *Shirodhara* would be brought about by three mechanisms: 1) the well-known relaxing action of essential oils from *Lavendula angustifolia* mediated by olfactory nerves, 2) the pharmacological action of substances absorbed through the skin or mucosa in the sesame oil or lavender essential oil, and 3) the physiological effect of sesame oil dripped on the forehead induced by the somato-autonomic reflex through thermosensors or pressure sensors in the skin or hair follicles via the trigeminal cranial nerve. The complicated pharmacophysio-psychological action of Ayurvedic oil treatment may provide a useful model for future pharmacophysio-psychotherapy.

3) **Xu FH., Ogawa H., Wang HB., Hisajima T., Uebaba K.: Different physiological changes in carbonated localized bathing of hands and feet in healthy males. J Jpn Soc Balneol Climatol Phys Med. 72(4):23-34,2008.**

Abstract: Physiological changes induced by localized bathing in hand, foot, and simultaneous hand-foot baths were studied and compared with each other in order to elucidate the physiological mechanism of hand and footbath. Fifteen healthy adult males (32 +/- 10 years old) took hand, foot, and simultaneous hand-foot carbonated (by Module mixture type artificial carbonated bath, at CO₂ concentration 1100 +/- 100 ppm, pH 4.8) and freshwater baths (pH 7.4) at 38°C, and assumed a control sitting position following a randomized controlled design. They took 7 kinds of localized baths mentioned above 1 week apart from each other. Each localized bath had a 5-minute rest in a sitting position, and a 30-minute bathing, followed by a 10-minute rest. Their physiological parameters, such as heart rate, blood pressure, near infrared spectroscopy at the forehead, laser Doppler flowmetric findings for immersed (foot) and

non-immersed (shoulder muscle) body surface capillary flow, as well as body temperatures of sublingual and tympanic membrane were monitored.

While any physiological changes occurred during the proximal 5-10 minutes after starting simultaneous hands-footbaths, the body temperature, cerebral tissue circulation, cutaneous blood flow of the non-bathed skin, and heart rate increased, and diastolic pressure decreased in the distal half of 30-minute baths of carbonated and freshwater. These physiological changes would probably be due to the thermal effect.

However, in the proximal 5-10 minutes after starting carbonated baths of the hand and foot showed the opposite autonomic change, which was cancelled out in the simultaneous hand-foot carbonated baths. Freshwater localized baths of hand and foot did not show such as different reaction. The cutaneous blood flow of the bathed skin of hands and feet was also significantly different only in the carbonated baths, while no differences were obtained in the freshwater hand and footbaths.

Taken together, 38°C and 1000ppm carbonated localized baths (hands and feet) showed the opposite heart rate variability just after starting bathing, and they induced different cutaneous blood flow changes during bathing. These physiological differences in hand and foot bathing may be owing to somato-autonomic and axon reflex induced by the skin nociceptive ion channels with different sensitivity and reaction due to different pH of bathed medium, and due to different hydrostatic pressure in hands and footbaths.

4) **Zhu Y., Origasa H., Uebaba K., Xu FH and Wang Q.: Development and validation of the Japanese Version of the Constitution in Chinese Medicine Questionnaire (CCMQ). *Kampo Med.*, 59: 783-792, 2008.**

Abstract: Objectives: The objective of this study is to develop a Japanese version of the Constitution in Chinese Medicine Questionnaire (CCMQ) in Chinese, which is composed of 60 items with 9 sub-scales, and evaluate its reliability and validity. Methods: We conducted a survey of 130 participants in the Toyama area of Japan from Dec. 2005, to Feb. 2006. A test-retest method was used. Feasibility was evaluated by the response times to the questionnaire, and the response rates of the CCMQ items. Internal consistency within the sub-scales was assessed by Cronbach's α coefficient. Reproducibility was confirmed between the first and second occasions using weighed kappa and Spearman correlation. Lastly, criterion validity was evaluated by correlation between CCMQ and SF-36 sub-scale. Results: Response time was 8 minutes on average and its rate was nearly 100 %. Internal consistency was achieved for each of the 9 sub-scales with a 0.65 to 0.79 α coefficient. Reproducibility ranged from 0.41 to 0.81 for the items, and 0.79 to 0.88 for the sub-scales. Regarding the criterion validity, the "Gentleness type" sub-scale was positively correlated with SF-36 (-0.35 to -0.50, $P < 0.001$) as expected. Conclusions: We developed a Japanese version of the CCMQ and found acceptable levels of reliability and validity using a 130 subjects in Japan. This suggests that the CCMQ could be a useful tool in comparing the constitution profiles between Chinese and Japanese.

5) **Suzuki N., Uebaba K., Kohama T., Moniwa N., Kanayama N., Koike K. X.: French maritime pine bark extract significantly lowers the requirement for analgesic medication in dysmenorrhea. *J Reprod. Med.*, 53(5): 338-346, 2008.**

Abstract: Objective: A previous open study demonstrated that French maritime pine bark extract (Pycnogenol) may soothe menstrual pain in dysmenorrheal. We thus investigated the effects of Pycnogenol on menstrual pain in a double-blind study. Study design: Subjects were 116 women aged 18-48 years. The first 2 menstrual cycles served as a control period; during the subsequent 2 menstrual cycles women received wither a Pycnogenol supplement (60 mg/day) or a placebo in identical capsule from. One further cycle was monitored after sessation of capsule administration. Women were assigned to either a group with low menstrual pain or a group with dysmenorrhea. The criterion for assignment to the first group was absence of analgesic medication. Results: In women with low menstrual pain, no significant difference for lowering of pain scores was found. In contrast, women with dysmenorrheal had a significantly lower pain score and required statistically significantly less analgesic medication during supplementation with Pycnogenol. The number of days women required analgesic medication was

likewise found to be statistically significantly lowered in the Pycnogenol group. Even after discontinuation of Pycnogenol supplementation, the required analgesic medication remained significantly decreased. Conclusion: The analgesic-sparing effect of Pycnogenol increases with duration of supplementation and benefits persist even after discontinuation.

- 6) **Funatsu Y., Nishimura Y., Ishioroshi M., Uebaba K., Nishio U., Terashima T., Mafune N.: Hypoglycemic effects of Tofu refuse-enriched cake on blood glucose level in Healthy subjects and its sensory attributes. Nippon Shokuhin Kagaku Kogaku Kaishi, 55(8), 55(8):67-372,2008**

Abstracts: In order to utilize efficiently dischargedtofu refuse (Okara), a *tofu* refuse-enriched cake (TREC) was prepared by addition of tofu refuse, sugar,egg, margarine, edible vegetable oil, salt, baking powder and vanilla essence, and its approximate compositions, hypoglycemic effect in vivo and sensory arrttributes were compared with those of wheat-based caked as a control. According to approximate composition analysis, dietary fiber was higher in TREC than in the control, in which the content of insoluble dietary fiber was extremely high. Single-dose oral administrationof TREC significantly lowered blood glucose 30 min after loading of 50 g of sugars in healthy subjects (p<0.05). Glycemic index was 39.1 % lowere in TREC than in the control. The results of sensory evaluation revealed that texture, easiness of swallowing and overall taste of TREC were more agreeable than those of the control (p<0.05). There was no significant difference of external appearance or smell between TREC and the control (p>0.05). The acceptability of TREC was also significantly higher than that of the control (p<0.001). These results suggested that TREC may not only prevent increases in postprandial glucose leble but also have good palatability.

- 7) **Hui S., Hayashi T., Sakurai T., Jin S., Ishii S., Murai T., Uebaba K., Ogawa H., Chiba H., Kurosawa T.: Quantitative analysis of curcuminoids in human plasma by means of HPLC with UV detection. Rinsho Kagaku, 38(1):59-67,2009**

Abstracts: Curcuminoids are the polyphenols contained in turmeric. They are getting more popular in Japan as as ingredient of health foods. However, little is known about the intestinal absorption, metabolites and pharmacokinetic profiles of orally administered curcuminoids in human. In this report, quantitative analysis of curcuminoids in human plasma after oral administration were done by using HPLC with the aid of synthetic curcuminoid derivatives as an internal standard. For non-reduced forms of curcuminoids, the average recoveries from plasma were 93.1%~114.8%, and the coefficients of variation were less than 16.2%. The enzymatic hydrolysis demonstrated the the non-reduced curcumiooids were glucuronides (50.0%), glucuronide/sulfate double conjugates (45.4%) and free (4.6%) at 1 hour after oral ingestion of 4 g turmeric powder. The maximum plasma concentrations of curcuminoids (non-reduced form) in the turmeric powder group (60 ~90 mg curcuminoids included, n=7) and the turmeric tablet group (90% purified curcuminoids 480 mg included, n=7) were 142.9 ±63.7 nmol/l (mean ±SD) at 1 hour and 26.9 ±17.7 nmol/l (mean ±SD) at 8 hour, respectively, indicating the different intestinal absorption rates. The present method will serve as a useful analytical tool for pharmacological studies of curcuminoids.

◇学会報告 (*: 特別講演, シンポジウム, ワークショップ等)

- 1) Uebaba K., Xu FH., Ogawa H., Origasa H.: Personalized effects of a Kampo herbal formulation, Fang Feng Tong Sheng San, on metabolism- A randomized, double-blind, placebo-controlled study -. Dague Hanny- Togi University Mutual Academic Conference, 8.21,2008 in Busan, Korea.(Invited lecture)
- 2) Xu FH., Ogawa H., UEBABA K.:Effect of Acupressure Points Stimulation on ocular fatigue caused by VDT work, International Conference on Fatigue Science and 51th Annual Conference of Japanese Association of Fatigue Science, 2008, 9,3-5, Okinawa.

- 3) 上馬場和夫：アロマ環境協会第15回専門セミナー：Pharmaco-physio-psycho-therapyとしてのアロマセラピー，アロマ環境協会特別セミナー，2008，10，19，東京&大阪。
- 4) 上馬場和夫，岩重健一，許鳳浩，富島三貴，胡莉珍 音響療法に関するダブルブラインド・ランダム化比較試験，第1回日本統合医療学会，2008，12，6-7，福岡。
- 5) 上馬場和夫：シンポジウム統合医療はわが国で正当医療になりうるか？統合医療は医療の当たり前，第1回日本統合医療学会，2008，12，6-7，福岡。
- 6) 許鳳浩，上馬場和夫，小川弘子：Effect of Acupressure Points Stimulation on ocular fatigue caused by VDT work，第51回疲労学会，2008，3，27，沖縄。
- 7) 許鳳浩，上馬場和夫，小川弘子，王紅兵，宝音倉：炭酸泉部分浴における nociceptive ion channels の役割に関する考察，第74回日本温泉気候物理医学会，2008，5，16-17，鳴子。
- 8) 上馬場和夫，許鳳浩，宝音倉，小川弘子，王紅兵，富島三貴：ステッピングマッサージによる生理・心理的变化，第74回日本温泉気候物理医学会，2008，5，16-17，鳴子。
- 9) 上馬場和夫：インド伝統医学におけるゴマ油。第23回日本ゴマ科学大会，2008，10，4，名古屋。
- 10) 小川弘子，八塚幸枝，許鳳浩，上馬場和夫，浦田哲郎，御影雅幸：アーユルヴェーダの概念と現代医学の対応-アーマと AGEs の類似性およびウコンによる AGEs 生成抑制-，第30回日本アーユルヴェーダ学会大阪研究総会，2008，11，24-26，大阪。
- 11) 上馬場和夫，許鳳浩，小川弘子，八塚幸枝，浦田哲郎，御影雅幸：インド伝統医学の未病概念と現代医学の対応-食品中 AGEs の毒性マーカーとしての可能性-，第15回日本未病システム学会，2008，11，1-2，東京。
- 12) 上馬場和夫，大野智，新井隆成，林浩孝，許鳳浩，小川弘子，鈴木信孝：ハーブティーのQOL増進作用に関する探索的研究-その1：頭痛と目の疲れに対するハーブティーの作用スペクトル-，第11日本補完代替医療学会総会，2008，11，8-9，横浜。
- 13) 上馬場和夫，大野智，新井隆成，林浩孝，許鳳浩，小川弘子，鈴木信孝：ハーブティーのQOL増進作用に関する探索的研究，-その2：更年期障害様症状に対する作用-，第11回日本補完代替医療学会，2008，11，8-9，横浜。

◇その他

- 1) 上馬場和夫：統合医療の伝統医学. Modern Physician, 28(11):1572-1574, 2008.
- 2) 上馬場和夫：統合医療とは，患者中心の医療.30回富山市薬剤師会研修会，2008，9，23，富山。

◇共同研究

- 1) 上馬場和夫：アガリクス (*Agaricus blazei*) 粉末食品の安全性と有効性に関する臨床試験：ビーエイチエヌ株式会社，金沢大学大学院医学系研究科臨床応用補完代替医療学講座，NPO 代替医療科学研究センター，医療法人ホスピター，2008，9～
- 2) 上馬場和夫：アロマセラピーの臨床薬理・生理・心理学的研究-被施術者と施術者におけるラベンダーの経皮吸収-，アロマ環境協会，医療法人ホスピター，2008，12～
- 3) 上馬場和夫：ヨーガとエアロビクスの生理・心理・生化学的変化の違い，日本ヨーガ療法学会，2008，12～
- 4) 上馬場和夫：冬虫夏草入りハーブ製剤の機能性研究，第一薬品工業，富山大学薬学部，医療法人ホスピター，2008，7～

◇研究費取得状況

- 1) 平成 20 年度 知的クラスター創成事業ほくりく健康創造クラスター富山県地域プログラム，富山型アンチエイジングシステムの開発研究（薬草温熱療法の研究），2008. 7～

◇人事異動

上馬場和夫：客員教授（2008，4，1～）

許鳳浩：客員助教（2008，4，1～）

小川弘子：教務補佐員（2008，4，1～）