Title	感染症薬物治療における漢方薬と抗菌薬の併用効果と腸内細菌叢との相関性の解析
Sub Title	Analysis of the correlation between the combined effect of Kampo medicines and antibiotics in drug treatment of infectious diseases and intestinal flora
Author	中村, 智徳(Nakamura, Tomonori)
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Abstract	感染症重症化のリスク因子や抗微生物薬に対する耐性化への漢方薬の併用効果と作用機構の解明を目的に、2つの研究課題（１）および（２）に取り組んだ。 （１）重症Clostridioides difficile感染モデルにおけるバンコマイシン（VCM）および漢方薬併用による重症化抑制効果の評価 感染症に対する効果が報告されている補中益気湯（HET）および柴苓湯（SRT）のVCMとの併用におけるin vitroの相乗効果（MIC測定、Time-kill curve）および重症マウスモデルを用いたin vivo実験（clinical sickness score, CSS）および細菌学的指標の検討を行った。 In vitroにおける漢方薬の併用効果は示されなかったが、HET併用群では体重減少、CSSスコア１以上の上昇を有意に抑制した。またSRT併用群ではVCM投与群と比較して漢方薬投与後にCSS（糞便状態の悪化、体重減少）を有意に抑制した。HETまたはSRT併用群では芽胞が検出されない個体が複数存在した。 以上より、重症CDIに対するVCM治療におけるこれら漢方薬の併用では、CDIの重症化抑制効果に寄与する可能性が示唆された。 （２）抗肥満作用を有する漢方薬の効果の分子機構および腸内細菌叢の関連に関する検討 肥満は脂質異常症、糖尿病、心血管疾患、癌、非アルコール性脂肪性肝疾患だけでなく、感染症重症化の重篤な危険因子となる。そこで、肥満に対し用いられる3種の漢方薬：防風通聖散（BTS）・防己黄耆湯（BOT）および大柴胡湯（DST）について抗肥満効果（体重増加抑制効果、血中脂質、内臓脂肪低減効果）を比較し、漢方薬の抗肥満効果の分子機構と腸内細菌叢との関連を検討した。 BTS・DSTは肥満指標のうち体重および内蔵脂肪組織重量を減少させ、抗肥満効果を示した。またBTS投与によりAkkermansia muciniphila等特定の腸内細菌の増減が見られた。 We worked on two research topics (1) and (2) with the aim of elucidating the effect and mechanism of action of Kampo medicines in combination with antimicrobial drugs on the risk factors for the severity of infectious diseases and the resistance. (1) Evaluation of the effect of suppressing aggravation of the combination of vancomycin (VCM) and Kampo medicines in a severe Clostridioides difficile infection model We examined the combination effects of Hochuekkito (HET) or Saireito (SRT) which have been reported to be effective against infectious diseases with VCM on ①in vitro synergistic effects (MIC measurement, time-kill curve), ②severe mouse model, ③in vivo experiments (clinical sickness score, CSS) and ④bacteriological indicators. Although no effect of combination of Kampo medicine and VCM was shown in vitro, weight loss and increase in CSS score of 1 or higher were significantly suppressed in the HET combination group. In addition, in the SRT combination group, CSS (deterioration of fecal condition and weight loss) was significantly suppressed after administration of Kampo medicine compared to the VCM alone administration group. There were multiple individuals in which spores were not detected in the HET or SRT combination group. From the above, it was suggested that the combination of these Kampo medicines in VCM treatment for severe CDI may contribute to suppressing the severity of CDI. (2) Study on the molecular mechanism of the effects of Kampo medicines with anti-obesity effects and the relationship with intestinal flora Obesity is a serious risk factor not only for dyslipidemia, diabetes, cardiovascular disease, cancer, and nonalcoholic fatty liver disease, but also for the aggravation of infectious diseases. Therefore, three types of Kampo medicines used for obesity: Bofutsushosan (BTS), Boiogito (BOT), and Daisaikoto (DST) have antiobesity effects (weight gain suppressive effect, blood lipids, internal organs, etc.). We investigated the molecular mechanism of the anti-obesity effect of Kampo medicine and its relationship with intestinal flora. BTS/DST decreased body weight gain and visceral adipose tissue weight among obesity

	indicators, and showed anti-obesity effects. Furthermore, an increase or decrease in specific intestinal bacteria such as Akkermansia muciniphila was observed due to BTS administration. Based on the above, it is necessary to focus on Kampo medicines that are expected to improve obesity, which is a risk factor for the severity of infectious diseases, and to elucidate its molecular pharmacological mechanism and investigate the involvement of intestinal flora in the future.
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研究代表者	所属	薬学部	職名	教授	補助額	300千円（A）
	氏名	中村 智徳	氏名（英語）	Tomonori Nakamura		

研究課題（日本語）

感染症薬物治療における漢方薬と抗菌薬の併用効果と腸内細菌叢との相関性の解析

研究課題（英訳）

Analysis of the correlation between the combined effect of Kampo medicines and antibiotics in drug treatment of infectious diseases and intestinal flora

１．研究成果実績の概要

感染症重症化のリスク因子や抗微生物薬に対する耐性化への漢方薬の併用効果と作用機構の解明を目的に、2つの研究課題（１）および（２）に取り組んだ。

（１）重症Clostridioides difficile感染モデルにおけるバンコマイシン（VCM）および漢方薬併用による重症化抑制効果の評価

感染症に対する効果が報告されている補中益気湯（HET）および柴苓湯（SRT）のVCMとの併用におけるin vitroの相乗効果（MIC測定、Time-kill curve）および重症マウスモデルを用いたin vivo実験（clinical sickness score, CSS）および細菌学的指標の検討を行った。

In vitroにおける漢方薬の併用効果は示されなかったが、HET併用群では体重減少、CSSスコア１以上の上昇を有意に抑制した。またSRT併用群ではVCM投与群と比較して漢方薬投与後にCSS（糞便状態の悪化、体重減少）を有意に抑制した。HETまたはSRT併用群では芽胞が検出されない個体が複数存在した。

以上より、重症CDIに対するVCM治療におけるこれら漢方薬の併用では、CDIの重症化抑制効果に寄与する可能性が示唆された。

（２）抗肥満作用を有する漢方薬の効果の分子機構および腸内細菌叢の関連に関する検討

肥満は脂質異常症、糖尿病、心血管疾患、癌、非アルコール性脂肪性肝疾患だけでなく、感染症重症化の重篤な危険因子となる。そこで、肥満に対し用いられる3種の漢方薬：防風通聖散（BTS）・防已黄耆湯（BOT）および大柴胡湯（DST）について抗肥満効果（体重増加抑制効果、血中脂質、内臓脂肪低減効果）を比較し、漢方薬の抗肥満効果の分子機構と腸内細菌叢との関連を検討した。

BTS・DSTは肥満指標のうち体重および内蔵脂肪組織重量を減少させ、抗肥満効果を示した。またBTS投与によりAkkermansia muciniphila 等特定の腸内細菌の増減が見られた。

２．研究成果実績の概要（英訳）

We worked on two research topics (1) and (2) with the aim of elucidating the effect and mechanism of action of Kampo medicines in combination with antimicrobial drugs on the risk factors for the severity of infectious diseases and the resistance.

(1) Evaluation of the effect of suppressing aggravation of the combination of vancomycin (VCM) and Kampo medicines in a severe Clostridioides difficile infection model

We examined the combination effects of Hochuekkito (HET) or Saireito (SRT) which have been reported to be effective against infectious diseases with VCM on ①in vitro synergistic effects (MIC measurement, time-kill curve), ②severe mouse model, ③in vivo experiments (clinical sickness score, CSS) and ④bacteriological indicators.

Although no effect of combination of Kampo medicine and VCM was shown in vitro, weight loss and increase in CSS score of 1 or higher were significantly suppressed in the HET combination group. In addition, in the SRT combination group, CSS (deterioration of fecal condition and weight loss) was significantly suppressed after administration of Kampo medicine compared to the VCM alone administration group. There were multiple individuals in which spores were not detected in the HET or SRT combination group.

From the above, it was suggested that the combination of these Kampo medicines in VCM treatment for severe CDI may contribute to suppressing the severity of CDI.

(2) Study on the molecular mechanism of the effects of Kampo medicines with anti-obesity effects and the relationship with intestinal flora

Obesity is a serious risk factor not only for dyslipidemia, diabetes, cardiovascular disease, cancer, and nonalcoholic fatty liver disease, but also for the aggravation of infectious diseases. Therefore, three types of Kampo medicines used for obesity: Bofutsushosan (BTS), Boiogito (BOT), and Daisaikoto (DST) have antiobesity effects (weight gain suppressive effect, blood lipids, internal organs, etc.). We investigated the molecular mechanism of the anti-obesity effect of Kampo medicine and its relationship with intestinal flora.

BTS/DST decreased body weight gain and visceral adipose tissue weight among obesity indicators, and showed anti-obesity effects. Furthermore, an increase or decrease in specific intestinal bacteria such as Akkermansia muciniphila was observed due to BTS administration.

Based on the above, it is necessary to focus on Kampo medicines that are expected to improve obesity, which

is a risk factor for the severity of infectious diseases, and to elucidate its molecular pharmacological mechanism and investigate the involvement of intestinal flora in the future.

３．本研究課題に関する発表

発表者氏名 （著者・講演者）	発表課題名 （著書名・演題）	発表学術誌名 （著書発行所・講演学会）	学術誌発行年月 （著書発行年月・講演年月）
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