品名，規格単位	適応，用法・用量	警告，禁忌，副作用等
顆 オースギ，ツムラ(TJ-79) 1g ¥7.9，テイコク，本草 〔含有生薬〕ソウジュツ，コウボク，チンピ，カンゾウ，タイソウ，ショウキョウ	食前又は食間2～3回に分服(ツ)	
臨床情報	薬学管理のPoint 併用時注意 カンゾウ1g/日	

防已黄耆湯(ボウイオウギトウ)

防已黄耆湯
顆 クラシエ，コタロー，ジュンコウ
顆 JPS，オースギ，太虎堂，ツムラ(TJ-20) 1g ¥10.5，テイコク，本草，マツウラ
錠 クラシエ
〔含有生薬〕ボウイ，オウギ，ソウジュツ，タイソウ，ショウキョウ，カンゾウ

腎炎，ネフローゼ，妊娠腎，陰嚢水腫，肥満症，関節炎，よう，癤，筋炎，浮腫，皮膚病，多汗症，月経不順(色白で筋肉軟らかく水ぶとりの体質で疲れやすく，汗が多く，小便不利で下肢に浮腫をきたし，膝関節の腫痛するもの)
➡ 顆 1日7.5g，食前又は食間2～3回分服(ク)，顆 1日7.5g，食前又は食間2～3回に分服(ツ)，錠 1日18錠，食前又は食間2～3回に分服

創 重大 間質性肺炎，偽アルドステロン症，ミオパチー，肝機能障害，黄疸
併注 カンゾウ含有製剤，グリチルリチン酸含有製剤

臨床情報
処方のPoint 変形性膝関節症を伴う肥満中高年女性がよい適応
薬学管理のPoint モニタ 肝機能 臨検 間質性肺炎の報告 併用時注意 カンゾウ1.5～2g/日 組成違い (ツ)はソウジュツ，(コ)(ク)はビャクジュツ 錠あり (ク)

防風通聖散(ボウフウツウショウサン)

防風通聖散
顆 クラシエ，コタロー，三和，東洋
顆 JPS，オースギ，太虎堂，ツムラ(TJ-62) 1g ¥9.1，テイコク，本草，マツウラ
錠 クラシエ
〔含有生薬〕オウゴン，カンゾウ，キキョウ，セッコウ，ビャクジュツ，ダイオウ，ケイガイ，サンシシ，シャクヤク，センキュウ，トウキ，ハッカ，ボウフウ，マオウ，レンギョウ，ショウキョウ，カッセキ，無水ボウショウ

高血圧の随伴症状(動悸，肩こり，のぼせ)，肥満症，むくみ，便秘(腹部に皮下脂肪が多く，便秘がちなもの)
➡ 顆 1日7.5g，食前又は食間2～3回に分服(ク)，顆 1日7.5g，食前又は食間2～3回に分服(ツ)，錠 1日27錠，食前又は食間2～3回に分服

創 重大 間質性肺炎，偽アルドステロン症，ミオパチー，肝機能障害，黄疸
併注 マオウ含有製剤，エフェドリン類含有製剤，MAO阻害薬，甲状腺製剤，カテコラミン製剤，キサンチン系薬，カンゾウ含有製剤，グリチルリチン酸含有製剤

臨床情報
処方のPoint メタボリック症候群の諸症状に有用．18種類の構成生薬があり，他の漢方と併用しない
薬学管理のPoint モニタ 肝機能 臨検 間質性肺炎の報告 マオウ含有 循環器系障害の患者等で注意 ダイオウ含有 妊婦等で注意 併用時注意 カンゾウ2g/日 錠あり (ク)

補中益気湯(ホチュウエッキトウ)

補中益気湯
錠 太虎堂
顆 クラシエ，コタロー，三和，ジュンコウ，東洋

夏やせ，病後の体力増強，結核症，食欲不振，胃下垂，感冒，痔，脱肛，子宮下垂，陰萎，半身不随，多汗症(消化機能が衰え，四肢倦怠感著

創 重大 間質性肺炎，偽アルドステロン症，ミオパチー，肝機能障害，黄疸
併注 カンゾウ含有製剤，グリ

品名，規格単位	適応，用法・用量	警告，禁忌，副作用等
顆 JPS，オースギ，太虎堂，ツムラ(TJ-41) 1g ¥25.1，テイコク，(東亜薬品)，本草 〔含有生薬〕オウギ，ソウジュツ，ニンジン，トウキ，サイコ，タイソウ，チンピ，カンゾウ，ショウマ，ショウキョウ	しい虚弱体質者) ➡ 錠 1日7.5g，食前又は食間3回に分服，顆 1日7.5g，食前又は食間2～3回に分服(ク)，顆 1日7.5g，食前又は食間2～3回に分服(ツ)	チルリチン酸含有製剤
臨床情報	処方のPoint 3大補剤の1つ，「医王湯」の別名を持つ補剤の王者で「気虚」の病態に広く使用．飲みやすい味で，癌患者の治療中に用いられる．夏バテや食欲不振時にも用いる 安全性情報 間質性肺炎(05年8月：216) 薬学管理のPoint モニタ 肝機能 臨検 間質性肺炎の報告 併用時注意 カンゾウ1.5g/日 組成違い (ツ)はソウジュツ，(コ)(ク)はビャクジュツ	

麻黄湯(マオウトウ)

麻黄湯
顆 クラシエ，コタロー，ジュンコウ
顆 ツムラ(TJ-27) 1g ¥8.1，テイコク，本草
〔含有生薬〕マオウ，キョウニン，ケイヒ，カンゾウ

感冒，インフルエンザ(初期のもの)，関節リウマチ，喘息，乳児の鼻閉塞，哺乳困難(悪寒，発熱，頭痛，腰痛，自然に汗の出ないもの)
➡ 顆 1日6g，食前又は食間2～3回に分服(ク)，顆 1日7.5g，食前又は食間2～3回に分服(ツ)

創 重大 偽アルドステロン症，ミオパチー
併注 マオウ含有製剤，エフェドリン類含有製剤，MAO阻害薬，甲状腺製剤，カテコラミン製剤，キサンチン系薬，カンゾウ含有製剤，グリチルリチン酸含有製剤

臨床情報
薬学管理のPoint マオウ含有 循環器系障害の患者等で注意 併用時注意 カンゾウ1.5g/日

麻黄附子細辛湯(マオウブシサイシントウ) 妊(ツ除く)

麻黄附子細辛湯
顆 三和
顆 ツムラ(TJ-127) 1g ¥19.8
カ コタロー
〔含有生薬〕マオウ，サイシン，修治ブシ末

感冒，気管支炎(悪寒，微熱，全身倦怠，低血圧で頭痛，めまいあり，四肢に疼痛冷感あるもの)
➡ 顆 1日4.5g，食前又は食間3回に分服，顆 1日7.5g，食前又は食間2～3回に分服，カ 1日6カプセル，食前又は食間2～3回に分服

創 重大 肝機能障害，黄疸
併注 マオウ含有製剤，エフェドリン類含有製剤，MAO阻害薬，甲状腺製剤，カテコラミン製剤，キサンチン系薬

臨床情報
薬学管理のPoint モニタ 肝機能 マオウ含有 循環器系障害の患者等で注意 ブシ含有 小児には慎重投与 カプセルあり (コ)

麻杏甘石湯(マキョウカンセキトウ)

麻杏甘石湯
顆 コタロー，ジュンコウ

小児喘息，気管支喘息
➡ 顆 1日6g，食前又は食間2～3回に分服(白)，顆 1日7.5g，食前又は食間2～3回に

創 重大 偽アルドステロン症，ミオパチー
併注 マオウ含有製剤，エフェドリン類含有製剤，MAO阻害

品名,規格単位	適応,用法・用量	警告,禁忌,副作用等
細 オースギ,ツムラ(TJ-55)1g¥69,テイコク,(東亜薬品),本草,マツウラ〔含有生薬〕セッコウ,キョウニン,マオウ,カンゾウ	分服(ツ)	薬,甲状腺製剤,カテコラミン製剤,キサンチン系薬,カンゾウ含有製剤,グリチルリチン酸含有製剤
臨床情報	薬学管理のPoint マオウ含有 循環器系障害の患者等で注意 併用時注意 カンゾウ2g/日	

麻杏薏甘湯(マキョウヨクカントウ)

麻杏薏甘湯 細 クラシエ,コタロー,三和 顆 JPS,オースギ,ツムラ(TJ-78)1g¥95,(東亜薬品) 〔含有生薬〕マオウ,キョウニン,ヨクイニン,カンゾウ	関節痛,神経痛,筋肉痛 ➡ 細 1日6g,食前又は食間2～3回に分服(ク),顆 1日7.5g,食前又は食間2～3回に分服(ツ)	副 重大 偽アルドステロン症,ミオパチー 併注 マオウ含有製剤,エフェドリン類含有製剤,MAO阻害薬,甲状腺製剤,カテコラミン製剤,キサンチン系薬,カンゾウ含有製剤,グリチルリチン酸含有製剤
臨床情報	薬学管理のPoint マオウ含有 循環器系障害の患者等で注意 併用時注意 カンゾウ2g/日	

麻子仁丸(マシニンガン)

麻子仁丸 細 コタロー 顆 オースギ,ツムラ(TJ-126)1g¥71 〔含有生薬〕マシニン,コウボク,キジツ,シャクヤク,キョウニン,ダイオウ	便秘 ➡ 細 1日6g,食前又は食間2～3回に分服,顆 1日7.5g,食前又は食間2～3回に分服(ツ)	
臨床情報	薬学管理のPoint ダイオウ含有 妊婦等で注意	

木防己湯(モクボウイトウ)

木防己湯 細 コタロー,三和 顆 ツムラ(TJ-36)1g¥141 〔含有生薬〕ボウイ,ケイヒ,ニンジン,セッコウ	心臓,あるいは腎臓に基づく疾患,浮腫,心臓性喘息(顔色がさえず,咳を伴う呼吸困難があり,心臓下部に緊張圧重感があるもの) ➡ 細 1日6g,食前又は食間2～3回に分服(ヨ),顆 1日7.5g,食前又は食間2～3回に分服	

薏苡仁湯(ヨクイニントウ)

薏苡仁湯 細 クラシエ,ジュンコウ,東洋 顆 オースギ,ツムラ(TJ-52)1g¥102,本草,マツウラ	関節痛,筋肉痛 ➡ 細 1日6g,食前又は食間2～3回に分服(ク),顆 1日7.5g,食前又は食間2～3回に分服(ツ),錠 1日18錠,食前又は食間2～3回に分服	副 重大 偽アルドステロン症,ミオパチー 併注 マオウ含有製剤,エフェドリン類含有製剤,MAO阻害薬,甲状腺製剤,カテコラミン製剤,キサンチン系薬,カンゾウ含有製剤,グリチルリチン

品名,規格単位	適応,用法・用量	警告,禁忌,副作用等
錠 クラシエ〔含有生薬〕マオウ,トウキ,ソウジュツ,ヨクイニン,ケイヒ,シャクヤク,カンゾウ		酸含有製剤
臨床情報	処方のPoint マオウ含有 循環器系障害の患者等で注意 併用時注意 カンゾウ2g/日 組成違い(ツ)(マ)のみソウジュツ,他はビャクジュツ 錠あり(ク)	

抑肝散(ヨクカンサン)

抑肝散 細 オースギ,ツムラ(TJ-54)1g¥118〔含有生薬〕ソウジュツ,ブクリョウ,センキュウ,チョウトウコウ,トウキ,サイコ,カンゾウ	神経症,不眠症,小児夜泣き,小児疳症(虚弱な体質で神経が高ぶるもの) ➡ 1日7.5g,食前又は食間2～3回に分服	副 重大 間質性肺炎,偽アルドステロン症,ミオパチー,肝機能障害,黄疸 併注 カンゾウ含有製剤,グリチルリチン酸含有製剤
臨床情報	処方のPoint 「肝」は肝臓ではなく精神活動を指し,本剤は精神安定作用を示す.イライラ感,興奮,不眠等の際に用いる.認知症にもよく用いられる 安全性情報 間質性肺炎,肝機能障害,黄疸(10年7月:271) 薬学管理のPoint モニタ 肝機能 指導 間質性肺炎の報告 併用時注意 カンゾウ1.5g/日	

抑肝散加陳皮半夏(ヨクカンサンカチンピハンゲ)

抑肝散加陳皮半夏 細 クラシエ,コタロー 顆 ツムラ(TJ-83)1g¥159〔含有生薬〕ハンゲ,ソウジュツ,ブクリョウ,センキュウ,チンピ,トウキ,チョウトウコウ,サイコ,カンゾウ	神経症,不眠症,小児夜泣き,小児疳症(虚弱な体質で神経が高ぶるもの) ➡ 細 1日7.5g,食前又は食間2～3回に分服(ク),顆 1日7.5g,食前又は食間2～3回に分服	副 重大 偽アルドステロン症,ミオパチー 併注 カンゾウ含有製剤,グリチルリチン酸含有製剤
臨床情報	薬学管理のPoint 併用時注意 カンゾウ1.5g/日 組成違い(ツ)はソウジュツ,(ヨ)(ク)はビャクジュツ	

六君子湯(リックンシトウ)

六君子湯 細 クラシエ,コタロー,三和,東洋 顆 オースギ,ツムラ(TJ-43)1g¥201,テイコク,本草,マツウラ〔含有生薬〕ソウジュツ,ニンジン,ハンゲ,ブクリョウ,タイソウ,チンピ,カンゾウ,ショウキョウ	胃炎,胃アトニー,胃下垂,消化不良,食欲不振,胃痛,嘔吐(胃腸の弱いもので,食欲がなく,みぞおちがつかえ,疲れやすく,貧血性で手足が冷えやすいもの) ➡ 細 1日6g,食前又は食間2～3回に分服(ク),顆 1日7.5g,食前又は食間2～3回に分服(ツ)	副 重大 偽アルドステロン症,ミオパチー,肝機能障害,黄疸 併注 カンゾウ含有製剤,グリチルリチン酸含有製剤
臨床情報	処方のPoint シスプラチンによる食欲不振に対して,グレリンを介した食欲増進効果あり 薬学管理のPoint モニタ 肝機能 併用時注意 カンゾウ1～1.5g/日 組成違い(ツ)はソウジュツ,(ヨ)(ク)はビャクジュツ	

品名，規格単位	適応，用法・用量	警告，禁忌，副作用等
立効散（リッコウサン）		
立効散 顆 ツムラ(TJ-110)1g ¥10.9 〔含有生薬〕サイシン，ショウマ，ボウフウ，カンゾウ，リュウタン	抜歯後の疼痛，歯痛 ➡ 1日7.5g，食前又は食間2～3回に分服	副 重大 偽アルドステロン症，ミオパチー 併注 カンゾウ含有製剤，グリチルリチン酸含有製剤
臨床情報	薬学管理のPoint 併用時注意 カンゾウ1.5g/日	
竜胆瀉肝湯（リュウタンシャカントウ）		
竜胆瀉肝湯 錠 太虎堂 細 コタロー，三和，ジュンコウ，太虎堂，東洋 顆 太虎堂，ツムラ(TJ-76)1g ¥11.7 〔含有生薬〕トウキ，ジオウ，モクツウ，オウゴン，タクシャ，シャゼンシ，カンゾウ，サンシシ，リュウタン	排尿痛，残尿感，尿の濁り，こしけ（比較的体力があり，下腹部筋肉が緊張する傾向があるもの） ➡ 錠 1日7.5g，食前又は食間3回に分服，細 1日9g，食前又は食間2～3回に分服（㋓），顆 1日7.5g，食前又は食間2～3回に分服（㋐）	副 重大 偽アルドステロン症，ミオパチー，肝機能障害，黄疸 併注 カンゾウ含有製剤，グリチルリチン酸含有製剤
臨床情報	安全性速報 肝機能障害，黄疸（10年12月：275） 薬学管理のPoint モニタ 肝機能 ジオウ含有 胃腸虚弱者注意 併用時注意 カンゾウ1～1.5g/日	
苓甘姜味辛夏仁湯（リョウカンキョウミシンゲニントウ）		
苓甘姜味辛夏仁湯 細 コタロー 顆 ツムラ(TJ-119)1g ¥21.4 〔含有生薬〕ブクリョウ，キョウニン，ハンゲ，サイシン，カンキョウ，カンゾウ，ゴミシ	気管支炎，気管支喘息，心臓衰弱，腎臓病（貧血，冷え症で喘鳴を伴う喀痰の多い咳嗽があるもの） ➡ 1日7.5g，食前又は食間2～3回に分服	副 重大 偽アルドステロン症，ミオパチー 併注 カンゾウ含有製剤，グリチルリチン酸含有製剤
臨床情報	薬学管理のPoint 併用時注意 カンゾウ2g/日	
苓姜朮甘湯（リョウキョウジュツカントウ）		
苓姜朮甘湯 細 コタロー，三和 顆 ツムラ(TJ-118)1g ¥9，本草 〔含有生薬〕ブクリョウ，ビャクジュツ，カンキョウ，カンゾウ	腰痛，腰の冷え，夜尿症（腰に冷えと痛みがあって，尿量が多いもの） ➡ 細 1日6g，食前又は食間2～3回に分服（㋒），顆 1日7.5g，食前又は食間2～3回に分服	副 重大 偽アルドステロン症，ミオパチー 併注 カンゾウ含有製剤，グリチルリチン酸含有製剤
臨床情報	薬学管理のPoint 併用時注意 カンゾウ2g/日	

品名，規格単位	適応，用法・用量	警告，禁忌，副作用等
苓桂朮甘湯（リョウケイジュツカントウ）		
苓桂朮甘湯 細 クラシエ，コタロー，三和，ジュンコウ，東洋 顆 JPS，オースギ，太虎堂，ツムラ(TJ-39)1g ¥7.3，本草，マツウラ 〔含有生薬〕ブクリョウ，ケイヒ，ソウジュツ，カンゾウ	神経質，ノイローゼ，めまい，動悸，息切れ，頭痛（めまい，ふらつきがあり，又は動悸があり尿量が減少するもの） ➡ 細 1日6g，食前又は食間2～3回に分服（㋕），顆 1日7.5g，食前又は食間2～3回に分服（㋐）	副 重大 偽アルドステロン症，ミオパチー 併注 カンゾウ含有製剤，グリチルリチン酸含有製剤
臨床情報	薬学管理のPoint 併用時注意 カンゾウ2g/日	
六味丸（ロクミガン）		
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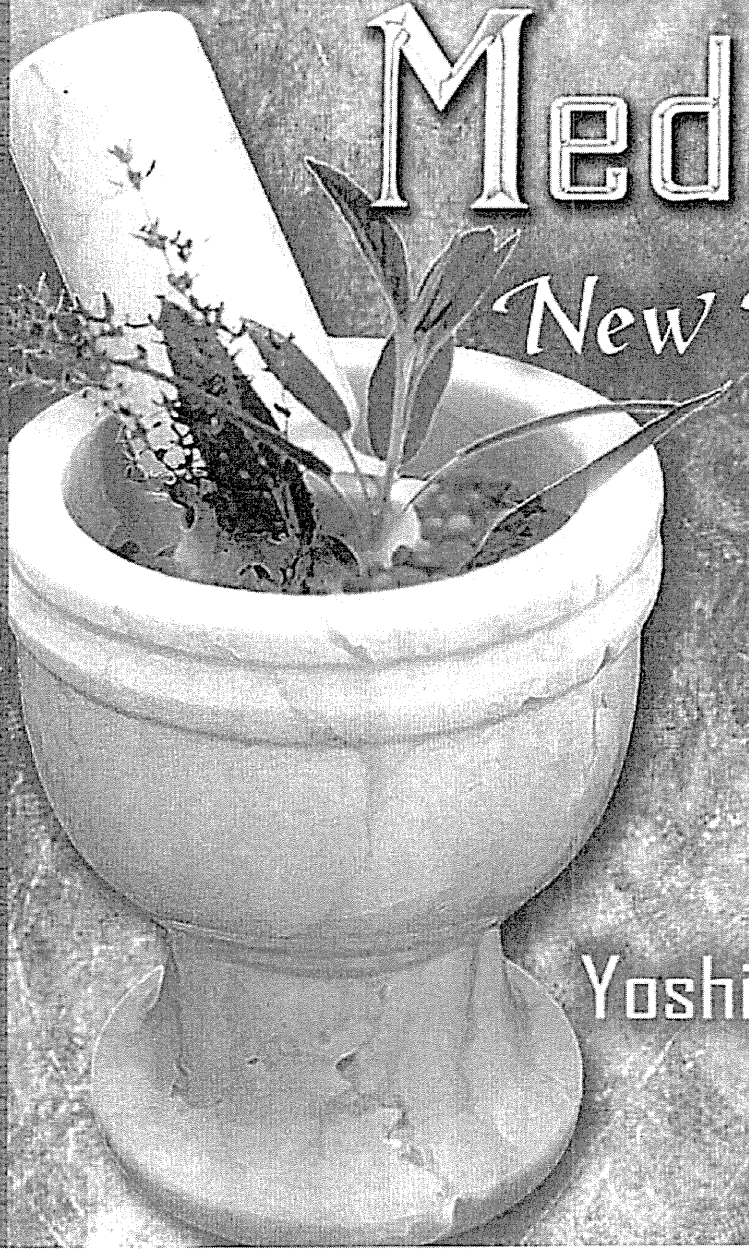

Yoshiharu Motoo
Editor

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MEDICAL PROCEDURES, TESTING AND TECHNOLOGY

TRADITIONAL MEDICINE

NEW RESEARCH

YOSHIHARU MOTOO
EDITOR

New York

Preface

Traditional Medicine (TM) is currently used widely in the world. However, TM is not as universal and standard as Western Medicine (WM). Each TM has its unique characters, and such diversity reflects its history of utilization in each country or region. Traditional East Asian Medicine (TEAM) is the TM, which originated from ancient Chinese Medicine and later developed to Kampo Medicine (Traditional Japanese Medicine), Traditional Korean Medicine (Korean Oriental Medicine), Traditional Vietnamese Medicine, etc. Kampo, with its high-quality finished products and the health insurance coverage, is well incorporated into a modern Westernized medical system in Japan. In China and Korea, TM is basically independent of WM, but recently combination of both TM and WM has been examined.

In this book, there are various unique chapters from molecular, pharmacognostic, pharmacoeconomic, and clinical viewpoints. Especially, several chapters focused on cancer patient care, regarding TM as an important supportive measure. We have other interesting issues such as ethics for East Asian Medicine and perspectives for TM systems. These new researches will surely stimulate future studies on TM.

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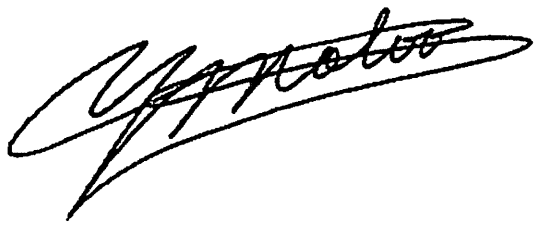

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Chapter 1

Kampo for Cancer Care: Significance as Supportive Measures

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Abstract

Kampo is the Japanese traditional herbal medicine. The aim of Kampo therapy is to improve patients' condition whatever their diseases are. Kampo Medicine plays more and more important roles in closing the gap between modern Western Medicine and demand of patients, especially for the cancer patient. It is also expected to solve the problems such as the side effects of chemotherapy or radiotherapy, appetite loss, and various types of general fatigue or malaise. For instance, rikkunshito (RKT) is the most frequently used and has been proved to be effective for CINV and anorexia. Hangeshashinto (HST) effectively prevents CPT-11-induced delayed diarrhea in animal experiments and in humans. Although Kampo methodology for diagnosis and treatment is referred to as "formulation corresponding to [sho]", some routine treatments as above have produced fruitful results, which were better than expected. In this chapter, we introduce some formulas and recent clinical research on Kampo supportive therapy for the following symptoms of cancer patients. However, it is important to understand that the concept of Kampo medicine is to improve the general condition of patients. The integration of western medicine and Kampo medicine would make new progress in cancer supportive therapy.

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Abbreviation of Kampo Formulas

Rikkunshito	RKT
Hangekobokuto	HKT
Goreisan	GRS
Hangeshashinto	HST
Orengedokuto	OGT
Daikenchuto	DKT
Shokenchuto	SHKT
Mashiningan	MNG
Goshajinkigan	GJG
Hochuekkito	HET
Ninjinyoeito	NYT
Juzentaihoto	JTT

Introduction

Kampo — Japanese traditional herbal medicine — is the most frequently used alternative and complementary medicine in Japan. The aim of Kampo therapy is to improve patients' condition whatever their diseases are. In this concept, Kampo medicine plays a more and more important role in closing the gap between Western Modern Medicine and demands of patients. In Japan, Kampo can be used easily for cancer patient because it is covered by the national health insurance system. It is also expected to relieve the symptoms such as the side effects of chemotherapy and radiotherapy, and various types of general fatigue or malaise. However, Kampo might have an adverse effect against the cytotoxic effects of chemotherapy. It must be continually examined by laboratory data, physical examination, and history of patients.

Although Kampo methodology for diagnosis and treatment is referred to as "formulation corresponding to sho", some routine treatments have been producing better results than expected. This leads to rising expectations for Kampo medicine. An increasing number of reports or studies have been made on Kampo medicine in cancer supportive therapy, from basic research to clinical studies. In this chapter, we introduce some formulas and recent clinical researches on Kampo supportive therapy for cancer patients and the concept of Kampo Medicine in supportive therapy.

1. Chemotherapy-induced Nausea, Vomiting, and Anorexia

Chemotherapy-induced nausea and vomiting (CINV) is potentially the most severe and the most distressing, which sometimes makes completion of chemotherapy impossible. Quite a few Kampo formulas are used to improve CINV and anorexia, for example, rikkunshito (RKT), hangekobokuto (HKT), or goreisan (GRS). Among these Kampo formulas, RKT is

the most frequently used and has been proved to be effective for CINV and anorexia. In this section, we introduce recent clinical and basic research on RKT.

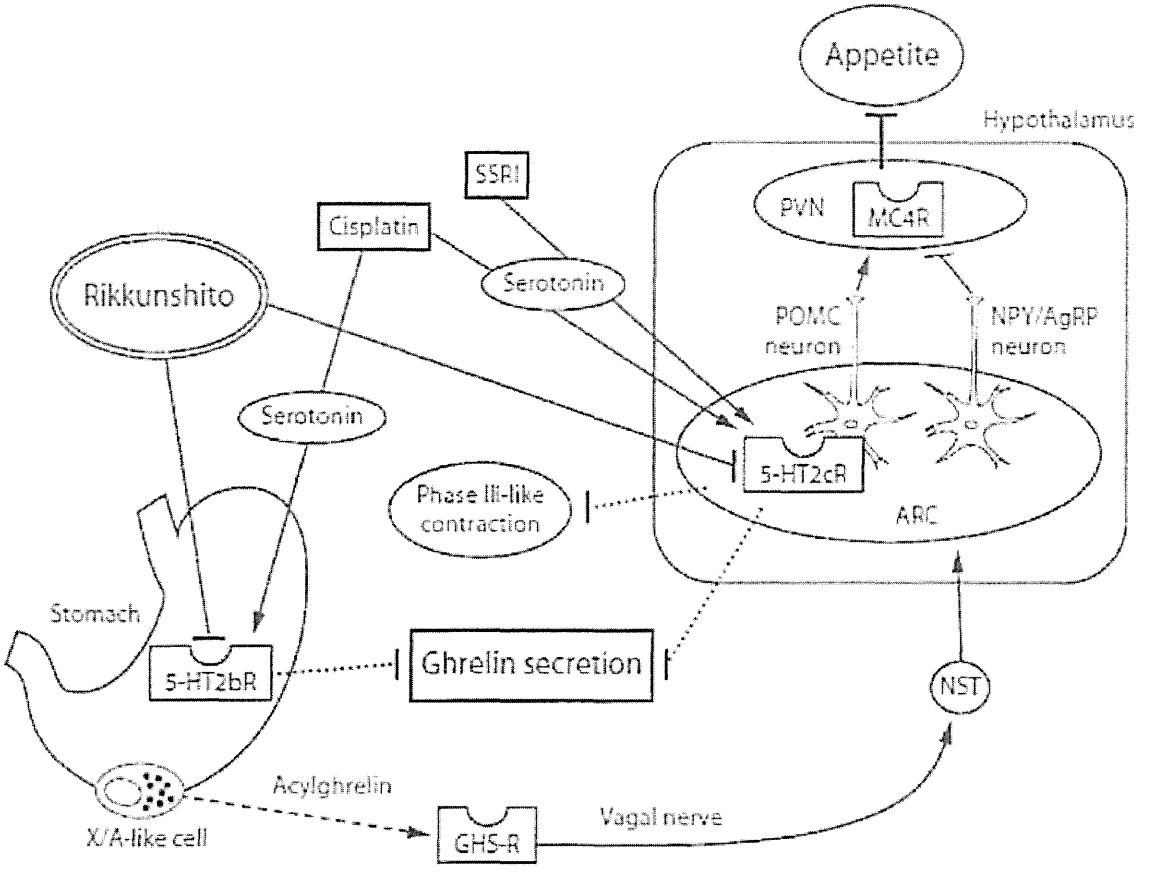

Figure1. Schematic diagram of action mechanisms of rikkunshito on appetite. (revised from [7]).

RKT is composed of eight crude drugs: Atractylodis Lanceae Rhizoma, Ginseng Radix, Pinelliae Tuber, Hoelen, Zizyphi Fructus, Aurantii Nobilis Pericarpium, Glycyrrhizae Radix and Zingiberis Rhizoma. RKT is the most popular Japanese traditional medicine for various gastrointestinal tract disorders, and has been used for patients with hypofunctional constitution and anorexia, heaviness of stomach, and stomach discomfort. In a double-blind controlled study, RKT significantly ameliorated dysmotility-like dyspepsia and upper gastric symptoms such as nausea and anorexia [1] [2]. Several studies in rats have proved the enhanced gastric emptying and a protective effect on gastric mucosa injury with RKT administration. These findings show that RKT might be useful for treatment of anorexia and may provide a new strategy for improvement of upper gastrointestinal dysfunction in cancer patients.

Ghrelin is the key factor of the mechanism of RKT. Ghrelin is a 28-amino-acid orexigenic hormone that stimulates growth hormone release and enhances feeding and weight gain to regulate energy homeostasis [3]. It has recently been shown that RKT ameliorates cisplatin-induced anorexia by an increase of the circulating ghrelin concentration. Cisplatin causes a significant decrease in plasma ghrelin and appetite loss in rodents, and intravenous injection of exogenous acylated ghrelin inhibits the appetite loss after cisplatin administration. It is also reported that RKT suppresses cisplatin-induced anorexia in rat via 5-HT2 receptor

antagonism [4]. Moreover, rat models with decreased contractions of the antrum and duodenum induced with a selective serotonin reuptake inhibitor were reversed by RKT via enhancement of the circulating ghrelin concentration [5]. It is also demonstrated that RKT improves anorexia of aging via inhibiting reduced hypothalamic ghrelin receptor reactivity [6]. RKT inhibits peripheral 5-HT2B and central 5-HT2C receptor and stimulates secretion of ghrelin from the stomach (Figure 1) [7]. Moreover, RKT also enhances ghrelin receptor reactivity via PDE3 inhibition. These studies show RKT is effective in treating anorexia in cancer patients.

In Kampo medicine, formulas that expel dampness are often used for patients with CINV. GRS is one of the most major formulas that expel dampness. GRS includes five crude drugs: Alismatis Rhizoma, Poria, Polyporus, Atractylodis macrocephalae Rhizoma, and Cinamomoni Cortex. GRS promotes urination, which is the principal way to expel dampness from the body. It is especially effective for severe vomiting immediately after drinking water, which is called "water rebellion disorder".

HKT is an important formula that can be used for many disorders with somatic and psychoemotional symptoms. It is also used to treat functional dyspepsia [8]. Since most of cancer patients feel anxiety, fear, or discomfort for their disease, their symptoms are often influenced by their emotion. Moreover, it is classically considered one of the representative formulations to improve abdominal bloating, which includes an excess of abdominal gas in its pathophysiology. Therefore, HKT seems to be very effective for CINV of patients with an excess of abdominal gas and anxiety.

2. Chemotherapy-induced Diarrhea

Irinotecan hydrochloride (CPT-11) possesses a wide antitumor spectrum against lung cancer, colon cancer, malignant lymphoma, and so on. It is a semisynthetic derivative of camptothecin and an anticancer drug which inhibits nucleic acid synthesis by topoisomerase I inhibition [9]. The leading side effects of CPT-11 include diarrhea, which occurs in 63–79% of the patients. This side effect is the main reason for discontinuing administration. There are two types of CPT-11-induced diarrhea: acute diarrhea that occurs during the early stages of drug administration, and delayed diarrhea that occurs during later stages. The former is thought to be caused by the anticholinesterase actions of CPT-11. It is mostly transient in nature, and can be treated effectively with anticholine drugs [10]. The latter sometimes develops into severe diarrhea, which is difficult to control. For this reason, other patients drop out from taking CPT-11 [10]. The mechanism of CPT-11-induced delayed diarrhea is as follows. CPT-11 is metabolized to 7-ethyl-10-hydroxycamptothecin (SN-38) in the liver, and inactivated by glucuronate conjugation as SN-38 glucuronide. It is deconjugated by β-glucuronidase of intestinal bacteria, and returns as SN-38 in the bile [11]. Activated SN-38 directly damages the intestinal mucous membrane and induces delayed diarrhea.

HST, containing baicalin, serves as a β-glucuronidase inhibitor, which prevents the deconjugation of inactive SN-38. Experiments with rats have shown that it effectively prevents CPT-11-induced delayed diarrhea [12], and HST can effectively prevent diarrhea caused by CPT-11 [13]. Moreover, a randomized comparative trial in combination therapy

with cisplatin and CPT-11 in advanced non-small-cell lung carcinoma (NSCLC) showed that HST reduces the rate of CPT-11-induced severe diarrhea (grade3 and 4) [14].

HST contains seven crude drugs: Pinellaiae Tuber, Scutellariae Radix, Glycyrrhizae Radix, Zizyphi Fructus, Ginseng Radix, Coptitis Rhizoma, and Zingiberis Siccatum Rhizoma. In Kampo medicine, HST is indicated for focal distention caused by clumping of constrained heat and fluids in the epigastrium. In this concept, it is used for nausea, emesis, diarrhea, acute and chronic gastroenteritis, or dysfunction of all digestive systems.

In a colitis animal model, HST down-regulates the pro-inflammatory prostaglandins. HST effectively prevents CPT-11-induced delayed diarrhea in animal experiments [12, 15]. Moreover, one of the main ingredients of HST, Coptis Rhizome, contains berberin. Berberine inhibits butyrate-induced colonic epithelial cell death. The other important ingredient, Scutellariae Radix, contains baicalin, which is an inhibitor of β-glucuronidase.

3. Chemotherapy-induced Oral Mucositis

Chemotherapy induced oral mucositis (COM) is a common adverse effect associated with cytotoxic cancer chemotherapy. COM results in severe discomfort and impairment of patients' ability to eat, swallow, or speak. COM sometimes demands an unfavorable modification or reduction of chemotherapy, which may affect the survival rate. Chemotherapy-induced myelosuppression places patients at significant risk of bacteremia and sepsis from oral microorganisms resulting in increased COM[16]. Factors that exacerbate COM also activate the cyclooxygenase pathway that mediates ulcer and pain through the upregulation of pro-inflammatory prostaglandins [17].

It is shown that hangeshashinto (HST) downregulates the pro-inflammatory prostaglandins, such as prostaglandin E2 in colitis animal models [18, 19]. As mentioned in diarrhea section, berberine in HST has broad-spectrum antibacterial activity and inhibits butyrate-induced colonic epithelial cell death [20, 21]. Repeated topical application of HST improved the COM symptoms in the majority of patients [22]. It is also noted that two-thirds of patients on FOLFIRI (leucovorin, 5FU, and irinotecan) treatment developed COM. Mucosal lesions typically appear between 7 and 14 days after the initiation of chemotherapy, mainly on the movable mucosa and rarely affecting the dorsum of the tongue, the hard palate, or the gingiva [22]. Compounds like berberine might be responsible for the antimicrobial and anti-inflammatory effects, suppression of prostaglandins, and alleviation of COM symptoms by HST. In Kampo medicine, oral mucositis is caused by excess heat in the chest and diaphragm. Those that clear heat in the chest and diaphragm are called "shashinto" group, which means "Drain the Heart". HST is the representative formula in this group. The other important formula in this group is orengedokuto (OGT). "Shashinto"s resolves anxiety, malaise, or pain. HST and OGT are both often used for oral mucositis.

4. Bowel Obstruction/Constipation

In cancer patients after laparotomy and intestinal manipulation, gastrointestinal motility decreases, gastrointestinal transit delays, and intra-abdominal adhesion occurs. Adhesion

may cause mechanical bowel obstruction and abdominal pain, resulting in prolonged hospitalization and greater health care utilization in postoperative cancer patients and survivors. In Japan, daikenchuto (DKT) is the most commonly used for prevention and treatment of postoperative bowel obstruction and gastrointestinal disorders. DKT is considered as a safe drug with only a rare incidence of minor side effects [23].

Morphine is one of the most effective anti-nociceptive agents used in pain management of terminal cancer patients. However, it induces severe constipation, causing an obvious reduction in quality of life (QOL) [24]. It is reported that about 60% of patients who take morphine-containing drugs suffer from severe constipation. Other side effects are nausea and vomiting (around 40%), impairment of consciousness (less than 20%) and dysuria (less than 3%). Magnesium oxide or sennoside-containing drugs are typically administered for treatment of constipation, but it is difficult to control the dose of these drugs, and these therapies often become intolerable to the patients. DKT relieves morphine-induced delay of gastrointestinal transit without affecting the anti-nociceptive effects of morphine. Furthermore, DKT causes moderate contraction of morphine-treated longitudinal muscle of ileum and relaxation of morphine-induced contractions of the circular muscle of ileum. These effects of DKT provide a pharmacological basis for recovery from morphine-induced disorder of gastrointestinal transit [25].

DKT is composed of four crude drugs: Zingiberis Siccatum Rhizome, Ginseng Radix, Zanthoxyli Fructus, and Maltosum. The chief ingredient of DKT is Maltosum, which confers a sweet taste and improves the palatability of this formula. DKT warms the intestine and cures abdominal pain, nausea and vomiting. The "kenchu" of DKT represents the reconstruction of gastrointestinal tract; therefore DKT can be translated as, "strong soup for reconstructing gastrointestinal tract."

The neuronal mechanism of DKT in morphine-induced constipation is partly associated with stimulation of serotonin receptors [26] and vanilloid receptors [27] by components of DKT such as (6)-shogaol and hydroxy-*L*-sanshool. Gastrointestinal transit may be coordinated by relaxation of the circular muscle and constriction of the longitudinal muscle through several neuronal networks including serotonin receptors [26, 28]. The accelerating effects of DKT on the rates of intestinal and colonic transits in morphine-treated mice would result from those of Zanthoxyli Fructus. The effect of hydroxy-*L*-sanshool was significantly inhibited by the capsaicin receptor antagonist, capsazepine [29]. Another DKT component, (6)-shogaol, isolated from Zingiberis Rhizome, acts on gastrointestinal motor neurons and facilitates an intestinal transit [30]. Moreover, it is suggested that (6)-shogaol exhibits a capsaicin-like effect on the terminals of primary afferent nerves containing substance P, causing the initial release of neuropeptides and finally depleting the contents of neuropeptides, by subsequent stimulation of the primary afferents [31].

Several important neurally mediated mechanisms are suggested as mediating the increased effective intestinal motility of DKT. One of these mechanisms of action involves the release of calcitonin gene-related peptide (CGRP), a neuropeptide produced by the sensory neurons of the gut. CGRP is the most powerful vasoactive substance and increases mucosal blood flow [32]. Serum calcitonin gene-related peptide level elevates after administration of DKT [33]. Therefore, CGRP in gut function may reveal diverse actions of DKT in the prevention of intestinal adhesions resulting from inflammation.

CGRP binds to the calcitonin receptor-like receptor (CRLR). The former receptor turns into the CRLR through binding of receptor activity modifying protein 1 (RAMP1), a specific

type of modulating membrane protein from the family of RAM proteins. The CRLR family can function as a CGRP receptor or as an adrenomedullin (ADM) receptor depending on the modifying membrane proteins; binding of RAMP2 and/or RAMP3 converts the receptor to the ADM receptor. ADM belongs to the same peptide family as CGRP and has potent vasodilatory effects in the microvascular system. The major difference between CGRP and ADM is that the latter is not produced by neuronal cells, but rather by epithelial, smooth muscle cells, and other non-neuronal tissues. One of the characteristics of the small intestines is the production of ADM from the intestinal epithelial cells. ADM also has anti-inflammatory and powerful anti-cytokine effects and especially inhibits TNFα.

The effect of DKT on blood flow in the rat gut with direct intra-intestinal administration of DKT was associated with the release of CGRP from the sensory nerve terminals of the mucosa, stimulating the expression and subsequent interaction of CGRP receptor and modifying proteins (CRLR and RAMP1), and thereby causing an immediate increase in colonic blood flow. This increase in intestinal blood flow, however, was not observed with oral administration of DKT, which suggested that the actions of DKT were mediated locally rather than systemically [34].

Distal gastrectomy (DG) and pylorus-preserving gastrectomy (PPG) have been employed for gastric cancer. PPG is reported to be superior to DG in regard to postoperative quality of life. However, some patients with PPG still suffer from gastric stasis. Rikkunshito (RKT) improves gastric emptying and postoperative symptoms of patients who have undergone a PPG [35].

In Kampo medicine, there are two popular formulas for constipation in cancer patients. Shokenchuto (SHKT) is in the same group as DKT. SHKT means "small soup for reconstructing gastrointestinal tract". The ingredients of SHKT are Ginger Rhizome, Maltosum, Zizyphi Fructus, Cinnamoni Cortex, Glycyrrhiza Radix, and Peony Radix. This is a popular formula for treating abdominal pain due to cold. It is indicated for those who are in a generally weak and debilitated disposition associated with the loss of essence such that the patient looks pale, is easily exhausted, or feels cold but sweats easily.

Mashiningan (MNG) is composed of Paeoniae Radix, Rhubarb Rhizome, Aurantii Fructus Immaturus Armeniacae Semen, Cannabis Semen and Magnoliae Cortex. MNG is a variation of shojokito that purges heat accumulation and relieves moderate constipation. The chief herb, Cannabis Semen, is rich in oil that moistens the intestine and facilitates bowel movement.

5. Neuropathy

Neuropathy is one of the major reasons that limit treatment tolerability, often necessitating treatment delay or cessation. Neuropathic symptoms may persist for a long time. All platinum analogs are potentially neurotoxic. Oxaliplatin is especially associated with a unique spectrum of neurologic symptoms. Severe oxaliplatin-induced neuropathy, such as sensory ataxia or functional impairment, occurs in 10–20% of patients receiving a higher cumulative dose [36, 37].

The Kampo medicine, goshajinkigan (GJG), is composed of 10 crude drugs: Rehmanniae Radix, Achyranthis Radix, Corni Fructus, Dioscoreae Radix, Plantaginis Semens, Alismatis

Rhizoma, Hoelen, Moutan Cortex, Cinnamomi Cortex, and Aconiti Tuber. It is traditionally used for the treatment of lower back pain, leg pain, difficulty of urination, or knee-joint deformities. It suggested that GJG improved vibration sensation in patients with diabetic neuropathy [38]. GJG is also reported to improve taxanes-induced neuropathy [39]. In a retrospective study, GJG was effective for peripheral neurotoxicity of oxaliplatin in patients with advanced or recurrent colorectal cancer [40]. GJG safely reduced the incidence of severe neuropathy by mFOLFOX6 regimen without any adverse influence on the response rate to mFOLFOX6. It is useful in preventing oxaliplatin-induced neuropathy in patients with non-resectable or recurrent colorectal cancer. Moreover, GJG did not have an influence on tumor response to mFOLFOX6 therapy [41].

GJG may alleviate peripheral neuropathy by several mechanisms [42–44]. The first is that GJG promotes the release of dynorphin, and thus improves numbness/pallesthesia via the opiate system. The second is that GJG promotes nitric oxide production, and thus improves the circulation and blood supply to the nerves. Additionally, oxaliplatin acts on IB4-positive C-fiber nociceptors to induce an oxidative stress-dependent acute painful peripheral neuropathy [45], and GJG reduces transmitter proteins and sensory receptors associated with C-fiber activation [46].

This effect may be one of the mechanisms of GJG that prevents oxaliplatin-induced neuropathy.

6. Vasomotor Symptoms Associated with Cancer Therapy

Vasomotor symptoms associated with cancer therapies are increasingly common problems for breast cancer survivors given the increasing use of ovarian suppression with anti-estradiol (E2) agents, adjuvant chemotherapy in premenopausal women, and aromatase inhibitors in postmenopausal women. Estrogen receptor (ER) positive breast cancers are with additional risks; approximately 60% of breast cancers are ER-positive [47]. In general, hormone replacement therapy (HRT) effectively treats estrogen-deficiency symptoms, but it is probably associated with an increase in breast cancer risk, especially with prolonged use. Thus, it is still difficult to manage estrogen-deficiency symptoms in breast cancer survivors with HRT. In Japan, for vasomotor symptoms of menopause, traditional herbal medicines (Kampo) have been widely used in primary health care. It is possible that Kampo medicines may also be beneficial for breast cancer survivors with estrogen deficiency symptoms. Some clinical use of Kampo medicines for breast cancer survivors has already been reported.

Nyoshinsan (NSS) is indicated for menopausal symptoms such as hot flashes and transient feelings of anxiety. Yet chemicals that possess E2-like activity have not been reported in NSS. NSS is composed of 12 crude drugs: Cyperi Rhizoma, Cnidii Rhizoma, Atractylodis Lanceae Rhizoma, Angelicae Radix, Cinamomi Cortex, Ginseng radix, Arecae Semen, Coptitis Rhizoma, Glycyrrhizae Radix, Carophyllis Flos, and Saussureae Radix. Although NSS contains various chemical substances, neither an elevation in the serum level of E2 nor a decrease in the serum level of FSH is observed. Therefore, the action of NSS may not be based on estrogenic behavior [8].

Unkeito (UKT) is another alternative for menopausal symptoms. UKT is composed of 12 crude drugs; Ophiopogonis Tuber, Pinelliae Tuber, Angelicae Radix, Glycyrrhizae Radix, Cinnamoni Cortex, Paeoniae Radix, Cnidii Rhizoma, Ginseng Radix, Moutan Radix, Evodiae Fructus, Zingiberis Rhizoma, and Asini Gelatum. UKT is used for dysmenorrhea, amenorrhea, or menopausal syndrome. Eight weeks of treatment with UKT enhanced the secretion of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol levels in hyper- (robust) and hypo- (asthenia) functioning patients with first and second grade amenorrhea during a 12-week follow-up. No significant difference was observed in the rate of change of these hormones between hyper- and hypo-functioning patients. It suggests that UKT could be used safely for cancer patients with menopausal symptoms.

7. General Fatigue

General fatigue is a common problem in cancer patients. The most important factors contributing to cancer-related fatigue are anemia, pain, emotional distress, sleep disturbance, and poor nutrition resulting from cancer therapy. Cancer-related fatigue is particularly prevalent with multimodality or dose-intense treatment protocols, and in patients with metastatic disease. In Western medicine, management of cancer-related fatigue involves specific treatment for potentially reversible causes (i.e., treating anemia or metabolic or endocrine abnormalities, as well as managing pain, insomnia, depression, or anxiety) and symptomatic measures. Nonspecific symptomatic treatment measures include education, counseling, and pharmacologic (e.g., psychostimulants) as well as non-pharmacologic (e.g., exercise, yoga, acupuncture) measures. In Kampo medicine, patients with pronounced general fatigue and malaise can be treated with Kampo formulas. In this condition, often considered as loss of vital energy, especially Ginseng Radix and Astragali Radix formulations "jingizai" are said to be effective. These formulas include hochuekkito (HET), jyuzentaihoto (JTT), or ninjin'yoeito (NYT), and are useful for cancer patients.

HET is composed of ten crude drugs: Astragali Radix, Atractylodis Lanceae Rhizoma, Ginseng Radix, Angelicae Radix, Bupleuri Radix, Zizyphi Fructus, Aurantii Nobilis Pericarpium, Glycyrrhizae Radix, Cimicifugae Rhizoma, and Zingiberis Rhizoma.

HET is distinguished from other jingizais by containing Bupleuri Radix, which relieves physical and psychological stress. One-week preoperative treatment with HET was effective for improving pre- and postoperative nutritional status and immune function in patients scheduled to undergo laparotomy for large intestine carcinoma in randomized controlled trial using sealed envelopes for allocation (RCT-envelope). Mean prealbumin level was higher in the HET group from the day before surgery to 7 days after surgery. IL-6 was lower in the HET group on postoperative day 1. It was suggested that preoperative treatment with HET is useful for early recovery from surgery for colorectal carcinoma [49]. It is also reported that HET during chemotherapy for lung cancer relieves and improves mood and general malaise [50, 51].

JTT is composed of 10 crude drugs: Astragali Radix, Cinnamoni Cortex, Rehmanniae Radix, Paeoniae Radix, Cnidii Rhizoma, Atractylodis Lanceae Rhizoma, Angelicae Radix, Ginseng Radix, Hoelen, and Glycyrrhizae Radix. NYT is composed of very similar components to JTT. NYT is consist of 12 crude drugs: Rehmanniae Radix, Paeoniae Radix,

Atractylodis Lanceae Rhizoma, Hoelen, Astragali Radix, Ginseng Radix, Cinnamoni Cortex, Angelicae Radix, Polygalae Radix, Schisandrae Fructus, and Glycyrrhizae Radix. JTT significantly prolonged survival rate for advanced breast cancer patients when the JTT group was stratified by Kampo diagnosis [52]. NYT is effective for patients with psychological fatigue and insomnia. The combination of NYT and JTT is effective for reducing myelosuppression and nephrotoxicity associated with chemotherapy [53]. These effects would alleviate general fatigue.

Conclusion

In this chapter, we introduce some formulas mainly with recent clinical and basic researches in Kampo supportive therapy for cancer patients. It is certain that the effort to clarify the mechanism of Kampo formulas, but it is important to understand that the concept of Kampo medicine is to understand and improve the general condition of patients. There are many things to learn from the method of Kampo examination. The integration of western medicine and Kampo medicine would make new progress in cancer supportive therapy.

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Research Article

Study of Factors Involved in Tongue Color Diagnosis by Kampo Medical Practitioners Using the Farnsworth-Munsell 100 Hue Test and Tongue Color Images

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In traditional Japanese medicine (Kampo medicine), tongue color is important in discerning a patient's constitution and medical conditions. However, tongue color diagnosis is susceptible to the subjective factors of the observer. To investigate factors involved in tongue color diagnosis, both color discrimination and tongue color diagnosis were researched in 68 Kampo medical practitioners. Color discrimination was studied by the Farnsworth-Munsell 100 Hue test, and tongue color diagnosis was studied by 84 tongue images. We found that overall color discrimination worsened with aging. However, the color discrimination related to tongue color regions was maintained in subjects with 10 or more years of Kampo experience. On the other hand, tongue color diagnosis significantly differed between subjects with <10 years of experience and ≥10 years of experience. Practitioners with ≥10 years of experience could maintain a consistent diagnosis of tongue color regardless of their age.

1. Introduction

In traditional Japanese medicine (Kampo medicine), observing the tongue shapes and colors is a method for diagnosing the patient's constitution and medical conditions. In addition to the information that the tongue reveals, Kampo evaluations are supplemented with data from questionnaires, pulse, and abdominal diagnosis. Tongue diagnosis is particularly useful for detecting *Mibyou*, the "disease-oriented" healthy stage in Kampo medicine. Kampo tongue information, such as tongue pain in the dental oral area, can be used to prevent potentially refractory diseases [1, 2]. Generally, tongue diagnosis focuses on tongue texture and tongue coating. The colors and shapes of each part can be investigated to diagnose medical conditions.

Mainly, tongue color is the result of light reflection and light absorption. The color of the tongue (tongue color) is especially dependent on internally diffused light. Tongue color diagnosis (TCD) can provide very useful information for medical conditions. By TCD, we can get useful information about the patient's reservoirs of heat and cold, exhaustion level, mental state, digestive system function, blood circulation dynamics, and water metabolic state. However, tongue color diagnosis is affected by two types of factors. One is environmental factors, such as light sources or room temperature, which influence impact diagnosis. The other type includes the subjective factors of the observers, especially their knowledge of Kampo and experience using it.

In recent years, to solve the problem of environmental factors (EF), many researchers have developed a tongue imaging system that operates at constant conditions [3–6]. Chiu devised the hardware and software for tongue imaging and examined the tongue surface and tongue coating, divided into areas related to concepts of traditional medicine [3]. Wang et al. introduced a method of evaluating the color of