Review

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Kampo medicine in the management of menopausal symptoms: A narrative review of therapeutic potential

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SUMMARY: Menopausal symptoms primarily result from ovarian dysfunction and declining estrogen levels, leading to multisystem disorders. Although hormone therapy remains the most effective treatment, its long-term use is associated with significant risks, prompting interest in alternative options. Kampo medicine, a traditional Japanese system derived from Chinese herbal medicine, has gained renewed attention as a complementary and personalized therapeutic approach to menopausal health. This review aims to systematically summarize the current application and clinical evidence of Kampo medicine in the management of menopausal symptoms across multiple domains, including vasomotor, neuropsychiatric, musculoskeletal, skeletal, and genitourinary systems. Furthermore, the review seeks to further validate its efficacy through the mechanistic actions of its key ingredients. While the therapeutic effects of Kampo medicine on hot flashes have been inconsistent, it has demonstrated significant efficacy in improving emotional disturbances, sleep disorders, and somatic symptoms, particularly among individuals whose conditions are not driven solely by hormonal imbalances. In the management of osteoporosis, the integration of Kampo medicine with conventional Western treatments not only enhances overall therapeutic outcomes but also contributes to the reduction of adverse effects. One limitation of current research is the lack of randomized controlled trials (RCTs) evaluating the efficacy of Kampo medicine in managing Genitourinary Syndrome of Menopause (GSM), highlighting the need for further investigation in this area. The integration of Kampo medicine into menopausal symptom management may contribute to a more holistic, patient-centered approach that offers both traditional and Western medical options. This integrative model has the potential to support shared decision-making and improve personalized care for menopausal women.

Keywords: menopausal symptoms, Kampo, traditional herbal medicine, key ingredients

1. Introduction

Menopausal symptoms arise as a consequence of ovarian dysfunction and reduced estrogen secretion, leading to autonomic and neuropsychiatric disturbances. These symptoms include hot flushes, night sweats, dizziness, palpitations, sleep disturbances, mood changes, headaches, musculoskeletal pain, atrophic vaginitis, bladder irritability, and general malaise (*1-3*). Moreover, menopause has been linked to an increased risk of osteopenia, osteoporosis, and ischemic heart disease (*4*).

Menopausal symptoms can last for 4–5 years, with 9% of women still experiencing symptoms at the age of 72 (*5*). Hormone therapy is widely recognized as the most effective treatment for menopausal symptoms. However, extensive research has documented its potential risks, including increased incidences of breast, ovarian, and endometrial cancer, as well as a heightened risk of stroke and thromboembolism, particularly with prolonged use (*6-10*). Since the early 2000s, the use of menopausal hormone therapy has exhibited a substantial decline, particularly among women aged 52 to 65, largely attributable to safety concerns following the initial results of the Women's Health Initiative trial (*6*). Consequently, both patients and healthcare professionals are increasingly seeking alternative therapeutic options that demonstrate efficacy while minimizing adverse effects. In the United States, 82% of physicians advocate for herbal therapies as a complementary approach for managing menopausal symptoms (*11*). Traditional Chinese herbal medicine, known for its relatively mild side effects, is a natural therapeutic approach that has been widely utilized in some Asian countries, such as China and Japan. Its popularity is attributable in part to the relatively mild side effects associated with its use.

In Japan, Kampo medicine has been officially

incorporated into the National Health Insurance System, enabling patients to freely choose between Western and Kampo treatments at an affordable cost. Kampo formulations have become the most widely used form of Complementary and Alternative Medicine recommended by physicians in Japan (*12*). The market size for prescribed Kampo formulations has steadily grown, reaching approximately 162 billion yen per year by 2020 (*13*). Given this growing interest in safer and evidence-based alternatives, Kampo medicine has attracted increasing attention for its therapeutic potential in menopausal care. This narrative review aims to systematically summarize the current applications and clinical evidence of Kampo medicine in managing menopausal symptoms across multiple domains, including vasomotor, neuropsychiatric, musculoskeletal, skeletal, and genitourinary systems.

2. Kampo's basic concepts

Kampo medicine is based on a diagnostic framework that integrates three fundamental dichotomies: Yin-You (yin-yang), Kyo-Jitsu (deficiency-excess), and Netsu-Kan (heat-cold), and three essential physiological substances: Ki (Qi), Ketsu (blood), and Sui (fluid) (*14-16*). According to the principles of Kampo medicine, the onset of menopausal disorders is attributed to imbalances in Ki (Qi), Ketsu, and Sui. These elements have historically been referred to as "Blood Path Syndrome", which is characterized by blood stasis and microcirculatory dysfunction. Ketsu stagnation was identified as the most prevalent pathological condition among menopausal women, with a prevalence of 36.5% among cases. This was followed by Ki regurgitation (25.9%) and Ki stagnation (24.8%) as relatively frequent patterns. Among women whose primary menopausal symptoms were headache, hot flushes, and dizziness, the most commonly associated patterns were Sui metabolism disorders (48.8%), Ketsu stagnation (48.1%), and again Sui metabolism disorders (48.0%), respectively (*17*).

According to Kampo theory, the optimal formula should be selected individually based on four traditional diagnostic methods: *i*) visual inspection, *ii*) auscultation, *iii*) palpation and olfaction, and *iv*) inquiry into the patient's subjective symptoms. These methods enable practitioners to ascertain not only the imbalanced substance (Ki, Ketsu, or Sui), but also the predominant pattern among the dichotomies (yin–yang, deficiency–excess, heat–cold), thereby guiding treatment selection. In accordance with these diagnostic principles, 25 commonly used Kampo formulations (Table 1) have been officially standardized for the treatment of menopausal symptoms, as listed in the official compendium of Kampo medicines and their constituent crude drugs published by the Ministry of Health, Labour and Welfare of Japan (*18*).

3. Kampo for menopausal symptoms

A growing body of research supports the efficacy and safety of Kampo medicine in managing a wide range of menopausal symptoms. The following section will review its studies across five key symptom domains. Table 1 and Table 2 summarize Kampo formulations with existing research evidence for each symptom domain, including their herbal components and mechanisms of action from both traditional and modern medical perspectives.

3.1. Kampo for hot flushes

Approximately 60–80% of menopausal women experience hot flushes and sweating, symptoms that typically peak during the late menopausal transition and the initial phase of menopause (*19*). Menopausal hot flashes are primarily attributed to dysregulation of the hypothalamic thermoregulatory center triggered by fluctuating or declining estrogen levels (*20*). This hormonal disturbance is believed to enhance the activity of neuropeptides such as calcitonin gene-related peptide (CGRP), a potent vasodilator (*21*). Elevated CGRP levels increase skin temperature and promote sweating, contributing directly to the onset of hot flashes (*22*). Keishibukuryogan may alleviate vasomotor symptoms by improving peripheral blood flow and lowering plasma CGRP concentrations, thereby modulating the underlying mechanisms of hot flashes (*23*). Notably, in one clinical study, Keishibukuryogan significantly increased blood flow in the toes, which associated with a reduction in upper body hot flashes and a relief of cold sensations in the lower extremities of postmenopausal women, whereas hormone replacement therapy (HRT) reduced peripheral blood flow (*24*). Similarly, Unkeito has been shown to relieve hot flashes and coldness in the lower limbs by improving poor circulation and modulating excessive peripheral blood flow (*25*). EH0202, a herbal supplement, significantly reduces facial flushing by decreasing facial skin surface blood flow, while also exerting lipid-lowering effects (*26*).

In addition to improving peripheral circulation, some Kampo formulations also appear to alleviate hot flashes by modulating inflammation-related thermoregulatory pathways. Both Keishibukuryogan and Kamishoyosan significantly reduce IL-8 levels, a key cytokine involved in thermoregulation (*27*). In addition, keishibukuryogan decreases circulating monocyte chemotactic protein-1 level in postmenopausal women, which is the primary chemokine responsible for the recruitment of monocytes to sites of active inflammation (*27,28*).

Although several Kampo formulations have demonstrated pharmacological activity and some efficacy in alleviating hot flashes and night sweats, current studies still reveal inconsistent therapeutic outcomes (*29,30*).

3.2. Kampo for emotional and sleep disorders

Table 1. Twenty-five standardized Kampo formulations for menopausal symptom treatment

Japanese name	Synonym	Ingredients	Effects	Ref.
Unkeito	Wen-Jing-Tang	*Angelica, Cnidium, Paeonia (lactiflora), Cinnamomum, Paeonia (suffruticosa), Panax, Glycyrrhiza, Ophiopogon, Pinellia, Zingiber, Colla Corii, Evodia*	Improvement of circulation, alleviation of hot flashes and cold limbs, alleviation of depressive symptoms and anxiety, prevention of bone loss, inhibition of osteoclast activity	(*24*) (*39*) (*57*)
Unseiin		*Rehmannia, Angelica, Cnidium, Paeonia, Coptis, Scutellaria, Gardenia, Phellodend*	—	
Orengedokuto	Huang-Lian-Jie-Du-Tang	*Coptis, Scutellaria, Phellodendron, Gardenia*	—	
Keishibukuryogan	Gui-Zhi-Fu-Ling-Wan	*Cinnamomum, Paeonia (lactiflora), Paeonia (suffruticosa), Prunus, Poria*	Improvement of peripheral blood flow, reduction of plasma CGRP levels, alleviation of vasomotor symptoms including hot flashes and cold sensations, alleviation of sleep disturbances, increase of bone mineral content, improvement of calcium metabolism	(*23*) (*24*) (*38*) (*59*)
Keishibukuryogankayokuinin	Keishibukuryoganyokuinin	*Cinnamomum, Paeonia (lactiflora), Paeonia (suffruticosa), Prunus, Poria, Rehmannia, Gardenia*	—	
Koujito		*Atractylodes, Poria, Alisma, Polyporus, Cinnamomum*	—	
Kousosan		*Citrus, Paeonia (lactiflora), Cyperus, Ligusticum, Glycyrrhiza*	—	
Goshakusan		*Paeonia (lactiflora), Glycyrrhiza, Zingiber, Cinnamomum, Jujube*	—	
Saikokaryukotsuboreito		*Bupleurum, Paeonia (lactiflora), Poria, Cinnamomum, Aconite*	Bone protection, anti-inflammatory effects	(*60*)
Saikokeishikankyoto		*Bupleurum, Paeonia (lactiflora), Scutellaria, Pinellia, Zingiber*	—	
San'oshashinto		*Rehmannia, Plantago, Dioscorea, Alisma, Poria*	—	
San'ousan		*Rehmannia, Plantago, Dioscorea, Alisma, Poria, Cinnamomum*	—	
Shimotsuto		*Angelica, Rehmannia, Paeonia (lactiflora), Cnidium, Atractylodes, Poria*	—	
Hachimisoyosan		*Bupleurum, Paeonia (lactiflora), Atractylodes, Poria, Glycyrrhiza, Angelica, Rehmannia, Cnidium*	—	
Kamishoyosan	Jia-Wei-Xiao-Yao-San	*Bupleurum, Paeonia (lactiflora), Atractylodes, Poria, Glycyrrhiza*	Anti-inflammatory effects, modulation of thermoregulatory pathways, anxiolytic effects, reduction of anxiety symptoms, immunomodulation, alleviation of sleep disturbances	(*27*) (*34*) (35-37) (*38*)
Kamishoyosangoshimotsuto	Kamishoyosankasenkyujio	*Bupleurum, Paeonia (lactiflora), Atractylodes, Poria, Glycyrrhiza, Angelica, Rehmannia, Cnidium*	—	

Table 1. Twenty-five standardized Kampo formulations for menopausal symptom treatment (continued)

Japanese name	Synonym	Ingredients	Effects	Ref.
Senkyuchachosan		*Cnidium, Angelica, Rehmannia, Paeonia (lactiflora)*	—	
Tsudosan		*Rhei, Angelica, Cnidium, Paeonia (lactiflora), Citrus*	—	
Tokishakuyakusan		*Angelica, Paeonia (lactiflora), Alisma, Poria, Atractylodes*	Alleviation of sleep disturbances	(*38*)
Tokishakuyakusankaninjin		*Angelica, Paeonia (lactiflora), Alisma, Poria, Atractylodes, Panax*	—	
Tokishakuyakusankabushi		*Angelica, Paeonia (lactiflora), Alisma, Poria, Atractylodes, Aconite*	—	
Nyoshinsan		*Atractylodes, Poria, Alisma, Polyporus, Cinnamomum*	Mood stabilization, improvement of sleep and depressive symptoms	(*45*)
Yokukansan		*Atractylodes, Poria, Angelica, Cnidium, Bupleurum, Glycyrrhiza*	Anxiolytic and hypnotic effects	(*40-42*)
Yokukansankashakuyakuoren		*Atractylodes, Poria, Angelica, Cnidium, Bupleurum, Glycyrrhiza, Paeonia (lactiflora), Coptis*	—	
Yokukansankachinpihange		*Atractylodes, Poria, Angelica, Cnidium, Bupleurum, Glycyrrhiza, Citrus, Pinellia*	Alleviation of sleep disturbances	(*43*)

Table 2. Additional Kampo formulations for menopausal symptoms identified in recent studies

Japanese name	Synonym	Ingredients	Effects	Ref.
EH0202		*Cucurbita, Plantago, Lonicera, Carthamus*	Reduction of facial flushing	(*26*)
Porcine Placental Extract (PPE)		*Extractum Placentae*	Alleviation of depression and anxiety	(*44*)
Hachimijiogan	Ba-Wei-Di-Huang-Wan	*Rehmannia, Cornus, Dioscorea, Poria, Alisma, Paeonia (suffruticosa), Cinnamomum, Aconitum*	Enhancement of calcium metabolism, prevention and treatment of osteoporosis	(*54*)
Kamikihito		*Panax, Astragalus, Atractylodes, Poria, Ziziphus, Polygala, Zingiber, Glycyrrhiza, Angelica, Paeonia (lactiflora), Zizyphus, Saussurea, Cinnamomum, Bupleurum, Ginseng*	Increase of bone mass	(*58*)
Keishibukuryogan and bushi		*Cinnamomum, Paeonia (lactiflora), Paeonia (suffruticosa), Prunus, Poria, Aconitum*	Alleviation of lower back pain	(*74*)
Boiogito		*Sinomenium, Astragalus, Ziziphus, Glycyrrhiza, Zingiber, Atractylodes (lancea)*	Alleviation of joint and muscle pain, improvement of mobility and physical function	(*64,66*)
Keishikaryoujutsubuto		*Cinnamomum, Paeonia (lactiflora), Glycyrrhiza, Zingiber, Ziziphus, Atractylodes (lancea), Poria*	Alleviation of joint and muscle pain	(*64-65*)

The menopausal transition is associated with an elevated risk of mood disorders (*31*), with the incidence of first-onset depression being approximately twice as high as in premenopausal women (*32*). Epidemiological surveys indicate that the incidence of anxiety and depression among perimenopausal women ranges between 21% and 25% (*33*). There is a bidirectional relationship between mood and sleep, and sleep disturbances are increasingly recognized as a core component of menopausal psychological symptoms rather than a secondary complaint. Anxiety and depression frequently coexist with insomnia, and all three are influenced by overlapping neuroendocrine and neurotransmitter mechanisms during the menopausal transition.

Higuchi *et al.* demonstrated that peri-menopausal women with nonspecific symptoms who were treated with Kamishoyosan exhibited significantly lower Hamilton anxiety scores compared to those receiving HRT (*34*). Beyond endocrine mechanisms, immune factors are also involved in the development and aggravation of menopausal symptoms (*35*). Kamishoyosan has been shown to alleviate these symptoms while reducing serum levels of IL-6 and sIL-6R (*36*). It also increases TNF-α concentrations, suggesting that cytokines may influence mood regulation *via* the central nervous system and can be modulated by herbal interventions (*37*). In addition, research has shown that Japanese Kampo formulations, such as Tokishakuyakusan, Kamishoyosan, and Keishibukuryogan, are effective in alleviating sleep disturbances in perimenopausal women, improving sleep onset, reducing sleep interruptions, and enhancing restorative sleep (*38*). Furthermore, the combined use of Unkeito and HRT has been found to significantly reduce scores on the Self-Rating Depression Scale and alleviate both depressive symptoms and anxiety levels, as measured by the State-Trait Anxiety Inventory (*39*).

The Japanese Kampo Medicine Clinical Practice Guidelines recommend Yokukansan for treating menopausal insomnia (*40*). Studies also have shown that it can reduce anxiety and improve sleep quality, likely through modulation of central neurotransmitter systems (*41*). Yokukansan has been shown to enhance the anxiolytic effect of fluvoxamine by downregulating 5-HT_{2A} receptor expression in the prefrontal cortex, suggesting that their combination may provide a synergistic approach for the treatment of anxiety disorders (*42*). YokuKansan-ka-chimpihange is a Kampo compound formula derived from the classical prescription Yokukansan, with the addition of *Citrus reticulata* and *Pinellia*. One polysomnographic study has shown that YokuKansan-ka-chimpihange significantly increases total sleep time in healthy adults and demonstrates a tendency to improve sleep efficiency and reduceP sleep latency (*43*).

Oral administration of porcine placental extract (PPE) over a 24-week period significantly reduced scores on the Simplified Menopausal Index, Zung's Self-Rating Depression Scale, and the State-Trait Anxiety Inventory, indicating notable improvements in anxiety and depressive symptoms (*44*). Nyoshinsan, one of the commonly used Kampo formulations for managing menopausal symptoms, has demonstrated clinical efficacy in alleviating psychiatric manifestations such as nocturnal awakening and depressive mood. Notably, its therapeutic effects appear to be more pronounced in women with a higher body mass index (*45*).

While HRT is effective in relieving vasomotor symptoms, its effects on psychiatric symptoms such as insomnia, anxiety, depression, dizziness, and irritability are limited (*46,47*). Not all climacteric symptoms can be explained by ovarian hypofunction alone (*48,49*), and estrogen therapy has significant limitations in addressing psychological manifestations.

3.3. Kampo for osteoporosis

Osteoporosis is a metabolic bone disease characterized by degenerative changes in bone microarchitecture, leading to increased bone fragility and a higher risk of fractures. It affects more than 200 million people worldwide (*50*), with postmenopausal women being particularly vulnerable due to estrogen deficiency. Estrogen deficiency accelerates trabecular bone loss and induces the production of proinflammatory cytokines such as IL-6, which enhance osteoclast activity and contribute to the development of postmenopausal osteoporosis (*51*). Currently, clinical management of osteoporosis primarily relies on two therapeutic strategies: anti-resorptive agents and bone anabolic agents. However, long-term use of anti-resorptive agents such as bisphosphonates may lead to complications like osteonecrosis of the jaw (*52*) or atypical fractures (*53*), while HRT also carries potential side effects.

Compared to synthetic drugs, Kampo medicines are known for their fewer adverse effects, making them more suitable for long-term use. Hachimi-jio-gan (HJG) has been shown to enhance calcium metabolism (*54*) and demonstrate efficacy in osteoporosis prevention and treatment (*55*). Furthermore, a study in ovariectomized rats found that HJG inhibited bone resorption without significantly affecting bone formation. Notably, combining HJG with alendronate significantly improved trabecular bone mass and microstructure compared to either treatment alone (*56*). Similarly, Unkeito (*57*) has been reported to suppress RANKL-induced osteoclastogenesis, promote osteoclast apoptosis, and prevent bone loss in ovariectomized mice, highlighting its potential as a therapeutic agent for postmenopausal osteoporosis. Kamikihito has been shown to effectively increase bone mass, improve anemia, and reduce menopausal symptom severity in women with osteoporosis (*58*). In an randomized controlled trial (RCT) involving women who had

undergone oophorectomy and entered surgically induced menopause, the combination of Keishibukuryogan and vitamin D3 significantly increased bone mineral content, as well as serum calcium and alkaline phosphatase levels, which shows a therapeutic effect on osteopenia caused by estrogen deficiency (*59*). Saikokaryukotsuboreito can prevent loss of bone volume and suppress serum IL-6 level in a postmenopausal model (*60*).

Kampo medicine offers a promising therapeutic approach for the treatment of postmenopausal osteoporosis, particularly for patients who are intolerant to conventional medications or unwilling to undergo hormone therapy.

3.4. Kampo for somatic symptoms

Some of the most common climacteric symptoms are somatic symptoms, such as muscle and joint pain, which cause limitations in performing daily tasks. Several evidence suggest that changes in or loss of sex hormones may enhance susceptibility to musculoskeletal pain and influence disease progression (*3,61*). These findings indicate a correlation between menopause and the increased incidence of joint pain and osteoarthritis (OA) (*62*).

Approximately 50% of menopausal women report arthralgia (*63*). Traditional herbal medicine has been utilized for centuries to treat various musculoskeletal pain conditions. Keishikaryoujutsubuto and Boiogito have been reported to alleviate menopausal hand joint pain, muscle pain, and stiffness, thereby significantly improving quality of life (*64*). A randomized, placebo-controlled clinical trial has demonstrated the efficacy and safety of Keishikaryoujutsubuto in managing pain associated with knee OA (*65*). Additionally, an RCT investigating the therapeutic effects of Boiogito on knee OA with joint effusion demonstrated that patients in the Boiogito group exhibited significant improvements in stair-climbing ability, as measured by the Knee Society Scoring System functional score (*66*). Sinomenium acutum, a substitute for Fangji in Japan due to concerns about aristolochic acid toxicity. Sinomenium acutum has long been used in traditional Chinese medicine to treat rheumatic diseases (*67*), and its main active compound, sinomenine, has demonstrated anti-inflammatory and analgesic effects in both animal and human models of OA (*66,68,69*).

In traditional Chinese medicine, the placenta is known as Ziheche (processed human placenta) and has been used for centuries in Asian countries to alleviate menopausal symptoms. In Japan, a commonly used pharmaceutical preparation derived from hydrolyzed human placenta is commercially available under the name Laennec (*70*). Recently, PPE has been developed as an oral supplement for therapeutic purposes similar to human placental extract. Oral administration of PPE, especially in combination with menopausal hormone therapy, has shown efficacy in relieving chronic shoulder stiffness and knee pain in postmenopausal women (*71*).

Low back pain is one of the most common pain conditions and tends to worsen during the perimenopausal and postmenopausal periods (*72*). Its causes are multifactorial, including hormonal decline, bone loss, muscle atrophy, and psychological stress. Although hormone therapy is effective for alleviating hot flashes, menopausal hormone therapy and oral contraceptives have been linked to an increased risk of Low back pain (*73*). Kampo medicine offers a unique advantage in that it can be modified based on an individual's menopausal constitution to simultaneously address systemic menopausal symptoms and musculoskeletal complaints. An RCT found that Keishibukuryogan combined with bushi (*Aconiti tuber*) was more effective than Keishibukuryogan alone in relieving nonspecific lumbago in menopausal women, with higher symptom relief rates (*74*).

Kampo formulations has demonstrated clinical efficacy in alleviating menopausal musculoskeletal symptoms. In addition, bioactive components from traditional remedies, such as Sinomenium acutum and PPE, show promise for pain relief and functional improvement.

3.5. Genitourinary Syndrome of Menopause (GSM)

GSM is a clinical condition resulting from decreased estrogen levels following menopause, affecting the genital and lower urinary tract. Common symptoms include vaginal dryness, burning sensations, dyspareunia, urinary frequency, and urgency (*75*). The prevalence of GSM has been documented to be approximately 64.7% one year after menopause, increasing to 84.2% after six years (*76*). Due to the intimate nature of its symptoms, many women may be reluctant to seek medical attention, leading to underreporting and undertreatment of this condition. MHT remains the primary treatment for GSM (*77*). Conversely, Kampo medicine's current scope is confined to the provision of symptomatic relief, and there is an absence of substantial clinical evidence, such as RCTs, specifically addressing GSM. Consequently, further research is warranted to explore Kampo's potential role in the comprehensive management of GSM.

4. Concise overview of key ingredients in the Kampo formulations discussed

In the management of menopausal syndrome, Kampo medicines have demonstrated promising clinical potential due to their multi-component and multi-target characteristics. In this review, we provide a concise overview of the key ingredients identified in the Kampo formulations discussed (Figure 1).

Glycyrrhizae radix and *cinnamomi cortex* exhibited

Estrogen Receptor β-dependent estrogenic activity, and unkeito, kamishoyosan, and nyoshinsan demonstrated estrogenic effects, potentially useful for treating menopausal syndrome (*78*). Cinnamaldehyde, a pivotal active constituent of Keishibukuryogan, has been demonstrated in earlier studies to activate the transient receptor potential ankyrin 1 channel (*79*), thereby promoting thermoregulatory responses such as increased brown adipose tissue activity and elevated rectal temperature. Moreover, cinnamaldehyde exerts anti-inflammatory effects in chondrocytes by inhibiting lipopolysaccharide -induced inflammation and attenuating cartilage degeneration through the suppression of the NF-kappaB signaling pathway (*80*). Glycyrrhizin and geissoschizine methyl ether are two active components of Yokukansan. Geissoschizine methyl ether acts as a partial agonist at serotonin 5-HT1A receptors and an antagonist at 5-HT7 receptors, primarily targeting neurons in the prefrontal cortex, thereby modulating emotional and anxiety-related behaviors (*81-84*). The glycyrrhizin metabolite, 18β-glycyrrhetinic acid, enhances glutamate uptake in the hippocampus by activating astrocytic glutamate transporters, which may contribute to alleviating depressive symptoms and improving sleep quality (*85*). Liquiritigenin, another active compound of *Glycyrrhiza*, exhibits estrogenic agonist activity by stimulating the expression of estrogen-regulated genes, indicating that it possesses characteristics of a selective estrogen receptor modulator (*86*). The lignan components contained in EH0202, such as secoiso and lariciresinol (*87*), exhibit phytoestrogenic activity and may contribute to the regulation of the central thermoregulatory system.

Paeoniflorin and paeonol, bioactive components derived from peony, demonstrate significant therapeutic potential in alleviating menopausal symptoms through multiple mechanisms. Paeoniflorin, an active compound in traditional Kampo formulations such as Unkeito, Tokishakuyakusan, Kamikihito, Keishibukuryogan, and Hachimijiogan, has multiple biological effects. It promotes non-rapid eye movement sleep *via* the adenosine A1 receptor (*88*) and helps improve osteoporosis caused by high-fat, high-carbohydrate diet-induced hyperlipidemia (*89*). Paeoniflorin also directly stimulates 3T3-L1 adipocytes to secrete estradiol, suggesting potential roles in managing ovarian dysfunction in postmenopausal women (*90*). Paeonol alleviates postmenopausal cognitive impairment, anxiety, and depression by upregulating G protein-coupled receptor 30 expression and activating the PI3K/Akt/mTOR signaling pathway with increased hippocampal brain-derived neurotrophic factor levels (*91*). Additionally, it prevents bone loss by suppressing RANKL-induced osteoclastogenesis *via* inhibition of ERK, p38, and NF-kappaB pathways (*92*).

The efficacy of Hachimijiogan in combating osteoporosis is attributable to the synergistic actions of its core components, including catalpol, loganin, and morroniside. Catalpol (*93*) has been shown to support bone formation while limiting bone breakdown. Loganin (*94*) has been demonstrated to promote osteogenesis and balance bone remodeling. Morroniside (*95*) has been shown to protect against inflammation-driven bone loss by modulating key signaling pathways, such as NF-kappaB and MAPK. Saikokaryukotsuboreito is traditionally employed in the treatment of Menopausal symptoms. Among its

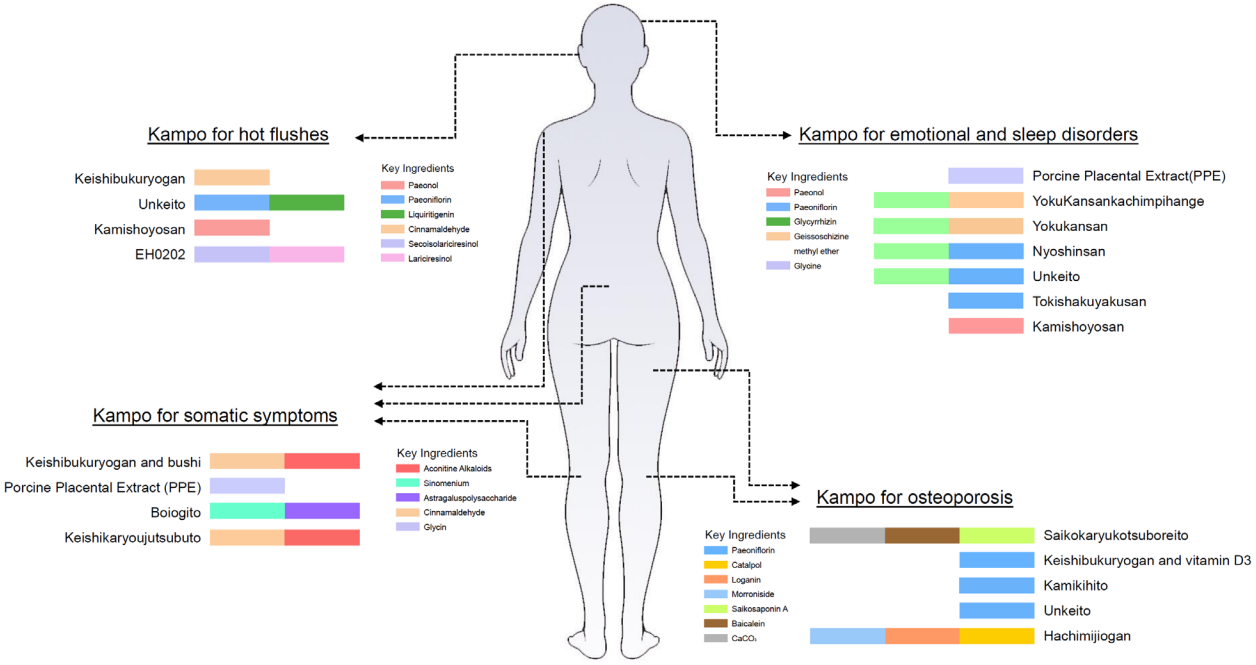

Figure 1. Kampo formulations and key ingredients for menopausal symptoms.

constituents, saikosaponin A, baicalein, and calcium carbonate are considered key contributors to its effects on bone health. Saikosaponin A (*96*) has been shown to mitigate bone loss by inducing ferroptosis in osteoclasts and inhibiting osteoclastogenesis. Baicalein (*97*) inhibits osteoclast differentiation and promotes apoptosis in mature osteoclasts, thereby reducing bone resorption. The use of oyster shell–fortified foods (*98*) has demonstrated efficacy in the prevention and treatment of osteoporosis by enhancing calcium intake and supporting bone mineralization. It is noteworthy that the oyster shell composition is predominantly calcium carbonate, constituting a bioavailable calcium source. Keishikaryoujutsubuto and Keishibukuryogan combined with bushi (*Aconiti tuber*) contain aconitine alkaloids, which are believed to improve peripheral circulation and reduce pain and stiffness (*99*). Boiogito includes sinomenium (*100*) and astragalus polysaccharides (*101*), which exhibit anti-inflammatory and immunomodulatory effects, aiding in the relief of musculoskeletal discomfort.

The efficacy of Kampo medicine in managing menopausal syndrome is substantiated by both formula-level clinical observations and component-level mechanistic evidence. These findings suggest that the therapeutic effects of Kampo formulations are attributable to their multi-component, multi-target actions, offering pharmacological plausibility for their traditional use.

5. Conclusion

Kampo medicine has experienced a resurgence in Japan following its official approval by the Ministry of Health and Welfare in 1976. Today, it is recognized as a principal therapeutic option for managing menopausal symptoms, alongside hormone therapy. Among the approximately 150 Kampo formulations currently in clinical use, Tokishakuyakusan, Kamishoyosan, and Keishibukuryogan are regarded as the most representative and frequently prescribed formulations for alleviating menopausal complaints in women (*38*).

Kampo medicine fundamentally differs from Western medicine in its underlying etiological concepts, diagnostic criteria, patient evaluation methods, and treatment selection strategies. Each system possesses distinct philosophical foundations and clinical approaches, and rather than being mutually exclusive, they may be considered complementary. In the treatment of hot flash and GSM, HRT remains the first-line approach. However, Kampo medicine has demonstrated significant effectiveness in managing emotional and sleep disturbances as well as various somatic symptoms. This may be attributed to Kampo's ability to interpret and treat the multifaceted physical and psychological manifestations of menopause as an integrated syndrome. By selecting from a small number of formulations tailored to the individual's overall symptom pattern, Kampo aligns closely with the heterogeneous and systemic nature of menopausal disorders.

Given the unique diagnostic and therapeutic principles of Kampo, future clinical research should not only pursue high-quality RCTs but also explore ways to incorporate Kampo-specific diagnostic frameworks into study designs. Instead of treating Western and Kampo medicine as opposing paradigms, a patient-centered model that presents both options clearly, along with their respective benefits and potential risks, should be encouraged. This integrative approach has the potential to empower women to make informed decisions and may lead to more personalized and effective management of menopausal health.

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