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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Traditional Chinese medicine valuably augments therapeutic options in the treatment of climacteric syndrome

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Abstract Climacteric syndrome refers to recurring symptoms such as hot flashes, chills, headache, irritability and depression. This is usually experienced by menopausal women and can be related to a hormonal reorganization in the hypothalamic–pituitary–gonadal axis. In Traditional Chinese Medicine, originating 1000s of years ago, abovementioned symptoms can be interpreted on the basis of the philosophic diagnostic concepts, such as the imbalance of Yin and Yang, the Zang-Fu and Basic substances (e.g. Qi, Blood and Essence). These concepts postulate balance and harmonization as the principle aim of a treatment. In this context, it is not astounding that one of the most prominent ancient textbooks dating back to 500–200 BC, Huang di Neijing: The Yellow Emperor's Classic of Internal Medicine gives already first instructions for diagnosis and therapy of climacteric symptoms. For therapy, traditional Chinese medicine comprises five treatment principles: Chinese herbal medicine, TuiNa (a Chinese form of manual therapy), nutrition, activity (e.g. QiGong) and acupuncture (being the most widespread form of treatment used in Europe). This review provides an easy access to the concepts of traditional Chinese medicine particularly regarding to climacteric syndrome and also focuses on current scientific evidence.

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Basic concepts of traditional Chinese medicine (TCM)

Yin and Yang constitute the principle concept in the understanding of Chinese philosophy [1]. As opposite yet complementing conditions, they emblematize a concept of dynamic balance. The Chinese ideogram for Yang (阳) originally means "the sunny side of a hill", while the ideogram for yin (阴) can be attributed as "the shady side of the hill". Therefore, Yang identifies active and dynamic principles while Yin is used to indicate more receiving and regenerative elements. Yin and Yang cannot exist without each other—they control one another and exist through this relation. Beyond that they are in a constant change of state and rise from one and another. Yin and Yang can be used to describe all kind of phenomena and relations in the macro- and microcosms of the universe. In traditional Chinese medicine, they possess a central meaning referring to body and mind. In a healthy person, they are at dynamic equilibrium and cause physical and mental well-being. One cannot be efficient all the time (being in a Yang-condition) without regeneration time (being in a Yin-state). The nature of Yin and Yang can also be transferred to physiological processes such as the menstrual cycle: during the follicular phase constructive processes dominate, whereas in the luteal phase receiving aspects are focused. Within the condition of Yin and Yang, aspects of Chinese culture and philosophy are deeply connected with the physiological aspects of Chinese medicine.

Based upon the concept of Yin and Yang and observations of nature and humans (such as seasons, climatic conditions, phases of life and emotions) other principles evolved, that are deeply woven to Chinese culture. The theory of the five phases (or elements) is one of the most-used conceptual schemes to describe symptoms and choose treatments. The five phases are an elaborated equivalence system and may explain complex interactions in our surrounding. Furthermore, they comprise one of the conceptual models of the physiological homeostasis in TCM. The elements water, wood, fire, earth and metal are associated with the Chinese organs kidney, liver, heart, spleen and lung. It is very important to consider these organs do not stand in the tradition of Western Medicine. The "Chinese organs", also called "Zang-Fu", have to be put into a more functional context based on a system of analogies (for examples, see below). Therefore, they assume not only structural duties, but also play an important role, e.g. in the regulation of emotions.

According to these models, health is regarded as balance. In terms of this balance, a harmony of dynamic nature exists between Yin and Yang, the Five Phases and several other conditions in our body. Moreover, externally or internally driven alterations of the flow of energy and matter in human body can reclaim imbalances. Therefore, the concept of Qi (氣) refers to a universal vital energy, which is responsible for all kind of vital processes.

In assumption of TCM, the flow of Qi can be influenced and harmonized by inserting acupuncture needles at defined acupuncture points. Treatment objective is to re-establish health by inducing the balance of the mentioned systems (for review: [2], [3]).

Menopause in TCM: a simplified overview of Chinese physiology

Western medicine connects climacteric symptoms to a reduced function of the hypothalamic–pituitary–gonadal axis. TCM frequently attributes "renal deficiency" as underlying mechanism. Normal functions of the "Chinese kidneys" including thermoregulation, sexuality and water homeostasis may be affected. Kidneys store the essence Jing (精), which is responsible for maturation and reproduction processes and circulates in 7-year-long cycles in females. In the course of life, Jing is consumed physiologically, which contributes normal aging processes. After the seventh cycle (49 years), the menstruation dries up, so that women are unable to conceive [4]. The physiological decrease of Jing may lead to an imbalance of Yin and Yang within the kidneys: symptoms subsumed under "kidney yin deficiency" are familiar to many menopausal women and comprise, e.g. hot flushes, dry mucosa, sleeping disorders and recurrent urinary tract infections. The relative excess of Yang (in comparison to the decreased Yin) causes more dynamic processes/symptoms (e.g. sleeping disorders, agitation). Tight interrelations between the different variables may cause further pathologies. The "Chinese spleen" being responsible for the regulation of digestion in TCM may get into a state of imbalance as well. All varieties of digestive disorders, rapid exhaustion and headaches can be interpreted on the background of a splenic Qi-deficit. Both the quantity and the harmonic flow of Qi essentially influence health. Of special susceptibility for the harmonic flow of Qi is the "Chinese liver", which has a principle role in the regulation of emotions in TCM. Therefore, an imbalance may take the form of emotional instability or fit of anger. The expression of being liverish or choleric can be considered as an analogy to the role of liver in the emotional regulation in TCM. The multiple interactions between Chinese organs and their role in the regulation of the Qi flow are simplified in Fig. 1.

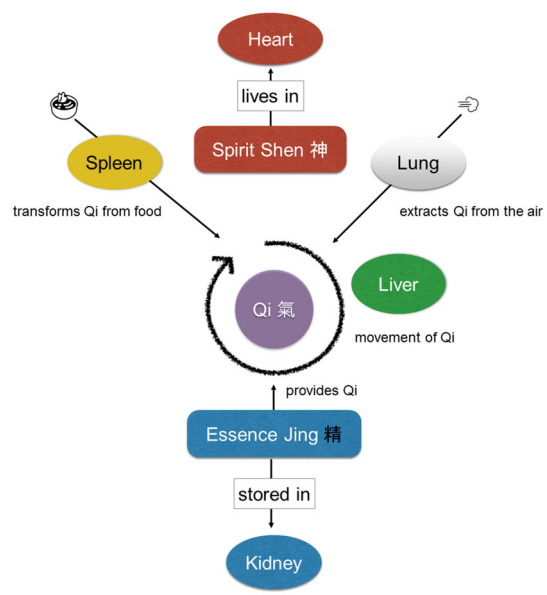

Fig. 1 The philosophic understanding of climacteric syndrome in traditional Chinese medicine. The *figure* illustrates the function of the five important Chinese organs kidney, liver, heart, spleen and lung. According to the ancient textbooks, women in menopause are already weakened regarding their Qi. If Qi cannot be nourished by the food we eat (transformed by spleen) and the air we breathe (extracted by lungs) above that, Essence (Jing; a form of hereditary energy stock) is consumed and kidneys are further impaired. This process aggravates the physiological decline of Essence and can be responsible for menopause symptoms based on a so-called *kidney-Yin-deficiency*. On the long run, this affects other organs: nausea, soft stools and poor appetite may be consequences of a weakened spleen. Excitability and migraine may be expressions of a *liver-Qi-stagnation* (smooth flow of Qi is blocked). The spirit Shen, usually residing in the heart and being responsible for consciousness, becomes deracinated thus the Yin root is weakened. Restless Shen appears in insomnia, anxiety and nervousness

In Chinese medicine, menopause is a physiological conversion process, which may cause individually experienced imbalances. Severity of symptoms depends on the ability of the body to harmonize these imbalances and are associated to both, physical (intrinsic) and environmental (extrinsic) factors. A general weakened condition, e.g. due to stress, chronic sleep disorders, many births or additional diseases can aggravate the severity of climacteric symptoms [5]. The five treatment principles of TCM [acupuncture, Chinese herbal medicine, TuiNa, activity (e.g. QiGong) and nutrition] have been described to enhance the process of harmonization.

As described above, menopause in TCM is characterized as a condition of deficiency. Acupuncture can reduce the severity of symptoms caused by imbalances but is not able to fill up deficiencies of the substances (as Qi, Yin and Yang). This aspect is traditionally subject to traditional Chinese herbal medicine. Over 12,000 traditional Chinese drugs (of herbal, mineral and animal origin) have been described and constitute a complex pharmacological system. The drugs are attributed to have the power to replenish basic substances like Qi, Yin and Yang and strengthen the Chinese organs. Some Chinese pharmaceuticals show analog mechanisms of action as classic drugs used in Western medicine (e.g. diuretics or anti-invectives). Artemisinin, recently honored in the context of the Nobel Prize winners 2015, is an example for a drug originating from Chinese herbal medicine, that researcher used as the basis for the development of a sufficient antimalaria treatment option [6]. Traditionally, drugs in Chinese herbal medicine are not given as single substances. They are combined in complex prescriptions individually for each patient and his disease. Traditionally prescriptions are prepared as decoction (raw materials are cooked over a longer period); over the last decades, several additional forms of application have been proposed and investigated (granular and powdered forms are more convenient in use).

Acupuncture: physiological mechanisms of action

Aforementioned concepts underlying traditional Chinese medicine are not scientific, and coherences have not been (and are not expected to be) verified or falsified by experiment. They have to be recognized in a more philosophical and humanistic context. However, treatment modalities which have arisen from these concepts have been accepted to effectively treat various diseases. Modern scientific methods assess physiological, anatomical and neurochemical mechanisms underlying acupuncture, a pivotal mechanism providing a simplified universal explanation is missing [7].

A milestone of acupuncture research was in 1976 the finding of endorphins being released from acupuncture treatment and playing a decisive role in mediating acupuncture analgesia [8, 9]. Further research confirmed the role of endorphins [10] and demonstrated an effect on central and peripheral neurotransmitters/modulators like serotonin [11] and adenosine [12] caused by acupuncture (for review: [13], [7]).

Insertion and stimulation of acupuncture needle induce cytoskeletal remodeling, not only in the area immediately surrounding the acupuncture needle. Fibroblasts further away from the stimulation location are influenced by mechanotransduction-based mechanisms [14]. Thus, functional muscle chains may be influenced by acupuncture. The anatomical correspondence of classical acupuncture points and trigger points goes in line with this thesis [15]. Integrative processes on all levels of the central nervous system (CNS) as essential effect of acupuncture have been emphasized by numerous studies. In acupuncture analgesia, neuronal mechanisms of endogenous analgesia play an important role. The involvement of segmental inhibition [16], "diffuse noxious inhibitory controls" (DNIC) and descending pain inhibitory systems represents important mechanisms [7, 17]. Brain response mediated by acupuncture stimulus includes somatosensory, cognitive and affective processes. These findings have been confirmed in several fMRI studies [18].

Traditional Chinese medicine postulates the stimulation of acupuncture points at the lower extremity particularly for gynecological indications. A possible conceptualization is the association of correspondent segmental innervation and sexual organs. Possible interrelations between female pelvic organs and acupuncture are illustrated in a hypothetical model (see Fig. 2): The insertion of a needle is a complex stimulus triggering several processes on a local and systemic base, as mentioned above. Aδ- and C-fibers transmit the signal conducted by acupuncture to the posterior horn of the spinal cord. Neural circuits may be responsible for direct influence on the organs (e.g. increased ovarian blood flow). Central effects are triggered in the CNS via supraspinal pathways. A connection of endorphin mechanisms and ovary function is assumed. Endorphins are involved in regulation and biosynthesis of gonadotropin-releasing hormone (GnRH), and therefore as well in the release of luteinizing hormone (LH) [19]. Besides, they influence the functioning of the hypothalamic thermoregulatory center [20]. Acupuncture strongly influences this release of endorphins (see above). Further effects of acupuncture on corticotrophin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) release have been described. The reduction of cortisol and catecholamines release in the adrenal gland decreases sympathetic tonus. The activity of vasomotor center (VMC) in

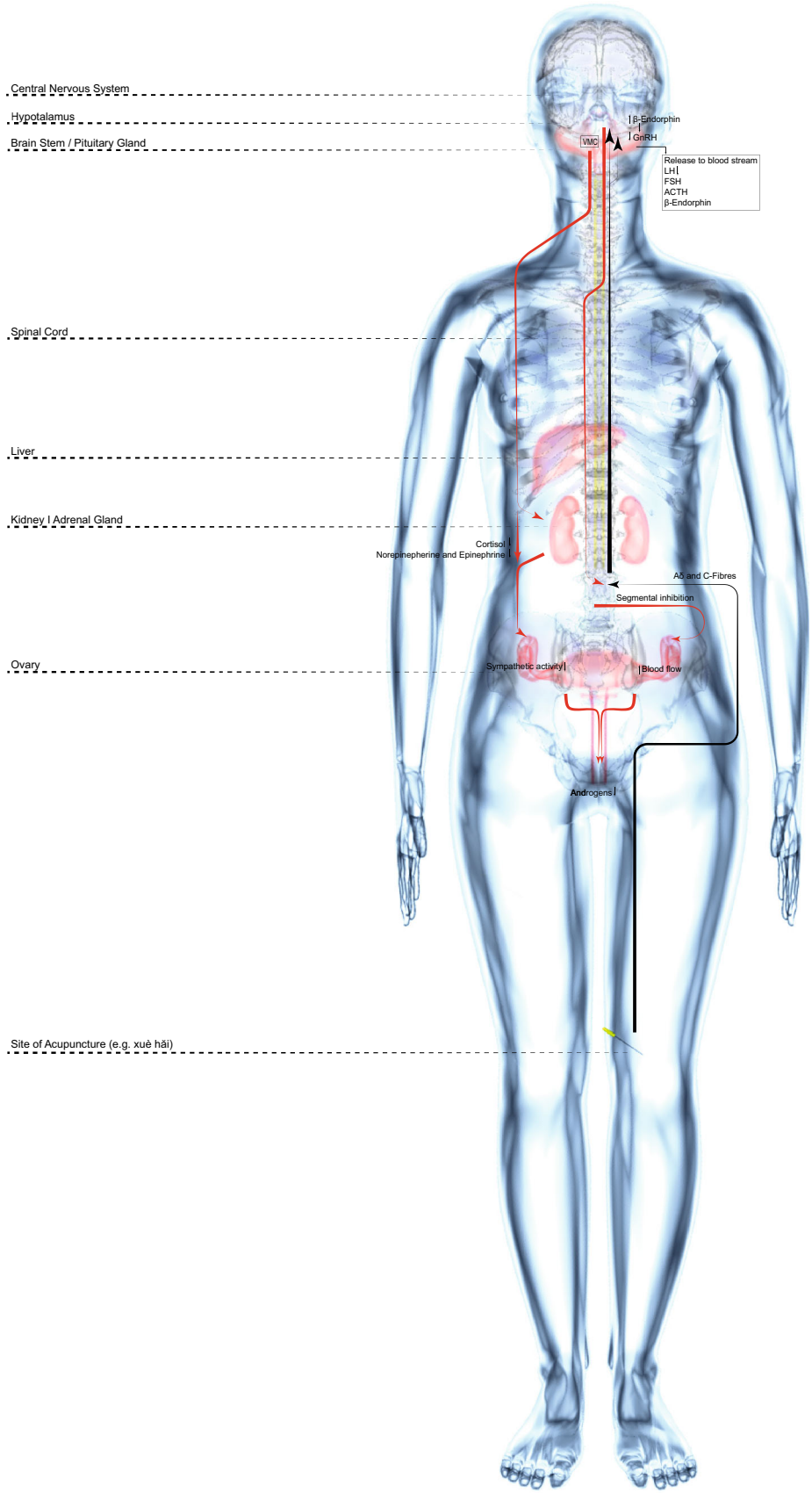

Fig. 2 Acupuncture: mechanism of action. After inserting the needle (in this illustration at the acupuncture point xuè hǎi, i.e. Spleen 10), afferent Aδ- and C-fibers transmit the signal conducted by acupuncture to the posterior horn of the spinal cord. Segmental neural circuits, a focus lies on segmental inhibition and also descending inhibitory neurons, directly influence the function of the according organs (*red arrows* next to the spinal cord). In consequence, the ovarian blood flow may increase. Secondary neurons forward the stimuli to the CNS and lead to the release of endorphins. These play a key role in the regulation and biosynthesis of gonadotropin-releasing hormone (GnRH), and therefore as well in the decreased release of luteinizing hormone (LH) and the regulation of follicle-stimulating hormone (FSH) or adrenocorticotropin (ACTH) [19]. Acupuncture affects the hypothalamic thermoregulatory center and decreases the activity of the vasomotor center (VMC) in the medulla oblongata. The reduction of cortisol and catecholamines release in the adrenal gland decreases sympathetic tonus. A decrease of androgens has been described. In summary, acupuncture has been shown to regulate several pathomechanism related to the neuroendocrine dysfunction in climacteric woman

medulla oblongata seems to be reduced as well [21–23]. Previous work in a model of polycystic ovaries in rats suggests that EA can modulate sympathetic nerve activities to improve the function of ovaries [24]. In summary, acupuncture seems to be thought to reduce climacteric symptoms by regulating the neuroendocrine function (for review: [25]).

Also, for some Chinese herbal medicine preparations treating menopausal symptoms, selective activating effects on estrogen receptor-β have been reported with potential synergistic effects of the herbal components [26, 27].

Chinese and evidence-based medicine

Numerous studies over the last decades investigated the efficacy of acupuncture for the treatment of climacteric symptoms. Methodological problems of acupuncture trials regard the inclusion of adequate placebo controls, since the need for sufficient blinding still remains unsolved [28]. Recent recommendations suggest to avoid sham-needling groups and to compare acupuncture to or in addition to standard regime [29]. Still, differentiating specific from unspecific treatment effects facilitated the understanding of sham effects and helped to estimate the overall effect of acupuncture [30].

Strong evidence, the latest Cochrane review was issued in 2015, emphasize the use of acupuncture in the treatment of nausea and vomiting (postoperative and chemotherapy-induced) [31–33]. Positive effects in pregnancy are assumed. Meta-analyses show effectiveness in the treatment of chronic pain [34].

Safety and side effects

Acupuncture is considered to be a safe treatment. Adverse effects occur in about 9 out of 100 treatments, but more than 99 % comprise little hematoma and small bleeding due to lesion of small vessels, pain sensations during needling or vegetative reactions [35]. In a cumulative review, serious adverse effects (e.g. infections, pneumothorax) were estimated to 0.05/10,000 [36]. Kang et al. found 16 minor adverse effects reported in a sample size of 22,279 patients treated for different gynecological indications [37]. A limiting factor is the unsystematically reporting of adverse effects in most of the studies.

Acupuncture in the reduction of hot flushes

The efficacy of acupuncture in the treatment of hot flushes has been illustrated by consistent data. In a multicenter study of 175 patients with hot flushes, acupuncture-treated patients showed an improvement of 62 % compared to 27 % in the control group (no treatment) over 24 h [38]. A Chinese study of a smaller sample ($n = 57$) showed comparable effects for the combination of Chinese herb medicine with acupuncture and hormonotherapy; further, reduced Kupperman index and reduced blood level of follicle-stimulating hormone (FSH) after treatment were detected [39]. Moreover, a Swiss pilot study detected a significant effect for acupuncture, sham acupuncture and Chinese herb medicine on the frequency and severity of hot flushes [40]. After an acupuncture treatment of 12 weekly sessions, a 50 % reduction of symptoms was reported. A recent meta-analysis showed small-size effects on reducing the hot flush frequency and the severity of menopause-related symptoms in 342 breast cancer survivors [41]. Same authors retrieved other 12 studies with 869 women experiencing natural menopause, showing in their meta-analysis that acupuncture improves hot flush frequency and severity, menopause-related symptoms, and quality of life (in the vasomotor domain) [42]. This is in contrast to a recent narrative review, doubting the effects of acupuncture on hot flushes but without adequate statistical methods [43]. This is in line with the statement of the North American Menopause Society, refusing the recommendation of acupuncture due to the potential sources of negative, insufficient, or inconclusive data [44]. Still, authors of this article disagree with this opinion. Current data are sound, the methodological design of the latest studies is state of the art, and risk–benefit ratio is in clear favor regarding the patient. As mentioned above, the debate on the specificity of acupuncture effects is ongoing and cannot be ruled out. A statement of opinion leaders in the UK health services recently claimed for the involvement of Chinese medicine in the treatment of menopausal symptoms [45].

Besides distinguishing verum and sham acupuncture effects, a 2013 Cochrane review showed benefits of acupuncture when compared with no treatment [46]. Eight of 16 included studies (1155 patients) compared acupuncture with sham acupuncture. Although no difference was detected considering the frequency of hot flushes between the two groups, a significant reduction of the severity of the symptoms was observed in the acupuncture group. The comparison of acupuncture patients with waiting list patients favored acupuncture as well. Three of the studies compared acupuncture treatment with hormonotherapy. Findings revealed superiority of hormonotherapy over acupuncture regarding the frequency of hot flushes, although no differences were detected between the groups, when changes of severity of symptoms were considered. Summing up, the meta-analysis notes that the interpretation of this data has to be conducted in light of important methodological shortcomings, restricted numbers of patients and big heterogeneity of the samples [46]. These

data are in agreement with the evidence of a previous study [36].

Reduction of side effects in adjuvant endocrine therapy

Several studies report on the benefit of acupuncture when added to an adjuvant endocrine therapy in cancer patients. There are severe restrictions regarding the treatment of climacteric symptoms in tamoxifen-medicated women with breast cancer. Pharmacological treatment based upon venlafaxine or gabapentine has been reported to show considerable side effects [47], while compliance raises a major issue. An American study compared the venlafaxine prescription with an acupuncture treatment over 12 weeks in a sample of 50 hormone therapy patients with hormone-positive breast cancer. Short- and long-term (follow-up after a year) effects were comparable between the study groups. Both groups reported reduction of hot flushes, depressive symptoms and improved life quality. However, no side effects were reported in the acupuncture group, contrastingly to the venlafaxine group, where 18 patients showed demonstrated side effects [48]. Considerations of a possible upturn of estradiol levels due to the acupuncture and therefore of an enhanced risk of relapse have been sufficiently rejected [49]. In this context, there is promising research addressing the severity of atrophic vaginitis in cancer patients treated with aromatase inhibitors [50]. A case report showed acupuncture and Chinese herbal medicine to completely reduce symptoms of vaginal discomfort, dryness and dyspareunia in postmenopausal women [51].

The role of Chinese herbal medicine

In the classical treatment of internal diseases, Chinese herbs play an important role. Still, their investigation has not been ruled out in the same extend than for acupuncture therapies. However, Chinese herbs are pharmaceutics and can be investigated in accordance to other medications in Western medicine.

Regarding climacteric symptoms, there are few minor studies investigating their effects. A recent study showed the semi-individualized mixture Tiáo Gēng Tāng to be similar effective than tibolone alleviating symptoms in 60 climacteric women, but with a significantly reduced ratio of side effects [52]. In contrast, the chosen herbs in a Swiss pilot study (mentioned above) were not effectual in this regard [40]. A randomized double-blind placebo-controlled trial investigated the effects of different Chinese herbal medicine granules for the treatment of climacteric symptoms by menopausal stages over 12 weeks in 389 subjects [53]. The results of subgroup analysis showed that the Danzhi Qing formula was more effective than placebo in improving the Menopause-Specific Quality of Life score for perimenopausal women at the end of week 12. Danzhi Qing displayed more favorable effects alleviating hot flushes and night sweats on early postmenopausal participants. This is in agreement with an animal study showing the Chinese herb Gengnianchun to exert phytoestrogen-like properties without the side effects of estradiol valerate in ovariectomized rats [54]. There is a large variety of potential substances subject to further research. A recent network pharmacological investigation found for example more than 20 potential effective ingredients out of 721 compounds resulting from one single decoction [55].

A topical review on Chinese medicine suggests promising effects of Chinese herbal medicine, and also acupuncture and moxibustion on symptoms co-occurring with hot flushes [56]. Yet, methodological issues limit the explanatory power. This is in agreement with a meta-analysis on 8 randomized controlled studies with 675 patients published in a Chinese journal, showing the clinical effect of the preparation Kuntai Capsule to be comparable to estrogen replacement with lower effects on hormone levels but less adverse effects [57]. Still, evidence is limited and subject to further research.

Acupuncture treatment of sleep disorders

Sleep disorders show a prevalence of 30–50 % in peri- and postmenopausal women. A double-blind randomized placebo-controlled trial of a small sample of postmenopausal women ($n = 18$) detected a sleep improving effect of acupuncture treatment; the improvement was observed in subjective questionnaires and validated by polysomnographic measures with enhanced amounts of deep sleep [58].

Conclusions

In summary, acupuncture is not a therapeutic option meant to replace standard hormone therapy in the alleviation of climacteric symptoms. Its therapeutic potential lies in the integrative combination with established methods. Data show acupuncture to improve patients' well-being, to reduce their symptom severity and to avoid medication-related side effects. In addition, traditional Chinese medicine can be considered an alternate in patients with contraindications to hormonal therapies such as breast cancer patients or patients with a thromboembolic history. The role of Chinese herbal medicine is promising, but big data are missing. Currently, a modern approach to climacteric syndrome should preferentially include at least acupuncture as one among several multimodal tools. To show the

superiority of such concepts is the challenge to the next generation of clinical studies.

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Compliance with ethical standards

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Human participant/animal statement This article does not contain any studies with human participants or animals performed by any of the authors.

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