Therapeutic effects of Chinese herbal medicine against neuroendocrinological diseases especially related to hypothalamus-pituitary-adrenal and hypothalamus-pituitary-gonadal axis

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Abstract: This is a systemic review of plants used traditionally for neuroendocrinological diseases related to hypothalamus-pitutary-adrenal (HPA) and hypothalamus-pitutary-gland (HPG) axis. By searching from PubMed literature search system (1950-2013), Medline (1950-2013) and CNKI (China Journals of Full-text database; 1989-2013), 105 papers met the inclusion criteria were displayed in this review. 96 herbal drugs were classified into two parts which include hormones mainly related to HPA and HPG axis. The full scientific name of each herbal medicine, dose ranges and routes, models or diseases, affect on hormones and pertinent references are presented via synoptic tables. Herbal remedies that have demonstrable the activities of hormones have provided a potential to various diseases related to neunoendocrine and deserve increased attention in future studies. This review provides a basis for herbs use in neuroendocrinological diseases. The data collected here will benefit to further research associated to herbal medicines and hormones.

Keywords: Herbal medicine, Neuroendocrinological diseases, hypothalamus-pitutary-adrenal (HPA) axis, hypothalamus-pitutary-gland (HPG) axis.

INTRODUCTION

Hormones play a crucial role in body metabolism, growth, development, reproduction, gender, sexuality, and sexual activities. Disorders of neunoendocrine may cause mental illness (Wingenfeld *et al*., 2009), chronic fatigue (Shi *et al*., 2004b) and hyperprolactinemia (Ishikawa *et al*., 1992). Though various medicines widely used for treating diseases related to hormone disorders, the therapeutic effects are still not satisfied; therefore, seeking help from herbal drugs is highly desired. Numerous herbs have been recorded in ancient pharmacopoeias from different regions in the world including China (Adams et al., 2009; Wei et al., 2009), Indian (Chanda *et al*., 2009; Teschke and Bahre, 2009), Japan (Kakizaki *et al*., 2009; Kishida *et al*., 2009) and Korea (Kim and Kim, 2008; Lee *et al*., 2009). Herbal drugs are recognized as an alternative to conventional medicine and most of them have already been used in clinics.

The therapeutic effects of herbal drugs on hormones have been widely reported in various syndromes and diseases. The studies are increasing every year; however, there is no paper to summarize these effects systematically. The aim of this systematic review is to estimate the prevalence studies on hormones, and if appropriate, to sum up the herbal drugs possess positive or negative regulatory effects on hormones related to hypothalamus-pitutary-adrenal (HPA) and hypothalamus-pitutary-gland (HPG) axis.

MATERIALS AND METHODS

Search strategy

The electronic databases of PubMed literature search system (1950-2013), Medline (1950-2013) and CNKI (China Journals of Full-text database; 1989-2013) were searched by using the keywords including "herbs", "herbal drugs", "herbal medicine" or "Traditional Chinese Medicine" plus at least one of the terms of hormones related to hypothalamus-pitutary-adrenal (HPA) and hypothalamus-pitutary-gland (HPG) axis: gonadotropin releasing hormone (GnRH), adrenocorticotropic hormone (ACTH), anti-diuretic hormone (ADH), growth hormone (GH), corticotropin releasing hormone (CRH), corticosterone (CORT), epinephrine hormone (E), noradrenaline hormone (NE), prolactin (PRL), growth hormone releasing hormone (GHRH), dihydrotestosteron (DHT), estradiol (E_2), testosterone (T), progesterone (P) and luteinizing hormone (LH).

Inclusion and exclusion criteria

Studies satisfying the following parameters were included: Firstly, model types of studies were belong to animal experiment and randomized controlled clinical research. Secondly, studies were related to single herb or herbal mixtures. Thirdly, herbs in the studies can change

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at least one of the hormones level significantly. Last, only studies demonstrating statistically significant results on the diseases or models were included. Studies associated with neuroimmunology were excluded.

RESULTS

413 titles and abstracts were reviewed for criteria, and 105 papers met the inclusion criteria were displayed in the present review. 96 herbal drugs were selected and classified through the effects on hypothalamus-pitutary-adrenal (HPA) and hypothalamus-pitutary-gland (HPG) axis. The full herb or herbal mixture name, dose ranges and routes, models or diseases, affect on hormones and pertinent references are listed in the tables (tables 1 and 2). Since the names of prescription in Chinese and in Japanese are different, in this paper, we summarized the names as the Chinese formation.

DISCUSSION

Effects of herbal medicines on HPA axis

The regulatory effects of 36 herbs on HPA activity associated with hormones including NE, GH, E, CORT, ACTH, CRH, ADH and GHRH are classified and discussed in this section. Nearly one third of them are related to stress administration. Amount of anatomical and physiological evidence suggest that monoamine neurotransmitter system is regulated via hypothalamic paraventricular nucleus in brain (Plotsky *et al*., 1989). During the stress state, the body appears the changes mainly on the sympathetic-adrenal medulla and HPA cortical response (Krupp and Pollina, 1996). Chronic stimulation promotes ACTH secretion and CRH gene expression in hypothalamic, and increases the secretion of glucocorticoid, which further leads to the continuous HPA axis hyperfunction. Moreover, as reported previously, HPA system disruption is observed in approximately one half of patients suffered with depression (Arana *et al*., 1985; Carroll *et al*., 1981; Holsboer, 1983). As shown in Tab.1, 6 single herbs and 9 prescriptions are used for stress treatment, which significantly reduce serum concentration of CORT or ACTH or both of them. *Jia-Wei-Si-Ni Decoction*, an herbal formula based on *Si-Ni Decoction,* is recorded in "Treatise on Exogenous Febrile Diseases". It participates effectively on HPA adjustment in rats with restraint psychological stress, and relieves the inhibitory effect of glucocorticoid on the thymus (Shi *et al*., 2007; Xu *et al*., 2002). *ChaiHu-Jia-LongGu-MuLi Decoction*, another famous herbal mixture recorded in "Treatise on Exogenous Febrile Diseases", displayed therapeutic effects on depression (Sarai, 1992), neurosis (Kanba *et al*., 1998), anxiety (Sarai, 1992) and insomnia (Kikutani, 1984). The prescription suppresses the high level of monoamine transmittance (Qu *et al*., 2003) and enhances serum ATCH and CORT concentration in rats (Kang *et al*., 2005). Additionally, it decreases nuclear glucocorticoid receptor (GR) in the hippocampus in chronically stressed rat model (Mizoguchi *et al*., 2007). Previous study demonstrates that *ChaiHu-Jia-LongGu-MuLi Decoction* significantly prevents the chronic stress-induced the decrement of extracellular dopamine (DA) and prefrontal cortex serotonin (5-HT) levels in rats (Mizoguchi *et al*., 2003). It ameliorates the abnormality of the neuroendocrine system during the recovery period (Mizoguchi *et al*., 2002). ADH, a peptide hormone secreted by hypothalami, promotes water absorption. It is considered as a key regulatory hormone for urine dilution. *Ba-Wei-Di-Huang Wan* decreases ADH level and further eases the stress caused by microgravity in mouse (Song *et al*., 2002).

Some herbs fail to regulate hormone secretion directly; however, they possess therapeutic effects on neuroendocrinological diseases. Treatment with 100 mg/kg *Withania somnifera* radix for 7 or 28 days, the levels of DA, 3,4-dihydroxy-phenylacetic acid (DOPAC) and homovanillic acid (HVA) are increased strikingly in mouse (RajaSankar *et al*., 2009). *Yi-Gan San* displays anti-anxiety activities via suppressing 5-HT2A receptor level in the prefrontal cortex (Egashira *et al*., 2008; Mizoguchi *et al*., 2009). *TangKui-ShaoYao San* prevents the reduction of dopamine metabolites, and immediately increases NGF contents in the olfactory bulb (Song *et al*., 2001). Wang, JX *et al* point that after *Guan-Yu Capsules* treatment, the content of 5-HT in depressive rat is increased (Wang *et al*., 2005). Moreover, *BuZhong-YiQi Tang* increases 5-HT and its metabolites in the cortex, hippocampus and hypothalamus in aging rats after 5 month treatment (Tsunemi *et al*., 2005). *KangZhen-ZhiJing Capsule* partially improves the rotational behavior in Parkinson's rat model associated with the reduction of free radical level and DA catabolism (Bao *et al*., 2001).

Effects of herbal medicines on HPG axis

The effects of herbs on HPG axis activity and sex hormone related diseases were summarized in this part (table 2). Hyperprolactimia (HyperPRL) is a common clinical disorder, which is defined as a blood PRL level greater than 25ng/ml for women and greater than 20 ng/ml for men (Halbreich and Kahn, 2003). Pathologically high levels of PRL have significant impacts on fertility. In women, a high level of PRL reduces the FSH concentration, resulting in an obstacle to follicular ovulation and a low level of progesterone, which may result in pregnancy failure and abortion (Chahal and Schlechte, 2008). In men, hyperPRL leads to steroidogenesis and impaired spermatogenesis. An abnormally high level of PRL inhibits the function of gonadal and results in low levels of sexual hormones. Urogenital atrophy, dyspareunia, loss of libido, repeated urinary tract infection, urinary frequency and dysuria can be observed in male patients with hyperPRL (Chahal and Schlechte, 2008; Mancini *et al*., 2008).

There have been numerous single and mixed herbal preparations regulates PRL secretion and synthesis. Among them, *Paeoniae-Glycyrrhiza Decoction* (PGD) is the most promising herbal preparation in alleviating hyperPRL. Clinical studies have well confirmed the therapeutic effects of PGD in treating conditions associated with hyperPRL. Two case reports have revealed that PGD treatment remarkably suppressed olanzapine-induced high blood level of RRL and reduced hyperPRL symptoms (Hori *et al*., 2013; Yamada *et al.*, 1997). PGD displays a significant therapeutic effect on risperidone-induced amenorrhea associated with hyperPRL (Yamada *et al.*, 1999). PGD is also an effective agent in treating female infertility and male impotence caused by hyperPRL (Xu, 2003; You, 1998). Our pilot trial has further demonstrated that PGD treatment produced a considerable decrease of serum PRL level and the decreased amplitude was similar to that of bromocriptine in risperidone-induced hyperPRL patients. Moreover, patients in PGD treatment had a significantly lower proportion of adverse effects associated with hyperPRL compared to bromocriptine (Yuan *et al*., 2008). PGD and its individual herbal preparations can significantly lower blood levels of T in rat models and in patients with polycystic ovarian disease and androgen sterilization (Takahashi and Kitao, 1994; Takeuchi *et al*., 1989; Yaginuma *et al*., 1982). Its main constituents, peoniflorin, 18b-glycyrrhetinic acid and glycyrrhizin also strikingly reduce T levels (Takeuchi *et al*., 1991).

There are 16 herbal preparations showing down-regulation of PRL secretion. Among them, *Panax Ginseng* is a well-investigated herb. *Hordeum Vulgare L.* is a common food of which alkaloid compounds are similar in structure to bromocriptine (Zhou *et al*., 2008). *Vitex Agnus-castus* can relieve pre-menstrual syndrome (Berger *et al*., 2000) and serve as a non-surgical therapeutic alternative for hyperPRL patients who cannot tolerate dopamine agonists treatment (Tamagno *et al*., 2007). Extractions of *Agnus castus fruit* can even regulate plasma P, E_2, and PRL concentration and increase the uterine weight in ovariectomized rats (Ibrahim *et al*., 2008). A large number of Chinese formulae have been used in the treatment of hyperPRL. *Xiao-Yao Wan* reduced PRL level and hyperPRL symptoms without changing body weight in risperidone-treated patients (Ren *et al*., 2008). *Jian-Ru-Ling* (Huang *et al*., 1999), *Li-Ru-Kang* (Qian *et al.*, 2007), and *Ru-Kuai-Xiao Decoction* (Chen *et al*., 2007a) have the therapeutic potential for hyperplasia of mammary gland, a common breast disease in middle-aged women, with a certain tendency to develop into cancer (Lakhani, 1999).

In addition, *BaoTai Granule* (Zhang and Gui, 2004), *Xiong-Gui-Tiao-Xue-Yin* (Ushiroyama *et al*., 2007), *Silybum marianum (L.) Gaertn* (Capasso *et al.*, 2009), and *MaiDang-RuTong* (Xu and He, 2007) *Granule* elevate blood PRL concentration. *Bao-Tai Granule* also can elevate serum P level (Zhang and Gui, 2004), suggesting broad effects of this herbal effects in modulating sex hormones (McNatty *et al*., 1974).

Sex hormone disorder is a risk factor for cardiovascular diseases and diabetes mellitus in females (Kuang *et al*., 1989). Premature ovarian failure, a kind of serious disease, impacts on women's reproductive, physical and mental health and low-E_2 symptoms are observed in the patients (Orshan *et al*., 2001; Pasquali, 1999). As reported, due to ovarian dysfunction and the reduction of sex hormone secretion, climacteric syndrome is occurred (Wu, 1986). Combining with the low-secretion of E_2, menopausal women have higher incidences of physiological and mental changes (Burger *et al*., 2007). Epidemiologic study revealed that there were more than 477 million menopausal women in the world in 1998, and the number is expected to reach 1.1 billion by 2025 (Uhl, 2008). Associated with ovarian hormone deficiency, postmenopausal osteoporosis is a common cause for age-related bone loss (Miksicek, 1994).

Several herbal teas have shown therapeutic effects on sex hormone-associated disorders. Spearmint herbal tea displayed a therapeutic effect on hirsutism (excessive hairiness) of women caused by pathological changes in menstrual cycle (Akdogan *et al*., 2004; Akdogan *et al*., 2007; Sun and Yu, 2000). Administration with spearmint herbal tea twice daily for 5 days significantly enhanced T, LH, E_2 and FSH secretion in patients (Akdogan *et al*., 2007). Peppermint tea treatment resulted in an increment of FSH and LH level and a reduction of T serum concentration in rat models (Akdogan *et al.*, 2004). A special herbal tea containing six herbs, is capable of reducing body weight and stimulating ovulation in rat model of obesity and anovulation (Sun and Yu, 2000).

DangGui-ShaoYao San has been widely used to treat menopausal syndrome (Hagino, 1993), dysmenorrheal (Kotani *et al.*, 1997), luteal insufficiency (Usuki *et al.*, 2002), amenorrhea (Hagino, 1996) and chills (Kobayashi *et al.*, 2004). *DangGui-ShaoYao San* can regulate various monoamine neurotransmitters and their metabolites, including norepinephrine, 4-hydroxy 3-methoxy benzene ethylene glycol, DA, DOPAC, 5-HT and 5-HIAA and adrenal cortical hormone (Ach) in the cerebral cortex, corpus striatum and hippocampus in mouse model (Itoh *et al.*, 1998). *Danggui-Shaoyao San* restored the decreased plasma estradiol concentration in women with menopausal syndromes (Chung *et al*., 2008), and regulated progestretone levels and activated ovarian function in women with ovarian insufficiency (Koyama *et al*., 1988).

Over the past decade, *ErXian Decoction* and its disassembled prescriptions have been well studied. *ErXian Decoction* is capable of delaying aging of the HPG axis, enhancing the axis function (Fang *et al.*, 1992), and protecting against free radicals. It can be beneficial in treating menopausal syndrome (Sze *et al.*, 2009).

Table 1: Effects of herbal drugs on HPA axis

Herbal preparations	Treatment methods	Duration	Models/diseases	Effect on Hormones	References
A. venetum L.	15- 250 mg/kg, QD, PO	8 weeks	Stress (Rat)	NE↓	(Butterweck *et al*., 2003)
Curcuma longa L.	5-10 mg/kg, QD, PO	20 days	Stress (Rat)	CORT↓	(Xu *et al*., 2006)
Ginkgo biloba	300 mg/kg, QD, PO	4 week	Neuromodulatory (Mouse)	PRL↑, GH↑	(Watanabe *et al*., 2001)
Glycyrrhizae Radix	20 μg/kg, PO	120 min	Normal (rat)	GH↑	(Kim *et al*., 2003; Lee *et al*., 2007)
Hypericum monogynum L.	0.25-0.5 g/kg QD, PO	14 days	Stress (Rat)	NE↑	(Calapai *et al*., 2001)
Panax notoginseng	0.2 g/kg; PO	10 days	Stress (Rat)	ACTH↓	(Wang *et al*., 2010)
Polygala tenuifolia Willd.	20-80 mg/kg, QD, PO	15 days	Aged and Amnesic (Mouse)	NE↑	(Zhang *et al*., 2008)
Pinelliae Tuber	6.0 g/d, PO	120 min	Stress (Human)	CORT↓, ACTH↓	(Katagiri *et al*., 2004)
Radix Angelicae dahurica	77.0 g/kg, QD, PO	4 days	Pain (Rat)	NE↑	(Nie and Shen, 2002)
Rhizoma Zingiberis,	6.0 g, PO	120 min	Stress (Human)	CORT↓, ACTH↓	(Katagiri *et al*., 2004)
Anke-meng Oral Liquid	25.0 g/kg, QD, PO	9 days	Chronic Fatigue (Rat)	E↑	(Shi *et al*., 2004b)
BanXia-HouPo Tang; BanXia-XieXin Tang	7.5 g/d, QD, PO	120 min	Stress (Human)	ACTH↓	(Naito *et al*., 2003)
Ba-Wei-Di-Huang Wan	1.0 g/kg, QD, PO	3 days	Water metabolism (Mouse)	ADH↓	(Song *et al*., 2002)
ChaiHu-Jia-LongGu-DuLi Tang	10-1000 mg/kg, QD, PO	21-28 days	Stress (Rat and Mouse)	CORT↓, ACTH↓	(Kang *et al*., 2005; Mizoguchi *et al*., 2003; Mizoguchi *et al*., 2002; Sasaki *et al*., 1995)
Da-Cheng-Qi Granules	6.0 g, BID, PO	7 days	Severe Sepsis (Human)	ACTH↓, CORT↓	(Yu *et al*., 2005)
Dan-Zhi-Xiao-Yao Powder	12.0 g, BID, PO	6 weeks	Stress (Human)	CORT↓	(Li *et al*., 2007)
Er-chen tang	6.0 & 7.5 g, PO	120 min	Stress (Human)	ACTH↓	(Katagiri *et al*., 2004; Naito *et al*., 2003)
Jia-Wei-Si-Ni Decoction	13.0 g/kg, QD, PO	2 weeks	Stress (Rat)	CRH↓, ACTH↓, CORT↓	(Shi *et al*., 2008; Xu *et al*., 2002)
Jia-Wei-Si-Wu pill	0.21-4.2 g/kg, QD,PO	3 month	Normal (Rat)	NE↑, E↑	(Yu *et al*., 2002)
Jie-Yu Wan	106, 212 mg/kg, QD,PO	21 days	Stress (Rat)	CORT↓, ACTH↓	(Shi *et al*., 2007)
Juzen-taihoto	3.6 g, QD,PO	5 month	Aging (Mouse)	NE ↑	(Tsunemi *et al*., 2005)
Kai-Xin-San	0.3-2.7 g/kg, QD,PO	5 weeks	Chronic Mild Stress (Rat)	NE↓	(Dang *et al*., 2009)
Liu-Jun-Zi Tang	7.5 g/d, PO	120 min	Stress (Human)	ACTH↓	(Naito *et al*., 2003)
ShuGan-JianNao-TiaoYu Tablets	1.8 & 3.6 g/kg, QD,PO	14 days	Post-stroke depression (Rat)	CRH↓	(Zhang, 2008)
ShuGan-LiFei Recipe	28.0-36.0 g/kg, QD, PO	3 weeks	Asthma (Rat)	CORT↓	(Tong *et al*., 2005)
SuanZaoRen-HeHuan Formula	50-200 mg/kg QD, PO	2 weeks	Depression (Mouse)	NE↓	(Zhang *et al*., 2012)
Tou-Feng-Yu Pill	180, 90, 45 mg/kg; 108, 54, 27 mg/kg; QD, PO	180 min	Migraine (Rat, Mouse and Rabbit)	NE↑	(Li *et al*., 2011)
Xiang-Su San	1.0 g/kg QD,PO	28 days	Stress (Mouse)	CORT↓	(Ito *et al*., 2009)
Xiao-Chai-Hu Tang	1.2 g/kg, QD, PO	45 days	Normal or Prednisolone-induced (Mouse)	CORT↑	(Iwama *et al*., 1986)

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Table 1: Continue…

Herbal preparations	Treatment methods	Duration	Models/diseases	Effect on Hormones	References
Xiao-Yao Powder	20.0 g/kg, QD, PO	30 days	Postanal Depression (Rat)	NE↓	(Wang and Qin, 2010)
Xiao-Yao Wan	8 pills, TID, PO	1 month	Liver stagnation and Spleen deficiency (Human)	E↓	(Chen *et al*., 2005)
YiNiao Recipe	15.98, 31.83 g/kg, QD, PO	30 days	Kidney-yang deficiency (Rat)	ADH↑	(Su *et al*., 2010)
Yi-Xin-Le Liquid	25.0, 50.0 g/kg, QD, PO	9 days	Chronic fatigue (Mouse)	E↓	(Shi *et al*., 2004a)
You-Gui-Yin	10.0 g/kg, QD, PO	14 days	Corticosterone-induced (Rat)	NE↓, CORT↑, ACTH↑	(Cai *et al*., 1995)
ZiBu-ShenJing Fang	10.0-20.0 g/kg QD, PO	21 days	Kidney-essence insufficiency (Mouse)	GH↑	(Shen *et al*., 2011)

NE: norepinephrine; GH: growth hormone; E: epinephrine; CORT: corticosterone; ACTH: adrenocorticotropic hormone; PRL: prolactin; CRH: corticotropin releasing hormone; ADH: anti-diuretic hormone; GHRH：growth hormone releasing hormone.
QD: Once a day; BID: Twice a day; TID: Three times a day; PO: Oral administration.
↑ The level of hormones enhanced; ↓ The level of hormones reduced

Table 2: Effects of herbal drugs on HPG axis

Herbal preparations	Treatment methods	Duration	Models/diseases	Effect on Hormones	References
Anemarrhena Asphodeloides	50-300 mg/kg, QD, PO	12 weeks	Ovariectomy-induced bone loss (rat)	E_2↑	(Nian *et al*., 2006)
Cajanus Cajan L.	50-200 mg/kg QD, PO	8 weeks	Bone loss (Rat)	FSH↓, LH↓	(Zheng *et al*., 2007)
Cordyceps Sinensis	0.02, 0.2 mg/g QD,PO	5 weeks	Normal (Mouse)	T↑	(Hsu *et al*., 2003)
Curculigo Orchioides	0.5-2.0 g/kg QD, PO	12 weeks	Bone loss (Rat)	ATCH↓, CORT↓	(Cao *et al*., 2008)
Epimedium brevicornu Maxim.	300 ml, QD, PO	3months	Menopause (Human)	E_2↑	(Yan *et al*., 2008)
Hordeum Vulgare L.	12.5-50g/kg, QD, PO	40 days	Hyperprolactinemic (Rat)	PRL ↓	(Zhou *et al*., 2008)
Kaempferia Paroiflora	1.0 g/kg, QD, PO	45 days	Normal (Rat)	T↓, P↓, CORT↓	(Trisomboon *et al*., 2008)
Lobed Kudzuvine Root	30,100 mg/kg QD, PO	7 days	Normal (Rat)	FSH↑, LH↑, E_2 ↓PRL ↓,	(Xue *et al*., 2003)
SemenCoicis	2.0 mg/kg, QD, Intravenous injection	360 min	Normal (Rat)	P↓, E_2↓	(Hsia *et al*., 2007)
Silybum marianum (L.) Gaertn	25-200 mg/kg, QD, PO	14 days	Normal (Rat)	PRL ↑	(Capasso *et al*., 2009)
Panax Ginseng	80 mg/ kg, QD, PO	8 weeks	Hyperprolactinemia (Rat)	PRL ↓	(Zhao *et al*., 2005)
Thallus Laminariae	100 mg/kg, QD, PO	14 days	Mating dysfunction induced by radiation (Rat)	FSH↑, LH↑, E_2↑, T↑	(Qiong *et al*., 2011)
Tremella Aurantia	0.25 g, QD, PO	15 days	Diabetes mellitus (Rat)	T ↓ CORT ↑, CORT ↓	(Lo *et al*., 2004)
Vitex Agnus-castus	0.6, 1.2 g/kg, QD, PO	5 days	Normal and Ovariectomy (Rat)	E_2↑, P↑, PRL ↓	(Ibrahim *et al*., 2008; Jarry *et al*., 1994)
Withania Somnifera Root	5 g/day, QD, PO	3 months	Infertile (Human)	T↑, LH↑, FSH ↓, PRL↓	(Ahmad *et al*., 2010)
Bao-Tai Granule	10.0 g, BID, PO	>0.5 month	Spontaneous abortion (Human)	PRL↑ , P↑	(Zhang and Gui, 2004)

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Table 2: Continue

Herbal preparations	Treatment methods	Duration	Models/diseases	Effect on Hormones	References
Ba-Wei-Di-Huang Wan	5.0-10.0 g, PO	> 3 months	Hyperprolactinemia (Human)	PRL↓	(Usuki and Usuki, 1989)
Bu Zhong Yi Qi Tang	7.5 g, PO	3 months	(Human)	PRL↓,E_2↓,	(Ishikawa *et al*., 1992)
BusShen Fang	3.75-15.0 g/kg ; PO	3 weeks	Testicular injury (Rat)	T↑	(Jin *et al*., 2011)
BuShen-ShuGan Recipe	26.3 g/kg, QD, PO	35 days	Anorexia (Rat)	E_2↑, LH↑	(Hu *et al*., 2010)
BuShen-HuaYu-QuTan Recipe	BID, PO	6 months	Polycystic ovarian syndrome (Human)	T↓, INS↓	(Wu *et al*., 2007)
BuShen-HuoXue Recipe	0.2 ml/10g, QD, PO	20 days	Premature ovarian failure (Mouse)	E_2↑,	(Cai *et al*., 2001)
XuanJu Capsule	1.0-4.0 g/kg, QD, PO	20 days	Testectomy (Rat)	LH↑, FSH↑	(Zhou *et al*., 2011)
ErXian Decoction	0.76, 1.52 g/kg QD, PO	6 weeks	Menopausal syndrome (Rat)	E_2↑	(Sze *et al*., 2009)
Geng-Nian-Kang	4.0 ml, QD, PO	3 months	Osteoporosis (Rat)	FSH↓, LH↓	(Wu *et al*., 2005)
GengNian-NingShen Tang	Dosis, BID, PO	3 months	Climacteric syndrome (Human)	E_2↑, LH↓, FSH↓	(Li *et al*., 2008)
Geng-Nian-Shu	Dosis, BID, PO	30 days	Menopausal syndrome (Human, Rat)	ACTH↓, FT4↓, NE↑	(Wang *et al*., 1994)
Jian-Ru-Ling	4 pills, TID, PO	25 days	Hyperplasia of mammary gland (Human)	E_2↓, PRL↓, P↑, T↑ ,	(Huang *et al*., 1999)
Jing-Qian-Shu Granule	100 mg/kg, QD, PO	56 days	Premenstrual depression (Monkeys)	PRL↓, E↓	(Qiao *et al*., 2007)
JinGui-ShenQi Pill	3.0 g, TID, PO	3 months	Partial Androgen Deficiency (Human)	T↑ LH↓, FSH↓	(Che *et al*., 2005)
Keishi-bukuryo-gan	300 mg/kg, QD, PO	14 days	Gonadal system (Rat, Human)	LH↓, FSH↓, E_2↓	(Sakamoto *et al*., 1988; Sakamoto *et al*., 1998)
Kidney-replenishing Herbs	20.0 g, TID, PO	30 days	Menopausal Osteoporosis (Human)	E_2↑,	(Huang and Ye, 1993)
Li-Ru-Kang	12.0 g, TID, PO	4 months	Hyperplasia of mammary gland (Human)	E_2↓, P↑, T↑, FSH↑, PRL↓	(Qian *et al*., 2007)
Li-Shen Injection	10% 8.0 ml, QD, Injection	2 weeks	Kidney Deficiency (Human)	E_2 (Diphasic regulatory)	(Qiu *et al*., 1996)
Liu-Wei–Di-Huang Decoction	5.0-15.0 g/ kg, QD, PO	20 days	Senescence accelerated (Mouse)	E_2↑, LH↓	(Ma *et al*., 2004)
MaiDan-RuTong Granule	2.0-8.0 g/kg, QD, PO	10 days	Galactozemia (Rat)	PRL↑	(Xu and He, 2007)
NingXin-HongQi Capsule	162-648 mg/kg, QD, PO	8 weeks	Menopause (Rat)	E↑, P↑, FSH↓, LH↓	(Lu *et al*., 2008)
PC-SPES	1.28 g, QD, PO	2 week	Prostate cancer (human)	T↓	(DiPaola *et al*., 1998)
Peony-Glycyrrhiza Decoction	45.0 g, QD,PO;2.5 g TID, PO 7.5 g; QD, PO	4 week; 8 week; 24 weeks	Hyperprolactinemia; Amenorrhea; Polycystic ovarian disease (Human)	PRL↓, T↓	(Takahashi and Kitao, 1994; Takeuchi *et al*., 1989; Yamada *et al*., 1996; Yamada *et al*., 1997; Yuan *et al*., 2008)
Peppermint Teas	5.0, 8.0 g, QD, PO	30 days	Digestion (Rat)	FSH↑, LH, T↓	(Akdogan *et al*., 2004)

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Table 2: Continue

Herbal preparations	Treatment methods	Duration	Models/diseases	Effect on Hormones	References
Qing'E Formula	0.85- 3.4 g/kg, QD,PO	4 weeks	Menopause (Human)	LH↑, E_2↑	(Xu *et al*., 2010)
Ru-kuai-xiao decoction	5.8- 23.2 g/kg, QD, PO	30 days	Hyperplasia of mammary gland (Rat)	E_2↓, PRL ↓, P↑	(Chen *et al*., 2007a)
Ruxian Pill	58-525 mg/kg, QD, PO	3 months	Mammary Gland Hyperplasi (Rabbit)	E_2 ↓, P ↑	(Chen *et al*., 2007b)
San-Zhuang Wan	1.0 g/kg QD, PO	10 days	Immature (Rat)	LH↑, T↓,	(Zhang and Pomerantz, 1989)
Sheng-Jing-Bao	2.0 g/kg QD, PO	36 days	Oligospermia (Mouse)	T↑	(Yang *et al*., 2007)
Spearmint Tea	5.0g, BID, PO	5 or 30 days	Hirsutism combined with polycystic ovarian syndrome (Human, Rat)	T ↓, LH↑, E_2 ↑, FSH↑, P↓	(Akdogan *et al*., 2007; Grant, 2010)
Special Herbal Tea	30 g/kg QD, PO	21 days	Androgen-induced sterility (Rat)	GnRH ↑, FSH↑, LH ↑, E_2↓	(Sun and Yu, 2000)
Tian-Kui Fang	3.42 g/kg QD, PO	9 days	Fat infertility (Rat)	GnRH↑, FSH ↑, LH↑, E_2↓, T↓	(Sun *et al*., 1999)
Tian-Kui-Geng-Nian Capsule	0.72-4.5 g/kg QD, PO	45 days	Aged female rat (Rat)	E_2↑	(Liu *et al*., 2006)
Tiao-Geng-Tang	3.87 g/day, QD,PO	8 weeks	Ovariectomy (Rat)	E_2↑, FSH↓	(Xu *et al*., 2011)
Tokishakuyakusan	0.5- 2 g/kg or 7.5 g, QD, PO	2 weeks or 20 days	Menopausal syndromes (Rat); Ovarian insufficiency (Human)	E_2↑, P↑	(Chung *et al*., 2008; Koyama *et al*., 1988)
Tong-Da Tang	Dosis , BID, PO	8 weeks	Galactorrhea amenorrhea syndrome (Human)	PRL↓	(Ding *et al*., 2008)
Wen-Jing Tang	2.5g, TID, PO	8 weeks	Polycystic ovary syndrome (Human)	LH↓, E_2↑, P ↑	(Koyama *et al*., 1988; Ushiroyama *et al*., 2006; Ushiroyama *et al*., 2001)
Xiao-Yao Wan	6.0 g, TID, PO	10 weeks	Hyperprolactinemia (Human)	PRL↓	(Ren *et al*., 2008)
Xiong-Gui-Tiao-Xue-Yin	6.0 g, QD,PO	6 days	Spontaneous labor pain (Human)	PRL↑	(Ushiroyama *et al*., 2007)
Yang-Jing Decoction	24.0g/kg QD, PO (Rat); TID, PO (Human)	3 months or 4 weeks	Anovulatory (Human, Rat)	FSH↑,LH↑, E_2↑,NE↑	(Liu *et al*., 2001)
Yi-Gu Capsule	4 capsules, TID, PO	6 months	Postmenopausal osteoporosis (Human)	E_2↑	(Zhang *et al*., 2005)
YiShen-TiaoJing Recipe	Dosis , QD,PO	3 months	Woman hypogonadism (Human)	E_2↑	(Mao *et al*., 2008)
Zi-Shen Pill	0.3-0.6 g/kg, QD,PO	28 days	Benign prostatic hyperplasia (Rat)	DHT↓	(Sun *et al*., 2008)
Zuo-Gui Pill	150 mg/ kg, QD,PO	7 weeks	Premature ovarian failure (Rat)	FSH↑, E_2 ↑,	(Zhu *et al*., 2005)

DHT: dihydrotestosterone; GnRH: gonadotropin releasing hormone; E_2: estradiol; T: testosterone; P: progesterone; ACTH: adrenocorticotropic hormone; LH: luteinizing hormone; FSH: Follicle stimulating hormone; PRL: prolactin.
QD: Once a day; BID: Twice a day; TID: Three times a day; PO: Oral administration.
↑ The level of hormones enhanced; ↓ The level of hormones reduced

Wen-Jing Tang is an extensively investigated herbal formula. It mainly acts at the hypothalamic-pituitary-ovarian axis (Koyama *et al.*, 1988). This mixture normalize menstrual cycle in women with high basal levels of LH secretion and an ovulation in patients with polycystic ovary syndrome (Ushiroyama *et al.*, 2006).

Although no direct experimental data reveal the regulatory effects of some herbs on sex hormone secretion, these herbs are successfully using disease administration. *Prunella vulgaris* displays significantly anti-estrogenic activity and changes the expressions of CYP1A1, CYP1B1 and aryl hydrocarbon receptor (Collins *et al.*, 2009). *Trifolium pretense* stimulates the secretion of alpha-estrogen receptor in the endometrium without increasing cell proliferation (Alves *et al.*, 2008). Moreover, *GuiZhi-FuLing Wan* possesses therapeutic effect on hot flashes in women who are undergoing medical ovariectomy (Noguchi *et al.*, 2005; Sakamoto *et al.*, 1992).

CONCLUSION

The current studies on the regulatory effects of herbal medicine on hormones related to HPA and HPG axis are still limited. Given the reported therapeutic success of these medicines by traditional cultures and modern clinicians, the activities of these herbs or herbal mixtures may be partially due to their effects on hormones regulation. Only a few herbal drugs have been approved in clinical use due to the complex mixture of chemical components. In this review, most herbal drugs have been displayed their effects on hormone regulation in animal models which may be approved in clinics. The data collected and reviewed here will benefit to further research on herbal medicines related to neuroendocrinological disease.

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