The Endocrine System

• No system in higher animals exists in isolation.
• The endocrine system is part of the psycho-neuro-immuno-endocrine (PNIE) system, which regulates and coordinates organ systems and their cellular function, as well as thinking, feeling, mood and behaviour.
• PNIE maintains stability in the process of change
• Health depends on successful adaption to change
• PNIE depends on feed-back to regulate health
Endocrine Function

- The endocrine system includes eight major glands throughout the body. These glands make hormones. Hormones are chemical messengers. They travel through the bloodstream to tissues or organs. Hormones work slowly and affect all body processes. These include
  - Growth and development
  - Metabolism - digestion, elimination, breathing, blood circulation and maintaining body temperature
  - Sexual function, Reproduction
  - Mood

<table>
<thead>
<tr>
<th>Endocrine Tissue</th>
<th>Hormone</th>
<th>Site of Action</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Pituitary</td>
<td>Growth Hormone</td>
<td>Most Cells Adrenals (cortex) Thyroid Gonads Gonads Breast</td>
<td>Stimulates Growth Release Cortisol &amp; Aldosterone Secretion of Thyroid Hormones Ovarian Follicles &amp; Testosterone Oestrogen/Progesterone &amp; “Breast Development &amp; Milk</td>
</tr>
<tr>
<td></td>
<td>ACTH</td>
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<tr>
<td></td>
<td>TSH</td>
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<td>FSH</td>
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<td></td>
<td>LH</td>
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<td></td>
<td>Prolactin</td>
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<td>Posterior Pituitary</td>
<td>ADH</td>
<td>Kidneys, Vessels Uterus &amp; Breast</td>
<td>Causes Retention Water &amp;BP Contractions, Breast Milk (Also Bonding)</td>
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<td>Pineal</td>
<td>Melatonin</td>
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<td>Sleep/Wake Cycle</td>
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<td>Thyroid</td>
<td>T3, T4</td>
<td>Most Cells Bones</td>
<td>Increases Metabolism Bone Mineralisation</td>
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<td></td>
<td>Calcitonin</td>
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<tr>
<td>Parathyroid</td>
<td>Parathormone (PTH)</td>
<td>Gut, Kidney, Bone</td>
<td>Increases Calcium in Blood</td>
</tr>
<tr>
<td>Endocrine Tissue</td>
<td>Hormone</td>
<td>Site of Action</td>
<td>Action</td>
</tr>
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</tr>
<tr>
<td>Adrenal Medulla</td>
<td>Adrenaline (Epinephrine) &amp; Noradrenaline (Norepinephrine)</td>
<td>Many Cells &amp; Organ Systems</td>
<td>Initiates Flight/Flight, Regulates Drive</td>
</tr>
<tr>
<td>Adrenal Cortex</td>
<td>Cortisol &amp; Aldosterone &amp; DHEA</td>
<td>Many Cells/Tissue Kidneys, Sweating Immune, Brain</td>
<td>Stress Response, Metabolism, Immune System, Mood Water/Sodium, Potassium Androgen, Immune, Mood</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Insulin &amp; Glucagon</td>
<td>Most Cells Liver, Fat, Muscles</td>
<td>Tissue Entry of Sugar ➔ Fat Increases Glucose &amp; Release</td>
</tr>
<tr>
<td>Ovaries</td>
<td>Oestrogens &amp; Progesterone</td>
<td>Sex Organs, Bone, Brain (Same)</td>
<td>Sexual Development, Uterine Tissue, Menstruation, Bone</td>
</tr>
<tr>
<td>Testes</td>
<td>Testosterone</td>
<td>Sex Organs, Bone</td>
<td>Sexual Development, Libido, Muscle Development</td>
</tr>
</tbody>
</table>

**Hypothalamus**

- Where it all Begins (or Ends)
Hypothalamus

• Zuogui Pill(左归丸) and Yougui Pill(右归丸) could improve the function of central nervous system and delay ageing by regulating the expression of amino acid neurotransmitter receptor in the hypothalamus (Kang et al, 2007).

(20 month old the rats were given Zuo Gui Wan and 20 plus were given You Gui Wan)

You Gui Wan
(Restore the Right Pill)

• Cinnamomi Cortex (rou gui)
• Aconiti Carmichaeli praeparata (fu zi)
• Radix Dioscoreae Oppositae (shan yao)
• Radix Rehmanniae Glutinosae Praeparata (shu di)
• Angelicae Sinensis (dang gui)

• Corni Officinalis Fructus (shan zhu yu)
• Lycii Fructus (gou qi zi)
• Eucommiae Cortex (du zhong)
• Cuscutae Chinensis Semen (tu si zi)
Zuo Gui Wan
(Restore the Left Pill)

• Radix Rehmanniae Glutinosae Praeparata (shu di)
• Corni Officinalis Fructus (shan zhu yu)
• Fructus Lycii (gou qi zi)
• Cuscutae Chinensis semen (tu si zi)
• Colla Plastrum Testudinis (gui ban jiao)

• Radix Dioscoreae Oppositae (shan yao)
• Colla Cornu Cervi (lu jiao jiao)
• Radix Cyathulae Officinalis (chuan niu xi)

Hypothalamus

• The antipyretic mechanism of Heat Clearing herbs; Scutellaria baicalensis (huang qin), Forsythia suspensa (lian qiao) and Lonicera japonica (jin yin hua) affected the metabolism of antipyretic central medium $\beta$-Endorphin (hippocampus and hypothalamus), raising its content and suppressing of raising temperature set point (Xu et al, 1998).

• The decline of hypothalamic-function in ageing was the reason for decreased pituitary-thyroid axis function. Tonifying herbs might regulate the function of hypothalamus in delaying the ageing changes of pituitary-thyroid axis.

• Treatment with kidney tonifying and vital energy benefiting prescription delayed increase of pituitary weight and delayed decrease in hypothalamic NE, DA, 5-HT, 5-HIAA, TEH (neuron) and pituitary TEH synaptic levels (Zhang et al, 1990)
**Hypothalamus**

- Active fraction A (Fr.A), isolated from Ramulus Cinnamomi Cassiae (gui zhi) decoction was related with promoting release of arginine vasopressin (AVP) in ventral septal area (VSA) and neurotensin (NT) in hypothalamus.
- It also inhibited the release and/or action of AVP and NT in the thermoregulatory center and was involved in regulating hypothermia (Huo et al, 1999).
- 10g/kg of decoction of Cinnamon Twigs (DCT) (gui zhi) was orally administered and the cAMP level in the hypothalamus or the plasma and the ratio of cAMP/cGMP increased thereafter.
- Result indicated that cyclic nucleotide in the thermoregulatory centre took part in the dual-directional regulation of DCT (Fu et al, 1994).

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**Hypothalamus**

- The Yang-strengthening Chinese herbs Radix Aconiti Praeparata (fu zi), Cortex Cinamomi (rou gui), Epimedium brevicorum (yin yang huo) and Herba Cistanchis (rou cong rong) were used in the study and the following were found:
  1: In the hypothalamus of cortisol-induced Yang-deficiency, rat Noradrenaline (NA) decreased and Adrenaline (A) increased when compared with that of the control.
  2: After 4 weeks of administration of Yang-strengthening herbs, the NA and A of the Yang-deficiency rats returned to nearly normal and it suggested these herbs have the effect of "supporting the right and recovering the source". Dopamine (DA) markedly increased both in control rats and Yang-deficiency rats.
Hypothalamus

3: The ratio of DA/3,4-dihydroxyphenylacetic acid (DOPAC) and Serotonin (5-HT)/5-hydroxyindole-3-acetic acid (5-HIAA) markedly increased both in the control and Yang-deficiency rats after using Yang-strengthening herbs.

- The study suggested Yang-strengthening herbs could inhibit the activity of monoamine oxidase (MAO) in hypothalamus (Chen et al, 1990).

Hypothalamus

- Guilingji decreased the levels of thiobarbituric acid reactive substances (TBARS) in the left cortex, midbrain, and olfactory lobe, and increased the SOD activity in the midbrain and hypothalamus.
- These results are the first to demonstrate that Guilingji may possess an antiepileptic effect further to its proposed antiageing action, because decreasing the TBARS elevation and increasing the SOD attenuation in the brain are suggested to be important characteristics of antiepileptic agents (Liu et al, 1990).
Gui Ling Ji

- Cornu Cervi (Lu Rong)
- Radix Ginseng (Ren Shen)
- Hippocampus (Hai Ma)
- Radix Rehmanniae Glutinosae Praeparata (Shu Di Huang)
- Herba Cistanches Deserticolae (Rou Cong Rong)
- Squama Manitis Pentadactylae (Chuan Shan Jia)
- Fructus Lycii (Gou Qi Zi)
- Radix Achyranthis Bidentatae (Huai Niu Xi)
- Fructus Amomi (Sha Ren)
- Cortex Eucommiae Ulmoidis (Du Zhong)
- Halitum (Rong Yan)
- Herba Cynomorii Songarici (Suo Yang)
- Flos Caryophylli (Ding Xiang)
- Cerebrum Passeris Montani (Que Nao)
- Semen Cuscutae Chinensis (Tu Si Zi)
- Fructus Psoraleae Corylifoliae (Bu Gu Zhi)
- Herba Epimedii (Yin Yang Huo)
- Radix Glycyrrhizae Uralensis (Zhi Gan Cao)
- Tuber Asparagi Cochinchinensis (Tian Men Dong)
- Fossilia Spirifera (Shi Yan)

Magnolol

- Magnolol, isolated from Magnolia officinalis produced a decrease in colon temperature, an increase in foot skin temperature, a decrease in metabolic rate and a decrease in the endogenous release of 5-HT in the rat hypothalamus.

- Data suggest that magnolol decreases body temperature due to increased heat loss and decreased heat production (Hsieh et al, 2007)
Hypothalamus & Immunity

- Kidney Tonifying Herbs (KTH) exerted effects on reserve function of the adrenal cortex and lymphocytic receptor glucocorticoid.
- The therapeutic mechanism of KTH was explored with respect of function in endocrine axis and neurotransmitter in hypothalamus.
- The senile hypothalamic function played an important role in the declining of neuroendocrine-immunity function. KTH might regulate the function of hypothalamus, delaying the ageing of neuroendocrine-immunity disturbance (Zhang et al, 1994).

Pituitary/Adrenal

- Social Stress & Ageing
Adrenals

<table>
<thead>
<tr>
<th>Adrenal Disorder</th>
<th>Major Signs &amp; Symptoms</th>
<th>Key Lab Tests</th>
<th>Conventional Approach</th>
<th>Complementary Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Aldosteronism (hyperaldosteronism)</td>
<td>Secondary Hypertension</td>
<td>High Aldo Levels also: Potassium, Magnesium, Alkalosis</td>
<td>Unilateral Adrenalectomy</td>
<td>Ginger extract (Jiang et al 2001) Fuzi, Paojiang &amp; Yuxingcao (Chen et al 2009) Past Tense</td>
</tr>
<tr>
<td>Pheochromocytoma (adrenal tumours)</td>
<td>Hypertension Headaches Palpitations</td>
<td>Catecholamines</td>
<td>Surgery Vincristine etc</td>
<td>Rauwolfia (she gen mu) alkaloids (Kahler, 1958). Ligusticum chuanxiong (Lin et al, 2007) Past Tense</td>
</tr>
<tr>
<td>Adrenal Insufficiency</td>
<td>Weakness, Fatigue Hypotension (Postural)</td>
<td>DHEA-S Cortisol</td>
<td>Steroids Salt</td>
<td>Adaptogenic Herbs (Friedman, 2008) Glycyrrhetinic Acid (Mackenzie et al 1990) Re)Cover, Panax Complex, Magnoli</td>
</tr>
</tbody>
</table>

Symptoms of Adrenal Insufficiency

- Excess Fatigue 94%
- Irritability 86%
- PMS 85%
- Salt Craving 84%
- Depression 79%
- Sweet Craving 75%
- Allergies 73%
- Headache 68%
- Alcohol Intolerance 66%
- Weakness 65%
- Neck/Shoulder Pain 65%
- Confusion 61%
- Poor Memory 59%
- Palpitations 57%
- Poor Digestion 51%
- Backache 48%
- IBS 45%
- Fainting 42%
- Insomnia 40%
- Dermatitis 39%

From: Friedman 2008
Signs of Adrenal Insufficiency

- Postural Hypotension 93%
- Dry Skin 91%
- Scanty Perspiration 91%
- Low Basal Body Temp 85%
- Sparse Body Hair 83%
- Underweight 78%

From: Friedman 2008

Causes of Adrenal Insufficiency

- High Levels of Ongoing, Unrelenting Psychological Stress
- Environmental Toxins
- Nutritional Insufficiency, Particularly Micronutrients & Antioxidants
- Lack of Sleep
- Lack of Exercise

From: Friedman 2008
Tests for Adrenal Insufficiency

- Twenty-four Hour Salivary Cortisol: Abnormal changes in cortisol levels may be due to hypothalamic, pituitary, or adrenal dysfunction. If undiagnosed and untreated, these disorders can be life threatening. In the diurnal rhythm of normal individuals, peak levels of cortisol are seen in the serum in the morning (6:00 a.m.), and the lowest levels are in the late evening (10:00 p.m.).
  - DHEA-S
  - Testosterone
  - Serum Na = low normal
  - Serum K = high normal
  - Eosinophils = high

Cortisol Levels
Magnol

- Honokiol, a neolignane derivative of Magnolia bark (chuan po), has central depressant action and, at much lower doses, anxiolytic activity. Results suggest that, in contrast with diazepam, honokiol selectively induces an anxiolytic effect with less liability of eliciting motor dysfunction and sedation or disinhibition (Kuribara et al, 2000)
- Honokiol inhibits catecholamine secretion induced by carbachol and DMPP. The results suggest that honokiol interferes with the interaction between the acetylcholine receptor and its agonists (Liu et al, 1989)

Magnol

- Salivary DHEA and cortisol measurements were taken.
- Using Honokiol and Magnolol, morning salivary cortisol levels dropped 37 percent, while DHEA levels rose 227 percent. Previously abnormal cortisol/DHEA levels returned to normal in all subjects by the study’s end (LaValle & Hawkins, 2003)
**Rhodiola rosea**

- Treatment of Rhodiola rosea extracts (RRE) for 4 weeks could reduce swimming-enhanced oxidative stress possibly via the reactive oxygen species scavenging capability and the enhancement of the antioxidant defense mechanisms (Huang 2009).
- Chronic administration of RRE results in potent inhibition of the behavioural and physiological changes induced by chronic exposure to mild stressors (Mattioli 2009).

**Stress Related Neurological Decline**

- A combination of Genistein, Resveratrol, Quercetin and Curcumin has been shown to prevent cognitive decline due to ageing, stress and endocrine disruption.
- Results suggest that the main improvement after 6 weeks of genistein supplementation was in frontal lobe function (File et al, 2005).
- Results suggest that the addition of genistein to the diet of ovariectomized female rats is likely to increase the rate of protein synthesis in the brain, and that RNA activity is at least partly related to the fractional rate of brain protein synthesis (Lyou et al 2002).
Panax Complex

• Gynostemma Herba Polysaccharide (GP), jiao gu lan plays a role in the enhancement of the antioxidant enzyme activity in some tissues of exhausted mice, and to a certain extent inhibit the lipid peroxidation damage (Wang & Chen, 2008), and Administration of GP increases ACTH levels (Chen & Chen P.854)

Panax Complex

• GP administration three times daily for 2 months reduced signs of ageing in 106 patients. Less fatigue and increased energy, decreased diarrhoea, increased memory and a reduction in insomnia (Chen & Chen P. 855)

• The gypenosides was used as an immune enhancer to cure the immune deficit mouse and observe non-specific immunological function (Zhou et al, 2006)
Panax Complex

• Panacis Quinquefolii radix/American Ginseng (AG), xi yang shen can significantly prolong the swimming time of yin-deficiency Jimpy mice, compared with model control group, the high-dose group and the low-dose group have the significant difference (Li et al 2007).

Panax Complex

• Ginsenoside Rb1 from AG can improve the mouse liver tissue regeneration, before raising the level of albumin, to improve liver after fatigue (Lu et al, 2008).

• Both AG and GP have a CNS depressive effect, Panax Complex increases energy and endurance, stimulates immunity, has an anti-ageing effect while reducing stress levels. GP has a particularly strong sedative effect.
Perimenopausal Depression

• The disorder of the hypothalamic-pituitary-ovarian (HPO) axis during perimenopause has been found to affect the levels of dopamine and serotonin, important mood-stabilising neurotransmitters. 8% to 47% of women undergo perimenopausal depression (Schmidt, 2005).
• The serotonin deficiency hypothesis is the most prominent biological theory of the aetiology of depression, and oestrogen has been found to modulate serotonergic function, through which oestrogen controls mood lowered level of oestrogen and the increased levels of FSH and LH are associated with depression during the menopausal transition.
• It may be partly through increasing the level of E2 and decreasing the levels of FSH that GNL herbal alleviated perimenopausal depression.
**Geng Nian Le (GNL)**

- All the herbs in GNL act together to supplement the Kidney, regulate the Liver, balance yin and yang, and supplement qi and Blood, thus relieving perimenopausal depression.
- After 12 weeks of treatment, Hamilton Depression Scale (HAMD) scores in both groups decreased significantly (p 0.05) with no significant difference between the GNL and the Tibolone (a synthetic steroid hormone) group (p 0.05).
- The levels of FSH decreased significantly and the level of E2 increased significantly in both groups, and they changed more in the control group (Qu et al, 2009).

**Geng Nian Le (GNL)**

- Concha margarita (zhen zhu)
- Semen Ziziphus Spinosae (suan zao ren)
- Radix Astragali (huang qi)
- Radix Polygalae (yuan zhi)
- Rhizoma Dioscoreae (shan yao)
- Semen platycladi (bai zi ren)
- Cortex Albiziae (he huan pi)
- Radix Codonopsis (dang shen)
- Semen Cuscutae (tu si zi)
Glucose Homeostasis Disorders

• Diabetes & Hypoglycaemia

Type 2 Diabetes

• Many type II diabetic patients have normal levels of insulin in the blood.
• The diabetes is not caused by the destruction of beta cells in the pancreas but by other mechanisms, such as insulin resistance, related to down-regulation of insulin receptors, defects in insulin secretion from the pancreatic beta cells and other changes to the glucose transporter system.
Type 2 Diabetes

• About 5%-10% of pre-diabetes will develop into diabetes within one year and the occurrence of cardiovascular events in patients with pre-diabetes are higher than in healthy individual. The rates of development of diabetes after 5.8-6.5 years follow-up from patients with normal glucose tolerance, single impaired fasting glucose (IFG), single Impaired Glucose Tolerance (IGT), both IGT and IFG people are 4.5%, 33.0%, 33.8% and 64.5%, respectively (Pan et al, 1995)

Blood Sugar Regulation

• The best evidence for efficacy in diabetes is from adequately designed randomised controlled trials (RCTs) for Coccinia indica (Hossain et al, 1992) and American ginseng (University Of Toronto 2000; Vuksan et al, 2000).

• Chromium has been the most widely studied supplement as is Gymnema sylvestre, Aloe vera, vanadium, Momordica charantia, and Opuntia fuliginosa (Trejo-González et al 1996; Yeh et al, 2003).
Blood Sugar Regulation

- Antioxidants have been considered as a useful remedy in diabetes therapeutics, and thus, herbal medicines with antioxidant properties may play major role in treating diabetes.
- American ginseng (AG) and Scutellaria baicalensis (SB) were tested to evaluate their anti-diabetic effect in obese diabetic ob/ob mice.
- AG at 300 mg/kg showed significant effects on fasting blood glucose levels ($P<0.01$) and glucose tolerance test ($P<0.01$). Animal body weights also reduced significantly after 12-day treatment ($P<0.01$). However, SB administered at 5-50 mg/kg for 12 days did not show any significant effects on blood glucose and body weight changes (Xie et al, 2009).

NT2

Jin Qi Jiang Tang (JQJT) formula:
- Flos Lonicerae (jin yin hua)
- Rhizome Coptidis (huang lian)
- Radix Astragali (huang qi)
- Panax Ginseng Berry (ren shen guo)
- Nelumbo nucifera (ou jie)

- Momoridica
- Chromium
- Theaflavin 3-O-gallate, Theaflavin 3'-O-gallate, Theaflavin 3, 3'di-O-gallate
Jin Qi Jiang Tang (JQJT): Dual deficiency of qi and yin or yin deficiency with heat.

• JQJT tablets can improve insulin resistance in humans (Shen, 2004).

• Gu wenyuan indicated that combination of JQJT tablets and Gliclazide can improve fasting blood-glucose (FBG) of 2 type diabetes patients (Gu, 2004).

• Zhang rongrong discovered that JQJT tablets can not only prevent the progression from pre-diabetes to diabetes but also delay development of diabetic nephropathy (Zhang & Liu, 2005).

• Three black tea theaflavins, theaflavin 3-O-gallate, theaflavin 3'-O-gallate, theaflavin 3,3’ di-O-gallate and thearubigins as novel mimics of insulin/IGF-1 action on mammalian FOXO1a, PEPCK (Cameron et al, 2008).

• A significant reduction in blood glucose level was observed at a dose of 10 mg/kg of theaflavin 3’-O-gallate (TF-3-O-Gal), demonstrating for the first time that TF-3-O-Gal can suppress glucose production from maltose through inhibition of α-glucosidase (AGH) in the gut (Matsui et al, 2007).
It is now largely established that the immune and neuroendocrine systems cross-talk by using similar ligands and receptors. In this context, the thymus-hypothalamus/pituitary axis can be regarded as a paradigm of connectivity in both normal and pathological conditions.

For example, cytokines and thymic hormones modulate hypothalamic-pituitary functions: (a) interleukin (IL)-1 seems to upregulate the production of corticotropin-releasing factor and by adrenocorticotropin by hypothalamic neurons and pituitary cells, respectively; (b) thymulin enhances LH secretion.
In addition to mutual effects, thymus-pituitary similarities for cytokine and hormone production have been demonstrated. Cytokines such as IL-1, IL-2, IL-6, interferon-\(\gamma\), transforming growth factor-\(\beta\) and others can be produced by hypothalamic and/or pituitary cells.

Conversely, hormones including GH, PRL, LH, oxytocin, vasopressin and somatostatin can be produced intra-thymically.

The thymus-pituitary connectivity can also be seen under pathological situations. In this regard, an altered HPA axis has been reported in AIDS, human falciparum malaria and murine rabies, that also show a severe thymic atrophy.

From: Savino et al 1999; Immunoneuroendocrine Connectivity: The Paradigm of the Thymus-Hypothalamus/Pituitary Axis

Serissa serissoides (liu yue xue) increased the weight and volume of thymus gland index in mice (Zhu et al, 2007).

According to the free radical theory of ageing, free radicals could initiate lipid peroxidation, and produce such metabolic products as malondialdehyde (MDA), which could form lipofuscin and deposit in the organs such as brain and liver, thus leading to the injury of structure and function in normal cells.

The thymus gland and spleen are the main immune organs in the human body, and the structural and functional ageing of the immune system impacts these organs.
Thymus & Lipofuscin

- Lipofuscin could decrease liver lipid peroxidation and increase thymus index. The liver lipid peroxidation was determined by thiobarbituric (TBA) method. The thymus index and spleen index were determined by weighing method.
- It suggested that it might be beneficial in retarding ageing and immune processes (Chu et al, 2000).
- Lipofuscin contains Polygonum Multiflori (he shou wu), Rhizoma Acori Gramineae (shi chang pu), Scutellaria baicalensis (huang qin) and Panax notoginseng (san qi), Rehmannia glutinosa (shu di) and Ligusticum chuanxiong (chuan xiong).

Thank You

The yin/yang of the psycho-neuro-immuno-endocrine system

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