Stress, Inflammation and Affect Disorders

The Hidden Fires of Metaflammation, Para-inflammation, and Smouldering Chronic Inflammation
Stress

- ‘Stress’ may be defined as any situation which tends to disturb the equilibrium between a living organism and its environment.
- From another perspective, stress may be the discrepancy between an internal psycho-physical resource and the magnitude of the external demand: more resource, less stress.
- As the environment (the world) changes we need to adapt, learn and evolve.
Stress

- The stress system coordinates the adaptive responses of the organism to stressors of any kind. The main components of the stress system are the corticotropin-releasing hormone (CRH) and locus ceruleus–norepinephrine (LC/NE)-autonomic systems and their peripheral effectors, the pituitary–adrenal axis (Tsigos & Chrousos 2002).

- Activation of the stress system leads to behavioural and peripheral changes that improve the ability of the organism to adjust homeostasis and increase its chances for survival (Tsigos 2002).
Allostasis

- Allostasis is the process of achieving stability through physiological or behavioural change. This can be carried out by means of alteration in HPA axis hormones, the autonomic nervous system, cytokines, or a number of other systems, and is generally adaptive in the short term (1998, doi: 10.1056/NEJM199801153380307).

- This is a process of reestablishing homeostasis, but one that responds to a challenge instead of to subtle ebb and flow. Allostasis is from the Greek *allo*, which means "variable;" thus, remaining stable by being variable
Stress and Adaptation

- Stress promotes adaptation (“allostasis”), but a perturbed diurnal rhythm or failed shutoff of mediators after stress (“allostatic state”) leads, over time, to wear and tear on the body (“allostatic load”). Neural changes mirror the pattern seen in the cardiovascular, metabolic, and immune systems, that is, short-term adaptation versus long-term damage.

- Allostatic load leads to impaired immunity, atherosclerosis, obesity, bone demineralization, and atrophy of nerve cells in brain. Allostatic load is seen in major depressive illness and may also be expressed in other chronic anxiety disorders such as PTSD and should be documented (McEwen 2003).
Allostastastic Load

- Type 1 allostatic overload occurs when energy demand exceeds supply, resulting in activation of the emergency life history stage. This serves to direct the animal away from normal life history stages into a survival mode.
- Type 2 allostatic overload begins when there is sufficient or even excess energy consumption accompanied by social conflict and other types of social dysfunction. Type 2 allostatic overload does not trigger an escape response, and can only be counteracted through learning and changes in the social structure (2003, doi:10.1016/S0018-506X(02)00024-7)
Epidemiological studies have shown that chronic work stress or unfavourable psychosocial work conditions are prospectively associated with different adverse health outcomes.

The relationship between work-related chronic stress as well as exhaustion and a cumulative measure of physiological wear-and-tear called allostatic load [AL]. AL could be a possible biological pathway for how chronic work stress and exhaustion lead to health impairments in the long run.
Allostatic Load and Reward

- Effort-Reward-Imbalance [ERI] is the underlying factor in whether the effort to reward expresses satisfaction [adaptation] or stress [failure to adapt].

- A value close to zero indicates relatively low effort and relatively high reward whereas values above 1.0 indicate a high amount of effort spent not matched by appropriate rewards (Bellingrath et al 2009).
Allostasis & Allostatic Load

- Allostasis is the process of adaptation that helps the body to maintain homeostasis. Allostatic load is the cost of excessive adaptation and reflects over-activity of chemical mediators involved in adaptation; it reflects an imbalance in the activities of mediators - e.g. inflammatory cytokines with inadequate glucocorticoids; or excess excitatory amino acids in brain after stress or during ageing; or elevated glucocorticoids, insulin and catecholamines in relation to abdominal obesity and Type 2 diabetes.

- Four conditions that lead to allostatic load are:
Allostasis & Allostatic Load

1. Repeated frequency of stress responses to multiple novel stressors
2. Failure to habituate to repeated stressors of the same kind
3. Failure to turn off each stress response in a timely manner due to delayed shut down
4. Inadequate response that leads to compensatory hyperactivity of other mediators. The effects of these forms of dysfunctional allostasis cause allostatic load and this in turn leads over time to diseases (McEwen et al 1997).
Psychological Stress

- In response to psychological stress, the level of various hormones changes. In response to psychological stress, the immune system is altered. In response to psychological stress may affect the production of pro-inflammatory and immunoregulatory cytokines.

- Psychological stress significantly increased the stimulated production of tumour necrosis factor α (TNF-α), interleukin 6 (IL-6), IL-1 receptor antagonist (IL-1Ra), interferon γ (IFN-γ) and IL-10.
Activation of Stress: Allostasis

HEALTHY ADAPTATION

UNHEALTHY; FAILURE TO ADAPT

Repeated Hits | Lack of Adaptation | Prolonged Response | Burnout Inadequate Response
Stress and Allostatic Load

- Often, we use the word "stress" to refer to biological factors, but this is an oversimplification because they are more than "stress" and include many aspects of lifestyle and daily experience and behaviour, including the adjustments to the circadian light-dark cycle.

- Moreover, the widespread use of the term "stress" in popular culture has made this word a very ambiguous term to describe the ways in which the body copes with psychosocial, environmental and physical challenges (McEwen 2000).
Stress and Allostatic Load

- Allostasis is positive and necessary to life. It is different from homeostasis in that it supports homeostasis—it supports physiological parameters essential for life, as environments and/or life changes (McEwen and Stellar 1993).
The 7 biological markers used to measure allostatic load scores

1. Waist-to-hip circumference ratio
2. Systolic & diastolic blood pressure
3. Urinary cortisol
4. Urinary norepinephrine
5. Urinary epinephrine
6. Serum Dehydroepiandrosterone sulphate (DHEA-S)
7. Glycosylated haemoglobin
The next 7 biological markers used to measure allostatic load scores

1. Serum LDL / HDL cholesterol
2. Total serum cholesterol / triglycerides
3. Insulin resistance
4. Tumour-necrosis-factor-α (TNF-α)
5. C-reactive protein (CRP)
6. Fibrinogen
7. D-dimer
Molecules

- Sufficient evidence is now available to accept the concept that the brain recognises cytokines as molecular signals of sickness (Dantzer 2006). Perhaps there is no causal link between personality, stress and cancer but they are all linked by an underlying factor; chronic systemic inflammation.

- Inflammatory cytokines, such as interleukin 1 (IL-1) and IL-6 are small enough to pass through the blood brain barrier (BBB) and when these cytokines bind to blood vessel receptors in the brain, they trigger other enzymes.
Psychological Stress & Inflammation

- Those with high anxiety response had a significantly higher production of IFN-γ and a lower production of the negative immunoregulatory cytokines, IL-10 and IL-4 (1998, https://doi.org/10.1006/cyto.1997.0290)

- Increasing amounts of data suggest that inflammatory responses have an important role in the pathophysiology of depression. Depressed patients have been found to have higher levels of proinflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules. In addition, therapeutic administration of the cytokine interferon-α leads to depression in up to 50% of patients (2006, http://doi.org/10.1016/j.it.2005.11.006).
Inflammation

- Inflammation underlies a wide variety of physiological and pathological processes. Although the pathological aspects of many types of inflammation are well appreciated, their physiological functions are mostly unknown.

- The classic instigators of inflammation — infection and tissue injury — are at one end of a large range of adverse conditions that induce inflammation.

- Chronic inflammation may add to the severity of cardiovascular disease burden by accelerating the development of atherosclerosis, as well as the link between chronic inflammation, atherosclerosis and cancer (Hasselbalch, 2012)
Inflammatory Cascade

• The body normally and naturally responds to stress by activating the inflammatory cascade. Nuclear factor-kappaB (NF-κB) has generated considerable attention as a promoter of the inflammatory cascade and COX 2 enzyme activity, which cause inflammation.

• NF-κB is a family of factors in the body that regulate immune and inflammatory responses. Inhibition of this family reduces production of the pro-inflammatory prostaglandins. However, the NF-κB system is essential to immune function so it is important to target only its cascade manifestations, not suppress NF-κB itself (Oechtinghaus & Ghosh, 2009).
Para-inflammation

- Tissue stress or malfunction similarly induces an adaptive response, which is referred to as para-inflammation or metaflammation. This response relies mainly on tissue-resident macrophages and is intermediate between the basal homeostatic state and a classic inflammatory response.

- Para-inflammation is probably responsible for the chronic inflammatory conditions that are associated with modern human diseases.

- Low-grade chronic inflammation is characterized by a two- to threefold increase in the systemic concentrations of cytokines such as TNF-α, IL-6, and CRP (Petersen & Pedersen, 2005).
Inflammation & Tissue Damage

(From: Suk, 2007)
<table>
<thead>
<tr>
<th></th>
<th><strong>Acute</strong></th>
<th><strong>Chronic</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Causative agent</strong></td>
<td>Bacterial Pathogens, injured tissues</td>
<td>Persistent acute inflammation due to non-degradable pathogens, viral infection, persistent foreign bodies, or autoimmune reactions, irritants, stress</td>
</tr>
<tr>
<td><strong>Major cells involved</strong></td>
<td>neutrophils (primarily), basophils (inflammatory response), and Eosinophils (response to worms and parasites), mononuclear cells (monocytes, macrophages)</td>
<td>Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts</td>
</tr>
<tr>
<td><strong>Primary mediators</strong></td>
<td>Vasoactive amines, eicosanoids</td>
<td>IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Few days</td>
<td>Up to many months, or years</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Resolution, abscess formation, chronic inflammation</td>
<td>Tissue destruction, fibrosis, necrosis</td>
</tr>
</tbody>
</table>

Generally speaking, acute inflammation is mediated by granulocytes, while chronic inflammation is mediated by mononuclear cells such as monocytes and lymphocytes.
Did You Know

- 35% of people have an undiagnosed chronic disease
- Cancer exists for 90% of its time before diagnosis
- 50% of the time a heart attack (Coronary Occlusion) is the first sign of a CVD
- Nearly 200,000 people die and 2.2 million injured each year by adverse reaction to prescribed drugs
- The use of prescription drugs and their interactions is the third leading cause of death

Did You Know

- Undiagnosed COPD in one study group was 27%, of which 45% were in stage 1, 53% in stage 2, 3% in stage 3 (Sandelowsky et al, 2011).

- One out of three people in an at-risk population has undiagnosed Chronic Kidney Disease (CKD) and poorly controlled CKD risk factors. Only 12% were aware of their condition. 4% of patients had stage 1 CKD, 6% stage 2, 18% stage 3, 2% stage 4, and 6% had stage 5 (Sumaili et al, 2009).
The term "cytokine" has been used to refer to the immunomodulating agents, such as interleukins and interferons. The anatomic and structural distinctions between cytokines and hormones is unclear as they are both signalling molecules.

The immunomodulating effects of cytokines are systemic rather than local and may be autocrine or paracrine in chemotaxis and endocrine as a pyrogen.
Cytokines

- Cytokines are a unique family of growth factors. Secreted primarily from leukocytes, cytokines stimulate both the humoural and cellular immune responses, as well as the activation of phagocytic cells.

- Many of the lymphokines are also known as interleukins (ILs), since they are not only secreted by leukocytes but also able to affect the cellular responses of leukocytes. Specifically, interleukins are growth factors targeted to cells of haematopoietic origin.
Tumour Necrosis Factor-α

- TNF is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. It is produced chiefly by activated macrophages.
- The primary role of TNF is in the regulation of immune cells. TNF, being an endogenous pyrogen, is able to induce fever, to induce apoptotic cell death, to induce sepsis (through IL1 & IL6 production), to induce cachexia, induce inflammation, and to inhibit tumorigenesis and viral replication.
In the basal state TNF is directly proportional to fat mass and has been shown to be involved in the development of insulin resistance. In-vitro studies have demonstrated that TNF decreases the insulin receptor tyrosine phosphorylation, and down regulates several steps in the insulin signaling pathway while neutralizing agents for TNF have been shown to improve insulin resistance.

Thus, *TNFα is not only a classical cytokine but may be causal in the insulin resistance of the metabolic syndrome of ageing* (Rudin & Barzilai, 2005).
Depression

- Stressful events promote neurochemical changes that may be involved in the provocation of depressive disorder. In addition to neuroendocrine substrates (e.g. corticotropin releasing hormone, and corticoids) and central neurotransmitters (serotonin and GABA), alterations of neuronal plasticity or even neuronal survival may play a role in depression.

- Stressors and cytokines share a common ability to impair neuronal plasticity and at the same time altering neurotransmission, ultimately contributing to depression (2005, http://doi.org/10.1016/j.neuroscience.2005.03.051).
Depression

- The public health burden of depression is also a serious issue; depression is currently ranked the fourth most burdensome disease in the world, and it is predicted that it will be the second most burdensome illness by the year 2020 for all ages, and both sexes (World Health Organisation, 2008).

- The economic burden of depression in the United States, including direct medical costs, suicide-related mortality costs, and workplace costs, was estimated at $83.1 billion in the year 2000 (Greenberg et al, 2003).
Hippocampal Apoptosis

Pre-frontal cortex locus ceruleus

Amygdala

Perceived Threat or Emotional Stress

3 Responses: Freeze, Flight, Fight

CRH/CRF

Adrenals

CRH/CRF

ACTH

Hypothalamus

Pituitary

SNS Norepinephrine

Blood Sugar

Blood Pressure

Epinephrine

Leaky Gut etc

Pancreas

Thyroid

Gonads & Auto-Immune

Resistance

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(From: Hedaya & Quinn 2008)
Network of bidirectional communication between CNS, peripheral nervous systems, endocrine, and immune systems.

From: Reiche, E., Nunes, S. & Morimoto, H. 2004
Depression & Inflammation

a) depression results from an increased production of pro-inflammatory cytokines, which may be triggered by external or internal stressors;

b) inflammation may induce depressive symptoms through different pathways, such as central neuro-inflammation, tryptophan degradation and an increased synthesis of neurotoxic tryptophan catabolites along the indoleamine oxidase pathway (TRYCATs);

c) increased inflammatory, oxidative and nitrosative (O&NS) levels may disrupt lipid membrane components and may modify protein structures thereby mounting an autoimmune response and interfere with functional proteins.
Depression & Inflammation

d) the clinical efficacy of antidepressants is at least in part related to their anti-inflammatory activity, for example, through their interactions with the inflammatory-serotonin pathway; and  
e) anti-inflammatory compounds including natural anti-O&NS (oxidative & nitrosative stress) substances (NAIOSs) may augment the efficacy of antidepressants or may have anti-depressive efficacy (Maes, 2008).
Depression & Inflammation

- Depression is accompanied by an inflammatory reaction as indicated by an increased production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, tumour necrosis factor-α (TNF-α) and interferon-γ (IFN)-γ. These cytokines are stress-sensitive and may cause depressive behaviours. The latter may be induced by an increased catabolism of tryptophan, the precursor of serotonin, to neurotoxic TRYCATs (tryptophan catabolites along the indoleamine oxidase pathway).
Cytokines & Depression

- People who are chronically ill often get depressed; depressed people are prone to a variety of medical illnesses; and pro-inflammatory cytokines can alter mood and promote illness. The effects of cytokines in the brain can induce depression in patients with these medical diseases.

- In the brain, these substances inhibit hippocampal neurogenesis; activate the hypothalamic-pituitary-adrenal axis, thus increasing cortisol production; and indirectly increase production of agonists of the N-methyl-d-aspartate receptor, which promotes apoptosis (Dowlati et al, 2010).
Cytokines & Depression

- IL-6 stimulates differentiation and proliferation of immunoglobulin-secreting B-lymphocytes, and TNF-α stimulates the release of other pro-inflammatory cytokines and inflammatory prostaglandins. In the brain, these substances inhibit hippocampal neurogenesis; activate the hypothalamic-pituitary-adrenal axis, thus increasing cortisol production; and indirectly increase production of agonists of the N-methyl-D-aspartate receptor, which promotes apoptosis.

- Concentrations of TNF-α and interleukin (IL)-6 were significantly higher in depressed patients than in controls. (Dowlati et al, 2010).
Inflammation & Depression

- Increasing amounts of data suggest that inflammatory responses have an important role in the pathophysiology of depression. Depressed patients have been found to have higher levels of proinflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules.
- Stress, which can precipitate depression, can also promote inflammatory responses through effects on sympathetic and parasympathetic nervous system pathways. (Raison et al, 2006).
An increase in inflammatory response and an imbalance between T-helper (Th) 1 and 2 functions have been implicated in major depression. Increased pro-inflammatory cytokine interleukin (IL)-1β and decreased anti-inflammatory cytokine IL-10 were found in the depressed patients. By contract, Th1 produced pro-inflammatory cytokines, TNF-α and IFN-γ were decreased, and Th2 produced cytokine IL-4 was significantly increased in depressed patients.

Electro-acupuncture treatment restored the balance between Th1 and Th2 systems by increasing TNF-α and decreasing IL-4 (Song et al, 2009).
IBD & Depression

- Depression may coexist with Crohn’s disease more often than would be expected by chance. Clinical and experimental evidence indicates that intestinal inflammatory conditions can be exacerbated by depression. The tonic counter-inflammatory influence mediated by the vagus nerve in experimental colitis provides a potential link between behaviour and gut inflammation.

- Depressive-like behaviours in mice increased susceptibility to intestinal inflammation by interfering with the tonic vagal inhibition of pro-inflammatory macrophages and produced a vulnerability to colitis by a mechanism involving parasympathetic transmission (Ghia et al, 2008).
Coronary Heart Disease (CHD)

- The current literature lends further support to the view that major depression is associated with a pro-inflammatory response, as indexed by elevation in C-reactive protein and cytokines such as interleukin 6 and tumour necrosis factor-α.

- Antidepressants suppress the inflammatory response, whereas electroconvulsive therapy acutely increases pro-inflammatory cytokine levels. Most, though not all, studies support a link between depression, inflammation and cardiovascular events. Depression is an inflammatory state that may increase the risk of cardiac disease (Dinan 2009).
Coronary Heart Disease (CHD)

- IL-6 is a powerful inducer of the hepatic acute phase response. Elevated concentrations of acute phase reactants, such as C-reactive protein (CRP), are found in patients with acute coronary syndromes, and predict future risk in apparently healthy subjects. The acute phase reaction is associated with elevated levels of fibrinogen, a strong risk factor for CHD, with autocrine and paracrine activation of monocytes by IL-6 in the vessel wall contributing to the deposition of fibrinogen.
Coronary Heart Disease (CHD)

- Circulating IL-6 stimulates the hypothalamic–pituitary–adrenal (HPA) axis, activation of which is associated with central obesity, hypertension and insulin resistance. Thus there is a role for IL-6 in the pathogenesis of CHD through a combination of autocrine, paracrine and endocrine mechanisms.

- The acute phase response is associated with increased blood viscosity, platelet number and activity. Raised serum amyloid A lowers HDL-cholesterol levels. IL-6 decreases lipoprotein lipase (LPL) activity and monomeric LPL levels in plasma, which increases macrophage uptake of lipids (Yudkin et al, 2000).
Immunity & Depression

- Studies have demonstrated increased levels of serum markers of systemic inflammation and immune system function among individuals with depressive symptoms. The risk of moderate to severe depression was significantly greater in the highest quartiles of C-reactive protein (CRP) (OR = 1.84, 95 percent confidence interval (CI) = 1.35–2.52), white blood cell counts (WBC) (OR = 1.70, CI = 1.31–2.19), and platelet counts (OR = 1.41, CI = 1.13–1.76) and highest quartile of WBC counts remained associated with depression (OR = 1.60, CI = 1.23–2.09) (Kobrosly & van Wijngaarden 2010).
Botanicals & Inflammation

- Pulsatilla chinensis' anti-inflammatory mechanisms may possibly be that it could suppress the secretion of TNF, IL-1 and IL-6 from Kupffer cells (KC) stimulated by Lipopolysaccharide (LPS) (Yang 2004). At the same time treatment with Pulsatilla chinensis specifically increases superoxide release by liver tissues and slightly increase extracellular SOD (ECSOD) activity in plasma and in particular it can markedly increase MnSOD activity in mitochondria in liver tissue (Yao et al, 2004).

- Lastly, a Glycoprotein Isolated from dried root of Pulsatilla Chinensis reduces NO and cytotoxicity (Bao et al, 1998).
Botanicals & Inflammation

- TNF-α, IL-6 and IL-8 may play a role in the pathophysiology after the trauma. The application of Rheum palmatum decreases the plasma TNF-α, IL-6 and IL-8 and obviously relieves general inflammatory reactions (Zhao 2007).

- Rheum (Emodin/Rhein) had good curative effects on stress ulceration and toxic gastrointestinal paralysis caused by sepsis. Furthermore, Rheum could improve the gastrointestinal blood perfusion and reduce the plasma concentrations of TNFα, IL6 and endotoxin (Chen et al 2000).
Botanicals & Inflammation

- Other studies demonstrate a reduction in IL-6 levels in neurons using Ganoderma lucidum (Wang 2005) and how Portulaca oleracea reduced cytokines TNF-\(\alpha\) and IL-6 secreted by adipose cells (Xiao 2005).
- Ethanol (EEP) and water (WSD) extracts of propolis showed an inhibiting function on oedema induced by Freund's adjuvant arthritis and decreased the degree of local inflammatory response. EEP and WSD inhibited the increase of IL-6 and PGE\(_2\) content in the inflammatory tissue fluid (Hu 2005).
Berberine shows inhibitory effects on the proliferation and reproduction of certain tumourigenic microorganisms and viruses, such as H. pylori and hepatitis B virus. Berberine is a broad spectrum enzyme inhibitor, which affects N-acetyltransferase, COX-2, and topoisomerase activities and gene/protein expression.

The suppression of tumour growth and metastasis, the beneficial application in combined medication, and the improvement of multidrug resistance both in vivo and in vitro clearly show its potential as an alternative medicine for tumour chemotherapy (Sun et al, 2009).
A methanolic extract (CM-ext) from Corydalis tuber (yan hu suo) has been screened for activity in experimental models of inflammation. CM-ext (200 or 500 mg/kg) inhibited an increase in vascular permeability in mice induced by acetic acid, and reduced acute paw oedema in rats. CM-ext suppressed the development of adjuvant-induced oedema in arthritic rats.

CM-ext was found to be effective in both the acute and chronic phases of inflammation (Kubo et al, 1994).
San Huang Xie Xin Tang

- San-Huang-Xie-Xin-Tang (SHXXT), an important Chinese medicine formula is abundant in anthraquinone and flavonoid polyphenols.
- Inhibitions on nitric oxide (NO) and cytokine production by SHXXT, were through reducing the protein expression of inducible NO synthase (iNOS). In addition, the serum metabolites significantly decreased the ratios of IFN-ϒ to interleukin (IL)-4 and is a promising remedy for immunomodulation through Th1/Th2 regulation.
San Huang Xie Xin Tang

- Rhizoma Coptidis Recens (huang lian)
- Radix Scutellariae Baicalensis (huang qin)
- Radix et Rhizoma Rhei (da huang)
The study was to explore the effect of HLJDT on serum anti-inflammatory cytokines IL-4 and IL-10 in experiments type II diabetic rats and its therapeutic mechanism on improving insulin resistance.

The serum levels of fasting blood glucose (FBG) were decreased, the variance of fasting plasma insulin (FINS) level was not significant, and the anti-inflammatory cytokines IL-4 and IL-10 were significantly increased in HLJDT group.

HLJDT and its main effective component Berberine could increase the levels of IL-4 and IL-10, and alleviate chronic inflammatory reaction in the diabetic pathogenic mechanism, and improve insulin resistance (Tan et al, 2005).
Huang Lian Jie Du Tang

- The study was to investigate the effect of HLJDT on Alzheimer’s disease, and its influence on cytokines.
- After Aβ injection, the study and memory ability of the rats was decreased, and would be improved by HLJDT. TNF, INF-γ and IL-2 levels of AD rats were higher than those in control group; and after the treatment of HLJDT, these levels all came down.
- HLJDT could improve the study and memory ability of AD rats by changing their immune state (Fang et al, 2004).
Huang Lian Jie Du Tang (Insulin Resistance formula)

- Rhizoma Coptidis Recens (huang lian)
- Radix Scutellariae Baicalensis (huang qin)
- Cortex Phellodendri (huang bai)
- Fructus Gardeniae Jasminoidis (zhi zi)
Huang Lian Jie Du Tang
(Insulin Resistance formula)

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- Radix Scutellariae Baicalensis (huang qin)
- Cortex Phellodendri (huang bai)
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<table>
<thead>
<tr>
<th>Herb or Isolate</th>
<th>Origin</th>
<th>Anti-cancer property</th>
<th>Anti-inflammatory / Immune property</th>
<th>Anti-depressive/Anxiolytic Effect</th>
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<tbody>
<tr>
<td>Honokiol</td>
<td>Magnolia officinalis</td>
<td>Decreases viability of PC-3 and LNCaP human prostate cancer cells (Hahm &amp; Singh, 2007). Inhibits the growth and depresses serum PSA (Shigemura et al., 2007)</td>
<td>Inhibits NF-κB induced oxidative stress and inflammation (Chiang et al., 2009). Inhibits high-glucose-induced up-regulation of inflammatory cytokine production (Wu et al., 2010) Anti-inflammatory bioactivities through Inhibition of Protein Kinase C (Chao et al., 2010)</td>
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<tr>
<td>Pulsatilla chinensis</td>
<td>Reduces NO and cytotoxicity (Bai, Xing, Yu, 1998)</td>
<td>Impact on Th1 and Th2 (Sun, Liu, Yu, &amp; Gong, 2010). Impact on secretion of TNF, IL-1 and IL-6 (Yang, 2004)</td>
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<tr>
<td>Rheum palmatum</td>
<td></td>
<td>Relieves inflammatory reactions through decrease of plasma TNF-α, IL-6 and IL-8 (Zhao, 2007). Improves gastrointestinal blood perfusion (Chen, D. C., Yang, Zhang, &amp; Chen X. Y. (1997))</td>
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<tr>
<td>Euphorbia kansui</td>
<td>Inhibitory effects and induction of apoptosis on human SGC-7901 cells (Yu, F-R. et al., 1997). Blocks IL-6 in human hepatoma cells (Chang, J. S. et al., 2010). May treat SAP by decreasing the levels of serum TNF-α and IL-6 (Zhang, 2007)</td>
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<tr>
<td>Curcuma longa (turmeric)</td>
<td>Reduces development of animal tumors in vitro and in vivo (Kuttan, Bhanumathy, Nirmala, &amp; George, 1985)</td>
<td>Inhibits TNF-α induced expression of adhesion molecules on human umbilical vein endothelial cells (Gupta &amp; Ghosh, 1999)</td>
<td></td>
<td>Inhibits the monoamine oxidize A (MAO) activity in mouse whole brain (Yu, Z. F., Kong, &amp; Chen, 2002)</td>
</tr>
<tr>
<td>Curcumin I, curcumin II (monodemethoxycurcumin), curcumin III (bisdemethoxycurcumin)</td>
<td>Curcuma longa</td>
<td>Inhibits proliferation and induces apoptosis in cancer cells through Bax and Bak regulation (Shankar &amp;</td>
<td>Showed cytotoxicity, antioxidant and anti-inflammatory activity against leukemia, colon, CNS,</td>
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<tr>
<td>Botanical</td>
<td>Preparation</td>
<td>Dose</td>
<td>Model</td>
<td>Cytokine</td>
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<tr>
<td>Sap Aloe</td>
<td>Aqueous</td>
<td>200 to 400mg/Kg</td>
<td>In vivo</td>
<td>IL-6</td>
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<tr>
<td>Radix Angelicae sylvestris</td>
<td>Aqueous</td>
<td>640 mg/Kg</td>
<td>In vivo</td>
<td>TNF</td>
</tr>
<tr>
<td>Radix Asparagus racemosus</td>
<td>80% ethanol</td>
<td>100 mg/Kg</td>
<td>In vivo</td>
<td>IL-1α, TNF</td>
</tr>
<tr>
<td>Bupleurum falcatum</td>
<td>Aqueous</td>
<td>640 mg/kg</td>
<td>In vivo</td>
<td>TNF</td>
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<tr>
<td>Cortex Cinnamommi cassia</td>
<td>Aqueous</td>
<td>560 mg/Kg</td>
<td>In vivo</td>
<td>TNF</td>
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<tr>
<td>Rhizoma Cnidium monnieri</td>
<td>Aqueous</td>
<td>560 mg/Kg</td>
<td>In vivo</td>
<td>TNF</td>
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<tr>
<td>Rhizoma Coptis chinensis</td>
<td>Powdered</td>
<td>1% Pwd in food</td>
<td>In vivo</td>
<td>IL-6</td>
</tr>
<tr>
<td>Radix Panax Ginseng</td>
<td>40% ethanol</td>
<td>150 mg/Kg</td>
<td>In vivo</td>
<td>IL-4, TNF, IFN-γ</td>
</tr>
<tr>
<td>Botanical</td>
<td>Preparation</td>
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</tr>
<tr>
<td>Folium Perilla frutescens</td>
<td>Aqueous</td>
<td>0.4 mL injection</td>
<td>In vivo</td>
<td>TNF</td>
</tr>
<tr>
<td>Rhizoma Picrorhiza kurroa</td>
<td>80% ethanol</td>
<td>100 mg/Kg</td>
<td>In vivo</td>
<td>IL-1α, TNF</td>
</tr>
<tr>
<td>Radix Polygala tenuifolia</td>
<td>Aqueous</td>
<td>2x10³ injection</td>
<td>In vivo</td>
<td>IL-4, IFN-Υ</td>
</tr>
<tr>
<td>Semen/Fructus Silybum marianum</td>
<td>Silymarin</td>
<td>10 mg/Kg injection</td>
<td>In vivo</td>
<td>IL-2, IL-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 mg/Kg Injection</td>
<td>In vivo</td>
<td>IL-1β, IL-6, TNF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 mg/Kg Injection</td>
<td>In vivo</td>
<td>IL-2, IL-4</td>
</tr>
<tr>
<td>Rhizoma Smilax cordifolia</td>
<td>Aqueous</td>
<td>400 mg/Kg</td>
<td>In vivo</td>
<td>IL-1, IL-2, TNF</td>
</tr>
<tr>
<td>Radix/Herba Tinospora cordifolia</td>
<td>80% ethanol</td>
<td>100 mg/Kg</td>
<td>In vivo</td>
<td>IL-1α, TNF</td>
</tr>
<tr>
<td>Radix/folium Withania somnifera</td>
<td>80% ethanol</td>
<td>100 mg/Kg</td>
<td>In vivo</td>
<td>IL-2, IFN-Υ</td>
</tr>
<tr>
<td>Botanical</td>
<td>Preparation</td>
<td>Dose</td>
<td>Model</td>
<td>Cytokine</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>---------------------------------------</td>
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<td>-----------------------------</td>
</tr>
<tr>
<td>Cortex Acanthopanax gracilistylus</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>In vitro (human cells)</td>
<td>IL-1, IL-6, TNF, IFN-γ</td>
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<td></td>
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<td>$20 \mu g/mL$ incubation</td>
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<tr>
<td>Radix Astragalus membranaceus</td>
<td>Aqueous</td>
<td>$1.5 \times 10^5 \mu g/mL$ incubation</td>
<td>In vitro (human cells)</td>
<td>IL-6</td>
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<td></td>
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<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td></td>
<td>IL-1</td>
</tr>
<tr>
<td>Radix Codonopsis pilosula</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>In vitro (human cells)</td>
<td>IL-1</td>
</tr>
<tr>
<td>Herba Epimedium brevicornum</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>IL-1</td>
</tr>
<tr>
<td>Radix Oldenlandia diffusa</td>
<td>Aqueous</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>$1.08 \times 10^3 \mu g/mL$ incubation</td>
<td>IL-1</td>
</tr>
<tr>
<td>Rhizoma Smilax glabra</td>
<td>Aqueous</td>
<td>$400 \text{mg/Kg QD}$</td>
<td>Ex vivo, Murine</td>
<td>IL-1, IL-2 TNF</td>
</tr>
<tr>
<td>Botanical</td>
<td>Preparation</td>
<td>Dose</td>
<td>Model</td>
<td>Cytokine</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------</td>
<td>-------------------------------</td>
<td>------------------------</td>
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</tr>
<tr>
<td>Fruiting body Cordyceps</td>
<td>50% Methanol</td>
<td>100 μg/mL incubation</td>
<td>In vitro, Human</td>
<td>IL-2, IFN-γ</td>
</tr>
<tr>
<td>Mycelia Coriolus versicolor</td>
<td>70% Ethanol</td>
<td>5 μL/mL Incubation</td>
<td>In vitro, Human</td>
<td>IL-1β</td>
</tr>
<tr>
<td></td>
<td>70% Ethanol</td>
<td>3 μL/mL Incubation</td>
<td></td>
<td>IL-6</td>
</tr>
<tr>
<td>Sclerotium Poria cocos</td>
<td>50% Hot Ethanol</td>
<td>800 μg/mL Incubation</td>
<td>In vitro, (Human cells)</td>
<td>IL-1β</td>
</tr>
<tr>
<td></td>
<td>Ethanol</td>
<td>400 μg/mL Incubation</td>
<td></td>
<td>IL-6</td>
</tr>
<tr>
<td></td>
<td>Ethanol</td>
<td>200 μg/mL Incubation</td>
<td></td>
<td>TGF-β</td>
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<td>Fruiting body Ganoderma lucidum</td>
<td>Aqueous Ethanolic precipitation</td>
<td>12.8 μg/mL incubation</td>
<td>In vitro</td>
<td>IL-12</td>
</tr>
<tr>
<td>Fruiting body Grifola frondosa</td>
<td>Ethanol</td>
<td>1x10³ μg/mL Incubation</td>
<td>In vitro</td>
<td>IL-12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5x10³ μg/kg body wt</td>
<td>In vivo</td>
<td>TNF, IFN-γ</td>
</tr>
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</table>
TChM, Inflammation and Cytokines

- Chinese traditional medicine had anti-inflammatory, blood circulation improving and immune regulating effects, and that’s due to its function of inhibiting inflammatory cells from producing cytokines.

- Anti-inflammatory Chinese traditional medicine could bi-directionally regulate the cytokines’ synthesis and secretions by inflammatory cells, significantly inhibit human macrophage from releasing inflammatory cytokines either induced or not induced by endotoxin (lipopolysaccharide), have the activities of stabilizing lysosome, inhibiting lipid peroxidization and reducing the release of TNF.
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