**Review**

# Potential Treatment of Autism with Traditional Chinese Medicine

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**Autism is a complex neurological disorder of largely unknown cause. According to recent epidemiologic studies, autism spectrum disorders are diagnosed in one of 88 children in the United States and cost more than $137 billion a year nationwide. There is no known medical cure. Four major drug categories are regularly used for symptomatic treatment; but because of large individual differences among patients, efficacy is quite limited. A recent study showed that autism may be accompanied by abnormalities in the inflammatory response system, specifically increases in the cytokines IL-6, IL-10, and TNF-α measured in whole blood. Clinical studies have also demonstrated that increased cytokines correlates well with GI symptoms. For instance, IL-1β, mainly produced by blood monocytes, is elevated in nearly 100% of autistic children. We have studied extensively the traditional Chinese medicine Huo Luo Xiao Ling Dan (HLXL) for the treatment of osteoarthritis, an inflammatory and autoimmune disease. In an animal model, we demonstrated that suppression of arthritis was associated with significant alterations in the T-cell proliferative and cytokine responses. There was a reduction in the level of the pro-inflammatory cytokines IL-17 and IL-1β and enhancement of the anti-inflammatory cytokine IL-10. HLXL may represent an alternative and complementary therapy for the treatment of autism.**
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**Key Words:** *Autism, herbal remedy, inflammation, immune-dysfunction, osteoarthritis, HLXL, traditional Chinese medicine*

## INTRODUCTION

Autism is a complex neurological disorder of largely unknown cause characterized by impairments in social interaction and communication and by restricted, repetitive, and stereotyped patterns of behavior, and is often accompanied by extreme behavioral challenges. Based on United States Centers for Disease Control data of 2008 and other recent epidemiologic studies, autism spectrum disorders (ASDs) are diagnosed in one of 88 children in the United States.[1] As many as 1.5 million Americans may have some form of autism, including milder variants, and the number is rising. Epidemiologists estimate that it could reach 4 million in the next decade. Autism costs more than $137 billion a year nationwide. Unraveling and treating this complex, devastating disorder remains an urgent challenge requiring a multidisciplinary effort.

## CURRENT MEDICATIONS

There is no known cure for ASD, but many doctors are prescribing medication. Not everyone with ASD has the same symptoms, and not all symptoms can be treated with the same drugs. Most often, the prescription is intended to address specific symptoms such as anxiety, depression, mood swings (bipolar disorder), obsessions, compulsions, inattention, and hyperactivity. Because of large individual differences, clinical improvement is quite limited despite a significant on-going effort in clinical trials of these agents and their combinations. Four major drug categories are used.

- SSRIs: Selective serotonin reuptake inhibitors are commonly known as antidepressants and are also used to treat anxiety and obsessive-compulsive disorder. Fluoxetine (Prozac™), fluvoxamine (Luvox™), sertraline (Zoloft™), and clomipramine (Anafranil™) are used in ASD. The FDA has issued an advisory to patients, families, and health professionals to closely monitor adults and children taking antidepressants for signs of suicide. This is especially important at the beginning of treatment and when the dose is changed.

- Antipsychotics: Older drugs such haloperidol, chlorpromazine, thioridazine, and fluphenazine reduce the action of the neurotransmitter dopamine in the brain. However, they have adverse effects such as sedation, muscle stiffness, and abnormal movements. Newer antipsychotics such as risperidone (Risperdal™) are effective against aggression and self-injury in autistic children and have fewer side effects but may increase appetite and weight gain. Olanzapine (Zyprexa™) and

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ziprasidone (Geodon™) also are used, and the antihypertensive clonidine is sometimes added.

- Anticonvulsants: One in four autistic patients has seizures, necessitating an anticonvulsant such as carbamazepine (Tegretol™), lamotrigine (Lamictal™), topiramate (Topamax™), or valproic acid (Depakote™). These drugs reduce but do not eliminate seizures.

- Stimulants: Stimulants reduce inattention and hyperactivity. Methylphenidate (Ritalin™), prescribed for attention deficit hyperactivity disorder, reduces the similar symptoms in autism.

It is important to ensure that individuals with autism and their families are adequately informed about potential risks and benefits. Most of these medications are used off-label, in that they are FDA approved for the treatment of some conditions across a certain age range (e.g., 12 and above) but are not specifically approved to treat autism. They give only symptomatic relief. There is an urgent need for a drug to treat ASD directly.

## POSSIBLE PATHOPHYSIOLOGY OF AUTISM: INFLAMMATION AND IMMUNE DYSFUNCTION

Many autistic children show allergy symptoms such as eczema, allergic rhinitis, asthma, and chronic infection or inflammation. Recent studies suggest that autism may be accompanied by abnormalities in the inflammatory response system (IRS). Products of the IRS, notably pro-inflammatory cytokines, may induce some of the behavioral symptoms such as social withdrawal, resistance to novelty, and sleep disturbances. Abnormally high levels of the interleukins IL-6, IL-10, and IL-1β, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) have been found in whole blood and serum.[2,3] There were no significant abnormalities in the serum concentrations of IL-6, IL-2, and IL-1β in normal children, suggesting that autism may be accompanied by an activation of the monocytic (increased IL-1β) and T-helper-1 (Th1)-like (increased IFN-γ) arm of the IRS.[4] It was hypothesized that increased production of pro-inflammatory cytokines could play a role in the pathophysiology of autism.[5,6,7] Ashwood reviewed the research linking the immune response with ASD and concluded that aberrant immune function during critical periods of neurodevelopment could participate in the generation of neurological dysfunction characteristic of ASD.[8] Clinical studies have also demonstrated immune dysfunction,[9] particularly in the brain and intestine, such as neurological activation in cerebellum, antibrain antibodies,[10,11] microvasculitis, and increased cytokines correlated with gastrointestinal symptoms.[12,13,14] Interestingly, IL-1β, mainly produced by blood monocytes, is significantly elevated in nearly 100% of autistic children. IL-1 receptor antagonists protect against placental and neurodevelopmental defects induced by maternal inflammation.[15] Children with ASD had increased activation of both Th1 and Th2 arms of the adaptive immune response, with Th2 predominance and without the compensatory increase in the regulatory cytokine IL-10.[16] These results showed that immune dysfunction as evidenced by elevated plasma cytokines is closely associated with impaired behavioral outcome in ASD.[17,18]

In our experience, gastrointestinal diseases caused by inflammation and immune dysfunction can be treated effectively by traditional Chinese medicine. Furthermore, a study by Dr. Shui Yin Lo (www.JoinAutismStudy.net) suggests that removing blockages along the gastrointestinal or yang meridians allows energy in the body to flow more freely and help reduce some of the effects of autism. More importantly, if blockages are seen at an early age, ASD may be detected before symptoms appear, and early detection of autism is a key factor in successful treatment. During a 12-week pilot study, Dr. Lo examined 11 male children with autism of varying levels of severity and took full-body thermographic images. The images showed a pattern of six hot regions in key areas along the yang meridians, or the meridians that connect the gastrointestinal tract to the brain and are believed to be linked to the major clinical symptoms of autism.[19] If thermal imaging can be confirmed in a larger clinical study as a reliable method for early detection, it can be applied to monitor the treatment effects of traditional Chinese medicine for gastrointestinal disorders. Interestingly, the signs of autism in the traditional Chinese medicine perspective are severe bronchitis, constant gastritis, recurrent hepatitis, distension of biceps, dizziness, nausea, peptic ulcer, copious phlegm, anxiety, unhealthy taste, shortage of consciousness, shyness, minor thirst, violet tongue, evasive-abrupt pulse, quick-wiry pulse, and spleen and kidney deficiency. Since the spleen is in charge of food essence and qi absorption and qi and fluid alteration and distribution, kidney deficiency causes excessive accumulation of fluid, leading to dampness in the gastrointestinal system that affects the function of kidney in nourishing muscles, causing underdevelopment of muscles and motor skills. Brain edema in children with autism may also be caused by the general excessive accumulation of fluid.

## POTENTIAL OF TRADITIONAL CHINESE MEDICINE: SCIENTIFIC BASIS

In traditional Chinese medicine, natural products are widely used to treat inflammatory disorders. Inflammation accounts for a significant proportion of disease, and macrophages play a crucial role in the initiation, maintenance, and resolution of inflammation. Signaling of overactive macrophages is associated with, but not limited to, tissue destructive inflammatory diseases such as diabetes, obesity, Alzheimer's, rheumatoid arthritis, endometriosis, atherosclerosis, and tumor metastasis. We reported an example of a botanical dietary supplement used to treat inflammatory and immunology related arthritis, namely Huo-Lou-Xiao-Lin Dan (HLXL), which consists of 11 herbs and is used in China for a variety of disorders, including arthritis.[20,21] It showed anti-inflammatory activity in an experimental model of paw edema. It suppressed inflammatory signaling by inhibiting NF-κB activation and CCL5 in vitro and expression of cytokines (IL-6, IL-17), angiogenic factors (VEGF), and proteolytic enzymes (MMP-2, MMP-9) in vivo.[22,23,24] The rationale for treating inflammation-associated processes including invasion, proliferation, angiogenesis, and pain is

summarized in **Table 1**. HLXL also has potent antiarthritic activity, as validated in the rat adjuvant-induced arthritis (AA) model (**Figure 1**). Arthritis was induced in Lewis (RT.11) rats by heat-killed M. tuberculosis H37Ra (Mtb) subcutaneously. HLXL (2.3 g/kg) was administered daily by gavage beginning at the onset of arthritis and continuing through the observation period of 25 days.

**Table 1.** Properties of Single Herbs in HLXL.

| English Name | *Enzymes/MMPs* | *Cytokines* | *NF-κB* | Pain |
|---|---|---|---|---|
| *Boswellia carterii* (Frankincense) | MMP-9↓, COX-2↓ | TNFα↓, IL-1,2↓, MCP-1↓ | p65↓ | ↓ |
| *Notopterygium incisum* | | ICAM-1, E-slectin | | |
| *Angelica sinensis* | MMP-2,9↓, TIMP-1↓ | TNFα↓ | p65↓ | ↓ |
| *Poeonia lactiflora* | COX-2↓ | TNFα↓, IL-1,6↓, MCP-1↓ | p65↓ | ↓ |
| *Glycyrrhiza uralensis* (Licorice) | COX-2↓ | TNFα↓, IL-8↓, MCP-1↓ | p65↓ | ↓ |
| *Corydalis yanhusuo* | MMP-9↓, | | p65↓ | ↓ |
| *Salvia miltiorrhiza* | $PGE_2$↓, COX-2↓ | TNFα↓, IL-1,6↓, MIP-1α↓ | p65↓ | ↓ |
| *Ligusticum chuanxiong* | COX-2↓, iNOS↓ | | | ↓ |
| *Gentiana macoprylla* | $PgE_2$↓ | | | |
| *Cinnamomum cassia* | COX-2↓ | MCP-1↓, TNFα↓, IL-1,6↓ | p65↓ | ↓ |
| *Angelica pubescens* | | | | ↓ |

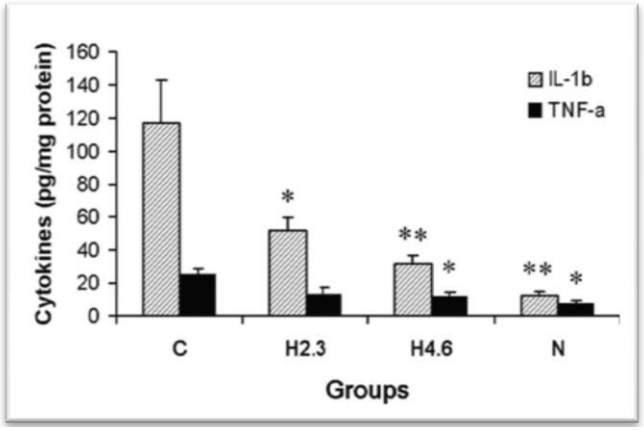


**Figure 1.** Effect of HLXL on IL-1β and TNF-α levels (pg/mg protein, mean ± S.E.) 25 days post-CFA injection.

The draining lymph node cells and synovium-infiltrating cells were tested in T-cell proliferation and cytokine assays using mycobacterial heat-shock protein 65 (Bhsp65); the sera were tested for anti-Bhsp65 antibodies and nitric oxide (NO). HLXL reduced the severity of AA. This suppression was associated with a reduction in the level of the pro-inflammatory cytokines IL-17 and IL-1β but enhancement of the anti-inflammatory cytokine IL-10. In addition, there was inhibition of both the anti-Bhsp65 antibody response and the serum level of NO. These results provide an immunological basis for the action of HLXL against autoimmune arthritis. A schematic representation of the diverse mechanisms involved in HLXL-induced immunomodulation of adjuvant arthritis is shown in **Figure 1**. HLXL suppresses arthritis via the induction of disease-regulating cytokines coupled with the inhibition of pathogenic events that facilitated the initiation and propagation of arthritis. Interestingly, one of the ingredients, frankincense (Boswellia serrata), has been shown to reduce cerebral edema as measured by MRI.[25] HLXL is undergoing Phase II clinical trial in arthritis patients in the US.

Tissue was obtained from four groups of rats: group C (arthritis + vehicle, n = 6), group H2.3 (arthritis + HLXL 2.3g/kg/day n = 6), group H4.6 (arthritis + HLXL 4.6g/kg/day, n = 7), and group N (no arthritis +vehicle, n = 4). Both IL-1β and TNF-α increased significantly in local tissue following development of arthritis. After HLXL treatment, local tissue IL-1β and TNF-α decreased significantly, *$p < 0.05$ and **$p < 0.01$.

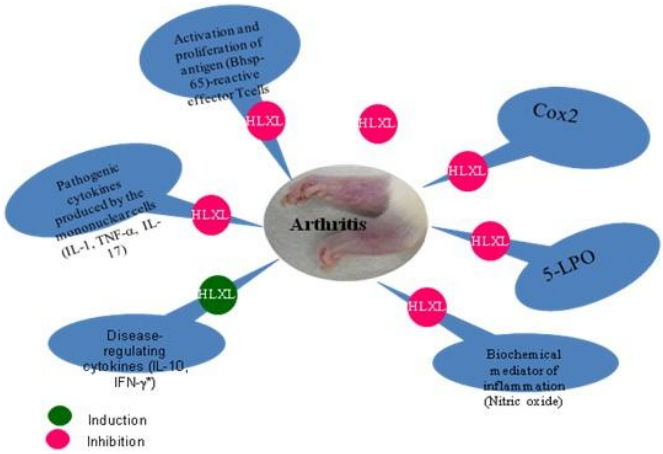


**Figure 2**. A schematic representation of the diverse mechanisms involved in HLXL-induced immunomodulation of adjuvant arthritis.

## CONCLUSION

Autism is a devastating neurological disorder of largely unknown cause and no known cure. Four major drug categories are regularly used for symptomatic treatment; but because of large individual differences among patients, efficacy is quite limited. In addition, too many psychiatric drugs are being prescribed to children with no solid understanding of long term adverse effects. For instance, one of the popularly prescribed drugs for autism is Ritalin, which behaves like cocaine. It can be addictive and can cause anxiety, paranoia, insomnia, headaches, nausea, and chromosome aberration, and physicians may not always warn parents about these effects. Indiscriminate use of powerful psychotropic drugs can do more harm than good. There is a tacit assumption that a single small molecule can address complex human diseases, particularly brain disorders. We believe a reexamination of the use of psychiatric drugs is needed, especially in children.

With a better understanding of the pathophysiology of autism, specifically the role of inflammation and immune dysfunction, we may be able to develop an herbal remedy. We have isolated 153 phytochemicals from 11 herbs of HLXL, and 56 of them are bioactive.[26] These compounds target two major inflammation pathways, COX2 and 5-LOP, and several immune-related cytokines. HLXL is a good example of a multi-component, multi-targeted approach with no major adverse effects. Based on these preliminary studies, we believe that it could lead to a viable alternative remedy for autism.

**CONFLICT OF INTEREST**

None.

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