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Herbs to Diminish Stealth Pathogens

Part 1 of the Stealth Pathogen Arsenal

Chronic low level exposure to a range of pathogens, for example, protozoa and bacteria, can lead to chronic debilitating disease. If left untreated, long-term consequences to the immune system and chronic ill-health may result.

Pathogenic microorganisms make use of two general strategies on their host: frontal assault and stealth assault. In frontal assaults the infecting pathogen rapidly replicates, causes symptoms that overwhelm the immune defences of the host, and find a new host before the immune system engages. Stealth assaults, on the other hand, typically involve a slower infection process in which the pathogens subvert the host's immune system to set up a chronic or persistent infection.[1]

Stealth is also a strategy used by organisms to maximise their probability of surviving in the host. For example, pathogens such as fungi may shield or camouflage themselves by producing a surface coating that is not recognised by the immune system or that is recognised but interpreted as "self" to the host.[2]

Stealth Pathogens & Persistent Infections

The concept 'stealth pathogen' originally referred to bacteria and closely-related organisms that were able to adopt a form that did not contain a cell wall or had lost some components of the cell wall.

- Changing to this form may allow the organism to survive for a long time in the host in a dormant stage and due to their persistence, contribute to chronic infection, and eventually disease (for example, via continuous low level stimulation of the immune system).[3]
- The ability to adopt the different form may be due to interaction between the pathogen and immune system of the host.[4]
- Suboptimal doses of certain drugs including antibiotics (which inhibit the cell wall) may create wall-deficient forms and over time encourage their persistence.[3]
- These pathogens, already present in the body, can cause disease after being activated by, for example, environmental, severe physical or emotional stress.[3]
- These forms have been difficult to detect which may have contributed to the conclusion of a non-infectious cause for certain diseases.[4]

The term, stealth pathogen, is also used to describe a pathogen that although not necessarily lacking a cell wall, is good at escaping immune detection, and is often not associated with the usual markers of infection.

In broad terms then, stealth pathogens are organisms that:[5]

- persist in their host, and
- have strategies to evade the host's immune system.

Stealth pathogens:

- can persist within cells;[3] they can take up residence in the immune system itself, such as in the phagocytic cells;
- are controversially implicated in the pathogenesis of chronic diseases including for example, chronic fatigue syndrome, fibromyalgia syndrome, chronic Lyme disease;
- may play a role in autoimmune diseases (for example, as a consequence of immune reactions triggered by persistent, cross reactions with host tissue antigens);[3]
- may increase systemic inflammation.

Examples of Pathogens that Operate by Stealth and/or Persistence

Borrelia burgdorferi and *Treponema pallidum*, which are a certain type of bacteria known as spirochetes, are responsible for Lyme disease and syphilis, respectively. These are chronic, multistage infections that are characterised by periods of remission and exacerbation. Underlying their episodic nature is the ability of both organisms to persist for prolonged periods despite the immune responses that they elicit in infected individuals.[5]

Stealthy and persistent bacteria have successful strategies that thwart host responses. Individual pathogens usually use multiple strategies. Examples of these strategies include:[5-7]

- modification of the intracellular environment (e.g. *Chlamydia* spp.);

- molecular mimicry (e.g. *E. coli*);
- unusual structure of the outer membrane, specifically non-inflammatory and with few antigen targets (e.g. *Treponema pallidum*);
- entry into intracellular niches (e.g. *Borrelia burgdorferi, Treponema pallidum*)
- ability to undergo variation of surface-exposed antigens (e.g. *Borrelia burgdorferi, Treponema pallidum*);
- ability to delay and/or suppress the onset of effective immune responses (e.g. *Borrelia burgdorferi, Treponema pallidum*);
- inhibition of phagocytosis (e.g. *Staphylococcus aureus*);
- survival in macrophages (e.g. *Mycobacterium tuberculosis*);
- disarming T-cells (e.g. *Helicobacter pylori*);
- ability to undergo genetic rearrangement (e.g. *Helicobacter pylori*).

Sweet Wormwood

Artemisia annua herb, also known as Qing Hao and Annual Wormwood, has been used in traditional Chinese medicine (TCM) for fevers, including in consumptive disease such as tuberculosis, and low grade fevers; nosebleeds, rash and the alternating fever and chills of malaria. It is described as bitter and aromatic.[8-10]

The aerial parts of *Artemisia annua* contain many constituents, the most important of which is the sesquiterpene lactone known as artemisinin, which was found to have antimalarial activity by Chinese scientists in the late 1970s. The chemical structure of artemisinin is highly oxygenated, and contains a unique 1,2,4-trioxane ring, which is responsible for the antimalarial activity.[11,12] Other constituents, which may be important for clinical activity, include other sesquiterpenes, monoterpenes, flavonoids and polyphenolic acids.[12-14]

Constituents other than artemisinin may also contribute to the antimalarial activity of Sweet Wormwood. Powder of the leaves of *Artemisia annua* was more effective in reducing parasitaemia in mice infected with *Plasmodium chabaudi* than an equivalent dose of artemisinin.[15] Animal testing has also shown that the plant material is far more resilient than pure artemisinin and so may delay the onset of resistance.[16]

Testing for other activity found that oral doses of artemisinin reduced the parasite burden in animals infected with the protozoan *Leishmania donovani*.[17] Hexane fraction of *Artemisia annua* leaves was more effective in this model than artemisinin.[18] In a model of congenital toxoplasmosis (infection with the protozoan *Toxoplasma gondii*), oral administration of *Artemisia annua* infusion containing 0.2% artemisinin, reduced the parasite load in the placenta and foetus, although treatment was not completely successful.[19] High oral dose of artemisinin to infected animals produced some detrimental changes in the tegument (outer membrane) of the trematode *Schistosoma mansoni*.[20]

Artemisinin has demonstrated activity against several organisms *in vitro*, although for this activity to be relevant *in vivo*, the metabolites of artemisinin need to also demonstrate this activity and/or sufficient artemisinin needs to be present in the blood after metabolism. (A pharmacokinetic study with healthy volunteers found that after consuming one litre of tea prepared from 9 grams of *Artemisia annua* dried plant, and containing 94.5 mg of artemisinin, the mean maximum plasma concentration of artemisinin was 240 ng/mL. The bioavailability of artemisinin from the tea preparation was similar to that from isolated artemisinin taken in capsules.[21]) *In vitro*, artemisinin:

- demonstrated good activity, which was similar to current drugs used to treat Lyme disease, against stationary phase *Borrelia burgdorferi*;[22]
- inhibited the growth of the protozoa *Trypanosoma cruzi* and *Trypanosoma brucei rhodesiense*;[23]
- inhibited the growth of the fungus *Pneumocystis carinii*;[24]
- inhibited production of hepatitis B virus,[25] and the replication of hepatitis C virus replicons in a concentration-dependent manner;[26]
- demonstrated antibacterial activity, at the lower end of the activity scale, against *Helicobacter pylori*.[27]

Artemisia annua tea infusion demonstrated anti-HIV activity *in vitro*. Testing suggests that artemisinin does not substantially contribute to the activity.[28]

Clinical Studies

Antiparasitic Effect

In August 1972, an official Chinese document reported that 21 patients with **malaria** had been successfully treated in Beijing with an extract of Sweet Wormwood.[29] The results of subsequent clinical studies of Sweet Wormwood in patients is *outlined in Table 1*.

Trial Details	Preparation	Results	Ref
unc; uncomplicated malaria due to *P. falciparum*; n = 49#	16.7 mL/kg/day of infusion of dried leaves (5 g per litre of water, sweetened with Stevia) for 6 days	• parasite density decreased from 1860 to 35 per microlitre of blood on day 2 and completely cleared by day 3 • on day 14, 94% had CPAR, 6% were late parasitological failures • on day 28, 8% had late clinical failure, 18% were late parasitological failures and the rest had CPAR • presence of gametocytes in the blood not detected during follow up in any patient • well tolerated except by children under 2 years	30
unc; malaria due to *P. falciparum*; patients undergoing orthopaedic surgery; n = 25*	capsules containing dried and powdered leaves, about 400-500 mg/day†, containing 0.1% artemisinin, for several days	• average parasitaemia decreased from 432 to 165 parasites/mL (62% improvement) • results were similar regardless of age or weight	31
unc; malaria; n = 54*	capsules; 15 g/day of dried leaf, providing 15 mg/day artemisinin for 10 days	• after 2 days all patients were free of fever and 94% were parasite free after 10 days	32
r, db, comp; uncomplicated malaria due to *P. falciparum*; n = 19*	1 L/day of infusion (5 g or 9 g of dried herb per litre of water, providing 70 mg and 126 mg of artemisinin, respectively) for 7 days compared to drug (sulfadoxine-pyrimethamine)	• at day 7 cure rate was 7/10 for the combined herb group (3/4 for 5-g dose, 4/6 for 9-g dose) compared to 7/9 for the drug group • the cure rate dropped in all groups at day 14 and day 28 - at day 28: 1/10 for the combined herb group; 3/8 for the drug group	33
unc; uncomplicated malaria due to *P. falciparum*; n = 44~	tablets made from dried and powdered leaves; 4 dosage groups within the range 2-5 g on day 1 then 1-4 g/day for 5 days,§ containing 0.75% artemisinin	• there were 4 treatment failures • across the 4 dosage groups: 10, 8, 9 and 8 patients had no malaria parasites at day 6, 5, 3 and 4 respectively • recrudescence occurred in 6 patients (13.6%) by day 14 or day 28 • the results were not dose-dependent	34
r, db, comp; uncomplicated malaria due to *P. falciparum*; n = 115‡	1 L/day of infusion (5 g or 9 g of dried herb per litre of water providing 70 mg and 126 mg of artemisinin, respectively) for 7 days compared to drug (quinine)	• after 7 days, cure rates were on average 74% for the herb groups compared with 91% for quinine • during follow up (days 14, 28, 35) cure rates in the herb groups dropped, indicating a higher rate of recrudescence - cure rates at day 28: 32% for the combined herb group; 79% for the drug group • the results in the herb groups were not dose-dependent	35
2 unc, pilot; malaria**; n = 22 and 48*	Study 1		36
	1 L/day of infusion (5 g of dried leaves per litre of water, providing 12 mg/day artemisinin) for 5 days	• 5 patients agreed to have their blood tested, and the parasite counts dropped rapidly to zero • of the other 17 patients, 15 reported disappearance of malaria symptoms within the course of treatment	
	Study 2		
	1 L/day of decoction (5 g of dried leaves per litre of water, providing 7.2 mg/day artemisinin) for 4 days	• disappearance of parasitaemia in 92% of patients at the end of treatment	
unc; severe malaria not responding to orally administered artemisinin combination (drug) therapy or intravenous artesunate; n = 18*	tablets; 1 g/day of powdered, dried leaf, providing 55 mg/day of artTestmisinin for 5 days (dose reduced for body weight under 30 kg)^	• all patients fully recovered: parasites were microscopically undetectable in blood and no symptoms present	37

Table 1. Clinical results for treatment of malaria with *Artemisia annua.*

Abbreviations: comp: comparative; CPAR: clinical and parasitological adequate response; db: double-blind; r: randomised; unc: uncontrolled
Definitions: cure rate: blood negative for parasite; recrudescence: reappearance of blood forms of parasites
Notes: # children aged 6 months to 10 years; * completed the study/treatment; † 22 children, 3 adults; the lower dose was for children under 20 kg; ~ 48 patients began treatment, one did not complete treatment, 3 were lost to follow up on days 3, 7 and 14; § i.e. one group received 2 g on day 1 then 1 g/day on days 2 to 6; the next group received 3 g on day 1 then 2 g/day on days 2 to 6 etc; ‡ 105 patients able to be evaluated on day 14, 98 on day 28, 96 on day 35; ** study 1: malaria due to due to *P. falciparum* and *P. malariae;* study 2: malaria due to *P. falciparum*; ^ herb administered 24 hours after last i.v. artesunate treatment

Artemisinin has been used on its own as an antimalarial therapy, although now combination with other drugs is desired to help prevent recrudescence[38] and the development and spread of resistance to artemisinin and its derivatives.[39] (The absorption of artemisinin is incomplete (it has low bioavailability) and derivatives of artemisinin were found to be more active, so these derivatives became more extensively used than artemisinin.[40]) The oral dose of artemisinin has varied from the standard 500 mg/day to over 2 g/day and more when administered according to body weight.[38] The following results were obtained from 4 trials that prescribed artemisinin at the oral dose of 500 mg/day for 5-6 days to patients with *P. falciparum* malaria:[41-44]

- parasite clearance time was 31-44 hours;
- clearance or subsidence of fever took 20-26 hours;
- parasites were detected in 23-41% of patients at 3 to 4 weeks after treatment.

The effect was inferior to an artemisinin derivative,[43] and when compared to artemisinin combined with drugs.[42,44]

Other factors to consider regarding the efficacy of artemisinin and/or its derivatives when used on their own.[38]

- Treatment of 5 to 7 days is required but as the clinical symptoms often improve rapidly, patients are less likely to continue treatment beyond 3 to 4 days.
- It is difficult to distinguish between reinfection and recrudescence unless patients are kept in a transmission-free area.

Two patients with uncomplicated **cutaneous leishmaniasis** were successfully treated with capsules of *Artemisia annua* leaf powder. Complete cure (100% closure of the ulcer and presence of scar in the lesion site) was observed on day 45 after the end of treatment. The patients remained disease-free after 2 years of follow-up. The patients consumed 30 g over 20 days, starting at 3 g/day, decreasing to 2 g/day then 1 g/day.[45]

Autoimmune Conditions

Sweet Wormwood has been used in clinical studies for the treatment of **rheumatoid arthritis** and **lupus**, although at high or very high doses. For example:

- *Artemisia annua* (20 g/day, as a decoction) for 12 weeks combined with low dose of methotrexate was better than methotrexate alone in decreasing levels of TNF-alpha in patients with rheumatoid arthritis.[46]
- *Artemisia annua* ethanolic extract (equivalent to 128 g/day of dried herb) plus leflunomide and methotrexate taken for 48 weeks produced greater improvement in measures of acute inflammation (pain, painful joints, erythrocyte sedimentation rate, C-reactive protein) at 12 weeks than drugs alone in patients with rheumatoid arthritis. Overall efficacy in the herb group was significantly better than the control group both at 24 and 48 weeks.[47]
- In an uncontrolled study, good or moderate effects occurred in a majority of patients with discoid lupus erythematosus treated with honeyed powder of the herb (36-54 g/day) or with the artemisinin derivative arteannuin (300-600 mg/day).[10]

Safety

Even in the high doses prescribed, artemisinin and its derivatives are regarded as quite safe. No serious adverse events or severe significant toxicity has been reported from clinical trials.[48] Drug-induced fever may occur. Artemisinin, when prescribed for malaria (i.e. at doses high in comparison with herb use), is contraindicated in pregnancy during the first trimester.[49] Artemisinin (500 mg/day) decreased the oral clearance of omeprazole in healthy volunteers.[50,51]

Clinical application in China indicates Sweet Wormwood to have low toxicity and to be well tolerated.[10] In clinical studies for malaria, Sweet Wormwood was well tolerated and without significant adverse effects in many trials,[30,31,33,35,37] although nausea was observed in 10% and 25% of patients in two trials, and was not related to dosage.[34,36] In the active rheumatoid arthritis trial that used a very high dose of *Artemisia annua*, a lower incidence rate of adverse effects was observed in the herb extract + drug group compared with the control (drugs only) group.[47]

Allergy to Sweet Wormwood leaf is possible, and is independent of the presence of pollen, as pollen-free plant extracts have produced allergenic responses in participants sensitive to the pollen of Artemisia species.[52]

According to TCM, Sweet Wormwood should be used with caution in those with loose bowels or weak digestion.[8,53]

Sarsaparilla

The word 'sarsaparilla' comes from the Spanish 'sarza', meaning a bramble and 'parilla' meaning a small vine.[54] Sarsaparilla root was used in a formulated syrup in the 1930s to mask the unpleasant taste of castor oil.[55] Sarsaparilla extracts have been used extensively as flavouring in beverages, such as root beer, even though they are essentially odourless and have hardly any taste.[56]

Sarsaparilla contains 1-3% steroidal saponins, including sarsasapogenin and smilagenin as aglycones as well as other saponins.[57]

The root of several species of Smilax have been used traditionally in western herbal medicine: *S. aristolochiaefolia, S. febrifuga, S. ornata, S. regelii* in Britain; *S. officinalis, S. medica* and other species in the

United States. It is a depurative or tissue cleanser, particularly indicated for chronic skin conditions and rheumatism, but has also been used to treat syphilis. It is also regarded as a tonic.[57,58]

It is thought that Sarsaparilla might also be of benefit to help the body detox if the adverse, Jarisch-Herxheimer ('herx') reaction occurs. This reaction has been associated with antimicrobial treatment of infections such as syphilis and Lyme disease.[59] Symptoms of the reaction can include headache, fever, chills, sweating, malaise and hypotension. The symptoms of the existing disease may also worsen.[60] The reaction was thought to be the result of endotoxin release from the dead or dying bacteria and an increase of inflammatory cytokines.[60] It is now thought that these, and other mechanisms, such as hypersensitivity to spirochetes, may not be causative. Instead, accelerated phagocytosis of spirochetes by polymorphonuclear leukocytes which provokes a strong inflammatory response, is a likely trigger.[59]

Supportive Formulation

These herbs complement each other to support the following actions:

- antiparasitic;
- febrifuge;
- depurative.

Indications

- As part of a stealth pathogen bioburden protocol focussing on treating stealthy and persistent organisms to support treatment of Lyme disease, autoimmune diseases, chronic fatigue syndrome, and particularly conditions where infection with multiple organisms is a causal factor.

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