Phytotherapy in the Treatment of Dysbiosis of the Small and Large Bowel

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The Human GIT Microbiota

Human GIT microbiota contains $10^{14}$ viable microorganisms. (Neish, 2009)

- this is **10 times** the number of cells in the human body!
  - from over **1000** different species

- a mutually beneficial symbiotic relationship
The Human GIT Microbiota

A vital, but under-appreciated human organ

– this “microbe” organ weighs 1-1.5 kg

– rivals the liver in the number of biochemical reactions in which it participates
C Bacterial population present

**Oral cavity:**
- Gemella (e.g., G. haemolyans), Granulicatella, Streptococcus (e.g., S. mitis), Veillonella, Prevotella, Porphyromonas, Rothia, Neisseria, Fusobacterium, Lactobacillus

Allochthonous microbes are generally outnumbered by autochthonous microbes.

**Stomach:**
- Helicobacter pylori

**Allochthonous:**
- Gemella (e.g., G. haemolyans), Granulicatella, Streptococcus (e.g., S. mitis), Veillonella, Prevotella, Porphyromonas, Rothia, Neisseria, Fusobacterium, Lactobacillus

**Small intestine:**
- Escherichia coli, Klebsiella, Enterococcus, Bacteroides, Ruminococcus, Dorea, Clostridium, Coprococcus, Weissella, Lactobacillus (some species)

**Allochthonous:**
- Granulicatella, Streptococcus (e.g., S. mitis), Veillonella, Lactobacillus

**Large intestine:**

Allochthonous microbes are generally outnumbered by autochthonous microbes.
The Human GIT Microbiota

Most important component of the GIT microbiota is believed to be the **colonic microbiota** – bacterial concentrations far outweigh those found elsewhere

- bacterial species here can be divided into potentially **harmful** or **health-promoting groups** (Gibson & Roberfroid, 1995)
harmful

pathogenic (incl. production of toxins)

- Ps. aeruginosa
- vibriocaece
- staphylococci
- clostridia

veillonellae

enterobacteria

E. coli

sulphate reducers

anaerobic G +ve cocci

methanogens
eubacteria
bifidobacteria
bacteroides

beneficial

inhibition of growth of exogeneous and/or harmful bacteria (competitive exclusion, antimicrobials, low pH)
stimulation of immune functions through non-pathogenic means, anti-tumour properties, cholesterol reduction

lower gas distension
aid in digestion and/or absorption of food ingredients/minerals

synthesis of vitamins

number/g faeces
log_{10} scale
What does our **Microbiota Organ** do for us?

- Modulates the immune system
  - protects against atopy development
  - up-regulates non-specific immunity and IgA production
- ‘Normal’ GIT motility
- Improves nutritional status
  - B vitamins
  - vitamin K
  - mineral absorption – Ca, Mg, Zn?
  - energy salvaging
- Xenobiotic metabolism
- Colonisation resistance
- Production of SCFAs
- Production of polyamines
- Weight management
- Mood management
- Helps us live longer?
Dysbiosis

‘Qualitative and quantitative changes in the intestinal flora, their metabolic activities or their local distribution that produces harmful effects on the host’

Modern diet and lifestyle, as well as the use of pharmaceutical drugs, has led to the disruption of the normal intestinal microbiota and/or its activities. (Hawrelak & Myers, 2004)
Dysbiosis

Two types of intestinal dysbiosis.

– Small intestinal dysbiosis
  • Small Intestinal Bacterial Overgrowth (SIBO)

– Colonic dysbiosis
Small Intestinal Bacterial Overgrowth (SIBO)
SIBO - Definition

- a heterogeneous syndrome characterised by an increased number and/or abnormal type of bacteria in the small bowel (Bures et al, 2010)
  - $\geq 10^5$ CFU of bacteria/mL in a proximal jejunal aspirate
  - 2 types (Gasbarrini et al, 2009)
    - Gram-positive bacteria from upper respiratory tract and oral cavity
    - colonic bacteria (anaerobes)
SIBO

Conditions associated with:

- IBS
  - SIBO may or may not be more common in IBS patients (Ford et al, 2009)
- Unresponsive coeliac disease (Tursi et al, 2003)
- Chronic prostatitis (Weinstock et al, 2011)
- Acne rosacea (Parodi et al, 2008)
- Systemic sclerosis (Marie et al, 2009)
- Fibromyalgia (Pimentel et al, 2004)
- Rheumatoid arthritis (Henriksson et al, 1993)
- Liver cirrhosis (Bauer et al, 2001)
- NAFLD (Compare et al, 2012)
- Parkinson’s disease (Gabrielli et al, 2011)
- Type 2 diabetes (Rana et al, 2011)
- Restless legs syndrome (Weinstock and Walters, 2011)
  - 2° to iron deficiency?
SIBO

• Normal Protective Mechanisms (Bures et al, 2010)
  – Gastric acid
  – Intestinal motility
    • migrating motor complex
  – Intact ileo-caecal valve
  – Intestinal immunoglobulin (IgA) secretion
  – Bacteriostatic properties of pancreatic and biliary secretions
SIBO

• Risk factors
  – Proton pump inhibitor (PPI) use (Compare et al, 2011)
    • 50% of patients taking PPIs longterm (median 36 months) had SIBO vs 6% of controls (Lombardo et al, 2010)
  – Narcotic use (Choung et al, 2011)
  – Gastrectomy (Paik et al, 2011)
  – Chronic pancreatitis (Choung et al, 2011)
  – AIDS (Quigley and Abu-Shanab, 2010)
  – Diabetic neuropathy (Quigley and Abu-Shanab, 2010)
  – Elderly (aged ≥75 years) (Riordan et al, 1997)
SIBO

• Risk factors
  – Small intestinal disorders
    • Small bowel diverticula (Choung et al, 2011)
    • Crohn’s disease (Choung et al, 2011)
    • Coeliac disease (Ghoshal et al, 2004)
    • Short bowel syndrome (DiBaise et al, 2006)
    • Radiation enteropathy (Husebye et al, 1995)
    • Ileocaecal valve resection (Quigley and Abu-Shanab, 2010)
  – Large bowel disorders
    • acute diverticulitis (Tursi et al, 2005)
SIBO - Microbiology

• Commonly cultured bugs in SIBO: (Bouhnik et al, 1999)
  • mean number of bacterial genera was 4.6 per person with SIBO
  - *Lactobacillus* – 75%
  - *Streptococcus* – 71%
  - *Escherichia coli* – 69%
  - *Bacteroides* – 29%
  - *Clostridium* – 25%
  - *Veillonella* – 25%
  - *Staphylococcus* – 25%
  - *Micrococcus* – 22%
  - *Klebsiella* – 20%
  - *Fusobacterium* – 13%
  - *Peptostreptococcus* – 13%
  - *Proteus* – 11%
Conventional Medicine

- Antibiotics
  - two most commonly used:
    - Metronidazole – 43.7% GBT normalisation (7-day txt) (Lauritano et al, 2009)
    - Rifaximin – 63.4% GBT normalisation (7-day txt)
      » degree of efficacy appears dose-dependent (Scarpellini et al, 2007)
SIBO - Txt

- High Relapse Rate post-AB txt
  - SIBO often returns after “successful” AB txt (Lauritano et al, 2008)
    • 12.6% recurrence at 3 months
    • 27.5% recurrence at 6 months
    • 43.7% recurrence at 9 months

- S&S can return quickly
  • one trial found an average duration of symptom improvement of only 22 days! (Di Stefano et al, 2005)

- patients can be recommended repeated courses of ABs (e.g., first week of every month) or even continuous AB txt for life (Quigley and Quera, 2006)
Natural Treatment of SIBO

• Probiotics

• Prebiotics

• Anti-bacterial herbs
• Herbal Anti-bacterials – Human research
  – SIBO case study \((n=1)\) found enteric-coated *Mentha piperita* oil to reduce symptoms and decrease LBT results \(\text{(Logan and Beaulne, 2002)}\)
    - LBT test results improved, but did not normalise
• Anti-bacterial herbal medicines

  – *Punica granatum* (fruit rind), *Allium sativum*, *Syzygium aromaticum* oil, *Thymus vulgaris* oil, *Origanum vulgare* oil

• Anti-bacterial herbal medicines

• Herbs active against *Clostridium spp.* (Hawrelak, unpublished data) (Bialonska et al, 2009) (Lee et al, 2006)(Dorman and Deans, 2000)

  - tea polyphenols, *Allium sativum*, *Syzygium aromaticum* oil, *Thymus vulgaris* oil
SIBO - Txt

• Anti-bacterial herbal medicines

  


  – *Punica granatum* (fruit rind), *Allium sativum*, *Origanum vulgare* oil and infusion, *Thymus vulgaris* oil, *Syzygium aromaticum* oil
• Herbal Anti-bacterial Therapy
  – Summary
  • most broad-acting herbs:
    – *Punica granatum* (fruit rind) (TCM – shi liu pi)
    – *Allium sativum* – fresh is best
    – Green tea polyphenols
    – *Origanum vulgare* oil
    – *Thymus vulgaris* oil
    – *Syzygium aromaticum* oil

– ensure essential oils are administered in an enteric-coated form!
Colonic Dysbiosis
Colonic Dysbiosis

Conditions associated with:

- IBS  (Lyra et al, 2009)
- Inflammatory bowel disease  (Walker et al, 2011)
- Atopic eczema  (Candela et al, 2012)
- Kidney stones  (Kaufman et al, 2008)
- Obesity  (Riley et al, 2013)
- Autism  (Finegold, 2011)
- Rheumatoid arthritis  (Scher & Abramson, 2011)
- Liver cirrhosis  (Bajaj et al, 2013)
- Breast cancer  (Xuan et al, 2014)
- Type 1 diabetes  (Mejia-Leon et al, 2014)
The Causes of Dysbiosis:

Antibiotics.

– of all the factors that can impact upon the GIT microbiota, antibiotics have the greatest detrimental effect (Hawrelak & Myers, 2004)

• research using culturing techniques suggested quantitative changes could last up to 40 days
• metabolic derangements can last up to 18 months!
The Causes of Dysbiosis:

**Antibiotics.** (Jernberg et al, 2010)(Cotter, 2012)

– New research using more sensitive molecular analysis techniques (16 sRNA) has revealed:
  
  • presence of antibiotic resistant microorganisms for up to 4 years post-treatment
  
  • alterations can last significantly longer than previously believed:
    – 18-24 months after a single course of clindamycin
    – 4 years after triple therapy for *H. pylori*

– some organisms never recover
Other Causes of Dysbiosis:

- Radiotherapy (Nam et al, 2013)
- Chemotherapy (Stringer et al, 2013)
- Stress (Hawrelak & Myers, 2004)
- C-section delivery (Mitsou et al, 2008)
- Formula feeding (Penders et al, 2006)
Dietary Causes of Colonic Dysbiosis:

Diet
– can also negatively impact GIT microbiota
  • sulphates and sulphites (Hawrelak & Myers, 2004)
  • high protein diets (Duncan et al, 2007)
  • high animal protein diets (Goldin and Gorbach, 1976)
  • high fat diets (Cani et al, 2008)
  • high in refined carbohydrates (low in colonic foods)
Animal-based Diet
(David et al, 2013)

- Subjects placed on an animal-based diet for 5 days
  - composed of meat, eggs and cheese (ad libitum)
    - dietary fat contributed 70% of calories and protein 30%
  - microbiota composition changed within 24 hours!
    - ↑ Bilophyla wadsworthia, Alistipes spp, and Bacteroides spp.
    - ↓ Roseburia spp., Eubacterium rectale and Ruminococcus bromii
  - decreased SCFA production
  - increases in protein putrefactive byproducts
  - increased concentrations of secondary bile acids
    - deoxycholic acid (DCA) - cancer promoter
  - WGTT slowed by 12 hours
  - these changes may contribute to the development of IBD and colon cancer

- weight decreased significantly by day 3
  - urinary ketones increased by day 2
Treatment of Colonic Dysbiosis

• Rectify dietary contributors
  • Probiotics
  • Prebiotics
  • Prebiotic-like foods
• Antimicrobial herbs?
Prebiotic-like Foods in General Dysbiosis

• Brown rice (Benno et al, 1989)

• Carrots (Tamura, 1983)

• Cocoa (Tzounis et al, 2011)

• Green tea (Goto et al, 1998)

• Almonds (Liu et al, 2014)
Green Tea

Human Trial (Goto et al, 1998)

- **Green tea**
  - 300 mg catechins/day
  - equivalent to 5-6 cups/day

Results:

- increased numbers of lactobacilli and bifidobacteria
- decreased numbers of bacteroides, clostridia and enterobacteria
- decrease in faecal pH
- decrease in faecal concentrations of ammonia, sulfide, skatol, indole and cresol
- increased production of SCFAs

Increased β-glucosidase activity (Molan et al, 2010)
Dark Cocoa

- **R, DB, PC, CO trial** (Tzounis et al, 2011)
  - n=22 healthy subjects
- Subjects consumed either high or low flavonol cocoa for 4 weeks
  - High = ~500 mg cocoa flavanols/day
  - equivalent 14 g cocoa powder/day
- **Results:**
  - increase in faecal bifidobacteria and lactobacilli
  - decreases in clostridia
  - reduction in plasma triglycerides and CRP
Treatment of General Colonic Dysbiosis

Research clearly shows that significant beneficial alterations in the GIT ecosystem can be induced through the use of:

- Probiotics
  - the right strain(s)

- Prebiotics

- Prebiotic-like foods
Is there a role for herbal antimicrobials in general colonic dysbiosis??
Weed, Seed and Feed Program

- **Weed** - use of “natural” antimicrobial agents to reduce the population of *unknown* pathogens or out of balance organisms in the GIT; +/- ‘bowel purge’

- **Seed** - the reintroduction of beneficial microbes (lactobacilli & bifidobacteria);

- **Feed** – introduction of foods and supplements that preferentially select for the growth of beneficial colonic bacteria (i.e., FOS)
Potential Problems with the ‘Weed, seed and feed’ Program

Do we really know what we are doing when ‘weeding’?

- What effects do these herbs have on the 1000+ species of bacteria in the gut?
Intensive ‘weeding’?
Intensive ‘weeding’ and ‘seeding’?
Potential Problems with the ‘Weed, seed and feed’ Program

Do we really know what we are doing when ‘weeding’?

- Could inappropriate use cause long-lasting detrimental changes in the flora?
- How long does it take for the microbiota to recover from ‘weeding’?
  - Short-term vs long-term
- Could this have long-term health implications?
  - Decreased efficacy of medicinal herbs?
    - Devil’s claw, red clover, flaxseeds, willow bark, soy foods, senna, cascara sagrada, Panax ginseng, and many more!!
  - Increased risk of breast or other cancers?? kidney stones?
Does this protocol follow natural medicine principles?
The Process of Healing & the Therapeutic Order

“In facilitating the process of healing, the... physician seeks to use those therapies which are most efficient in stimulating the self-healing mechanisms and which have the least potential to harm the patient.” (Zeff, 1997)
The ‘Therapeutic Spectrum’?

This concept results in the **therapeutic spectrum**:

- treatments can be ordered in a spectrum from those which act generally and gently to promote the health of the individual with little potential to do harm \(\rightarrow\) to those that act very specifically and have a greater potential to cause harm
My Antimicrobial Research
<table>
<thead>
<tr>
<th>Botanical Name</th>
<th>Common Name</th>
<th>Extract type</th>
<th>Test Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bacteroides fragilis</td>
</tr>
<tr>
<td>Allium sativum</td>
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</tr>
<tr>
<td>Allium sativum</td>
<td>Garlic</td>
<td>Fr</td>
<td>2.75</td>
</tr>
<tr>
<td>Artemisia annua</td>
<td>Sweet Annie</td>
<td>Eth</td>
<td>18.5</td>
</tr>
<tr>
<td>Berberis vulgaris</td>
<td>Barberry</td>
<td>Eth</td>
<td>&gt;18.5</td>
</tr>
<tr>
<td>Citrus spp.</td>
<td>Citrus seed</td>
<td>gly</td>
<td>0.02</td>
</tr>
<tr>
<td>Coptis chinensis</td>
<td>Goldthread root</td>
<td>Eth</td>
<td>9.5</td>
</tr>
<tr>
<td>Hydrastis canadensis</td>
<td>Golden seal</td>
<td>Eth</td>
<td>2.2</td>
</tr>
<tr>
<td>Mahonia aquifolium</td>
<td>Oregon grape</td>
<td>Eth</td>
<td>&gt;18.5</td>
</tr>
<tr>
<td>Origanum</td>
<td>Oregano</td>
<td>EO</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Results:

Herbs with little-to-no effect on the microbiota or pathogens:

- *Artemisia annua* (sweet Annie or Chinese wormwood)
- *Artemisia absinthium* (wormwood)
- *Berberis vulgaris* (barberry)
- *Mahonia aquifolium* (Oregon grape)

NB – these herbs displayed very little antimicrobial activity at clinically-relevant doses.
Results:

Herbs that demonstrated substantial selectivity of action:

- *Allium sativum* (fresh)
Results:

Herbs that demonstrated some degree of selectivity:

- *Allium sativum* (dry tableted extract)
Results:

Herbs that demonstrated little selectivity:

• Berberine-containing herbs
  – *Coptis chinensis* (goldthread root)
  – *Hydrastis canadensis* (golden seal)

• *Origanum vulgare* (e.o.)
Results:

Herbs with no selectivity:

• citrus seed extract (grapefruit seed extract)
Implications of Results:

- citrus seed extract
  - should be viewed as an extremely potent, broad-acting antimicrobial that may decimate the GIT microbiota
  - more active against beneficial members of the GIT microbiota than potentially pathogenic members

- compare to clindamycin, which causes:
  » colonic SCFA production to decrease by ~ 90%
  » 4-6 log ↓ in bifidobacteria (10,000 -1 million x decrease)
  » 4-6 log ↓ in Bacteroides spp.
  » 2 log ↓ in lactobacilli (100 x decrease)
Implications of results:

– Citrus seed extract

• **No** tradition of use
• **Not** a natural product
  – appears to be spiked with benzethonium chloride, triclosan and/or methylparaben (von Woedtke et al, 1999)(Takeoka et al, 2005)(Avula et al, 2007)

• Displays human cytotoxicity
  – in any dilution more concentrated than 1:256 (Heggers et al, 2002)
My Research - Summary

Use of some medicinal herbs commonly advocated to treat dysbiosis may:

– be a waste of time/effort
– actually **cause** harmful alterations to the GIT ecosystem

• reserve use of more broad-acting, less targeted herbal antimicrobials to situations of specific pathogen eradication and as second lines of treatment
  – e.g., confirmed Giardia or *H. pylori* infection

– **avoid the use of CSE (GSE) completely**
Other Implications of Results:

– probiotic supplementation recommended concurrently with- and post-administration of:
  – fresh *Allium sativum* (in single doses $\geq$ 2.75 g)
  – dried *Allium sativum* (in single doses $\geq$ 8.5 g)
  – *Coptis chinensis* (in single doses $\geq$ 0.6 g)
  – *Hydrastis canadensis* (in single doses $\geq$ 0.6 g)
Other Selectively-Acting GIT Antimicrobials

**Essential Oils** (Hawrelak et al, 2009)

- *Carum carvi* (caraway seeds)
- *Lavandula angustifolia* (lavender flowers)
- *Trachyspermum copticum* (ajwain seeds)

- All these oils were selective in activity
  - Inhibited the growth of potential pathogens
    - *Candida albicans, Clostridium spp.*, *Bacteroides fragilis*
  - **No effect** on lactobacilli or bifidobacteria
Other Selectively-Acting GIT Antimicrobials


– Antibacterial

  • *E. coli, Campylobacter jejuni, Salmonella spp.*, *Shigella spp.*, *Vibrio spp.*
  • *Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus, Proteus spp.*, *Listeria monocytogenes, Yersinia enterocolitica*
  • inhibits *Pseudomonas aeruginosa* and dental organism biofilm formation
Other Selectively-Acting GIT Antimicrobials


– Antiprotozoal
  • Giardia spp., Blastocystis spp., Entamoeba histolytica, Cryptosporidium parvum, Trichomonas vaginalis

– Anthelmintic
  • widely used in Ayurveda, TCM and in the past WHM
  • in vitro

– Antifungal
  • Candida albicans

– No negative impact on lactobacilli + enhanced growth of bifidobacteria  (Bialonska et al, 2009)(Neyrinck et al, 2013)
Green Tea Polyphenols – Antimicrobial & Anti-biofilm Effects

• **Candida albicans** (Evensen & Braun, 2009)
  – Inhibits growth of *C. albicans*
  – Prevents formation of biofilms
  – **80% reduction** in established *C. albicans* biofilm

• Prevents formation of biofilm by *E. coli* (Faraz et al, 2012), *streptococci* (Cho et al, 2010) **and** *staphylococci* (Blanco et al, 2005)

• Inhibits bacterial drug-resistant pump activity (Sudano Roccaro et al, 2004)(Kurincic et al, 2012)
Recommended Colonic Dysbiosis Treatment Approach

Seed and Feed

– Use appropriate probiotic strains, prebiotics and prebiotic-like foods to beneficially alter the out-of-balance GIT ecosystem
Recommended Colonic Dysbiosis Treatment Approach

Selective Weeding - choose selectively-acting antimicrobials first before considering broad-spectrum options

- Green tea extract
  - ~300 mg catechins/day
- Pomegranate husk
- Garlic
  - preferably raw
- Caraway, lavender or ajwain essential oils (preferably enteric-coated)
Recommended Colonic Dysbiosis Treatment Approach

Leave more broad-acting, potentially microbiota-damaging options as last resort

– **Berberine-rich** herbs

– Enteric-coated essential oils
  • Oregano, thyme, clove, cinnamon

– Antibiotics (SIBO)
The ‘Therapeutic Spectrum’

- Stimulates self-healing mechanisms
- Little potential to harm patient
- Acts gently and non-specifically
- Nurtures and supports, rather than controls

- Little potential to stimulate *vis medicatrix naturae*
- Greater potential to cause harm and suppression
- Acts specifically and with greater force
- Controls function
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