Multi-Stage Probabilistic Bipartite Graph Algorithm - Effect of Herbal Medicines on the Gut Ecosystem

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Presenter: Suganya Chandrababu
Straightforward Overview

- Purpose/value of the study
- Effect of Herbs on the Gut Ecosystem
- Our Contribution
- Multi-stage Graph Probabilistic Algorithm
- Dataset Used
- Results and Discussion
- Conclusion
- Limitations
- Future Work
Such imbalance could result in intestinal and extra-intestinal disorders, including inflammatory bowel disease (IBD), diabetes mellitus (DM), obesity, etc.
Pharmacological Effects of Natural Products

**Role of Gut Microbiota in the Pharmacological Effects of Natural Products**

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**Berberine Regulates Treg/Th17 Balance to Treat Ulcerative Colitis Through Modulating the Gut Microbiota in the Colon**

Huantian Cui, Yuxi Cai, Li Wang, Bettiian Jia, Junchen Li, Shuwu Zhao, Xiaoqian Chu, Jin Lin, Xiaoyu Zhang, Yuhong Bian, and Pengwei Zhuang

1 Tianjin University of Traditional Chinese Medicine, Tianjin, China; 2 Tianjin Second People’s Hospital, Tianjin, China

Published online at [ScienceDirect](https://www.sciencedirect.com)

**Anthocyanins as inflammatory modulators and the role of the gut microbiota**

Carina Almeida Morais, Veridiana Vera de Rasso, Débora Estadella, Luciana Pellegrini Pisani

Departamento de Nutrição, Faculdade de Saúde e Ciências da Saúde da Universidade Federal de São Paulo, São Paulo, SP, Brazil

Received 14 August 2017; accepted 16 November 2017

**Ginseng polysaccharides enhanced ginsenoside Rb1 and microbial metabolites exposure through enhancing intestinal absorption and affecting gut microbial metabolism**

Published online at [ScienceDirect](https://www.sciencedirect.com)
Herbs Modulate Gut Bacterial Metabolism

Bioactive Compound

Target

Microbial Enzymes

Enzyme Activity
- Activate
- Inhibit
- Directly Bind

Functions

Can be directly metabolized by GI microbiota upon ingestion
- NO$_3^-$
- NH$_3$

Can be metabolized by GI microbiota after conjugation by the liver
- GSH

Can interfere with enzymatic activity of GI microbiota

Bacterial products

https://media.springernature.com/lw685/springer-static/image/art%3A10.1038%2FJPinpbiolstrms%2F2016.3/MediaObjects/41522_2016_Article_BFJpinpbiolstrms20163_Fig1_HTML.jpg
Why Hear the Talk?

To

- understand a comprehensive method that integrates knowledge from multiple sources.
- know how to characterize the microbial dysbiosis.
- evaluate the pharmacological value of herbal medicine.
- learn how and which herbs can modulate the gut microbial functions.
What is our contribution?

We

- provide a **systems-level characterization** of the effects of the small molecules in herbs on the bacterial genes and metabolic pathways.

- propose a **computational network-based approach**—the **Multi-stage Probabilistic Bipartite graph Algorithm (MPBA)**, which integrates the complex heterogeneous metabolism/pathway data from herbs to gut bacteria.
Background Work

◆ The human colon modulates of gut immune function, protects the host against pathogens and diseases. [D. C. Savage, et al., 1997, R. E. Ley, et al., 2010]

◆ Variations in products of bacterial metabolism have been implicated as a causative agent in serious diseases, including cancer (example: Helicobacter pylori). [Flint, Harry J., et al., 2012]

◆ Herbal medicine are useful in the treatment of dysbiosis and serve as a multi-targeting complementary/alternative medicine/probiotic in the management of colon health, [M. Sałaga, et al., 2014, F. Ke, et al., 2012]
Multi-Stage Probabilistic Bipartite Graph Algorithm
Our Prediction Model

Bacterial metabolism

Herbs modulating bacterial functions

Herbal pharmacology

MPBA
Graph Approximation

\[ z_{ij} \approx \sum_{q=1}^{k} \frac{x_{iq} y_{jq}}{\sigma_q} \]

where

\[ \sigma_q = \sum_{i=1}^{m} x_{iq} + \sum_{j=1}^{n} y_{jq} \]

It denotes the degree of the pathway nodes.

Matrix Form

\[ Z \approx X \Sigma Y^T \]

where \( \Sigma \) is a diagonal matrix, with \( \left( \Sigma \right)_{qq} = \frac{1}{\sigma_q} \)
The Divergence Loss Function

- To evaluate how well the algorithm models the data, we use the divergence loss function

The approximation $Z \approx X\Sigma Y^T$, can be done minimizing

$$l(Z, X\Sigma Y^T)$$

Divergence Loss

$$l(Z, X\Sigma Y^T) = \sum_{i=1}^{m} \sum_{j=1}^{n} \left( z_{ij} \log \frac{z_{ij}}{(X\Sigma Y^T)_{ij}} - z_{ij} + (X\Sigma Y^T)_{ij} \right)$$

, which equal zero when $Z = X\Sigma Y^T$
Probabilistic Graph Model

- We can interpret the same equation using *Markov random walks* on graphs as done using PLSA [T. Hoffman, 200].

- The weight \( z_{ij} \) is essentially a quantity proportional to the stationary probability of direct transitions between \( h_i \) and \( b_j \), denoted by \( p(h_i, b_j) \).

\[
\text{z}_{ij} = p(h_i, b_j)
\]

\[
p(h_i, b_j) = p(h_i)p(b_j|h_i)
\]

- In a tripartite graph there is no direct edge between the \( h_i \) node and the \( b_j \) node, and they can only be connected through the pathway nodes \( pq \).
Probabilistic Graph Model

\[ p(h_i, b_j) = p(h_i) p(b_j | h_i) \]  

Transition probability

\[ p(b_j | h_i) = \sum_{q=1}^{k} p(b_j | p_q) p(p_q | h_i) \]  

Tripartite Network

\[ p(h_i, b_j) = p(h_i) \sum_{q=1}^{k} p(b_j | p_q) p(p_q | h_i) \]  

Back Substitution

\[ p(h_i, b_j) = \sum_{q=1}^{k} \frac{p(h_i, p_q) p(b_j, p_q)}{p(p_q)} \]  

\[ \Rightarrow z_{ij} \approx \sum_{q=1}^{k} \frac{x_{iq} b_{yq}}{\sigma_q} \]
Unsupervised Learning by Probabilistic Latent Semantic Analysis

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3.2. Model fitting with the EM algorithm

The standard procedure for maximum likelihood estimation in latent variable models is the Expectation Maximization (EM) algorithm (Dempster, Laird, & Rubin, 1977). EM

![Graphical model representation of the aspect model in the asymmetric (a) and symmetric (b) parameterization.](image)

*Figure 1.* Graphical model representation of the aspect model in the asymmetric (a) and symmetric (b) parameterization.
Bayesian Formula

For the E-step we apply Bayes’ formula to obtain

$$p(p_q | h_i, b_j) = \frac{p(h_i, b_j | p_q)p(p_q)}{p(h_i, b_j)}$$

And in the M-step one has to maximize the expected complete data log-likelihood given by,

$$E[\mathcal{L}^c] = \sum_{i=1}^{N} \sum_{j=1}^{M} n(h_i, b_j) \sum_{q=1}^{K} P(p_q | h_i, b_j) \log \left[ P(b_j | p_q) P(p_q | h_i) \right]$$

where $n(h_i, b_j)$ is the frequency or the number of paths from herb to bacteria through the pathway node.
Dataset Used
Differential Abundant Pathways in IBD

- Nitrogen metabolism
- Fructose and mannose metabolism
- Riboflavin metabolism
- Sulfur metabolism
- Bacterial secretion system
- Cysteine and methionine metabolism
- Butanoate metabolism
- Lysine biosynthesis
- Pentose phosphate pathway

- UC
- CD without ileal
- CD with ileal
- Healthy

2. X. C. Morgan, T. L. Tickle, H. Sokol, D. Gevers, K. L. Devaney,  
### Dataset and Source

**8** Most affected Pathways and enzymes in IDB

Source: KEGG

Bacteria harbors **273** enzymes belonging to the pathways

**235** bacterial species and **273** bacterial enzymes

Source: Uniprot, NCBI Genome

Targeting **262** bacterial enzymes belonging to the pathways

**Herbal compounds target**

**24** Culinary herbs, **132** bioactive compounds and **262** compound target enzymes

Source: PhytoChem NAL, PubChem

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03/06/2020

University of Nebraska at Omaha

GRACA 2019
Results and Discussion
Case Study

- Most Affected Microbial Metabolic Pathways and Enzymes In Both UC And CD

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Map</th>
<th>Enzyme Count</th>
<th>Bacteria Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysteine and methionine metabolism</td>
<td>map00270</td>
<td>86</td>
<td>235</td>
</tr>
<tr>
<td>Butanoate metabolism</td>
<td>map00650</td>
<td>67</td>
<td>222</td>
</tr>
<tr>
<td>Fructose and mannose metabolism</td>
<td>map00051</td>
<td>60</td>
<td>235</td>
</tr>
<tr>
<td>Pentose phosphate pathway</td>
<td>map00030</td>
<td>53</td>
<td>235</td>
</tr>
<tr>
<td>Lysine biosynthesis</td>
<td>map00300</td>
<td>46</td>
<td>234</td>
</tr>
<tr>
<td>Niripartiterogene metabolism</td>
<td>map00910</td>
<td>37</td>
<td>217</td>
</tr>
<tr>
<td>Sulfur metabolism</td>
<td>map00920</td>
<td>44</td>
<td>195</td>
</tr>
<tr>
<td>Riboflavin metabolism</td>
<td>map00740</td>
<td>33</td>
<td>235</td>
</tr>
</tbody>
</table>

- Routes were traced through the metabolic model of the gut microbiota, and the organism(s) harboring the necessary genes identified.
The network consists of 8 pathways, 273 bacterial enzymes, 235 bacterial species, and 18060 distinct interactions.

- **EC 1.2.1.11-aspartate-semialdehyde dehydrogenase**
# Uniquely Encoded Bacterial Enzymes

## Potential Drug Targets

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Pathway</th>
<th>Bacterium</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC1.1.1.122 - L - fucosedehydrogenase</td>
<td>Fructose and mannose metabolism</td>
<td>CentipedaparidontiiDSM2778</td>
</tr>
<tr>
<td>EC7.6.2.7 - taurineABC transporter</td>
<td>Sulfur metabolism</td>
<td>Enterobacteriaceaebacterium9254FAA</td>
</tr>
<tr>
<td>EC1.3.5.4 - fumaratereductase (quinol)</td>
<td>Butanoate metabolism</td>
<td>Enterobacteriaceaebacterium9254FAA</td>
</tr>
<tr>
<td>EC2.3.1.184 - acyl - homoserine - lactonesynthase</td>
<td>Cysteine and methionine metabolism</td>
<td>Enterobacteriaceaebacterium9254FAA</td>
</tr>
<tr>
<td>EC5.1.2.3 - 3 - hydroxybutyryl - CoApimerase</td>
<td>Butanoate metabolism</td>
<td>Enterobacteriaceaebacterium9254FAA</td>
</tr>
<tr>
<td>EC2.3.1.46 - homoserineO - succinyltransferase</td>
<td>Sulfur metabolism, Cysteine and methionine metabolism</td>
<td>Enterobacteriaceaebacterium9254FAA</td>
</tr>
<tr>
<td>EC2.7.4.23 - ribose1, 5 - bisphosphoephosphokinase</td>
<td>Pentose phosphate pathway</td>
<td>Enterobacteriaceaebacterium9254FAA</td>
</tr>
<tr>
<td>EC2.7.1.51 - L - fuculokinase</td>
<td>Fructose and mannose metabolism</td>
<td>Enterobacteriaceaebacterium9254FAA</td>
</tr>
<tr>
<td>EC3.1.3.7 - phosphoadenylate - nucleotidase</td>
<td>Sulfur metabolism</td>
<td>Enterobacteriaceaebacterium9254FAA</td>
</tr>
<tr>
<td>EC2.7.1.55 - allosekinase</td>
<td>Fructose and mannose metabolism</td>
<td>EubacteriumventriosumATCC27560</td>
</tr>
<tr>
<td>EC1.13.12.16 - nitronatemonooxygenase</td>
<td>Nitrogen metabolism</td>
<td>Fusobacteriumnucleatumsubsp. animalisATCC51191</td>
</tr>
<tr>
<td>EC3.2.2.16 - methylthioadenosinenucleosidase</td>
<td>Cysteine and methionine metabolism</td>
<td>FusobacteriumvariumATCC27725</td>
</tr>
<tr>
<td>EC1.1.1.36 - acetoacetyl - CoA reductase</td>
<td>Butanoate metabolism</td>
<td>GranulicatellaadiacensATCC49175</td>
</tr>
<tr>
<td>EC4.1.1.12 - aspartate4 - decarboxylase</td>
<td>Cysteine and methionine metabolism</td>
<td>LactobacillusantriDSM16041</td>
</tr>
<tr>
<td>EC1.7.7.1 - ferredoxin -- -- nitrifereductase</td>
<td>Nitrogen metabolism</td>
<td>Lactobacillusbrevisubsp. gravesensisATCC27305</td>
</tr>
<tr>
<td>EC3.1.3.46 - fructose - 2, 6 - bisphosphatase</td>
<td>Fructose and mannose metabolism</td>
<td>Lactobacillusdelbrueckiiusubsp. lactisDSM20072</td>
</tr>
<tr>
<td>EC1.4.7.1 - glutamatesynthase</td>
<td>Nitrogen metabolism</td>
<td>LactobacillushamnosusLMS2 - 1</td>
</tr>
<tr>
<td>EC4.1.2.43 - 3 - hexulose - 6 - phosphatesynthase</td>
<td>Pentose phosphate pathway</td>
<td>Paenibacillussp.HGF7</td>
</tr>
<tr>
<td>EC1.1.1.215 - gluconate2 - dehydrogenase</td>
<td>Pentose phosphate pathway</td>
<td>Paenibacillussp.oraltaxon786str.D14</td>
</tr>
<tr>
<td>EC1.4.1.2 - glutamate dehydrogenase</td>
<td>Nitrogen metabolism</td>
<td>Parvimonassp.oraltaxon110str.F0139</td>
</tr>
<tr>
<td>EC2.3.3.14 - homocitratesynthase</td>
<td>Lysine biosynthesis</td>
<td>Peptostreptococcusanaerobius553 - L</td>
</tr>
<tr>
<td>EC2.7.7.22 - GDPmannosephosphorylase</td>
<td>Fructose and mannose metabolism</td>
<td>Selenomonassp.oraltaxon149str.6TH29BP</td>
</tr>
<tr>
<td>EC2.8.3.35 - 3 - oxoacidCoA - transferase</td>
<td>Butanoate metabolism</td>
<td>Sporosarcinaneuerykonsis2681</td>
</tr>
<tr>
<td>EC6.2.1.16 - acetoacetyl - CoA synthetase</td>
<td>Butanoate metabolism</td>
<td>Sporosarcinaneuerykonsis2681</td>
</tr>
<tr>
<td>EC6.2.1.2 - butyryl - CoA synthetase</td>
<td>Butanoate metabolism</td>
<td>StaphylococcusepidermidisW23144</td>
</tr>
<tr>
<td>EC2.4.2.28 - MesAdoprophosphorylase</td>
<td>Cysteine and methionine metabolism</td>
<td>Veillonellasp.oraltaxon158str.F0142</td>
</tr>
</tbody>
</table>
Bacterial metabolism

- Paenibacillus sp. HGF7, Staphylococcus epidermidis W23144, Streptococcus sanguinis SK1087, Lactobacillus buchneri ATCC 11577

- Sulphur and Nitrogen metabolism has enzymes uniquely encoded by bacterial species

03/06/2020

map00051  Fructose and Mannose metabolism
map000650  Butanoate metabolism
map00030  Pentose Phosphate metabolism
map00910  Nitrogen metabolism
map00740  Riboflavin metabolism
map00270  Cysteine and Methionine metabolism
map00300  Lysine biosynthesis
The network 5623 unique herb-target interactions.

Dill, fennel, parsley, ginseng, french tarragon, basil, coriander, mint, and thyme, were capable of targeting 262 enzymes.

aldehyde reductase – most targeted enzyme, causes imbalances in 5-HT levels. [D. Keszthelyi, et al., 2009]
# Compounds Targeting Enzymes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Enzyme_count</th>
<th>Herbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td>185</td>
<td>Borage, Basil, Fennel, Dill, Chives, Coriander, Cloves, French Tarragon, Garlic, Oregano, Parsley, Ginger</td>
</tr>
<tr>
<td>Luteolin</td>
<td>180</td>
<td>Thyme, French Tarragon, Mint, Oregano, Rosemary, Sage</td>
</tr>
<tr>
<td>Curcumin</td>
<td>176</td>
<td>Ginger</td>
</tr>
<tr>
<td>Gallic-Acid</td>
<td>170</td>
<td>Thyme, Cloves, French Tarragon, Oregano, Sage</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>168</td>
<td>Ginseng</td>
</tr>
<tr>
<td>Coumarins</td>
<td>167</td>
<td>Dill, Lovage</td>
</tr>
<tr>
<td>O-Methoxycinnamaldehyde</td>
<td>167</td>
<td>Basil, Cinnamon</td>
</tr>
<tr>
<td>Guaiacol</td>
<td>167</td>
<td>Cinnamon, Mint</td>
</tr>
<tr>
<td>Lutein</td>
<td>167</td>
<td>Ginseng</td>
</tr>
<tr>
<td>Esculin</td>
<td>167</td>
<td>Basil</td>
</tr>
<tr>
<td>Linoleic-Acid</td>
<td>167</td>
<td>Borage, Basil, Cardamom, Fennel, Dill, Thyme, Chervil, Chives, Coriander, Garlic, Ginseng, Majoram, Mint, Oregano, Rosemary, Sage, Ginger</td>
</tr>
<tr>
<td>Estradiol</td>
<td>167</td>
<td>Ginseng</td>
</tr>
<tr>
<td>Apigenin</td>
<td>167</td>
<td>Basil, Dill, Thyme, Coriander, French Tarragon, Garlic, Oregano, Parsley, Rosemary, Sage</td>
</tr>
<tr>
<td>Myricetin</td>
<td>69</td>
<td>Cloves, Garlic, Ginger</td>
</tr>
<tr>
<td>Chlorogenic-Acid</td>
<td>49</td>
<td>Fennel, Dill, Thyme, Coriander, French Tarragon, Garlic, Majoram, Mint, Oregano, Parsley, Rosemary, Ginger</td>
</tr>
<tr>
<td>Esculetin</td>
<td>45</td>
<td>Basil, Dill, French Tarragon</td>
</tr>
<tr>
<td>Bergapten</td>
<td>16</td>
<td>Fennel, Dill, Coriander, Lovage, Parsley</td>
</tr>
<tr>
<td>5-Methoxy-Psoralen</td>
<td>16</td>
<td>Fennel, Dill, Coriander, Lovage, Parsley</td>
</tr>
<tr>
<td>Scopoletin</td>
<td>15</td>
<td>Fennel, Dill, Coriander, French Tarragon, Parsley</td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>14</td>
<td>Basil, Cinnamon, Cloves, Lemon Balm, Ginseng, Parsley</td>
</tr>
</tbody>
</table>
The HT network has **5623** unique herb-target interactions.

The average degree (connectivity) of the HT network (**39.32**) and most herbs targeted on an average of **23.3** enzymes which is significantly higher than the modern synthetic drugs (**1.8**) [M.AY, et al., 2017].
Herb-target-pathway (HTP) network was constructed with 24 herbs, 262 target enzymes, 8 metabolic pathways, and 5893 distinct interactions.
Fructose and Mannose metabolism (map00051) is the pathway targeted by most herbs including, coriander, chives, thyme, parsley, ginger, garlic, mint, basil, etc.

Butanoate and Pentose Phosphate metabolism are targeted by fewer no. of herbs.
Herb-Pathway-Bacteria Net.

- What are the potential herbs which can regulate bacterial functions and compositions?
- What are the bacterial species a given herb can target?
- And what are the metabolic functions the herbs can regulate?

map00051 Fructose and Mannose metabolism
map00650 Butanoate metabolism
map00030 Pentose Phosphate metabolism
map00910 Nitrogen metabolism
map00740 Riboflavin metabolism
map00270 Cysteine and Methionine metabolism
map00920 Sulphur metabolism
Herb-Bacteria Analysis

- Species including *Sporosarcina newyorkensis* 2681, *Centipeda periodontii DSM 2778*, *Enterobacteriaceae bacterium 92 54FAA*, *Staphylococcus epidermidis W23144*, are targeted by various herbs - mint, garlic, ginger, thyme, and, basil.

- Alternatively, species including *Helcococcus kunzii ATCC 51366*, *Facklamia ignava CCUG 37419*, *Eubacterium infirmum F0142*, and *Fusobacterium necrophorum subsp. funduliforme 1 1 36S* are found to harbor unique enzymes which are not commonly encoded by the bacterial genes and are targeted by fewer herbs like sage, borage, etc.
Herbal medicines, when exposed to gut microbes, metabolizes into active or absorbable compounds which are accomplished by the secreted enzymes of intestinal microflora.

Results show ginseng has an effect on 6 out of the 8 given pathways such as, Nitrogen metabolism, Fructose, and mannose metabolism, Riboflavin metabolism, Cysteine and methionine metabolism, Butanoate metabolism, and Pentose phosphate pathway, and can target 237 enzymes belonging to these pathways which can be harbored by 235 bacterial species.

Ginseng exerted a weight loss effect (antiobesity) on gut microbiota in all participants, which differed depending on the composition of gut microbiota. [Mi-YoungSong, et al., 2014]
Conclusion

MPBA allows us to:

**Identify what herbal compounds can affect the bacterial composition**

- Understand the gut bacterial metabolism under normal or diseased condition.

- Functionally classify the gut microbiome through their metabolic pathways and the secreted enzymes.

- Understand the pharmacology and mechanism of action of the herbs.

- Model the effect of natural drug mechanism on the gut microbiome and in turn the host health.

- Integrate heterogeneous data and predict critical associations.

- Mathematically model complex biological systems like the herbs and gut ecosystem and provides a systems approach for characterizing the functions of the system.
Limitations

- The potential limitation that we encounter lies in the *incompleteness of the networks due to unavailable compound-target knowledge*.

- Difficulty in *differentiating the therapeutic effects from the side effects*, in spite of the large volume of data that currently exist.

- The proposed method could not identify *the type of activity of the bioactive compounds on the target enzymes*, except for some supporting literatures.
Future Work

- Include abundance information from clinical samples.

- Include other factors like, age, gender, environment, lifestyle, etc., which also play a vital role in shaping the microbiome of an individual.
Thank you
Questions

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University of Nebraska at Omaha