

The Future of Research in Chinese Herbal Pharmacology

Keywords: pharmacology, microbiome, evolution biology, Bayes' statistics, prebiotics long lasting effects

Abstract

Classical statistics and the direct effects of pharmacology on human cells were a hallmark of medical research for many years, but with new knowledge available our diagnosis and therapy can improve in the future:

By combining empirical observation with modern research we found the key why herbal pharmacology in comparison to chemical pharmacology is superior in regard to long-term effects:

By causing a lasting change in the relation of different reproducing microorganisms in the human body, herbal pharmacology restores the evolutionary developed relation between the human body and its microorganisms, thus leading to an indirect but long-lasting effect of treatment. For instance: the reproduction of intestinal bacteria will continue, while a chemical action on human cells only lasts when the medication continues.

Including evolution biology thus improves the understanding of disease and treatment, as a second example shows:

Since Bayesian statistics is very similar to the neural network of the human brain, i.e. including „fuzzy“ information of different sources (pulse, tongue, body odour, questioning etc.), the outcome of diagnosis by Chinese medicine can be calculated with a much more precise result, than by classical statistics which relies mostly on repetition of „cleaned“ digital input and is easily disturbed by outliers.

These examples show, that the combination of empirical experience from Chinese medicine with a systemic approach of understanding networking relations of the cell system leads to a new step of progress in diagnosis and therapy.

Why do have Chinese herbs lasting effects?

In the 1990's we gladly studied in Tianjin the combination of the experience in treating diseases gained by thousands of minds over centuries with the newest technical and methodological ideas from the presence worldwide.

This knowledge turned out to be very successful in treating patients in Germany for almost a decade. But while the written experience of the ancestors is still not completely available to everybody, methods in modern science have evolved and are waiting to be combined with it.

Take for example the Bayesian Statistics and Markov-Chains, which seem to fit much better to complex medical analysis, as in Chinese Medicine, than the older methods like the Chi-squared-test.

Some research has been done on that¹, but there are still a lot of interesting combinations with Bayesian Statistics and Chinese Medicine, since our brain seems to gain knowledge in a Bayesian way.²

Also, thanks to modern research like Evidence Based Chinese Medicine (EBCM)³ the methods of Chinese medicine, although by history different from biomedicine, become more accepted by western physicians.

But for patients in our clinic and also to ourselves, one of the greatest mysteries in phytotherapy remained:

While commercial pharmaceuticals of biomedicine rarely leave a long-time effect, i.e. after discontinuing a drug like an antihypertensive one, the symptoms (essential hypertension) return, but after taking Chinese phytotherapy for a year, the blood pressure remains in a normal range.

Also most patients with multiple sclerosis stopped having new attacks and this remained true even for years after ceasing to take herbs. The same goes for many rheumatic diseases, allergies and many other diseases. Why?

In TCM we were told, this is because it treats the pattern (Zheng), not the symptoms. If patients asked why, we tell them, that the herbs just brought their body back into the stage, before the disease began.

While patients accepted this explanation, I was still wondering whether there was a scientific explanation for this lasting effect of herbs in the health of the body.

Why do the effects of plant based therapies continue, even after ceasing the drug?

Microbiology and Evolutionary Biology

The phytochemicals of a prescription are a very complicated mixture, which not only differs from plant to plant, but also differ in each year of harvest and according to soil, weather, and other conditions. Therefore their precise compositions' effects in our bodies are also very hard to analyse or standardize. Thus it seems too complicated to find out which changes exactly occur in the patient's body after some time. But this way of analysing each part, down to the trace elements in order to find out its effects originates from the early approach in pharmacy, where frequency analysis was used, while more modern Bayesian statistic looks at the whole effects. But how can we get closer to the answer of how plant ingredients work for much longer than single chemical substances?

¹ 兰州大学，硕士论文，（2017）：张彦净：基于贝叶斯方法进行中医证候诊断的研究：

<http://www.doc88.com/p-1344878139071.html> , and
贝叶斯法在医学诊断中的应用：

<https://wenku.baidu.com/view/937618c708a1284ac85043a7.html>

² Sharon Bertsch McGrayne: **THE THEORY THAT WOULD NOT DIE**, at Yale University Press (2012), pp.233-251

³Evidence-based Chinese medicine : theory and practice, by:

Jun-Hua Zhang · You-Ping Li · Bo-Li Zhang, in: Zhongguo Zhong yao za zhi, Jan 2018; and
Toward evidence-based Chinese medicine: Status quo, opportunities and challenges, Chen, Y., Zhao, C., Zhang, L. et al. Chin. J. Integr. Med. (2018). <https://doi.org/10.1007/s11655-017-2795-2>

In 2012, I (Dr Neeb) stumbled into a new field, that seemed being not much connected to Chinese medicine: The human microbiome or microbiota. For this 400-pages book, I collected the newest research about bacteria, viruses, fungi and other organisms that live in, on, and around each „planet“ which we know as a human body.

It was a surprising and shocking journey into the world of the smallest beings of which each body consists. Would you believe, that i.e. most bacteria on earth are not interested at all in us? And of those, who live in and on us, only a very small part is causing disease, while the others protect us from them. This was very different from the older view, that most bacteria are evil and need to be killed.

The truth was, that ocean of microorganisms in which our species evolved, was there - long before plants and animals came to life on the earth. In evolution multi-cell organisms arranged their cells fitting into the conditions that both single cell organisms in air, water, and soil provided for them. The higher species depended on the existence of their „old friends.“

To name a few examples: Plants needed nitrogenic-producing bacteria to grow, trees needed fungi to connect their roots, some viruses (bacteriophages) specialized in attacking the streptococcus bacteria, which would cause sore throats in humans and thus prevented this disease.

There would be hundreds of examples more that sound amazing, how important those microorganism are to our life, but still the question remains:

How is this connected to phytotherapy?

While I just became interested in this topic, one of my patients, a 30-year old worker from Russia came to my clinic, returning ten years after I had cured his asthma without reoccurrence.

But since then, he gradually caught colds and took more and more antibiotics, often without seeing his physician first. But he caught a recurring bronchitis and even pneumonias. Since each of the antibiotics seem to work ever less, his physician tried different classes of them.

Gradually his stool became softer and he developed chronic diarrhea with green excrements.

Finally, when he came to my clinic, his feces was green and tinged with blood. As I found out, he had taken all major classes of antibiotics over the last three years. After what I knew about the gut microbiome, it must have been ruined by then. Due to his permanent colds, he also was now unemployed.

I prescribed some spleen tonifying herbs as decoction (Yu Ping Feng Tang, etc.) as well as a few known to regulate the intestinal microbiome as Jiang Huang. I was worried that the reconstitution of his bowels and immune response might take a long time, but to my surprise, the patient stated after two months, that he was free of any infections now. Besides this, his excretions were of normal consistency and colour. He then suggested that the treatment could be ended, but I could not believe such a fast recovery. After altogether six month, came once more and was completely recovered and meanwhile able to work again. He did not take anything besides the decoctions. I was amazed, how good these plants worked on such a seemingly difficult case.

But meanwhile some answers came up to the effects of Chinese herbs on autoimmune diseases of the bowels.⁴

When writing my book, I found out, that many diseases of the immune system were found to be connected to the microbiome of the intestines: Infections, allergies, autoimmune and even metabolic and mental diseases seemed to be connected to the absence of certain bacteria in our bowels or the dysbiosis of the wrong microorganisms in them.

Nowadays, after DNA-sequencing (in bacteria mostly 16S-ribosomal RNAs) became much cheaper, it was possible to know those really important anaerobic bacteria, which formerly could not be found in stool-tests. So after some very successful research with the transplantation of stools of a healthy patient into diseased patients, the „Fecal microbiota transplant“ (FMT) became renown, in China invented in the 4th Century as „Huang Tang“ and later listed in the „Ben Cao Gang Mu“ of Li Shi-Zhen.

But sadly this method employed by enema, nasoduodenal tube or capsule is only used in some hospitals as a last resort, when vancomycine has lost the fight against *clostridia difficile* bacteria in autoimmune gut inflammations.

So after looking for the biological connections, I found that many antibiotics were developed from fungi, which produce those „weapons“ in their constant fight for territory against bacteria. On the other hand, lactic-acid bacteria by changing the environments PH, restrain the spread of fungi as an answer. But multi-cell organisms like Plants also produce substances against bacteria like Huang Lian's *berberine*, or to nourish them like oligosaccharides. By now, there are many known antibiotic or antimycotic substances in the pharmakopoeia of plants.

But – different from western biomedicine which has in the times of epidemics developed into a purely attacking approach, in Chinese medicine there are the concepts of attack (Gong) and supplementation (Bu).

Research has shown that our intestines' composition as compared to hunter-gatherer tribes, has not only decreased by 50% in amount and biodiversity. So maybe due to our modern food and lifestyle we created an advantage for opportunistic microbes to attack us?

Our species is a latecomer on this planet, but therefore we have more co-evolved friends than enemies among microorganisms, would it not be a smarter approach to support our many friends than to kill the few enemies and leave those areas vulnerable for new attacks?⁵

Microbiome modulation: The Bu-Fa with phytochemicals

⁴ Journal of Ethnopharmacology, Volume 162, 13 March 2015, Pages 7-13:

Red Ginseng and Semen Coicis can improve the structure of gut microbiota and relieve the symptoms of ulcerative colitis, by: Ming zhang Guo, Shuo Ding, Changhui Zhao, Xinxu Gu, et al.; <https://doi.org/10.1016/j.jep.2014.12.029>

⁵ Recurrence up to 3.5 years after antibiotic treatment of acute otitis media in very young Dutch children: survey of trial participants, in; BMJ 2009;339:b2525 , doi:10.1136/bmj.b2525, and: Older Age, Long-term Antibiotic Use Linked to Mortality Risk - Medscape - Apr 02, 2018.

Since this relation was made, we began to look for connections between patients, whose disease was connected to the gut-microbiome (and later the other microbiota, too, like skin, mouth, nose etc.).

Meanwhile some other researchers asked similar questions.⁶ So in 2014, I took part of the World Microbiome Conference in Heidelberg/Germany. Unfortunately, only other researcher who tried to connect Chinese medicine with the gut microbiome I met, was Dr Zhao Li-ping from Shanghai⁷, whose research was on the treatment of overweight Prader-Willy-patients with Chinese herbs. This is called **pre**-biotic treatment, since the phytochemicals provide better conditions for the growth of beneficial bacteria.

Everybody else was looking for a **pro**-biotic approach, where the main question was, how those known anaerobic bacteria, which were lacking could be brought alive into the patients intestines.

The Canadians built an artificial machine-gut-system, to produce artificial feces. The French thought about methane-filled capsules for the anaerobic bacteria, the Americans collected lots of data from stool samples (American Gut-Project) and so did the British. Their data gathering of the intestinal microbiota was only surpassed by a very big project from the Research Institute Shenzhen⁸.

By now, most countries are busy in collecting data, but recently, I also found a few reports, which were trying to figure out, which herbs in Chinese medicine have beneficial effects on the microbiome.⁹

But except for a broader acceptance of the FMT, it might still take many years until the technical preparation of anaerobic bacteria is available to patients. My personal concerns after participating in the conference of 2014 is, that due to the last-century-pharmaceutical approach, the conservative companies will be picking a few champions of the intestines like *Akkermansia muc.* or *Fec.*

⁶ Journal of Ethnopharmacology, Volume 179, 17 February 2016, Pages 253-264; Journal of Could the gut microbiota reconcile the oral bioavailability conundrum of traditional herbs? By: Feng Chen, Qi Wen, Jun Jiang, Hai-Long Li et al.; <https://doi.org/10.1016/j.jep.2015.12.031> Targeting the Human Genome-Microbiome Axis for Drug Discovery: Inspirations from Global Systems Biology and Traditional Chinese Medicine, by: Liping Zhao, Jeremy K. Nicholson, Aiping Lu, Zhengtao Wang, Huiru Tang, Elaine Holmes, Jian Shen, Xu Zhang, Jia V. Li, and John C. Linton, Journal of Proteome Research 2012 11 (7), 3509-3519, DOI: 10.1021/pr3001628; and: 赵立平, 张晨虹; Zhao Liping, Zhang Chenhong, 建议启动“国际华族健康微生物组研究计划”; Proposal on International Healthy Chinese Microbiome Project, 中国科学院院刊, 2017, 32(3): 251-259; Bulletin of Chinese Academy of Sciences, 2017, 32(3): 251-259, at: <https://baike.baidu.com/item/赵立平/56059>

⁸ 华大基因, <https://zh.wikipedia.org/wiki/华大基因>;

https://web.archive.org/web/20100925040752/http://english.cas.cn/Ne/CASE/200908/t20090805_44705.shtml

⁹ Ethanol extract of *Atractylodes macrocephala* Rhizoma ameliorates insulin resistance and gut microbiota in type 2 diabetic db/db mice; by: Wen-You Zhang, Huan-Huan Zhang, Chen-Huan Yu, Jie Fang, Hua-Zhong Ying, Key Laboratory of Experimental Animal and Safety Evaluation, Zhejiang Academy of Medical Sciences, Hangzhou 310013, China, <https://doi.org/10.1016/j.jff.2017.10.020>; and

Ganoderma lucidum reduces obesity in mice by modulating the composition of the gut microbiota by: Chih-Jung Chang, Chuan-Sheng Lin, Chia-Chen Lu, Jan Martel et al., in: Nature Communications volume 6, 2015 <Article number: 7489>, doi:10.1038/ncomms8489

Prausnitzii and packing them into oxygen-free capsules, thus hoping they will score the necessary goals is like mediocre local soccer-team buying two champions.

But our body with the complete microbiota is a system, like a football team that cooperates to pass the ball to the scorers. This network has a systemic effect on the network that is our body. For such a complex system, behaving like a black box, the simple extraction of plant ingredients and insulation of a few compounds is a pharmaceutical approach from the last century, that should be updated.

For me, the diagnostic approach in Chinese medicine always was a way to find out what is wrong, in the black box **without** taking it apart. If an alien would find an alarm clock, taking it apart would be less helpful to understand it, than observing the movement of the hands and its ringing.

So while supplementation of a few lacking bacteria even after solving the technical problems might have faster improvement on changing the intestinal mucosa, we do not how effective this non-systemic approach will be.

Therefore I do not think, that pro-biotic treatments in the near future will be as effective as pre-biotic therapy with plant prescriptions.

One might ask, which of the billion plants may turn out to be the right ones.

To our experience, the major role in improving the microbiota it will be the tonifying plants, a completely different approach compared to western pharmacy, where microorganisms usually are attacked.

Recent reports seem to share this view.¹⁰

What makes the permanence in Chinese medicine with plants?

Speaking of attack- if we consider the three worst inventions mankind has made, atomic bombs, biological warfare and chemical attacks – which is the worst?

Chemical attacks will be over first, since the poison will be diluted or destroyed after a while.

Much worse are the effects of radioactivity, since they can last for many generations. But when will living microbes stop to attack? If they reproduce, they will never stop, as long as there is something to feed on.

But the good news is, as long as microbes live in the kind of environment in which they evolved, they will also continue to live forever by reproducing. For example: *Escherichia coli* is normally a harmless bacterium digesting saccharose in our bowels. As long as it has to compete with all other bacteria it is harmless, but if it is alone without any competitor, it becomes inflammatory.

So reducing the biodiversity with attacking methods leads to disease, because the system becomes lopsided, while increasing the biodiversity leads to balance, which is needed for „normal“ maintainance.

¹⁰ Chinese Journal of Natural Medicines: Volume 15, Issue 4, April 2017, Pages 241-254; Impact of Qi-invigorating traditional Chinese medicines on intestinal flora: A basis for rational choice of prebiotics; by: Xiao-Meng WANG, Xiao-Bo LI, Ying PENG; <<https://doi.org/10.1016/S1875-536430041-9>>

Thus, if any disease like „essential hypertension“, of which we do not know exactly how it occurs, is caused by autoimmune and inflammatory reactions of the blood vessels by substances from the wall of the intestines (**Intestinal permeability**¹¹), the restoring of the mucosal barrier will result in ceasing of this kind of hypertension.

Since this mechanism is also said to be connected to intestinal diseases like Crohn's disease, celiac disease, but also to type 1 and type 2 diabetes, rheumatoid arthritis, spondyloarthropathies, inflammatory bowel disease, irritable bowel syndrome, schizophrenia, certain types of cancer, obesity, fatty liver, atopy and allergic diseases, among many others, the application of prebiotic plants to restore the intestinal microbiome with Chinese herbs, has to offer many more applications.

In our experience, it is no coincidence that many of those diseases above have responded with very good results in our patients.

But also, this view of the effects of phytochemicals in Chinese herbs on the microbiome would finally explain, why the treatments have long lasting effects, that even continue, when no more prescriptions are taken by the patients.

Conclusion

Since many data of healthy subjects are sampled by now¹², the next step in research might be an analysis of the intestinal microbiota in patients before and after taking Chinese herbal medicine and some follow-ups after ceasing the treatment.

The impact of this new paradigm to understand and treat diseases by developing and applying prebiotic herbal medicine could have not only an economical impact on healthcare systems in the world – but also on research directions for new pharmaceutical products and is therefore of truly earth-shattering dimensions.

2018, April 16th, Wiesbaden, Germany

Dr. Bi-Xia Yeh
Prof. Dr. Gunter Neeb

For the 50-Year Anniversary Conference of The
TIANJIN UNIVERSITY OF CHINESE MEDICINE

¹¹ https://en.wikipedia.org/wiki/Intestinal_permeability#Clinical_significance

¹² <http://www.microbiome-standards.org>; <http://www.sciencemag.org/news/2015/07/head-chinas-leading-genome-sequencing-organization-steps-down-discusses-what-s-next>