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**Fecal microbiota transplantation: Historical review and current perspective**

Leung PC *et al.* Fecal microbiota transplantation: Review and perspective

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**Abstract**

There is a growing interest in the use of fecal transplantation for chronic intestinal conditions. We aim to review the methodology and safety of fecal microbiota transplantation and the evidence to support its use in treating a variety of diseases. We reviewed the history of fecal transplantation in China and found that there were varieties of fecal material used in ancient China. The first written record on fecal treatment was found in an ancient tomb in Middle China. This paper explores the historical and current perspectives of fecal microbiota transplantation. The ancient fecal transplantations did not have any background support from life science. In those ancient days, short of knowledge about bacteria, clinicians were aiming at a change of intestinal environment. Today, we aim at a change of the intestinal microbiome.

**Key words:** Fecal transplantation; Microbiota; Intestinal microbiome; Microenvironment

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**Core tip:** There is a growing interest in the use of fecal transplantation for chronic intestinal conditions. In the article, we reviewed the history of fecal transplantation in China. in . Although the ancient fecal transplantations did not have any evidence from life science, the ancient healers were fully aware of the acting value of gastrointestinal variety. Today, researchers in the field are working on various ways to change the microbiome at different levels of the gut.

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**Introduction**

The gastrointestinal tract harbors a diversity of microflora, and any alterations may contribute to problems like chronic gastrointestinal infections and inflammatory bowel diseases[1,2]. Recently, the microflora has also been shown to be potentially responsible for cardiac, metabolic and autoimmune conditions and some neoplasms[3-5]. In 1958, Eisman *et al*[6]reported the first four cases of fecal transplantation for the control of pseudomembranous enterocolitis. The successful control of chronic diarrhea was assumed to be due to a change of the intestinal microflora.

In recent years, there is a growing interest in the use of fecal transplantation for chronic intestinal conditions, including ulcerative colitis, celiac disease, irritable bowel syndrome and *Clostridium difficile* infection[7-10]. Many assumed that fecal transplantation was new technique not realizing that it was an established practice in ancient China. We aim to review the historical methodology and safety of fecal microbiota transplantation and the evidence to support its use in treating a variety of diseases.

**HISTORICAL REVIEW OF FECAL TRANSPLANTATION IN CHINA**

The first written record on the oral use of fecal matter was contained in one of the oldest Text of Chinese Medicine excavated in an ancient tomb in Middle China, called “Fifty-two Treatment Formulae”[11]. It was estimated that the document was written in 770 BC. Some details of the preparation of a fecal product called “golden juice” were given, and it was indicated for detoxication[12]. The authors did not encounter stories about medicinal use of fecal material in other ancient cultures while searching through relevant literature (British Encyclopedia).

The next record appeared in an important classic for medical teaching in the Han Dynasty (206 BC to AD 220), and the indications given were gastrointestinal emergencies[13]. Fecal material was reported to be used during epidemics.

Ge Hong (AD 284-364), a well-known Taoist healer, compiled a treatment guide “Handbook of Emergency Conditions” in which many medicinal items and formulae containing fecal matter of human, chicken, dog, cattle, horse, *etc.* were described[12].

Subsequently, classics compiled in the following dynasties,Song (AD 960-1279), Ming (AD 1368-1644) and Qing (AD 1644-1912), all contained supplemented versions of fecal preparations, which had already been described or were new inventions[14]. Clinical applications ranged from detoxication in emergency events, removal of harmful causes in infections, treatment of severe gastrointestinal problems like uncontrolled diarrhea and vomiting and most recently as an anti-allergic decoction in severe anaphylaxis-like emergencies[15].

Many different types of “fecal medicine” have been described. A table of eleven frequently described items is given (Table 1). Over 1550 recorded prescriptions containing different fecal substances are available for scrutiny[16].

The unfavorable stigma attached to the use of fecal matter in the past is unavoidable. Obviously, the majority of the items described have become less popular, although they remain respectable. Herb Books and some senior traditional practitioners still favor these applications[16]. While it is easy to be skeptical about ancient practices and label them as simple superstition or folk lore, one may objectively analyze the logic behind the historical uses. In return to this objective exercise, lessons can be learned that may serve the current field and help the further development of fecal transplantation.

**VARIETIES OF FECAL MATERIAL USED IN ANCIENT CHINA**

Looking at the variety of fecal products and their ancient applications, their correlation with the ancient logic of Traditional Chinese Medicine could be identified as follows.

***Principle of detoxication***

This principle is using a toxic agent to counteract an intoxicated state. Ge Hong used “golden juice” in emergency gastrointestinal disorders coupled with high fever[17].

***Principle of homeopathic medicine***

This principle is using fecal material in a situation of uncontrolled continuous gastrointestinal upset. It was believed that in an event of uncertain pathological cause, pushing the clinical problem to the extreme would allow a natural defense to better develop[18].

***Principle resembling vaccination***

Life substances from the guts, *i.e.* fecal matter, were used for severe gastrointestinal problems[19].

***Principle of anti-allergy***

Skin allergy and infections caused by insects and small animals were treated with their fecal material[20].

**Procedures of fecal formulation**

The procedures described in the classic literature describing the preparation of fecal material is illustrated below.

***Simple collection and drying of fecal material***

This crude method was reserved for the droppings of insects and small animals. The products were to be used externally[20].

***Adding special herbal components to initiate specific effects***

Prescriptions of Traditional Chinese Medicine demanded one champion herb to be supported by one or more partners. Glyzrrhiza was the component widely used with human fecal matter since its most ancient description[12].

***Creating an acceptable outlook of the fecal preparation***

Detailed instructions for maintaining cleanliness and screening unfavorable components were given. As an example, Ge Hong’s well respected “golden juice” followed this procedure: (1) Feces were collected form healthy boys; (2) Clean spring water was used to form a suspension; (3) The suspension was put into a red earth vase to be buried underground for up to 12 mo; and (4) On maturity, the fecal fluid already separated into three layers: the surface yellow layer was the “golden juice,” and the middle brownish layer and the bottom debris were to be discarded.

This way of preparation must have involved fermentation not actual feces, which would have influenced the replication and selection of the microbiome involved. If “golden juice” were providing any bioactive influence, it is to be speculated whether the effect was biotic or antibiotic. Whether the juice could just be giving a special environment for microbiome adaptations remains obscure[12,20].

**Patient and public involvement**

We did not directly include patient and public involvement in this study because this study was a manuscript of historical review and current perspective; however, the database used in the study was developed with patient and public involvement and is updated by a committee that includes patient representatives.

**Discussion**

***What do we learn from the ancient history of fecal transplantation?***

The ancient fecal transplantations did not have any evidence from life science. However, healers of those days were fully aware that fecal matter may be toxic or harmful. However, under special circumstances the fecal matter could provide unexpected and favorable outcomes. This plausible explanation matches quite well with today’s practice of fecal transplantation. Today, we aim at a change of the intestinal microbiome. In those ancient days, clinicians were aiming at a change of the intestinal environment (without the knowledge about bacteria)[21,22]. The benefits from the old practice were not related to a live microbiome. It could only be the provision of a specific microenvironment through the return of unwanted metabolized wastes that went through various forms of artificial treatment.

Today, we are working on various ways to changes the microbiome at different levels of the gut for a variety of gastrointestinal disorders, which are likely to be related to odd bacterial flora or infection[23,24]. Because the microbiome in the gut represents a healthy symbiosis between the human body and the organisms, a microenvironment suitable for a stable healthy symbiotic situation is of vital importance to maintain the stability. While we may still need fecal transplant in situations when immediate results are needed, the research direction should include studies on the provision of a favorable microenvironment for the usual symbiotic microbiome. Provision of the vital microenvironment could be preventive against the loss of the normal microbiome in inflammatory conditions. A suitable microenvironment for a healthy microbiome should also be the result after fecal transplantation. In the future, creating suitable oral prescriptions acceptable to all users with the aim of maintaining a favorable microenvironment could be the research direction. Obviously, more details about the symbiotic microbiomes at different levels of the gastrointestinal tract will need to be defined first[25].

Transplantation of a living microbiome has the intention of providing active, beneficial organisms to the gut, which for various reasons has failed to maintain their satisfactory survival. An unsatisfactory microenvironment necessary for microbial replication could be the cause. After all, it has been reported that as much as 20% to 60% of the human associated microbiome is uncultivable[26]. Instead of reintroduction of the microbiome, which is difficult to control and lacks standards, a satisfactory restoration of the microenvironments in the gut might be an alternative. With a suitable microenvironment, the spontaneous replication of the original microbiome that should have remained in small quantities would become possible[27].

The strength of the study was found in the basis of modern therapy from ancient records. The limitation of the study was that more ancient references would strengthen the basis of today’s practice of fecal transplantation.

**Conclusion**

Ancient fecal transplantations were not supported by evidence from life science. However, healers of those days were fully aware that even though fecal matter may be toxic or harmful, under special circumstances it could provide unexpected and beneficial outcomes. Today, we aim to change the intestinal microbiome. In those ancient days without knowledge of bacteria, clinicians aimed to change the intestinal environment.

**References**

1 **Smits LP**, Bouter KE, de Vos WM, Borody TJ, Nieuwdorp M. Therapeutic potential of fecal microbiota transplantation. *Gastroenterology* 2013; **145**: 946-953 [PMID: 24018052 DOI: 10.1053/j.gastro.2013.08.058]

2 **Dethlefsen L**, McFall-Ngai M, Relman DA. An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature* 2007; **449**: 811-818 [PMID: 17943117 DOI: 10.1038/nature06245]

3 **Tremaroli V**, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. *Nature* 2012; **489**: 242-249 [PMID: 22972297 DOI: 10.1038/nature11552]

4 **Mills KH**. TLR-dependent T cell activation in autoimmunity. *Nat Rev Immunol* 2011; **11**: 807-822 [PMID: 22094985 DOI: 10.1038/nri3095]

5 **Wiedermann CJ**, Kiechl S, Dunzendorfer S, Schratzberger P, Egger G, Oberhollenzer F, Willeit J. Association of endotoxemia with carotid atherosclerosis and cardiovascular disease: prospective results from the Bruneck Study. *J Am Coll Cardiol* 1999; **34**: 1975-1981 [PMID: 10588212 DOI: 10.1016/s0735-1097(99)00448-9]

6 **Eiseman B**, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery* 1958; **44**: 854-859 [PMID: 13592638]

7 **Gough E**, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. *Clin Infect Dis* 2011; **53**: 994-1002 [PMID: 22002980 DOI: 10.1093/cid/cir632]

8 **Brandt LJ**. American Journal of Gastroenterology Lecture: Intestinal microbiota and the role of fecal microbiota transplant (FMT) in treatment of C. difficile infection. *Am J Gastroenterol* 2013; **108**: 177-185 [PMID: 23318479 DOI: 10.1038/ajg.2012.450]

9 **Vermeire S,** Joossens M, Verbeke K, Hildebrand F, Kathleen M, Broeck KV. Sa1922 Pilot study on the safety and efficacy of faecal microbiota transplantation in refractory Crohn’s disease. *Gastroenterology* 2013; **142**: S-360 [ DOI: 10.1016/S0016-5085(12)61356-0]

10 **Borody TJ**, Khoruts A. Fecal microbiota transplantation and emerging applications. *Nat Rev Gastroenterol Hepatol* 2011; **9**: 88-96 [PMID: 22183182 DOI: 10.1038/nrgastro.2011.244]

11 **Shi XH**. Fecal therapy and Fecal Microecology. *Zhongguo Weishengtaixue Zazhi* 2017; **11**: 128-131

12 **Ge Hong**. Handbook of Emergency Conditions. 1st edition. Beijing: China Chinese Medicine Publisher, 2016

13 **Zhang ZJ**. Interpretation of Jin-Kui. 1st edition. Beijing: Peoples Health Publisher, 2005

14 **Qiu LX.** Intelligent use of child feces. *Guangming Zhongyi Zazhi* 2012; **27**: 2069-2070

15 **Yang YS,** Wang ZK. Advance in study on fecal microbiota transplantation. *Weichangbingxue Zazhi* 2014, **19**: 1-5 [DOI: 10.3969/j.issn.1008-7125.2014.01.001]

16 **Su ZQ,** Zhang WJ, Zhang YS, Wang DC, Meng XM, Wang WX, Wu JR, Li J, Ding X. Literature Study on Fecal Class Chinese Medicines and their application in the ancient prescriptions. *Beijing Zhongyiyao Daxue Xuebao Zazhi* 2016; **39**: 376-382 [DOI: 10.3969/j.issn.1006-2157.2016.05.006]

17 **Yin H.** Fundamentals of Traditional Chinese Medicine. 1st edition. Beijing: Foreign Language Press Beijing, 1992

18 **Wheeler CE**. An Introduction to the Principles and Practice of Homeopathy. London: London Publisher, 1983

19 **O’brien KA,** Xue CC. A Comprehensive Guide to Chinese Medicine. In: The Theoretical Framework of Chinese Medicine. Singapore: World Scientific Publisher, 2003: 47-84 [DOI: 10.1142/9789812794987\_0003]

20 **Shi XH**. Feces Therapy and Fecal Microecology. *Zhongguo Weishengtaixue Zazhi* 2017; **29**: 128-131

21 **Zhang F**, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? *Am J Gastroenterol* 2012; **107**: 1755; author reply p.1755-1755; author reply p.1756 [PMID: 23160295 DOI: 10.1038/ajg.2012.251]

22 **El-Matary W**, Simpson R, Ricketts-Burns N. Fecal microbiota transplantation: are we opening a can of worms? *Gastroenterology* 2012; **143**: e19; author reply e19-e19; author reply e20 [PMID: 22732575 DOI: 10.1053/j.gastro.2012.04.055]

23 **Bakken JS**, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, Kelly C, Khoruts A, Louie T, Martinelli LP, Moore TA, Russell G, Surawicz C; Fecal Microbiota Transplantation Workgroup. Treating Clostridium difficile infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol* 2011; **9**: 1044-1049 [PMID: 21871249 DOI: 10.1016/j.cgh.2011.08.014]

24 **Frank DN**, Robertson CE, Hamm CM, Kpadeh Z, Zhang T, Chen H, Zhu W, Sartor RB, Boedeker EC, Harpaz N, Pace NR, Li E. Disease phenotype and genotype are associated with shifts in intestinal-associated microbiota in inflammatory bowel diseases. *Inflamm Bowel Dis* 2011; **17**: 179-184 [PMID: 20839241 DOI: 10.1002/ibd.21339]

25 **Arumugam M**, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, de Vos WM, Brunak S, Doré J; MetaHIT Consortium, Antolín M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Mérieux A, Melo Minardi R, M'rini C, Muller J, Oozeer R, Parkhill J, Renault P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. *Nature* 2011; **473**: 174-180 [PMID: 21508958 DOI: 10.1038/nature09944]

26 **NIH HMP Working Group**; Peterson J, Garges S, Giovanni M, McInnes P, Wang L, Schloss JA, Bonazzi V, McEwen JE, Wetterstrand KA, Deal C, Baker CC, Di Francesco V, Howcroft TK, Karp RW, Lunsford RD, Wellington CR, Belachew T, Wright M, Giblin C, David H, Mills M, Salomon R, Mullins C, Akolkar B, Begg L, Davis C, Grandison L, Humble M, Khalsa J, Little AR, Peavy H, Pontzer C, Portnoy M, Sayre MH, Starke-Reed P, Zakhari S, Read J, Watson B, Guyer M. The NIH Human Microbiome Project. *Genome Res* 2009; **19**: 2317-2323 [PMID: 19819907 DOI: 10.1101/gr.096651.109]

27 **Johnsen PH**, Hilpüsch F, Cavanagh JP, Leikanger IS, Kolstad C, Valle PC, Goll R. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *Lancet Gastroenterol Hepatol* 2018; **3**: 17-24 [PMID: 29100842 DOI: 10.1016/S2468-1253(17)30338-2]

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**Table 1 Eleven Chinese Medicine fecal compositions**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No** | **Official name** | **Classic medical monograph** | **Fecal origin** | **Property and flavor** | **Clinical indications** |
| 1 | White clove | Yunnam Bencas (Herb Book) | Sparrow | Bitter, Warm | Gastrointestinal disorder |
| 2 | Silk worm sand | Bencao Gangmu (Herb Dictionary) | Silk worm | Sweat, Bitter, Warm | Vomit, diarrhea, rheumatism |
| 3 | Chicken white | Ancient Bencao (Ancient Herb Book) | Chicken | Bitter, Salty, Cold | Detoxicate, diuretic |
| 4 | Golden juice | Handbook of Emergency Conditions | Human male | Slight-bitter, Cold | Detoxicate, severe fever |
| 5 | Bipolar pin | Handbook of Distinguished Clinician | Rat | Bitter, Salty | Abdominal cramp, fever |
| 6 | Perfume of Dragon | Ancient Bencao (Herb Book) extension | Whale | Sweet, Sour, Warm | Analgesia, diuretic, bronchial spasm |
| 7 | Human Yellow | Special Bencao (Herb Book) | Human | Bitter, Salty, Cold | Detoxicate, severe infection |
| 8 | Moon Sand | Original classic | Rabbit | Bitter, Cold | External infection |
| 9 | Penta Crease | Original Bencao (Herb Book) | Small bat | Sweat, Bitter, Warm | External use |
| 10 | Moonlight Sand | Special Bencao (Herb Book) | Bat | Bitter, Cold | External use, eye infection |
| 11 | Flying Dragon | Bencao Gangmu (Herb Dictionary) | Pigeon | Bitter, Warm | Infection |