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## Fecal microbiota transplantation: Historical review and current 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. The first written record on the oral use of fecal matter was in 770 BC. 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<sup>[1,2]</sup>. Recently, the microflora has also been shown to be potentially responsible for cardiac, metabolic and autoimmune conditions and some neoplasms<sup>[3-5]</sup>. In 1958, Eisman *et al*<sup>[6]</sup> 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<sup>[7-10]</sup>. 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"<sup>[11]</sup>. 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<sup>[12]</sup>. 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<sup>[13]</sup>. 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<sup>[12]</sup>.

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<sup>[14]</sup>. 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<sup>[15]</sup>.

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<sup>[16]</sup>.

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<sup>[16]</sup>. 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.

**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

**Principle of detoxication**

This principle advocates the use of a toxic agent to counteract an intoxicated state. Ge Hong used “golden juice” in emergency gastrointestinal disorders presenting with high fever<sup>[17]</sup>.

**Principle of homeopathic medicine**

This principle advises the use of fecal material in a situation of uncontrolled repeated 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<sup>[18]</sup>.

**Principle resembling vaccination**

Life substances from the guts, *i.e.* fecal matter, were used for severe gastrointestinal problems resistant to standard treatment<sup>[19]</sup>.

**Principle of anti-allergy or anti-poisonous invasion**

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

## PROCEDURES OF FECAL FORMULATION IN ANCIENT CHINA

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<sup>[20]</sup>.

**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. Glycyrrhiza was the component widely used with human fecal matter in the most ancient description<sup>[12]</sup>.

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

Detailed instructions for maintaining cleanliness and filtering out unfavorable components were given. As an example, Ge Hong’s well respected “golden juice” followed this procedure: (1) Feces were collected from 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 and the fecal matter 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 providing a special environment for the gastrointestinal microbiome to change, adapt and reorganize



deserves careful speculations<sup>[12,20]</sup>.

## DISCUSSION

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

The ancient fecal transplantations did not have any evidence related to modern 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)<sup>[21,22]</sup>. The concept and benefits from the old practice were not linked with today's microbiome. Ancient fecal treatment could only be the provision of a specific gastrointestinal environment through the return of unwanted metabolized food and various forms of artificial treatment have been completed (like to "golden juice") before its application as a drug.

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<sup>[23,24]</sup>. 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 micro-environment 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<sup>[25]</sup>.

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<sup>[26]</sup>. 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 suitable quantities would become possible<sup>[27]</sup>.

## CONCLUSION

Ancient fecal transplantations were not supported by life science evidences. 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. Current research on intestinal microbiomes could include study of the intestinal environment that normally sustain their healthy growth.

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