Research Progress and Analysis of Moxibustion in Prevention and Treatment of Acute Infectious Diseases

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Abstract
To introduce and evaluate current research progress of moxibustion in the prevention and treatment of acute infectious diseases, related literature in CNKI, Wanfang Data, and SinoMed was retrieved and analyzed by the present study. Results showed abundant studies on the mechanism of action of moxibustion in the prevention and treatment of acute infectious diseases with remarkable clinical efficacy. The present study also summarizes the commonly-occurring problems and found out the deficiencies in existing studies in hope of providing more reference for further research.

Keywords: Acute infectious diseases, Chinese medicine, experimental research, literature research, mechanism of moxibustion

INTRODUCTION
With advances in modern medicine, various infectious diseases have been largely brought under control, but some have not completely eliminated and some are still emerging.

Moxibustion therapy has played an important part in the prevention and treatment of epidemics in traditional Chinese medicine (TCM). In moxibustion, moxa smoke kills germs and cauterizing reinforces healthy qi and eliminates pathogenic factors, so as to harmonize Yin and Yang, “prevent disease before its onset, control development of existing disease and prevent disease relapse after recovery.”[1]

In the last half century, although moxibustion therapy was used to prevent and treat major outbreaks of severe infectious diseases, its value is controversial in intervention of related diseases. Studies on the infectious diseases treated by moxibustion included epidemic hemorrhagic fever (EHF), influenza, and dysentery have been published, but there has been insufficient systematic review of studies on moxibustion in the prevention and treatment of acute infectious diseases. The authors hope to provide more reference for future research, thus to retrieve and analyze related literature to introduce research progress of moxibustion in the prevention and treatment of acute infectious diseases and supplement the deficiencies in existing studies.

MATERIALS AND METHODS

Literature sources and retrieval strategy
Databases including CNKI, Wanfang data and SinoMed were searched for and the diseases searched for were acute infectious diseases included in Law of the People’s Republic of China on the Prevention and Treatment of Infectious Diseases (revised after Announcement No. 1, 2020 by the National Health Commission of the People’s Republic of China). Advanced search was carried out using the computer retrieval formula of “灸法” or “艾灸” or “针灸”+ the name of acute infectious disease (“灸法” and “艾灸” refer to moxibustion, “针灸” refers to acupuncture and moxibustion).

Inclusion criteria
(1) Medical records of moxibustion for the prevention and treatment of acute infectious diseases; (2) animal
experiment on moxibustion for the prevention and treatment of acute infectious diseases; (3) clinical observation of moxibustion in the prevention and treatment of acute infectious diseases; and (4) studies on the mechanism of action of moxibustion in the prevention and treatment of acute infectious diseases.

Exclusion criteria
(1) Literature review; (2) studies with unspecified diagnosis of disease; (3) studies that used acupuncture combined with moxibustion and had only pre- and post-treatment comparison and no intergroup comparison; and (4) moxibustion studies that used sulfur or medicated threads instead of moxa.

Studies included
The above databases were searched for and full-text literature that met the inclusion criteria was read, and 25 eligible papers were obtained after screening by the exclusion criteria. Study subjects and methods are shown in Table 1. One of the papers involved two kinds of studies, namely case studies and clinical case series observation.[2] Twelve diseases were identified, with EHF occurring frequently.

Literature analysis and summary
Mechanism of action of moxibustion in epidemic prevention
In terms of study subjects, there were a total of 9 papers about the mechanism of action of moxibustion in intervention of acute infectious diseases that included EHF, leptospirosis, dysentery and influenza virus pneumonia, and all of the studies were animal randomized controlled trials. After full-text reading, the authors analyzed and summarized the pathways at different levels in the mechanism of action of moxibustion in the prevention and treatment of acute infectious diseases.

Enhancing the immune activity of body cells
In an experimental study by Song Xiaoge on moxibustion in the treatment of rats with EHF,[1] the activity of erythrocyte C3b receptor rosette (E-C3bRR) was investigated. 33 Wister rats were used in the study. The number of yeast rosettes in 200 erythrocytes observed under a microscope was counted experimentally, converted to percentages and used as indicator of the erythrocyte C₃b receptor activity. Virus inoculation and treatment were not performed for rats in the blank group, and EHF virus was inoculated in both the infection group and the treatment group. Moxibustion was not given in the infection group. Animals in the treatment group were treated as follows: At day 2 after EHF virus inoculation, moxibustion was performed at the kidney acupoint area for 30 min, once daily for 7 days. At 14 days after inoculation of EHF virus, the E-C3bRR rate was calculated as shown above.

The E-C3bRR rate (X ± standard deviation [SD]) was 4.23 nda. 07, 6.55 nda. 76 and 9.13 nda. 67 in the normal (blank) group, infection (control) group and treatment (moxibustion) group, respectively. It was higher in the infection group than in the normal group (P < 0.05) and was higher in the treatment group than in the infection group (P < 0.02), indicating that the activity of E-C3bRR was increased in the rats infected with EHF virus compared to that in the healthy rats, and moxibustion was effective in enhancing the activity of E-C3bRR.

In a study of the same type by the same authors,[4] percentage of peritoneal macrophage (PM) phagocytosis was used as another indicator. Twenty-two rats were used in the study. With exactly the same experimental design with the previous study, 120–160 macrophages were obtained experimentally and counted under a microscope at 14 days after viral inoculation, and the percentage of PM phagocytosis was calculated.

The percentage of PM phagocytosis (X ± SD) was 27.63 goc. 78, 19.00 goc. 20 and 29.8 dgo. 20 in the normal (blank) group, infection (control) group and treatment (moxibustion) group, respectively. It was higher in the treatment group than in the infection group (P < 0.05), indicating that moxibustion could significantly enhance the phagocytic function of PMs in rats infected with EHF virus.

The E-C3bRR rate was one of the indicators reflecting erythrocyte immune function, and PMs themselves participated in cell immunity. Moxibustion improved the activity of E-C3bRR and the phagocytic function of PMs, suggesting its potential in boosting immunity of the body.

Correct fluid disorders and stabilize the inner environment of the body
There was a total of 4 papers on this subject and all studies were animal randomized controlled trials that used EHF virus as the challenge virus. Immunofluorescence assay and radioimmunoasay were performed. There were a normal (blank) group, an infection (control) group and a treatment (moxibustion) group in the trials, with 10 rats in each group. Except for the number of animals and the indicators, the study design was the same with the previous studies. Comparison of indicators in the three groups was described below with the following data.

In a study with norepinephrine (NE) and dopamine (DA) as indicators (X ± s, ng/ml),[13] NE and DA were 192.66 emlt. 79 and 840.02 emlt. 73, respectively, in the normal group; 265.91 uplt. 33 and 1159.07 9plt. 01, respectively, in the

| Study subjects         | Study methods            | Number of papers (%) |
|------------------------|--------------------------|----------------------|
| Mechanism of action    | Animal randomized controlled trial | 9 (37.50) |
| Efficacy evaluation    | Clinical randomized controlled trial | 6 (25.00) |
|                        | Clinical case study       | 3 (12.50) |
|                        | Clinical case series observation | 6 (25.00) |
|                        | Animal randomized controlled trial | 1 (4.17) |
infection group; and 194.74 ± 56.12 and 816.50 ± 56.91 respectively in the treatment group. The levels of NE and DA were significantly higher in the infection group than in the normal group ($P_{\text{NE}} < 0.01, P_{\text{DA}} < 0.001$) and they were significantly lower in the treatment group than in the infection group ($P_{\text{NE}} < 0.05, P_{\text{DA}} < 0.001$), with no significant difference between treatment and normal groups ($P > 0.05$). The above data indicated that the levels of NE and DA increased in rats infected with EHF virus, and moxibustion reduced the levels, hence able to promote the levels of NE and DA to return to normal.

In a study with 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) used as indicators, the data also suggested that the levels of 5-HT and 5-HIAA were significantly higher in the infection group than in the normal group ($P_{\text{5-HT}} < 0.05, P_{\text{5-HIAA}} < 0.001$), and the levels were significantly lower in the treatment group than in the infection group ($P_{\text{5-HT}} < 0.001, P_{\text{5-HIAA}} < 0.05$). The level of 5-HT was not significantly different ($P_{\text{5-HT}} > 0.05$) and the level of 5-HIAA was significantly different ($P_{\text{5-HIAA}} < 0.05$) between treatment and normal groups. In addition, it was shown in a related study that the level of 5-HT had the same pattern of changes in lung and kidney tissues as in the above plasma samples. These data indicated that the level of 5-HT in plasma increased in rats infected with EHF virus, and moxibustion reduced the level, hence able to promote the level of 5-HT in plasma and lung and kidney tissues to return to normal.

The same pattern of changes was revealed in studies using the metabolite (TXB$_2$) of thromboxane (TXA$_2$), the metabolite (6-K-PGF$_1$) of prostacyclin (PGI$_1$), and the TXB$_2$/6-K-PGF$_1$ ratio as indicators as in the above studies.

Studies under this category were performed by Tang Zhaoliang et al. In these studies, the roles of the two catecholamine adrenergic neurotransmitters – NE and DA, the two monoamine neurotransmitters – 5-HT and 5-HIAA, and the two prostaglandins – TXB$_2$ and 6-K-PGF$_1$ in the body were described in detail. Results of the studies suggested that in the treatment of experimental animals with EHF, moxibustion had the effects of correcting fluid disorders and stabilizing the inner environment of the body, but there were few descriptions of the correlation between moxibustion and the disease course of EHF. Whether this mechanism of action can be supported in the treatment of other acute infectious diseases is to be further investigated.

**Inducing production of interferons and exerting antiviral effects**

There was a total of 3 papers on antiviral effects of moxibustion in the treatment of acute infectious diseases. The diseases in question were influenza, leptospirosis, and bacillary dysentery, and the studies were animal randomized experimental studies. In one of the studies, there were four groups, namely acupuncture group, treatment group, infection (control) group and blank control group. Potency of serum interferon in mice was used as the indicator and microdose cytopathogenic effect inhibition assay was carried out to determine serum interferon in mice. Animals in the moxibustion group were treated as follows: The Guanyuan point was selected for direct moxibustion with a 10–15 mg moxa cone, 4 cones at a time, once daily for 3 days. At day 3, mice were anesthetized lightly with ether after moxibustion, and under this condition, the nasal cavity of mice was attacked with influenza virus PR$_8$. Then, mice were treated with moxibustion for 3 times using the same method as above. Blood was collected from the mice after 48 h for the detection of serum interferon. It is worth mentioning that in the studies on mechanism of action that were included in this review, the experimental method in this study was one of the few methods in which moxibustion was carried out before viral inoculation for animals, and its results were significant for explaining the mechanism of action of moxibustion in the prevention of infection with influenza virus.

Based on experimental results, the potency of interferon ($\bar{X} \pm SD$) was 4.22 erf. 23, 2.63 erf. 22 and 2.93 erf. 19 in the moxibustion, infection and blank control groups, respectively. It was lower in the infection group than in the blank control group ($P < 0.05$), and was significantly higher in the moxibustion group than in the infection group ($P < 0.001$), indicating that moxibustion increased the potency of interferon in mice.

It is well-known that as a cytokine, serum interferon has broad-spectrum antiviral activity. Inducing production of interferons is an important approach of moxibustion to exert its antiviral effects. In this paper, the phagocytic function of PMs in mice was also investigated experimentally, and a possibility was proposed that interferons activated macrophages to improve immune function, thus it can be reasonably inferred that further investigation of the correlation between the antiviral effects of moxibustion in the prevention and treatment of acute infectious diseases and the mechanism of immune response is another approach to studying the mechanism of action of moxibustion. In mechanism studies on moxibustion exerting antiviral effects in intervention in other infectious diseases, there were also studies with other indicators demonstrating the antiviral mechanism of moxibustion, including studies on indicators of antibody titer and on endotoxins. Although further mechanism studies were not as definite as studies on interferons, they affirmed the antiviral effects of moxibustion in the prevention and treatment of acute infectious diseases.

**Efficacy evaluation of moxibustion in the prevention and treatment of acute infectious diseases**

In terms of study subjects, there were a total of 15 papers on efficacy evaluation of moxibustion in the prevention and treatment of acute infectious diseases and the study designs were clinical randomized controlled trial, clinical case study, clinical case series observation, and animal randomized controlled trial. Eleven diseases were involved, including EHF, viral hepatitis, hand-foot-and-mouth disease, malaria, rubella, hepatic echinococcosis, COVID-19, severe acute respiratory syndrome (SARS), amoebic dysentery, epidemic parotitis, and leptospirosis. It can be seen that
moxibustion had a broad spectrum of disease in the prevention and treatment of acute infectious diseases.

Clinical efficacy of moxibustion in the treatment of acute infectious diseases
In clinical observations included in the review, the total effective rate of moxibustion was 88.07% in the treatment of diseases. The effects mainly included improving symptoms and shortening the course of disease [Take a study on moxibustion in the treatment of 6 patients with acute amoebic dysentery as an example], as well as reducing sequelae [Take a study on moxibustion in the treatment of SARS as an example]. In this study by Zhao Hong, moxibustion was used to treat 9 SARS patients in recovery, and it was shown that moxibustion significantly improved sequelae of SARS, including low fever, chest tightness, fatigue, head and body aches, chest and abdominal distension pain, anorexia, constipation). In treatment of diseases, functions of the respiratory, digestive and urinary systems were improved, especially those of the digestive system, accounting for 66.67% [Table 2].

The assessment of study design in trials on moxibustion in intervening acute infectious diseases
According to preliminary classification of literature, there were only 6 clinical randomized controlled trials, accounting for 42.86% in clinical studies. In nonrandomized controlled studies, there were narrative reports of small-scale case series and case studies, and one of the papers was about two types of studies, namely case series observation and case study. Diseases involved are shown in Table 3. The study design was assessed considering several elements by further analyzing the literature.

1. Diagnostic criteria and efficacy indicator design: In all of the clinical trials included in the review, only 42.86% of the trials had definite criteria of disease diagnosis and efficacy indicator judgment, among which the trials on COVID-19 accounted for 50%. In most of the trials, there were shortcomings as follows: lack of diagnostic criteria; lack of standardization in efficacy indicator judgment, i.e., using subjective indicators and not using current reference standards formulated in guidelines or by international conferences.

2. Design of control group: In all of the clinical observations included in the review, the controlled studies and the randomized controlled studies accounted for 42.86% each, and the rest of the studies had indefinite control groups. In addition, in six of the randomized controlled studies, there were 4 studies with strictly balanced control and statistical methods to support insignificant inter-group differences, accounting for 66.67%. The rest of the studies were flawed in design of control group and thus less persuasive.

3. Design of treatment group: In self-controlled studies, since it was considered in exclusion of literature that the controlled studies using treatment with not only moxibustion could not support the effectiveness of moxibustion, the studies using treatment with only moxibustion were included in the review, accounting for 42.86%. Design of treatment group in randomized controlled studies is shown in Table 4. There were mainly a moxibustion group, a Western medicine group, and a group of moxibustion combined with Western medicine.

In addition, there was also an animal randomized controlled trial that was one of the few studies included in the review in which moxibustion was carried out before attack of pathogens. The disease studied was leptospirosis and expression of the c-Fos gene in the medulla oblongata of guinea pigs infected with leptospira was used as an indicator to show the degree of injury in the animals (expression of the c-Fos gene indicates noxious stimulation in the central and peripheral nervous system).

OmpL39 antigen injection was performed in the trial except for moxibustion (The Zusanli and Guanyuan points were selected. The Zusanli point was used for grain-sized moxibustion, 3 moxa cones at a time, 0.5 mg per cone; and the Guanyuan point was used for suspended moxibustion for 5 min. Moxibustion was carried out once every other day). There were a group of moxibustion + OmpL39 antigen injection, an OmpL39 antigen injection group, a moxibustion group and a control group. The effect of different prevention methods

Table 2: Improvement of functions of various systems by moxibustion

| Systems         | Functions improved                                                                 | Diseases involved                                  | Number of papers (%) |
|-----------------|-------------------------------------------------------------------------------------|----------------------------------------------------|----------------------|
| Digestive       | Hepatic functions (nausea, vomiting, abdominal distension, fatigue, ascites and liver echinococci calcification) and gastrointestinal functions (constipation, diarrhea, abdominal pain, poor appetite, and emaciation) | Viral hepatitis, hand-foot-mouth disease, hepatic echinococcosis, SARS, amoebic dysentery and COVID-19 | 8 (66.67)            |
| Respiratory     | Cough and chest tightness                                                           | COVID-19                                           | 1 (8.30)             |
| Urinary         | Renal functions (oliguria, dysuria, and proteinuria)                                 | Epidemic hemorrhagic fever                         | 3 (25.00)            |

SARS: Severe acute respiratory syndrome
was observed on visceral bleeding and c-Fos expression in guinea pigs attacked by viable leptospira. Results showed that visceral bleeding and c-Fos expression were reduced in the moxibustion group, the group of moxibustion + OmpL39 antigen injection and the OmpL39 antigen injection group compared to the control group ($P < 0.05$); they were reduced in the group of moxibustion + OmpL39 antigen injection and the OmpL39 antigen injection group compared to the moxibustion group ($P < 0.05$); expression of the c-Fos gene was significantly reduced in the group of moxibustion + OmpL39 antigen injection compared to the OmpL39 antigen injection group ($P < 0.05$). It was suggested that therapy with moxibustion alone was effective and moxibustion combined with antigen injection was more effective in reducing the noxious manifestations in the course of leptospirosis. However, since it was an animal trial that could not provide evidence for clinical efficacy, it could only support the therapeutic effect of moxibustion in the treatment of animals infected with leptospira and provide reference for further clinical study.

### Discussion

Although it was revealed that[23] infectious disease was not the high-frequency disease in the spectrum of disease intervened by moxibustion, it was found out in the studies included in this review that there was a wide scope of acute infectious diseases intervened by moxibustion, and moxibustion showed effect generally in the treatment of these diseases. According to this review, there were still shortcomings in the studies on moxibustion in the treatment of acute infectious diseases as follows: (1) There were few homogeneous studies evaluating the efficacy of moxibustion in treating certain disease, making it difficult to thoroughly evaluate the efficacy of moxibustion in the prevention and treatment of acute infectious diseases and to obtain evidence for evidence-based treatment of each disease. (2) There was almost no study on different diseases that elaborated the same mechanism of action, making it difficult to show universality of the epidemic prevention mechanism. There is currently no solution to the above two problems, thus apart from the approaches proposed in this paper, new methodology is needed concerning this subject for more objective and reliable data evaluation on existing studies.

Moreover, the studies on the diseases involved in this review were still isolated except those wide-scope and standard studies on EHF. Therefore, the authors believe that studies on other diseases may learn from the experience as follows. (1) After selection of a disease, the study protocol is designed based on an evaluation indicator with high disease relevance or commonly used in guidelines. (2) In performance of a mechanism study, efficacy indicators can also be used. For instance, in a study on the effect of moxibustion on 5-HT in lung tissue of rats infected with EHF virus, evaluation on pulmonary index can be included to explore the relevance between the therapeutic effect and the mechanism of action, so that the epidemic prevention mechanism of moxibustion can be more convincing. (3) In performance of related studies, correlation study can be performed on several indicators for which satisfactory effect has been obtained. For instance, evaluation indicators of relevance between different mechanisms can be added, or, further study can be carried out on current study results about the prevention mechanism of moxibustion for a certain disease (EHF), in hope of elaborating the relationship among and the focus in the antiviral mechanism, neurohumoral regulatory effect, and immunity-enhancing effect. After outbreak of the COVID-19, papers discussing the feasibility of using moxibustion to prevent and treat this disease proposed that the immunity-enhancing effect might be the basis of the antiviral effect of moxibustion. As is known to all, the nervous, endocrine, and immune systems have an impact on each other, but it can be seen from this review that there was no correlation study on such mechanism in specific infectious disease, warranting further investigation.

In addition, it is noticed that in previous studies, although various diseases were involved in clinical studies on moxibustion in the prevention and treatment of infectious diseases, high-quality studies with efficacy observation were few, thus, it is difficult to provide a reliable and systematic study basis for a persuasive result. The reasons lie in inadequate

### Table 3: Categories of clinical studies on moxibustion in intervening acute infectious diseases

| Types of literature                  | Diseases involved                                      | Number of papers (%) |
|--------------------------------------|--------------------------------------------------------|----------------------|
| Clinical randomized controlled trial | EHF, viral hepatitis and hand-foot-mouth disease       | 6 (42.86)            |
| Case series observation              | COVID-19, SARS, amoebic dysentery, epidemic parotitis and hepatic echinococcosis | 6 (42.86)            |
| Case study                          | Malaria, rubella and hepatic echinococcosis            | 3 (21.43)            |

EHF: Epidemic hemorrhagic fever, SARS: Severe acute respiratory syndrome

### Table 4: Categories of design of treatment group

| Groups                                                      | Diseases involved                  | Number of papers (%) |
|-------------------------------------------------------------|-----------------------------------|----------------------|
| Western medicine group and group of moxibustion combined with Western medicine | EHF                               | 2 (14.29)            |
| Moxibustion group, Western medicine group and group of moxibustion combined with Western medicine | EHF and hand-foot-mouth disease    | 3 (21.43)            |
| Moxibustion group and group of moxibustion combined with Western medicine | Viral hepatitis                    | 1 (7.14)             |

EHF: Epidemic hemorrhagic fever
emphasis on methodology and nonstandard study design that were common to these studies. Most studies included in this review were observations on symptom improvement and statistics about cure rate, and few of them included prevention observations, which indicates that clinical study on moxibustion in the prevention of acute infectious diseases is still a challenge.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Translator: Shuna Zhang (张淑娜)

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