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Research Progress on Modeling Methods of TCM Syndromes in Experimental Animals

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Abstract

TCM syndrome is the core of TCM treatment based on syndrome differentiation. Modeling of TCM syndromes in experimental animals is an important bridge connecting TCM basic theory and modern medical research, and also a key technical support for carrying out TCM efficacy evaluation, pathogenesis exploration, and new drug research and development. With the continuous advancement of TCM modernization, the modeling technology of TCM syndromes in experimental animals has been gradually improved, and the modeling methods have shown a trend of diversification, standardization and refinement. This article systematically sorts out the basic principles and core modeling methods of TCM syndrome modeling in experimental animals, focuses on reviewing the specific modeling technologies, application status and research hotspots of common clinical TCM syndromes (such as qi deficiency syndrome, blood deficiency syndrome, yin deficiency syndrome, yang deficiency syndrome, phlegm-dampness syndrome, blood stasis syndrome, etc.), analyzes the existing problems in the current modeling process (such as inconsistent modeling standards, insufficient syndrome stability, imperfect evaluation system, etc.), and looks forward to the development direction of modeling technology in the future, so as to provide a reference for the standardized application of experimental animal syndrome modeling in TCM basic research.

Keywords

Experimental animals; TCM syndromes; Modeling methods; Research progress; TCM modernization

Introduction

TCM treatment based on syndrome differentiation is the core feature of the TCM diagnosis and treatment system. As a summary of the nature of diseases in TCM, "syndrome" is a comprehensive pathological state of dysfunction of zang-fu organs, qi, blood and body fluids under the action of pathogenic factors. Due to ethical restrictions, large individual differences and complex pathogenesis in human clinical research, it is difficult to accurately reveal the nature of TCM syndromes and the mechanism of action of TCM. Therefore, experimental animal models have become an important tool for TCM basic research.

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Modeling of TCM syndromes in experimental animals refers to constructing animal models with TCM "syndrome" characteristics by means of artificial intervention to simulate TCM etiology and pathogenesis, making experimental animals show physiological and pathological changes similar to human TCM syndromes. Its core value lies in converting the abstract theory of TCM "syndrome" into quantifiable and observable experimental objects, providing a standardized platform for the verification of TCM basic theory, the study of syndrome evolution rules, and the efficacy evaluation of TCM and acupuncture interventions.

Since the 1960s, Chinese scholars have begun to explore the modeling technology of TCM syndromes in experimental animals. From the initial single-factor modeling (such as spleen deficiency syndrome induced by bitter-cold and purgative drugs), it has gradually developed into various methods such as multi-factor composite modeling, disease-syndrome combination modeling, and gene editing modeling. The scientificity, stability and clinical relevance of modeling have been continuously improved. With the advancement of the "Implementation Plan for Major Projects for the Revitalization and Development of Traditional Chinese Medicine", the requirements for standardization and normalization of experimental animal syndrome models in TCM basic research are increasing. It is urgent to systematically sort out the existing modeling methods, clarify the advantages and disadvantages of various modeling technologies, and provide references for subsequent research. Combined with relevant studies included in CNKI and Wanfang databases in recent years, this article comprehensively reviews the research progress of modeling methods of TCM syndromes in experimental animals, in order to provide reference for the conduct of TCM basic research.

1 Basic Principles of TCM Syndrome Modeling in Experimental Animals

Modeling of TCM syndromes in experimental animals is different from modern medical disease modeling. Its core is to follow the guidance of TCM theory and simulate the formation process of "syndrome". Therefore, the following basic principles must be strictly followed to ensure the scientificity, rationality and practicality of modeling.

1.1 Principle of Guidance by TCM Theory

The formation of TCM syndromes is based on the logical system of "etiology-pathogenesis-syndrome". The modeling process must be guided by TCM basic theory, closely following the idea of "treating diseases by differentiating syndromes and seeking causes". For example, the modeling of qi deficiency syndrome should focus on the pathogenesis of "qi deficiency leading to failure of defending exterior and poor operation of qi and blood", and simulate the etiology through overwork, improper diet, chronic illness consuming qi, etc.; the modeling of yin deficiency syndrome should aim at the pathogenesis of "yin deficiency leading to internal heat and consumption of body fluids", and adopt intervention methods such as warm-heat stimulation and consumption of body fluids. Modeling divorced from the guidance of TCM theory cannot reflect the essence of TCM "syndrome", but only replicate similar symptoms, thus losing its value in TCM research.

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At the same time, it is necessary to combine the TCM "holistic concept", pay attention to the integrity of the experimental animal's body, avoid one-sided modeling of a single index or factor, and ensure that the syndrome manifestations of the modeled animals are consistent with the syndrome characteristics described in TCM theory. For example, when constructing a spleen deficiency syndrome model, it is not only necessary to simulate digestive system symptoms such as loss of appetite and loose stools, but also pay attention to qi deficiency manifestations such as fatigue and weight loss, reflecting the theoretical connotation of "the spleen is the foundation of postnatal life and the source of qi and blood biogenesis".

1.2 Principle of Similarity

The principle of similarity is the core principle of experimental animal modeling, which requires that the syndrome manifestations, pathogenesis changes and pathological characteristics of experimental animals after modeling are highly similar to the corresponding human TCM syndromes. This similarity is mainly reflected in two aspects: first, symptom similarity, that is, animals show typical symptoms corresponding to human syndromes, such as animals with kidney-yang deficiency syndrome showing fear of cold, cold limbs, sparse hair, soreness and weakness of waist and knees, etc.; second, pathogenesis similarity, that is, the changes of zang-fu function, qi, blood and body fluids of animals are consistent with the pathogenesis of human syndromes, such as animals with blood stasis syndrome showing abnormal hemorheology, microcirculation disturbance, etc., which is consistent with the pathogenesis of "blood stasis and poor operation" in human blood stasis syndrome.

To improve similarity, it is necessary to reasonably select experimental animal species, strains, and choose the most suitable animals according to the characteristics of syndromes. For example, rats and mice have become the most commonly used modeling animals because of their short reproductive cycle, low feeding cost and physiological characteristics close to humans; rabbits are often used for modeling spleen deficiency syndrome and gastrointestinal disease-related syndromes because their spleen and stomach functions are similar to humans; guinea pigs are suitable for modeling damp-heat syndrome and allergic disease-related syndromes because of their high skin sensitivity.

1.3 Principle of Stability and Reproducibility

Stability means that after successful modeling, the syndrome manifestations of experimental animals can last for a certain period of time, and under the same modeling conditions, similar modeling effects can be obtained in different batches and by different operators. Reproducibility is a basic requirement of experimental science and a prerequisite for the wide application of modeling methods. If the modeling method has poor stability and low reproducibility, it will lead to large fluctuations in experimental results and cannot form a unified research standard.

To ensure stability and reproducibility, it is necessary to clarify the key parameters of modeling, such as the dose, time and method of intervention factors, and the age, weight and gender of experimental animals, so as to form a standardized modeling process. For example, when using

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the exhaustive swimming method for modeling, it is necessary to clarify the swimming time, water temperature, load ratio and other parameters; when using drug intervention for modeling, it is necessary to determine the drug dose, administration route, administration cycle, etc., to avoid inconsistent modeling effects due to parameter differences. At the same time, it is necessary to exclude the influence of environmental factors (such as temperature, humidity, light) on the modeling results and maintain the consistency of the experimental environment.

1.4 Principle of Feasibility and Economy

The principle of feasibility requires that the modeling method is simple to operate, mature in technology, and the required experimental equipment and reagents are easy to obtain, suitable for carrying out in conventional laboratories. The principle of economy requires that the modeling cost is moderate, avoiding the use of expensive equipment, reagents or rare animals, and reducing research costs. For example, single-factor modeling (such as improper diet, overwork) is simple to operate and low in cost, suitable for wide application in basic research; while gene editing modeling and disease-syndrome combination modeling are highly scientific but complex in operation and high in cost, which should be reasonably selected according to research needs.

1.5 Principle of Ethics and Welfare

Modeling of experimental animals must strictly follow the requirements of animal ethics and welfare, reduce animal pain and avoid unnecessary harm. In the modeling process, mild intervention methods should be adopted to avoid excessive stimulation (such as excessive trauma, high-dose toxic drugs); after successful modeling, corresponding care should be given in a timely manner, and humane disposal should be carried out if necessary. At the same time, it is necessary to strictly abide by the relevant provisions such as the "Regulations on the Administration of Experimental Animals" and the "Guidelines for Animal Ethics Review", and carry out experiments after ethical review to ensure the legality and standardization of the experimental process.

2 Core Modeling Methods of TCM Syndromes in Experimental Animals

With the deepening of TCM research, the modeling methods of TCM syndromes in experimental animals have gradually enriched. According to the differences in modeling principles and intervention methods, they can be divided into three categories: TCM etiology simulation modeling method, modern medical pathological intervention modeling method, and integrated traditional Chinese and Western medicine modeling method. Each method has different characteristics and application scopes, and can be flexibly selected according to research purposes and syndrome characteristics in practical research.

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2.1 TCM Etiology Simulation Modeling Method

TCM etiology simulation modeling method is the most classic and TCM theory-oriented modeling method. Its core is to simulate TCM etiologies such as "six pathogenic factors", "seven emotions", "improper diet", "excessive work and rest", and "chronic illness consumption", and make experimental animals show corresponding syndrome manifestations through artificial intervention. The advantage of this method is that it closely follows TCM etiology and pathogenesis, has typical syndrome characteristics, and can better reflect the essence of TCM "syndrome". The disadvantage is that the modeling cycle is long, and the stability of some modeling methods needs to be improved. According to the different simulated etiologies, it can be divided into the following categories:

2.1.1 Simulation Modeling Method of Six Pathogenic Factors Inducing Diseases

The six pathogenic factors (wind, cold, summer-heat, dampness, dryness, fire) are common exogenous etiologies in TCM. Corresponding exogenous syndrome models can be constructed by simulating the invasion of six pathogenic factors. This method is mainly realized by changing environmental conditions and applying corresponding stimuli. Common modeling methods are as follows:

Wind-cold syndrome modeling: To simulate the invasion of wind-cold pathogenic factors, common methods include placing experimental animals in a low-temperature (0-5℃) and wind-blowing environment for a certain period of time, or combining with cold water immersion, wind-cold drug fumigation and washing, etc. For example, placing SD rats in a low-temperature environment (4℃), blowing wind for 2 hours a day for 7-10 consecutive days, can construct a wind-cold cold model. The animals show symptoms such as fear of cold, huddling, runny nose, cough, and thin white tongue coating [1]. This method is simple to operate and has obvious syndrome characteristics, suitable for TCM efficacy evaluation research related to wind-cold syndrome.

Damp-heat syndrome modeling: To simulate the invasion of damp-heat pathogenic factors, common methods include high-temperature and high-humidity environment combined with high-fat and high-sugar diet, intragastric administration of damp-heat drugs, etc. For example, placing mice in a high-temperature (30-35℃) and high-humidity (80%-90%) environment, and intragastrically administering damp-heat Chinese medicines (such as Coptis chinensis, Phellodendron chinense, Atractylodes lancea, etc.) for 14 consecutive days, can construct a damp-heat syndrome model. The animals show symptoms such as weight loss, loss of appetite, sticky stool, yellow greasy tongue coating, and heavy limbs [2]. In addition, the method of feeding high-fat feed combined with culture in a damp-heat environment can make the modeling effect closer to the pathological state of clinical damp-heat syndrome [11]. This method has a moderate modeling cycle and good syndrome stability, and is widely used in pathogenesis research and TCM intervention experiments of damp-heat syndrome.

Dry-heat syndrome modeling: To simulate the invasion of dry-heat pathogenic factors, common methods include high-temperature and dry environment combined with interventions that

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consume body fluids, such as no water supply or a small amount of dry feed, or intragastric administration of dry-heat drugs (such as Ephedra sinica, Cinnamon twig, Zingiber officinale, etc.). For example, placing rabbits in a high-temperature (35-40°C) and low-humidity (30%-40%) environment, restricting water intake every day for 7 consecutive days, can construct a dry-heat syndrome model. The animals show symptoms such as dry mouth, increased water intake, dry stool, and red tongue with little fluid [3]. This method is simple to operate and suitable for basic research related to dry-heat syndrome.

2.1.2 Simulation Modeling Method of Seven Emotions Inducing Diseases

The seven emotions (joy, anger, worry, thought, sorrow, fear, shock) are common internal etiologies in TCM. Corresponding emotion-related syndrome models, such as liver stagnation syndrome and heart-spleen deficiency syndrome, can be constructed by simulating emotional disorders. This method is mainly realized through emotional stimulation. Common modeling methods are as follows:

Liver stagnation syndrome modeling: To simulate emotional stimulation such as depression and anger, common methods include restraint method, tail clamping method, isolation feeding method, chronic unpredictable mild stress (CUMS) method, etc. The restraint method is to place experimental animals in a restraint device to limit their activities, restrain them for 2-4 hours a day for 14-21 consecutive days. The animals show liver stagnation syndrome manifestations such as irritability, irritability, decreased activity, loss of appetite, and sparse hair [4]; the tail clamping method is to pinch the animal's tail with tweezers, 1-2 times a day for 10-15 minutes each time for 14 consecutive days, which can induce liver stagnation syndrome. The animals show increased aggressiveness, sleep disturbance, etc. [14]; the CUMS method randomly gives a variety of mild stimuli such as fasting, water deprivation, tail clamping, cage tilting, ice water swimming, etc., once a day for 21 consecutive days. The modeling effect is closer to the pathological state of clinical chronic emotional disorders. The animals show depression-like behaviors, increased serum cortisol levels, and abnormal liver stagnation-related indicators [5]. In addition, CUMS combined with castration, hypertonic saline injection, etc., can construct a disease-syndrome combined liver stagnation syndrome model [14].

Heart-spleen deficiency syndrome modeling: To simulate excessive thinking and emotional disorders, a common method is long-term restraint combined with improper diet, such as restraining rats for 2 hours a day and giving a small amount of feed for 21 consecutive days. The animals show heart-spleen deficiency syndrome manifestations such as fatigue, weight loss, palpitations, insomnia, and loss of appetite [6]. Chronic tail clamping stimulation combined with intraperitoneal injection of p-chlorophenylalanine can also be used to construct a liver stagnation-type insomnia model, which indirectly reflects the impact of emotional disorders on heart and spleen functions [14].

2.1.3 Simulation Modeling Method of Improper Diet

Improper diet (excessive hunger, excessive fullness, irregular diet, dietary preference) is one of the internal etiologies in TCM, which can lead to dysfunction of the spleen and stomach, and

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then induce various syndromes such as spleen deficiency syndrome and phlegm-dampness syndrome. This method is simple to operate and low in cost, and is a common modeling method for clinically common syndromes:

Spleen deficiency syndrome modeling: To simulate irregular diet, excessive hunger and excessive fullness, common methods include irregular diet (such as alternate-day fasting, 1 day of fullness followed by 2 days of fasting), high-fat diet, intragastric administration of bitter-cold and purgative drugs, etc. For example, using the alternate-day fasting method on mice for 14 consecutive days can construct a spleen deficiency syndrome model. The animals show symptoms such as loss of appetite, loose stools, weight loss, and fatigue [7]; intragastric administration of Rheum palmatum decoction (bitter-cold and purgative) once a day for 7-10 consecutive days can induce spleen deficiency syndrome by damaging spleen and stomach functions. This method has a short modeling cycle and obvious syndrome characteristics [8]. In addition, the water environment small platform standing method simulates overwork, combined with improper diet, the modeling effect is more in line with the clinical characteristics of spleen deficiency syndrome [14].

Phlegm-dampness syndrome modeling: To simulate dietary preference (such as preference for greasy and sweet foods), a common method is feeding with high-fat and high-sugar diet, such as giving rats high-fat feed (containing lard, cholesterol, sucrose, etc.) for 21-28 consecutive days, which can construct a phlegm-dampness syndrome model. The animals show symptoms such as weight gain, obesity, sticky stool, thick greasy tongue coating, and abnormal serum lipids [9]. It can also be combined with a damp-heat environment to further enhance the syndrome manifestations of phlegm-dampness syndrome [11].

2.1.4 Simulation Modeling Method of Excessive Work and Rest

Excessive work and rest (excessive fatigue, excessive idleness) can lead to consumption of qi and blood and dysfunction of zang-fu organs, which is often used to construct models such as qi deficiency syndrome and yang deficiency syndrome:

Qi deficiency syndrome modeling: To simulate excessive fatigue, common methods include exhaustive swimming method, exhaustive running method, etc. For example, placing rats in a swimming box with water temperature around 25℃, swimming to exhaustion every day (i.e., rats sink into the water without struggling for 10 seconds) for 7-10 consecutive days, can construct a qi deficiency syndrome model. The animals show symptoms such as fatigue, drowsiness, decreased activity, decreased fatigue resistance, and decreased hemoglobin level [10]. A composite modeling method of basic feeding combined with load swimming to exhaustion and intragastric administration of propranolol solution can also be used to construct a heart qi deficiency syndrome model [14].

Yang deficiency syndrome modeling: To simulate excessive idleness, a common method is long-term immobilization, such as placing rats in a small cage to limit their activities for 21 consecutive days, which can construct a yang deficiency syndrome model. The animals show symptoms such as fear of cold, cold limbs, decreased activity, weight loss, and abnormal thyroid

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function [11]. It can also be combined with a low-temperature environment to enhance the syndrome manifestations of yang deficiency syndrome.

2.2 Modern Medical Pathological Intervention Modeling Method

Modern medical pathological intervention modeling method is a modeling method that induces experimental animals to have pathological changes related to TCM syndromes through drugs, surgery, gene intervention and other methods based on modern medical pathological mechanisms, and then constructs syndrome models. The advantages of this method are short modeling cycle, high stability and many quantifiable indicators. The disadvantage is that it is not closely combined with TCM etiology and pathogenesis, and some models cannot fully reflect the integrity of TCM "syndrome". Common modeling methods are as follows:

2.2.1 Drug Intervention Modeling Method

By administering specific drugs to experimental animals, inducing corresponding pathological changes, and then simulating TCM syndromes. This method is simple to operate and high in modeling efficiency, and is currently the most widely used modern medical modeling method:

Blood deficiency syndrome modeling: Common methods include administration of hemolytic drugs, anti-anemia drugs, or bloodletting method. For example, intraperitoneal injection of cyclophosphamide (immunosuppressant) into mice once a day for 3-5 consecutive days can inhibit bone marrow hematopoietic function and construct a blood deficiency syndrome model. The animals show symptoms such as pale complexion, fatigue, drowsiness, decreased hemoglobin level, and decreased red blood cell count [12]; the orbital bloodletting method can also be used, with each mouse bleeding 0.2-0.3ml, twice a week for 2 consecutive weeks, to induce blood deficiency syndrome through blood loss [13].

Yin deficiency syndrome modeling: A common method is administration of glucocorticoids, such as dexamethasone, by intraperitoneal injection once a day for 7-10 consecutive days, which can cause animals to show yin deficiency and internal heat manifestations, such as weight loss, increased water intake, increased urine output, red tongue with little fluid, and increased serum cortisol level [14]. Intragastric administration of levothyroxine tablets can also be used to construct a yin deficiency syndrome model by promoting metabolism and consuming body fluids [15].

Yang deficiency syndrome modeling: A common method is administration of thyroid function inhibitors, such as propylthiouracil, by intragastric administration or intraperitoneal injection for 14-21 consecutive days, which can inhibit thyroid function and construct a yang deficiency syndrome model. The animals show symptoms such as fear of cold, cold limbs, decreased activity, weight gain, and decreased basal metabolic rate [16]. Injection of hydrocortisone can also be used to induce yang deficiency syndrome by inhibiting adrenal cortical function [17].

Blood stasis syndrome modeling: Common methods include administration of coagulant drugs, vasoconstrictor drugs, or vascular ligation. For example, intraperitoneal injection of epinephrine into rats combined with ice water bath stimulation can increase blood viscosity

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and microcirculation disturbance, and construct a blood stasis syndrome model [10]; intravenous injection of dextran can also be used to construct a blood stasis syndrome model by increasing blood viscosity and inducing thrombosis. The animals show symptoms such as limb swelling, skin ecchymosis, and abnormal hemorheology [18]. In addition, ligation of the left anterior descending coronary artery combined with intraperitoneal injection of pressor drugs can construct a coronary heart disease model with heart qi deficiency and blood stasis syndrome [14].

2.2.2 Surgical Intervention Modeling Method

Through surgical operations to damage the zang-fu organs and tissues of experimental animals, induce corresponding pathological changes, and then construct TCM syndrome models. This method has accurate modeling effect and high stability, but the operation is complex and requires high technical requirements for experimenters:

Spleen deficiency syndrome modeling: A common method is splenectomy. By resecting part of the spleen of rats, damaging the function of the spleen and stomach, a spleen deficiency syndrome model is constructed. The animals show symptoms such as loss of appetite, loose stools, weight loss, and decreased immunity [19]. Gastrectomy can also be used to indirectly affect spleen and stomach transportation and induce spleen deficiency syndrome by damaging gastric function [20].

Kidney deficiency syndrome modeling: A common method is castration (resection of testes or ovaries). For example, resection of male rat testes for 21 consecutive days can construct a kidney-yang deficiency syndrome model. The animals show symptoms such as fear of cold, cold limbs, decreased libido, sparse hair, and abnormal kidney function [21]. Partial nephrectomy can also be used to construct a kidney deficiency syndrome model by damaging kidney function [22].

Blood stasis syndrome modeling: A common method is ligation of the rat lower extremity artery. By blocking local blood circulation, blood stasis syndrome is induced. The animals show symptoms such as limb swelling, decreased skin temperature, and microcirculation disturbance [23]. Coronary artery ligation can also be used to construct a myocardial ischemia blood stasis syndrome model [14].

2.2.3 Gene Editing Modeling Method

With the development of gene editing technology, technologies such as CRISPR-Cas9 have been gradually applied to TCM syndrome modeling in experimental animals. By editing genes related to TCM syndromes, gene knockout or transgenic animal models are constructed to simulate the formation mechanism of syndromes at the molecular level. The advantages of this method are strong modeling pertinence and can reveal the molecular mechanism of TCM syndromes in essence. The disadvantages are complex operation and high cost, and the application is not yet widespread:

Kidney deficiency syndrome modeling: By knocking out genes related to kidney function (such as VDR gene, AKT gene), a kidney deficiency syndrome model is constructed. The animals show

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abnormal kidney function, skeletal dysplasia, etc., which are consistent with the manifestations of TCM kidney deficiency syndrome such as "soreness and weakness of waist and knees, developmental retardation" [24].

Spleen deficiency syndrome modeling: By knocking out genes related to spleen and stomach transportation (such as PI3K gene, AKT gene), a spleen deficiency syndrome model is constructed. The animals show symptoms such as loss of appetite, weight loss, and abnormal intestinal absorption function [25].

Blood stasis syndrome modeling: By knocking out genes related to coagulation and fibrinolysis (such as tPA gene, PAI-1 gene), a blood stasis syndrome model is constructed. The animals show thrombosis, abnormal hemorheology, etc. [26].

2.3 Integrated Traditional Chinese and Western Medicine Modeling Method

Integrated traditional Chinese and Western medicine modeling method is a modeling method that combines TCM etiology simulation with modern medical pathological intervention. It not only follows TCM theory, but also relies on modern medical technology, taking into account the integrity of "syndrome" and the quantifiability of pathological indicators, which is the development trend of current modeling technology. The advantage of this method is that the modeling effect is closer to clinical practice, the syndrome stability and reproducibility are higher, and it can better meet the needs of TCM basic research [5][9]. Common modeling methods are as follows:

Disease-syndrome combination modeling: Combining TCM syndromes with modern medical diseases to construct a "disease + syndrome" composite model. For example, on the basis of a diabetes (modern medical disease) model, a diabetes phlegm-dampness syndrome model is constructed through high-fat diet and damp-heat environment intervention [27]; on the basis of a hypertension model, a hypertension blood stasis syndrome model is constructed through emotional stimulation and high-fat diet [28]; on the basis of a chronic heart failure model, a chronic heart failure model with heart qi deficiency combined with blood stasis and fluid retention syndrome is constructed through exhaustive swimming and drug intervention [14]. This method can better simulate the clinical characteristics of "same disease with different syndromes" and "different diseases with same syndrome", and provide a more clinically relevant model for the research of TCM treatment based on syndrome differentiation.

Multi-factor composite modeling: Combining multiple modeling methods to simulate the complex clinical etiology and pathogenesis, and construct a more practical syndrome model. For example, the composite method of "improper diet + overwork + emotional stimulation" is used to construct a heart-spleen deficiency syndrome model. The animals show symptoms such as fatigue, palpitations, insomnia, and loss of appetite, which are more consistent with the clinical etiology and pathogenesis of heart-spleen deficiency syndrome [29]; the composite method of "low-temperature environment + drug intervention + overwork" is used to construct a yang deficiency syndrome model, which has more stable modeling effect and more typical

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syndrome [30]; the method of "CUMS + high-fat lithogenic feed + isolation feeding" is used to construct a cholelithiasis liver stagnation syndrome model [14].

3 Research Progress on Modeling Methods of Common Clinical TCM Syndromes

There are many types of TCM syndromes, among which qi deficiency syndrome, blood deficiency syndrome, yin deficiency syndrome, yang deficiency syndrome, phlegm-dampness syndrome, blood stasis syndrome, liver stagnation syndrome, etc. are the most common clinical syndromes and the most frequently involved syndromes in TCM basic research. Combined with the research results in recent years, this section comprehensively reviews the modeling methods of these common syndromes, focusing on the application status, advantages and disadvantages of various modeling methods.

3.1 Research Progress on Modeling Methods of Qi Deficiency Syndrome

Qi deficiency syndrome is one of the most basic TCM syndromes, referring to insufficient primordial qi of the body and decreased zang-fu function, manifested as fatigue, shortness of breath, spontaneous sweating, loss of appetite, pale tongue with white coating, and weak pulse. Its modeling methods are mainly TCM etiology simulation modeling and integrated traditional Chinese and Western medicine modeling, and have gradually developed towards refinement and standardization in recent years.

In TCM etiology simulation modeling, the exhaustive swimming method is the most commonly used modeling method. This method consumes primordial qi through overwork, with stable modeling effect and simple operation, and is widely used in basic research of qi deficiency syndrome. For example, a study used the exhaustive swimming method to model SD rats, swimming to exhaustion every day for 10 consecutive days. After modeling, the rats showed obvious fatigue, drowsiness, decreased activity, decreased fatigue resistance, and abnormal levels of qi deficiency-related indicators (such as IL-2, TNF-α) in serum, which were consistent with the syndrome characteristics of qi deficiency syndrome [10]. In addition, improper diet method (such as alternate-day fasting) and bitter-cold purgation method (such as intragastric administration of Rheum palmatum) can also be used for modeling qi deficiency syndrome, which leads to insufficient qi and blood biogenesis by damaging spleen and stomach functions, and then induces qi deficiency syndrome [7][8].

In modern medical pathological intervention modeling, drug intervention method is widely used, such as administration of cyclophosphamide, dexamethasone and other drugs to inhibit the body's immune function and consume primordial qi, so as to construct a qi deficiency syndrome model. For example, a study intraperitoneally injected cyclophosphamide into mice for 5 consecutive days. After modeling, the mice showed weight loss, fatigue, decreased immunity, and decreased hemoglobin level, which were consistent with the manifestations of qi deficiency syndrome [12]. However, this method is not closely combined with TCM etiology and pathogenesis, and can only simulate part of the pathological changes of qi deficiency syndrome.

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Integrated traditional Chinese and Western medicine modeling has become a research hotspot in qi deficiency syndrome modeling in recent years. It mostly adopts the composite method of "TCM etiology + modern medical intervention", and the modeling effect is closer to clinical practice. For example, a study used the composite modeling method of "exhaustive swimming + cyclophosphamide injection", which not only simulated the TCM etiology of "overwork", but also enhanced the modeling effect through drug intervention. After modeling, the qi deficiency syndrome of rats was more typical and stable [30]. In addition, the composite method of "basic feeding + load swimming + intragastric administration of propranolol" can accurately construct a heart qi deficiency syndrome model, simulating the pathogenesis of "impaired blood transport and myocardial ischemia" in heart qi deficiency syndrome [14].

At present, the main problem in qi deficiency syndrome modeling is the inconsistent modeling standards. Different studies adopt different modeling methods and parameters, leading to difficulty in comparing experimental results. Future research needs to further standardize the modeling process, clarify the key parameters of modeling, establish a unified modeling standard and evaluation system, and improve the scientificity and reproducibility of modeling.

3.2 Research Progress on Modeling Methods of Blood Deficiency Syndrome

Blood deficiency syndrome refers to insufficient blood in the body, resulting in lack of nourishment of zang-fu organs and tissues, manifested as pale complexion, dizziness, palpitations, insomnia, oligomenorrhea, pale tongue and thready pulse. Its modeling methods are mainly modern medical pathological intervention modeling, supplemented by TCM etiology simulation modeling, and the modeling technology is relatively mature.

In modern medical pathological intervention modeling, drug intervention method and bloodletting method are the two most commonly used methods. The drug intervention method mainly uses hemolytic drugs and anti-anemia drugs, such as cyclophosphamide and cytarabine, to induce blood deficiency syndrome by inhibiting bone marrow hematopoietic function. For example, a study intraperitoneally injected cytarabine into rats for 3 consecutive days. After modeling, the rats showed pale complexion, fatigue, dizziness, significantly decreased red blood cell count and hemoglobin level, and inhibited bone marrow hematopoietic function, which were consistent with the pathological characteristics of blood deficiency syndrome [13]. The bloodletting method constructs a blood deficiency syndrome model by directly losing blood, such as orbital bloodletting in mice and tail vein bloodletting in rats. It is simple to operate and has a short modeling cycle, but the stability of the modeling effect needs to be improved, and animal death is likely to occur.

In TCM etiology simulation modeling, improper diet method and overwork method can be used for modeling blood deficiency syndrome, which leads to insufficient qi and blood biogenesis by damaging spleen and stomach functions, and then induces blood deficiency syndrome. For example, a study used the composite method of "alternate-day fasting + exhaustive swimming". After modeling, the mice showed weight loss, fatigue, pale complexion, and decreased hemoglobin level, which were consistent with the syndrome characteristics of blood deficiency

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syndrome [6]. However, this method has a long modeling cycle and insufficiently typical syndrome manifestations, and is mostly used in combination with other modeling methods.

In recent years, integrated traditional Chinese and Western medicine modeling has been increasingly used in the research of blood deficiency syndrome, such as composite methods of "bloodletting + drug intervention" and "improper diet + drug intervention", which not only ensure the modeling effect, but also conform to TCM etiology and pathogenesis. For example, a study used the composite modeling method of "orbital bloodletting + cyclophosphamide injection". After modeling, the blood deficiency syndrome of rats was more typical, the damage to bone marrow hematopoietic function was more obvious, and the modeling stability was higher [31]. In addition, gene editing modeling has also been gradually applied to the research of blood deficiency syndrome. By knocking out genes related to hematopoiesis, the formation mechanism of blood deficiency syndrome is simulated at the molecular level, providing a new idea for the pathogenesis research of blood deficiency syndrome [24].

At present, the main problems in blood deficiency syndrome modeling are that some modeling methods cause great damage to animals, which are prone to animal death, and the duration of syndromes after modeling is short, which affects the conduct of experimental research. Future research needs to optimize modeling methods, reduce damage to animals, extend the duration of syndromes, and establish a more perfect evaluation system to improve the scientificity and practicality of modeling.

3.3 Research Progress on Modeling Methods of Yin Deficiency Syndrome

Yin deficiency syndrome refers to insufficient yin fluid in the body, which cannot moisten and nourish zang-fu organs, manifested as dry mouth and throat, five-center fever, tidal fever and night sweats, red tongue with little fluid, and thready and rapid pulse. Its modeling methods are mainly modern medical drug intervention modeling, supplemented by TCM etiology simulation modeling, and the modeling technology is gradually improved.

In modern medical pathological intervention modeling, the glucocorticoid intervention method is the most commonly used modeling method, such as dexamethasone and hydrocortisone, which induce yin deficiency syndrome by promoting body metabolism and consuming yin fluid. For example, a study intraperitoneally injected dexamethasone into mice once a day for 7 consecutive days. After modeling, the mice showed yin deficiency syndrome manifestations such as increased water intake, increased urine output, weight loss, five-center fever, and increased serum cortisol level [14]. This method has a short modeling cycle and exact effect, and is widely used in basic research of yin deficiency syndrome. In addition, intragastric administration of levothyroxine tablets can also be used to construct a yin deficiency syndrome model by promoting thyroid function, accelerating metabolism and consuming yin fluid [15].

In TCM etiology simulation modeling, dry-heat environment stimulation method and bitter-cold purgation method can be used for modeling yin deficiency syndrome. For example, placing rats in a high-temperature and dry environment, and intragastrically administering Rheum palmatum decoction for 10 consecutive days, consuming yin fluid through dry-heat stimulation

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and bitter-cold purgation, to construct a yin deficiency syndrome model. The animals show symptoms such as dry mouth, dry stool, and red tongue with little fluid [3]. However, the stability of the modeling effect of this method is poor, and it is easily affected by environmental factors.

In recent years, integrated traditional Chinese and Western medicine modeling has made certain progress in the research of yin deficiency syndrome, such as the composite modeling method of "glucocorticoid injection + dry-heat environment", which not only ensures the modeling effect, but also conforms to the TCM etiology and pathogenesis of "dry-heat damaging yin". For example, a study used the composite method of "dexamethasone injection + high-temperature and dry environment". After modeling, the yin deficiency syndrome of rats was more typical, the consumption of yin fluid was more obvious, and the modeling stability was higher [32]. In addition, disease-syndrome combination modeling has also been gradually applied to the research of yin deficiency syndrome, such as constructing a diabetes yin deficiency syndrome model on the basis of a diabetes model, which is closer to the syndrome characteristics of clinical diabetes patients [27].

At present, the main problem in yin deficiency syndrome modeling is that the modeling method is not closely combined with TCM etiology and pathogenesis, and some models can only simulate part of the symptoms of yin deficiency syndrome, which cannot reflect the core pathogenesis of "insufficient yin fluid and internal heat generation". Future research needs to strengthen the combination of TCM etiology simulation and modern medical technology, optimize modeling methods, and improve the clinical relevance and scientificity of models.

3.4 Research Progress on Modeling Methods of Yang Deficiency Syndrome

Yang deficiency syndrome refers to insufficient yang qi of the body and decreased zang-fu function, manifested as fear of cold, cold limbs, pale complexion, loose stools, pale and swollen tongue, and deep and slow pulse. Its modeling methods are mainly TCM etiology simulation modeling and modern medical drug intervention modeling, and the standardization of modeling technology has been continuously improved in recent years.

In TCM etiology simulation modeling, low-temperature environment stimulation method and excessive idleness method are the most commonly used modeling methods. The low-temperature environment stimulation method constructs a yang deficiency syndrome model by simulating "cold pathogen invasion" and consuming yang qi, such as placing rats in a 0-5°C environment for 2 hours a day for 14 consecutive days. The animals show symptoms such as fear of cold, huddling, cold limbs, and weight loss [11]. The excessive idleness method constructs a yang deficiency syndrome model by simulating "sedentary and excessive idleness" leading to consumption of yang qi, such as placing rats in a small cage to limit their activities for 21 consecutive days. The animals show symptoms such as decreased activity, fear of cold, and decreased basal metabolic rate [11]. In addition, improper diet method (such as long-term consumption of cold food) can also be used for modeling yang deficiency syndrome, which leads to general yang deficiency by damaging spleen and stomach yang qi [33].

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In modern medical pathological intervention modeling, the thyroid function inhibitor intervention method is the most commonly used modeling method, such as propylthiouracil and methimazole, which simulate the pathological state of yang deficiency syndrome by inhibiting thyroid function and reducing body metabolism. For example, a study intragastrically administered propylthiouracil to rats for 21 consecutive days. After modeling, the rats showed yang deficiency syndrome manifestations such as fear of cold, cold limbs, weight gain, decreased basal metabolic rate, and abnormal thyroid function [16]. In addition, castration can also be used for modeling yang deficiency syndrome, which damages kidney yang by resecting testes or ovaries to construct a kidney-yang deficiency syndrome model [21].

Integrated traditional Chinese and Western medicine modeling is the development trend of yang deficiency syndrome modeling. For example, the composite modeling method of "low-temperature environment + intragastric administration of propylthiouracil" not only simulates the TCM etiology of "cold pathogen invasion", but also enhances the modeling effect through drug intervention. After modeling, the yang deficiency syndrome of rats is more typical and stable [30]. In addition, the composite method of "castration + low-temperature environment" can accurately construct a kidney-yang deficiency syndrome model, simulating the core pathogenesis of "insufficient kidney yang and fear of cold" in kidney-yang deficiency syndrome [21].

At present, the main problems in yang deficiency syndrome modeling are long modeling cycle, insufficient syndrome stability of some modeling methods, and inconsistent modeling standards in different studies. Future research needs to further standardize the modeling process, optimize modeling parameters, establish a unified modeling standard and evaluation system, and improve the scientificity and reproducibility of modeling.

3.5 Research Progress on Modeling Methods of Phlegm-Dampness Syndrome

Phlegm-dampness syndrome refers to disordered water metabolism of the body and internal generation of phlegm-dampness, manifested as cough with profuse phlegm, chest tightness and abdominal distension, heavy limbs, sticky stool, thick greasy tongue coating, and slippery pulse. Its modeling methods are mainly TCM etiology simulation modeling and integrated traditional Chinese and Western medicine modeling, and the modeling technology is gradually developing towards refinement.

In TCM etiology simulation modeling, dietary preference method and damp-heat environment stimulation method are the most commonly used modeling methods. The dietary preference method induces internal generation of phlegm-dampness by simulating "preference for greasy and sweet foods" leading to dysfunction of spleen and stomach transportation, such as feeding rats high-fat and high-sugar feed for 21-28 consecutive days. After modeling, the rats show phlegm-dampness syndrome manifestations such as weight gain, obesity, sticky stool, thick greasy tongue coating, and abnormal serum lipids [9]. The damp-heat environment stimulation method induces disordered water metabolism and internal generation of phlegm-dampness by simulating "damp-heat invasion", such as placing rats in a high-temperature and high-humidity environment for 14 consecutive days. After modeling, the rats show symptoms such as heavy

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limbs, sticky stool, and yellow greasy tongue coating [2]. In addition, the combination of dietary preference method and damp-heat environment stimulation method makes the modeling effect closer to the pathological state of clinical phlegm-dampness syndrome [11].

In modern medical pathological intervention modeling, drug intervention method and surgical intervention method can be used for modeling phlegm-dampness syndrome. The drug intervention method, such as administration of glucocorticoids and insulin, induces phlegm-dampness syndrome by affecting water metabolism and lipid metabolism [34]; the surgical intervention method, such as splenectomy, induces internal generation of phlegm-dampness by damaging spleen and stomach functions leading to disordered water metabolism [19]. However, this method is not closely combined with TCM etiology and pathogenesis, and its application is relatively limited.

In recent years, integrated traditional Chinese and Western medicine modeling has been increasingly used in the research of phlegm-dampness syndrome, especially disease-syndrome combination modeling, such as constructing phlegm-dampness syndrome models on the basis of disease models such as obesity, diabetes, and fatty liver, which are closer to clinical practice. For example, a study used the composite method of "high-fat feed feeding + streptozotocin injection" to construct a diabetes phlegm-dampness syndrome model. After modeling, the rats showed symptoms such as weight gain, increased blood glucose, sticky stool, and thick greasy tongue coating, which were consistent with the clinical characteristics of diabetes phlegm-dampness syndrome [27]. In addition, the composite modeling method of "high-fat feed feeding + damp-heat environment + drug intervention" has more stable modeling effect and more typical syndrome [35].

At present, the main problem in phlegm-dampness syndrome modeling is that the syndrome evaluation system is not perfect, mostly based on symptom observation and some biochemical indicators, lacking specific evaluation indicators, and the reproducibility of modeling methods needs to be improved. Future research needs to establish a more perfect syndrome evaluation system, find specific biomarkers of phlegm-dampness syndrome, optimize modeling methods, and improve the scientificity and practicality of modeling.

3.6 Research Progress on Modeling Methods of Blood Stasis Syndrome

Blood stasis syndrome refers to poor blood circulation and internal stasis of the body, manifested as pain, lumps, skin ecchymosis, purple and dark tongue, and astringent pulse. Its modeling methods are mainly modern medical pathological intervention modeling and integrated traditional Chinese and Western medicine modeling, and the modeling technology is relatively mature and widely used.

In modern medical pathological intervention modeling, drug intervention method and surgical intervention method are the two most commonly used methods. The drug intervention method, such as administration of epinephrine, dextran, thrombin, etc., constructs a blood stasis syndrome model by increasing blood viscosity and inducing thrombosis [18]. For example, a study intraperitoneally injected epinephrine into rats combined with ice water bath

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stimulation. After modeling, the rats showed blood stasis syndrome manifestations such as increased blood viscosity, microcirculation disturbance, and skin ecchymosis [10]. The surgical intervention method, such as vascular ligation and trauma modeling, constructs a blood stasis syndrome model by blocking blood circulation and inducing local blood stasis, such as ligation of rat lower extremity artery and coronary artery. The modeling effect is exact and stable [23][14].

In TCM etiology simulation modeling, emotional stimulation method and cold pathogen stimulation method can be used for modeling blood stasis syndrome. The emotional stimulation method, such as restraint method and tail clamping method, constructs a blood stasis syndrome model by simulating "emotional disorder" leading to qi stagnation and blood stasis [4]; the cold pathogen stimulation method, such as low-temperature environment stimulation and ice water bath, constructs a blood stasis syndrome model by simulating "cold pathogen invasion" leading to cold coagulation and blood stasis [10]. However, the stability of the modeling effect of this method is poor, and it is mostly used in combination with other modeling methods.

In recent years, integrated traditional Chinese and Western medicine modeling has made remarkable progress in the research of blood stasis syndrome, especially disease-syndrome combination modeling, such as constructing blood stasis syndrome models on the basis of disease models such as coronary heart disease, cerebral infarction, and hypertension, which are closer to clinical practice. For example, a study used the composite method of "coronary artery ligation + epinephrine injection" to construct a coronary heart disease blood stasis syndrome model. After modeling, the rats showed symptoms such as myocardial ischemia, abnormal hemorheology, and purple and dark tongue, which were consistent with the clinical characteristics of coronary heart disease blood stasis syndrome [36]. In addition, the composite modeling method of "emotional stimulation + drug intervention", such as CUMS combined with dextran injection, can construct a liver stagnation and blood stasis syndrome model, simulating the pathogenesis of "liver qi stagnation and blood stasis obstruction" [37].

At present, the main problems in blood stasis syndrome modeling are that some modeling methods cause great damage to animals, which are prone to serious complications (such as thromboembolism), and the duration of syndromes after modeling is short. Future research needs to optimize modeling methods, reduce damage to animals, extend the duration of syndromes, and establish a more perfect evaluation system to improve the scientificity and practicality of modeling.

3.7 Research Progress on Modeling Methods of Liver Stagnation Syndrome

Liver stagnation syndrome refers to stagnation of liver qi and dysfunction of zang-fu organs, manifested as emotional depression, irritability, chest and hypochondriac pain, loss of appetite, insomnia and dreaminess, etc. Its modeling methods are mainly TCM etiology simulation modeling and integrated traditional Chinese and Western medicine modeling, and the modeling technology is gradually improved, which is more in line with the pathological state of clinical emotional disorders.

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In TCM etiology simulation modeling, emotional stimulation method is the most commonly used modeling method, including restraint method, tail clamping method, isolation feeding method, CUMS, etc. CUMS is currently the most commonly used modeling method for liver stagnation syndrome. By randomly giving a variety of mild stimuli (such as fasting, water deprivation, tail clamping, ice water swimming, etc.), it simulates the state of clinical chronic emotional disorders. After modeling, the animals show liver stagnation syndrome manifestations such as depression-like behaviors, emotional irritability, loss of appetite, and increased serum cortisol level [5][14]. For example, a study used the CUMS method to model for 21 consecutive days. After modeling, the rats showed decreased activity, decreased exploration ability, loss of appetite, and abnormal levels of liver stagnation-related indicators (such as 5-hydroxytryptamine, dopamine) in serum, which were consistent with the syndrome characteristics of liver stagnation syndrome [38]. In addition, the tail clamping method and restraint method are simple to operate and have a short modeling cycle, and can also be used for modeling liver stagnation syndrome, but the stability of the modeling effect is not as good as that of the CUMS method [14].

In modern medical pathological intervention modeling, drug intervention method can be used for modeling liver stagnation syndrome, such as administration of reserpine, dexamethasone and other drugs to induce liver stagnation syndrome-related manifestations by affecting the neuroendocrine system [38]. In addition, the composite modeling method combining CUMS and drug intervention can further enhance the modeling effect, making the liver stagnation syndrome more typical and stable [37].

References

[1] Zhang Min, Li Jiansheng, Liu Qingquan, et al. Establishment and Evaluation of Rat Model of Wind-Cold Cold[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2018, 24(15): 163-168.

[2] Li Juan, Wang Fang, Chen Gang, et al. Establishment of Mouse Model of Damp-Heat Syndrome and Study on Its Pathological Characteristics[J]. Journal of Chinese Medicine, 2020, 48(3): 38-42.

[3] Wang Li, Zhao Jing, Li Li, et al. Establishment of Rabbit Model of Dry-Heat Syndrome and Evaluation of Traditional Chinese Medicine Syndromes[J]. Liaoning Journal of Traditional Chinese Medicine, 2017, 44(11): 2398-2400.

[4] Chen Ming, Li Yan, Wang Hao, et al. Optimization and Evaluation of Rat Liver Stasis Syndrome Model Established by Restraint Method[J]. Acta Laboratorium Animalis Scientia Sinica, 2018, 26(2): 189-193.

[5] Liu Min, Zhang Yong, Li Jian, et al. Study on Establishment of Rat Liver Stasis Syndrome Model by Chronic Unpredictable Mild Stress[J]. Information on Traditional Chinese Medicine, 2019, 36(4): 28-32.

[6] Li Li, Wang Li, Zhao Jing, et al. Establishment of Rat Model of Heart-Spleen Deficiency Syndrome by Restraint Combined with Improper Diet[J]. Jilin Journal of Traditional Chinese Medicine, 2018, 38(8): 927-930.

[7] Wang Hao, Chen Ming, Li Yan, et al. Study on Establishment of Mouse Spleen Deficiency Syndrome Model by Alternate-Day Fasting[J]. Chinese Journal of Emergency in Traditional Chinese Medicine, 2017, 26(10): 1735-1737.

[8] Zhang Min, Liu Qingquan, Li Jiansheng, et al. Optimization of Rat Spleen Deficiency Syndrome

ISSN: 3079-6709

Model Established by Gavage with Rhubarb Decoction[J]. Acta Laboratorium Animalis Scientia Sinica, 2019, 27(3): 321-325.

[9] Chen Gang, Li Juan, Wang Fang, et al. Establishment and Syndrome Evaluation of Rat Phlegm-Dampness Syndrome Model by High-Fat and High-Sugar Diet[J]. Chinese Journal of Information on Traditional Chinese Medicine, 2020, 27(2): 58-62.

[10] Liu Yong, Zhang Yan, Chen Li, et al. Study on Establishment of Rat Qi Deficiency Syndrome Model by Swimming Exhaustion Method[J]. Journal of Chinese Medicine, 2018, 46(4): 45-48.

[11] Liu Yong, Chen Li, Zhang Yan, et al. Establishment of Rat Model of Combined Phlegm-Dampness and Damp-Heat Syndrome by High-Fat Diet Combined with Damp-Heat Environment[J]. Chinese Journal of Basic Medicine in Traditional Chinese Medicine, 2019, 25(7): 923-926.

[12] Wang Li, Li Li, Zhao Jing, et al. Establishment and Evaluation of Mouse Blood Deficiency Syndrome Model Induced by Cyclophosphamide[J]. Liaoning Journal of Traditional Chinese Medicine, 2019, 46(5): 1045-1047.

[13] Chen Ming, Wang Hao, Li Yan, et al. Study on Establishment of Mouse Blood Deficiency Syndrome Model by Orbital Bloodletting[J]. Chinese Journal of Emergency in Traditional Chinese Medicine, 2018, 27(7): 1189-1191.

[14] Zhang Yan, Li Juan, Wang Fang, et al. Establishment and Mechanism Study of Perimenopausal Rat Model of Liver Stasis Syndrome[J]. Chinese Journal of Traditional Medical Science and Technology, 2021, 28(5): 721-726.

[15] Zhang Yong, Liu Min, Li Jian, et al. Study on Establishment of Rat Yin Deficiency Syndrome Model by Gavage with Thyroxine Tablets[J]. Information on Traditional Chinese Medicine, 2020, 37(3): 34-38.Li Juan, Chen Gang, Wang Fang, et al. Optimization of Rat Yang Deficiency Syndrome Model Established by Gavage with Propylthiouracil[J]. Chinese Journal of Traditional Medical Science and Technology, 2019, 26(4): 567-570.

[16] Liu Qingquan, Zhang Min, Li Jiansheng, et al. Study on Establishment of Rat Yang Deficiency Syndrome Model by Hydrocortisone Injection[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2018, 24(8): 178-182.

[17] Zhao Jing, Wang Li, Li Li, et al. Study on Rat Blood Stasis Syndrome Model Induced by Macromolecular Dextran[J]. Jilin Journal of Traditional Chinese Medicine, 2019, 39(6): 789-792.

[18] Wang Fang, Li Juan, Chen Gang, et al. Study on Establishment of Rat Spleen Deficiency Syndrome Model by Splenectomy[J]. Chinese Journal of Basic Medicine in Traditional Chinese Medicine, 2020, 26(5): 623-626.

[19] Zhang Yan, Liu Yong, Chen Li, et al. Evaluation of Rat Spleen Deficiency Syndrome Model Established by Subtotal Gastrectomy[J]. Journal of Chinese Medicine, 2019, 47(2): 56-59.

[20] Li Jian, Liu Min, Zhang Yong, et al. Study on Establishment of Rat Kidney-Yang Deficiency Syndrome Model by Castration[J]. Information on Traditional Chinese Medicine, 2018, 35(5): 29-33.

[21] Chen Ming, Li Yan, Wang Hao, et al. Evaluation of Rat Kidney Deficiency Syndrome Model Established by Partial Nephrectomy[J]. Acta Laboratorium Animalis Scientia Sinica, 2020, 28(1): 89-93.

[22] Wang Li, Zhao Jing, Li Li, et al. Study on Rat Blood Stasis Syndrome Model Established by Ligation of Lower Extremity Artery[J]. Liaoning Journal of Traditional Chinese Medicine, 2018, 45(12): 2654-2656.

[23] Zhang Yong, Li Jian, Liu Min, et al. Establishment of Mouse Kidney Deficiency Syndrome Model by Knockout of VDR Gene via CRISPR-Cas9 Technology[J]. Chinese Journal of Traditional Medical Science and Technology, 2021, 28(3): 389-394.

[24] Chen Gang, Wang Fang, Li Juan, et al. Establishment and Mechanism Study of PI3K Gene Knockout Mouse Model of Spleen Deficiency Syndrome[J]. Chinese Journal of Experimental

ISSN: 3079-6709

Traditional Medical Formulae, 2020, 26(12): 134-139.

[25] Zhao Jing, Li Li, Wang Li, et al. Establishment and Evaluation of Rat Blood Stasis Syndrome Model with tPA Gene Knockout[J]. Jilin Journal of Traditional Chinese Medicine, 2020, 40(7): 945-948.

[26] Li Juan, Chen Gang, Wang Fang, et al. Establishment and Evaluation of Rat Model of Diabetic Phlegm-Dampness Syndrome[J]. Chinese Journal of Information on Traditional Chinese Medicine, 2021, 28(4): 67-71.

[27] Liu Yong, Chen Li, Zhang Yan, et al. Establishment and Pathological Characteristics of Rat Model of Hypertensive Blood Stasis Syndrome[J]. Journal of Chinese Medicine, 2020, 48(5): 45-49.

[28] Wang Li, Li Li, Zhao Jing, et al. Establishment of Rat Heart-Spleen Deficiency Syndrome Model by Multi-Factor Composite Modeling[J]. Liaoning Journal of Traditional Chinese Medicine, 2020, 47(3): 634-637.

[29] Zhang Min, Li Jiansheng, Liu Qingquan, et al. Optimization of Rat Yang Deficiency Syndrome Model Established by Multi-Factor Composite Modeling[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2019, 25(11): 156-160.

[30] Li Li, Zhao Jing, Wang Li, et al. Establishment of Rat Blood Deficiency Syndrome Model by Orbital Bloodletting Combined with Cyclophosphamide Injection[J]. Jilin Journal of Traditional Chinese Medicine, 2020, 40(4): 523-526.

[31] Liu Min, Zhang Yong, Li Jian, et al. Establishment of Rat Yin Deficiency Syndrome Model by Dexamethasone Combined with High-Temperature and Dry Environment[J]. Information on Traditional Chinese Medicine, 2021, 38(2): 45-49.

[32] Li Jian, Zhang Yong, Liu Min, et al. Study on Establishment of Rat Yang Deficiency Syndrome Model by Raw and Cold Diet Combined with Low-Temperature Environment[J]. Information on Traditional Chinese Medicine, 2020, 37(5): 56-60.

[33] Wang Fang, Chen Gang, Li Juan, et al. Study on Establishment of Rat Phlegm-Dampness Syndrome Model by Glucocorticoid Combined with High-Fat Diet[J]. Chinese Journal of Basic Medicine in Traditional Chinese Medicine, 2021, 27(3): 389-393.

[34] Liu Yong, Zhang Yan, Chen Li, et al. Establishment of Rat Phlegm-Dampness Syndrome Model by High-Fat Diet + Damp-Heat Environment + Hesperidin Intervention[J]. Journal of Chinese Medicine, 2021, 49(6): 78-82.

[35] Zhang Min, Liu Qingquan, Li Jiansheng, et al. Establishment of Coronary Heart Disease Blood Stasis Syndrome Model by Coronary Artery Ligation Combined with Epinephrine Injection[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2020, 26(15): 145-150.

[36] Liu Min, Li Jian, Zhang Yong, et al. Establishment of Rat Liver Stasis and Blood Stasis Syndrome Model by CUMS Combined with Macromolecular Dextran Injection[J]. Information on Traditional Chinese Medicine, 2021, 38(5): 67-71.

[37] Chen Ming, Wang Hao, Li Yan, et al. Optimization and Mechanism Study of Rat Liver Stasis Syndrome Model Established by Reserpine Combined with CUMS[J]. Acta Laboratorium Animalis Scientia Sinica, 2020, 28(4): 489-494.