



Review article

Research advances on the restorative effect of *Periplaneta americana* extracts on mucosa

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ABSTRACT

In addition to the pharmacological effects of *Periplaneta americana* extracts (PAEs), including their antitumor, hepatic protection, antioxidant, antibacterial, anti-inflammatory, and tissue regeneration characteristics, their mucosal restorative effects have also attracted significant attention. The mucosa serves as a “gateway” into the body and its functions include the surveillance and clearance of bacteria and pathogens; it also has the immunological function of acquiring beneficial antigens from the external environment and removing non-beneficial ones, a mechanism controlled by the mucosal immune system. In the present study, the relevant modern research literature on the mucosal restorative effect of PAEs was reviewed via a summarization of its restorative effects on respiratory, digestive, dermal, and genitourinary mucosa. The aim of doing so was to present a comprehensive understanding of the mucosal restorative effect of PAEs and their related mechanisms and to provide a reference for their further development and clinical application.

1. Introduction

Periplaneta americana (*P. americana*) spreads pathogenic bacteria and parasites and is considered a pest worldwide. However, *P. americana* extract has a long history of clinical application in traditional Chinese medicine (TCM) and has been recorded in herbal medicine works for generations. In the *Zhong Jing of Shen Nong Ben Cao Jing*, it is noted that “*P. americana*, salty in taste and cold in nature, was mainly used to treat blood stasis, crux, chills and fever, eliminate mass, sore throat, internal wind and cold, and infertility, [and] can promote generating body liquids.” The Standards of Chinese Medicinal Materials in Yunnan Province note that the dried insect worms of *P. americana*, which belongs to the Blattidae family, is salty and flat in nature, and affects the heart, liver, spleen, and kidney meridians. It is administered orally to strengthen the spleen and eliminate infantile malnutrition, invigorate blood circulation, and promote water retention and swelling as well as muscle production. It can be used to treat hypochondriac pain, gynecologic abdominal lumps, infantile malnutrition, palpitation, asthma, edema, hot water and fire burns, and various types of wounds and ulcers

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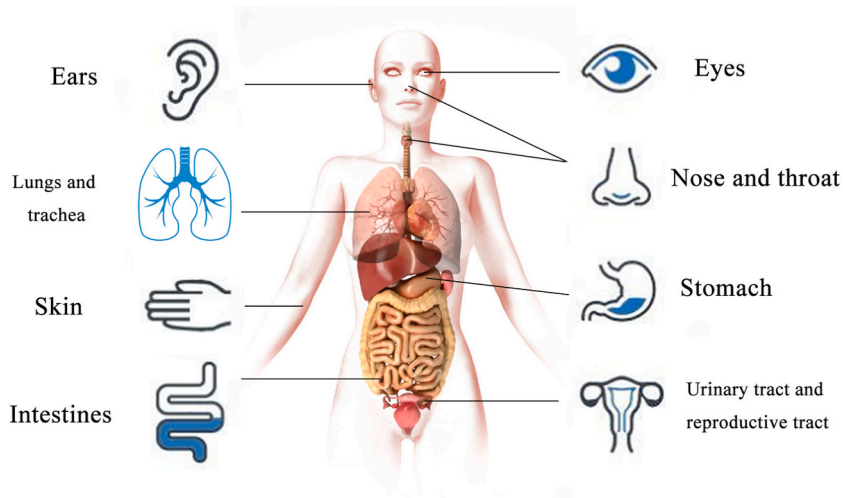


Fig. 1. Human mucosa.

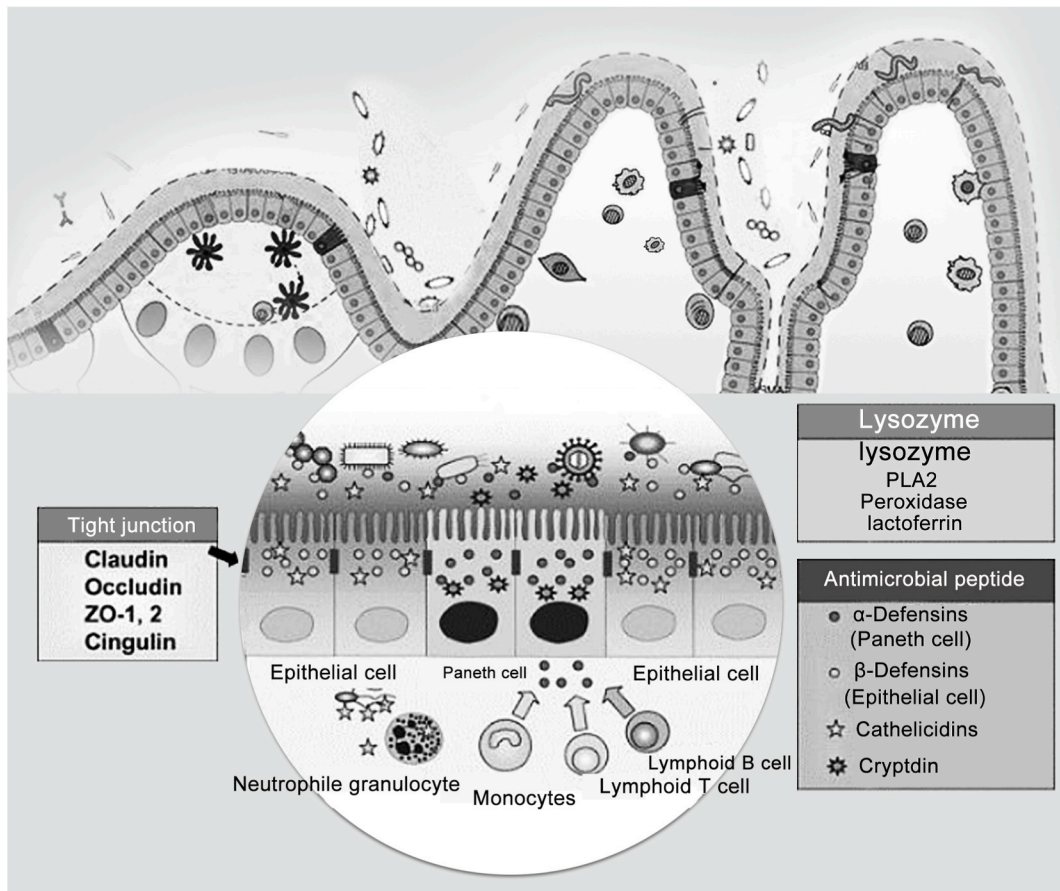


Fig. 2. Biological immune molecules on mucosal surface.

[1]. *Periplaneta americana* extracts is valued for its precise clinical efficacy. Since the 1970s, national and international pharmaceutical researchers have conducted extensive research on the chemical composition and pharmacological mechanisms of *P. americana* extracts. Yang et al. [2] isolated three novel isocoumarin glycoside components from *P. americana* extracts, among which (3

R)-3-ethyl-7-hydroxymethyl-8-hydroxy-3,4-dihydroisocoumarin-6-O- β -D-glucopyranoside could stimulate human dermal fibroblasts to produce collagen (31.2%) at a concentration of 30 $\mu\text{mol}\cdot\text{L}^{-1}$, thereby promoting the restoration of dermal mucosal tissue.

The mucosa is a membranous structure in organisms (e.g., the oral cavity, viscus, the stomach, intestines, and urethra) that comprises epithelial and connective tissue, the latter of which is called the lamina propria and the former the mucosal epithelium, which includes blood vessels and nerves and is capable of secreting mucus. Important mucosa in the human body includes the respiratory mucosa (including nasal, bronchial, and pulmonary mucosa), digestive mucosa (e.g., oral, esophageal, gastric, and intestinal mucosa), eyelid mucosa, and mucosa of the rectum and vulva (Fig. 1). The mucosa separates the body's internal environment from external settings, and the area of mucosa inside the body that has direct contact with external antigens exceeds 400 m². The mucosal immune cells account for approximately 80% of all immune cells in the body. To prevent the occurrence of local mucosal lesions in an environment with multiple antigens, the mucosa in the body forms a complex and constricted defense system known as the mucosal immune system (MIS) [3]. Accordingly, mucosa acts as the first line of defense for the body's immune system.

The MIS refers to the lymphoid tissue that is distributed in the respiratory tract, oral cavity, and gastrointestinal tract, as well as the submucosa of the genitourinary tract and selected exocrine glands and is the main site for conducting local specific immune functions. Some organs of the respiratory, digestive, and reproductive systems are located inside the body; others (e.g., the mouth, nose, and vulva) are always exposed to the external environment. Approximately more than 90% of pathogenic infections occur in the mucosa of the body or are invaded by mucosa. These organs are at high risk of a pathogenic microbial invasion when the host absorbs oxygen through the respiratory organs, essential nutrients through the digestive tract, or (in the case of women) when receiving sperm through the reproductive tract. Mucosal epithelial cells cover the surface of these organs, just as skin covers the exterior of the body, thereby creating a physical immune barrier against the invasion of harmful substances. The barrier function of intact mucosal epithelial tissue (EC) is an important factor in local mucosal innate immunity. Epithelial tissue consists of the skin and gastrointestinal tract, respiratory tract, genitourinary tract and other inner surface mucosal epithelia. Its barrier function includes epithelial cilia movement (peristalsis) and secretion of mucus (kill or inhibit microorganisms and pathogens), such as lysozyme, stomach acid, upper gastrointestinal digestive enzymes, criptidine or α -defensin in the lower digestive tract, colicin produced by *Escherichia coli*, pulmonary β -defensins that promote phagocytosis of surfactant proteins A and D, and normal microflora.

Biological immune molecules on mucosal surfaces must distinguish between beneficial and harmful substances as well as between resident pathogenic bacteria and pathogens. It manages the active uptake of beneficial substances or resident bacteria, and the selective removal of harmful bacteria and pathogens (Fig. 2). In addition, except for the lower respiratory tract (i.e., the lungs), most mucosa-associated organs have "resident flora" that coexist peacefully with the host, creating a mutually beneficial environment. Accordingly, while acting as a gateway into the body, the mucosa concurrently surveys and clears bacteria and pathogens and has the immunological function of acquiring beneficial antigens from the external environment and removing non-beneficial counterparts, a mechanism that is controlled by the MIS [4].

The mucosal barrier is as effective as the skin barrier at maintaining the health of the human body. It comprises mechanical, chemical, microbial, and immune barriers that are unified and coordinated through different molecular regulatory mechanisms, signaling pathways, and biological functions to protect the body against pathogenic bacteria and other harmful substances. Damaged mucosa poses a serious threat to the body in the case of failure of the mucosal barriers and their functions.

The causes of mucosal damage can be divided into internal and external factors. Internal factors occur due to damage caused by the body itself, such as septic inflammation, edema, ulcers, systemic stress, and mucosal damage caused by the malfunctioning of cellular metabolism. External factors, such as outside stimulation, drug therapy, acidic and alkaline stimulation, infection, burns, radiotherapy, and fasting can lead to mucosal barrier damage. Mucosal restoration involves reducing the mucosal inflammatory response, improving mucosal barrier function, and restoring the immunological function of the MIS.

Currently, the research on PAEs is primarily focused on their pharmacological effects, which include hepatic protection anti-tumor, antioxidant, anti-bacterial, and anti-inflammatory influences. A variety of modern TCM preparations have been developed, such as Kangfuxin liquid, Xinmailong injection, Ganlong capsules, and Xiaozheng Yigan tablets. Gao et al. [5] found that PAEs could affect the entire restoration process of trauma (mucosal injury), including reducing the inflammatory response, improving the body's immunity and enhancing antioxidant levels during inflammation, regulating cell growth factors during the formation of new tissue and in regeneration phases, and participate in several cytokine-mediated signaling pathways to achieve the final effect of trauma (mucosal injury) restoration. In the present study, the restorative effects of PAEs on the respiratory, digestive, dermal, and genitourinary mucosa were reviewed to gain a comprehensive understanding of their restorative effects on the body's mucosa and the related mechanisms involved and provide references for their further development and clinical applications.

2. The restorative effects of *Periplaneta americana* extracts on the respiratory mucosa

As an important part of the MIS, the respiratory MIS is a central barrier that protects the respiratory tract from the invasion of pathogens. Secretory immunoglobulin A plays a major role in specific immunity in the respiratory mucosa and is secreted in large quantities by plasma cells that play a key role in the invasion of pathogens. Secretory immunoglobulin A may prevent pathogens from entering the epithelium by blocking contact with the mucosal surface and reducing the adsorption of pathogens to the mucosa [6].

2.1. The restorative effects of *Periplaneta americana* extracts on the nasal mucosa

Nasal mucosal erosion is generally believed to be caused by an immune or vitamin deficiency as well as atmospheric dryness; the pathogenic mechanisms in this regard are mucosal vasoconstriction, local ischemia, and reduced secretion caused by inflammation,

followed by mucosal congestion, edema, excessive mucus secretion, and mucosal epithelial peeling. These factors will lead to mucosal roughness and erosion due to exposure of the submucosal vessels and result in a bleeding tendency. The clinical treatment of nasal mucosal erosion focuses on the restoration of the nasal mucosa. The external use of Kangfuxin liquid (the main component was *Periplaneta americana* extract) was adopted by Luo et al. for wounds with nasal mucosal erosion in combination with an internally administered self-prepared hemostatic formula for the treatment of bleeding in the mucosal region of the anterior nasal septum. The total effective rate was 97.91% after three weeks of continuous administration. The researchers applied Kangfuxin liquid to repair the mucosal erosion wounds of the nasal septum via transnasal administration, thereby solving the problem of nasal bleeding with remarkable efficacy. The above results indicated that Kangfuxin liquid may have the effect of promoting mucosal restoration, revascularization, and the healing of various types of ulcers and wounds [7].

Cheng et al. applied Kangfuxin Liquid for the postoperative irrigation treatment of patients with sinusitis. The duration of mucosal epithelium formation in the study group was significantly shorter than that in the control group. The levels of IL-6 (interleukin-6), TNF (tumor necrosis factor) and Hs-CRP (hypersensitive C-reactive protein) in the study group were lower than those in the control group, and the level of IL-10 (interleukin-10) was higher than that in the control group [8].

2.2. The restorative effects of *Periplaneta americana* extracts on tonsil mucosa

Acute and chronic tonsillitis are common infectious diseases of the upper respiratory tract and are also commonly (and frequently) diagnosed in children. The abundance of lymphoid tissue such as tonsils in children compared to adults, resistance is relatively weak. Moreover, the tonsils are located in the tonsillar fossa of the pharynx, which is easily affected by residual food, pollutants, and pathogenic bacteria, which can result in recurrent tonsillitis and long-lasting illnesses. Chen et al. added Kangfuxin liquid for the anti-infection treatment containing 10 ml/time, 4 min/time, swallowed after containing, 3 times/d and 3 days administration as a course. This was administered three times daily for three days as a course of therapy, based on anti-infection treatment. The clinical results showed that the average time for relieving a sore throat and reducing fever, and the average length of treatment in the Kangfuxin liquid group were significantly shorter than those in the control group (a total therapeutic efficiency of 97.8%) [9].

Liu et al. studied the effect of Kangfuxin liquid oxygen pump atomization on pharyngeal pain, incidence of infection, and wound healing time in patients after low-temperature plasma tonsillectomy. The results showed that the pharyngeal pain score and wound healing time in the experimental group were better than those in the control group at 48 h, 72 h and 96 h after operation [10].

2.3. The restorative effects of *Periplaneta americana* extracts on lower respiratory tract mucosa

Lower respiratory tract infections include acute bronchitis, bronchitis, pneumonia, and tuberculosis, which can be caused by infection, chemotherapy, allergies and other factors. Gu et al. used bronchoscopic injection of Kangfuxin solution combined with anti-tuberculosis drugs to treat cavitary pulmonary tuberculosis. During each treatment, the lesion was cleaned for approximately 5 min under bronchoscopy with normal saline-diluted Kangfuxin solution. The results showed that local drug injection through bronchoscopy was effective in the treatment of cavitary pulmonary tuberculosis, which could effectively control the development of the disease, and the prognosis was good without serious adverse reactions [11].

He et al. adopted Kangfuxin liquid for nebulized inhalation in the treatment of 32 patients with moderate-to-severe inhalation injuries. The clinical results showed that the healing time for these injuries in different areas was significantly shortened, and the incidence of airway stenosis was significantly reduced in the Kangfuxin liquid treatment group. These results suggested that the nebulized inhalation of Kangfuxin liquid could accelerate the shedding of necrotic tissue in the airway, promote the regeneration of airway mucosa, shorten the airway healing time, and reduce the incidence of respiratory tract infection in patients with an inhalation injury [12].

3. The restorative effects of *Periplaneta americana* extracts on digestive mucosa

3.1. The restorative effects of *Periplaneta americana* extracts on oral mucosa

Radiotherapy in the facial-cervical region is generally adopted in the treatment of head and neck tumors, and the oral mucosa is often included in the radiation field. The direct or indirect action of radiation will destroy the compensatively proliferative mechanism of oral mucosal cells and cause damage to the oral mucosal epithelium, resulting in radiation-induced oral mucositis [13,14]. Yuan et al. showed that Kangfuxin Liquid had a significant effect on oral mucositis caused by radiotherapy in patients with head and neck squamous cell carcinoma. Oral mucositis and oral pain scores in the experimental group were lower than those in the control group at 21 and 42 days after radiotherapy. Salivary flow rate, salivary pH, Epidermal Growth Factor (EGF), and amylase levels, CD4⁺ (cluster of differentiation 4)/CD8⁺, CD19⁺/CD69⁺, and natural killer (NK) cell levels were higher in the experimental group. At 21 and 42 days after radiotherapy, the serum levels of TGF- β 1, IL-6, and hs-CRP in the experimental group were lower than those in the control group [15].

Song et al. showed that Kangfuxin Liquid combined with Triamcinolone Acetonide had a significant effect in the treatment of elderly patients with suboral fibrosis, and the total effective rate of the study group was significantly higher than that of the control group. After treatment, the visual analogue scale (VAS), oral mucosal lesion area, and mouth opening degree of the two groups decreased, and the improvement in the study group was better than that in the control group. After treatment, the levels of inflammatory factors including transforming growth factor (TGF)- β 1, interleukin (IL) -2, and tumor necrosis factor (TNF) - α , in the two

groups decreased, and those in the study group were lower than those in the control group. After treatment, the whole blood middle shear rate (MS), plasma viscosity (PV), and fibrinogen (FIB) in the two groups decreased, and those in the study group were lower than those in the control group [16].

3.2. The restorative effects of *Periplaneta americana* extracts on the esophageal mucosa

Esophageal mucosal injury is a common condition of the digestive system with a complex etiology that is influenced by a variety of factors. Common etiologies include smoking, alcohol consumption, diabetes mellitus, and obesity. The different refluxes in patients with common gastroesophageal reflux disease may cause different degrees of damage to the esophageal mucosa in clinical practice. Kangfuxin liquid is a liquid extraction from *P. americana*, the active ingredients of which includes polyols, peptides, and mucoglycosine. Polyols and peptides not only promote mucosal capillary proliferation and improve local blood circulation but also promote the growth of epidermal cells and the proliferation of granulation tissue to enhance wound repair. Mucoglycosine may activate the cellular immune function, promote the phagocytosis of natural killer cells and macrophages, and secrete leukotrienes, interleukin (IL), interferons, and prostaglandins. It can quickly eliminate inflammatory edema while inhibiting the secretion and reducing the acidity of gastric juices, thereby diminishing the excretion of pepsin and forming attack factors for enhancing defensive action. Xu applied Kangfuxin Liquid combined with omeprazole in the treatment of reflux esophagitis (RE). After treatment, the endoscopic grading of the study group was better than that of the control group; the levels of gastrin (GAS) and motilin (MOT) were (176.96 ± 15.43) pg/ml and (324.25 ± 22.56) ng/L, respectively, which were higher than those in the control group. The GerdQ score was (5.32 ± 1.07) points lower than the control group [17].

Radiotherapy provided for patients with thoracic tumors may damage the esophageal mucosa, which can lead to radiation-induced esophagitis. Patients with this condition will experience congestion and edema of the esophageal mucosa, difficulty swallowing, and aching during food intake, resulting in nutritional deficiencies. A study by Xu et al. showed that the application of Kangfuxin liquid, combined with recombinant human granulocyte colony-stimulating factor, was effective in the treatment of radiation esophagitis, which could effectively lower pH in the mouth, alleviate pain, and effectively delay the onset of radiation-induced esophagitis, as well as reduce the overall incidence and the incidence of grade 2 or above radiation-induced mucosal injury [18].

3.3. The restorative effects of *Periplaneta americana* extracts on gastric mucosa

The components involved in the five-level gastric mucosal protection mechanism are collectively known as “gastric mucosal protective factors”, while components with an aggravating and damaging effect on gastric mucosa are called “gastric mucosal aggressive factors.” The underlying mechanism of gastric mucosal damage is an imbalance between these protective and aggressive factors. Gastric ulcer is a multifactorial disease with a complex etiology, the pathogenesis of which is not yet fully understood and is currently generally considered to result from a combination of multiple factors. The recurrence of gastric ulcers is closely related to the quality of ulcer healing, which requires not only the restoration of mucosal defects but also the restoration and reconstruction of submucosal structures. Therefore, the key to the clinical treatment of gastric ulcers is the restoration of the gastric mucosa.

Fu et al. revealed that PAE was able to reduce ethanol stimulation of the NLRP3 inflammasome/Caspase-1 pathway while affecting inflammation and oxidative stress by regulating pro-inflammatory cytokines (IL-18, tumor necrosis factor alpha [TNF- α], IL-6, and IL-1 β) and oxidative stress factors (myeloperoxidase [MPO] and superoxide dismutase [SOD]), thus suggesting a significant protective effect of PAE against gastric injury caused by ethanol, both in vitro and in vivo [19].

Zhou et al. observed the effect of Kangfuxin Liquid on gastric ulcers and gastrointestinal hormone levels. The results showed that the level of TNF- α in the Kangfuxin Liquid group was lower than that in the control group, and the level of SOD was higher than that in the control group. After treatment, the level of gastrin in the Kangfuxin Liquid group was higher than that in the control group, and the level of pepsinogen I was lower than that in the control group [20]. Kang studied the effect of Kangfuxin Liquid on oxidative stress and cellular immune status in patients with gastric ulcer. The clinical results showed that the total effective rate in the observation group was 97.67% higher than that in the control group (81.40%). After 2 and 4 weeks of treatment, the serum superoxide dismutase (SOD) in the observation group were (75.65 ± 7.56) and (78.61 ± 7.91) U/ml, respectively, which were higher than those in the control group. The catalases (CAT) were (12.59 ± 1.78) and (15.56 ± 2.03) U/ml, respectively, which were higher than those in the control group. Serum malondialdehyde (MDA) were (4.01 ± 0.53) and (3.71 ± 0.43) nmol/ml, respectively, which were lower than those in the control group. After 2 and 4 weeks of treatment, the levels of CD3⁺ and CD4⁺ in the observation group were higher than those in the control group, and the level of CD8⁺ was lower than that in the control group [21].

3.4. The restorative effects of *Periplaneta americana* extracts on intestinal mucosa

Ulcerative colitis (UC) has a recurrent and long-lasting course, and many researchers believe that multiple factors, such as persistent and recurrent intestinal infections, an impaired intestinal mucosal barrier, an imbalance in intestinal MIS, genetics, and environment all contribute to the development of UC. Previous studies have shown Traditional Chinese medicines are efficacious against UC.

Xue et al. applied PAEs to a rat model with UC and showed that PAE could promote intestinal mucosal restoration by inhibiting IL-13 expression in rats with UC. The findings also suggested that the expression of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) release were increased in an oxazolone (OXZ)-induced colitis model, and NO and iNOS were positively correlated with myeloperoxidase (MPO) activity. Following PAEs treatment, the expressions of NO and iNOS were significantly decreased in budesonide

(BUN) and *P. americana* extract –40 treatment groups. These results further confirmed the therapeutic effect of PAEs on OXZ-induced colitis [22].

Chen et al. studied the effects of Kangfuxin Liquid combined with mesalazine on inflammatory factor levels, oxidative stress response, and prognosis in patients with ulcerative colitis. The clinical results showed that the total effective rate in the observation group increased, and the recurrence rate decreased. The disappearance time of symptoms (diarrhea, tenesmus, vomiting, and abdominal pain) was shorter in the observation group than in the control group. After one month of treatment, the levels of serum interleukin-23 (IL-23), interleukin-17 (IL-17), interleukin-1 β (IL-1 β), lipid peroxide (LPO), and nitric oxide (NO) in the two groups decreased, and those in the observation group were lower than those in the control group. The levels of serum superoxide dismutase (SOD) in the two groups were increased, and the observation group was higher than the control group [23].

3.5. Repair effect of *Periplaneta americana* extracts on anorectal mucosa

Acute suppurative infection of the anorectal soft tissue and the surrounding space is called a perianal abscess. Luo et al. used Kangfuxin Liquid to treat perianal abscess and observed its effect on wound healing and inflammatory response after perianal abscess surgery. The clinical results showed that after 14 days of treatment, the total effective rate of the observation group was 98.04, which was significantly higher than that of the control group. The wound edema score at the third day after operation, wound exudation score at the 7th day after operation and VAS score in the observation group were lower than those in the control group. The levels of serum inflammatory factors IL-8, IL-17, and ACTA in the observation group were significantly lower than those in the control group [24].

4. The restorative effects of *Periplaneta americana* extracts on dermal wound mucosa

Dermal mucosal injuries are classified into infectious lesions (e.g., herpes zoster, herpes simplex, warts, fungi, bacterial infections), non-infectious lesions (acute injuries, blood contamination, chemical injuries, burns), and skin tumors (malignant melanoma, Kaposi's sarcoma, lymphoma). Ordinary dermal mucosal injuries typically heal spontaneously. Clinically, the dermal mucosal wounds that are caused by various external or intrinsic factors and are slow to heal or have not healed after more than one month of treatment are called chronic refractory wounds, such as diabetic dermal ulcers, acquired immunodeficiency syndrome combined with dermal mucosal lesions, tumor radiation skin mucosal injury, post-operative anal fistula wounds, and pressure sores.

4.1. The restorative effects of *Periplaneta americana* extracts on dermal wounds in diabetes mellitus

Diabetic dermal wounds heal difficultly because of impaired local blood perfusion, the reduced phagocytosis of leukocytes under a hyperglycemic internal environment, and a decreased resistance to infection. In the pathogenesis of diabetic wounds, the elevated expressions of matrix metalloproteinase-9 (MMP-9) will disrupt the balance of synthesis and degradation of extracellular matrix, resulting in difficult wound healing. In addition, the expression of MMP9 gradually decreases as the wound-healing process progresses. Therefore, PAEs may promote diabetic anal fistula wound-healing through multicomponent regulation and multi-target synergy [25].

Zhang et al. used Kangfuxin Liquid combined with cilostazol to treat diabetic foot (DF). After 2 weeks of continuous medication, the total effective rate of treatment in the observation group was 95.35%, which was higher than 81.40% in the control group. The wound area shrinkage rate of the observation group was $(84.26 \pm 6.71) \%$, which was higher than that of the control group $(66.35 \pm 4.89) \%$; the healing time of foot wound was $(10.31 \pm 1.05) \text{ d}$, which was shorter than $(12.26 \pm 1.75) \text{ d}$ in the control group; the motor nerve conduction velocity and sensory nerve conduction velocity of the observation group were $(44.58 \pm 4.75) \text{ m/s}$ and $(40.59 \pm 3.87) \text{ m/s}$, respectively, which were faster than those of the control group $(39.75 \pm 4.15) \text{ m/s}$ and $(34.18 \pm 3.09) \text{ m/s}$ [26].

4.2. The restorative effects of *Periplaneta americana* extracts on dermal wounds of the radiation dermatitis

Ma et al. used Kangfuxin Liquid combined with basic fibroblast growth factor (bFGF) in the treatment of radiation dermatitis in elderly patients with breast cancer. The VAS visual analogue score of the observation group was lower than that of the control group at 3 days and 7 days after treatment. After 2 weeks of treatment, the curative effect of the observation group was significantly higher than that of the control group (89.19% VS 70.45%), and the average wound healing time was significantly less than that of the control group $[(18.81 \pm 2.59) \text{ d VS } (25.34 \pm 2.43) \text{ d}]$. The levels of IL-6 and TNF- α were lower than those in the control group, and the level of EGF was higher than that in the control group. The radiation skin reaction RISRAS score was lower than the control group, and the KPS functional status score was higher than the control group [27].

Radiotherapy for cervical cancer almost inevitably causes perineal skin and mucosal damage. Yu et al. used Kangfuxin Liquid to wash the perineum to prevent and treat radioactive skin mucosal injury caused by radiotherapy for cervical cancer. The results showed that compared with the control group, the degree of skin mucosal injury in the treatment group was significantly reduced, and the degree of pain was significantly reduced [28]. Zhuang et al. showed that the application of Kangfuxin liquid and *P. americana* powder combined with Dermlin for the treatment of radiation dermatitis, significantly reduced the severity of radiation dermal damage and avoided the occurrence of grade-4 dermal damage, while concurrently prolonging the occurrence of dermal lesions and accelerating the healing of dermal damage [29].

4.3. The restorative effects of *Periplaneta americana* extracts on dermal wounds caused by injury

Liang used Kangfuxin Liquid in mouse dermal cell injury model to evaluate the anti-fibrosis effect of Kangqi in mouse dermal cell injury model. Cell biology experiments showed that the treatment with Kangfuxin liquid increased cell proliferation and repaired skin wounds in animal models. It was also found that the activation of signal transducer and activator of transcription 3 (STAT3) signaling pathway was the core molecular mechanism of Kangfuxin liquid in repairing skin wounds [30].

Lia et al. revealed that applying PAEs to skin injuries promoted the proliferation of epidermal cells and fibroblasts to promote early wound healing and granulation tissue maturation, together with the proliferation of epidermis during the middle and late stages of healing. The possible mechanism here may be related to the proliferative effect of PAE on various dermal cells, chemotaxis, the migration of fibroblasts, a pro-angiogenic effect, and stimulating the secretion of growth factors [31].

4.4. The restorative effects of *Periplaneta americana* extracts on dermal wound mucosa caused by burning

Patients with large/severe burns primarily experience clinical problems, such as the poor regeneration of granulation in the wound, a long wound-exposure time that makes it vulnerable to infection, and poor blood circulation in local tissue, all of which require timely and appropriate treatments according to the actual situation of the patients. Wang et al. found that the PAE emulsion had a good protective effect on deep degree-II burns in rats and may have accelerated the healing of these burn types in rats. The mechanism in this instance may have been related to promoting the release of vascular endothelial growth factor from the traumatized tissue and reducing the level of TNF- α and IL-1 in rats [32].

Wang et al. used Kangfuxin Liquid to treat children's burns and scalds, and observed its repair effect on children's wounds. After 2 weeks of continuous treatment, the levels of IL-6 and IL-7 in the observation group were significantly lower than those in the control group, the wound healing time was shorter than that in the control group, and VancouverScarScale (VSS) was lower than that in the control group [33].

4.5. The restorative effects of *Periplaneta americana* extracts on wound mucosa in pressure sores

A pressure sore is a common chronic ulcer, the main clinical manifestation of which is that it does not heal over time and causes localized superficial dermal lesions. Dong et al. used Kangfuxin Liquid combined with Jingwanhong Ointment to treat patients with bedsore. The clinical results showed that after 4 weeks of continuous administration, the VAS scale data of the observation group were lower than those of the control group. The data of inflammatory factors such as IL-1 β were lower than those in the control group; the clinical symptom data such as the disappearance time of bedsore exudate in patients were lower than those in the control group [34].

A study conducted by Li employed the topical application of Kangfuxin liquid in the treatment of pressure sores; the results showed that this could accelerate the detachment of necrotic tissue, improve local blood circulation, and promote the growth of granulation tissue, thus supporting the healing of pressure sores [35].

5. The restorative effects of *Periplaneta americana* extracts on genitourinary mucosa

Mucosal injury is the pathological basis for a range of bladder inflammations, e.g., chemical, radiation, glandular, chronic bacterial refractory, and interstitial cystitis. Hu et al. used bladder perfusion of Kangfuxin solution combined with thrombin and epidermal growth factor to treat 34 cases of radioactive hemorrhagic cystitis of cervical cancer. The study showed that 31 (91%) patients had hematuria and LUTS (Lower Urinary Tract Symptoms) disappeared after 6–13 days of continuous treatment without recurrence. Three patients (9%) with cervical cancer had hematuria again and continued treatment. Finally, all 34 patients with and without recurrent hematuria (3 and 31, respectively) and LUTS achieved a complete remission rate (CR) of 100% after 6–22 days of intravesical instillation. No adverse events were reported during treatment and 2-year follow-up [36].

Xie et al. confirmed that PAE could not only reduce bladder mucosal defects and inflammatory infiltration but also the expression of heat shock proteins 60 and 70 in bladder mucosa, thus repairing damaged bladder mucosa, strengthening the barrier effect of the bladder wall, and stopping inflammation [37].

Li used Kangfuxin Liquid combined with recombinant human interferon α -2 b to treat cervicitis. Continuous treatment for a week, the observation group in the vulva pruritus reduction time, burning fever reduction time, leucorrhea abnormal reduction time, lumbar acid symptom reduction time, urine pain reduction time were shorter than the control group. After treatment, the levels of inflammatory factors IL-6, hs-CRP and PCT in the observation group were significantly lower than those in the control group [38].

Kangfuxin liquid combined with a Baofukang suppository was adopted by Wang et al. in the treatment of chronic cervicitis with human papillomavirus infection. Here, Kangfuxin liquid could eliminate inflammatory edema, improve microcirculation in the wound, accelerate the mucosal repair of damaged tissue, and improve the immune protection of the body in multiple aspects [39].

Scrotal gangrene is necrotizing fasciitis involving the perineum, external genitalia, and perianal region. The early symptoms include edema and skin redness of the scrotum, hard nodules, increased skin sensitivity, blister formation, and pain. Dressing changes using a gauze strip containing Kangfuxin liquid was adopted by Xue et al. in the treatment of scrotal gangrene. The results showed that, in the experimental group, the therapeutic duration was significantly shortened, and the average length of hospital stay was reduced from 45 to 18 days [40]. Additionally, research conducted by Li et al. showed that the treatment of patients with erosive glansitis using Kangfuxin liquid significantly improved clinical efficacy, reduced the incidence of adverse effects, decreased the recurrence rate, and improved prognosis [41].

Table 1*Periplaneta americana* extract regulates mucosal-related inflammatory factors and immune factors.

Mucosal site	Reduce (inflammation related factors)	Elevated (immune-related factors)
Nasal mucosa [8]	IL-6, TNF, Hs-CRP	IL-10
Oral mucosa [15,16]	TGF- β 1, IL-2, IL-6, Hs-CRP	EGF, CD4 ⁺ /CD8 ⁺ , CD19 ⁺ /CD69 ⁺ , NK
Gastric mucosa [19,20]	IL-18, TNF- α , IL-6, IL-1 β	MPO, SOD, CAT, CD3 ⁺ , CD4 ⁺
Intestinal mucosa [23]	NO, iNOS, IL-1 β , IL-1 β , IL-17, IL-23, LPO	SOD
Anorectal mucosa [24]	IL-18, IL-17	
Skin mucosa [25,27,32]	MMP-9, IL-1, IL-6, IL-17, TNF- α	EGF, VEGF
Urinary and Reproductive mucosa [38]	IL-6, hs-CRP, PCT	

6. Discussion

Mucosal damage refers to mucosal damage that occurs in the body's five senses, digestive tract, respiratory tract, urogenital tract, and anus, and can accompany or exist independently of skin and systemic diseases. Mucosal injury first destroys the physical barrier of the mucosa, which then leads to loss of mucosal immune function, invasion of microorganisms and pathogens, and ultimately leads to the occurrence of diseases.

Periplaneta americana extract is a clinically effective drug for mucosal repair. A literature search revealed that *Periplaneta americana* extract could regulate the expression of inflammatory and immune factors related to the body's mucosa (Table 1), thereby producing a repair effect on the mucosa.

However, in actual clinical use, there are still problems with the formulation of *Periplaneta americana* extract, such as a single dosage form and unclear dose effect. Currently, commercially available cockroach extract drugs are represented by Kangfuxin liquid, and their indications are for oral administration: for blood stasis, stomachache and bleeding, and gastric and duodenal ulcers, as well as auxiliary treatment for yin deficiency pulmonary tuberculosis and pulmonary tuberculosis. External use: For wounds such as golden sores, trauma, ulcers, fistulas, burns, scalds, and bedsores. Despite recent research and reports on the use of Kangfuxin Liquid in the repair of mucous membranes in the oral cavity, tonsils, nasopharynx, esophagus, and genitourinary tract, its efficacy is accurate; However, due to the fact that the above applications are not within the scope of drug indications, they have not received widespread attention and application in practical clinical applications, resulting in certain limitations in the clinical application of Kangfuxin Liquid.

7. Summary and future research prospects

Currently, the clinical treatment of mucosal injury is based on immunosuppressive or hormonal therapy, and the guidelines for administering these drugs are extremely strict. In addition to being highly susceptible to adverse reactions, irregular administration may also lead to drug resistance in patients. In recent years, there has been significant progress in research on the restorative effect of PAEs on mucosa in China and abroad. Research on the restorative effects of PAEs on the mucosa of the digestive tract has achieved particular breakthroughs, revealing part of the molecular mechanism of PAEs in the restorative effect of the oral and gastrointestinal mucosa.

Although the efficacy of *Periplaneta americana* extract in the clinical repair of respiratory tract mucosa, skin mucosa, and urogenital mucosa is accurate, its pharmacological mechanism is not yet in-depth, and further research is needed for the selection of drug dosage forms, pharmacokinetics, and dosage. This requires a large number of scientific researchers to attach importance to the clinical repair of body mucosa with *Periplaneta americana* extract, use existing new technologies and methods to conduct more in-depth research and development, and further explore the molecular mechanism of a single substance in the mixture of *Periplaneta americana* extract in the repair of different parts of the body mucosa, and clarify its dose-effect relationship, with a view to developing new drugs for clinical repair of body mucosa with *Periplaneta americana* extract, providing reference for formulation improvement and dosage optimization.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article. </p>

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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