Mechanistic evaluation of gastro-protective effects of KangFuXinYe on indomethacin-induced gastric damage in rats

LI Qi-Juan¹, WANG Zhan-Guo², XIE Yu¹, LIU Qiao¹, HU Hui-Ling¹,* , GAO Yong-Xiang³,*

¹ College of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China; ² Metabonomics Synergy Innovation Laboratory, School of Medicine and Nursing, Chengdu University, Chengdu 610106, China; ³ College of Basic Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China

Available online 20 Jan., 2020

[ABSTRACT] KangFuXinYe (KFX), the ethanol extract of the dried whole body of Periplaneta americana, is a well-known important Chinese medicine preparation that has been used to treat digestive diseases such as gastric ulcers for many years in China. However, its therapeutic effect and mechanism are not yet well understood. Thus, the aim of this study was to investigate the gastro-protective effects of KangFuXinYe (KFX) in indomethacin-induced gastric damage. Rats were randomly divided into six groups as follows: control, treated with indomethacin (35 mg·kg⁻¹), different dosages of KFX (2.57, 5.14 and 10.28 mL·kg⁻¹, respectively) plus indomethacin, and sucrafate (1.71 mL·kg⁻¹) plus indomethacin. After treatment, rat serum, stomach and gastric homogenates were collected for biochemical tests and examination of histopathology firstly. Rat serum was further used for metabolomics analysis to research possible mechanisms. Our results showed that KFX treatment alleviated indomethacin-induced histopathologic damage in rat gastric mucosa. Meanwhile, its treatment significantly increased cyclooxygenase-1 (COX-1), prostaglandin E₂ (PGE₂) and epidermal growth factor (EGF) levels in rat serum and gastric mucosa. Moreover, KFX decreased cyclooxygenase-2 (COX-2) and interleukin-6 (IL-6) levels. Nine metabolites were identified which intensities significantly changed in gastric damage rats, including 5-hydroxyindoleacetic acid, sphingosine 1-phosphate, and indometacin. These metabolic deviations came to closer to normal levels after KFX intervention. The results indicate that KFX (10.28 mL·kg⁻¹) exerts protective effects on indomethacin-induced gastric damage by possible mechanisms of action (regulating tryptophan metabolism, protecting the mitochondria, and adjusting lipid metabolism, and reducing excessive indomethacin).

[KEY WORDS] KangFuXinYe; Indomethacin-induced gastric damage; Inflammation; Metabonomic analysis


Introduction

As early as about two thousand years BC, animal medicine has been recorded in the Oracle of the Yin Ruins. Although the number of animal medicine is less which compared with plant medicine, it has significant physiological activity, and is considered as “sentient flesh and blood products” in the theory of traditional Chinese medicine [1]. Cockroach is an ancient insect and it’s also one of the most adaptable insects among the entire animal kingdom which is usually known as a global health pest [2]. However, cockroach has another identity which could treat the illness as a medicine in China. In southern China, there is a kind insect of cockroach, Periplaneta americana (PA), as the dominant species which is a cockroach variety for medicinal purposes in modern medicine. Researches on PA mainly focus on pest control in the past, but the new discoveries in the PA has emerged in modern researches. It was found that PA has antitumor [3-5], antioxidative [6-7], antibacterial [8-9], anti-inflammatory [10], tissue-repairing [11] and wound-healing activities [12].

KangFuXinYe (KFX), the ethanol extract of the dried whole body of PA, has been used generously in treatments for digestive system diseases such as gastric ulcer [13], ulcerative colitis [14], peptic ulcer [15], gastro-esophageal reflux disease by the method of drug combination [16] and others like burns [17], dental ulcer [18], anal fistula healing [19], and Pediatric hand, foot and mouth disease [20]. It has been reported that KFX has a protective effect on gastric mucosa by increasing its mucus, bicarbonate and blood flow, improving microcirculation, promoting gastric mucosal repair [21], and inhibiting...
the activation of NF-κB pathway \[22\].

Gastric ulcer, one of the most commonly gastrointestinal diseases in clinic, could be caused by inadequate dietary habits, cigarette smoking, stress, infection by *Helicobacter pylori*, and excessive use of non-steroidal anti-inflammatory drugs (NSAIDs) \[23\]. Indomethacin is a kind of the NSAIDs with analgesic and antipyretic effects for the treatment of arthritis, gout, and tendinitis \[24\]. Additionally, indomethacin could induce gastric ulcers in rats or mice mainly through the inhibition of cyclooxygenases (COX) which exists in two isozymes, COX-1 and COX-2 \[25-26\]. COX-1 is considered to be basically associated with the production of prostaglandins (PGs) under normal physiological conditions, and COX-2 expression and activities are extremely low in the normal gastrointestinal tract \[27\]. Inhibition of COX causes the PG deficiency that is important to the gastric ulcerogenic response such as inflammation, erosions and ulcers \[25-28\]. However, few scientific studies have showed the influences of KFX on COX in indomethacin-induced gastrical damage model. Thus, we used indomethacin-induced gastric damage in rats as the model and tested the gastro-protective effects of KFX in this model. On the other hand, metabolomics allows quantitative analysis of the dynamic changes of metabolites which are influenced by organismal responses to physiological, pathological and various chemical stimulation \[29\]. Metabolites in vivo levels reflect the regulatory effects of medication on metabolisms relative to pharmacology \[30\]. Therefore, in this study, metabolites in serum were profiled using a liquid chromatography time-of-flight mass spectrometry (LC/TOF-MS) approach, and the metabonomics data were processed using multivariate statistic analysis. The potential biomarkers were further identified to better understand therapeutic efficacies and mechanisms of KFX in treating indomethacin-induced gastric damage.

**Materials and Methods**

**Animals and groups**

6-Week-old male Sprague-Dawley (SD) rats (body weight, 200 ± 20 g) were purchased from Dossy Biological Technology Co., Ltd. (Chengdu, China). All the animals were housed in a conventional animal house with controlled temperature (24 ± 2 °C) and 12 h light/dark cycles. The rats were supplied with free access to food and water during accommodation for 1 week and experimental periods. Experiments adhered to the guidelines of Experimental Animal Ethics Committee of Chengdu University of Traditional Chinese Medicine [the protocol number: 2014 DL-023]. The rats were randomly divided into six groups (n = 8 for each group) and treated as follows: (i) control group (oral supplementation with double distilled water); (ii) indomethacin 35 mg·kg⁻¹ (Huaxia Chemical Reagent Co., Ltd., China); (iii) indomethacin 35 mg·kg⁻¹ and KFX 2.57 mL·kg⁻¹ (Goooddoctor Pharmaceutical Group, China); (iv) indomethacin 35 mg·kg⁻¹ and KFX 5.14 mL·kg⁻¹; (v) indomethacin 35 mg·kg⁻¹ and KFX 10.28 mL·kg⁻¹; (vi) indomethacin 35 mg·kg⁻¹ and sucralfate 1.71 mL·kg⁻¹. The rats were orally given indomethacin once for 1 h and then treated with KFX or sucralfate once for an additional 4 h by the method of intragastric administration.

**Collection of gastric sample for histopathology**

After 4 h of treatment, the rats were sacrificed and the stomach was excised carefully, opened along the greater curvature, and then washed with ice-cold saline solution. The gastric lesion in the rats was observed in a thread-like pattern and the length of the ulcerous lesion was measured immediately using calipers at the end of the experiments. The gastric mucosal damages were expressed as an ulcer index, in which the ulcer index was calculated using a 0–3 scoring system to evaluate the severity of each damage. The scoring system was defined based on the length of the damage as follows: 0 = no ulcerous lesion; 1 = ulcerous lesion < 1 mm length; 2 = ulcerous lesion 2–4 mm length and 3 = ulcerous > 4 mm length \[31\]. Then, the gastric tissues were fixed in 10% formalin and embedded in paraffin, followed by being sectioned into 2 μm samples using a microtome. The paraffin embedded tissues were dried at 60 °C for 1 h and deparaffinized using a dip of xylene and a gradient concentration of ethanol. The microslide was stained with hematoxylin and eosin stain, and observed under a microscope (BX51, Olympus, Tokyo, Japan).

**Cytokines**

The concentrations of COX-1, COX-2, PGE₂, IL-6, TNF-α, and EGF in blood serum and supernates of homogenised stomach tissue were measured by enzyme-linked immunosorbent assay using commercial ELISA kits (Jingkang Biological engineering Co., Ltd., Shanghai, China) according to the manufacturer’s instructions.

**Metabonomic analysis**

**Sample collection**

Blood was also collected from tail vein after 4 h of the treatment of KFX or sucralfate, and let stand for 20 mins at room temperature.

**Sample preparation**

The blood of each rat was centrifuged at 3500 r·min⁻¹ for 10 min at 4 °C, and the supernatant was stored at −80 °C and was thawed prior to analysis. A total of 100 μL of the supernatant was added to 200 μL of methanol, and then the mixture was shaken vigorously for 1 min. It was centrifuged at 12 000 r·min⁻¹ for 10 min at 4 °C before LC/TOF-MS analysis.

**QC samples and sequence analysis**

A total of 100 μL from all blood samples was pooled to generate a pooled quality control (QC) sample, and was prepared in the same preparation method that described above for the blood. This pooled sample was used to validate the stability of the LC-MS system. All samples were randomly coded and subjected into LC/TOF-MS analysis. A QC sample was run every 6 samples to monitor the stability of the LC-MS system.

**LC/TOF-MS analysis**

A Shimadzu LC-30A system equipped with an AC-
Table 1  Effects of KangFuXinYe (KFX) on indomethacin-induced gastric ulcer index and ulcerous incidence in rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence /%</th>
<th>Ulcer index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0/8 (0)</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>Indomethacin 35 mg·kg⁻¹</td>
<td>7/8 (87.5)</td>
<td>13.1 ± 11.4</td>
</tr>
<tr>
<td>Indomethacin 35 mg·kg⁻¹ + KFX 2.57 mL·kg⁻¹</td>
<td>6/8 (75)</td>
<td>6.0 ± 3.4*</td>
</tr>
<tr>
<td>Indomethacin 35 mg·kg⁻¹ + KFX 5.14 mL·kg⁻¹</td>
<td>5/8 (62.5)</td>
<td>5.0 ± 2.6**</td>
</tr>
<tr>
<td>Indomethacin 35 mg·kg⁻¹ + KFX 10.28 mL·kg⁻¹</td>
<td>2/8 (25)</td>
<td>4.0 ± 2.0**</td>
</tr>
<tr>
<td>Indomethacin 35 mg·kg⁻¹ + sucralfate 1.71 mL·kg⁻¹</td>
<td>3/8 (37.5)</td>
<td>3.3 ± 1.2**</td>
</tr>
</tbody>
</table>

*P < 0.01 vs the control group, †P < 0.05 vs the indomethacin-treated group, ‡P < 0.01 vs the indomethacin-treated group.
Fig. 1  Effects of KFX on indomethacin-induced gastric damage in rats. Macroscopic (upper panel) and histopathological (lower panel) observation of gastric mucosa. The solid arrows indicated the ulcerations (upper panel); the solid and dotted arrows indicated erosion and blood congestion, respectively (lower panel).
high dose effectively increased the contents of PGE$_2$, COX-1 and EGF, and decreased the levels of COX-2 and IL-6 ($P < 0.05$).

Compared with the gastric homogenates of the control group, the levels of PGE$_2$, COX-1, TNF-α and EGF were appreciably lower ($P < 0.05$). The levels of COX-2 were significantly higher in the model group ($P < 0.05$), and the content of IL-6 was decreased with no significant difference (Fig. 2B). It is similar to the results of the serum, KFX treatment could regulate the levels of cytokines, which were that the levels of COX-2 and IL-6 were reduced and the levels of PGE$_2$, COX-1, TNF-α and EGF were augmented, especially in high dose of KFX ($P < 0.05$).

**Effects of KFX based on metabolite profiling**

To investigate the global metabolism variations and evaluate the therapeutic effects of KFX in the rats, all observations acquired in both positive and negative ion mode were analysed with multivariate analyses. PCA, the most common unsupervised method for handling metabonomics data, was applied to obtain an overview of metabolic changes. As shown in score plots of PCA (Fig. 3A), an approximate separation was observed among normal control group, model group and KFX-treated group (green circles, red circles and blue circles, respectively). PLS-DA was further performed for clearer separation, and exhibited satisfactory classification (Fig. 3B). As showed in Fig. 3B, the metabolic profiling of serum in gastric damaged rats deviated considerably from those normal rats. This observation indicated that indomethacin-induced gastric damage disturbed the endogenous substances metabolism and significantly altered the metabolite fingerprints of serum compared to the normal state. After treatment with KFX (high dose), the altered metabolite profiling found in model group was significantly reversed and was much closer to the normal control group. The metabolic pro-

---

**Fig. 2** The concentration of serum (A) and gastric homogenates (B) on indomethacin-induced gastric damage in rats (mean ± SD, n = 8). *P < 0.05 vs control group, #P < 0.05 vs model group.
filing was near the normal physiological position, indicating a recovery of the disturbed metabolic state and which revealed good performance of the KFX in the recovery of the indomethacin-induced inflammatory metabolic state.

Given the VIP values (> 1.0) and statistical tests (P < 0.05), 17 metabolites in the positive mode and 18 in the negative mode were selected for HPLC-MS/MS experiments. A total of 9 metabolites (3 in the positive mode and 6 in the negative) were confirmed by online databases (Table 2). The intensities of 7 biomarkers decreased significantly in model group relative to those in normal control group (P < 0.05 or 0.01), which include pantothenic acid, isobutyryl carnitine, 5-hydroxyindoleacetic acid, 4-hydroxyindole, indoxylsulfuric acid, indolelactic acid, and sphingosine 1-phosphate. By contrast, the intensities of these markers increased markedly in KFX-treated group (P < 0.05 or 0.01) except that the intensity of pantothenic acid showed no significant change. Simultaneously, the intensities of 3-methyl-2-oxovaleric acid and

Table 2  Identification of potential biomarkers in rat serum

<table>
<thead>
<tr>
<th>tR/min</th>
<th>Measured</th>
<th>Calculated</th>
<th>Error (ppm)</th>
<th>Elemental composition</th>
<th>Scan mode</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.85</td>
<td>218.1034</td>
<td>219.2350</td>
<td>−1.1316</td>
<td>C7H17NO5</td>
<td>-</td>
<td>Pantothenic acid</td>
</tr>
<tr>
<td>5.01</td>
<td>232.1548</td>
<td>231.2887</td>
<td>0.8661</td>
<td>C11H21NO4</td>
<td>+</td>
<td>Isobutyryl carnitine</td>
</tr>
<tr>
<td>6.11</td>
<td>190.0502</td>
<td>191.1834</td>
<td>−1.1332</td>
<td>C10H9NO3</td>
<td>-</td>
<td>5-Hydroxyindoleacetic acid</td>
</tr>
<tr>
<td>6.14</td>
<td>134.0589</td>
<td>133.0528</td>
<td>1.0061</td>
<td>C6H19NO</td>
<td>+</td>
<td>4-Hydroxyindole</td>
</tr>
<tr>
<td>6.21</td>
<td>212.0024</td>
<td>213.21</td>
<td>−1.2076</td>
<td>C6H19NO4S</td>
<td>-</td>
<td>Indoxylsulfuric acid</td>
</tr>
<tr>
<td>6.54</td>
<td>129.0556</td>
<td>130.1418</td>
<td>−1.0862</td>
<td>C6H19O3</td>
<td>-</td>
<td>3-Methyl-2-oxovaleric acid</td>
</tr>
<tr>
<td>7.82</td>
<td>204.0664</td>
<td>205.2100</td>
<td>−1.1436</td>
<td>C11H21NO5</td>
<td>-</td>
<td>Indolelactic acid</td>
</tr>
<tr>
<td>11.76</td>
<td>378.2359</td>
<td>379.4718</td>
<td>−1.2359</td>
<td>C13H18NO4P</td>
<td>-</td>
<td>Sphingosine 1-phosphate</td>
</tr>
<tr>
<td>14.99</td>
<td>358.0839</td>
<td>357.0768</td>
<td>1.0071</td>
<td>C11H16ClNO4</td>
<td>+</td>
<td>Indometacin</td>
</tr>
</tbody>
</table>

The metabolites were confirmed by databases and identified by reference compound.
indometacin were significantly enhanced in model group relative to those in normal control group ($P < 0.05$ or 0.01) but significantly depressed in KFX-treated group relative to those in normal control group ($P < 0.05$ or 0.01). For the abovementioned metabolites, there was the significant difference between normal control group and KFX-treated group ($P < 0.05$) in addition to 5-hydroxyindoleacetic acid and indolelactic acid ($P > 0.05$).

**Discussion**

Although KFX has a definite protective effect on gastrointestinal tract, the exact mechanism of KFX remains poorly understood. Thus, we attempted to examine the effects of KFX on indometacin-induced gastric damages in rats and explore key potential biomarkers involved in the pharmacological process of KFX treating for indometacin-induced gastric damages and to assess the integral efficacy of KFX on it in rats by a HPLC/TOF-MS-based metabonomic study.

In recent researches, we found the reason of gastrointestinal side effects of NSAIDs is that NSAIDs can cause gastrointestinal damage by chemical-biochemical actions on the intestinal epithelial cells. And in general, there are three biochemical actions that contribute to the cellular damage for conventional NSAIDs. Here, we focused on third point that KFX may play a role in the regulation of COX-1/COX-2 to combat the ulcerogenic activity of indometacin. And the key point is the prostaglandin synthesis.

COX is closely connected with biosynthesis of PGs, including the constitutively expressed COX-1 and the inducible COX-2. Studies have showed that the inhibition of both COX-1 and COX-2 is required for NSAID-induced gastric injury, suggesting a ‘housekeeping’ role of COX-2 as well as COX-1 in the stomach. In our study, we found that the expression of COX-1 was inhibited, the expression of COX-2 was up-regulated in rats, and the level of PGE$_2$ was significantly decreased following administration of indometacin, which were consistent with previous experimental results. Hereon, our findings revealed that pre- and post-supplementation with KFX significantly increased the indometacin-reduced COX-1 and PGE$_2$ content, decreased the level of COX-2, leading to inhibition of the indometacin-induced gastric ulcers in the rats. Especially, it’s obvious that KFX has a very clear effect on PGs, three doses show good effect of increasing PGs content. It may be assumed that KFX prevented the development of gastric lesions induced by indometacin.

It was shown that indometacin treatment increased IL-6 expression in rat serum and gastric mucosa as previously reported. Treatment with high dose of KFX promoted a reduction in cytokine production to levels similar to those in normal control group, which contributed to further alleviate inflammation.

Surprisingly, indometacin administration decreased TNF-$\alpha$ level in serum and gastric mucosa. The reason for this change might be the anti-inflammatory activity of indometacin and the characteristics of TNF action in vivo. Indometacin is one of NSAIDs which can inhibit the release of pro-inflammatory cytokines such as TNF-$\alpha$, and it might lead to the decrease of TNF-$\alpha$ level in model group. In addition, it was also reported about the existence of negative feedback mechanisms that do restrict TNF formation and function, which perhaps influenced the expression of TNF-$\alpha$. After the treatment with KFX, it was observed that high dose of KFX regulated TNF-$\alpha$ expression and made it approach the level of TNF-$\alpha$ in normal rats. To further find and verify the possible mechanisms of KFX on gastric damage induced by indometacin, we attempted to identify the key molecules involved in the pharmacological process of acute gastric mucosa injury to potentially explain its complex biochemical mechanisms using a metabonomics approach.

In our study, 9 metabolites were identified in serum samples as potential biomarkers. Among these molecules, the most obvious change was the imbalance of tryptophan metabolism. In the model group, the levels of 5-hydroxyindoleacetic acid, indoxylsulfuric acid, indolelactic acid, and 4-hydroxyindole were all reduced which were metabolites in the tryptophan metabolic pathway.

L-tryptophan, in addition to being an essential amino acid for protein synthesis, serves as an important precursor molecule for production of active metabolites involved in regulation of immunity, inflammation, neurotransmission and circadian rhythm. Those biologically active metabolites are produced via two major pathways: (1) indoleamine 2, 3 dioxygenase (IDO) pathway which generates kynurenines, and (2) tryptophan hydroxylase (TPH) pathway which was originally thought to produce neurotransmitters and neural function modulators notably serotonin and melatonin. In addition, there is also 5-methoxytryptophan (5-MTP) pathway which metabolite could inhibit COX-2 expression. 5-Methoxyindole metabolites of L-tryptophan notably 5-MTP encompass a novel class of endogenously produced compounds to modulate the inflammatory response to environmental insults and control neoplastic growth and cancer metastasis.

Related to the results of the literature, we found that the concentration of COX-2 was significantly increased, and the levels of metabolites associated with tryptophan metabolism were significantly decreased in the model group. After treatment of KFX, the concentration of COX-2 was significantly decreased, and the levels of metabolites associated with tryptophan metabolism were significantly increased in the model group. The inflammatory state of rats was improved. The experimental results suggest the reason why KFX inhibits expression of COX-2 may be that KFX can influence the formation of 5-methoxyindole metabolites by regulating tryptophan metabolism (Fig. 4A).

Pantothenic acid is essential for the synthesis of coenzyme A (CoA), and the latter is a critical cofactor involved in multiple pathways (e.g., the TCA cycle and fatty acid biosynthesis). An increased demand on CoA, for example, in mitochondrial $\beta$-oxidation or the TCA cycle, could reduce pan-
Indolelactic acid 5-hydroxyindoleacetic acid 5-hydroxytryptophan 5-methoxytryptophan COX-2 expression Indoxylsulfuric acid Tricarboxylic acid cycle Coenzyme A ROS Production

Fig. 4 The network of the potential biomarkers in serum that changed between normal control group, model group and KFX-treated group. Metabolite names in red indicate that they were detected in our study. Box-whisker plots of biomarkers were based on ANOVA analysis. Green colour: normal control group; red colour: model group; blue colour: KFX-treated group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) A: Regulating tryptophan metabolism (action pathway 1); B: Protecting the mitochondria, and regulating lipid metabolism (action pathway 2); C: Reducing excessive indomethacin (action pathway 3)

tothenic acid levels. This metabolite was markedly increased in the model group, indicating the TCA cycle was enhanced and the oxidation was intensified.

However, other metabolites showed the opposite results. 3-methyl-2-oxovaleric acid (KMV), a 2-oxoglutarate analog and OGDH inhibitor, can inhibit the formate-induced increase in pyruvate-driven ROS production. In other words, KMV has antioxidant effect, and its level in the model rats was increased in the model group. It suggests that the obvious antioxidant process occurred in the rats.

Mitochondrion is a crucial place for many important physiological processes in vivo, such as the TCA cycle, energy transformation. Mitochondrial oxidative system is a major part in biological oxidation, in addition, there are cellular antioxidative system and non-mitochondrial redox reaction system in vivo. These systems jointly maintain the balance of redox process in cells. Normally, oxidation and antioxidant are in a dynamic equilibrium state in cells, but we found that the equilibrium was destroyed in rats with acute gastric injury from our research. It was indicated that the function of mitochondria is affected and disordered in pathological condition as acute gastric damage. Compared with the levels in model group, those two metabolites were elevated in KFX-treated group, indicating that KFX could regulate mitochondrial function, further improves the inflammatory state.

Furthermore, we observed the levels of isobutyryl carnitine and sphingosine 1-phosphate (S1P) were decreased in the model group. The former is a short-chain acylcarnitine species, is formed within the mitochondria and participates in fatty acid metabolism. Similar to that in pantothenic acid, the decrease in isobutyryl carnitine levels in the model group may be associated with dysfunction in the mitochondria and fatty acid oxidation. The latter, a kind of sphingolipid, is a vasoprotective lipid mediator with pleiotropic biological effects. Alteration in the metabolism of sphingolipid, such as S1P, can broadly disturb lipid metabolism. Treatment results indicated that KFX increased isobutyryl carnitine and S1P levels in rat serum, and influenced lipid metabolism in rats.

In addition to the above, the most obvious effect of KFX is to eliminate excess indomethacin in rat serum. The pathological model used in the experiment is based on the inhibitory action of NSAIDs to COX, that is to say, indomethacin is the most direct factor to cause acute gastric injury. After treatment of KFX, the level of indomethacin was notably declined, indicating that KFX accelerates indomethacin metabolism, and promptly eliminates materia peccans.

To our knowledge, this work is the first to explore the effects of KFX on indomethacin-induced gastric damage at the metabolic level. Our results demonstrated that KFX (10.28 mL·kg⁻¹) exerts protective effects on indomethacin-induced gastric damage through the following possible mechanisms about regulating tryptophan metabolism, protecting the mitochondria, and regulating lipid metabolism, and reducing excessive indomethacin. Further studies based on multiple inflammatory disease models, other omics techniques and novel research approaches such as through model simulation to further investigate the core pathways of inflammation and its induced diseases development are necessary to achieve a more integrative understanding of related anti-inflammatory mechanisms.
Acknowledgements

The authors thank Smartnuclide Co., Ltd., Suzhou, China, for providing help in performing metabolomic analysis using the LC-MS.

References


