Latifolin protects against myocardial infarction by alleviating myocardial inflammatory via the HIF-1α/NF-κB/IL-6 pathway

Xiao-Xiao Laia, Ni Zhangb, Lan-Ying Chena, Ying-Ying Luo, Bin-Yao Shoua, Xin-Xu Xiea and Rong-Hua Liub

aNational Pharmaceutical Engineering Centre for Solid Preparation of Chinese Herbal Medicine, Jiangxi University of Traditional Chinese Medicine, Nanchang, China; bSchool of Pharmacy, Jiangxi University of Traditional Chinese Medicine, Nanchang, China

ABSTRACT
Context: The Traditional Chinese herb medicine Dalbergia odorifera T. Chen (Fabaceae), exerted a protective effect on myocardial ischaemia. Latifolin is a neoflavonoid extracted from Dalbergia odorifera. It has been reported to have the effects of anti-inflammation and cardiomyocyte protection.

Objective: To investigate whether latifolin can improve myocardial infarction (MI) through attenuating myocardial inflammatory and to explore its possible mechanisms.

Materials and methods: Left coronary artery was ligated to induce a rat model of MI, and the rats were treated with sodium carboxymethyl cellulose (CMC-Na) or different doses of latifolin (25, 50, 100 mg/kg/d) by oral gavage for 28 days. Serum contents of myocardial enzyme were measured at seven and fourteen days after treatment. Cardiac function, infarct size, histopathological changes and inflammatory cells infiltration was assessed at 28 days after treatment. Western blotting was used to investigate the underlying mechanisms.

Results: Latifolin treatment markedly decreased the contents of myocardial enzymes, and increased left ventricular ejection fraction (85.27% vs. 59.11%) and left ventricular fractional shortening (62.71% vs. 45.53%). Latifolin was found to significantly reduced infarction size (27.78% vs. 39.07%), myocardial fibrosis and the numbers of macrophage infiltration (436 cells/mm² vs. 690 cells/mm²). In addition, latifolin down-regulated the expression levels of hypoxia-inducible factor-1α (0.95-fold), phospho-nuclear factor-κB (0.2-fold) and interleukin-6 (1.11-fold).

Discussion and conclusions: Latifolin can protect against myocardial infarction by improving myocardial inflammation through the HIF-1α/NF-κB/IL-6 signalling pathway. Accordingly, latifolin may be a promising drug for pharmacological treatment of ischaemic cardiovascular disease.

Introduction
Myocardial infarction (MI) refers to myocardial necrosis brought about by acute, persistent coronary artery ischaemia and hypoxia. Postinfarction will lead to poor ventricular remodelling and heart failure; it may be accompanied by severe, excruciating non-cardiac conditions. Although the treatment of MI has been greatly improved in recent decades, MI remains a leading killer disease or a leading cause of death in the world (Benjamin et al. 2018; Zhang et al. 2019).

Previous studies have shown that MI can quickly induce an inflammatory response, then release massive inflammatory cells and inflammatory factors to clear the necrotic heart (Fang et al. 2015; Libby et al. 2016; Gombozhapova et al. 2017). Inflammation is believed to be a critical and dangerous participant after MI, plays a two-way regulatory role in the acute phase and healing process of MI. Excessive inflammation in the acute phase of MI will aggravate myocardial injury, ventricular remodelling and cardiac dysfunction (Frangogiannis 2014; Wang et al. 2018, 2019). Subsequent development of modest inflammation will lay good foundations for heart healing (Frangogiannis 2006; Spinales 2007; Prabhu and Frangogiannis 2016). Therefore, effective anti-inflammatory therapy will help to improve post-infarct recovery function (Dobaczewski et al. 2010; Saxena et al. 2016; Dai et al. 2019).

Dalbergia odorifera T. Chen (Fabaceae), a traditional Chinese herb medicine, has the effects of promoting blood circulation, resolving blood stasis, regulating Qi and relieving pain. Chinese medicine believes that Qi is the driving force for blood circulation. Dalbergia odorifera promotes the patency of the blood vessels and the dissipation of blood stasis by regulating Qi. It can be used to treat chest impediment with stabbing pain. Flavonoids are one of the main active components in Dalbergia odorifera. So far, about 99 flavonoids have been isolated and identified from Dalbergia odorifera. These can be divided into 9 categories: flavones, isoflavones, flavanones, flavans, isoflavanones, isosilavans, neoflavones, chalcones, and bioflavonoids. Modern pharmacological studies (Zhao et al. 2020) have indicated that the flavonoids of Dalbergia odorifera have vasodilating, anti-inflammatory, antioxidant activities, etc. Latifolin is a neoflavone isolated from Dalbergia odorifera. We found that the maximum tolerated dose (MTD) was 15 g/kg in Kunming mice after a single administration of latifolin. This indicates that latifolin is...
a safe and low-toxic drug. Findings from early research (Lee et al. 2014) report latifolin inhibits the activation of nuclear factor-κB (NF-κB) through nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated haem oxygenase-1 (HO-1) expression, thus easing the inflammatory reactions of peritoneal macrophages induced by lipopolysaccharide (LPS). The previous studies of this subject (Li et al. 2017) showed that latifolin improved acute myocardial ischaemia in rats by reducing the degree of inflammatory cell infiltration and myocardial necrosis in myocardial tissue. Moreover, Zhang et al. (2020) also revealed that latifolin could protect the heart from doxorubicin (DOX)-induced cardiotoxicity by mediating the polarization phenotype change of M1/ M2 macrophages. Therefore, we hypothesized that latifolin can play a role in the treatment of MI by improving myocardial inflammation.

We conducted experimental research through using coronary artery ligation to induce myocardial infarction in rats and administering latifolin for 28 consecutive days. It was found that latifolin improved myocardial inflammation, alleviated myocardial fibrosis, attenuated myocardial damage, and reduced myocardial infarction area in rats with myocardial infarction. Moreover, latifolin may inhibit myocardial inflammation through the HIF-1α/NF-κB/IL-6 signalling pathway.

Materials and methods

Drugs

Latifolin [chemical structure name (-)-(R)-latifolin] was provided by the School of Pharmacy, Jiangxi University of Traditional Chinese Medicine, and the purity is more than 98%. We purchased primary antibodies against antihypoxia-inducible factor-1α (HIF-1α), anti-phospho-nuclear factor-κB (p-NF-κB) and anti-interleukin-6 (IL-6) from OriGene, USA. Anti-CD68 and anti-MPO primary antibodies were purchased from Abcam, USA.

Animals

Fifty male SPF grade Sprague-Dawley (SD) rats (weighing 260 ± 20 g) aged 8 weeks from Hunan SJA Laboratory Animal Co., Ltd., (Changsha, China). Rats were raised in the animal facility with controlled room temperature 23 ± 2°C and 12 h light/dark cycle and unlimited access to food and water. All animal care and experimental procedures were consistent with the guidelines of the Animal Management Rules of the Ministry of Health of the People’s Republic of China and approved by the Institutional Animal Care and Use Committee of Jiangxi University of Traditional Chinese Medicine.

MI Model

Rats were anaesthetized with isoflurane gas inhalation for 2 min after intraperitoneal injection of urethane (0.6 g/kg). Limb lead II electrocardiogram (ECG) was monitored using power lab electrophysiology recorder (ADI Instruments, Australia). We cut a small incision in the skin of the rat’s left chest, bluntly separated its subcutaneous tissues and muscles, cut off the left third rib, quickly exposed the heart, and identified the range of the anterior descending branch. Using the flush position of the inferior edge of the left atrial appendage as a mark, the left coronary artery was ligated with 6-0 ligation line 2 mm below the lower edge of the left atrial appendage. Successful MI model was confirmed by the typical ST segment elevation on synchronous ECG and whitening of the left ventricular anterior wall. After 20 min of ECG stabilization, the air in the chest cavity was exhausted and the wound was sutured. After the operation, rats were placed in separate cages and returned to larger cages after they return to normal autonomous activity.

Experimental groups

The experiment is conducted on 5 groups, with 10 rats in each group. The rats with left anterior descending coronary artery ligation were randomly divided into 4 experimental groups: including a model group, and groups treated with latifolin 25, 50 or 100 mg/kg. In addition, rats who underwent thoracotomy but not ligated are called the sham group as control group. Rats in the latifolin treatment group were orally administered latifolin 25, 50 or 100 mg/kg/d, respectively. The model group and the sham group were governed with equal volume of 0.5% sodium carboxymethyl cellulose (CMC-Na). After 28 days of continuous gavage, all rats were sacrificed.

Detection of myocardial injury markers

Blood samples were collected from the orbital venous plexus at 7 and 14 days after the surgery. After standing for 2 h, the blood was centrifuged at 3000 g for 15 min to obtain the serum. The levels of lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB) in the serum were detected by fully automatic biochemical analyser.

Evaluation of cardiac function

Rat heart function was monitored by echocardiography at 4 weeks after surgery. The rats were anaesthetized with intraperitoneal injection of urethane (1.4 g/kg), sheared the thorax hair, and then fixed on the test table in the supine position. Left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) as the evaluation indicators of cardiac function were automatically calculated by the echocardiographic system (Ottawa, Canada).

Measurement of myocardial infarction area

Twenty-eight days later, rats were anaesthetized followed by cardiac perfusion with normal saline to eliminate the blood in the cardiac chamber. After freezing at −20°C for about 20 min, the myocardium was cut into 4 slices from the ligation site to the apex. The slices were incubated in a 1% solution of buffered triphenyl tetrazolium chloride (TTC) solution for 15 min at 37°C. During the staining process, the sections were carefully flipped every 5 min. Finally, stained slices were photographed and infarction size was calculated by Image J software.

Histopathology

To observe the histopathological changes in experimental rats, fresh heart tissues were fixed in 4% paraformaldehyde for over 24 h, washed with running water, dehydrated in automatic organizations dehydration machine (Beijing Jiayuan Xingye Science and Technology), and embedded in wax using a paraffin embedding machine (Hubei Xiaogan Yaguang Medical Electronic
Technology Co., Ltd.). Next, tissue blocks were cut into 5 µm thickness sections using a paraffin-slicing machine (Leica, Germany), and mounted onto anti-shedding glass slides. Sections were stained with haematoxylin and eosin (H&E) and Masson’s trichrome stain. All images were obtained using an inverted optical microscope (Nikon, Japan).

**Figure 1.** Latifolin reduces myocardial enzyme contents after MI. A. 7 days after operation, the contents of LDH and CK-MB in serum of rats. B. 14 days after operation, the contents of LDH and CK-MB in serum of rats. Data are presented as Mean ± SD. N = 3. *p < 0.05, **p < 0.01 vs. sham group. #p < 0.05, ##p < 0.01 vs. model group.

**Figure 2.** Latifolin improves cardiac function after MI. A. Representative M-mode echocardiograms of rats. B. LVEF and LVFS were measured by echocardiography. Data are presented as Mean ± SD. N = 4. *p < 0.05 vs. sham group. #p < 0.05, ##p < 0.01 vs. model group.
**Immunohistochemistry**

After deparaffinization and rehydration, paraffin sections of heart tissue were subjected to antigen retrieval in a sodium citrate buffer (pH 6.0, 95°C/100°C). After the slides were cooled to room temperature, they were incubated with anti-CD68 or anti-MPO primary antibody at 4°C overnight and then with secondary antibody at room temperature. At last, 3,3-diaminobenzidine (DAB) was used to develop the stain, haematoxylin was used for counterstain and neutral gum sealing the slides. In each slide, 5 different visual fields were randomly selected and photographed under an optical microscope (Nikon, Japan) at 200× magnification. Using Image-Pro Plus software to determine the positive staining cells.

**Western blotting**

Total protein was extracted from the left ventricular myocardial tissues using tissue homogenates and centrifugation. The total protein concentration was determined by BCA protein assay kit. The protein was denatured on a 95~100°C for 5 min. The protein lysate of 20 μg was fractionated by electrophoresis on a 10% SDS-PAGE gel. Protein was then transferred to the PVDF membrane. After 1 h of blocking at room temperature in 5% skim milk, PVDF membrane incubated overnight with primary antibodies at 4°C with anti-HIF-1α, anti-p-NF-κB, anti-IL-6. Then the membrane was incubated with horseradish peroxidase labelled secondary antibody at room temperature for 1.5 h and visualized by chemiluminescence (ECL) with a Western blotting detection system (Bio-Rad, USA). The protein expression levels of the stripes were analysed by Image J software, and normalized based on the grey value of β-tublin.

**Statistical analysis**

All results were expressed as mean values ± standard deviations (mean ± SD). Statistical analyses were performed using one-way analysis of variance by SPSS 20.0 software. For data not conforming to the normal distribution and equal variance criteria, nonparametric tests were used. Differences were considered statistically significant when \( p < 0.05 \) or \( p < 0.01 \).

**Results**

**Latifolin reduces myocardial enzyme content after MI**

On the 7th and 14th day after operation, the contents of LDH and CK-MB in the serum of rats were measured. As presented in Figure 1(A), the results showed that rats in the model group had higher levels of LDH and CK-MB compared the sham group on the 7th day after surgery: the levels in the model group were 21358.93 U/L and 2953.00 U/L, and significantly increased than the sham group (9746.73 U/L for LDH and 1352.33 U/L for CK-MB; \( p < 0.01 \)). Compared with the model group, LDH content in the 25 mg/kg latifolin group was significantly lower (14080.05 U/L; \( p < 0.05 \)) and the CK-MB content in the three treatment groups was markedly decreased (1357.33 U/L for 25 mg/kg latifolin group, 1500.67 U/L for 50 mg/kg latifolin group, 1149.00 U/L for 100 mg/kg latifolin group; \( p < 0.01 \)) (Figure 1(A)). On the 14th day after surgery, LDH content was 21359.97 U/L for the sham group and 32347.00 U/L for the model group (\( p < 0.05 \)), while the CK-MB content increased from 2977.00 U/L (sham group) to 3493.50 U/L (model group; \( p < 0.05 \)) (Figure 1(B)). As shown in Figure 1(B), LDH content in all treatment groups was lower than in the model group (21852.95 U/L for 25 mg/kg latifolin group, 22952.04 U/L for 50 mg/kg latifolin group, 23202.25 U/L for 100 mg/kg latifolin group; \( p < 0.05 \)). In addition, the
CK-MB content in the 25 mg/kg latifolin group and the 50 mg/kg latifolin group decreased dramatically compared with the model group, and the value was statistically significant (21,852.95 U/L for 25 mg/kg latifolin group, 22,952.04 U/L for 50 mg/kg latifolin group; \( p < 0.01 \)).

Latifolin improves cardiac function after MI

At the 28th day after MI, we found that the systolic function and cardiac output of the model group were much worse than the sham group (\( p < 0.01 \); Figure 2(A)). It should be noted that the LVEF increased significantly from 59.11% (model group) to 85.27% (100 mg/kg latifolin group; \( p < 0.01 \)), while the LVFS increased from 45.53% (model group) to 58.17% (50 mg/kg latifolin group; \( p < 0.05 \)) and to 62.71% (100 mg/kg latifolin group; \( p < 0.01 \)) (Figure 2(B)). It shows that latifolin has better cardiac function improvement to a certain extent.

Latifolin reduces myocardial infarction size after MI

At the 28th day after MI, we observed the appearance of the rat heart. The results showed that compared with the sham group, the rats in the model group had significantly enlarged heart,
thinned left ventricular wall, obvious infarcts under the ligation site, and whitened heart tissue. The infarction area in the model group was 39%. Compared with the model group, the appearance of the 50 mg/kg latifolin group was significantly improved. The degree of heart enlargement is smaller than that of the model group, and it is more elastic (Figure 3(A)). The area of myocardial infarction in the latifolin treatment group was significantly smaller than in the model group, and the decrease of the 50 mg/kg latifolin group was the most significant (27.78% for 50 mg/kg latifolin group; \( p < 0.01 \); Figure 3(B)).

**Latifolin ameliorates the histopathological changes of myocardial tissue after MI**

Figures 4 and 5 show the pathological changes and the degree of fibrosis of myocardial tissues in rats in the sham group, the model group and latifolin treatment group. As shown in Figure 4(H&E) showed that in the sham group, the myocardial tissue structure was normal, the myocardial cells were arranged neatly, and the myocardial fibres were arranged regularly. However, in the model group, myocardial cells had obvious vacuole degeneration, myofilament lysis, and myocardial fibres showed wavy disturbances. The latifolin

![Figure 5. Latifolin reduces the area of myocardial fibrosis in rats. 50x magnification and Masson’s trichrome stain. (A) A representative picture of myocardial fibrosis. (B) Statistical analysis of fibrosis area. Data are presented as Mean±SD. \( N=3 \). *\( p < 0.05 \), **\( p < 0.01 \) vs. sham group. #\( p < 0.05 \), ##\( p < 0.01 \) vs. model group.](image)
treatment group significantly improved the morphology of the myocardium tissue. Masson’s trichrome stain showed that there was no obvious fibrosis in the myocardial tissue of the sham group, while fibrosis is particularly significant in the model group (Figure 5(A)). Compared with the model group, the 50 mg/kg latifolin group significantly reduced the degree of fibrosis ($p < 0.01$; Figure 5(B)).

Latifolin reduces macrophage infiltration after MI

Immunohistochemical analysis of left ventricular sections of animals 28 days after MI confirmed that there were many CD68-positive cells and few MPO-positive cells in the myocardial tissue of the model group, indicating the presence of a large number of macrophage infiltration (690 cells/mm$^2$ for model group; $p < 0.01$ vs. sham group; Figure 6(A,B)). On the contrary, the number of macrophages in the latifolin treatment group was significantly reduced (462 cells/mm$^2$ for 25 mg/kg latifolin group, 425 cells/mm$^2$ for 50 mg/kg latifolin group, 436 cells/mm$^2$ for 100 mg/kg latifolin group; $p < 0.05$ vs. model group; Figure 6(B)), but the drug had no obvious effect on neutrophils (Figure 7).

These results suggest that latifolin can improve the inflammatory response after MI.

Latifolin down-regulates the expression of inflammatory pathway-related proteins

To determine the effect of latifolin on myocardial inflammation-related protein expression, we performed western blotting analysis of HIF-1$\alpha$, p-NF-κB and IL-6 (Figure 8(A)). Our results indicated that the expression levels of HIF-1$\alpha$ and IL-6 were significantly down-regulated by latifolin compared with model group ($p < 0.01$, $p < 0.05$; Figure 8(B–D)). As shown in Figure 8(C), 25 mg/kg latifolin group and 100 mg/kg latifolin group significantly decreased p-NF-κB protein levels than the model group ($p < 0.01$).

Discussion

A disturbed inflammatory response is associated with increased tissue damage and poor prognosis following myocardial...
In myocardial infarction (Christia and Frangogiannis 2013), inhibition of myocardial inflammatory response is effective for improving myocardial infarction (Morishita et al. 2016; Gao et al. 2019). In this study, we ligated the left coronary artery of rats to simulate myocardial infarction, and investigated the role of latifolin in myocardial infarction, especially its effect on myocardial inflammation. We found that latifolin can reduce myocardial injury, improve myocardial inflammatory environment and fibrosis by reducing macrophage infiltration in myocardial tissue. In addition, latifolin down-regulated the expression levels of HIF-1α, p-NF-κB and IL-6.

In the initial stage of MI (the inflammatory phase), large amounts of neutrophils and monocytes/macrophages infiltrate into the myocardium (Weirather et al. 2014), causing increased release of inflammatory factors to resolve the harsh inflammatory environment, which further aggravates myocardial injury. In the later stage of MI (the proliferation phase), chronic inflammation is mainly regulated by macrophages (Lambert et al. 2008). When the intense inflammatory phase has subsided, macrophages secrete chemokines to recruit and activate fibroblasts and endothelial cells. Transforming growth factor-β (TGF-β) is one of the important factors for macrophage release. It is involved in the transformation of fibroblasts into myofibroblasts, which in turn the vast production and deposition of extracellular matrix proteins for scar formation (Serini et al. 1998). In the last phase of MI (the maturation phase), the infarct evolves into a mature scar with cross-linked collagen fibres leads to the myocardial infarct area continues to expand, which further aggravate the progression of myocardial fibrosis and poor ventricular remodelling. As inflammatory response plays an important role in all stages of the development of MI, an increasing number of studies consider anti-inflammatory as a strategy for the treatment of MI. Xu et al. (2020) demonstrated that the Gal-3 inhibitor modified citrus pectin ameliorated cardiac dysfunction, decreased myocardial injury and reduced collagen deposition through inhibiting inflammation. Liu et al. (2019) found that fisetin treatment improved cardiac function, inhibited macrophage recruitment into the left atrium and production of interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α), and attenuated adverse atrial fibrosis following acute myocardial infarction.

In this study, it was found that the latifolin treatment group significantly reduced the levels of LDH and CK-MB, significantly increased LVEF and LVFS, and significantly alleviated myocardial fibrosis. It shows that latifolin protects against myocardial

**Figure 7.** Latifolin had no significant effect on neutrophil infiltration. ×200 magnification. N = 3.
injury in animals. Moreover, the immunohistochemical results showed that latifolin treatment group significantly inhibited macrophage infiltration in myocardial tissue. It was indicated that latifolin may protected myocardial injury by affecting the recruitment of macrophages. Interestingly, it also was noted that there were fewer neutrophils in myocardial tissue after MI, and the drug had no significant effect on it (Figure 7). After 28 days of MI, the myocardium is in the proliferative phase or the maturation phase, so no effect of the drug on neutrophils was observed.

Myocardium after myocardial infarction is in a state of long-term ischaemia and hypoxia. Under hypoxia, degradation of HIF-1α was reduced, causing accumulation of HIF-1α intracellular. HIF-1 is an important transcriptional regulator of oxygen homeostasis in vivo, which can regulate the expression of various genes, such as NF-κB. HIF-1α is not only a key mediator of cell metabolism, but also affects the development of inflammation and fibrosis (Xu and Dong 2016; Thiele et al. 2019). In recent years, HIF-1 is being increasingly recognized as a critical factor in the inflammatory response (Feinman et al. 2010). Hong et al. (2014) report that the regulation of HIF-1 expression may improve the poor wound healing process. NF-κB is a key transcription factor in regulating inflammation. Activation of NF-κB pathway produces a series of inflammatory cytokines, such as IL-6, IL-1β, interleukin-12 (IL-12), TNF-α. In this inflammatory cytokines, IL-6 plays a central role in body defense by stimulating various cell populations and is an essential part of the inflammatory mediator network. Lee et al. (2014) has found that latifolin mediate the expression of HO-1 through inhibiting the activation of NF-κB in LPS-induced peritoneal macrophages. Similarly, the results from the present study showed that latifolin could inhibit the activation of NF-κB, following suppression of IL-6. In addition, the results showed that latifolin significantly reduced the accumulation of HIF-1α in myocardial. It was indicated that latifolin may inhibit macrophages inflammation by regulating HIF-1α/NF-κB/IL-6 signalling pathway.

Although our data provide strong evidence that latifolin could protect against myocardial infarction by inhibited myocardial

Figure 8. Latifolin down-regulates the expression of inflammatory pathway-related proteins. (A) Representative photos of western blot. (B) HIF-1α grey value analysis. (C) p-NF-κB grey value analysis. (D) IL-6 grey value analysis. Data are presented as Mean ± SD. N = 3. *p < 0.05, **p < 0.01 vs. sham group. #p < 0.05, #p < 0.01 vs. model group.
inflammation through regulating HIF-1α/NF-kB/IL-6 signalling pathway, this study still has several limitations. Firstly, macrophages can be further divided into pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. This study was primarily focussed on the whole macrophages, but the effects of the drugs on M1 macrophages and M2 macrophages, respectively, are not clear. Secondly, there are multiple ways to degrade HIF-1α, such as promoting prolyl hydroxylation, Von Hippel-Lindau (VHL), etc. This study found that latifolin reduced the accumulation of HIF-1α, but how it degrades HIF-1α is unknown. Further investigations are therefore required in this area.

Conclusions

This study further confirmed the anti-inflammatory and myocardial protective effects of latifolin. Furthermore, the current study also found that the mechanism of latifolin in reducing myocardial inflammation may be closely related to regulating the HIF-1α/NF-kB/IL-6 pathway. This study provides a strong foundation for latifolin in the clinical therapies of ischaemic cardiovasculardisease.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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