Pharmacological Effects of Piceatannol on Anti-tumor, Anti-inflammatory, Antiviral, and Liver Protection

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Abstract Piceatannol (PIC) is a natural stilbene polyphenol found in various plants, which has pharmacological effects such as anti-tumor, anti-inflammatory, antiviral, liver protection, myocardial protection, and eye tissue protection. PIC can inhibit the proliferation of liver cancer cells and induce apoptosis and autophagy by activating the ULK1/Atg13 signaling pathway. PIC can reduce HBV inflammation by downregulating the Notch pathway. Through antioxidant, anti-inflammatory, and anti abnormal autophagy, PIC can relieve vomiting toxin induced liver injury. By inhibiting the HMGB1/TLR4/NF-κB pathway, PIC can protect myocardium. By activating the SIRT1/FOXO3a/BNIP3 pathway, PIC can protect corneal epithelial cells from oxidative damage. PIC can directly inhibit rotavirus and conduct antiviral biosynthesis. PIC has high safety, multi-target regulation, and good development prospects, but its molecular mechanism and clinical efficacy still need to be further studied.

Key words Piceatannol, Anti-tumor, Anti-inflammatory, Liver protection, Antiviral, Myocardial protection

0 Introduction

Natural polyphenolic compounds have become a research focus in the fields of modern medicine and functional food due to their wide sources, diverse biological activities, and good safety[1-2]. As a natural stilbene polyphenol, piceatannol (PIC) is widely distributed in various plants and Chinese medicinal materials such as *Vitis vinifera*, *Passiflora edulis*, *Vaccinium* spp., *Rheum palmatum*, *Reynoutria japonica*, *Pleuropterus multiflorus*. It is an important plant antitoxin produced by plants to cope with external stress. In recent years, a large number of *in vivo* and *in vitro* experiments have confirmed that PIC can play multiple pharmacological effects such as anti-inflammatory, antiviral, anti-tumor, and organ protection by regulating multiple signal pathways, and show good intervention effects in multiple disease models such as liver injury, myocardial toxicity, neurodegenerative diseases, metabolic diseases, and infectious diseases[3-5]. With the continuous deepening of pharmacological mechanism research on natural products, the multi-target and multi-pathway regulatory characteristics of PIC have gradually been revealed. In this paper, the pharmacological effects and molecular mechanisms of PIC in recent years are systematically reviewed, providing theoretical support for the basic research, new drug development, and clinical application of PIC.

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1 Anti-tumor effect of PIC and its molecular mechanism

Liver cancer is one of the most common malignant tumors worldwide, with insidious onset, rapid progression, and poor prognosis, posing a serious threat to human life and health. Zhang Shasha *et al.*[6] investigated the regulatory effects of PIC on the proliferation, apoptosis, and autophagy of HepG2 liver cancer cells, as well as its impact on the ULK1/Atg13 signaling pathway, using biological methods such as MTT assay, flow cytometry, MDC staining, RT-qPCR, and Western blot. It was found that the HepG2 cells did not form autophagosomes in control group; cells in the cisplatin group showed a large number of autophagosomes; the number of autophagosomes formed by cells in the low, medium, and high concentrations of PIC groups increased sequentially, but none were as high as those in the cisplatin group. Cell proliferation and apoptosis detection showed that the proliferation rate of the control group was (100.00 ± 0.00)%, and the apoptosis rate was (5.79 ± 1.25)%. The proliferation rate of the cisplatin group decreased to (39.59 ± 5.19)%, and the apoptosis rate increased to (24.75 ± 4.18)%. However, the proliferation rate in the high concentration group of PIC was (52.64 ± 9.32)%, and the apoptosis rate was (19.54 ± 4.10)%. The detection results at molecular level showed that the relative mRNA expression levels of LC3 II, ULK1, Atg13, and Bax in the control group were all around 1.00, while those in the cisplatin group increased to 2.49 ± 0.55, 3.67 ± 0.62, 2.85 ± 0.53, 2.66 ± 0.51, and those in the high concentration group of PIC were 2.15 ± 0.50, 2.86 ± 0.45, 2.27 ± 0.41, and 2.02 ± 0.31, respectively. The change trend of protein level was consistent with mRNA, with LC3 II/GAPDH of 0.29 ± 0.06 in the control group, 0.91 ± 0.13 in the cisplatin group, and 0.73 ± 0.11 in the high concentration group of PIC. The above results indicate that PIC can dose dependently inhibit the proliferation of liver cancer HepG2 cells, promote its apoptosis and autophagy, and its molecular mechanism may be related to the activation of the ULK1/Atg13 signaling pathway. By upregulating the expression of ULK1 and Atg13, autophagosome formation is

promoted, and the expression of pro apoptotic protein Bax is up-regulated, jointly regulating the biological behavior of liver cancer HepG2 cells. This provides new experimental evidence and potential natural drug candidates for the treatment of liver cancer, and also provides a basis for further exploration of the ULK1/Atg13 signaling pathway as a therapeutic target for liver cancer.

2 Anti-inflammatory effect of PIC and its molecular mechanism

Inflammation is a defensive response of the body to injury, infection, and stress, and excessive or sustained inflammation can lead to tissue and organ damage. PIC has significant anti-inflammatory activity and can exert anti-inflammatory effects by inhibiting inflammatory signaling pathways, reducing the release of pro-inflammatory factors, and alleviating inflammatory cell infiltration.

Liu Qi *et al.* [7] used biological methods such as animal experiments, HE staining, enzyme-linked immunosorbent assay (ELISA), Western blot, and fully automated biochemical detection to study the effect of PIC on the inflammatory response of HBV infected rats by regulating the Notch signaling pathway and its molecular mechanism. The results showed that compared with the control group, the levels of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the model group rats were significantly increased, and the liver tissue showed severe pathological damage, manifested as hepatocyte degeneration and necrosis, hepatic lobular structural disorder, local necrosis accompanied by fibrous connective tissue proliferation and inflammatory cell infiltration. The levels of pro-inflammatory cytokine inducible nitric oxide synthase (iNOS) and tumor necrosis factor-α (TNF-α) in serum and liver tissue were significantly increased, while the level of anti-inflammatory cytokine interleukin-10 (IL-10) was significantly decreased. The expression of liver tissue Notch signaling pathway related proteins Notch1, Delta like ligand 4 (DLL4), and Split hairy enhancer 1 (Hes1) was significantly upregulated, and the negative conversion rates of hepatitis B surface antigen (HBsAg) and hepatitis B E antigen (HBeAg) were both 0. Compared with the model group, the levels of AST and ALT in rats in the low and high dose groups of PIC were significantly reduced, and the pathological damage to liver tissue was significantly alleviated. The levels of iNOS and TNF-α in serum and liver tissue were significantly downregulated, while the level of IL-10 was significantly up-regulated. The expression of Notch1, DLL4, and Hes1 proteins was significantly reduced, while the negative conversion rates of HBsAg and HBeAg were significantly increased, and the improvement effect of high-dose PIC was more significant. Further verification of the mechanism revealed that compared with the high-dose group of PIC, the high-dose group of PIC + Jagged1 rats showed significant reversal of the above pathological indicators: the levels of AST, ALT, iNOS, and TNF-α were significantly increased, IL-10 level was significantly decreased, expression of Notch1, DLL4, Hes1 proteins were significantly up-regulated, negative conversion rates of HBsAg and HBeAg were significantly reduced, and pathological damage to liver tissue was aggravated, indicating that Jagged1 can counteract the protective effect of PIC. The Western blot results showed that the relative expression levels of Notch1/β-actin, DLL4/β-actin, and Hes1/β-actin in the model group were significantly higher than those in the control group. However, the relative expression levels of these proteins in the high-dose group of PIC were close to those in the control group, but significantly increased after adding Jagged1, further confirming that the Notch signaling pathway is a key target of PIC. The above results indicate that PIC can block the Notch signaling transduction by downregulating the expression of Notch1, DLL4, and Hes1 proteins, thereby reducing the production of pro-inflammatory factors iNOS and TNF-α, increasing the expression of anti-inflammatory factor IL-10, inhibiting the inflammatory response induced by HBV infection, reducing liver cell damage, improving liver function, and increasing the negative conversion rate of HBsAg and HBeAg. The Notch signal activator Jagged1 can reverse its protective effect, clarifying the core mechanism by which PIC regulates the inflammatory response in HBV infected rats, and providing new experimental evidence and potential natural drug candidates for the prevention and treatment of HBV infectious hepatitis.

3 Liver protective effect of PIC and its molecular mechanism

The liver is an important organ for drug metabolism, detoxification of toxins, and regulation of inflammation. It is susceptible to damage from fungal toxins, viruses, drugs, alcohol, oxidative stress, and other factors, leading to diseases such as hepatitis, fatty liver, and liver fibrosis. PIC exhibits significant protective effects in liver injury models, improving liver function, reducing pathological damage, and inhibiting inflammation and apoptosis.

Cheng Yujie *et al.* [8] studied the protective effect and mechanism of PIC on vomiting toxin induced liver injury in mice through biological methods such as animal experiments, HE staining, ELISA, and RT-qPCR. The results showed that compared with the CON group, the mice in DON group showed a significant decrease in body weight, a significant increase in liver index, disordered arrangement of hepatic cords, swelling and degeneration of liver cells, and significant infiltration of inflammatory cells. The activities and total antioxidant capacities (T-AOC) of glutathione peroxidase (GSH-Px) and catalase (CAT) in the liver were significantly reduced, while the content of malondialdehyde (MDA) was significantly increased. The contents of total cholesterol (TC), triglycerides (TG), and ALT and AST activities in the serum were significantly increased. Compared with the DON group, the PIC + DON group showed a significant increase in body weight, a significant decrease in liver index, and a significant improvement in liver tissue pathological damage. The above antioxidant and liver function indicators were significantly reversed. At the molecular level, PIC can significantly downregulate the mRNA expression of pro-inflammatory genes such as interleukin-6 (IL-6), IL-1β, TNF-α, and nuclear factor-κB (NF-κB) in the liver, as well as pro apoptotic genes such as Bax, Caspase-3, Caspase-9, and

Caspase-1. At the same time, it upregulates the mRNA expression of anti apoptotic and antioxidant genes such as B-cell lymphoma 2 (Bcl-2) and nuclear factor E2 related factor 2 (Nrf2). Further detection of autophagy related gene microtubule associated protein 1 light chain 3β (LC3B) expression by RT-qPCR was performed to validate the protective mechanism of PIC. The results showed that compared with the CON group, the relative mRNA expression level of *LC3B* gene in the liver of DON group mice was significantly increased. Compared with the DON group, the expression of *LC3B* gene in the PIC + DON group was significantly reduced, indicating that PIC can inhibit abnormal autophagy of liver cells induced by vomitoxin. The above results indicate that PIC can effectively alleviate vomiting toxin induced liver injury in mice by increasing liver antioxidant enzyme activity, inhibiting NF-κB mediated inflammatory response, regulating the Bcl-2/Bax apoptosis pathway, and inhibiting abnormal autophagy. This provides experimental evidence for the prevention and control of vomiting toxin pollution and the application of PIC in livestock and poultry production.

4 Cardioprotective effect and its molecular mechanism

Myocardial cells are highly sensitive to oxidative stress and inflammatory damage, and factors such as chemotherapy drugs, ischemia-reperfusion, sepsis, *etc.* can all lead to myocardial injury and cause cardiac dysfunction. PIC can exert significant cardioprotective effects by inhibiting oxidative stress, reducing cell apoptosis, and regulating inflammatory signaling pathways.

Using biological methods such as MTT assay, Hoechst 33342 staining, flow cytometry, DCFH-DA fluorescence staining, and Western blot, Wu Qirui *et al.* [9] investigated the protective effect and molecular mechanism of PIC on doxorubicin (DOX) induced H9c2 rat cardiomyocytes injury. The results showed that DOX intervention could significantly reduce the survival rate of H9c2 cardiomyocytes, while 20 μmol/L of PIC had no significant improvement on cell survival rate. 40 and 60 μmol/L of PIC could significantly improve cell survival rate, and the effect by 60 μmol/L of PIC was the best. Hoechst 33342 staining and Annexin V-FITC/PI flow cytometry results showed that DOX could significantly induce apoptosis in H9c2 cardiomyocytes, with apoptotic features such as chromatin condensation and division in the nucleus, and a significant increase in apoptosis rate. Meanwhile, 60 μmol/L of PIC could significantly reduce the number of apoptotic cells and decrease the apoptosis rate, with an effect similar to that of the positive control group. The DCFH-DA fluorescence staining results showed that compared with the normal control group, DOX intervention significantly increased the ROS levels in H9c2 cardiomyocytes, while 60 μmol/L of PIC could significantly reduce intracellular ROS accumulation and alleviate oxidative stress damage. Western blot results showed that DOX intervention significantly downregulated the expression of anti apoptotic protein Bcl-2 and upregulated the expression of pro apoptotic proteins Bax and Cleaved caspase-3. Compared with the model control group, 40 and 60 μmol/L of PIC significantly upregulated Bcl-2 expression and downregulated Bax and Cleaved caspase-3 expression in a dose-dependent manner. Molecular mechanism studies have shown that DOX intervention can significantly upregulate the protein expression levels of HMGB1, TLR4, NF-κB, and p-IκBα in H9c2 cardiomyocytes, while different concentrations of PIC can downregulate the expression of these proteins to varying degrees, with 60 μ mol/L of PIC showing the most significant downregulation effect. After adding the TLR4 agonist LPS, the downregulation of TLR4 and p-IκBα protein by PIC can be significantly reversed, offsetting its cardioprotective effect. The above results indicate that PIC can exert cardioprotective effects by reducing DOX induced ROS generation and inhibiting cardiomyocyte apoptosis in H9c2 cardiomyocytes. Its molecular mechanism is closely related to the inhibition of HMGB1/TLR4/NF-κB signaling pathway activation, reduction of IκBα phosphorylation levels, and blockade of NF-κB nuclear translocation. It could provide new experimental evidence and potential natural drug candidates for the prevention and treatment of DOX induced cardiac toxicity.

5 Protective effect on eye tissue and its molecular mechanism

As an important component of the ocular surface barrier, functional damage of human corneal epithelial cells (HCECs) is one of the key pathogenic mechanisms of ocular surface diseases such as dry eye disease (DED). Studies have shown that PIC can exert a protective effect on eye tissue and has potential applications in ocular surface damage.

Using biological methods such as cell counting kit-8 (CCK-8), lactate dehydrogenase (LDH) release detection, 2', 7'-dichlorofluorescein diacetate (DCFH-DA) probe detection, scratch assay, flow cytometry, and Western blot experiments, Wang Yaling *et al.* [10] investigated the protective effect and mechanism of PIC on hydrogen peroxide (H_2O_2)-induced HCECs damage. The results showed that H_2O_2 treatment significantly reduced HCECs activity, increased LDH release level and intracellular ROS accumulation, inhibited cell migration ability and promoted apoptosis, while downregulating the expression of anti apoptotic protein Bcl-2 and upregulating the expression of pro apoptotic proteins Bax and Cleaved caspase-3. Compared with the model group, treatment with PIC (40, 80 μmol/L) significantly increased HCECs activity, reduced LDH release and ROS levels, enhanced cell migration ability and reduced cell apoptosis, while reversing the expression changes of apoptosis related proteins mentioned above. At the molecular level, PIC can significantly upregulate the protein expression levels of SIRT1, FOXO3a, and BNIP3 in HCECs by activating the SIRT1/FOXO3a/BNIP3 signaling pathway, thereby alleviating H_2O_2 induced cellular oxidative stress damage. Further validation of the action mechanism of PIC was conducted using SIRT1 agonist SRT1720 and inhibitor EX527. HCECs were divided into a control group, inhibitor group (EX527), low concentration group of PIC (EX527 + 40 μmol/L of PIC), high concentration group of PIC (EX527 + 80 μmol/L of PIC), and agonist group (EX527 + 80 μmol/L of PIC + SRT1720). The results

showed that compared with the control group, the inhibitor group had significantly reduced expression of SIRT1, FOXO3a, and BNIP3 proteins in HCECs. Compared with the inhibitor group, the expression of the three proteins mentioned above was significantly increased in the low and high concentration groups of PIC, indicating that PIC can reverse the inhibitory effect of EX527 on the SIRT1/FOXO3a/BNIP3 signaling pathway. Compared with the high concentration group of PIC, the expression of three proteins in the agonist group further increased. The above results indicate that PIC may improve H_2O_2 induced oxidative stress damage in HCECs by activating the SIRT1/FOXO3a/BNIP3 signaling pathway, providing new experimental evidence for the treatment of DED.

6 Antiviral effect and its molecular mechanism

Rotavirus (RV) is the main pathogen causing viral diarrhea in infants and young children under 5 years old. Approximately 130 million children worldwide are infected each year, and in severe cases, it can cause complications such as epilepsy, viral encephalitis, and even death. PIC has been proven to have significant antiviral effects by inhibiting various viral infections such as influenza A virus and human cytomegalovirus.

Using MTT assay, half tissue culture infectious dose (TCID50) method, molecular docking, RT-qPCR, indirect immunofluorescence, Western blot, ELISA and other biological methods, Yuan Yue *et al.* [11] studied the *in vitro* anti RV effect and molecular mechanism of PIC. The results showed that the maximum non-toxic concentration of PIC on MA104 cells was 64 μmol/L, and there was no significant toxicity to cells within this concentration range. Research on the anti RV effect shows that PIC has a dual effect of directly inhibiting RV and anti RV biosynthesis, without anti RV adsorption. In the direct inhibition of RV, the inhibition rates of PIC at concentrations of 32 and 64 μmol/L on RV-Wa strain were 81.31% and 94.74%, respectively, with a therapeutic index (TI) of 14.07; the inhibition rates on RV-SA11 strain were 81.82% and 88.25%, respectively, with a TI value of 11.62, showing a significant dose dependence and being independent of the virus strain. In the anti RV biosynthesis process, at a concentration of 64 μmol/L, the inhibition rates of PIC on RV-Wa and RV-SA11 strains were 58.36% and 82.03%, respectively, with TI values of 12.63 and 12.02, both meeting the antiviral research value criteria of TI ≥ 4. TCID50 method detection showed that co-incubation of 8 – 64 μmol/L of PIC with virus solution for 2 h could dose dependently reduce RV titers, with the strongest effect observed at 64 μmol/L, further confirming its direct inhibitory effect on RV. The molecular docking results showed that PIC has a good binding ability with the VP8* protein of RV-Wa strain, with a binding energy of −26.7 kJ/mol, and it can form three hydrogen bonds with SER-197, TRP-102, and ARG-144. It suggested that VP8* protein is a key target for PIC to directly inhibit RV, and RV invasion into cells can be prevented by binding to this protein. In terms of anti RV biosynthesis mechanism, the results of RT-qPCR, indirect immunofluorescence and Western blot all indicated that PIC can significantly downregulate the mRNA and protein expression of RV structural protein VP6, prevent RV structural protein synthesis, and interfere with virus replication. Western blot results showed that RV infection significantly downregulated the expression of IκBα protein and upregulated the expression of p-NF-κBp65 protein. However, treatment with PIC significantly reversed these changes, inhibiting the degradation of IκBα protein and the phosphorylation of NF-κBp65. The ELISA results showed that PIC can significantly reduce the levels of IL-1β, IL-6, and TNF-α in the cell supernatant after RV infection, and alleviate RV induced inflammatory response. The above results indicate that PIC has a dual *in vitro* anti RV effect of directly inhibiting RV and anti RV biosynthesis. Its mechanism of action may be: by binding to the VP8* protein of RV-Wa strain outside the cell, it can prevent RV from invading host cells; by inhibiting NF-κBp65 phosphorylation within cells, reducing the release of pro-inflammatory cytokines, alleviating inflammatory responses, and downregulating VP6 protein expression, it interferes with RV biosynthesis. This study confirmed for the first time the *in vitro* anti RV activity of PIC, providing new experimental evidence and potential natural drug candidates for the development of anti RV drugs, and laying the foundation for further exploration of its *in vivo* anti RV effects and molecular mechanisms.

7 Conclusions and prospects

As a natural polyphenolic active ingredient with wide sources, high safety, and multi-target regulation, PIC has various pharmacological effects such as antioxidant, anti-inflammatory, antibacterial, antiviral, anti-tumor, liver protection, myocardial protection, neuroprotection, and eye tissue protection, and shows a wide range of development and utilization value. However, its specific pharmacological molecular mechanism and clinical effects are not yet clear. More systematic and in-depth research is needed at the molecular, cellular, and animal levels, and further clinical experiments are conducted to comprehensively evaluate its effectiveness, safety, applicability, *etc.*, providing theoretical basis for the pharmacological action research and further development and utilization of PIC.

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strong support from government policies, deep integration of industry, academia, and research, as well as the establishment of farmer training and technical service systems.

4 Conclusions and prospects

Entomopathogenic fungi are now widely acknowledged as multifunctional microbial agents that combine insect pathogenicity with plant growth promotion, offering considerable ecological value and application potential in agroecosystems. This review provides a systematic overview of recent advances in understanding their growth-promoting effects. The principal findings are summarized below. (i) Entomopathogenic fungi display extensive strain diversity and functional versatility. Representative species such as *Beauveria bassiana* and *Metarhizium* spp. stimulate crop growth through diverse mechanisms, including phytohormone production, nutrient transfer, nutrient mobilization, and emission of volatile signals. (ii) The plant-fungus interaction is underpinned by an intricate network of molecular events, notably MAMP perception, effector secretion, hormonal signal modulation, and the induction of systemic resistance. (iii) Field trials confirm that entomopathogenic fungi deliver dual benefits (enhanced growth and yield alongside effective pest suppression) in staple food and cash crops, with recorded yield increments of 15% – 46%. (iv) The benefits of entomopathogenic fungi span environmental, economic, and social dimensions, positioning them as a key technological choice for driving the green transformation and long-term sustainability of agriculture.

As interdisciplinary research continues to advance and technology innovation systems steadily improve, entomopathogenic fungi are expected to play an ever more significant role in sustainable agriculture throughout the 21st century. They will contribute substantially to global food security, environmental protection, and the long-term sustainability of agricultural systems.

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