The Chinese University of Hong Kong

1. Sub-chronic toxicity of the active fraction of a modified Huang-Lian-Jie-Du Decoction

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Toxicology Reports, 2024, 13, 101682

Abstract

A traditional Chinese herbal medicine formula named Huang-Lian-Jie-Du Decoction (HLJDD) has been used to cure various inflammatory diseases with a long history. However, one component of HLJDD Gardeniae fructus has remarkable liver and kidney toxicities. Therefore, it was altered with Dictamni cortex to form a modified HLJDD (MHLJDD). In this study, we aimed to evaluate the sub-chronic toxicity of the active fraction of MHLJDD (MHLJDD-F) in rats. Adult rats of both sexes were intragastrically administered with vehicle or MHLJDD-F (at the dose of 170, 340, and 680 mg/kg/day) once daily for 90 days. Half of the rats from each group were kept for an additional 30-day period to observe the drug withdrawal effect. The signs of toxicity and mortality of the rats were observed, and the body weight and food consumption were recorded. Blood was collected for hematological and biochemical analyses and major organs were weighed and harvested for histopathological examinations. The results revealed that no systemic toxicity of MHLJDD-F was found during the experiments. Organ coefficients and pathological alterations of major organs were comparable to the control rats. The no-observed adverse effect level (NOAEL) of MHLJDD-F was found up to 680 mg/kg/day. All these results demonstrated that long-term oral administration of MHLJDD-F did not cause significant toxicity, which is worthy to be widely applied as a new herbal medicine in pre-clinical and clinical studies.

2. Brusatol alleviates pancreatic carcinogenesis via targeting NLRP3 in transgenic Krastm4Tyj Trp53tm1Brn Tg (Pdx1-cre/Esr1*)# Dam mice

J. Zhang, Y.L. Wu, H.X. Xu, Y.B. Zhang, P.Y. Ren, Y.F. Xian, Z.X. Lin

Biomedicine & Pharmacotherapy, 2024, 177, 116977

Abstract

Background

Pancreatic cancer (PanCa), ranked as the 4th leading cause of cancer-related death worldwide, exhibits an dismal 5-year survival rate of less than 5 %. Chronic pancreatitis (CP) is a known major risk factor for PanCa. Brusatol (BRT) possesses a wide range of biological functions, including the inhibition of PanCa proliferation. However, its efficacy in halting the progression from CP to pancreatic carcinogenesis remains unexplored.

Methods

We assess the effects of BRT against pancreatic carcinogenesis from CP using an experimentally induced CP model with cerulein, and further evaluate the therapeutic efficacy of BRT on PanCa by employing Krastm4Tyj Trp53tm1Brn Tg (Pdx1-cre/Esr1) #Dam/J (KPC) mouse model.*

Results

Our finding demonstrated that BRT mitigated the severity of cerulein-induced pancreatitis, reduced pancreatic fibrosis and decreased the expression of α-smooth muscle actin (α-SMA), which is a biomarker for pancreatic fibrosis. In addition, BRT exerted effects against cerulein-induced pancreatitis via inactivation of NLRP3 inflammasome. Moreover, BRT significantly inhibited tumor growth and impeded cancer progression.

Conclusions

The observed effect of BRT on impeding pancreatic carcinogenesis through targeting NLRP3 inflammasome suggests its good potential as a potential agent for treatment of PanCa.

3. Tianma-Gouteng pair ameliorates the cognitive deficits on two transgenic mouse models of Alzheimer's disease

M. Zhong, Q.Q. Xu, Z. Hu, W. Yang, Z.X. Lin, Y.F. Xian

Journal of Ethnopharmacology, 2024, 328, 118113

Abstract

Ethnopharmacological relevance

Alzheimer's disease (AD) is a progressive neurodegenerative disease. Tianma-Gouteng Pair (TGP), commonly prescribed as a pair-herbs, can be found in many Chinese medicine formulae to treat brain diseases. However, the neuroprotective effects and molecular mechanisms of TGP remained unexplored.

Aim of the study

This study investigated the difference between the TgCRND8 and 5 × FAD transgenic mice, the anti-AD effects of TGP, and underlying molecular mechanisms of TGP against AD through the two mouse models.

Methods

Briefly, three-month-old TgCRND8 and 5 × FAD mice were orally administered with TGP for 4 and 6 months, respectively. Behavioral tests were carried out to determine the neuropsychological functions. Moreover, immunofluorescence and western blotting assays were undertaken to reveal the molecular mechanisms of TGP.

Results

Although TgCRND8 and 5 × FAD mice had different beta-amyloid (Aβ) burdens, neuroinflammation status, and cognition impairments, TGP exerted neuroprotective effects against AD in the two models. In detail, behavioral tests revealed that TGP treatment markedly ameliorated the anxiety-like behavior, attenuated the recognition

memory deficits, and increased the spatial learning ability as well as the reference memory of TgCRND8 and 5 × FAD mice. Moreover, TGP treatment could regulate the beta-amyloid precursor protein (APP) processing by inhibiting the Aβ production enzymes such as β- and γ-secretases and activating Aβ degrading enzyme to reduce Aβ accumulation. In addition, TGP reduced the Aβ42 level, the ratio of Aβ42/Aβ40, Aβ accumulation, and tau hyperphosphorylation in both the 5 × FAD and TgCRND8 mouse models. Furthermore, TGP ameliorated neuroinflammation by decreasing the densities of activated microglia and astrocytes, and inhibiting the production of inflammatory cytokines. TGP upregulated the SIRT1 and AMPK, and downregulated sterol response element binding protein 2 (SREBP2) in the brain of TgCRND8 mice and deactivation of the EPhA4 and c-Abl in the brain tissues of 5 × FAD mice.

Conclusion

Our experiments for the first time revealed the neuroprotective effects and molecular mechanism of TGP on 5 × FAD and TgCRND8 transgenic mouse models of different AD stages. TGP decreased the level of Aβ aggregates, improved the tauopathy, and reduced the neuroinflammation by regulation of the SIRT1/AMPK/SREBP2 axis and deactivation of EPhA4/c-Abl signaling pathway in the brains of TgCRND8 and 5 × FAD mice, respectively. All these findings unequivocally confirmed that the TGP would be promising in developing into an anti-AD therapeutic pharmaceutical.

4. Improvement effects of a novel Chinese herbal formula in imiquimod and IL-23-stimulated mouse models of psoriasis

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Chinese Medicine, 2024, 19,81

Abstract

Background

Psoriasis is a long-term inflammatory skin disease. A novel herbal formula containing nine Chinese herbal medicines, named Inflammation Skin Disease Formula (ISDF), has been prescribed in clinics for decades.

Aims

To investigate the efficacy and action mechanisms of ISDF on psoriasis using imiquimod (IMQ) and Interleukin-23 (IL-23)-induced models in mice and reveal the pharmacokinetics profile of ISDF in rats.

Methods

Topical administration of IMQ and intradermal injection with IL-23 respectively induced skin lesions like psoriasis on the dorsal area of Balb/c and C57 mice. The mice's body weight, skin thickness, and psoriasis area and severity index (PASI) were assessed

weekly. SD rats were used in the pharmacokinetics study and the contents of berberine and baicalin were determined.

Results

The PASI scores and epidermal thickness of mice were markedly decreased after ISDF treatment in both models. ISDF treatment significantly decreased the contents of IL-17A and IL-22 in the serum of IMQ- and IL-23-treated mice. Importantly, ISDF markedly downregulated IL-4, IL-6, IL-1β, and tumor necrosis factor α (TNF-α) gene expression, and the phosphorylation of NF-κB p65, JNK, ERKs and MAPK p38 in IMQ-treated mice. The protein phosphorylation of Jak1, Jak2, Tyk2 and Stat3 was significantly mitigated in the ISDF-treated groups. The absorption of baicalin and berberine of ISDF through the gastrointestinal tract of rats was limited, and their distribution and metabolism in rats were also very slow, which suggested ISDF could be used in the long-term application.

Conclusions

ISDF has a strong anti-psoriatic therapeutic effect on mouse models induced with psoriasis through IMQ and IL-23, which is achieved by inhibiting the activation of the Jak/Stat3-activated IL-23/Th17 axis and the downstream NF-κB signalling and MAPK signalling pathways. ISDF holds great potential to be a therapy for psoriasis and should be further developed for this purpose.

5. Modified Qing-Zao-Jiu-Fei decoction attenuated pulmonary fibrosis induced by bleomycin in rats via modulating Nrf2/NF-κB and MAPKs pathways

J.Q. Zhu, Y.Y. Tian, K.L. Chan, Z. Hu, Q.Q. Xu, Z.X. Lin, Y.F. Xian

Chinese Medicine, 2024, 19,10

Abstract

Background

Qing-Zao-Jiu-Fei Decoction (QZJFD) is a famous herbal formula commonly prescribed for the treatment of lung-related diseases in the ancient and modern times. Trichosanthis Fructus (TF) and Fritillariae Thunbergii Bulbus (FTB) are widely used for treatment of cough and pulmonary disease. In order to identify a more effective formula for treatment of pulmonary fibrosis, we intend to add TF and FTB in QZJFD to form a modified QZJFD (MQZJFD). In this study, we aims to explore MQZJFD as an innovative therapeutic agent for pulmonary fibrosis using bleomycin (BLM)-treated rats and to unravel the underlying molecular mechanisms.

Methods

BLM was given to SD rats by intra-tracheal administration of a single dose of BLM (5

mg/kg). QZJFD (3 g/kg) and MQZJFD (1, 2 and 4 g/kg) was given intragastrically daily to rats for 14 days (from day 15 to 28) after BLM administration for 14 consecutive days.

Results

MQZJFD was found to contain 0.29% of amygdalin, 0.020% of lutin, 0.077% of glycyrrhizic acid and 0.047% of chlorogenic acid. BLM treatment could induce collagen deposition in the lung tissues of rats, indicating that the pulmonary fibrosis rat model had been successfully established. MQZJFD have better effects than the original QZJFD in reducing the pulmonary structure damage and collagen deposition of rat lung fibrosis induced by BLM. MQZJFD could reduce the hydroxyproline content in lung tissues of BLM-treated rats. The biomarkers of fibrosis such as matrix metalloproteinase 9 (MMP9), collagen I and α-smooth muscle actin (α-SMA) were remarkably reduced after treatment with MQZJFD. MQZJFD also have anti-oxidant stress effects by inhibiting the level of malondialdehyde (MDA), but enhancing the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), and the level of glutathione (GSH) in the lung tissues of BLM-treated rats. Moreover, the MQZJFD markedly suppressed the over expressions of p-p65/p65 and p-IκBα/IκBα, but upregulated the Nrf2. MQZJFD also suppressed the protein expressions of p-ERK1/2/ERK1/2, p-p38/p38 and p-JNK/JNK in the lung tissues of BLM-treated rats.

Conclusions

MQZJFD could improve the pulmonary fibrosis induced by BLM in rats via inhibiting the fibrosis and oxidative stress via suppressing the activation of NF-κB/Nrf2 and MAPKs pathways.

6. Synergistic Anti-Tumor Effect of Toosendanin and Paclitaxel on Triple-Negative Breast Cancer via Regulating ADORA2A-EMT Related Signaling

J. Zhang, H.X. Xu, Y.L. Wu, W.C.S. Cho, Y.F. Xian, Z.X Lin

Advanced Biology, 2023, 7, 2300062

Abstract

Triple negative breast cancer (TNBC) is an aggressive cancer with very poor prognosis. Combination therapy has proven to be a promising strategy for enhancing TNBC treatment efficacy. Toosendanin (TSN), a plant-derived triterpenoid, has shown pleiotropic effects against a variety of tumors. Herein, it is evaluated whether TSN can enhance the efficacy of paclitaxel (PTX), a common chemotherapeutic agent, against TNBC. It is found that TSN and PTX synergistically suppress the proliferation of TNBC cell lines such as MDA-MB-231 and BT-549, and the combined treatment also inhibits the colony formation and induces cell apoptosis. Furthermore, this combination shows more

marked migratory inhibition when compared to PTX alone. Mechanistic study shows that the ADORA2A pathway in TNBC is down-regulated by the combination treatment via mediating epithelial-to-mesenchymal transition (EMT) process. In addition, the combined treatment of TSN and PTX significantly attenuates the tumor growth when compared to PTX monotherapy in a mouse model bearing 4T1 tumor. The results suggest that combination of TSN and PTX is superior to PTX alone, suggesting that it may be a promising alternative adjuvant chemotherapy strategy for patients with TNBC, especially those with metastatic TNBC.

7. Patchouli alcohol attenuates the cognitive deficits in a transgenic mouse model of Alzheimer's disease via modulating neuropathology and gut microbiota through suppressing C/EBPβ/AEP pathway

Q.Q. Xu, Z.R. Su, W. Yang, M. Zhong, Y.F. Xian, Z.X. Lin

Journal of Neuroinflammation, 2023, 20,19

Abstract

Background

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by progressive cognitive dysfunctions and behavioral impairments. Patchouli alcohol (PA), isolated from Pogostemonis Herba, exhibits multiple pharmacological properties, including neuroprotective effects. This study aimed to investigate the therapeutic effects of PA against AD using the TgCRND8 transgenic AD mouse model, and to explore the underlying mechanisms targeting CCAAT/enhancer-binding protein β/asparagine endopeptidase (C/EBPβ/AEP) signaling pathway.

Methods

After genotyping to confirm the transgenicity, drug treatments were administered intragastrically once daily to 3-month-old TgCRND8 mice for 4 consecutive months. Several behavioral tests were applied to assess different aspects of neurological functions. Then the brain and colon tissues were harvested for in-depth mechanistic studies. To further verify whether PA exerts anti-AD effects via modulating C/EBPβ/AEP signaling pathway in TgCRND8 mice, adeno-associated virus (AAV) vectors encoding CEBP/β were bilaterally injected into the hippocampal CA1 region in TgCRND8 mice to overexpress C/EBPβ. Additionally, the fecal microbiota transplantation (FMT) experiment was performed to verify the potential role of gut microbiota on the anti-AD effects of PA.

Results

Our results showed that PA treatment significantly improved activities of daily living (ADL), ameliorated the anxiety-related behavioral deficits and cognitive impairments in TgCRND8 mice. PA modulated the amyloid precursor protein (APP) processing. PA also markedly reduced the levels of beta-amyloid (Aβ) 40 and Aβ42, suppressed Aβ plaque burdens, inhibited tau protein hyperphosphorylation at several sites and relieved

neuroinflammation in the brains of TgCRND8 mice. Moreover, PA restored gut dysbiosis and inhibited the activation of the C/EBPβ/AEP signaling pathway in the brain and colon tissues of TgCRND8 mice. Interestingly, PA strikingly alleviated the AD-like pathologies induced by the overexpression of C/EBPβ in TgCRND8 mice. Additionally, the FMT of fecal microbiota from the PA-treated TgCRND8 mice significantly alleviated the cognitive impairments and AD-like pathologies in the germ-free TgCRND8 mice.

Conclusion

All these findings amply demonstrated that PA could ameliorate the cognitive deficits in TgCRND8 mice via suppressing Aβ plaques deposition, hyperphosphorylation of tau protein, neuroinflammation and gut dysbiosis through inhibiting the activation of C/EBPβ/AEP pathway, suggesting that PA is a promising naturally occurring chemical worthy of further development into the pharmaceutical treatment of AD.

8. Quercetin Ameliorates Neuropathic Pain after Brachial Plexus Avulsion via Suppressing Oxidative Damage through Inhibition of PKC/MAPK/NOX Pathway

Y. Huang, X. Zhang, Y. Zou, Q. Yuan, Y.F. Xian, Z.X. Lin

Current Neuropharmacology, 2023, 21, 2343-2361

Abstract

Background: Brachial plexus avulsion (BPA) animally involves the separation of spinal nerve roots themselves and the correlative spinal cord segment, leading to formidable neuropathic pain of the upper limb.

Methods: The right seventh cervical (C7) ventral and dorsal roots were avulsed to establish a neuropathic pain model in rats. After operation, rats were treated with quercetin (QCN) by intragastric administration for 1 week. The effects of QCN were evaluated using mechanical allodynia tests and biochemical assay kits.

Results: QCN treatment significantly attenuated the avulsion-provoked mechanical allodynia, elevated the levels of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) and total antioxidant capacity (TAC) in the C7 spinal dorsal horn. In addition, QCN administration inhibited the activations of macrophages, microglia and astrocytes in the C6 dorsal root ganglion (DRG) and C6-8 spinal dorsal horn, as well as attenuated the release of purinergic 2X (P2X) receptors in C6 DRG. The molecular mechanism underlying the above alterations was found to be related to the suppression of the PKC/MAPK/NOX signal pathway. To further study the anti-oxidative effects of QCN, we applied QCN on the H2O2-induced BV-2 cells in vitro, and the results attested that QCN significantly ameliorated the H2O2-induced ROS production in BV-2 cells, inhibited the H2O2-induced activation of PKC/MAPK/NOX pathway.

Conclusion: Our study for the first time provided evidence that QCN was able to attenuate pain hypersensitivity following the C7 spinal root avulsion in rats, and the

molecular mechanisms involve the reduction of both neuro-inflammatory infiltration and oxidative stress via suppression of P2X receptors and inhibition of the activation of PKC/MAPK/NOX pathway. The results indicate that QCN is a natural compound with great promise worthy of further development into a novel therapeutic method for the treatment of BPA-induced neuropathic pain.

9. Therapeutic effect of Duhuo Jisheng Decoction add-on Tui-na manipulation on osteoarthritis of knee: a randomized controlled trial

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Chinese Medicine, 2023, 18, 82

Abstract

Background: Knee osteoarthritis (KOA) is a common degenerative joint condition that causes disability and pain in the elderly population. The prevalence of KOA among persons aged 63 or above is approximately 30%. Previous studies have reported the positive effects of Tui-na treatment and the Chinese herbal formula Du-Huo-Ji-Sheng Decoction (DHJSD) for KOA treatment. The current study aims to evaluate the add-on therapeutic effect of oral administration of DHJSD on KOA in addition to Tui-na.

Methods: We conducted a prospective, randomized, controlled clinical trial. Seventy study subjects with KOA were randomly assigned to the treatment and control groups in a 1:1 ratio. Both two groups received eight sessions of Tui-na manipulation for 4 weeks. The DHJSD was only administered to the study subjects in the treatment group. The primary outcome measure was rated using the WOMAC at the end of treatment (4 weeks). Secondary outcomes were assessed using EQ-5D-5L, a health-related quality of life with 5-level EQ-5D version at end of treatment (week 4) and follow-up (week 8).

Results: No statistically significant difference was found between two groups on WOMAC scores at the end of treatment. The mean WOMAC Pain subscale score was significantly lower in the treatment group than control group at week 8 follow up (mean difference, MD - 1.8, 95% CI - 3.5 to - 0.02, P = 0.048). The mean WOMAC Stiffness subscale score was significantly lower in the treatment group than in the control group at week 2 (MD 0.74, 95% CI 0.05 to 1.42, P = 0.035) and week 8 follow up (MD 0.95, 95% CI 0.26 to 1.65, P = 0.008). The mean EQ-5D index value was significantly improved in the treatment group than in the control group at week 2 (MD 0.17, 95% CI 0.02 to 0.31, P = 0.022). The analysis of WOMAC scores and EQ-5D-5L in both groups showed statistically significant improvement with time. No significant adverse effect was found during the trial.

Conclusion: DHJSD may have an add-on effect in addition to Tui-na manipulation relieving pain and improving stiffness as well as quality of life (QOL) in patients with KOA. The combined treatment was generally safe and well tolerated. Trial registration The study was registered at the ClinicalTrials.gov (website:

https://clinicaltrials.gov/ct2/show/NCT04492670, registry number: NCT04492670), registered on 30 July 2020.

10. Brusatol suppresses the tumor growth and metastasis of colorectal cancer via upregulating ARRDC4 expression through modulating PI3K/YAP1/TAZ Pathway

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Phytomedicine, 2023, 109, 154567

Abstract

Background

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers with high metastasis and lethality. Arrestin domain-containing 4 (ARRDC4) is involved in inhibiting cancer glycolytic phenotypes. Brusatol (BR), extracted from Bruceae Fructus, exerts good anti-cancer effects against a number of cancers.

Purpose

In the present study, we aimed to explore the efficacy of BR on inhibiting CRC metastasis and elucidate the underlying mechanisms involving the upregulation of the ARRDC4 expression.

Methods

Cell viability, colony formation, wound healing and transwell assay were used to detect the anti-proliferative and anti-metastatic effects of BR against CRC in vitro. Microarray analysis was performed to find out differential genes in CRC cells after treatment with BR. Analysis of the CRC patients tumor samples and GEPIA database were first conducted to identify the expression of ARRDC4 on CRC. Stable overexpression and knockdown of ARRDC4 CRC cells were established by lentiviral transfection. The role of ARRDC4 in mediating the anti-metastatic effects of BR on CRC was measured using qRT-PCR, western blotting, immunohistochemical and immunofluorescence analysis. Orthotopic xenograft and pulmonary metastasis mouse models of CRC were established to determine the anti-cancer and anti-metastatic effects of ARRDC4 and BR.

Results

BR markedly suppressed the cell proliferation, migration, invasion and inhibited tumor growth and tumor metastasis. Microarray analysis demonstrated that BR treatment markedly increased the gene expression of ARRDC4 in CRC cells. ARRDC4 was significantly repressed in CRC in the clinical samples and GEPIA analysis. ARRDC4 overexpression plus BR produced better inhibitory effects on CRC metastasis than BR treatment alone, while ARRDC4 knockdown could partially eliminate the inhibitory effects of BR against CRC metastasis. BR exerted anti-metastatic effects against CRC via upregulating ARRDC4 and inhibiting epithelial-mesenchymal transition (EMT) processing through modulating PI3K/Hippo pathway.

Conclusion

This study reported for the first time that BR is a potent ARRDC4 agonist, and is worthy of further development into a new therapeutic strategy for CRC.

11. The efficacy and safety of Yupingfeng Powder with variation in the treatment of allergic rhinitis: Study protocol for a randomized, double-blind, placebo-controlled trial

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Frontiers in Pharmacology, 2022, 13, 1058176

Abstract

Background. Allergic rhinitis (AR) is an upper airways chronic inflammatory disease mediated by IgE, which affects 10-20% of the population. The mainstay for AR nowadays include steroids and antihistamines, but their effects are less than ideal. Many patients therefore seek Chinese medicine for treatment and Yupingfeng Powder is one of the most common formulae prescribed. In this study, we aim to investigate the efficacy and safety of Yupingfeng Powder with variation for the treatment of AR. Study Design. This is a double-blind, randomized, placebo-controlled trial. A 2-week screening period will be implemented, and then eligible subjects with AR will receive interventions of either "Yupingfeng Powder with variation" granules or placebo granules for 8 weeks, followed by post treatment visits at weeks 12 and 16. The change in the Total Nasal Symptom Score (TNSS) will be used as the primary outcome. Discussion. This trail will evaluate the efficacy and safety of Yupingfeng Powder in treating AR. that tThe study may provide the solid evidence of Yupingfeng Powder with variation can produce better clinical efficacy than the placebo granules. Trial registration. ClinicalTrials.gov identifier: NCT04976023, Registered 26 July 2021.

12. Efficacy and safety of modified Xiao-Feng Powder in the treatment of chronic urticaria: protocol of a randomized double-blind placebo-controlled study

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Chinese Medicine, 2022, 17, 87

Abstract

Background

Chronic Urticaria (CU), a common skin disorder known as Yin Zhen in Chinese medicine, is characterized by recurrent, pruritic, pink-to-red edematous lesions and wheals on the skin. Xiao-Feng Powder (XFP, meaning Wind-Dispersing Powder), is reported to be one

of the most frequently used Chinese herbal formulae for CU. In this study, we aim to investigate the effectiveness and safety of modified Xiao-Feng Powder (mXFP) for the treatment of CU.

Methods

In this randomised double-blind placebo-controlled clinical trial, 58 subjects identified as having mild to severe urticaria (Urticaria activity score greater than 10) will be recruited and randomised into two groups to receive antihistamine Bilastine with either mXFP or placebo for 12 weeks, followed by post treatment visits at week 16. The primary outcome measure is the change of weekly urticaria activity score (UAS7) at week 12. Secondary outcome measures include the Urticaria Control Test (UCT), Visual Analog Scale of Itch Severity (VAS), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), Angioedema Activity Score (AAS), immunoglobulin E (IgE) test, gut microbiota test and use of antihistamines during study period. The trial will be conducted at three Chinese medicine clinics in Hong Kong.

Expected outcomes

The results of this study will establish robust clinical evidence about the efficacy and safety of mXFP in the treatment of CU. A specific feature of this trial is that it is a integrative medicine trial with subjects being allowed to take the Western and Chinese medicine together for the treatment.

13. Brucein D augments the chemosensitivity of gemcitabine in pancreatic cancer via inhibiting the Nrf2 pathway

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Journal of Experimental & Clinical Cancer Research, 2022, 41, 1-19

Abstract

Gemcitabine (GEM) is the first-line chemotherapeutic drug used to treat pancreatic ductal adenocarcinoma carcinoma (PDAC), but chemoresistance is often encountered clinically. Nrf2, an oxidative stress responsive transcription factor, is an important contributor to chemoresistance and poor prognosis of PDAC. Brucein D (BD), a naturally occurring quassinoid, has been reported to exert anti-tumor effect in several cancers including PDAC. In this study, we aimed to investigate the efficacy of BD and the role of Nrf2 axes on the chemosensitivity of GEM and elucidate the underlying molecular mechanisms. Analyses of clinical samples of PDAC and GEPIA database were first conducted to identify the expression of Nrf2 in PDAC. We then established cell lines with stable deletion of Nrf2 through transfecting lentivirus into PDAC cells. Quantitative real-time PCR (qRT-PCR) and Western blotting were performed to determine the expression of Nrf2 in these cell lines. The effects of BD and Nrf2 axes on PDAC cell proliferation, colony-formation, tumor growth and chemosensitivity were determined both in vitro and in vivo. Orthotopic xenograft and genetically engineered KPC mouse models of PDAC

were used to evaluate the anti-pancreatic cancer effects of BD and GEM. Nrf2 was highly expressed in PDAC in the clinical samples and GEPIA analysis. Gain- and lost-function study demonstrated that Nrf2 affected the chemosensitivity of GEM on PDAC cells both in vitro and in vivo. We further found that BD effectively inhibited PDAC cell proliferation and enhanced the chemosensitivity of GEM. Mechanistic studies revealed that BD sensitized GEM in PDAC cells through the ubiquitin–proteasome-dependent degradation of Nrf2, and downregulating the Nrf2 pathway. Silencing of Nrf2 plus BD treatment resulted in more potent inhibitory effects of GEM. In contrast, Nrf2 activation attenuated the chemosensitivity of GEM, indicating that the action of BD was Nrf2 dependent. Finally, the efficacy of BD alone and in combination with GEM on PDAC was validated on both orthotopic xenograft and genetically engineered KPC mouse models. Conclusions

BD was able to enhance the chemosensitivity of GEM in PDAC through inhibition of the Nrf2 pathway. Our experimental findings indicate that BD, a potent Nrf2 inhibitor, holds promise for further development into a novel adjuvant therapy for PDAC.

14. Anti-atopic dermatitis effect of a modified Huang-Lian-Jie-Du decoction and its active fraction on 2, 4-dinitrobenzene and MC903-induced mouse models

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Phytomedicine, 2022, 104, 154346

Abstract

Huang-Lian-Jie-Du Decoction is a traditional Chinese medicine formula which has long been used to treat inflammatory skin disease including AD. However, Gardeniae Fructus, a component herb of HLJDD, has noticeable toxicity in liver and kidney. We therefore replaced Gardeniae Fructus with Dictamni Cortex with a hope to derive at a modified HLJDD (MHLJDD) with better safety profile. The present study aimed to develop MHLJDD and identify its active fraction as innovative therapeutic agents for AD using 2,4-dinitrobenzene (DNCB) and calcipotriol (MC903)-sensitized mouse models of AD. MHLJDD and the combination of the 1-butanol-soluble-fraction and the water-soluble-fraction (MHLJDD-F) were given intragastrically to the DNCB-induced mice and MC903-induced mice for two weeks. The body weight, dorsal skin/ear thickness and severity of AD symptoms of the mice were measured throughout the study. Scratching behaviors were observed after drug treatment. The blood and dorsal skin/ear tissues of mice were harvested for histopathological examination and biochemical analyses. The results revealed that DNCB- and MC903-induced AD symptoms, including skin thickening, dryness, erythema and excoriations, in the dorsal skin and ears were significantly alleviated in the MHLJDD and MHLJDD-F-treated mice. Ceramides content and protein expressions of filaggrin and loricrin were also up-regulated after treatment

with MHLJDD and MHLJDD-F. In addition, skin inflammation induced by DNCB and MC903 were markedly suppressed in the MHLJDD and MHLJDD-F-treated mice, and the action mechanisms involve suppression of the release of inflammatory cytokines, as well as downregulation of the activation of NF-κB and MAPKs pathways. Besides, MHLJDD and MHLJDD-F could reverse the abundance of gut microbiota induced by DNCB in mice. MHLJDD and MHLJDD-F could markedly relieve AD-like symptoms induced by DNCB and MC903 in mice through, at least in part, improving the epidermal barrier function and inhibiting skin inflammation via suppressing the activation of NF-κB and MAPKs pathways and regulation of the gut microflora dysbiosis. This study reported for the first time that MHLJDD and its active fraction could be used as innovative therapeutic agents for AD.

15. Major Constituents from Brucea javanica and Their Pharmacological Actions

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Frontiers in Pharmacology, 2022, 13, 853119

Abstract

Brucea javanica (Ya-dan-zi in Chinese) is a well-known Chinese herbal medicine, which is traditionally used in Chinese medicine for the treatment of intestinal inflammation, diarrhea, malaria, and cancer. The formulation of the oil (Brucea javanica oil) has been widely used to treat various types of cancer. It has also been found that B. javanica is rich in chemical constituents, including quassinoids, triterpenes, alkaloids, and flavonoids, which exhibit various biological properties. Pharmacological studies have revealed that chemical compounds derived from B. javanica exhibit multiple bioactivities, such as anti-cancer, anti-bacterial, anti-diabetic, and others. This review provides a comprehensive summary on the pharmacological properties of the main chemical constituents presented in B. javanica and their underlying molecular mechanisms. Moreover, the review will also provide scientific references for further research and development of B. javanica and the chemical constituents into novel pharmaceutical products for disease management.

16. Baicalin ameliorates 2, 4-dinitrochlorobenzene-induced atopic dermatitis-like skin lesions in mice through modulating skin barrier function, gut microbiota and JAK/STAT pathway

L. Wang, Y.F. Xian, S.K.F. Loo, S.P. Ip, W. Yang, W.Y. Chan, Z.X. Lin, J.C.Y. Wu

Bioorganic Chemistry, 2022, 119, 105538

Abstract

Baicalin has distinct therapeutic effects in various skin diseases animal models such as

atopic dermatitis (AD) and psoriasis. In this study, we aimed to investigate the anti-atopic dermatitis (AD) effects of baicalin in 2,4-dinitrochlorobenzene (DNCB)-treated mice. Female BALB/c mice treated with DNCB to induce AD-like skin lesions and orally administrated with baicalin daily for 14 consecutive days. Baicalin significantly inhibited dorsal skin thickness and trans-epidermal water loss and epidermal thickness in dorsal skin. In addition, baicalin also significantly up-regulated the protein expressions of filaggrin, involucrin, and loricrin, but inhibited the inflammatory response and the activation of NF-κB and JAK/STAT pathways in the dorsal skin of the DNCB-treated mice. Furthermore, baicalin significantly restored the abundance of probiotics in the gut microbiota of the DNCB-treated mice. Pseudo germ-free (GF) DNCB-treated mice receiving fecal microbiota from baicalin donors reduced the dorsal skin thickness and skin EASI score, and inhibited the release of IgE, histamine, TNF-α and IL-4 in serum of mice. In summary, baicalin ameliorates AD-like skin lesions induced by DNCB in mice via regulation of the Th1/Th2 balance, improvement of skin barrier function and modulation of gut dysbiosis, and inhibition of inflammation through suppressing the activation of NF-κB and JAK/STAT pathways.

17. Nano-Honokiol ameliorates the cognitive deficits in TgCRND8 mice of Alzheimer's disease via inhibiting neuropathology and modulating gut microbiota

C. Qu, Q.P. Li, Z.R. Su, S.P. Ip, Q.J. Yuan, Y.L. Xie, Q.Q. Xu, W. Yang, Y.F. Huang, Y.F. Xian, Z.X. Lin

Journal of advanced research, 2021, 35, 231-243

Abstract

Introduction: Honokiol (HO) exerts neuroprotective effects in several animal models of Alzheimer's disease (AD), but the poor dissolution hampers its bioavailability and therapeutic efficacy.

Objectives: A novel honokiol nanoscale drug delivery system (Nano-HO) with smaller size and excellent stability was developed in this study to improve the solubility and bioavailability of HO. The anti-AD effects of Nano-HO was determined.

Methods: Male TgCRND8 mice were daily orally administered Nano-HO or HO at the same dosage (20 mg/kg) for 17 consecutive weeks, followed by assessment of the spatial learning and memory functions using the Morris Water Maze test (MWMT).

Results: Our pharmacokinetic study indicated that the oral bioavailability was greatly improved by Nano-HO. In addition, Nano-HO significantly improved cognitive deficits and inhibited neuroinflammation via suppressing the levels of TNF-α, IL-6 and IL-1β in the brain, preventing the activation of microglia (IBA-1) and astrocyte (GFAP), and reducing β-amyloid (Aβ) deposition in the cortex and hippocampus of TgCRND8 mice. Moreover, Nano-HO was more effective than HO in modulating amyloid precursor protein (APP)

processing via suppressing β-secretase, as well as enhancing Aβ-degrading enzymes like neprilysin (NEP). Furthermore, Nano-HO more markedly inhibited tau hyperphosphorylation via decreasing the ratio of p-Tau (Thr 205)/tau and regulating tau-related apoptosis proteins (caspase-3 and Bcl-2). In addition, Nano-HO more markedly attenuated the ratios of p-JNK/JNK and p-35/CDK5, while enhancing the ratio of p-GSK-3β (Ser9)/GSK-3β. Finally, Nano-HO prevented the gut microflora dysbiosis in TgCRND8 mice in a more potent manner than free HO.

Conclusion: Nano-HO was more potent than free HO in improving cognitive impairments in TgCRND8 mice via inhibiting Aβ deposition, tau hyperphosphorylation and neuroinflammation through suppressing the activation of JNK/CDK5/GSK-3β signaling pathway. Nano-HO also more potently modulated the gut microbiota community to protect its stability than free HO. These results suggest that Nano-HO has good potential for further development into therapeutic agent for AD treatment.

18. Comparison of the chemical constituents and anti-Alzheimer's disease effects of Uncaria rhynchophylla and Uncaria tomentosa

Q.Q. Xu, P.C. Shaw, Z. Hu, W. Yang, S.P. Ip, Y.F. Xian, Z.X. Lin

Chinese Medicine, 2021, 16, 110

Abstract

Background: Uncaria tomentosa, which has similar chemical constituents with Uncaria rhynchophylla, has been reported to alleviate cognitive impairments in Alzheimer's disease (AD) animal models. This study aimed to compare the chemical constituents and anti-AD effect of the ethanol extracts of U. tomentosa (UTE) and U. rhynchophylla (URE).

Methods: The high-performance liquid chromatography (HPLC) was used to compare the chemical constituents of UTE and URE. Streptozotocin (STZ) was intracerebroventricularly (ICV) injected into adult male Sprague-Dawley (SD) rats to establish AD model. UTE (400 mg/kg) or URE (400 mg/kg) was administrated intragastrically once daily to the rats for 6 consecutive weeks. Morris water maze (MWM) test was conducted to assess the neurological functions in the STZ-induced AD rats. The brain tissues of the rats were harvested for further biochemical assay.

Results: The MWM test results showed both UTE and URE could significantly improve the learning and memory impairments induced by STZ in rats. Both UTE and URE could significantly inhibit the hyperphosphorylation of tau protein, reduce the elevated levels of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), enhance activities of antioxidant enzymes (SOD, CAT and GPx) and increase the protein expression of HO-1. In addition, UTE could decrease the malondialdehyde (MDA) level. Furthermore, both UTE and URE significantly enhanced Akt activation, down regulated the activation of glycogen synthase kinase 3β (GSK-3β), and induced the nuclear translocation of Nrf2 in the STZ-induced AD rats.

Conclusions: UTE and URE contained similar chemical constituents. We found for the first time that both of them could ameliorate cognitive deficits in the STZ-induced AD rats. The underlying molecular mechanism involve suppression of tau hyperphosphorylation, anti-oxidant and anti-neuroinflammation via modulating Akt (Ser473)/GSK3β (Ser9)-mediated Nrf2 activation. These findings amply implicate that both of UTE and URE are worthy of being developed clinically into pharmaceutical treatment for AD.

19. Efficacy and action mechanisms of a Chinese herbal formula on experimental models of atopic dermatitis

L. Wang, Y.F. Xian, Z. Hu, S.K.F. Loo, S.P. Ip, W.Y. Chan, Z.X. Lin, J.C.Y. Wu

Journal of Ethnopharmacology, 2021, 274, 114021

Abstract

Ethnopharmacological relevance: Atopic dermatitis (AD) is a skin inflammatory disease characterized by erythema, eruption, lichenification and pruritus. Shi Zhen Formula (SZF), an empirical Chinese herbal preparation, has clinical efficacy in relieving the symptoms of AD patients. However, the underlying molecular mechanisms of SZF remained unclear.

Aim of the study: We aimed to investigate the anti-AD effects of SZF and elucidate its underlying molecular mechanisms using in vitro and in vivo models of AD.

Materials and methods: High-performance liquid chromatography analysis was performed for quality control of SZF extract. The anti-inflammatory effect of SZF was investigated through evaluating the levels of nitric oxide (NO), chemokines and pro-inflammatory cytokines in the lipopolysaccharide (LPS) stimulated RAW264.7 cells. AD-like skin lesions in female BALB/c mice were induced by 2,4-dinitrochlorobenzene (DNCB). SZF (3.15, 6.30 and 9.45 g/kg) and dexamethasone (5 mg/kg) were administered by gavage daily for 15 consecutive days. The body weight, skin thickness, skin dermatitis severity and scratching behaviors were recorded throughout the study. Histological analysis, reverse transcription-quantitative polymerase chain reaction (RT-PCR), western blot (WB) and ELISA analysis were used to illuminate the molecular targets associated with the anti-AD effects of SZF.

Results: SZF markedly decreased the epidermal thickening and infiltration of mast cells in the ears and dorsal skin of the 2,4-dinitrochlorobenzene (DNCB)-treated mice. SZF not only suppressed the levels of immunoglobulin E (IgE), histamine, thymic stromal lymphopoietin (TSLP) and IL-4 in the serum but also suppressed the over-production of IL-4 and IL-6 and gene expressions of IL-4, IL-13, IL-31 and TSLP in the dorsal skin. Moreover, SZF improved epidermal barrier by increasing the protein expressions of filaggrin, involucrin and loricrin and inhibited the activation of NF-κB p65 pathway in the dorsal skin of the DNCB-treated mice.

Conclusion: SZF alleviates DNCB induced AD-like skin lesions in mice through regulating

Th1/Th2 balance, improving epidermal barrier and inhibiting skin inflammation. Our research findings provide scientific footing on the use of this Chinese herbal formula for the treatment of AD.

20. Herb–drug interactions between androgenic Chinese herbal medicines and androgen receptor antagonist on tumor growth: Studies on two xenograft prostate cancer animal models

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Phytotherapy Research, 2021, 35, 2758-2772

Abstract

Our previous study revealed that Epimedii Folium (EF) and Codonopsis Radix (CNR) significantly promoted tumor growth on a subcutaneous mouse model of prostate cancer (PCa) via enhancing the mRNA and protein expressions of androgen receptor (AR), while Astragali Radix (AGR) inhibited tumor growth via suppressing the protein expression of AR. In the present study, we aimed to investigate the potential interactions between EF, CNR or AGR and AR antagonist (abiraterone acetate [ABI]) on the tumor growth using subcutaneous and orthotopic PCa mouse models. EF, CNR, AGR and ABI were intragastrically given to mice once every 2 days for 4 weeks. The pharmacokinetics of ABI were evaluated in the plasma of rats when combined with EF, CNR, or AGR. Our results demonstrated that EF or CNR could weaken the anti-tumor effects of ABI via increasing the AR expression involving activation of the PI3K/AKT and Rb/E2F pathways and decreasing the bioavailability of ABI, while AGR could enhance the anti-tumor effects of ABI through suppressing the AR expression via inhibiting the activations of PI3K/AKT and Rb/E2F pathways and increasing the bioavailability of ABI. These findings imply that cautions should be exercised when prescribing EF and CNR for PCa patients.

21. Anti-atopic dermatitis effects of dictamni cortex: Studies on in vitro and in vivo experimental models

Y. Chen, Y.F. Xian, S. Loo, W.Y. Chan, L. Liu, Z.X. Lin

Phytomedicine, 2021, 82, 153453

Abstract

Background: Dictamni Cortex (DC), a Chinese herbal medicine with wind dispelling and itchiness relieving effects, is the most popular single herb prescribed for the treatment of atopic dermatitis (AD), as it is used in up to 12.68% of all herbal prescriptions for AD.

Purpose: The present study aimed to evaluate the anti-AD effect of Dictamni Cortex extract (DCE) and elucidate the underlying molecular mechanisms of its action using the 1-chloro-2,4-dinitrobenzene (DNCB)-induced AD-like mouse model and a relevant in

vitro experimental model.

Methods: Female Balb/c mice were sensitized with 200 μl 0.5% DNCB for three days. After sensitization, mice were challenged with 200 μl 1% DNCB on the same dorsal skin and also 20 μl 1% DNCB on each ear every 3 days, and orally administrated by gavage with DCE (0.6, 1.2 and 2.4 g/kg) daily from day 14 to day 29 for 16 consecutive days. At the end of experiment, the clinical scores for AD on the mice were calculated to evaluate the therapeutic effect of DCE; and serum, ears and dorsal skin of the mice were collected for mechanistic study. The anti-allergic activity of DCE was also evaluated using antigen-induced RBL-2H3 cell line. The release of selected cytokines, chemokines and β-hexosaminidase was measured to determine the anti-allergic activity of DCE. In addition, intracellular Ca2+ level, MAPKs and Lyn phosphorylations were further investigated to reveal its anti-allergic molecular mechanisms.

Results: Our results demonstrated that DCE could markedly improve the AD-like symptoms in AD-like mice by inhibiting the mast cell infiltration, suppressing the production of Th2-associated cytokine (IL-4) and pro-inflammatory cytokines (TNF-α), and enhancing the protein expression of filaggrin through inhibition of the MAPKs and NF-κB pathways. Moreover, DCE suppressed mast cell degranulation through decreasing the intracellular Ca2+ level and inactivation of Lyn, Syk and PLCγs, suggesting DCE could regulate mast-cell-mediated allergic response.

Conclusion: Our experimental results unambiguously indicate that DCE possesses potent anti-allergic effect, and help place the application of DC for the treatment of AD on a scientific footing.

22. Evaluation of the effects of androgenic Chinese herbal medicines on androgen receptors and tumor growth in experimental prostate cancer models

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Journal of Ethnopharmacology, 2020, 260, 113058

Abstract

Ethnopharmacological relevance: Many prostate cancer (PCa) patients in Mainland China and other Asian countries often use Chinese herbal medicines as an adjuvant treatment while receiving Western medicines. However, concerns have been raised about the potential herb-drug interaction when using herbal medicines containing phytoandrogens.

Aim of the study: This study aimed to investigate the effects of the selected 21 Chinese herbal medicines on the proliferation and tumor growth using the relevant in vitro and in vivo models of PCa.

Materials and methods: After treatment of LNCaP and 22Rv1 cells with different concentrations of 70% ethanol extracts of the 21 selected herbal medicines for 48 h, the

proliferative activity, the effects on androgen receptor (AR) and prostate specific antigen (PSA) were determined. The anti-tumor effects of the 21 herbs on PCa growth were also investigated on a subcutaneous mouse model of PCa.

Results: The results showed that Epimedii Folium (EF) and Codonopsis Radix (CNR) could significantly increase the cell viability in LNCaP cells ($p < 0.05$ for both) and 22Rv1 cells ($p < 0.05$ for both), protein expressions of AR in LNCaP cells ($p < 0.05$ for both) and 22Rv1 cells ($p < 0.05$ for both), and PSA ($p < 0.05$ for both) in LNCaP cells. EF, CNR, and Cistanches Herba (CCH) markedly accentuated the tumor growth ($p < 0.05$ for three drugs) and AR expression ($p < 0.05$ for three herbs) in tumor tissues. On the other hand, treatment with Astragali Radix (AGR), Chuanxiong Rhizoma (CXR) and Bruceae Fructus (BF) significantly inhibited the cell viability in LNCaP cells ($p < 0.05$, $p < 0.05$ and $p < 0.001$, respectively) and in 22Rv1 cells ($p < 0.05$, $p < 0.05$ and $p < 0.001$, respectively), and the protein expression of AR in LNCaP cells ($p < 0.05$ for three herbs) and 22Rv1 cells ($p < 0.05$, $p < 0.05$ and $p < 0.001$, respectively), and the protein expression of PSA ($p < 0.05$ for three herbs) in LNCaP cells, as well as tumor growth ($p < 0.05$ for three herbs) and the AR expression ($p < 0.05$ for AGR and CXR, $p < 0.001$ for BF) in tumor tissues.

Conclusion: Our results revealed that AGR, CXR and BF suppressed the PCa development via inhibition of AR expression, while EF, CNR and CCH promoted the development and progression of PCa via enhancement of AR expression. The results strongly suggest that caution should be exercised when using androgenic Chinese herbal medicines in PCa patients.

23. Magnolol ameliorates behavioral impairments and neuropathology in a transgenic mouse model of Alzheimer's disease

Y.F. Xian, C. Qu, Y. Liu, S.P. Ip, Q.J. Yuan, W. Yang, Z.X. Lin

Oxidative medicine and cellular longevity, 2020, 2020, 5920476

Abstract

Alzheimer's disease (AD) is a common neurodegenerative disease characterized by progressive memory loss. Magnolol (MN), the main active ingredient of Magnolia officinalis, possesses anti-AD effects in several experimental models of AD. In this study, we aimed to explore whether MN could ameliorate the cognitive deficits in TgCRND8 transgenic mice and to elucidate its molecular mechanisms. Male TgCRND8 mice were orally administered with MN (20 and 40 mg/kg) daily for 4 consecutive months, followed by assessing the spatial learning and memory functions using the open-field, radial arm maze, and novel object recognition tests. The results demonstrated that MN (20 and 40 mg/kg) could markedly ameliorate the cognitive deficits in TgCRND8 mice. In addition, MN significantly increased the expression of postsynaptic density protein 93 (PSD93), PSD-95, synapsin-1, synaptotagmin-1, synaptophysin (SYN), and interleukin-10 (IL-10),

while markedly reduced the protein levels of tumor necrosis factor alpha (TNF-α), IL-6, IL-1β, Aβ 40, and Aβ 42, and modulated the amyloid precursor protein (APP) processing and phosphorylation. Immunofluorescence showed that MN significantly suppressed the activation of microglia (Iba-1) and astrocytes (GFAP) in the hippocampus and cerebral cortex of TgCRND8 mice. Mechanistic studies revealed that MN could significantly increase the ratios of p-GSK-3β (Ser9)/GSK-3β, p-Akt (Ser473)/Akt, and p-NF-κB p65/NF-κB p65. These findings indicate that MN exerted cognitive deficits improving effects via suppressing neuroinflammation, amyloid pathology, and synaptic dysfunction through regulating the PI3K/Akt/GSK-3β and NF-κB pathways, suggesting that MN is a promising naturally occurring polyphenol worthy of further developing into a therapeutic agent for AD treatment.

24. Huang-Lian-Jie-Du extract ameliorates atopic dermatitis-like skin lesions induced by 2, 4-dinitrobenzene in mice via suppression of MAPKs and NF-κB pathways

Y. Chen, Y.F. Xian, S. Loo, Z. Lai, W.Y. Chan, L. Liu, Z.X. Lin

Journal of Ethnopharmacology, 2020, 249, 112367

Abstract

Ethnopharmacological relevance: Huang-Lian-Jie-Du Decoction (HLJDD), is a well-known traditional Chinese herbal formula first written in the Tang dynasty. In Chinese medicine practice, HLJDD is commonly prescribed to treat various inflammatory skin diseases, such as atopic dermatitis (AD) and psoriasis.

Aim of the study: The present study aimed at investigating the therapeutic effect of HLJDD extract (HLJDE) and to elucidate the underlying molecular mechanisms of action in the 1-chloro-2,4-dinitrobenzene (DNCB)-induced AD-like mice.

Materials and methods: Female Balb/c mice were sensitized with DNCB for three days. After sensitization, mice were challenged with DNCB every three days and orally administrated with HLJDE (150, 300 and 600 mg/kg) daily from day 14 to day 29 for consecutive 16 days. At the end of experiment, the clinical AD scores of the mice were calculated to evaluate the therapeutic effect of HLJDE, and serum, ears and dorsal skin of the mice were collected for unravelling molecular mechanisms.

Results: HLJDE significantly reduced the clinical symptoms in the AD-like mice by inhibiting eosinophil and mast cell infiltration, suppressing the production of Th2-associated cytokine (IL-4) and pro-inflammatory cytokines (TNF-α). In addition, HLJDE significantly suppressed the NF-κB and MAPKs pathways. Moreover, HLJDE was able to accentuate filaggrin expression in the skin lesion when compared to the sensitized mouse without treatment.

Conclusion: HLJDE significantly improved the AD-like symptoms on the DNCB-sensitized mice through mitigating the production of inflammatory mediators via

suppressing MAPKs and NF-κB pathways. Additionally, the elevated expression of filaggrin in the skin lesion by HLJDE contributes to the recovery of dysfunctional skin barrier on the DNCB-sensitized mice.

25. Berberine enhances survival and axonal regeneration of motoneurons following spinal root avulsion and re-implantation in rats

X. Zhang, X.D. Liu, Y.F. Xian, F. Zhang, P.Y. Huang, Y. Tang, Q.J. Yuan, Z.X. Lin

Free Radical Biology and Medicine, 2019, 143, 454-470

Abstract

Brachial plexus avulsion (BPA) occurs when the spinal nerve roots are pulled away from the surface of the spinal cord and disconnects neuronal cell body from its distal downstream axon, which induces massive motoneuron death, motor axon degeneration and de-innervation of targeted muscles, thereby resulting in permanent paralysis of motor functions in the upper limb. Avulsion injury triggers oxidative stress and intense local neuroinflammation at the lesioned site, leading to the death of most motoneurons. Berberine (BBR), a natural isoquinoline alkaloid derived from medicinal herbs of Berberis and Coptis species, has been reported to possess neuro-protective, anti-inflammatory and anti-oxidative effects in various animal models of central nervous system (CNS)-related disorders. In this study, we aimed to investigate the effect of BBR on motoneuron survival and axonal regeneration following spinal root avulsion plus re-implantation in rats. Our results indicated BBR significantly accelerated motor function recovery in the forelimb as revealed by the increased Terzis grooming test score, facilitated motor axon regeneration as evidenced by the elevated number of Fluoro-Gold-labeled and P75-positive regenerative motoneurons. The survival of motoneurons was notably promoted by BBR administration presented with boosted ChAT-immunopositive and neutral red-stained neurons. BBR treatment efficiently alleviated muscle atrophy, attenuated functional motor endplates loss in biceps and prevented the reduction of motor axons in the musculocutaneous nerve. Additionally, BBR treatment markedly mitigated the avulsion-induced neuroinflammation via inhibiting microglial and astroglial reactivity, up-regulated the expression of antioxidative indicator Cu/Zn SOD, and down-regulated the levels of nNOS, 3-NT, lipid peroxidation and NF-κB, as well as promoted SIRT1, PI3K and Akt activation. Collectively, BBR might be a promising therapy to assist re-implantation surgery for the treatment of BPA.

26. Isorhynchophylline exerts antidepressant-like effects in mice via modulating neuroinflammation and neurotrophins: involvement of the PI3K/Akt/GSK-3β signaling pathway

Y.F. Xian, S.P. Ip, H.Q. Li, C. Qu, Z.R. Su, J.N. Chen, Z.X. Lin

The FASEB Journal, 2019, 33, 10393-10408

Abstract

Isorhynchophylline (IRN), an oxindole alkaloid isolated from Uncaria rhynchophylla, elicited distinct antidepressant-like activity in mice. The present study aimed to investigate the antidepressant-like effects of IRN in chronic unpredictable mild stress (CUMS)-induced depressive-like behaviors in mice and to illustrate its possible mechanisms of action. The mice were subjected to CUMS for 6 wk and administered with IRN (20 or 40 mg/kg) daily by oral gavage for 3 wk. The PI3K/protein kinase B (Akt) inhibitor and glycogen synthase kinase-3β (GSK-3β) inhibitors were used to determine the involvement of the PI3K/Akt/GSK-3β pathway in the antidepressant-like effects of IRN in the mice. The results showed that CUMS caused depression-like behaviors in the mice, such as behavioral despair by the forced swim test (FST) and anhedonia by the sucrose preference test. In addition, CUMS could significantly reduce the levels of nerve growth factor and brain-derived neurotrophic factor but markedly increase the release of TNF-α and IL-6 in the hippocampus and cerebral cortex of the mice. Western blotting analysis showed that CUMS markedly suppressed the levels of phosphorylated GSK-3β (Ser9) and phosphorylated Akt (Ser473) but significantly enhanced the translocation of NF-κB p65 from cytosol to nuclei in the hippocampus and cerebral cortex of the mice. CUMS could also significantly increase the NF-κB binding activity in the hippocampus and cerebral cortex of the mice, whereas IRN treatment could significantly reverse the behavioral and biochemical changes induced by CUMS in the mice. Moreover, the antidepressant-like effect of IRN was completely abolished by the PI3K/Akt inhibitor. Combination treatment with IRN and GSK-3β inhibitors in the mice exerted a synergistic anti-immobility action in the FST. The results of mechanistic investigations indicated that the antidepressant-like action of IRN was mediated, at least in part, by enhancing neurotrophins and attenuating neuroinflammation via modulating the PI3K/Akt/GSK-3β pathway

27. Pharmacokinetic Study on Bruceoside A Revealed the Potential Role of Quassinoid Glycosides for the Anticancer Properties of Fructus Bruceae

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Journal of Pharmaceutical and Biomedical Analysis, 2019, 170, 264-272

Abstract

Bruceoside A, an abundant quassinoid glycoside in Fructus Bruceae, was chosen for the pharmacokinetic study. It is the first case report on the pharmacokinetic study of quassinoid glycosides so far. A sensitive, accurate, and repeatable UHPLC-MS/MS method was developed for the determination of bruceoside A and its major metabolite.

The results showed bruceoside A could be transformed into the potent anticancer component brusatol in vivo, rather than its direct deglycosylated metabolite bruceosin and the intestinal bacteria were proposed to take a potential role during such transformation. Based on the present study, it could be concluded that the quassinoid glycosides possessing weak activities in vitro could do contribution to the anticancer properties of Fructus Bruceae in vivo via transforming into more active metabolites.

28. Ameliorative effect of supercritical fluid extract of Chrysanthemum indicum Linnén against D-galactose induced brain and liver injury in senescent mice via suppression of oxidative stress, inflammation and apoptosis

X. Zhang, J.Z. Wu, Z.X. Lin, Q.J. Yuan, Y.C. Li, J.L. Liang, J.Y.X. Zhan, Y.L. Xie, Z.R. Su, Y.H. Liu

Journal of ethnopharmacology, 2019, 234, 44-56

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:

Chrysanthemum indicum Linne (C. indicum), a healthy food and folk medicine in China for thousands of years, has been reported to exert heat-clearing and detoxifying effects and extensively applied to treat various symptoms such as inflammation diseases, hepatitis and headache.

AIM OF THIS STUDY:

The purpose of the present study was to investigate the protective effect of the supercritical carbon dioxide fluid extract from flowers and buds of C. indicum (CISCFE) on D-galactose-induced brain and liver damage during aging process and to illuminate the underlying mechanisms.

MATERIALS AND METHODS:

Mice were orally administrated with CISCFE (100, 150 and 300 mg/kg) after injection with D-galactose. 24 h after the last administration, the blood samples, whole brain and liver tissues were collected for biochemical analysis, histological examination and western blot analysis. The body weight, spleen and thymus indexes, alanine transaminase (ALT), aspartate transaminase (AST), total antioxidant capacity (T-AOC), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), malondialdehyde (MDA) in brain and liver, interleukin-1β (IL-1β), interleukin-6 (IL-6), and necrosis factor-α (TNF-α) were detected. Besides, the expressions of Bax, Bcl-2 and cleaved caspase-3 were determined by western blot assay.

RESULTS:

The results indicated that CISCFE effectively increased the suppressed body weight, attenuated the decline of thymus and spleen indexes, and reduced the elevated levels of ALT and AST induced by D-gal. Furthermore, CISCFE might notably alleviate

D-gal-induced abnormal alterations in structure and function of brain and liver dose-dependently via renewing normal antioxidant enzymes activities (SOD, CAT, GSH-Px), reducing MDA accumulation, decreasing inflammatory cytokines productions (IL-1β, IL-6, TNF-α), as well as attenuating the increase of Bax/Bcl-2 ratio and cleaved caspase-3 activation in the liver and brain.

CONCLUSIONS:

Taken together, our present results suggested that CISCFE treatment could effectively mitigate the D-gal-induced hepatic and cerebral injury, and the underlying mechanism might be tightly related to the decreased oxidative stress, inflammation and apoptosis, indicating CISCFE might be an alternative and promising agent for the treatment of aging and age-associated brain and liver diseases.

29. Synergistic antitumor effect of brusatol combined with cisplatin on colorectal cancer cells

H.M. Chen, Z.Q. Lai, H.J. Liao, J.H. Xie, Y.F. Xian, Y.L. Chen, S.P. Ip, Z.X. Lin, Z.R. Su

International Journal of Molecular Medicine, 2018, 41, 1447-1454

Abstract

Colorectal cancer (CRC) is a common and life‑threatening type of malignant cancer, which is associated with a high mortality rate. Cisplatin (CDDP) is a commonly used chemotherapy drug with significant side effects. Brusatol (BR) is one of the principal chemical compounds isolated from the Chinese herb Bruceae Fructus, which has been reported to markedly inhibit the proliferation of numerous cancer cell lines. The present study aimed to investigate the possible synergistic anticancer effects of CDDP combined with BR on CT‑26 cells, and to evaluate the underlying mechanisms of action. The growth inhibitory effects of BR, CDDP, and BR and CDDP cotreatment on CT‑26 cells were assessed by MTT assay. Cell apoptosis were determined by flow cytometry and western blot analysis. The results indicated that compared with single‑agent treatment, cotreatment of CT‑26 cells with CDDP and BR synergistically inhibited cell proliferation and increased cellular apoptosis. Furthermore, treatment of CT‑26 cells with CDDP and BR resulted in a marked increase in the release of cytosolic cytochrome c, decreased expression of procaspase‑3 and procaspase‑9, and upregulation of the B‑cell lymphoma 2 (Bcl‑2)‑associated X protein/Bcl‑2 ratio compared with treatment with BR or CDDP alone. These results strongly suggested that the combination of CDDP and BR was able to produce a synergistic antitumor effect in CRC cells, thus providing a solid foundation for further development of this combination regimen into an effective therapeutic method for CRC.

30. Isorhynchophylline alleviates learning and memory impairments induced by aluminum chloride in mice

H.Q. Li, S.P. Ip, G.Q. Zheng, Y.F. Xian, Z.X. Lin

Chinese Medicine, 2018, 13, 29

Abstract

Background: To evaluate the effect of Isorhynchophylline (IRN) on the learning and memory impairments induced by aluminum chloride (AlCl3) in mice. Methods: Fifty male Balb-c mice (4-month-old) were randomly divided into five groups: control, AlCl3 plus vehicle, AlCl3 plus IRN (20 mg/kg), AlCl3 plus IRN (40 mg/kg) and AlCl3 plus donepezil (5 mg/kg). Learning and memory impairments were induced in mice by subcutaneously injecting with AlCl3 (50 mg/kg) once a day for 8 consecutive weeks. At the same time, mice were intragastrically given vehicle or IRN (20 and 40 mg/kg) or donepezil (5 mg/kg) 30 min before each AlCl3 injection. The spatial learning and memory function was assessed using radial arm maze. After sacrificed, the parameters of oxidative stress and cholinergic system in the brain tissues were examined with ELISA kits. Moreover, the expression of nuclear factor kappa B (NF-κB) signaling pathway was analyzed with western blotting. Results: The results showed that treatment with IRN could significantly ameliorate the cognitive deficits induced by AlCl3 in mice. In addition, treatment with IRN was found to reduce the level of malondialdehyde, enhance the activities of superoxide dismutases and catalase, increase the level of glutathione, and markedly inhibit the activity of acetylcholinesterase (AChE) in the brain tissues of the AlCl3-treated mice. Moreover, IRN significantly suppressed the phosphorylation of NF-κB p65 and IκBα in the brain tissues of AlCl3-treated mice. However, IRN did not show significant effect on the activity of butyrylcholinesterase. Conclusion: Our findings demonstrated for the first time that IRN could alleviate learning and memory impairments induced by AlCl3 in mice. The neuroprotective effect of IRN against AlCl3-induced AD is probably mediated, at least in part, through inhibiting the AChE activity and reducing the oxidative damage of brain tissue via suppress the NF-κB signaling pathway. These results contributed to a better understanding of the in vivo anti-AD mechanism of IRN. It was concluded that IRN could protect the learning and memory function.

31. Brucein D, a Naturally Occurring Tetracyclic Triterpene Quassinoid, Induces Apoptosis in Pancreatic Cancer through ROS-Associated PI3K/Akt Signaling Pathway

Z.Q. Lai, S.P. Ip, H.J. Liao, Z. Lu, J.H. Xie, Z.R. Su, Y.L. Chen, Y.F. Xian, P.S. Leung, Z.X. Lin

Frontiers in Pharmacology, 2017, 8, 936

Abstract

Brucein D (BD), a major active quassinoid in Brucea javanica, has exhibited pronounced anticancer activities. However, the biologic mechanisms have not been fully explored. In this study, BD exhibited more potent cytotoxic effect on pancreatic cancer (PanCa) cell lines, while exerted weaker cytotoxic effects on GES-1 cells (non-tumorigenic). BD was shown to elicit apoptosis through inducing both the intrinsic and extrinsic mitochondria-mediated caspase activations. Furthermore, the BD-induced apoptotic effects were dependent on the accumulated reactive oxygen species (ROS) and inactivation of PI3K/Akt signaling pathway. Pretreatment with tempol completely prevented the cellular apoptosis induced by BD, and recovered the inactivation of AKT, which suggested ROS essentially involved in BD-elicited apoptosis and down-regulation of PI3K/Akt pathway. In addition, the results obtained from orthotopic xenograft in nude mice were congruent with those of the in vitro investigations. These results support the notion that BD held good potential to be further developed into an effective pharmaceutical agent for the treatment of PanCa.

32. Antidepressant-Like Effect of Isorhynchophylline in Mice

Y.F. Xian, D. Fan, S.P. Ip, Q.Q. Mao, Z.X. Lin

Neurochemical Research, 2017, 42, 678-685

Abstract

Isorhynchophylline (IRN), an oxindole alkaloid, has been identified as the main active ingredient responsible for the biological activities of Uncaria rhynchophylla (Miq) Miq ex Havil. (Rubiaceae). Previous studies in our laboratory have revealed that IRN possesses potent neuroprotective effects in different models of Alzheimer's disease. However, the antidepressant-like effects of IRN are remained unclear. The present study aims to evaluate the antidepressant-like effects of IRN. The antidepressant-like effects of IRN was determined by using animal models of depression including forced swimming and tail suspension tests. The acting mechanism was explored by determining the effect of IRN on the levels of monoamine neurotransmitters and the activities of monoamine oxidases. Intragastric administration of IRN at 10, 20 and 40 mg/kg for 7 days caused a significant reduction of immobility time in both forced swimming and tail suspension tests, while IRN did not stimulate locomotor activity in the open-field test. In addition, IRN treatment antagonized reserpine-induced ptosis and significantly enhanced the levels of monoamine neurotransmitters including norepinephrine (NE) and 5-hydroxytryptamine (5-HT), and the activity of monoamine oxidase A (MAO-A) in the hippocampus and frontal cortex of mice. These results suggest that the antidepressant-like effects of IRN are mediated, at least in part, by the inhibition of monoamine oxidases.

33. Neuroprotective effects of honokiol against beta-amyloid-induced neurotoxicity via GSK-3β and β-catenin signaling pathway in PC12

cells

Y.F. Xian, S.P. Ip, Q.Q. Mao, Z.X. Lin

Neurochemistry International, 2016, 97, 8-14

Abstract

Beta-amyloid (Aβ) accumulation, one of the most important pathogenic traits of Alzheimer's disease (AD), has been reported to induce neurotoxicity in vitro as well as in vivo. Honokiol, isolated from the bark of Magnolia officinalis, has neuroprotective effects in different models of AD in vivo and in vitro. However, the exact mechanism for its neuroprotective effect is not well understood. The present study aimed to investigate the molecular mechanisms underlying the protective action of honokiol against Aβ1-42-induced neurotoxicity in cultured rat pheochromocytoma (PC12) cells. The results revealed that honokiol protected PC12 cells from Aβ1-42 induced cytotoxicity with increases in cell viability, GSH production and Bcl-2 expression, but decreases in the release of lactate dehydrogenase and cytochrome c, the amount of DNA fragmentation and MDA level, as well as Bax expression. Mechanistic study showed that honokiol could inhibit the activation of glycogen synthase kinase (GSK)-3β, attenuate the nuclear accumulation of β-catenin and suppress the phosphorylation of β-catenin (Ser33/Ser37/Thr41 site) in the Aβ1-42-treated PC12 cells. These results indicate that the anti-oxidative and anti-apoptotic effects of honokiol in Aβ1-42-treated PC12 cells may be mediated, at least in part, by regulation the GSK-3β and β-catenin signaling pathways.

34. Sonodynamic action of curcumin on foodborne bacteria Bacillus cereus and Escherichia coli

X.N. Wang, M. Ip, A.W.N. Leung, Z.R. Yang, P. Wang, B.T. Zhang, S.P. Ip, C.S. Xu

Ultrasonics, 2015, 62, 75-79

Abstract

Bacterial contamination is an important cause of foodborne diseases. The present study aimed to investigate sonodynamic action of curcumin on foodborne bacteria Bacillus cereus (B. cereus) and Escherichia coli (E. coli). The uptake of curcumin was measured for optimizing the concentration incubation time before ultrasound sonication, and colony forming units (CFU) were counted after ultrasound treatment. The chromosomal DNA fragmentation of bacteria was analyzed and the effect of hypoxic condition on the antibacterial efficacy of sonodynamic action of curcumin was also assessed in this study. The results showed that the maximum uptake of curcumin in B. cereus and E. coli occurred in 50min after curcumin incubation. Curcumin had sonodynamic bactericidal activity in a curcumin dose-dependent manner, and 5.6-log reduction in CFU of B. cereus was observed after curcumin treatment (2.0 μM), however, only 2-log reduction in CFU of E. coli after 40μM curcumin treatment. No significant change in chromosomal DNA was

found after the combined treatment of curcumin and ultrasound. The survival of B. cereus and E. coli after sonodynamic treatment in hypoxic group was significantly higher than that in normal oxygen group. These findings indicated that sonodynamic action of curcumin had significant inactivation effect on foodborne bacteria, and B. cereus was more sensitive to sonodynamic treatment of curcumin than E. coli. Sonodynamic antibacterial activity of curcumin might be dependent on the oxygen environment.

35. Honokiol improves learning and memory impairments induced by scopolamine in mice

X.F. Xian, S.P. Ip, Q.Q. Mao, Z.R. Su, J.N. Chen, X.P. Lai, Z.X. Lin

European Journal of Pharmacology, 2015, 760, 88-95

Abstract

Honokiol, a lignan isolated from the bark of Magnolia officinalis, has been reported to ameliorate the learning and memory impairments in senesed (SAMP8) mice. However, whether honokiol could improve scopolamine (SCOP)-induced learning and memory deficits in mice is still unknown. In this study, we aimed to investigate whether honokiol could reverse the SCOP-induced learning and memory impairments in mice and to elucidate its underlying mechanisms of action. Mice were given daily intraperitoneal injection of honokiol (10 and 20mg/kg) for 21 consecutive days. The results showed that honokiol significantly improved spatial learning and memory function (as assessed by the Morris water maze test) in the SCOP-treated mice. In addition, treatment with honokiol significantly decreased the protein and mRNA levels of interleukin (IL)-1β and the activity of acetylcholinesterase (AChE), while significantly increased the protein and mRNA levels of IL-10, and the level of acetylcholine (Ach) in the brain of the SCOP-treated mice. Moreover, honokiol also significantly suppressed the production of prostaglandin E 2 (PGE2) and mRNA expression of cyclooxygenase-2 (COX-2) in the brain of the SCOP-treated mice. Mechanistic investigations revealed that honokiol could markedly reverse the amount of phosphorylated Akt and extracellular regulated kinases 1/2 (ERK1/2) changes in the brain of the SCOP-treated mice. These results amply demonstrated that honokiol could improve learning and memory impairments induced by SCOP in mice, and the protective action may be mediated, at least in part, by inhibition of AChE activity, and amelioration of the neuroinflammatory processes in the SCOP-treated mice.

36. Piperine reverses chronic unpredictable mild stress-induced behavioral and biochemical alterations in rats.

Q.Q. Mao, Z. Huang, X.M. Zhong, Y.F. Xian, S.P. Ip

Cellular and Molecular Neurobiology, 2014, 34, 403-308

Abstract

Previous studies in our laboratory have demonstrated that piperine produced antidepressant-like action in various mouse models of behavioral despair, which was related to the serotonergic system. The present study aimed to examine the behavioral and biochemical effects of piperine in rats exposed to chronic unpredictable mild stress (CUMS). The results showed that CUMS caused depression-like behavior in rats, as indicated by the significant decrease in sucrose consumption and increase in immobility time in the forced swim test. In addition, it was found that serotonin (5-HT) and brain-derived neurotrophic factor (BDNF) contents in the hippocampus and frontal cortex were significantly decreased in CUMS-treated rats. Treating the animals with piperine significantly suppressed behavioral and biochemical changes induced by CUMS. The results suggest that piperine produces an antidepressant-like effect in CUMS-treated rats, which is possibly mediated by increasing 5-HT and BDNF contents in selective brain tissues.

37. Isorhynchophylline treatment improves the amyloid-β-induced cognitive impairment in rats via inhibition of neuronal apoptosis and tau protein hyperphosphorylation

Y.F. Xian, Q.Q. Mao, J.C. Wu, Z.R. Su, J.N. Chen, X.P. Lai, S.P. Ip, Z.X. Lin

Journal of Alzheimer's Disease, 2014, 39, 331-346

Abstract

The progressive accumulation of amyloid-β (Aβ) in the form of senile plaques has been recognized as a key causative factor leading to the cognitive deficits seen in Alzheimer's disease (AD). Recent evidence indicates that Aβ induces neurotoxicity in the primary neuronal cultures as well as in the brain. Previously, we have demonstrated that isorhynchophylline (IRN), the major chemical ingredient of Uncaria rhynchophylla, possessed potent neuroprotective effects. In the present study, we aimed to investigate the effect of IRN on cognitive function, neuronal apoptosis, and tau protein hyperphosphorylation in the hippocampus of the Aβ25-35-treated rats and to elucidate its action mechanisms. We showed that Aβ25-35 injection caused spatial memory impairment, neuronal apoptosis, and tau protein hyperphosphorylation. Treatment with IRN (20 or 40 mg/kg) for 21 days could significantly ameliorate the cognitive deficits induced by Aβ25-35 in the rats. In addition, IRN attenuated the Aβ25-35-induced neuronal apoptosis in hippocampus by down-regulating the protein and mRNA levels of the ratio of Bcl-2/Bax, cleaved caspase-3 and caspase-9, as well as suppressing the tau protein hyperphosphorylation at the Ser396, Ser404, and Thr205 sites. Mechanistic study showed that IRN could inhibit the glycogen synthase kinase 3β (GSK-3β) activity, and activate the phosphorylation of phosphatidylinositol 3-kinase (PI3K) substrate Akt.

These results indicate that down-regulation of GSK-3β activity and activation of PI3K/Akt signaling pathway are intimately involved in the neuroprotection of IRN. The experimental findings provide further evidence to affirm the potential of IRN as a worthy candidate for further development into a therapeutic agent for AD and other tau pathology-related neurodegenerative diseases.

38. Liquid Chromatography – Mass spectrometry method for the simultaneous determination and confirmation of seven active components in Chinese medicine Kumu injection

Z.Q. Lai, H.J. Liao, S.P. Ip, Y.Y. Yi, S.J. Shi, J.Y. Su, X.P. Lai, Z.R. Su and Z.X. Lin

Tropical Journal of Pharmaceutical Research, 2014, 13, 141-148

Abstract

Purpose: To develop and validate a simple and selective high performance liquid chromatography photo diode array mass spectrometry (HPLC-PDA-MS/MS) method for simultaneous determination and confirmation of seven major active alkaloids (6-Hydroxy-ß-Carboline-1-carboxylic acid, ß-Carboline-1- carboxylic acid, ß-Carboline-1-propanoic acid, 3-Methylcanthin-5,6-dione, 4-Methoxy-3-methylcanthine-5,6-dione, 5-Hydroxy-4- methoxycanthin-6-one, 4,5-Dimethoxycanthin-6-one) in Kumu injections (KMIs)

Methods: For the analysis of the preparation, the optimal chromatographic condition was achieved on a Phenomenex Gemini C18 column with gradient elution of 25 mM aqueous ammonium acetate (pH = 4.0 adjusted by glacial acetate acid) and acetonitrile with flow rate at 1.0 mL/min, column temperature at 35oC and detection wavelengths at 245, 260 and 271 nm.

Results: Excellent linear behavior over the investigated concentration ranges was observed with regression coeffcient (R2) > 0.9997 for all analytes. Intra- and inter-day precisions for all studied constituents ranged from 0.20 to 1.80 %. Recoveries of the assayed constituents were in the range of 98.73 to 100.34 %. The results showed the contents of these seven marker compounds differed significantly among different batches of KMIs both from the same and different manufacturers.

Conclusion: The validated method was reliable, accurate, repeatable, and can be applied to routine quality assessment of these active components in KMIs.

39. Brain-derived neurotrophic factor signalling mediates the antidepressant-like effect of piperine in chronically stressed mice.

Q.Q. Mao, Z. Huang, X.M. Zhong, Y.F. Xian, S.P. Ip

Behavioural Brain Research, 2014, 261, 140-145

Abstract

Previous studies in our laboratory have demonstrated that piperine produced antidepressant-like action in various mouse models of behavioral despair. This study aimed to investigate the role of brain-derived neurotrophic factor (BDNF) signalling in the antidepressant-like effect of piperine in mice exposed to chronic unpredictable mild stress (CUMS). The results showed that CUMS caused depression-like behavior in mice, as indicated by the significant decrease in sucrose consumption and increase in immobility time in the forced swim test. It was also found that BDNF protein expression in the hippocampus and frontal cortex were significantly decreased in CUMS-treated mice. Chronic treatment of piperine at the dose of 10mg/kg significantly ameliorated behavioural deficits of CUMS-treated mice in the sucrose preference test and forced swim test. Piperine treatment also significantly decreased immobility time in the forced swim test in naive mice. In parallel, chronic piperine treatment significantly increased BDNF protein expression in the hippocampus and frontal cortex of both naive and CUMS-treated mice. In addition, inhibition of BDNF signalling by injection of K252a, an inhibitor of the BDNF receptor TrkB, significantly blocked the antidepressant-like effect of piperine in the sucrose preference test and forced swim test of CUMS-treated mice. Taken together, this study suggests that BDNF signalling is an essential mediator for the antidepressant-like effect of piperine.

40. Isorhynchophylline protects PC12 cells against beta-amyloid-induced apoptosis via PI3K/Akt signaling pathway

Y.F. Xian, Z.X. Lin, Q.Q. Mao, J.N. Chen, Z.R. Su, X.P. Lai, S.P. Ip

Evidence-Based Complementary and Alternative Medicine. Volume 2013 (2013), Article ID 163057, 8 pages. doi: 10.1155/2013/163057.

Abstract

The neurotoxicity of amyloid-β (Aβ) has been implicated as a critical cause of Alzheimer's disease. Isorhynchophylline (IRN), an oxindole alkaloid isolated from Uncaria rhynchophylla, exerts neuroprotective effect against Aβ25–35-induced neurotoxicity in vitro. However, the exact mechanism for its neuroprotective effect is not well understood. The present study aimed to investigate the molecular mechanisms underlying the protective action of IRN against Aβ25–35-induced neurotoxicity in cultured rat pheochromocytoma (PC12) cells. Pretreatment with IRN significantly increased the cell viability, inhibited the release of lactate dehydrogenase and the extent of DNA fragmentation in Aβ25–35-treated cells. IRN treatment was able to enhance the protein levels of phosphorylated Akt (p-Akt) and glycogen synthase kinase-3β (p-GSK-3β). Lithium chloride blocked Aβ25–35-induced cellular apoptosis in a similar manner as IRN, suggesting that GSK-3β inhibition was involved in neuroprotective action of IRN.

Pretreatment with LY294002 completely abolished the protective effects of IRN. Furthermore, IRN reversed Aβ25–35-induced attenuation in the level of phosphorylated cyclic AMP response element binding protein (p-CREB) and the effect of IRN could be blocked by the PI3K inhibitor. These experimental findings unambiguously suggested that the protective effect of IRN against Aβ25–35-induced apoptosis in PC12 cells was associated with the enhancement of p-CREB expression via PI3K/Akt/GSK-3β signaling pathway.

41. Comparison the neuropreotective effect of Cortex Phellodendri Chinensis and Cortex Phellodendri Amurensis against beta-amyloid-induced neurotoxicity in PC12 cells

Y.F. Xian, Z.X. Lin, S.P. Ip, Z.R. Su, J.N. Chen, X.P. Lai

Phytomedicine, 2013, 20, 187-193

Abstract

Cortex Phellodendron chinensis (CPC) and Cortex Phellodendron amurensis (CPA) derived from the dried bark of Phellodendron chinense Schneid. or Phellodendron amurense Rupr., respectively, are used interchangeably in clinical practice under the name "Huang Bai" for centuries in Chinese medicine for the treatment of various inflammatory conditions. Previous study in our laboratory demonstrated that CPC and CPA had different anti-diarrheal, anti-bacterial and anti-inflammatory effects. In this present study, we aimed to compare the protective effect of ethanol extract of Cortex Phellodendri chinensis (ECPC) and Cortex Phellodendri Amurensis (ECPA) against beta-amyloid (Aβ)-induced neurotoxicity in PC12 cells, a typical model of Alzheimer's disease. The results showed that ECPC and ECPA contain four common chemical markers such as berberine, but palmatine and jatrorrhizin were not found in CPC in contrast to the presence in CPA. In addition, both ECPC and ECPA can significantly increase the cell viability in Aβ-treated PC12 cells. Moreover, ECPC and ECPA can markedly elevate the ratio of the protein and mRNA levels of Bcl-2/Bax, while remarkably decrease the release of cytochrome c, and the protein and mRNA expression of caspase-3. Interestingly, ECPA has better protective effect than ECPC against Aβ-induced neurotoxicity in PC12 cells. These results indicate that both ECPC and ECPA have potential protective effect against Aβ-induced neurotoxicity in PC12 cells, and ECPA is more potential of the two species to be used in traditional medicine as a neuroprotective agent for the treatment of AD. The neuroprotective effect of the two species may be mediated, at least in part, via suppressing of the cellular apoptosis.

Acknowledge to the support of Department of Health

42. Mechanistic study on the antidepressant-like effect of Danggui-Shaoyao-San, a Chinese herbal formula

Z. Huang, Q.Q. Mao, X.M. Zhong, Z.Y. Li, F.M. Qiu, S.P. Ip

Evidence-Based Complementary and Alternative Medicine. Volume 2012 (2012), Article ID 173565, 7 pages. doi:10.1155/2012/173565.

Abstract

Danggui-Shaoyao-San (DSS), a famous Chinese herbal formula, has been widely used in the treatment of various diseases. Previous studies have shown that DSS produces antidepressant-like effect in rodents. This study aims to investigate the mechanism(s) underlying the antidepressant-like action of DDS. The results showed that DSS treatment significantly antagonized reserpine-induced ptosis in mice. In addition, DSS treatment significantly increased sucrose consumption in chronic unpredictable stress- (CUS-) treated mice. DSS treatment also markedly attenuated CUS-induced decreases in noradrenaline and dopamine concentrations in mouse brain. Furthermore, DSS treatment significantly reversed CUS-induced increase in serum malondialdehyde (MDA) content and decrease in serum superoxide dismutase (SOD) activity in mice. The results suggest that the antidepressant-like activity of DSS is probably mediated by the modulation of central monoamine neurotransmitter systems and the reduction of oxidative stress.

43. Quantitative analysis of biologically active ingredients of Five Seeds Combo by liquid chromatography-quadrupole time-of-flight mass spectrometry for quality control of commercial herbal product

M.L. Chen, L. Miao, J. Cao, S.P. Ip, C.T. Che

Journal of Separation Science, 2012, 35, 1612-1618

Abstract

Five Seeds Combo (wu zi yan zong wan) is a traditional Chinese herbal formula composed of fructus Lycii, semen Cuscutae, fructus Rubi, semen Plantaginis, and fructus Schisandrae. This herbal prescription has been developed into herbal products by many pharmaceutical manufacturers for treating age-related symptoms. The present study aims to develop an analytical method for the quality control of this herbal drug. Nine active ingredients including schisantherin A, schisandrin B, schisandrin, schisandrin A, quercitrin, betaine, verbascoside, hyperoside, and kaempferol were selected as the targeted analytes for the analysis. By using liquid chromatogram/quadrupole time-of-flight mass spectrometry (MS), the nine chemical compounds were determined simultaneously from the chromatogram. The parameters for MS were optimized by orthogonal array testing and the best condition of the MS for the determination of the nine

marker compounds was found to be 175, 75, and 700 V for fragmentor, skimmer, and voltage of capillary, respectively. The method validation showed that this analytical method had high precision and sensitivity (limit of quantitation was smaller than 10 ng/mL for most of the analytes). The method was found to be able to demonstrate the quality of Five Seeds Combo from different manufacturers.

44. Bioassay-Guided Isolation of Neuroprotective Compounds from *Uncaria rhynchophylla* against Beta-Amyloid-Induced Neurotoxicity

Y.F. Xian, Z.X. Lin, Q.Q. Mao, Z. Hu, M. Zhao, C.T. Che, S.P. Ip

Evidence-Based Complementary and Alternative Medicine. Volume 2012 (2012), Article ID 802625, 8 pages. doi:10.1155/2012/802625.

Abstract

Uncaria rhynchophylla is a component herb of many Chinese herbal formulae for the treatment of neurodegenerative diseases. Previous study in our laboratory has demonstrated that an ethanol extract of Uncaria rhynchophylla ameliorated cognitive deficits in a mouse model of Alzheimer's disease induced by D-galactose. However, the active ingredients of Uncaria rhynchophylla responsible for the anti-Alzheimer's disease activity have not been identified. This study aims to identify the active ingredients of Uncaria rhynchophylla by a bioassay-guided fractionation approach and explore the acting mechanism of these active ingredients by using a well-established cellular model of Alzheimer's disease, beta-amyloid- (Aβ-) induced neurotoxicity in PC12 cells. The results showed that six alkaloids, namely, corynoxine, corynoxine B, corynoxeine, isorhynchophylline, isocorynoxeine, and rhynchophylline were isolated from the extract of Uncaria rhynchophylla. Among them, rhynchophylline and isorhynchophylline significantly decreased Aβ-induced cell death, intracellular calcium overloading, and tau protein hyperphosphorylation in PC12 cells. These results suggest that rhynchophylline and isorhynchophylline are the major active ingredients responsible for the protective action of Uncaria rhynchophylla against Aβ-induced neuronal toxicity, and their neuroprotective effect may be mediated, at least in part, by inhibiting intracellular calcium overloading and tau protein hyperphosphorylation.

45. Protective roles of Cordyceps on lung fibrosis in cellular and rat models

M. Chen, F.W. Cheung, M.H. Chan, P.K. Hui, S.P. Ip, Y.H. Ling, C.T. Che, W.K. Liu

Journal of Ethnopharmacology, 2012, 143, 448-454

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE: Cordyceps sinensis is a fungus used in

traditional Chinese medicine as a tonic to soothe the lung for the treatment of fatigue and respiratory diseases. Idiopathic pulmonary fibrosis is a chronic, irreversible and debilitating lung disease showing fibroblast/myofibroblast expansion and excessive deposition of extracellular matrix in the interstitium leading to breathing difficulty. Our previous observation revealed a partial relief of lung fibrosis in patients suffering from severe acute respiratory syndrome (SARS). We hypothesize that Cordyceps has beneficial effects on lung fibrosis and the objective of this study is to explore the target(s) of Cordyceps in the relief of lung fibrosis in animal and cell models and to gain insight into its underlying mechanisms.

MATERIAL AND METHODS: A rat model of bleomycin (BLM)-induced lung fibrosis and a fibrotic cell model with transforming growth factor beta-1 induction were employed in the studies.

RESULTS: Reduction of infiltration of inflammatory cells, deposition of fibroblastic loci and collagen, formation of reactive oxygen species, and production of cytokines, as well as recovery from imbalance of MMP-9/TIMP-1, were observed in fibrotic rats after treatment with Cordyceps in preventive (from the day of BLM administration) and therapeutic (from 14 days after BLM) regimens. In a fibrotic cell model with transforming growth factor beta-1 induction, the human lung epithelial A549 acquired a mesenchymal phenotype and an increase of vimentin expression with a concomitant decrease of E-cadherin. This epithelial-mesenchymal transition could be partially reverted by cordycepin, a major component of Cordyceps.

CONCLUSION: The findings provide an insight into the preventive and therapeutic potentials of Cordyceps for the treatment of lung fibrosis.

46. Schisandra chinensis reverses visceral hypersensitivity in a neonatal-maternal separated rat model

J.M. Yang, Y.F. Xian, P.S.P. Ip, J.C.Y. Wu, L.X. Lao, H.H.S. Fong, J.J.Y. Sung, B. Berman, J.H.K. Yeung, C.T. Che

Phytomedicine, 2012,19, 402-408

Abstract

Visceral hypersensitivity is an important characteristic feature of functional gastrointestinal disorders, such as irritable bowel syndrome (IBS). This study evaluated the effect of Schisandra chinensis on visceral hyperalgesia induced by neonatal maternal separation (NMS) in an IBS rat model. The visceromotor responses to colorectal balloon distension (CRD) were measured by abdominal withdrawal reflex (AWR) and electromyographic (EMG) activities. NMS control rats (receiving vehicle) underwent aggravated visceral pain in response to CRD as compared to normal rats, evidenced by the reduced pain threshold, enhanced AWR scores and EMG responses. Treatment with a 70% ethanol extract of S. chinensis (0.3g/kg and 1.5g/kg/day) for 7 days resulted in an

increase in the pain threshold (NMS control: 19.1±1.0mmHg vs low-dose: 24.8±1.3mmHg and high-dose: 25.2±1.8mmHg, p<0.01), and abolished the elevated AWR and EMG responses to CRD in NMS rats (AUC values of EMG response curve were: 1952±202 in NMS control group vs 1074±90 in low-dose group and 1145±92 in high-dose group, p<0.001), indicating that S. chinensis could reverse the visceral hypersensitivity induced by early-life stress event. The result of ELSA measurement shows that the elevated serotonin (5-HT) level in the distal colon of NMS rats returned to normal level after treatment with S. chinensis. Moreover, the increase in pain threshold in rats treated with S. chinensis was associated with a decline of the mRNA level of 5-HT(3) receptor in the distal colon. All available results demonstrate that S. chinensis can reverse visceral hypersensitivity induced by neonatal-maternal separation, and the effect may be mediated through colonic 5-HT pathway in the rat.

47. Impact of the Herbal Medicine Sophora flavescens on the Oral Pharmacokinetics of Indinavir in Rats: The Involvement of CYP3A and P-Glycoprotein

J.M. Yang, S.P. Ip, Y. Xian, M. Zhao, Z.X. Lin, J.H. Yeung, R.C. Chan, S.S. Lee, C.T. Che

PLoS One, 2012; 7, e31312.

Abstract

Sophora flavescens is a Chinese medicinal herb used for the treatment of gastrointestinal hemorrhage, skin diseases, pyretic stranguria and viral hepatitis. In this study the herb-drug interactions between S. flavescens and indinavir, a protease inhibitor for HIV treatment, were evaluated in rats. Concomitant oral administration of Sophora extract (0.158 g/kg or 0.63 g/kg, p.o.) and indinavir (40 mg/kg, p.o.) in rats twice a day for 7 days resulted in a dose-dependent decrease of plasma indinavir concentrations, with 55%-83% decrease in AUC(0-∞) and 38%-78% reduction in C(max). The CL (Clearance)/F (fraction of dose available in the systemic circulation) increased up to 7.4-fold in Sophora-treated rats. Oxymatrine treatment (45 mg/kg, p.o.) also decreased indinavir concentrations, while the ethyl acetate fraction of Sophora extract had no effect. Urinary indinavir (24-h) was reduced, while the fraction of indinavir in faeces was increased after Sophora treatment. Compared to the controls, multiple dosing of Sophora extract elevated both mRNA and protein levels of P-gp in the small intestine and liver. In addition, Sophora treatment increased intestinal and hepatic mRNA expression of CYP3A1, but had less effect on CYP3A2 expression. Although protein levels of CYP3A1 and CYP3A2 were not altered by Sophora treatment, hepatic CYP3A activity increased in the Sophora-treated rats. All available data demonstrated that Sophora flavescens reduced plasma indinavir concentration after multiple concomitant doses, possibly through hepatic CYP3A activity and induction of intestinal and hepatic P-gp. The animal

study would be useful for predicting potential interactions between natural products and oral pharmaceutics and understanding the mechanisms prior to human studies. Results in the current study suggest that patients using indinavir might be cautioned in the use of S. flavescens extract or Sophora-derived products.

48. Peony glycosides reverse the effects of corticosterone on behavior and brain BDNF expression in rats

Q.Q. Mao, Z. Huang, S.P. Ip, X.F. Xian, C.T. Che

Behavioural Brain Research, 2012, 277, 305-309

Abstract

Repeated injections of corticosterone (CORT) induce the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in depressive-like behavior. This study aimed to examine the antidepressant-like effect and the possible mechanisms of total glycosides of peony (TGP) in the CORT-induced depression model in rats. The results showed that the 3-week CORT injections induced the significant increase in serum CORT levels in rats. Repeated CORT injections also caused depression-like behavior in rats, as indicated by the significant decrease in sucrose consumption and increase in immobility time in the forced swim test. Moreover, it was found that brain-derived neurotrophic factor (BDNF) protein levels in the hippocampus and frontal cortex were significantly decreased in CORT-treated rats. Treatment of the rats with TGP significantly suppressed the depression-like behavior and increased brain BDNF levels in CORT-treated rats. The results suggest that TGP produces an antidepressant-like effect in CORT-treated rats, which is possibly mediated by increasing BDNF expression in the hippocampus and frontal cortex.

49. Comparison on anti-inflammatory effect of Cortex Phellodendri Chinensis and Cortex Phellodendri Amurensis in 12-O-tetradecanoylphorbol-acetate-induced ear edema in mice

X.F. Xian, Q.Q. Mao, S.P. Ip, Z.X. Lin, C.T. Che

Journal of Ethnopharmacology, 2011, 137, 1425-1460

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE: Cortex Phellodendri is derived from the dried bark of Phellodendron chinense Schneid. or Phellodendron amurense Rupr. Traditionally, Cortex Phellodendron Chinensis (CPC) and Cortex Phellodendron Amurensis (CPA) are used interchangeably under the name "Huang Bai" for the treatment of gastroenteritis, abdominal pain or diarrhea. The present study aims to compare the anti-inflammatory effect of ethanol extracts of Cortex Phellodendri

Chinensis (ECPC) and Cortex Phellodendri Amurensis (ECPA) in a mouse model of inflammation induced by 12-O-tetradecanoylphorbol-acetate (TPA).

MATERIALS AND METHODS: The anti-inflammatory effect was evaluated by measuring the ear thickness, activity of myeloperoxidase (MPO) and the production reactive oxygen species (ROS). The anti-inflammatory mechanism was explored by determining the protein and mRNA levels of cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6.

RESULTS: The results showed that both ECPC and ECPA significantly decreased the ear thickness, MPO activity and the ROS level in mouse model of inflammation induced by TPA. In addition, ECPC and ECPA also remarkably inhibited the protein and mRNA levels of TNF-α, IL-1β, IL-6 and COX-2. Interestingly, ECPC has better anti-inflammatory effect than that of ECPA.

CONCLUSIONS: These results indicate that both ECPC and ECPA have potential anti-inflammatory effect on TPA-induced inflammatory in mice, and ECPC is more effective than ECPA. The anti-inflammatory effect of the herbal drugs may be mediated, at least in part, by down-regulating the mRNA expression of a panel of inflammatory mediators including TNF-α, IL-1β, IL-6 and COX-2.

Acknowledge to the support of Department of Health

50. Analgesic Effect of Coptis chinensis rhizomes (Coptidis Rhizoma) Extract on Rat Model of Irritable Bowel Syndrome

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Journal of Ethnopharmacology, 2011, 135, 754-761

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE: Coptis chinensis rhizomes (Coptidis Rhizoma, CR), also known as "Huang Lian", is a common component of traditional Chinese herbal formulae used for the relief of abdominal pain and diarrhea. Yet, the action mechanism of CR extract in the treatment of irritable bowel syndrome is unknown. Thus, the aim of our present study is to investigate the effect of CR extract on neonatal maternal separation (NMS)-induced visceral hyperalgesia in rats and its underlying action mechanisms.

MATERIALS AND METHODS: Male Sprague-Dawley rats were subjected to 3-h daily maternal separation from postnatal day 2 to day 21 to form the NMS group. The control group consists of unseparated normal (N) rats. From day 60, rats were administrated CR (0.3, 0.8 and 1.3 g/kg) or vehicle (Veh; 0.5% carboxymethylcellulose solution) orally for 7 days for the test and control groups, respectively.

RESULTS: Electromyogram (EMG) signals in response to colonic distension were measured with the NMS rats showing lower pain threshold and increased EMG activity

than those of the unseparated (N) rats. CR dose-dependently increased pain threshold response and attenuated EMG activity in the NMS rats. An enzymatic immunoassay study showed that CR treatment significantly reduced the serotonin (5HT) concentration from the distal colon of NMS rats compared to the Veh (control) group. Real-time quantitative PCR and Western-blotting studies showed that CR treatment substantially reduced NMS induced cholecystokinin (CCK) expression compared with the Veh group. CONCLUSIONS: These results suggest that CR extract robustly reduces visceral pain that may be mediated via the mechanism of decreasing 5HT release and CCK expression in the distal colon of rats.

51. Involvement of serotonergic system in the antidepressant-like effect of piperine

Q.Q. Mao, X.F. Xian, S.P. Ip, C.T. Che

Neuro-Psychopharmacology & Biological Psychiatry, 2011, 35, 1144-1147

Abstract

Piperine is a major alkaloid of black pepper (Piper nigrum Linn.) and long pepper (P. longum Linn.), and its antidepressant-like effect has been previously demonstrated. The purpose of this study was to explore the possible contribution of the serotonergic system in the antidepressant-like effect of piperine in mice. The results showed that piperine significantly reduced the immobility time in the forced swim test and tail suspension test in mice. The anti-immobility effect of piperine in the forced swim test and tail suspension test was completely abolished by pre-treating the mice with pCPA (an inhibitor of 5-HT synthesis). Piperine treatment also significantly potentiated the number of head-twitches of mice induced by 5-HTP (a metabolic precursor to 5-HT). In addition, the neurochemical assays showed that piperine produced a marked increase of 5-HT level in both the hippocampus and frontal cortex of mice. Taken together, these results clearly suggest that serotonergic system is involved in the antidepressant-like effect of piperine.

52. HPLC-MS analysis of Schisandra lignans and their metabolites in Caco-2 cell monolayer and rat everted gut sac models and in rat plasma

J.M. Yang, P.S.P. Ip, J.H.K. Yeung, C.T. Che

Acta Pharmaceutica Sinica B, 2011, 1, 46-55

Abstract

The absorption profiles of Schisandra chinensis were evaluated using the human Caco-2 cell monolayer and rat everted gut sac models, as well as in rat plasma. By analyzing the

chromatographic and MSn characteristics of individual peak acquired by HPLC-DAD-APCI-MSn determination, thirteen lignans were identified as the major in vitro absorbable components of the Schisandra extract. Most of these compounds were also detected and identified in rat plasma after an oral administration of the Schisandra extract, except for angeloyl(tigloyl)gomisin H and angeloyl(tigloyl)gomisin Q, whose structures possess an ester group at the cyclooctadiene ring. In addition, four metabolites, corresponding to the hydroxylation and demethylation products of schisandrin and the hydrolysis derivative of angeloyl(tigloyl)gomisin Q, were tentatively identified. The results demonstrate that Schisandra lignans are the major absorbable components of this crude drug, and hydroxylation, demethylation and hydrolysis are important metabolic transformations of the absorbable lignans.

53. Inhibitory effect of schisandrin on spontaneous contraction of isolated rat colon

J.M. Yang, J.H.K. Yeung, S.P. Ip, C.T. Che

Phytomedicine, 2011, 18, 998-1005

Abstract

This study examined the effect of schisandrin, one of the major lignans isolated from Schisandra chinensis, on spontaneous contraction in rat colon and its possible mechanisms. Schisandrin produced a concentration-dependent inhibition (EC50 = 1.66 μM) on the colonic spontaneous contraction. The relaxant effect of schisandrin could be abolished by the neuronal Na+ channel blocker tetrodotoxin (1 μM) but not affected by propranolol (1 μM), phentolamine (1 μM), atropine (1 μM) or nicotine desensitization, suggesting possible involvement of non-adrenergic non-cholinergic (NANC) transmitters released from enteric nerves. Nω-nitro-L-arginine methyl ester (100-300 μM), a nitric oxide synthase inhibitor, attenuated the schisandrin response. The role of nitric oxide (NO) was confirmed by an increase in colonic NO production after schisandrin incubation, and the inhibition on the schisandrin responses by soluble guanylyl cyclase inhibitor 1H-[1,2,4] oxadiazolo[4,3-α]-quinoxalin-1-one (1-30 μM). Non-nitrergic NANC components may also be involved in the action of schisandrin, as suggested by the significant inhibition of apamin on the schisandrin-induced responses. Pyridoxal phosphate-6-azo(benzene-2,4-disulfonic acid) tetrasodium salt hydrate (100 μM), a selective P2 purinoceptor antagonist, markedly attenuated the responses to schisandrin. In contrast, neither 8-cyclopentyl-1,3-dipropylxanthine, an antagonist for adenosine A1 receptors, nor chymotrypsin, a serine endopeptidase, affected the responses. All available results have demonstrated that schisandrin produced NANC relaxation on the rat colon, with the involvement of NO and acting via cGMP-dependent pathways. ATP, but not adenosine and VIP, likely plays a role in the non-nitrergic, apamin-sensitive

component of the response.

54. A proteomic approach in investigating the hepatoprotective mechanism of schisandrin b: role of Raf kinase inhibitor protein

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Journal of Proteome Research, 2011, 10, 299–304

Abstract

To identify key proteins involved in the hepatoprotection afforded by Sch B, a proteomic approach was used to screen proteins that were specifically regulated by Sch B in mouse livers and the role of the proteins in the hepatoprotection was investigated. Thirteen proteins were specifically activated or suppressed by schisandrin B treatment. Among the thirteen proteins, Raf kinase inhibitor protein (RKIP) was postulated to be the key regulator involved in the development of hepatotoxin-induced cellular damage. The results indicated that the down-regulation of RKIP by antisense RKIP vector transfection led to the activation of Raf-1/MEK/ERK signaling pathway, as evidenced by increases of MEK/ERK phosphorylation and the level of nuclear factor erythroid 2-related factor 2 in the nucleus. The signaling effect produced by RKIP down-regulation resembled that triggered by schisandrin B, wherein both treatments resulted in a decrease in the extent of carbon tetrachloride-induced apoptotic cell death in AML12 hepatocytes. Over-expression of RKIP by sense RKIP transfection vector or the inhibition of MEK kinase by PD98059 were able to abrogate the cytoprotective effect of Sch B in the hepatocytes. The results indicate that schisandrin B triggers the Raf/MEK/ERK signaling pathway, presumably through down-regulating RKIP, thereby protecting against carbon tetrachloride-induced cytotoxicity.

55. Long-term treatment with a “Yang-invigorating” Chinese herbal formula, Wu-Zi-Yan-Zong-Wan, reduces mortality and liver oxidative damage in chronic alcohol intoxicated rats

M.L. Chen, S.H. Tsai, S.P. Ip, K.M. Ko, C.T. Che

Rejuvenation Research, 2010, 13, 459-467

Abstract

Long-term alcohol consumption has been reported to increase oxidative stress in multiple organs and accelerate the aging process. A previous study in our laboratory has shown that Wu-Zi-Yan-Zong-Wan, a “Yang- invigorating” Chinese herbal formula, protected against ethanol-induced toxicity in HepG2 cells transfected to express human CYP2E1, presumably by enhancing mitochondrial antioxidant status and functional ability. The

present study aims to investigate whether Wu-Zi-Yan-Zong-Wan extract treatment can afford protection against chronic ethanol-induced oxidative stress (a major risk factor of aging) and mortality in rats. The effect of the extract (1.8 g, 4.5 g and 9 g raw materials/kg/day) on chronic ethanol hepatotoxicity was investigated in rats receiving steady intragastric infusion of ethanol-containing liquid diet. The results showed that long-term (42 days) herbal co-treatment protected against chronic ethanol-induced mortality and hepatotoxicity and in rats, as evidenced by decreased plasma transaminases activities. The extract also suppressed the pathological development of fatty liver, as assessed by histopathological examination and the ratio of liver weight to body weight. The hepatoprotection afforded by the extract was associated with decreases in the extents of reactive oxygen species production, lipid peroxidation, and oxidative modification of proteins, as well as the reversal of altered mitochondrial reduced glutathione level. The results suggest that the suppressive effect of Wu-Zi-Yan-Zong-Wan on chronic ethanol-induced oxidative stress and mortality may be attributed to the antioxidant action, particularly in mitochondria.

56. Chemical and biological differentiation of Cortex Phellodendri Chinensis and Cortex Phellodendri Amurensis

M.L. Chen, S.P. Ip, Y.F. Xian, S.H. Tsai, J.Y. Yang, C.T. Che

Planta Medica, 2010, 76,1530-1535

Abstract

The Chinese herbal drug Cortex Phellodendri is derived from two species of Phellodendron, P. chinensis Schneid. and P. amurense Rupr. Traditionally, Cortex Phellodendri Chinensis (CPC) and Cortex Phellodendri Amurensis (CPA) are used interchangeably because they are believed to share the same clinical efficacy. Berberine has been believed to be the active ingredient of the herbs. However, recent studies have shown that the content of berberine is much higher in CPC than in CPA. Interestingly, the majority of researches deal with CPA, the one with lower content of berberine. These observations arouse us to reconsider the active ingredients of Cortex Phellodendri. In this study, two traditional usages (antidiarrhea and antibacteria) of Cortex Phellodendri were compared with the chemical analysis of the two herbs. The results suggest that berberine is one of the active ingredients for the antidiarrheal and antibacterial activities of the herbs, but other chemical ingredients are also involved in regulating the biological actions of the herbal drug. These chemical ingredients may have same or opposite effect as berberine. The effectiveness of the herbs is more likely to correlate to the content of total alkaloids rather than the content of berberine.

Acknowledge to the support of Department of Health

57. Biochemical mechanism of Wu-Zi-Yan-Zong-Wan, a traditional Chinese herbal formula, against alcohol-induced oxidative damage in CYP2E1 cDNA-transfected HepG2 (E47) cells

M.L. Chen, S.P. Ip, S.H. Tsai, K.M. Ko, C.T. Che

Journal of Ethnopharmacology, 2010, 128, 116-122

Abstract

Wu-Zi-Yan-Zong-Wan (WZ) is a traditional Chinese herbal formula which is commonly used for treating patients with "Yang deficiency". In the present study, the effect of WZ on ethanol-induced toxicity in CYP2E1 cDNA-transfected HepG2 (E47) cells was investigated. WZ extract was obtained by extracting the herbal powder with 50% ethanol (v/v, in water) and used for all experiments. The results showed that the treatment with WZ extract (12.5-200 μg/mL) for 24 h dose-dependently protected against ethanol-induced toxicity in E47 cells, as evidenced by the enhanced cell viability and decreased extent of lactate dehydrogeanse leakage. The cytoprotection against ethanol-induced toxicity was associated with decreases in the extents of reactive oxygen species production and lipid peroxidation, as well as increases in mitochondrial reduced glutathione and membrane potential. In addition, WZ extract treatment also suppressed the formation of DNA fragments in ethanol-intoxicated E47 cells. In conclusion, WZ extract was found to protect against the ethanol-induced toxicity in E47 cells, possibly by virtues of its antioxidant activity.

58. Long-term treatment with peony glycosides reverses chronic unpredictable mild stress-induced depressive-like behavior via increasing expression of neurotrophins in rat brain

Q.Q. Mao, Y.F. Xian, S.P. Ip, S. H. Tsai, C.T. Che

Behavioural Brain Research. 2010, 210, 171-177

Abstract

The root part of Paeonia lactiflora Pall., commonly known as peony, is a commonly used Chinese herb for the treatment of depression-like disorders. Previous studies in our laboratory have showed that total glycosides of peony (TGP) produced antidepressant-like action in various mouse models of behavioral despair. The present study aimed to investigate the mechanism(s) underlying the antidepressant-like action of TGP by measuring neurotrophins including brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in non-stressed and chronic unpredictable mild stress (CUMS)-treated rats. TGP (80 or 160 mg/kg/day) was administered by oral gavage to the animals for 5 weeks. The results showed that CUMS caused depression-like behavior in rats, as indicated by the significant decreases in sucrose consumption and

locomotor activity (assessed by open-field test). In addition, it was found that BDNF contents in the hippocampus and frontal cortex were significantly decreased in CUMS-treated rats. CUMS treatment also significantly decreased the level of NGF in the frontal cortex of the animals. Daily intragastric administration of TGP (80 or 160 mg/kg/day) during the five weeks of CUMS significantly suppressed behavioral and biochemical changes induced by CUMS. Treating non-stressed animals with TGP (160 mg/kg) for 5 weeks also significantly increased BDNF contents in the hippocampus and frontal cortex, and NGF contents in the frontal cortex. The results suggest that the antidepressant-like action of TGP is mediated, at least in part, by increasing the expression of BDNF and NGF in selective brain tissues.

59. Quality assurance for Chinese herbal formulae: standardization of IBS-20, a 20-herb preparation

S.P. Ip, M. Zhao, Y.F. Xian, M.L. Chen, Y.Y. Zong, Y.W. Tjong, S.H. Tsai, J.J. Sung, A . Bensoussan, B. Berman, H.H. Fong, C.T. Che

Chinese Medicine, 2010, 5, 8

Abstract

BACKGROUND: The employment of well characterized test samples prepared from authenticated, high quality medicinal plant materials is key to reproducible herbal research. The present study aims to demonstrate a quality assurance program covering the acquisition, botanical validation, chemical standardization and good manufacturing practices (GMP) production of IBS-20, a 20-herb Chinese herbal formula under study as a potential agent for the treatment of irritable bowel syndrome. METHODS: Purity and contaminant tests for the presence of toxic metals, pesticide residues, mycotoxins and microorganisms were performed. Qualitative chemical fingerprint analysis and quantitation of marker compounds of the herbs, as well as that of the IBS-20 formula was carried out with high-performance liquid chromatography (HPLC). Extraction and manufacture of the 20-herb formula were carried out under GMP. Chemical standardization was performed with liquid chromatography-mass spectrometry (LC-MS) analysis. Stability of the formula was monitored with HPLC in real time. RESULTS: Quality component herbs, purchased from a GMP supplier were botanically and chemically authenticated and quantitative HPLC profiles (fingerprints) of each component herb and of the composite formula were established. An aqueous extract of the mixture of the 20 herbs was prepared and formulated into IBS-20, which was chemically standardized by LC-MS, with 20 chemical compounds serving as reference markers. The stability of the formula was monitored and shown to be stable at room temperature. CONCLUSION: A quality assurance program has been developed for the preparation of a standardized 20-herb formulation for use in the clinical studies for the treatment of irritable bowel syndrome (IBS). The procedures developed in the present

study will serve as a protocol for other poly-herbal Chinese medicine studies.

60. Determination of aflatoxins in Chinese medicinal herbs by high-performance liquid chromatography using immunoaffinity column cleanup. Improvement of recovery

S.P. Ip, C.T. Che

Journal of Chromatography A, 2006, 1135, 241-244

Abstract

Although analytical methods are available for the determination of aflatoxins in medicinal herbs, none of them can be applied satisfactorily to all sample matrices. The difficulty arises from the complex chemical composition of the herbs. Recovery is generally low by using immunoaffinity column cleanup due to the acidity of the water extractive leading to a weakened binding affinity. As a solvent for dilution and neutralization, phosphate buffer saline is useful for certain herbs but not for others that have high acidity. The problem can be solved by using 0.1 M phosphate buffer, which has a higher buffering capacity and eliminates sodium chloride. The modified method was validated by the analysis of a certified reference material and shown to be useful for the determination of aflatoxins in herbal samples of high acidity.