藥物化學暨藥理學組

壁報論文摘要集

A 組 藥物化學暨藥理學組

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A-001

A Novel Histone Deacetylase 6 Selective Inhibitor YH309Inhibits Triple Negative Breast Cancer Cell Migration and Enhances Anti-metastatic Effect of Taxol

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Triple negative breast cancer(TNBC) is more invasive and has higher potential for metastasis compared to other breast cancers. Patients with TNBC have poor prognosis with high risk of relapse and metastasis. This study investigated the impact of YH309, a novel histone deacetylase6 (HDAC6) inhibitor, on cell migration of triple negative MDA-MB-231 cell lines and hormone receptor positive MCF-7 cell lines as comparison. We also examined the combinatorial effect of YH309with a microtubule stabilizing agent, taxol, which is commonly used as chemotherapy in TNBC. Cell migration was evaluated by wound healing assay. mRNA and protein expression level were determined by QPCR and western blot. Protein-protein interaction was studied by immunoprecipitation. YH309 has high selectivity and great potency against HDAC6 (IC_{50}=4.41nM), which is more potent than a well-known HDAC6 selective inhibitor, tubastatin-A (IC_{50}=26nM). YH309decreased MDA-MB-231 cell migration and also significantly enhanced the inhibition of taxol. Since Aurora kinase A (Aur-A)is frequentlyoverexpressed in a number of human cancersand promotes cell migration through regulatingcofilin-mediated actin reorganization, we found YH309 depletes Aur-A levels partly through reduction of mRNA transcription and partly through inhibition of chaperone association with hsp90 in MDA-MB-231 and MCF-7 cell lines. It increased hsp90 acetylation resulting in disassociation with Aur-A and then unprotected Aur-A was degraded by proteasome, which could be reversed by MG132 treatment. YH309 significantly increased cofilin phosphorylation in MDA-MB-231 cells, whereas in MCF-7 cells only a slight increase was observed. This suggested that cofilin-F-actin-mediated cell migration has more important role in invasive MDA-MB-231 cells but not in non-invasive MCF-7 cell lines. In addition, YH309 dramatically elevated α-tubulin acetylation, which would enhance taxol-induced microtubule stabilization and interrupt microtubule dynamics. All of these results indicate that YH309 suppresses breast cancer cell motility and has great combinatorial effect with taxol, suggesting that combination of YH309 and taxol may provide a treatment with lower toxicity but higher efficacy for invasive TNBC.

A-002

YH309, a novel HDAC6-selective inhibitor combine with bortezomibinduces synergisticantitumor activity in multiple myeloma.

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Multiple myeloma (MM) is a plasma cell malignancy predominantly localized in the bone marrow and characterized clinically by paraproteinemia (M-protein), destructive bone disease, hypercalcemia, renal failure, and hematologic dysfunction. It is the second most common hematologic malignancy after non Hodgkin's lymphoma, accounting for more than 10% of all hematologic cancers and 2% of annual cancer-related deaths.

Recent studies have shown that unfolded ormisfolded proteins are bound by ubiquitinatin, and be degraded not only by proteasomes pathway, but also by aggresomes pathway.In aggresomal protein degradation pathway, HDAC6 plays an important role because it can bind both polyubiquitinated proteins and dynein motors, and then acting to recruit protein cargo to dynein motors for transport to aggresomes. The inhibition of both proteasomal and aggresomal protein degradation systems could induce accumulation of polyubiquitinated proteins and significant cell stress, followed by activation of apoptotic cascades.

In this study, we investigated the activity of YH308, an HDAC6-selective inhibitor, alone and in combination with bortezomib (a proteasome inhibitor) in MM. First, we successfully found the most specific HDAC6 inhibitor, YH308 from the derivatives that we synthesis. Second, we prove the combination of YH308 with bortezomib induces synergistic anti-MM viability resulting in apoptosis via caspase-3, caspase-8, and caspase-9. In vivo, the anti-MM viability of YH308 was confirmed by using xenograft SCID mouse model. Tumor growth was significantly delayed in YH308 treated sample. To further characterize the activity of YH308 against HDAC6 activity in vivo, we used IHC and western blot analysis. The results did not show a significant increase in acetylated histone H3, while demonstrating, more acetylation of α-tubulin. Our studies therefore demonstrate that YH308 combined with bortezomib has significant anti-MM viability, providing the framework for clinical evaluation of combined therapy to improve patient outcome in MM.

A-003

Application of Galactose-Modified Liposomes as a Potent Antigen Presenting Cell Targeted Carrier for Intranasal Immunization

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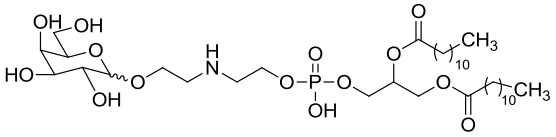
The mucosal immune system produces secretory IgA (sIgA) as the first line of defense against invasion by foreign pathogens. Our aim was to develop a galactose-modified liposome as a targeted carrier which can be specifically recognized by macrophage, one of the most important antigen presenting cells. First, galactose was covalently conjugated with 1,2-didodecanoyl-sn-glycero-3-phosphoethanolamine (DLPE) to give a targeted ligand, a galactosyl lipid. The galactosyl lipid was then incorporated into a liposomal bilayer to form a galactosylated liposome carrier. Further, the ovalbumin (OVA) was encapsulated into the galactosylated liposome carriers and mice were intranasally immunized. Confocal laser scanning microscopy and flow cytometry analysis showed that the targeted galactosylated liposome carrier had a higher uptake rate than unmodified liposomes. The targeted galactosylated liposome induced higher levels of tumor necrosis factor-α and interleukin-6 production than unmodified liposomes ($P<0.05$). Furthermore, 6-week-old BALB/c female mice immunized with the OVA-encapsulated targeted galactosylated liposome had significantly higher OVA-specific s-IgA levels in the nasal and lung wash fluid ($P<0.05$). In addition, the targeted galactosylated liposome simultaneously augmented the serum IgG antibody response. In summary, the OVA-encapsulated targeted galactosylated liposome induced significantly higher mucosal IgA and systemic IgG antibody titers and is a potential antigen delivery carrier for further clinical applications.



A-004

Synthesis of C-aryl D-glucofuranosides as Sodium-Dependent Glucose Cotranporter 2 (SGLT2) Inhibitors for Type 2 Diabetes Treatment

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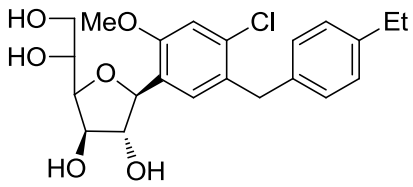
Type 2 diabetes mellitus (T2DM) affect more than 150 million people worldwide and the number of patient has been rapidly increasing in developing countries. T2DM is a metabolic disorder caused by high blood glucose and insulin resistance. Type 2 sodium-dependent glucose co-transporter (SGLT2) appeared to be a promising target for treating T2DM as it works independent from the action of insulin. By inhibiting SGLT2, the reabsorption of renal glucose at S1 of proximal convoluted tubule will be attenuated and decrease the blood glucose level to achieve glycemic control.

We proposed and successfully synthesized novelC-aryl-D-glucofuranosides to inhibit human hSGLT2 and hSGLT1.TheSAR studied relating to the substitution of various groups on the aromatic rings and their effect on SGLT inhibition conducted. Compound **21** demonstrated the best in vitro inhibitory activity against SGLT2 in this series (EC_{50} = 0.62 μM).



21

A-005

2-*O*-*N*-benzylcarbamate Promoted β-Selective Glycosylation and Its Application in the Stereoselective Synthesis of Oligosaccharides

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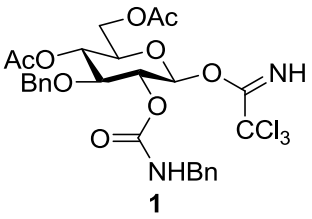
Stereoselective glycosidic bond formation is challenging in oligosaccharide synthesis. Several strategies have been developed to improve stereoselectivity, such as solvent effect, neighboring-group participation, promoters and reaction temperature.

We introduced 2-*O*-*N*-benzylcarbamoyl group as a new protecting group for β-selective glacosylation. 2-*O*-*N*-benzylcarbamoyl group is resistant to basic, acid or hydrogenation conditions, and it can be selectively removed by tetrabutylammonium nitrate. The 2-*O*-*N*-benzylcarbamoyl group successfully facilitates β-selective glycosylation of glycosyl donor **1** and various primary acceptors in moderate to good yield. The glycosylation of donor **1** and secondary acceptors afforded low yield or no reaction, in particular glucose 4-OH acceptors. Consequently, the activated intermediate was analyzed by nuclear magnetic resonance for mechanistic study, and the less reactive 1-OTf intermediate was identified. This observation could explain the limitation of the glycosylation with steric hindered glucose 4-OH acceptors.



1

A-006

Functional Study of the Fibrin-DerivedFg Bβ_{15-42} Peptide on Blood Pressure Regulation

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The previous studies have demonstrated that the Fg Bβ_{15-42}peptide, a fibrin(ogen)-derived productwhich consists of28 amino acids corresponding to the *N*-terminal sequence of the fibrin β-chain, exert a potent cardioprotective effect of ischemia/reperfusion injury or organ transplantation,. The antihypertensive activities of this fibrin-derivedpeptide are, however, currently unknown. Therefore, we aimed to investigate the antihypertensive effects of the Fg Bβ_{15-42}in anesthetizedspontaneously hypertensive rats (SHR). The change of mean systemic arterial pressure (MSAP), heart rate (HR), cardiac contractility and sympathetic vasomotor tone after systemic administration of Fg Bβ_{15-42} (0.25-1 mg/kg) were examined for at least 60 min. Control injection of the same volume of isotonic normal saline and heat-inactivatedFg Bβ_{15-42}(1 mg/kg, 60℃, 15 min) served as vehicle and negative control, respectively.In SHR with established hypertension, the intravenous bolus administration of the Fg Bβ_{15-42} (0.25,0.5 and 1 mg/kg) produced potent dose-related antihypertensive effects, and decreases in heart rate, cardiac contractility and the power density of the vasomotor components of SAP spectrum, our experimental index for sympathetic neurogenic vasomotor tone.The dose-dependentcardiovascular depressive effects ofFg Bβ_{15-42} commenced approximately 3-5 min and lasted for at least 60 min postinjection. Duration ofcardiovascular depressive responses of Fg Bβ_{15-42} (0.25-1 mg/kg) was also dose dependent. At a lower dose (0.25 mg/kg), Fg Bβ_{15-42} promoted vasodepressor responses that lasted for approximately 90 min postinjection, whereas at higher doses (0.5 or 1mg/kg) Fg Bβ_{15-42} produced cardiovascular depressive responses that sustained more than 2hrspostinjection.Together these resultsdemonstrate for the first time that Fg Bβ_{15-42} peptide promoted a delayed but long-lasting antihypertensive effect in SHR and provides novel evidence for potential therapeutic applications of this peptide in hypertensive state.

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A-007

Cytotoxic constituents from *Celastruspaniculatus* induce apoptosis and autophagy in breast cancer cells

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Celastruspaniculatus is a traditional medicinal plant with diverse pharmacological activities. To identify its bioactive constituents, we isolated three new β-dihydroagarofuranoidsesquiterpenes from the whole plant, of which the major constituent [(1α,2α,8β,9β)-1,8-bis(acetyloxy)-2,9-bis(benzoyloxy)-14-hydroxy-β-dihydroagarofuran; compound **3**] was assessed for its antiproliferative activity. Compound **3** suppressed the viability of MCF-7 breast cancer cells with IC_{50} of 17 ± 1 μM. This growth inhibition was, in part, attributable to apoptosis. Moreover, this drug treatment led to LC3B-II accumulation, indicative of autophagy. Western blot analysis revealed the ability of compound **3** to target a broad range of signaling effectors related to survival and cell cycle progression, including Akt, NF-κB,p53, and MAP kinases. In addition, flow cytometry analysis indicates increased reactive oxygen species production in response to compound **3**. Taken together, these findings suggest a pleiotropic mode of mechanism that underlies the antiproliferative activity of compound **3** in MCF-7 breast cancer cells.

A-008

Betulinic acid, a pentacyclictriterpene,promotesgastric cancer celldeath and inhibitscancer-associated fibroblast activation

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Tumor stromal myofibroblasts(cancer-associated fibroblasts; CAFs) in cancer microenvironments have recently been implicated in tumor growth and metastasis ofvarious cancers. A hallmark of myofibroblastactivation is the induction of α-smooth muscleactin (α-SMA) expression. NF-κBand TGF-β signaling may link with promoting fibroblasttransdifferentiationby up-regulation of α-SMA expression during tumor development.As these cellspromote amicroenvironmentthat is permissive for tumor growth, there has been enormous interest in developing targetedmolecular therapies against them. Betulinic acid (BA), a pentacyclictriterpene isolated from the bark of the white birch tree, has been reported to exhibit anti-inflammatory andanti-tumor properties.However, the mechanisms of BA responsible for the regulation of gastric CAFsremain unclear.In this study, we demonstrated that BA not only induced gastric cancer cell apoptosis, attenuated TGF-β secretion by gastric cancer through HOXA9-mediated pathway, but also inhibited TGF-β-induced CAFs activation.Our results providea molecular basis for the ability of BA to mediate gastric cancer death,suppress CAFs activation.BAmay be regarded as a promising agent in anti-gastric tumortherapy.

A-009

Targeting signal transducer and activator of transcription 3 pathway by cucurbitacin I diminishes self-renewing and radiochemoresistant abilities in thyroid cancer-derived CD133+ cells.

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Anaplastic thyroid cancer (ATC) is a lethal solid tumor with poor prognosis because of its invasiveness and its resistance to current therapies. Recently, ATC-CD133+ cells were found to have cancer stem cell (CSC) properties and were suggested to be important contributors to tumorigenicity and cancer metastasis. However, the molecular pathways and therapeutic targets in thyroid cancer-related CSCs remain undetermined. In this study, ATC-CD133+ cells were isolated and found to have increased tumorigenicity, radioresistance, and higher expression of both embryonic stem cell-related and drug resistance-related genes compared with ATC-CD133 cells. Microarray bioinformatics analysis suggested that the signal transducer and activator of transcription 3 (STAT3) pathway could be important in regulating the stemness signature in ATC-CD133+ cells; therefore, the effect of the potent STAT3 inhibitor cucurbitacin I in ATC-CD133+ cells was evaluated in this study. Treatment of ATC-CD133+ cells with cucurbitacin I diminished their CSC-like abilities, inhibited their stemness gene signature, and facilitated their differentiation into ATC-CD133$^-$ cells. Of note, treatment of ATC-CD133+ cells with cucurbitacin I up-regulated the expression of thyroid-specific genes and significantly enhanced radioiodine uptake. Furthermore, cucurbitacin I treatment increased the sensitivity of ATC-CD133+ cells to radiation and chemotherapeutic drugs through apoptosis. Finally, xenotransplantation experiments revealed that cucurbitacin I plus radiochemotherapy significantly suppressed tumorigenesis and improved survival in immunocompromised mice into which ATC-CD133+ cells were transplanted. In summary, these results show that the STAT3 pathway plays a key role in mediating CSC properties in ATC-CD133+ cells. Targeting STAT3 with cucurbitacin I in ATC may provide a new approach for therapeutic treatment in the future.

A-010

Hepatoprotective Activity of *Antrodia camphorata* Mycelium form Strain B86 Against Carbon Tetrachloride Induced Hepatotoxicity in Rats

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The product of *Antrodia camphorata* mycelium form strain B86 (AC-B86) were studied for hepatoprotective activity against SD rats with liver damage induced by carbon tetrachloride (CCl_4). It was found that the AC-B86 at a dose of 200, 400, and 1000 mg/kg body weight exhibited protective effect dose-dependently by lowering the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and total bilirubin to a significant extent. The highest activity of observed for AC-B86 at a dose of 1000 mg/kg body weight and the reduction of serum level of AST, ALT, alkaline phosphatase and total bilirubin were 79.9 %, 75.5 %, 43.2 % and 52.4 %, respectively. The hepatoprotective activity was also supported by histopathological studies of liver tissue. The effects of AC-B86 at the dose of 1000 mg/kg body weight were comparable with that of a known hepatoprotective agent, silymarin. Since results of biochemical studies of blood samples of carbon tetrachloride treated rats showed significant increase in the levels of serum enzyme activities, reflecting the liver injury caused by CCl_4 and blood samples from the animals treated with AC-B86 showed significant decrease in the levels of serum markers, indicating the protection of hepatic cells, the AC-B86 could afford significant dose-dependent protection against CCl_4 induced hepatocellular injury.

A-011

Synthesis Quinazoline Derivatives and Evaluation Anti-Proliferation Ability on Nasopharyngeal Cancer (NPC-TW01)

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The quinazoline (QA) is a heterocyclic compound with benzene fused to pyrimidine and is a well-leading structure for new drug development because it displays a wide spectrum of pharmacological activities such as neuron protective, anti-bacterial and anti-cancer properties. In this study, a series of novel QA derivatives were synthesized and their anti-proliferative mechanisms were studied. Firstly, QA series were subjected to MTT assay to examine the growth-inhibitory abilities against three human cancer cell lines, including nasopharyngeal cancer (NPC-TW01), leukemia (Jurkat), and lung carcinoma (NCI-H226). Among them, **4e** treatment showed dramatic growth-inhibitory effect on NPC-TW01 cells with IC_{50} of 4.7 μM. Furthermore, cell cycle analysis showed that **4e** could cause TW-01 cells arrest in ***S*** phase. Detail anti-proliferation mechanisms of **4e** against human NPC are actively investigated in our laboratory. In conclusion, **4e** is a promising novel anti-proliferation drug and worthy of further investigation.

A-012

Synthesis and Anti-proliferative Evaluation of Amide-Containing Anthraquinone, Xanthone, and Carbazole

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Nasopharyngeal carcinoma (NPC) is an uncommon type of head-and-neck cancer in Western countries, but is relatively endemic in southern regions of China. It occurs in about 25 cases per 100,000 people in this region, 25 times higher than the rest of the world. It is also quite common in Taiwan. Despite an initial response to chemotherapy, the majority of patients with advanced NPC succumb to this disease. Therefore, it is in an urgently need to search for new treatment and/or effective chemotherapeutical agents. We were especially interest in the identification of new compounds which selectively active against nasopharyngeal carcinoma. Recently, we have prepared certain *N*-(naphthalen-2-yl)acetamide and *N*-(substituted phenyl)acetamide bearing quinolin-2(1*H*)-one and 3,4-dihydroquinolin-2(1*H*)-one derivatives and evaluated *in vitro* for their anti-proliferative activities against a panel of human cancer cell lines including nasopharyngeal (NPC-TW01), lung carcinoma (H661), hepatoma (Hep3B), renal carcinoma (A498), and gastric cancer (MKN45). Among them, *N*-(naphthalen-2-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)acetamide (**3**) was the most active and selective against NPC-TW01 with an IC_{50} value of 0.6 μM. In continuation of our studies to explore active and selective anti-NPC agents and establish structure-activity relationships, the present report describes the preparation of certain amide-containing anthraquinone, xanthone, and carbazole derivatives whose structures are similar to the lead compounds **1** – **3** (*Figure*). Their 4-substituted *N*-phenyl counterparts have also been synthesized for anti-proliferative evaluation.

A-013

Inoscavin A Inhibits Metastasis of Lung Cancer Cell by Reducing Matrix Metalloproteinases-9Expression

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Lung cancer is the leading cause of cancer mortality, and metastasis is responsible for approximately 40% of death in lung cancer patients. Matrix metalloproteinases (MMPs) are the key enzymes in the degradation of extracellular matrix, and MMP-2 and -9 are critical for cell migration leading to invasion and metastasis of cancer.The inhibition of MMP-2 and -9 is therefore considered that might suppress the occurrence of tumor invasion and metastasis. Inoscavin A was isolated from Chinese medicine *Phellinuslinteus*, a medicinal mushroom that has recently been shown to have antioxidant and anticancer activities.However, the literature regarding the effect of inoscavin A on the metastatic potential of lung cancer cells and the detailed mechanism of its anti-metastatic activity have not been examined previously. In this study, we investigated that the effect of inoscavin A on lung cancer cell proliferation, MMP-2 and-9 activities, migration as well as invasion activities in human lung adenocarcinoma A549 cell and Lewis lung carcinoma cell (LLC).The data demonstrated that inoscavin A did not effectively inhibit the viability of A549 and LLC cells. When treated with non-toxic doses of inoscavin A, cell migration and invasion is markedly suppressed in a dose-dependent manner by Boyden chamber assay.Mechanistically, inoscavin A decreased the enzymatic activity level of MMP-9 in a concentration-dependent manner by gelatin zymography.These results demonstrated that the inhibition A549 and LLC cells invasion and migration may be through reducing matrix metalloproteinases-9 expression.These findings suggested that inoscavin A may be used as an antimetastatic agent.

A-014

Effects of ginseng flower on hyperglycemia and dyslipidemia in high fructose-fed rats

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Type 2 diabetes is a chronic disorder in metabolism of carbohydrates, proteins, and fat due to absolute or relative deficiency of insulin secretion with/without varying degree of insulin resistance. At the turn of this century 171 million individuals were estimated to have diabetes, and this is expected to increase to 366 million by 2030. The main clinical manifestations of DM are polydipsia, polyuria, andpolyphagia, accompanied with high blood glucose level.The aim of thepresent investigation was to evaluate the effects of ginseng floweron hyperglycemia and dyslipidemia in high fructose-fed rats.

Sixty days after high fructose feeding with rats, higher levels of plasma glucose and triglycerides were observed. The levels of AST and ALT and the relative hepatic weight of high fructose-fed rats were higher than those of normal diet-fed rats. But the relative brain weight of high fructose-fed rats were lower than those of normal diet-fed rats. Thus high fructose-fed rats prolonged the reached time to the hidden platform in the spatial performance of Morris water maze and shortened the time spent in the platform area. Ginseng flower could decreased the levels of plasma glucose, triglyceride, AST and ALT in high fructose-fed rats. Ginseng flower also reversed the impairment of spatial performance and probe test of Morris water maze in high fructose-fed rats. In conclusion, we suggested that ginseng flower could attenuate the plasma biochemical confusion and related cognitive dysfunction in high fructose-fed rats.

A-015

Hepatoprotective effect of *Cuscutacampestris* ethanol extract oncarbon tetrachloride-induced liver damage in mice.

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The liver is the body's vital metabolic organ. According to Ministry of Health and Welfare statistics show people death caused by liver disease is one of the top ten diseases.

Contemporary studies have shown that flavonoids can effectively prevent or treat liver diseases. Therefore, this study used ***Cuscutacampestris*** (CC_{EtOH})contained flavonoid as study sample. The experiments conducted using ICR male mice in chronic hepatitis tests are divided into six groups, the first one is normal group, the secondary group is mice treated with CCl_4, the third group is positive control group (silymarin, 200 mg/kg) and the last three groups were three doses of $CC_{EtOH.}$ The study period was last for 8 weeks.

The results showed that the body weight, sALT, sAST, and TG of mice treated with carbon tetrachloride were significant differences as compared with the normal group. CC_{EtOH} was significant decreased the body weight, sALT, sAST, and TG induced by CCl_4.

These results show that CC_{EtOH} could improve the CCl_4-induced liver injury. The action of mechanism of CC_{EtOH} on carbon tetrachloride induced chronic liver fibrosis need to be further studied in the future.

A-016

Lobelia chinensis Lour inhibits inflammation in RAW 264.7 macrophage cells

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Lobelia chinensis Lour (Campanulaceae) is distributed in oriental countries and has been traditionally used for the treatment of snake bites, carbuncles, boils, inflammation, pain, liver cirrhosis and various cancers; chinensis has been shown to possess some pharmacological effects such as anti-inflammatory, anticancer and immunomodulatory activities

Macrophages play important roles in inflammatory diseases through the release of factors such as ROS and cytokines. Production of these macrophage mediators has been determined in many inflammatory tissues following exposure to immune stimulants including bacterial endotoxin lipopolysaccharide (LPS) and interferon-gamma (IFN-γ). Inappropriate macrophage activation is responsible for the pathogenesis of certain acute and chronic inflammatory diseases such as allergic reactions and hypersensitivity. Chronic inflammation leads to up-regulation of signaling proteins in affected tissues and cells. -Inducible nitric-oxide synthase (iNOS) and cyclooxygenase (COX-2) are two of the most commonly known pro-inflammatory enzymes involved in various chronic diseases including multiple sclerosis, Parkinson's disease, Alzheimer's diseases and lung cancer . Thus, agents that suppress iNOS and COX-2 overexpressions in inflammation and carcinogenic processes have potential therapeutic values.

In this study, we examined the anti-inflammatory effects of the methanol extract of *Lobelia chinensis* Lour (MLcL) as well as its fractions. Its fractions were further examined for their anti-inflammatory effects in a LPS induce RAW 264.7 macrophage cells model.

A-017

The Anti-angiogenic Effect of Anthraquinone Derivatives

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Angiogenesis plays an important role in many physiological and pathological phenomena. Some anti-angiogenesis drugs have been used in the clinical treatment of diseases such as malignant tumors and macular degeneration. Vascular endothelial growth factor (VEGF), the major pro-angiogenesis factor, is known as stimulate various steps of angiogenic endothelial cells, such as proliferation, migration and differentiation of vessel tube. In an effort to discover more efficacious inhibitors to block tumor angiogenesis, we investigated a series of anthraquinone derivatives for their anti-angiogenic effect and explored the em026 inhibitory mechanisms in human umbilical vascular endothelial cells (HUVECs). The em026 significantly inhibited VEGF-induced proliferation, migration, invasion, and tube formation of HUVECs. The em026 also attenuated VEGF-induced microvessel sprouting from aortic rings *ex vivo* and suppressed new vasculature formation in implanted matrigel plugs in *in vivo* angiogenesis animal models. Furthermore, em026 inhibited VEGF-induced phosphorylation of VEGFR2 and its downstream protein kinases including Akt, focal adhesion kinase, extracellular signal-regulated kinase and Src. Taken together, this study provides evidence that em026 may suppress tumor angiogenesis and consequently tumor growth through inhibiting VEGFR2 signaling pathways. These results also support that em026 is a potential drug candidate for developing anti-angiogenic agent in field of cancer and angiogenesis-related diseases.

A-018

Buyang Huanwu Decoction on Ischemic Stroke Mice by Proteomics Study

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Stroke is one of the top five leading causes of death in the worldwide, and most of the cases are caused by ischemic stroke. An unmet need for the safe and efficient treatment, there is great urgency to develop drug with less side effect and more potency for stroke's patients. Our previous metabolomics study demonstrated Buyang Huanwu Decoction (BHD), a Chinese herbal decoction, has long been used for stroke in Chinese medicine, ameliorates the dysmetabolism of brain in a cerebral ischemic/reperfusion (CI/R) injury and displays a neuroprotective effect on the sub-acute stroke mice. In this study, we characterized the neuroprotective effect of BHD on CI/R mice by iTRAQ proteomics approach using the UPLC/MS/MS and further confirmed the target proteins by Western blotting. Results showed that treatment with BHD (10 mg/kg) significantly ameliorated the damage to brain function caused by CI/R injury. There were 1310 and 1206 proteins identified and quantified, respectively. Major cellular protein functions were affected by CI/R but remained unchanged after BHD treatment. Those protein are associated with oxidation-reduction and homeostasis in molecular function and biological process, respectively. In addition, several important proteins involved in the cell apoptosis, neuroprotection and neurogenesis, were regulated by BHD treatment was further verified by the immunoblotting. BHD play as a GSK-3 inhibitor *via* activated Akt and its downstream MAPK pathway in ischemic stroke mice represented their therapeutic effects.