团队自主学习模式在中药药理学教学中的应用

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摘要:目的 探索团队自主学习(TBL)模式在中药药理学教学中的应用。**方法** 选取本校中药学长学制的30名学生,自主选择学习小组,在规定的时间内自由安排时间和空间,学习中药药理学教材中相关章节内容,团队学习的成果以ppt、文献综述和汇报讨论等形式进行展示,经教师、团队之间和团队成员之间评估计入中药药理学课程成绩。**结果** 通过学习成果的展示,首先可以看到团队学习中,均采用组长负责制,对团队成员有明确分工,学习地点和时间多样化,口头汇报中,团队成员相互支持回答问题,体现出团队协作的意识。其次,团队自主学习不局限于中药药理学课本内容,对课本中表述不清晰,机理研究不深入的内容进行了讨论和补充,反映出同学们探究问题的兴趣和拓展学习的能力。第三,各团队学习成果统一放到班级群中共享,让全体同学在有限的时间里充分获得学习资料,促进团队之间互助。最后,让学生个体和团体参与学习评价,调动了学习的积极性和竞争性。**结论** 中药药理学理论教学中引入TBL教学法,借助客观的评价方法,可有效发挥学生的主观能动性,培养学生团队协作意识和提高对中药药理学学习的兴趣。

关键词: 团队; 自主学习; 中药药理学
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T5 肾脏药理学

肾脏中G蛋白偶联受体信号转导的多样性

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摘要: G蛋白偶联受体(GPCR)是最重要的药物靶点之一;临床有超过30%处方药是直接作用在GPCR上的。在肾脏中,升压素受体、血管紧张素受体、内皮素受体、前列腺素受体和嘌呤受体等都对肾脏的多种功能有重要的调控作用,也是重要的治疗肾病的药物靶点。多种靶向这些肾脏GPCR的激动剂或者拮抗剂已经进入临床应用或者临床测试阶段。然而,这些GPCR药物的设计主要以激动剂和拮抗剂进行区分,与GPCR的功能多样性存在着一定的鸿沟。我们最近在研究靶向血管紧张素受体(AT1R)的药理学研究过程中,不仅发现了高同型半胱氨酸是血管紧张素受体的内源性配体,还发现Arrestin偏向性信号途径不仅可以介导传统的第二波信号途径,还可以在时序上进行第一波信号转导,通过激活TRPC3来促进肾上腺素的释放,从而产生在治疗心血管疾病时的有害作用。我们据此提出了更合理的靶向AT1R开发药物的方法。不仅如此,我们还针对升压素受体的磷酸化编码,阐明了Arrestin对GPCR的磷酸化编码的识别机制,Arrestin的多聚脯氨酸码头的分选机制,以及配体通过操控受体7此跨膜核心与Arrestin的相互作用来指导Arrestin功能的机制。这些研究工作为以后特异性的靶向GPCR的Arrestin 信号通路开发药物奠定了基础。

关键词: G蛋白偶联受体; 血管紧张素受体; Arrestin 信号通路
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线粒体:急性肾损伤治疗的新靶标

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摘要: 线粒体是细胞的"能量工厂",是合成三磷酸腺苷的主要场所,为细胞的生命活动提供能量来源。正常肾单位依赖线粒体生成的ATP以维持对肾小球滤过液体的重吸收。线粒体对各种损伤性刺激敏感,线粒体功能障碍是急性肾损伤(AKI)的早期事件,在AKI的发生与进展中发挥重要作用,维持线粒体结构和功能的完整,有助于防治AKI的发生发展。

在缺血再灌注大鼠肾脏组织中MPTP开放增加、ROS产生增加、ATP下降,而缺血后处理的肾组织MPTP开放减少、损伤较轻。应用线粒体靶向的多肽SS-31可抑制ROS产生、MPTP开放,对肾损伤起保护作用。免疫抑制剂环孢素A是一种mPTP的抑制剂,亦可抑制MPTP开放,从而发挥肾保护作用。线粒体形态学的改变也是缺血再灌注肾损伤的重要机制之一。将线粒体分裂主要的调控因子Drp1抑制可以显著抑制缺血再灌注诱导的线粒体分裂,并抑制小管细胞凋亡,减轻肾损伤。在体外培养的猪肾小管上皮细胞中,顺铂处理后出现激活线粒体信号通路包括开放MPTP、释放细胞色素c、活化胱天蛋白酶等,诱导细胞损伤。应用线粒体主要的抗氧化蛋白MnSOD的类似物MnTBAP可阻断顺铂诱导的线粒体活性氧产生以及细胞损伤。通过调控MnSOD信号可减少顺铂诱导的肾组织氧化应激以及凋亡。顺铂刺激亦可诱导肾小管上皮细胞自噬及线粒体自噬,促进线粒体自噬能够保护线粒体功能进而减轻顺铂诱导的肾小管上皮细胞损伤,抑制线粒体自噬损伤线粒体功能进一步加重顺铂诱导的肾小管上皮细胞损伤。

随着对线粒体功能障碍在AKI发病机制的研究不断深入,多种靶向线粒体的药物被证实可通过调节线粒体的功能对抗肾脏损伤,这些药物包括线粒体分裂的抑制剂、MPTP孔抑制剂、线粒体抗氧化蛋白的类似物、线粒体靶向的醌类化合物以及多肽等,部分药物已经在临床试验中应用并验证,然而将其应用于临床急性肾损伤的防治仍需要更多以及更深入的工作。

关键词: 急性肾损伤; 线粒体功能障碍; 线粒体靶向药物; 线粒体分裂; 氧化应激; 线粒体自噬
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FOXO1 inhibition prevents renal ischemia-reperfusion injury via promotion of CREB/PGC-1α-mediated mitochondrial biogenesis

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Abstract: OBJECTIVE Growing evidence indicates targeting mitochondrial dynamics and biogenesis could accelerate recovery from renal ischemia-reperfusion (I/R) injury, but the underlying mechanisms remain elusive. Transcription factor fork head box O1 (FOXO1) is a key regulator of mitochondrial homeostasis and plays a pathologic role in the progression of renal disease. The present study was designed to determine the involvement of FOXO1 in mitochondrial dynamics in diabetes and investigate underlying mechanisms. **METHODS** A mouse model of renal I/R injury and a hypoxia/reoxygenation (H/R) injury model for human renal tubular epithelial cells (HK2s) were used. **RESULTS** I/R injury up-regulated renal expression of FOXO1, and treatment with FOXO1-selective inhibitor AS1842856 prior to I/R injury decreased serum urea nitrogen, serum creatinine and the tubular damage score after injury. Post-I/R injury AS1842856 treatment could also ameliorate renal function and improve the survival rate of mice following injury. AS1842856 administration reduced mitochondrial mediated apoptosis, suppressed the overproduction of mitochondrial reactive oxygen species (mtROS) and accelerated recovery of ATP both *in vivo* and *in vitro*. Additionally, FOXO1 inhibition improved mitochondrial biogenesis and suppressed mitophagy. Expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), a master regulator of mitochondrial biogenesis, was down-regulated in both I/R and H/R injury, which could be abrogated by FOXO1 inhibition. Experiments using integrated bioinformatics analysis and coimmunoprecipitation established that FOXO1 inhibited PGC-1α transcription by competing with CREB for its binding to transcriptional coactivators CREBBP/EP300 (CBP/P300). **CONCLUSION** These findings suggested that FOXO1 was critical to maintain mitochondrial function in renal tubular epithelial cells and FOXO1 may serve as a therapeutic target for pharmacologic intervention in renal I/R injury.

Key words: FOXO1; ischemia-reperfusion injury; apoptosis; mitochondria; PGC-1α
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Petroleum ether extract of *Derris eriocarpa* How. (PEEDEH) investigate antidiabetic nephropathy effect and mechanism through TLR4/NF-κB/caspase-3 pathways

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Abstract: OBJECTIVE To investigate anti-diabetic nephropathy effect and mechanism through Toll-like receptor 4 (TLR4)/NF-κB/Caspase-3 pathway of petroleum ether extract of *Derris eriocarpa* How. (PEEDEH). **METHODS** Type 2 diabetes was induced in male Kunming (KM) mice through a combination of high-sugar and high-fat diet for 2 months, after that, which was injected with streptozotocin (STZ, 80 mg·kg^{-1}) via tail vein. After 3 d, mice with a fasting blood glucose (FBG)≥ 11.1 mmol·L^{-1} were considered diabetic. The mice were randomly assigned to normal control group, model group, metformin positive group (320 mg·kg^{-1}) and once that received low-, middle-, high-dose (200, 400, 800 mg·kg^{-1}) of PEEDEH for 21 days. **RESULTS** The intraperitoneal administration of PEEDEH reduced the levels of FBG, blood urine nitrogen (BUN), serum creatinine(Scr), kidney index, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Pathological changes of kidney observed by HE staining revealed that the pathology was improved. The expression of TLR-4, NF-κB, caspase-3 and COX-2 detected using immunohistochemical analysis indicated that their expressions were reduced after PEEDEH administration. PEEDEH also significantly reduced mRNA and protein expression levels of TLR-4/NF-κB/caspase-3 pathway in kidney compared to the diabetic group. **CONCLUSION** PEEDEH ameliorated DN through TLR-4/NF-κB/Caspase-3 signaling pathways.

Key words: petroleum ether extract of *Derris eriocarpa* How.; type 2 diabetes; antidiabetic nephropathy
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Contribution of TFEB-mediated autophagy totubulointerstitial fibrosis in mice with adenine-induced chronic kidney disease

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Abstract: OBJECTIVE Autophagy has been implicated in the pathogenesis of chronic kidney disease (CKD). Transcription factor EB (TFEB) is a master controller of autophagy. However, the pathophysiological roles of TFEB in modulating autophagy and tubulointerstitial injury in CKD are unknown. The present study aimed to determine whether TFEB-mediated autophagy contributes to the tubulointerstitial injury in mice with CKD. **METHODS and RESULTS** By treating mice with an adenine diet (0.2% adenine) for 8 weeks, we observed the development of CKD as characterized by increased levels of plasma blood urea nitrogen (BUN) and creatinine (Cre), and tubulointerstitial inflammation and fibrosis. Immunohistochemical analysis further revealed that in the adenine-induced CKD mice, TFEB and autophagy genes were significantly up-regulated in the kidney, and such increase was mostly found in the tubular epithelial cells. Interestingly, we observed a similar expression pattern of TFEB-autophagy genes in tubular epithelial cells in kidney tissue from Immunoglobulin A (IgA) nephropathy patients. Moreover, we speculated a pathogenic role of TFEB in adenine-induced CKD because pharmacological activation of TFEB by trehalose failed to protect mice from tubulointerstitial injuries. In cultured rat tubular epithelial cells (NRK-52E), we demonstrated that activation of TFEB by trehalose increased autophagy induction, cell death, and interleukin-6 release. **CONCLUSION** These results suggest that activation of TFEB-mediated autophagy may cause autophagic cell death and inflammation in tubular epithelial cells contributing to renal fibrosis in adenine-induced CKD.

Key words: chronic kidney disease; inflammation; fibrosis; TFEB; autophagy; adenine diet
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Morin reduce uric acid level in hyperuricemia mice

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Abstract: OBJECTIVE To explore morin´s effect on hyperuricemia mice. **METHODS** Mice were grouped as control, model, morin low dose, middle dose, high dose, allopurinol, benzbromarone. Hyperuricemia model was built by 300 mg·kg^{-1} potassium oxonate intraperitoneal injection. After model built, administrated morin two weeks and sampled serum, kidneys, ileum and liver. Assay UA, BUN, CRE, AST, ALT, TG, CHO, ALB, HDL, LDL by Biochemical analyzer. **RESULTS** Morin groups can reduce the serum uric acid. Compared with allopurinol, morin have less BUN level and CRE level in serum. Morin can reduce ALT level and high dose of morin group significantly reduce LDH level. **CONCLUSION** morin can reduce the serum uric acid on hyperuricemia mice, meanwhile, has liver and kidneys protective effects in some degrees.

Key words: hyperuricemia; morin; uric acid
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姜黄素对TNF-α诱导人肾小球系膜细胞增殖及PTX3表达的作用研究

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摘要：目的 本实验研究姜黄素(Cur)对TNF-α诱导人肾小球系膜细胞过度增殖以及PTX3过度表达的影响，并对其作用机制进行初步探究。**方法** 本实验选择人肾小球系膜细胞进行体外研究。实验共分为6组：空白对照组、TNF-α组、Cur 20，40和80 μmol·L^{-1}组和PDTC组。1. Cur对TNF-α诱导人肾小球系膜细胞过度增殖及PTX3过度表达的影响。① 使用MTT法检测Cur对人肾小球系膜细胞过度增殖的影响。② 使用免疫荧光法检测Cu对人肾小球系膜细胞PTX3过度表达的影响。2. Cur对TNF-α诱导人肾小球系膜细胞PTX3过度表达的作用机制研究。① 使用Western印迹法检测Cur对人肾小球系膜细胞内NF-κB信号通路中蛋白水平及PTX3蛋白表达的影响。② 使用qRT-PCR法检测Cu对人肾小球系膜细胞内NF-κB信号通路中mRNA水平及*PTX3* mRNA表达的影响。**结果** ① Cur对TNF-α诱导人肾小球系膜细胞PTX3的过度表达有良好的抑制作用。② Western印迹结果表明，Cur明显抑制NF-κB P65和IKKβ的蛋白表达，增加IκBα的蛋白表达。③ qRT-PCR结果表明，Cur明显抑制*NF-κB*、*P65*和*IKKβ* mRNA表达，增加*IκBα*的mRNA表达。**结论** ① Cur可有效抑制TNF-α诱导人肾小球系膜细胞的过度增殖。② Cur对TNF-α诱导人肾小球系膜细胞PTX3的过量表达产生良好的抑制效果，极有可能是通过抑制NF-κB信号通路的激活而达到。

关键词： 姜黄素；狼疮性肾炎；PTX3；NF-κB

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endophilin A2抑制小鼠肾间质纤维化的形成

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摘要：目的 探讨endophilin A2(EndoA2)对肾间质纤维化的抑制作用，为评估EndoA2是否可作为肾脏纤维化防治的新靶点提供实验室依据。**方法** EndoA2转基因小鼠通过单侧输尿管结扎手术，形成肾间质纤维化。造模结束后，分离小鼠肾脏并作石蜡切片。Masson染色检测小鼠肾间质纤维化程度，并检测纤维胶原相关分子的蛋白表达情况。另外，HK2细胞过表达EndoA2，观察细胞形态变化与上皮间质转分化(EMT)标志物的蛋白表达以及TβRI与TβRⅡ的mRNA和蛋白表达；检测EndoA2对TGF-β/smad通路的影响。**结果** 造模后的EndoA2转基因小鼠肾间质纤维化程度明显减弱，而且肾皮质中多个纤维胶原相关分子的蛋白表达均明显降低；EndoA2可明显抑制TGF-β_1诱导的HK2细胞EMT及TGF-β/Smad通路，而且TβRⅠ的mRNA和蛋白表达均明显降低；EndoA2可抑制TβRⅡ的蛋白表达但并不影响其mRNA水平。**结论** EndoA2可通过抑制TβRⅠ和TβRⅡ的蛋白表达，从而抑制TGF-β/Smad通路，最终抑制肾间质纤维化的形成。

关键词： endophilin A2；肾间质纤维化；EMT；TGF-β/smad通路
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圆锥绣球提取物治疗慢性肾功能不全的临床前开发及药理机制

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摘要：目的 随着老龄化的到来，肾脏疾病的发病率逐年上升，糖尿病肾病和慢性免疫性肾病是导致终末期肾功能不全的最主要病因，严重威胁着我国人民的健康，然而临床上缺乏特异性的针对肾病病理机制的药物，因此开发新的肾脏保护药物是当务之急。**方法** 基于民间用药经验和我们所前期的工作基础，初步发现广泛分布于我国南方的植物圆锥绣球(Hydangea paniculata)茎提取物(简称HP)有肾保护的药理活性。目前提取工艺已经确定，且HP所含的成分90%都已经结构明确，主要为香豆素类衍生物和少部分环烯醚萜类化合物。本实验室通过近10年的研究，利用LPS诱发的脓毒性免疫肾损伤、糖尿病肾病、阳离子白蛋白诱发的免疫性肾病模型，系统性的评价HP对肾脏保护作用的药效。结合药代分析，初步证实了HP中有效成分在体内的代谢产物，明确其发挥药效的物质基础，深入阐明HP肾保护作用的分子机制。**结果** 研究发现，HP对3种肾病模型均展现出良好的治疗效果，分述如下：① HP显著降低了LPS诱发的AKI小鼠血中BUN和NGAL的含量，减轻肾病理损伤；显著减轻LPS诱导的肾组织中氧化应激和炎症因子的表达，减少炎性细胞对肾组织的侵润，以及减轻肾小管细胞凋亡(通过抑制caspase家族的剪切激活)。分子生物学研究表明，HP可以显著抑制LPS刺激下巨噬细胞Ana1中NFκB的表达和核转位，抑制Ana1细胞中STAT3的磷酸化；HP对LPS刺激的人肾小管上皮细胞HK2中STAT1和ERK1/2的磷酸化有显著抑制作用，提示这可能是HP发挥抗炎免疫所依赖的信号通路。② HP显著改善c-BSA诱导的免疫性肾病大鼠肾功能，显著降低肾病大鼠BUN和SCr，增加肌酐清除率，同时降低了免疫性肾病引起的血中甘油三酯和低密度脂蛋白胆固醇的升高。病理检测证实，HP显著改善了肾小球硬化、系膜增生、肾间质炎性细胞侵润、空泡变性和蛋白管型等病理特征。我们通过全基因组测序和肠道菌群测序，明确了HP的肾保护药效主要来自免疫抑制、抑制纤维化和致病肠道菌群正常化。③ 通过糖尿病肾病模型，证实HP可以显著改善肾病后期的肌酐清除率下降，改善病理中出现的空泡变性。机制研究证实，HP对肾的保护可能来自对TGFβ-Smad信号通路的抑制和Nrf2的激活。另外，研究还提示，HP对糖尿病导致的白内障和心血管损伤也有改善作用。HP的初步药代动力学证实，现HP中主要成分茵芋苷(skimmin)口服生物利用度为14.2%，同时HP中的香豆素

类化合物可以在体内代谢成血药浓度相对较高的7-羟基香豆素和6,7-二羟基香豆素,体外证实其具有较强的抗炎和抗氧化活性,为理解HP的体内药效提供了一定的物质基础。**结论** 圆锥绣球作为一个全新的药用资源,对其进行较为系统的肾保护作用研究,具有一定的创新性。HP成为药品注册新政下一个中药1类药物,处于临床前开发阶段。

关键词: 圆锥绣球; 免疫性肾病; 临床前开发

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T6 民族药物生化与分子机制

冠心活血胶囊的药效学研究

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摘要:目的 研究冠心活血胶囊对心肌缺血及心肌梗死的保护作用。**方法** 在建立犬急性心肌缺血模型、大鼠急性心肌缺血模型、小鼠耐缺氧模型和离体大鼠心肌缺血再灌注模型的基础上,通过观察冠心活血胶囊对犬的血压、心率、冠脉血流量、冠脉阻力、心输出量、心脏膜表面ECG的影响;对大鼠血清中LDH、CK活力及心肌组织中SOD活力、MDA含量的影响;记录小鼠在缺氧状态下的平均存活时间以及测定心肌组织中超氧化物歧化酶(SOD)、乳酸脱氢酶(LDH)、肌酸激酶(CK)、Ca^{2+}-ATP酶、Ca^{2+}- Mg^{2+}-ATP酶、Na^{+}- K^{+}-ATP酶的活力和丙二醛(MDA)的含量变化,以探讨冠心活血胶囊对心肌缺血的保护作用。再通过冠心活血胶囊对大、小鼠血液流变学的影响,探讨其对心肌梗死对保护作用。**结果** 冠心活血胶囊给药后能明显增加冠脉血流量、改善缺血区供血,缩小心肌梗死范围,降低心肌损伤程度,降低心肌耗氧量,提高小鼠耐缺氧能力的作用。对离体大鼠心肌细胞缺血再灌注损伤具有一定的保护作用,且具有抑制红细胞聚集并改善急性血瘀模型大鼠血液流变学指标的作用。**结论** 冠心活血胶囊对动物具有心肌缺血及心肌梗死的保护作用。

关键词: 冠活血胶囊; 心肌缺血; 心肌梗死

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Pharmacological and toxicological studies of famous Chinese medicine Hua-Feng-Dan

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Abstract: Hua-Feng-Dan (HFD) is a famous traditional Chinese medicine with 370 years of clinical use for stroke paraplegia, epilepsy, facial nerve palsy, mouth-eye skewed, and other neurodegenerative diseases, and is listed as an intangible cultural heritage of China. HFD contains 15 herbs, minerals and animal products undergoing a special fermentation process to satisfy the "lifting and floating" theory of Chinese medicine. However, the pharmacological basis of HFD remains elusive. We initially discovered its anti-inflammatory effects in rat neuron-glia co-cultures. Further studies found that 35 d administration of HFD at the clinical dose ameliorated the dopaminergic neuron loss and microglia activation in chronic LPS+rotenone rat PD models and in chronic LPS+MPTP mouse PD models, with significant reduction of pro-inflammatory cytokine production and cellular ROS levels. HFD contains heavy metals with increasing concern of its safety. However, removal or reduction of realgar and cinnabar from HFD resulted in abolished or reduced beneficial effects. To further evaluate the safety of HFD, a series of experiments were conducted, including cultured cells, acute and subacute toxicity studies in rodents, and the results clearly demonstrated that realgar (As_4S_4) and cinnabar (HgS)-containing HFD is much less toxic than environmental arsenic compounds ($NaAsO_2$ and NaH_2AsO_4) and mercury compounds ($HgCl_2$ and MeHg), with much less absorption from the gastrointestinal tract. The gut-brain axis is now implicated in neurodegeneration, and LPS+rotenone or LPS+MPTP induced alterations in gut microbiota, which were significantly ameliorated by HFD. HFD itself also modulates gut microbiome, shedding light on gut-brain axis as one of the possible pharmacological mechanisms. In summary, HFD is effective in preventing dopaminergic neuron loss in both *in vivo* and *in vitro* models, and this effect appears to be related to its anti-inflammatory effects and modulation effects on gut microbiota. Realgar and cinnabar are effective ingredients in HFD recipe and the use of $NaAsO_2$ or $HgCl_2$ to make risk assessment of realgar (As_4S_4) and cinnabar (HgS) is inappropriate.

Key words: Hua-Feng-Dan; neuroprotection; hepatotoxicity; nephrotoxicity; arsenic; mercury

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Melanin homeostasis plays an important role in kaempferide-induced melanogenesis

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