

## SELEZIONE BIBLIOGRAFICA SU POLYGONUM CUSPIDATUM E RESVERATROLO

1. Phytomedicine. 2012 Apr 4. [Epub ahead of print]

Polydatin protects learning and memory impairments in a rat model of vascular dementia.

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Polydatin is one of the most common encountered stilbenes of nature and a key component of the Chinese herb *Polygonum cuspidatum*. This study is to investigate the effects of polydatin on learning and memory impairments induced by chronic cerebral hypoperfusion in rats, as well as the potential mechanism. Both common carotid arteries and both vertebral arteries occlusion (four-vessel occlusion, 4-VO) induced severe cognitive deficits tested by water maze task, along with oxidative stress in hippocampus. Oral administration of polydatin for 30 days markedly attenuated cognitive deficits compared with the control ( $p < 0.05$ ). Biochemical determination revealed that polydatin decreased the production of malondialdehyde (MDA) and significantly increased the activities of superoxide dismutase (SOD) and catalase (CAT). Additionally, polydatin effectively alleviated the injuries of cultured neurons induced by oxygen-glucose deprivation (OGD). These results suggest that polydatin exhibit therapeutic potential for vascular dementia, which is most likely related, at least in part, to its anti-oxidant activity and the direct protection of neurons.

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2. J Ethnopharmacol. 2012 Mar 26. [Epub ahead of print]

The effects of *Polygonum cuspidatum* extract on wound healing in rats.

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**AIM OF THE STUDY:** *Polygonum cuspidatum* has long been used as a traditional medicine inducing wound healing. In this study, the extract from the Chinese medicinal herb *Polygonum cuspidatum* was investigated on its wound healing activity, in order to obtain an accurate elucidation of its traditional use value. **MATERIALS AND METHODS:** After creating wound healing model on the back of rats, the extract from the Chinese medicinal herb *Polygonum cuspidatum* was applied. Wound healing rates were calculated at 3, 7, 14, and 21 days after the wounding, and tissues were harvested at 1, 3, 7, 14 and 21 days for histological and immunohistochemistry analysis. The stages of wound granulation tissues were evaluated histopathologically. The expression of TGF- $\beta$ 1 was determined by immunohistochemically. **RESULTS:** Wound healing rates were significantly higher at 3, 7, 14 and 21 days in the extract group than in the control ( $p < 0.05$ ). Histological results showed more well-organized bands of collagen, more fibroblasts and hair follicle and less inflammatory cells in the extract group. The immunohistochemical results revealed that TGF- $\beta$ 1 increased in the extract group on day 1, 3 and 7 post-wounding ( $p < 0.05$ ). **CONCLUSION:** The present study has shown that the extract from the Chinese medicinal herb *Polygonum cuspidatum* possesses wound healing activity, and thus provided the evidence for its traditional use value.

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3. J Clin Endocrinol Metab. 2011 May;96(5):1409-14. Epub 2011 Feb 2.

A resveratrol and polyphenol preparation suppresses oxidative and inflammatory stress response to a high-fat, high-carbohydrate meal.

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**BACKGROUND:** High-fat, high-carbohydrate (HFHC) meals are known to induce oxidative and inflammatory stress, an increase in plasma endotoxin concentrations, and an increase in the expression of suppressor of cytokine signaling-3 (SOCS-3). **HYPOTHESIS:** The intake of a nutritional supplement containing resveratrol and muscadine grape polyphenols reduces HFHC meal-induced oxidative and inflammatory stress and stimulates the activity of the antioxidant transcription factor, NF-E2-related factor-2 (Nrf-2), and its downstream targets. **METHODS:** Ten normal, healthy subjects were given a 930-kcal HFHC meal either with placebo or with the supplement. Indices of oxidative stress, inflammation, Nrf-2 binding activity, the concentrations of endotoxin (lipopolysaccharide) and lipoprotein binding protein (LBP), and the expression of toll-like receptor 4 (TLR-4), CD14, IL-1 $\beta$ , TNF $\alpha$ , SOCS-3, Keap-1, NAD(P)H:quinone oxidoreductase-1 (NQO-1), and GST-P1 were measured. **RESULTS:** The intake of the supplement suppressed the meal-induced elevations of plasma endotoxin and LBP concentrations, the expression of p47(phox), TLR-4, CD14, SOCS-3, IL-1 $\beta$ , and Keap-1, while enhancing Nrf-2 binding activity and the expression of NQO-1 and GST-P1 genes. **CONCLUSION:** A supplement containing resveratrol and muscadine polyphenols suppresses the increase in oxidative stress, lipopolysaccharide and LBP concentrations, and expression of TLR-4, CD14, IL-1 $\beta$  and SOCS-3 in mononuclear cells after an HFHC meal. It also stimulates specific Nrf-2 activity and induces the expression of the related antioxidant genes, NQO-1 and GST-P1. These results demonstrate the acute antioxidant and antiinflammatory effects of resveratrol and polyphenolic compounds in humans in the postprandial state.

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PMID: 21289251 [PubMed - indexed for MEDLINE]

4. J Nat Med. 2010 Apr;64(2):146-52.

Free radical scavenging activity and antiproliferative potential of Polygonum cuspidatum root extracts.

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*Polygonum cuspidatum* is widely used as a medicinal herb in Asia. In this study, ethanol and ethyl acetate extracts of *P. cuspidatum* root were assayed for their 1,1-diphenyl-2-hydrazyl (DPPH) and hydroxyl free radical scavenging activities, total phenolics content, protective effect against DNA damage, and antiproliferative activity on human lung cancer cells. The ethanol and ethyl acetate (lipophilic phase) extracts of *P. cuspidatum* had significant scavenging effects on DPPH and hydroxyl radicals. Total phenolics content of ethanol and ethyl acetate (lipophilic phase) extracts of *P. cuspidatum* were 276.78 +/- 39.31 and 231.73 +/- 5.04 mg/ml, respectively; both extracts protected against hydroxyl radical-induced DNA strand scission. Furthermore, the extracts of *P. cuspidatum* induced apoptosis and inhibited cell growth in A549 and H1650 cell lines, suggesting that *P. cuspidatum* root extracts exhibit an antiproliferative effect on human lung cancer cells.

PMID: 20082145 [PubMed - indexed for MEDLINE]

5. Biol Res. 2007;40(1):13-21. Epub 2007 Jul 19.

Antioxidant activity of extract from Polygonum cuspidatum.

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Numerous diseases are induced by free radicals via lipid peroxidation, protein peroxidation and DNA damage. It has been known that a variety of plant extracts have antioxidant activities to scavenge free radicals. Whether *Polygonum cuspidatum* Sieb. et Zucc. has antioxidant activity is unknown. In this study, dried roots of *Polygonum cuspidatum* were extracted by ethanol and the extract was lyophilized. Free radical scavenging assays, superoxide radical scavenging assays, lipid peroxidation assays and hydroxyl radical-induced DNA strand scission assays were employed to study antioxidant activities. The results indicate that the IC<sub>50</sub> value of *Polygonum cuspidatum* extract is 110 microg/ml in free radical scavenging assays, 3.2 microg/ml in superoxide radical scavenging assays, and 8 microg/ml in lipid peroxidation assays, respectively. Furthermore, *Polygonum cuspidatum* extract has DNA protective effect in hydroxyl radical-induced DNA strand scission assays. The total phenolics and flavonoid content of extract is 641.1 +/- 42.6 mg/g and 62.3 +/- 6.0 mg/g. The results indicate that *Polygonum cuspidatum* extract clearly has antioxidant effects.

PMID: 17657351 [PubMed - indexed for MEDLINE]

6. *Drugs Exp Clin Res.* 2001;27(5-6):233-48.

Benefits of resveratrol in women's health.

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Resveratrol and trans-resveratrol are powerful phytoestrogens, present in the skins of grapes and other plant foods and wine, which demonstrate a broad spectrum of pharmacological and therapeutic health benefits. Phytoestrogens are naturally occurring plant-derived nonsteroidal compounds that are functionally and structurally similar to steroidal estrogens, such as estradiol, produced by the body. Various studies, reviewed herein, have demonstrated the health benefits of phytoestrogens in addressing climacteric syndrome including vasomotor symptoms and postmenopausal health risks, as well as their anticarcinogenic, neuroprotective and cardioprotective activities and prostate health and bone formation promoting properties. Conventional HRT drugs have been demonstrated to cause serious adverse effects including stroke and gallbladder disease, as well as endometrial, uterine and breast cancers. Recent research demonstrates that trans-resveratrol binds to human estrogen receptors and increases estrogenic activity in the body. We investigated the effects of protykin, a standardized extract of trans-resveratrol from *Polygonum cuspidatum*, on cardioprotective function, the incidence of reperfusion-induced arrhythmias and free radical production in isolated ischemic/reperfused rat hearts. The rats were orally treated with two different daily doses of protykin for 3 weeks. Coronary effluents were measured for oxygen free radical production by electron spin resonance (ESR) spectroscopy in treated and drug-free control groups. In rats treated with 50 and 100 mg/kg of protykin, the incidence of reperfusion-induced ventricular fibrillation was reduced from its control value of 83% to 75% ( $p < 0.05$ ) and 33% ( $p < 0.05$ ), respectively. Protykin was seen to possess cardioprotective effects against reperfusion-induced arrhythmias through its ability to reduce or remove the reactive oxygen species in ischemic/reperfused myocardium. Taken together, these data suggest that trans-resveratrol supplementation may be a potential alternative to conventional HRT for cardioprotection and osteoporosis prevention and may confer other potential health benefits in women.

PMID: 11951581 [PubMed - indexed for MEDLINE]

7. *Vascul Pharmacol.* 2004 Jan;40(6):279-84.

Inhibitory effects of *Polygonum cuspidatum* water extract (PCWE) and its component resveratrol [correction of rasveratrol] on acyl-coenzyme A-cholesterol acyltransferase activity for cholesteryl ester synthesis in HepG2 cells.

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The pharmacological effects of *Polygonum cuspidatum* water extract (PCWE) on lipid biosynthesis were investigated in cultured human hepatocyte HepG2 cells. The addition of PCWE (5 and 20 microg/ml), which had no effect on cell

proliferation and cellular protein content, caused a marked decrease in the cellular cholesterol content, particularly, the cholesteryl ester content following 24 h of incubation. The incorporation of (14)C-oleate into the cellular cholesteryl ester fraction was also reduced remarkably during incubation for 6 and 24 h. The effect of PCWE on acyl-coenzyme A-cholesterol acyltransferase (ACAT) activity were studied in vitro to explore the mechanism by which PCWE inhibits cholesterol ester formation. The data confirmed that PCWE, in a dose dependent manner, remarkably inhibits ACAT activity. Among the main active chemicals of *P. cuspidatum*, resveratrol, a kind of flavonoid, decreased ACAT activity in a dose-dependent manner from the level of 10(-3) M. These results strongly suggest that PCWE reduces the cholesteryl ester formation in human hepatocytes by inhibiting ACAT.

PMID: 15063831 [PubMed - indexed for MEDLINE]

1. PLoS One. 2012;7(4):e35092. Epub 2012 Apr 13.

Acute Activation of AMP-Activated Protein Kinase Prevents H<sub>2</sub>O<sub>2</sub>-Induced Premature Senescence in Primary Human Keratinocytes.

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We investigated the effects of AMPK on H<sub>2</sub>O<sub>2</sub>-induced premature senescence in primary human keratinocytes. Incubation with 50 μM H<sub>2</sub>O<sub>2</sub> for 2 h resulted in premature senescence with characteristic increases in senescence-associated β-galactosidase (SA-gal) staining 3 days later and no changes in AMPK or p38 MAPK activity. The increase in SA-gal staining was preceded by increases in both p53 phosphorylation (S15) (1 h) and transactivation (6 h) and the abundance of the cyclin inhibitor p21(CIP1) (16 h). Incubation with AICAR or resveratrol, both of which activated AMPK, prevented the H<sub>2</sub>O<sub>2</sub>-induced increases in both SA-Gal staining and p21 abundance. In addition, AICAR diminished the increase in p53 transactivation. The decreases in SA-Gal expression induced by resveratrol and AICAR were prevented by the pharmacological AMPK inhibitor Compound C, expression of a DN-AMPK or AMPK knock-down with shRNA. Likewise, both knockdown of AMPK and expression of DN-AMPK were sufficient to induce senescence, even in the absence of exogenous H<sub>2</sub>O<sub>2</sub>. As reported by others, we found that AMPK activation by itself increased p53 phosphorylation at S15 in embryonic fibroblasts (MEF), whereas under the same conditions it decreased p53 phosphorylation in the keratinocytes, human aortic endothelial cells, and human HT1080 fibrosarcoma cells. In conclusion, the results indicate that H<sub>2</sub>O<sub>2</sub> at low concentrations causes premature senescence in human keratinocytes by activating p53-p21(CIP1) signaling and that these effects can be prevented by acute AMPK activation and enhanced by AMPK downregulation. They also suggest that this action of AMPK may be cell or context-specific.

PMCID: PMC3325987

PMID: 22514710 [PubMed - in process]

2. J Gerontol A Biol Sci Med Sci. 2012 Jan 4. [Epub ahead of print]

Age-Associated Proinflammatory Secretory Phenotype in Vascular Smooth Muscle Cells From the Non-human Primate *Macaca mulatta*: Reversal by Resveratrol Treatment.

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There is increasing evidence that age-associated chronic low-grade inflammation promotes the development of both large-vessel disease (myocardial infarction, stroke, peripheral arterial disease) and small-vessel pathologies (including vascular cognitive impairment) in older persons. However, the source of age-related chronic vascular inflammation remains unclear. To test the hypothesis that cell-autonomous mechanisms contribute to the proinflammatory changes in vascular phenotype that accompanies advancing age, we analyzed the cytokine secretion profile of primary vascular smooth muscle cells (VSMCs) derived from young (~13 years old) and aged (~21 years old) *Macaca mulatta*. Aged

VSMCs cultured in the absence of systemic factors exhibited significantly increased secretion of interleukin-1 $\beta$ , MCP-1, and tumor necrosis factor $\alpha$  compared with young control cells. Secretion of interleukin-6 also tended to increase in aged VSMCs. This age-associated proinflammatory shift in the cellular secretory phenotype was associated with an increased mitochondrial O(2)(-) production and nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells activation. Treatment of aged VSMCs with a physiologically relevant concentration of resveratrol (1  $\mu$ M) exerted significant anti-inflammatory effects, reversing aging-induced alterations in the cellular cytokine secretion profile and inhibiting nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells. Resveratrol also attenuated mitochondrial O(2)(-) production and upregulated the transcriptional activity of Nrf2 in aged VSMCs. Thus, in non-human primates, cell-autonomous activation of nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells and expression of an inflammatory secretome likely contribute to vascular inflammation in aging. Resveratrol treatment prevents the proinflammatory properties of the aged VSMC secretome, an effect that likely contributes to the demonstrated vasoprotective action of resveratrol in animal models of aging.

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3. Chem Biol Interact. 2012 Feb 5;195(3):199-205. Epub 2011 Dec 27.

Differential protective effects of quercetin, resveratrol, rutin and epigallocatechin gallate against mitochondrial dysfunction induced by indomethacin in Caco-2 cells.

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The beneficial effects of dietary polyphenols on health are due not only to their antioxidant properties but also to their antibacterial, anti-inflammatory and/or anti-tumoral activities. It has recently been proposed that protection of mitochondrial function (which is altered in several diseases such as Alzheimer, Parkinson, obesity and diabetes) by these compounds, may be important in explaining the beneficial effects of polyphenols on health. The aim of this study was to evaluate the protective effects of dietary polyphenols quercetin, rutin, resveratrol and epigallocatechin gallate against the alterations of mitochondrial function induced by indomethacin (INDO) in intestinal epithelial Caco-2 cells, and to address the mechanism involved in such damaging effect by INDO, which generates oxidative stress. INDO concentration dependently decreases cellular ATP levels and mitochondrial membrane potential in Caco-2 cells after 20min of incubation. INDO also inhibits the activity of mitochondrial complex I and causes accumulation of NADH; leading to overproduction of mitochondrial O(2)(-), since it is prevented by pyruvate. Quercetin (0.01mg/ml), resveratrol (0.1mg/ml) and rutin (1mg/ml) protected Caco-2 cells against INDO-induced mitochondrial dysfunction, while no protection was observed with epigallocatechin gallate. Quercetin was the most efficient in protecting against mitochondrial dysfunction; this could be due to its ability to enter cells and accumulate in mitochondria. Additionally its structural similarity with rotenone could favor its binding to the ubiquinone site of complex I, protecting it from inhibitors such as INDO or rotenone. These findings suggest a possible new protective role for dietary polyphenols for mitochondria, complementary of their antioxidant property. This new role might expand the preventive and/or therapeutic use of PPs in conditions involving mitochondrial dysfunction and associated with increased oxidative stress at the cellular or tissue levels.

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4. Metabolism. 2011 Dec 28. [Epub ahead of print]

Resveratrol improves insulin resistance of catch-up growth by increasing mitochondrial complexes and antioxidant function in skeletal muscle.

Zheng J, Chen LL, Zhang HH, Hu X, Kong W, Hu D.

Caloric restriction followed by refeeding, a phenomenon known as catch-up growth (CUG), affects mitochondrial function and results in systemic insulin resistance (IR). We investigated the potential of resveratrol (RES) in CUG to prevent IR by increasing activity of the mitochondrial respiratory chain and antioxidant enzymes in skeletal muscle. Rats (8 weeks of age) were divided into 3 groups: normal chow, CUG, and CUG with RES intervention. Skeletal muscle and systemic IR were measured in each group after 4 and 8 weeks. Mitochondrial biogenesis and function, oxidative stress levels, and antioxidant enzyme activity in skeletal muscle were assessed. Catch-up growth-induced IR resulted in significant reductions in both average glucose infusion rate(60-120) at euglycemia and skeletal muscle glucose uptake. Mitochondrial citrate synthase activity was lower; and the activity of complexes I to IV in the intermyofibrillar and subsarcolemmal (SS) mitochondria were reduced by 20% to 40%, with the decrease being more pronounced in the SS fraction. Reactive oxygen species levels were significantly higher in intermyofibrillar and SS mitochondria, whereas activities of antioxidant enzymes were decreased. Oral administration of RES, however, increased silent information regulator 1 activity and improved mitochondrial number and insulin sensitivity. Resveratrol treatment decreased levels of reactive oxygen species and restored activities of antioxidant enzymes. This study demonstrates that RES protects insulin sensitivity of skeletal muscle by improving activities of mitochondrial complexes and antioxidant defense status in CUG rats. Thus, RES has therapeutic potential for preventing CUG-related metabolic disorders.

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5. Mini Rev Med Chem. 2011 Dec 1;11(14):1200-15.

Polyphenols: skin photoprotection and inhibition of photocarcinogenesis.

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Polyphenols are a large family of naturally occurring plant products and are widely distributed in plant foods, such as, fruits, vegetables, nuts, flowers, bark and seeds, etc. These polyphenols contribute to the beneficial health effects of dietary products. Clinical and epidemiological studies suggest that exposure of the skin to environmental factors/pollutants, such as solar ultraviolet (UV) radiation induce harmful effects and leads to various skin diseases including the risk of melanoma and non-melanoma skin cancers. The incidence of non-melanoma skin cancer, comprising of squamous cell carcinoma and basal cell carcinoma, is a significant public health concern world-wide. Exposure of the skin to solar UV radiation results in inflammation, oxidative stress, DNA damage, dysregulation of cellular signaling pathways and immunosuppression thereby resulting in skin cancer. The regular intake of natural plant products, especially polyphenols, which are widely present in fruits, vegetables, dry legumes and beverages have gained considerable attention as protective agents against the adverse effects of UV radiation. In this article, we first discussed the impact of polyphenols on human health based on their structure-activity relationship and bioavailability. We then discussed in detail the photoprotective effects of some selected polyphenols on UV-induced skin inflammation, proliferation, immunosuppression, DNA damage and dysregulation of important cellular signaling pathways and their implications in skin cancer management. The selected polyphenols include: green tea polyphenols, pomegranate fruit extract, grape seed proanthocyanidins, resveratrol, silymarin, genistein and delphinidin. The new information on the mechanisms of action of these polyphenols supports their potential use in skin photoprotection and prevention of photocarcinogenesis in humans.

PMCID: PMC3288507

PMID: 22070679 [PubMed - in process]

6. J Nutr Metab. 2011;2011:525094. Epub 2011 Oct 1.

Distinct effects of calorie restriction and resveratrol on diet-induced obesity and Fatty liver formation.

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The potential of resveratrol to mimic beneficial effects of calorie restriction (CR) was investigated. We compared the effects of both CR (70% of ad libitum energy intake) or resveratrol (2 g/kg or 4 g/kg food) on high-fat diet-induced obesity and fatty liver formation in C57Bl/6J mice, and we examined their effects on calorimetry, metabolic performance, and the expressions of inflammatory genes and SIRT proteins. We found that resveratrol with 4 g/kg dose partially prevented hepatic steatosis and hepatocyte ballooning and induced skeletal muscle SIRT1 and SIRT4 expression while other examined parameter were unaffected by resveratrol. In contrast, CR provided superior protection against diet-induced obesity and fatty liver formation as compared to resveratrol, and the effects were associated with increased physical activity and ameliorated adipose tissue inflammation. CR increased expressions of SIRT3 in metabolically important tissues, suggesting that the beneficial effects of CR are mediated, at least in part, via SIRT3-dependent pathways.

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