

Pomegranate

POMEGRANATE DERIVED PRODUCTS FOR CANCER CHEMOPREVENTION.

Because treatment options for advanced metastasized cancers remain inadequate, developing effective approaches for the prevention of cancer has become an important goal to reduce cancer burden. One such strategy is through chemoprevention, preferably by the use of non-toxic dietary substances and botanical products. Pomegranate, used for centuries for its medicinal properties is now being recognized as a potential chemopreventive and anticancer agent. Increasing body of evidence has underscored the cancer preventive efficacy of pomegranate both in vitro and in vivo animal models. The emerging data provide new insights into the molecular framework needed to establish novel mechanism-based chemopreventive strategies for various human cancers.

Semin Cancer Biol. 2007 Oct;17(5):377-85

ELLAGIC ACID, POMEGRANATE AND PROSTATE CANCER—A MINI REVIEW.

There is currently a shifting focus towards finding natural compounds that may prevent or treat cancer, due to the problems that exist with current chemotherapeutic regimens. The fruit of the *Punica granatum* (pomegranate) contains hundreds of phytochemicals and pomegranate extracts have recently been shown to exhibit antioxidant properties, thought to be due to the action of ellagic acid, the main polyphenol in pomegranate. In this mini review the effects of pomegranate extracts and ellagic acid on the proliferation of prostate cancer cells and their future potential are discussed.

J Pharm Pharmacol. 2008 Feb;60(2):139-44

POLYPHENOL-RICH POMEGRANATE FRUIT EXTRACT (POMX) SUPPRESSES PMACI-INDUCED EXPRESSION OF PRO-INFLAMMATORY CYTOKINES BY INHIBITING THE ACTIVATION OF MAP KINASES AND NF-KAPPAB IN HUMAN KU812 CELLS.

ABSTRACT: **BACKGROUND:** Mast cells and basophils are multifunctional effector cells and contain plentiful secretory granules in their cytoplasm. These cell types are involved in several inflammatory and immune events and are known to produce an array of mediators including a broad spectrum of cytokines. Pomegranate fruit is rich in anthocyanins and hydrolysable tannins; a group of polyphenolic compounds shown to be potent antioxidant with anti-inflammatory activity. However, no studies have been undertaken to investigate whether a polyphenol-rich pomegranate fruit extract (POMx) inhibits the inflammatory activity of activated human mast cells and basophils. The aim of this study was to examine whether POMx modulates inflammatory reactions using human basophilic cell line KU812. **METHODS:** KU812 cells were stimulated with phorbol-12-myristate 13-acetate plus calcium ionophore A23187 (PMACI). The inhibitory effect of POMx on pro-inflammatory cytokine gene expression and production by stimulated KU812 cells was measured by quantitative RT-PCR, and cytokine-specific ELISA assays, respectively. Western blotting was used to analyze the effect of POMx on the activation of mitogen-activated protein kinases (MAPKs), and the nuclear factor (NF)-kappaB in PMACI stimulated KU812 cells. Effect on the activity of NF-kappaB was determined using Luciferase reporter assay. Significance of differences from control values were analyzed by means of standard statistical methods. **RESULTS:** POMx significantly decreased PMACI stimulated inflammatory gene expression and production of interleukin (IL)-6 and IL-8 in KU812 cells. The inhibitory effect of POMx on the pro-inflammatory cytokines was MAPK subgroups c-jun N-terminal kinase (JNK)- and extracellular-regulated kinase (ERK) dependent. In addition, POMx suppressed the NF-kappaB activation induced by PMACI by inhibiting IkappaB-degradation in human basophil cells. POMx also suppressed the powerful induction of NF-kappaB promoter-mediated luciferase activity in transiently transfected KU812 cells. **CONCLUSION:** These novel pharmacological actions of POMx provide new suggestion that POMx or POMx-derived compounds may be of therapeutic use for the treatment of inflammatory diseases by suppressing mast cells/basophils activation.

J Inflamm (Lond). 2009 Jan 8;6:1

POMEGRANATE EXTRACT INHIBITS ANDROGEN-INDEPENDENT PROSTATE CANCER GROWTH THROUGH A NUCLEAR FACTOR-KAPPAB-DEPENDENT MECHANISM.

Constitutive nuclear factor-kappaB (NF-kappaB) activation is observed in androgen-independent prostate cancer and represents a predictor for biochemical recurrence after radical prostatectomy. Dietary agents such as pomegranate extract (PE) have received

increasing attention as potential agents to prevent the onset or progression of many malignancies, including prostate cancer. Here, we show that PE inhibited NF-kappaB and cell viability of prostate cancer cell lines in a dose-dependent fashion in vitro. Importantly, maximal PE-induced apoptosis was dependent on PE-mediated NF-kappaB blockade. In the LAPC4 xenograft model, PE delayed the emergence of LAPC4 androgen-independent xenografts in castrated mice through an inhibition of proliferation and induction of apoptosis. Moreover, the observed increase in NF-kappaB activity during the transition from androgen dependence to androgen independence in the LAPC4 xenograft model was abrogated by PE. Our study represents the first description of PE as a promising dietary agent for the prevention of the emergence of androgen independence that is driven in part by heightened NF-kappaB activity.

Mol Cancer Ther. 2008 Sep;7(9):2662-71

ANTI-LISTERIA MONOCYTOGENES ACTIVITY OF HEAT-TREATED LYOPHILIZED POMEGRANATE JUICE IN MEDIA AND IN GROUND TOP ROUND BEEF.

Heat treatment can affect antimicrobial activity of plant by-products by altering phenolic content and composition and forming melanoidins. The antilisterial efficacy of heat-treated and unheated lyophilized pomegranate juice (LPJ) was determined. The LPJ was heated at 100 degrees C for 0, 30, 60, or 120 min and added at 2% (wt/wt) to ground top round beef, which was then cooked and inoculated with individual *L. monocytogenes* strains. Samples of meat stored at 5 degrees C were taken at days 1, 8, 14, and 21 and plated onto Oxford medium for enumeration of bacteria. The MIC of LPJ was determined, and agar well diffusion assays were conducted. Against five *L. monocytogenes* strains, LPJ had a MIC of 1.50 to 1.75% (wt/vol) and 16.8- to 20.0-mm zones of inhibition. In general, no significant differences in *L. monocytogenes* levels between the various treatments, including the commercial sodium lactate-sodium diacetate combination, were detected at days 1 and 8. The LPJ (0, 30, 60, and 120 min of heating) significantly inhibited growth of all five *L. monocytogenes* strains in refrigerated ground cooked beef by 1.80 to 4.61 log CFU/g at day 21. Heating did not negatively impact LPJ antilisterial activity. Addition of LPJ lowered pH values by 0.3 units. The L^* , a^* , and b^* values of cooked ground beef with LPJ changed during the study by 3.4 to 4.43, 0.44 to 0.8, and 0.57 to 1.36 units, respectively, compared with the control. This is the first investigation to confirm pomegranate's antilisterial activity in vitro and in ground beef.

J Food Prot. 2009 Dec;72(12):2508-16

POMEGRANATE FLOWER IMPROVES CARDIAC LIPID METABOLISM IN A DIABETIC RAT MODEL: ROLE OF LOWERING CIRCULATING LIPIDS.

Excess triglyceride (TG) accumulation and increased fatty acid (FA) oxidation in the diabetic heart contribute to cardiac dysfunction. *Punica granatum* flower (PGF) is a traditional antidiabetic medicine. Here, we investigated the effects and mechanisms of action of PGF extract on abnormal cardiac lipid metabolism both in vivo and in vitro. Long-term oral administration of PGF extract (500 mg kg⁻¹) reduced cardiac TG content, accompanied by a decrease in plasma levels of TG and total cholesterol in Zucker diabetic fatty (ZDF) rats, indicating improvement by PGF extract of abnormal cardiac TG accumulation and hyperlipidemia in this diabetic model. Treatment of ZDF rats with PGF extract lowered plasma FA levels. Furthermore, the treatment suppressed cardiac overexpression of mRNAs encoding for FA transport protein, peroxisome proliferator-activated receptor (PPAR)-alpha, carnitine palmitoyltransferase-1, acyl-CoA oxidase and 5'-AMP-activated protein kinase alpha2, and restored downregulated cardiac acetyl-CoA carboxylase mRNA expression in ZDF rats, whereas it showed little effect in Zucker lean rats. The results suggest that PGF extract inhibits increased cardiac FA uptake and oxidation in the diabetic condition. PGF extract and its component oleanolic acid enhanced PPAR-alpha luciferase reporter gene activity in human embryonic kidney 293 cells, and this effect was completely suppressed by a selective PPAR-alpha antagonist MK-886, consistent with the presence of PPAR-alpha activator activity in the extract and this component. Our findings suggest that PGF extract improves abnormal cardiac lipid metabolism in ZDF rats by activating PPAR-alpha and thereby lowering circulating lipid and inhibiting its cardiac uptake.

Br J Pharmacol. 2005 Jul;145(6):767-74

POMEGRANATE FLOWER: A UNIQUE TRADITIONAL ANTIDIABETIC MEDICINE WITH DUAL PPAR-ALPHA/-GAMMA ACTIVATOR PROPERTIES.

PPARs are transcription factors belonging to the superfamily of nuclear receptors. PPAR-alpha is involved in the regulation of fatty acid (FA) uptake and oxidation, inflammation and vascular function, while PPAR-gamma participates in FA uptake and storage, glucose homeostasis and inflammation. The PPARs are thus major regulators of lipid and glucose metabolism. Synthetic PPAR-alpha or PPAR-gamma agonists have been widely used in the treatment of dyslipidaemia, hyperglycaemia and their complications. However, they are associated with an incidence of adverse events. Given the favourable metabolic effects of both PPAR-alpha and PPAR-gamma activators, as well as their potential to modulate vascular disease, combined PPAR-alpha/-gamma activation has recently emerged as a promising concept, leading to the development of mixed PPAR-alpha/-gamma activators. However, some major side effects associated with the synthetic dual activators have been reported. It is unclear

whether this is a specific effect of the particular synthetic compounds or a class effect. To date, a medication that may combine the beneficial metabolic effects of PPAR-alpha and PPAR-gamma activation with fewer undesirable side effects has not been successfully developed. Pomegranate plant parts are used traditionally for the treatment of various disorders. However, only pomegranate flower has been prescribed in Unani and Ayurvedic medicines for the treatment of diabetes. This review provides a new understanding of the dual PPAR-alpha/-gamma activator properties of pomegranate flower in the potential treatment of diabetes and its associated complications.

Diabetes Obes Metab. 2008 Jan;10(1):10-7

POMEGRANATE FLOWER EXTRACT DIMINISHES CARDIAC FIBROSIS IN ZUCKER DIABETIC FATTY RATS: MODULATION OF CARDIAC ENDOTHELIN-1 AND NUCLEAR FACTOR-KAPPAB PATHWAYS.

The diabetic heart shows increased fibrosis, which impairs cardiac function. Endothelin (ET)-1 and nuclear factor-kappaB (NF-kappaB) interactively regulate fibroblast growth. We have recently demonstrated that Punica granatum flower (PGF), a Unani anti-diabetic medicine, is a dual activator of peroxisome proliferator-activated receptor (PPAR)-alpha and -gamma, and improves hyperglycemia, hyperlipidemia, and fatty heart in Zucker diabetic fatty (ZDF) rat, a genetic animal model of type 2 diabetes and obesity. Here, we demonstrated that six-week treatment with PGF extract (500 mg/kg, p.o.) in Zucker diabetic fatty rats reduced the ratios of van Gieson-stained interstitial collagen deposit area to total left ventricular area and perivascular collagen deposit areas to coronary artery media area in the heart. This was accompanied by suppression of overexpressed cardiac fibronectin and collagen I and III mRNAs. Punica granatum flower extract reduced the up-regulated cardiac mRNA expression of ET-1, ETA, inhibitor-kappaBbeta and c-jun, and normalized the down-regulated mRNA expression of inhibitor-kappaBalpha in Zucker diabetic fatty rats. In vitro, Punica granatum flower extract and its components oleanolic acid, ursolic acid, and gallic acid inhibited lipopolysaccharide-induced NF-kappaB activation in macrophages. Our findings indicate that Punica granatum flower extract diminishes cardiac fibrosis in Zucker diabetic fatty rats, at least in part, by modulating cardiac ET-1 and NF-kappaB signaling.

J Cardiovasc Pharmacol. 2005 Dec;46(6):856-62

MACROPHAGE PEROXONASE 2 (PON2) EXPRESSION IS UP-REGULATED BY POMEGRANATE JUICE PHENOLIC ANTI-OXIDANTS VIA PPAR GAMMA AND AP-1 PATHWAY ACTIVATION.

Peroxisome proliferator-activated receptor 2 (PON2), a member of the paraoxonase gene family, was shown to protect macrophages against oxidative stress. Pomegranate juice (PJ), which contains potent polyphenol anti-oxidants, exhibits similar effects. We questioned possible association between PJ polyphenolics, macrophage oxidative stress, and cellular PON2 expression, in relation to the activation of specific PON2 transcription factors. Incubation of J774A.1 macrophages with PJ (0-50 microM of total polyphenols) dose-dependently increased expression (mRNA, protein) and activity and reduced macrophage oxidative status. These effects could be attributed to the PJ unique polyphenols, punicalagin and gallic acid. PJ polyphenol-induced up-regulation of PON2 was inhibited by 40% upon using the PPAR gamma inhibitor GW9662 (50 microM). Accordingly, the PPAR gamma ligand, rosiglitazone, dose-dependently stimulated macrophage PON2 expression, by up to 80%. Inhibition of AP-1 activation with SP600125, attenuated PJ-induced up-regulation of PON2 by 40%. Similarly, incubation of macrophages with PJ polyphenols in the presence of GW9662 or SP600125, significantly reduced their capacity to protect the cells against oxidative stress. We conclude that the anti-oxidative characteristics of PJ unique phenolics punicalagin and gallic acid could be related, at least in part, to their stimulatory effect on macrophage PON2 expression, a phenomenon which was shown to be associated with activation of the transcription factors PPAR gamma and AP-1.

Atherosclerosis. 2007 Dec;195(2):313-21

POMEGRANATE FLOWER AMELIORATES FATTY LIVER IN AN ANIMAL MODEL OF TYPE 2 DIABETES AND OBESITY.

AIMS OF THE STUDY: Fatty liver is the most common cause of abnormal liver function tests. We investigated the effect and its underlying mechanism of pomegranate flower (PGF), a traditional antidiabetic medicine, on fatty liver. **MATERIALS AND METHODS:** At the endpoint of treatment of male Zucker diabetic fatty (ZDF) rats with PGF extract (500 mg/kg, p.o. x 6 weeks), liver weight index, hepatic lipid contents (enzymatic colorimetric methods) and droplet accumulation (Oil Red O staining) were determined. Gene profiles (RT-PCR) were analyzed in the liver of ZDF rats and in human liver-derived HepG2 cell line. **RESULTS:** PGF-treated ZDF rats showed reduced ratio of liver weight to tibia length, hepatic triglyceride contents and lipid droplets. These effects were accompanied by enhanced hepatic gene expression of peroxisome proliferator-activated receptor (PPAR)-alpha, carnitine palmitoyltransferase-1 and acyl-CoA oxidase (ACO), and reduced stearoyl-CoA desaturase-1. In contrast, PGF showed minimal effects on expression of genes responsible for synthesis, hydrolysis or uptake of fatty acid and triglycerides. PGF treatment also increased PPAR-alpha and ACO mRNA levels in HepG2 cells. **CONCLUSION:** Our findings suggest that this Unani medicine ameliorates diabetes and obesity-associated fatty liver, at least in part, by activating hepatic expression of genes responsible for fatty acid oxidation.

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