

A QUERCETIN CONTAINING SUPPLEMENT REDUCES NIACIN-INDUCED FLUSH IN HUMANS

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Coronary artery disease is associated with increased serum levels of cholesterol, triglycerides and LDL, but low levels of HDL. The most potent agent capable of reversing this trend is the vitamin nicotinic acid (niacin). However, compliance even with extended-release preparations and addition of acetylsalicylic acid (ASA) is hampered by the development of a feeling of erythema and burning (“flush”), especially on the face. We recently showed that the natural flavonoids quercetin and luteolin can eliminate “flush”, as well as inhibit both niacin-induced plasma prostaglandin D₂ (PGD₂) and serotonin increase in an animal model. We conducted a pilot clinical study in humans. Four normal male subjects received (a) 1 g immediate release niacin either alone or after (b) the dietary formulation (Algonot-plus[®]) containing 150 mg quercetin per capsule. Subjects completed a visual scale (1=no, 5=worst response) symptom assessment. Erythema and burning sensation scores were both 4.75±0.50 and lasted for 3.63±1.11 hours. After Algonot-plus[®] administration, both scores were reduced to 2.5±0.58 and lasted for only 1.68±0.70 hours. Quercetin also inhibited methylnicotinate-induced human mast cell PGD₂ release. These preliminary results suggest that quercetin could reduce niacin-induced “flush” in humans.

Ingestion of the B₃-vitamin niacin (nicotinic acid) has been repeatedly shown to improve hypercholesterolemia and other lipoprotein abnormalities, while it also increases HDL levels (1). Moreover, the combination of niacin with lovastatin has been shown to be superior to either agent alone (2-4). However, a serious limiting adverse effect is the development of significant facial erythema and warmth, known as “flush” that is more intense with

immediate release than with extended release niacin (2, 5-6). Moreover, most of the over-the-counter formulations either do not contain sufficient niacin to have any effect or contain niacin metabolites that are ineffective (7).

Niacin is thought to induce flush by stimulating the release of prostaglandin D₂ (PGD₂) from the skin (8-9), most likely from dermal macrophages (10). However, co-administration of acetylsalicylic acid

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(ASA) does not reduce PGD_2 levels more than about 30% (11). Other measures used to reduce flush have included avoidance of alcohol and spicy foods with little benefit (12).

We recently used a rat model of flush (13) and showed that niacin-induced skin vasodilation was accompanied by increased plasma PGD_2 , but also serotonin increases, both of which were inhibited along with the flush by the flavonoids quercetin and luteolin (14). We therefore conducted a pilot clinical trial to investigate if a quercetin containing dietary supplement could inhibit niacin-induced flush in humans.

MATERIALS AND METHODS

Materials

Immediate release niacin caplets (250 mg each, SLO-NIACIN®) were obtained commercially (Upsher-Smith Laboratories, Inc., Minneapolis, MN). Quercetin were obtained from Sigma (St. Louis, MO) and were dissolved in olive kernel extract. Four normal male subjects (mean age = 28 ± 3 years) received: (a) 1 g niacin (4 caplets) at 2 pm on days 1 and 2; (b) 2 capsules of a dietary formulation (Algonot-plus®) containing 150 mg quercetin/capsule (with 450 mg of olive kernel extract to increase absorption) at 8 am on days 3 and 4; and (c) 2 Algonot-plus® capsules at 8 am and 1 g niacin at 2 pm on days 4 and 6. Skin temperature was measured with a digital pyrometer (Model OS613A, Omega Co., Stamford, CT) at 4 facial sites (forehead, both cheeks and chin) at 15, 30, 45, 60, 75 and 90 min post niacin administration. Subjects completed a visual scale (1=no, 5=worst response) symptom assessment (erythema, edema, pruritus and burning sensation).

Blood was obtained from the antecubital vein, serum was separated, aliquoted and frozen at -80°C until it was assayed. PGD_2 and serotonin were measured by ELISA.

Isolation of CD34^+ cells and mast cell culture

Human umbilical cord blood was collected as approved by the Tufts Medical Center's Human Investigation Review Board (protocol # 7305). Non-phagocytic mononuclear cells were separated by density-gradient centrifugation using Lymphocyte Separation Medium (LSM) from Organon Teknika Corp (Durham, NC). The isolation of hematopoietic stem cells (CD34^+) was performed by positive selection of $\text{CD34}^+/\text{AC133}^+$ cells by magnetic associated cell sorting (MACS) using an AC133^+ cell isolation kit (Milltenyi Biotec, Auburn, CA). Human cord blood mast cells (hCBMCs) were cultured as previously reported (15-16). Briefly, CD34^+ cells were suspended in

Iscove's Modified Dulbecco's Medium (IMDM; GIBCO BRL, Grand Island, NY), supplemented with 100 ng/ml recombinant human stem cell factor (rhSCF), 50 ng/ml IL-6, 10% fetal bovine serum (FBS; Biowhittaker, Walkesville, MD), 5×10^{-5} M 2-Mercaptoethanol, and 1% penicillin-streptomycin (GIBCO BRL) for 12 to 16 weeks. The purity of hCBMCs was evaluated by immunocytochemical staining for tryptase as previously described (15) and mast cell viability was determined by trypan blue (0.3%) exclusion.

Statistical analysis

The four temperature measurements were averaged for each point. Data are presented as mean \pm SD or scattergrams. Paired comparisons between niacin and control or niacin and drug pretreatment followed by niacin were analyzed with the two-tailed Student's *t* test and the non-parametric Mann-Whitney U test. Multi-variant ANOVA analysis was performed on all other comparisons. Significance is denoted by $p < 0.05$.

RESULTS

There was no significant increase in skin temperature with niacin administration (results not shown). However, erythema and burning sensation were quite intense, with the highest corresponding scores of 4.75 ± 0.50 and 2.25 ± 0.50 , respectively; the least impressive symptom was edema with a score of 0.50 ± 0.58 (Table I).

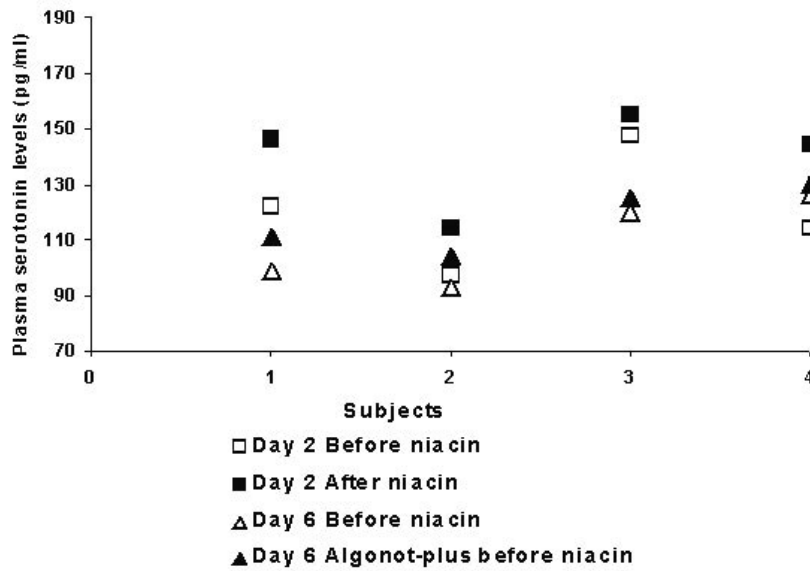
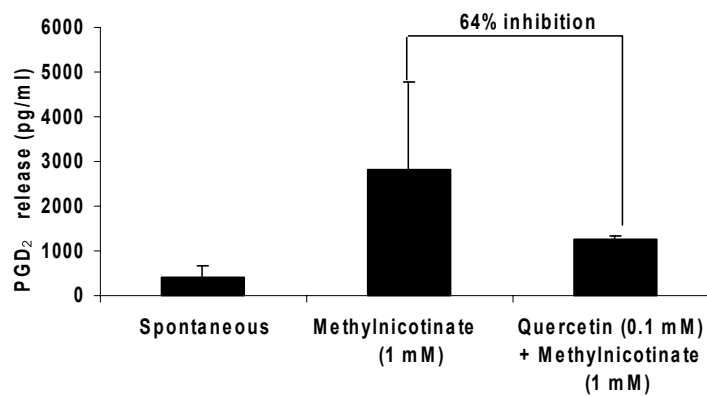
After Algonot-plus® administration, both the erythema and burning scores were reduced from the maximum of 4.75 ± 0.50 to 2.5 ± 0.58 (50% inhibition, $p < 0.05$). Pruritus was reduced from 2.25 ± 0.50 to 1.25 ± 0.50 ($p < 0.05$). The duration of symptoms was reduced from 3.63 ± 0.58 hours before Algonot-plus® to 1.68 ± 0.70 hours (55% inhibition, $p < 0.05$) (Table I).

Plasma serotonin was increased from an average of 120 pg/ml to 140 pg/ml, a 16% increase; individual values are shown as a scattergram (Fig. 1). When Algonot-plus® was administered before niacin on Day 6, plasma serotonin was decreased (Fig. 1).

Given the symptoms of erythema, burning and itching, we investigated if methylnicotinate could stimulate human mast cell secretion. Methylnicotinate (1 mM) resulted in significant increase in PGD_2 release (Fig. 2). Pretreatment of mast cells for 15 min with quercetin (0.1 mM) reduced PGD_2 release by 64% (Fig. 2).

Table I. Effect of Algonot-plus® on niacin-induced flush.

Symptoms	Day 1	Day 2	Day 5	Day 6
Erythema	4.75±0.50	4.50±0.58	3.25±0.50*	2.5±0.58*
Edema	0.50±0.58	0.50±0.58	0.25±0.50*	0.25±0.50*
Pruritus	2.25±0.50	2.0±0.82	1.75±0.50	1.25±0.50*
Burning	4.75±0.50	4.0±0.82	3.0±0.82	2.5±0.58*
Duration (hr)	3.63±1.11	2.75±0.87	1.68±0.40*	1.68±0.70*

* $p < 0.05$ **Fig. 1.** Effect of niacin and Algonot-plus® on plasma serotonin levels in the 4 subjects.**Fig. 2.** Inhibitory effect of quercetin on methylnicotinate-induced PGD₂ release from human cultured mast cells ($n=3-6$, $p < 0.05$).

DISCUSSION

Here, we show for the first time to our knowledge, that the quercetin-containing dietary supplement Algonot-plus® is effective in reducing niacin-induced flush in humans. We also show that, in addition to the reported plasma PGD₂ increases, niacin raises plasma serotonin levels and this dietary supplement also inhibits serotonin increase. The plasma serotonin increase is small, but reflects only part of the total since serotonin is metabolized rapidly in humans to its metabolite 5-hydroxyindoloacetic acid (5-HIAA) measured in 24-hour urine. We also show that quercetin can inhibit methyl nicotinate-induced PGD₂ release from human cultured mast cells.

The ability of Algonot-plus® to inhibit niacin flush appears to be related to the flavonoid quercetin, which exhibits strong anti-oxidant and anti-inflammatory activity (17). We recently showed that the flavonoids quercetin and luteolin could inhibit niacin-induced skin vasodilation in a rat model of niacin-induced flush (14). Quercetin (18) and luteolin (19-20) can inhibit mast cell secretion. Luteolin also inhibits cyclooxygenase 2 (21). Quercetin seems to be a preferential agent in reducing niacin-associated flush because it can also reduce systolic blood pressure, plasma, cholesterol and triglycerides, as well as inflammation (22).

We recently showed that niacin induces serotonin release from platelets in a rat model (23). Serotonin has superficial vasodilatory actions (24), and elevated plasma serotonin levels (25) are associated with the facial flush characteristic of the Carcinoid syndrome (26).

Increasing evidence indicates that niacin can reduce triglycerides, LDL, cholesterol and apolipoprotein E, while increasing HDL (5, 27-31). Recent studies have confirmed the superior efficacy of combining extended release niacin and simvastatin (3-4). However, the rate of niacin discontinuation due to flushing is over 80% even with extended release niacin (32), and increases over the course of treatment (33-34); moreover, the flush can not be reduced by ASA (325 mg/day), ibuprofen (200 mg/day) or selective PGD₂ receptor antagonists by more than 30% (11-12, 35). Inhibition of niacin-induced flush is, therefore, of critical importance for compliance.

The present findings suggest the possibility of inhibiting the niacin flush by administration of niacin together with select flavonoids. A randomized, double-blind, placebo-controlled trial is now in its planning stage for a new formulation that contains niacin together with quercetin and luteolin (CardioProtek®) to evaluate its ability to correct the lipid profile without flush in patients with dyslipidemia.

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DISCLOSURE

US Patents No. 7,115,278, and 11/99,991 as well as EPO No. 1365777, awarded to (TCT) cover methods and composition claims for blocking niacin-induced flush.

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