Effects of Curcumin Chewing Gum on Pro-Inflammatory Cytokines Compared to Capsule Formulation of Curcumin

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Abstract

Poor bioavailability of curcumin has prevented the routine use of curcumin in chemoprevention of HNSCC. We have shown mucosal absorption of curcumin with a micro granular formulation resulted in improved bioavailability of curcumin when compared to capsular formulation. We now report results of a curcumin chewing gum as an extension of the mucosal absorption concept and its effects on cytokine levels in patient's serum.

10 healthy volunteers were administered a one-time dose of curcumin capsule, followed by curcumin chewing gum at least 1 week apart. Serum was assayed for 15 pro-inflammatory cytokines via multiplex analysis at various time points after dosing.

We identified significant decreases in Gro-α as well as TNFα in patient serum after curcumin gum compared to baseline levels ($p=0.036$, $p<0.001$ respectively). TNFα, VEGF, IFNγ, EGF, and IL-13 in the gum group at 4 hours were significantly lower than the capsule group at 4 hours ($P < .05$).

This is the first study reporting significantly decreased Gro-α in patient serum after curcumin. Gro-α and TNFα both represent excellent targets for curcumin therapy of HNSCC. Gro-α mediates angiogenesis and promotes invasion of HNSCC, while TNFα is a critical player in chronic inflammation via NF-κB pathway.

Introduction

High incidence of locoregional recurrence and second primaries in HNSCC can be explained by field cancerization, there is a drastic need for chemoprevention to decrease recurrence rates. Mucosal injury leads to local expression of pro-inflammatory cytokines, creating a micro-environment which promotes malignant degeneration of precursor lesions.

Bioavailability of standard curcumin capsules is low due to low systemic absorption and also degradation by first pass metabolism. To circumvent this, we have engineered a curcumin chewing gum which bypasses first pass metabolism by promoting direct mucosal absorption and activity at the site of field cancerization.

Curcumin decreases NF-κB signaling and scavenges free radicals, and it has also been shown to demonstrate anti-carcinogenic properties. Chronic inflammation induces a metastasis-prone micro-environment by promoting a positive feedback loop between NF-κB and Gro-α 1/2 which Curcumin has been reported to disrupt. A previous study by our group demonstrated that levels of pre-inflammatory differ between patients with HNSCC and healthy patients. Here, we investigated the effect of our formulated curcumin chewing gum on levels of pro-inflammatory cytokines in human serum compared to standard curcumin capsules.

Methods

- 10 healthy volunteers were administered standard Curcumin capsule, and then 7 days later those same 10 volunteers were administered 3 pieces our formulated Curcumin chewing gum (each containing 4g of curcumin)
- 15-panel cytokine profile from the chewing gum group was compared to that of the capsule group
- Whole blood was collected from each at 3 time points: immediately prior to ingestion (baseline), 30 minutes, and 4 hours post administration
- Cytokine expression levels were measured using a bead-based multiplex immunoassay kit for 15 analytes: EGF, FGF-2, Flt-3, GM-CSF, IFNγ, Gro-α, IL-13, IL-17, IL-1β, IL-6, IL-8, IP-10, MIP-1β, TNFα, and VEGF
- Independent two-tailed t-test and Mann-Whitney-U test was used to find differences in cytokine levels between each group

Results

Demographics	Number (%)
Total Patients:	10
Gender:	
Male	4 (40)
Female	6 (60)
Ethnicity:	
African American	3 (30)
Caucasian	7 (70)
Tobacco Use	2 (20)

Table 1: Demographic information for the 10 volunteers.

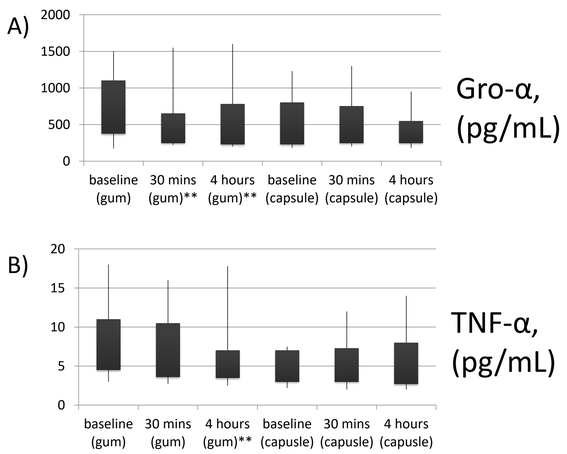

Figure 1: Serum levels of pro-inflammatory cytokines after curcumin gum and capsule administration compared to baseline: A) In the gum group, Gro-α was significantly decreased at 30 mins and 4 hours compared to its baseline ($p= 0.049$, and 0.036 respectively). No significant decreases for serum levels of Gro-α in capsule group. B) In the gum group, TNF-α was significantly decreased at 4 hours compared to baseline ($p<0.001$). In capsule group, serum levels of TNF-α were increased from baseline.

Results Cont.

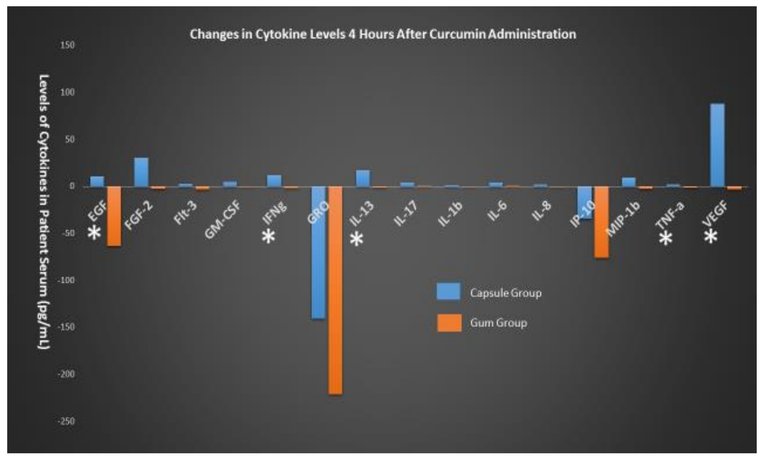

Figure 2: A cytokine profile comparison between treatment groups at 4 hours after administration, capsule group (blue), gum group (orange). EGF, IFNγ, IL-13, TNF-α, VEGF were significantly lower in gum group at 4 hours compared to capsule group at 4 hours ($p= 0.002, 0.03, 0.01, 0.004, 0.038$ respectively)

Discussion

Here we have demonstrated that curcumin chewing gum has superior biologic effect on pro-inflammatory cytokines compared to standard curcumin capsule. Our formulated curcumin chewing gum significantly decreased levels of TNFα and Gro-α compared to their respective baselines. Increased TNFα leads to transformation, tumor cell proliferation, and evasion of apoptosis while increased Gro-α leads to leukocyte recruitment, angiogenesis, invasion, and metastasis.

A total of 5 pro-inflammatory cytokines were significantly lower in serum at 4 hours of the gum group compared to the capsule group (TNFα, VEGF, IL-13, EGF, and IFNγ). Each of these cytokines have been proven to contribute to the tumor microenvironment.

This is the first study reporting decreased levels of Gro-α in human patient serum after curcumin chewing gum, previous studies have reported this finding only at the in-vitro and mouse model level. Gro-α has been proven to be implicated in tumor progression by various mechanisms.

Conclusion

- Our novel curcumin chewing gum formulation has demonstrated the ability to significantly decrease the levels of Gro-α and TNFα in serum, both of which are quintessential to cancer-related inflammation
- Each of the 5 pro-inflammatory cytokines that were found to be significantly decreased in the gum group are directly implicated in HNSCC immunopathogenesis in various ways
- These findings lay the foundation for future prospective trials using curcumin gum as a chemopreventative agent in patients with premalignant lesions

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