Enhanced Systemic Bioavailability of Curcumin Through Transmucosal Administration of a Novel Microgranular Formulation

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Abstract. *Background/Aim: Curcumin is a promising nutraceutical for chemoprevention of head and neck squamous cell carcinoma (HNSCC). Capsular formulations of curcumin demonstrate low systemic bioavailability. We aimed to determine if curcumin levels were higher in healthy volunteers and cancer patients with microgranular curcumin that allows for transmucosal absorption and identify a consistent biomarker. Patients and Methods: Eight healthy volunteers and 15 HNSCC patients completed the trials. Serum levels of curcumin were measured by HPLC. Biological activity of curcumin was assessed with Multiplex Immunoassay and immunohistochemistry. Results: We achieved higher serum levels of curcumin compared to trials using capsular formulation. In cancer patients a significant decrease in expression of fibroblast growth factor-2 (FGF-2) in post-biopsy samples and decreased serum levels of FGF-2, granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin-17 (IL-17) ($p<0.05$) was observed. Conclusion: Transmucosal administration of microgranular curcumin leads to enhanced curcumin bioavailability that is associated with significant biological effects.*

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Key Words: Curcumin, bioavailability, microgranules, head and neck squamous cell carcinoma.

Head and neck cancer develops through a multi-step process of genetic, epigenetic, and metabolic changes resulting from carcinogen exposure (1-3). Alcohol and tobacco use are the leading causes of HNSCC (4). The oral mucosa exposed to carcinogens in tobacco undergoes pre-cancerous changes that often progress to devastating and debilitating oral cancer (5). Moreover, recurrences and second primary tumors are common among HNSCC patients (6), because the entire mucosa has undergone pre-cancerous changes, a phenomenon known as field cancerization (7). Thirty to 45% of patients with dysplasia progress to invasive cancer which occurs in a multi-step process (8). One of the molecular changes that occurs during progression of pre-cancer to cancer is a switch to an angiogenic phenotype known to be regulated by cytokines and angiogenic factors, such as basic fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF) (9).

Most chemopreventives to date, such as retinoids and cyclooxygenase-2 inhibitors, have had significant side-effects when taken over a prolonged period of time (10). When

these agents are discontinued as a result of these side-effects, reversal of clinical effects is observed (11). Although some trials utilizing natural products have shown much promise, unsuccessful trials (such as that of β-carotene) have highlighted the importance of gaining adequate understanding over underlying mechanisms and pharmacology of novel compounds rather than relying primarily on epidemiological data (12). Hence, there is a need for safe, continuous and effective agents thoroughly tested in clinical trials. Curcumin, a polyphenol compound derived from the South Asian spice turmeric (Curcuma longa), is one such promising nutraceutical (13). Curcumin is the most prominent curcuminoid, while desmethoxycurcumin and bis-desmethoxycurcumin are the other two curcuminoids present in turmeric. Curcumin has been found to have anti-inflammatory, anti-oxidative, and anti-carcinogenic properties (14). However, most current supplements of curcumin are hampered by poor bioavailability. Aside from being poorly absorbed by the gut, curcumin undergoes sulfation and glucuronidation at various tissue sites and is rapidly metabolized to these intermediates in the liver (13, 15). In Anand's review article (13), five methods were devised to improve the compound's bioavailability. The use of piperine to reduce metabolite formation, liposomal curcumin, curcumin nanoparticles, and structural analogues of curcumin were some of the attempted modifications. None of these methods revealed conclusive evidence of improving curcumin bioavailability (13). To date, most clinical trials have used Curcumin C^3 Complex™ capsules (Sabinsa Corporation, CA, USA) that contain a curcuminoid mix of 79.85% curcumin, 17.5% demethoxycurcumin, and 2.65% bisdemethoxycurcumin with serum curcumin/metabolite levels typically non-detectable or near the limit of detection (16-20). Poor bioavailability has negatively impacted its clinical development. However, curcumin has maintained its promise in the treatment of colorectal cancer due to its ability to bathe the intestinal mucosa over time and bypass the aforementioned constraints of poor bioavailability (17). We attempted to adapt this concept of direct tissue contact to the treatment of HNSCC by administering microgranules of curcumin, so that oral mucosal exposure would allow for direct mucosal absorption into the bloodstream.

Given the problems with curcumin's bioavailability, transmucosal administration of curcumin will allow for prolonged contact with oral mucosa and for direct absorption into the blood stream, by-passing the poor stomach absorption and hepatic first-pass metabolism, thus leading to improved systemic bioavailability. Hence, we hypothesized that oral transmucosal administration of curcumin in the form of microgranules that can be pouched in the sub-lingual area of the mouth will improve the systemic bioavailability of the compound, achieving biological effects at the dose tested. We conducted a clinical trial and compared the serum levels of microgranular curcumin achieved in our study to historical published studies of the capsular formulation of curcumin C^3 Complex™ manufactured by the same company, Sabinsa, to determine whether transmucosal administration enhances its bioavailability. We also evaluated whether improved bioavailability of curcumin translates into biological activity in HNSCC patients.

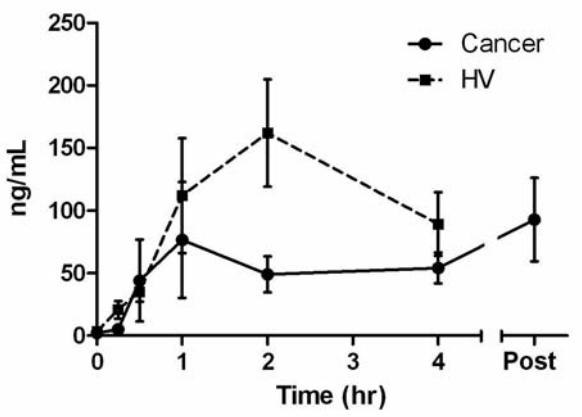

Figure 1. *Serum levels of curcumin. Head and neck cancer patients (Cancer) and healthy volunteers (HV) consumed 4 g of microgranular formulation of curcumin: one time dose for healthy volunteers and twice daily for 3-4 weeks in cancer patients. Serum samples were collected at 0, 0.25, 0.5, 1, 2, 4 h after the initial dose for both groups, and for cancer patients only, at 3-4 weeks (Post) after daily curcumin consumption. Mean±SEM is shown.*

Materials and Methods

Formulation, dose, and clinical trial design. The clinical trial was performed at the Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center-Shreveport (LSUHSC-S). The study was approved by the Institutional Review Board of LSUHSC-S.

We first enrolled healthy volunteers who were administered a one-time dose of curcumin to determine time points for blood draw as well as to analyze any potential differences between cancer patients and healthy subjects. Nine healthy volunteers were recruited and screened with 8 completing the trial. The study schedule was similar to day 1 of the cancer patients as healthy volunteers received only a one-time dose of 4 g.

Patients with newly-diagnosed HNSCC of the oral cavity, oropharynx, hypopharynx or larynx with an accessible tumor for biopsy were enrolled in the trial. The curcumin C^3 Complex™ was in the form of small beadlets (microgranules), manufactured by Sabinsa. Following the standard diagnostic incisional biopsy, patients self-administered a 4 g dose of C^3 Complex™ microgranules and were instructed to hold it in the mouth for 10 minutes. Serum was collected at 15 min, 30 min, 1 h, 2 h, and 4 h after administration. The final serum collection occurred between days 21-28, after patients completed a 3-4 week regimen of 4 g twice daily dosing of curcumin. Patient's HPV status was determined as described previously (21).

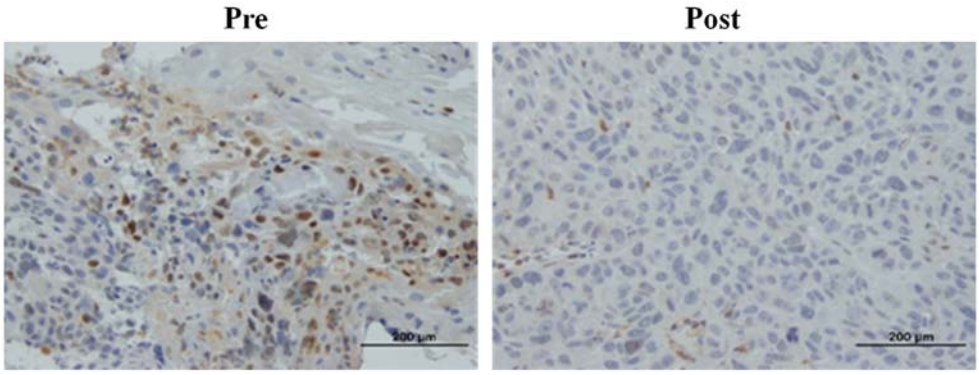

Figure 2. *Analysis of FGF-2 expression by immunohistochemistry. Representative matched tumor samples collected before (Pre; note strong positive brown staining) and after consumption of 8 g of curcumin daily for 3-4 weeks (Post) are shown.*

Pharmacological Analysis. Preparation of serum samples for High-Performance Liquid Chromatography (HPLC) analysis. A standard curve was established by serial dilutions of curcumin from a 1 mM stock of C^3 Complex™ in 1 mM ascorbic acid in MeOH (pH 4.6) with a detection limit of 9 ng/ml. The acidic pH of the solvent is critical, since curcumin is unstable at basic pH and undergoes slower degradation under acidic conditions (22). Since most solid tumors exhibit acidic conditions in their core, curcumin in direct contact with tumors may present an ideal absorptive environment (23). Samples were prepared in the dark or under yellow-filtered light conditions to prevent curcumin degradation (22) using Axygen 2-ml microtubes (MCT-200-C-S) because curcumin reacts with the plastic in traditional Eppendorf tubes.

Serum samples were mixed with β-Glucuronidase (500 units/50 µL in 0.1M sodium acetate, pH 5.0) that also contains sulfatase activity (catalog #G1512; Sigma-Aldrich, St. Louis, Missouri, USA) and incubated at 37˚C to convert all conjugates to parent compound. Post incubation, enzymatic reactions were quenched using 1 mM ascorbic acid, pH 4.6 in methanol. Each sample was extracted with 1 mL of 5% methanol/95% ethyl acetate, vortexed, and spun for 30 min at 14,000 rpm in a cold room centrifuge. The upper organic phase layer was then removed and placed in separate microcentrifuge tubes. The procedure was repeated twice, and pooled serum extracts were concentrated using a Savant SpeedVac. Samples were reconstituted in 100 µl of 1 mM ascorbic acid/methanol solution, mixed in a sonication bath for 2 min, and 75 µl were injected on-column.

HPLC parameters. Reverse-phase HPLC (Agilent 1100 series) with a Waters uBondapak C18 10-µm 4.6×250 mm analytical column operated at ambient temperature was used to quantify curcumin in serum. The mobile phase was 0.1% glacial acetic acid (Mobile A) and 100% methanol (Mobile B). Extracted serum samples were eluted using a gradient starting at 40% of Mobile A/60% of Mobile B over 5 min, then 35% of Mobile A/65% of Mobile B for 5-15 min, 25% of Mobile A/75% of Mobile B for 15-30 min, and finally 100% of Mobile B for 30-35 min. The column was cleaned of residual curcumin using an injection of 100 µL of isopropanol in 100% of Mobile B for 23 min. With all analyses performed at a 1 ml/min flow rate and fluorescence detection at Ex 420 nm and Em 524 nm, curcumin eluted at about 23 min.

Efficacy Studies. Immunohistochemical analysis of molecular markers. IHC staining for FGF-2 (Santa Cruz Biotechnology, Santa Cruz, CA), metalloproteinase-9 (MMP-9), phospho-S6, phospho-Akt, phospho-mTOR and phospho-eukaryotic translation initiation factor 4E-binding protein 1 (Cell Signaling, Beverly, MA, USA) was performed using the streptavidin conjugated detection system (Biogenex, San Ramon, CA, USA) according to the manufacturer's instructions. Staining intensity of patients' tissue samples from diagnostic incisional biopsies was scored semi-quantitatively by the study pathologist (FA) who was unaware of the clinical details.

Multiplex immunoassay analysis of serum cytokines and growth factors. The serum samples were analyzed using MILLIPLEX multi-analyte panels (MAP) Human Cytokine/Chemokine Magnetic Bead multiplex assay on the Bio-Plex® 200 system. 13 different analytes were measured: FGF-2, GM-CSF, Interferon γ (IFNγ), Growth-Related Oncogene (GRO), Interleukin (IL)-13, IL-17, IL-1β, IL-6, IL-8, Inducible Protein (IP)-10, Macrophage inflammatory protein-1β (MIP-1β), Tumor necrosis factor α (TNFα), and VEGF.

Statistical analysis. Spearman rank correlation analysis was used to correlate curcumin serum levels with a decrease in biomarker levels at different time points post-curcumin consumption, as well as associations between the changes in biomarkers and clinicopathological variables. Paired t-test or the Wilcoxon signed rank test were used to determine significant changes in curcumin levels or biomarker expression at various time points compared to baseline values. Unless otherwise stated, values in the text represent the mean+the SD.

Results

Characteristics of cancer patients and healthy volunteers. Demographic and baseline characteristics of cancer patients and healthy volunteers are shown in Tables I and II, correspondingly. Thirty-three cancer patients were enrolled, 18 were withdrawn and 15 completed the trial. Eighteen patients were withdrawn either voluntarily or by the principle investigator due to the following reasons: primary treatment was initiated early after patient's enrollment in the curcumin

Table I. *Patients' characteristics.*

	N (%) or Mean±SD; Median (Range)
Sex	
Male	14 (93.3%)
Female	1 (6.7%)
Race	
Caucasian	10 (66.7%)
African American	5 (33.3%)
Age (years)	52.7±11.5, 52.0 (36-76)
Site	
Oral cavity	3 (20.0%)
Oropharynx	12 (80.0%)
HPV status	
Positive	6 (40.0%)
Negative	3 (20.0%)
Not determined	6 (40.0%)
Cancer stage	
1, 2 or 3	4 (26.7%)
4	11 (73.3%)
T-stage	
1 or 2	7 (46.7%)
3 or 4	8 (53.3%)
N-stage	
0 or 1	6 (40%)
2	9 (60%)
M-stage	
0	15 (100%)

Table II. *Characteristics of healthy volunteers.*

	N (%) or Mean±SD; Median (Range)
Sex	
Male	5 (62.5%)
Female	3 (37.5%)
Race	
Caucasian	6 (75.0%)
African American	2 (25.0%)
Age (years)	41.8±13.4; 42.5 (22-63)

trial; non-compliance with dosing, blood draws or biopsy; baseline blood chemistry eligibility failure; one patient was unable to take curcumin as suggested due to tumor size; one patient had diarrhea after taking the first dose of curcumin (see below). Curcumin treatment was well-tolerated in most subjects. One subject experienced diarrhea within 24 h of taking the first dose of curcumin C^3 Complex™. At this time the subject notified us of a history of Crohn's disease that had not been active for over a year. The subject was advised to skip a dose and diarrhea resolved within 24 h. The principle investigator decided to discontinue curcumin in this patient.

The median age of cancer patients was 52 years (range=36-76 years). Fourteen out of fifteen patients were men (Table I). All but one of the patients had a history of tobacco use and 9/15 reported present or past heavy alcohol use. The median age of healthy volunteers was 42.5 years (range=22-63 years). Five out of eight healthy volunteers were men (Table II). A history of tobacco and alcohol use was not collected on healthy volunteers.

Curcumin pharmacology. Serum levels of curcumin in both cancer patients and healthy volunteers are shown in Figure 1. Compared to baseline levels, there was a significant increase in curcumin levels in cancer patients starting at the 30-min time point and thereafter ($p<0.05$). On day 1 of the study, the average serum curcumin concentration peaked at 76.51±179.00 ng/ml around 1 h following intake of the first dose in cancer patients. Curcumin was undetectable in the serum of two patients on day 1 of the study. At the post time-point (3-4 weeks after steady daily dosing), the average level of curcumin was 92.88±129.09 ng/ml and the maximum concentration was 403.52 ng/ml. All but one patient had detectable levels of curcumin at the post time-point. The majority of patients, 8 of 15, achieved the highest concentration of curcumin at the post time point. The average C_{max}, which included 0.25-4 h and the post samples, was 127.14±186.65 ng/ml (maximum level of curcumin) with a range of 19.09-711.29 ng/ml.

There was a significant increase in curcumin levels at all time points compared to baseline in the healthy volunteers ($p<0.05$). Serum concentrations peaked 2 h after ingestion of curcumin, with an average concentration of 162.04±121.37 ng/ml. The average C_{max} was 170.55±131.79 ng/mL with a range of 33.05-406.49 ng/ml.

Comparison of curcumin pharmacology for microgranular formulation administered transmucosally to historical published studies of oral capsular formulation. We compared serum levels of curcumin after administration of the microgranular formulation of curcumin to historical controls, *i.e.* trials where curcumin from the same company was taken in a capsular formulation at approximately the same dose (Table III). In the dose escalation study on the capsular formulation, Lao *et al.* reported that no curcumin was detected in the serum of subjects although escalating single doses of up to 8,000 mg of curcumin were administered (24). Several other studies were unable to detect curcumin in serum samples of patients consuming 3.6 g daily of curcumin. Dr. Sharma studied the effects of capsular curcumin on colon cancer patients that were administered oral doses of 3.6 g of curcumin daily. The study yielded average levels (curcumin+metabolites) of 16.99 ng/mL 1 h following curcumin ingestion (19), whereas the average level of total curcumin detected for our microgranular formulation was 76.51±179.00 ng/mL at the same time point. Dhillon's study at MD Anderson evaluated

Table III. *Comparison of our findings using microgranular formulation of curcumin with published studies of capsular formulation of curcumin.*

Published Studies	Capsular formulation of curcumin	Microgranular formulation of curcumin (*this study*)
Sharma Colon Cancer (19):	16.99 ng/ml mean curcumin at 1 h[a]	76.51±179.00 ng/ml and 111.88±129.71
3.6 g daily with 30 min, 1 h, 2 h, 3 h, 6 h and 8 h collection time points		ng/ml mean curcumin (+SD) at 1 h time point[a] among HNSCC patients and healthy volunteers, respectively
Garcea Metastatic Colon Cancer (20): 3.6 g daily dose for 1 week with collection at 1hr time points.	Curcumin and its metabolites measured separately. Peak areas for all measurements below or near LOD[b]	
Garcea Colon Cancer Study (17): 3.6 g daily for 1 week with collection at 1 h timepoint on day 7.	Free curcumin detected below the LOD and no metabolites detected[b]	
Dhillon Advanced Pancreatic Cancer Study (16): 8 g daily for 8 weeks.	Conjugated curcumin in plasma measured at steady state=22-41 ng/ml.	Post (3-4 weeks) was 92.88±129.09 ng/ml (Mean±SD)[c] among HNSCC patients

[a]Quantified as parent compound plus metabolites. [b]Below the limit of detection (LOD), which was 1 ng/mL. [c]Total curcumin at steady state.

the effects of an 8 g daily dose of capsular curcumin in advanced pancreatic cancer patients and reported steady state serum total curcumin levels of 22-41 ng/mL (16). Our novel microgranular formulation resulted in more than double these values, with average steady state levels of 92.88±129.09 ng/ml.

Efficacy studies. To determine the biologic effects of microgranular curcumin and identify potential biomarkers for future chemopreventive studies, we tested the effects of curcumin on tissue biomarkers, as well as on angiogenic and anti-inflammatory cytokines in serum.

Previously, we demonstrated robust anti-proliferative effects of curcumin in a panel of nine HNSCC cell lines which were associated with inhibition of the AKT/mTOR pathway and downregulation of FGF-2 and MMP-9, both biomarkers of angiogenesis and invasion regulated by the AKT/mTOR pathway (25). Therefore, we chose to evaluate these biomarkers in HNSCC patients enrolled in the trial. Only FGF-2 was significantly decreased in post-treatment tumor samples in 7 out of 11 patients when compared to evaluable matched pre-treatment tumor samples (p=0.0261; Figure 2).

As immunohistochemical staining is subject to inconsistent results due to tumor heterogeneity and sampling errors, we also analyzed serum for changes in cytokine and growth factor levels. Also, in future chemoprevention clinical trials of curcumin in subjects with a high risk of developing cancer, tumor tissue would not be available, thereby making serum cytokine analysis an important biomarker to establish. There was a significant effect of curcumin on the serum level of FGF-2 at time points 4 h (p=0.0078) and a trend towards decreased levels of FGF-2 at 15 min, 30 min and 1 h (p=0.084) after curcumin administration. The serum levels of GM-CSF significantly decreased between 15 min and 2 h (p<0.05) as well as those of IL-17 at 1 h (p=0.0342) post-curcumin consumption (Table IV). Curcumin caused a noticeable decrease in the levels of IFNγ, IL-13, TNFα and VEGF at various time points and an increase in the level of MIP1β. However, because of data variability, there was no statistically significant difference at the various time points for the aforementioned serum biomarkers. We did not detect any associations between curcumin serum levels or changes in biomarkers and clinicopathological variables.

Discussion

Curcumin is a natural dietary compound that has shown promise across many therapeutic areas, including cancer. However, most current supplements of curcumin are hampered by poor bioavailability and have not been proven to be clinically effective. We addressed curcumin bioavailability using a unique microgranular formulation administered transmucosally in HNSCC patients and healthy volunteers. We achieved much higher levels of curcumin in serum compared to trials that evaluated the standard capsular formulation of curcumin. This improved bioavailability was also associated with significant biologic effects.

Retinoids are the best-studied class of chemopreventive agents with multiple randomized trials conducted in premalignant oral lesions, prevention of recurrences and decreasing second primary tumors (11). Although the trials showed significant response rates, dose-related mucocutaneous toxicity has been the major adverse effect. High relapse rates

Table IV. *Baseline serum levels of cytokines and growth factors and responses to consumption of microgranular curcumin in HNSCC patients* ‡

	Serum levels (pg/ml)						
Analytes	Baseline	15 min	30 min	1 h	2 h	4 h	Post (3-4 weeks)
FGF-2	90.4±142.6	53.4±96.7$^{\Phi}$	52.4±101.6$^{\Phi}$	57.0±115.5$^{\Phi}$	45.7±78.9	35.9±75.9*	40.8±53.7
GM-CSF	30.7±59.8	17.7±48.1*	10.5±24.8*	10.2±18.9*	4.4±3.0*	7.3±13.6	19.4±46.6
IL-17	29.4±89.7	7.4±13.3	6.1±11.2	4.5±7.4*	6.2±12.8	4.9±3.9	5.3±6.1

‡No significant changes were observed in the other multiplex measures (data not shown). *$p<0.05$. $^{\Phi}0.05 < p<0.10$.

noted on withdrawal of the medication indicate the need for prolonged maintenance therapy. NSAIDs have also been widely investigated as chemoprevention agents, but demonstrated an increased risk of cardiovascular events and toxicities (26). Given the need for a safer agent and the long-term use of chemopreventive agents, curcumin has attracted attention due to its antitumor activity and negligible toxicity in animals and humans. Adverse events are limited to grade 1 toxicity even at high doses, mostly involving headache and yellow, loose stools one day after dosing (14). However, curcumin's primary cellular targets are not clearly defined and attempts to improve the compound's bioavailability were not successful (27). The purpose of this study was to investigate the effects of a novel microgranular formulation of curcumin administered via transmucosal route on the drug's bioavailability and efficacy in HNSCC.

In our study we observed a significant increase in serum levels of curcumin at 30 min after ingestion of curcumin in both cancer patients and healthy volunteers. When we compared the results of our study with microgranular curcumin administered transmucosally to historical controls, *i.e.* trials where curcumin from the same company was taken in a capsular formulation at approximately the same dose, our patient serum levels showed appreciable increases in curcumin/metabolite levels relative to previously reported results. Since the datasets and/or standard deviations were not provided in historical published studies of oral capsular formulation we could not determine if the difference between our results and historical controls was statistically significant. Therefore a head-on comparison of two curcumin formulations is being proposed. Our simple innovation to deliver curcumin to patients *via* prolonged contact with the oral mucosa (transmucosal absorption), given our strong preliminary data, could be an exciting approach to effective and cost-friendly biodelivery.

Higher plasma levels of curcumin do not necessarily translate to biological activity. Hence, biomarkers of response were tested to determine if increased curcumin concentrations had any biological effects. Also, identifying a consistent biomarker that can be validated in chemoprevention trials is critical, as the occurrence of cancer as an end-point could take years. Furthermore, in future chemoprevention clinical trials of curcumin in subjects with a high risk of developing cancer, no tumors would be available, making serum cytokine analysis an important serum biomarker. Although many serum biomarkers appear promising and trend towards significance, only FGF-2 was consistently affected as we found its inhibition in HNSCC cells (25), and in this study in post-biopsy tumor samples and in serum, indicating that FGF-2 is potentially an important biomarker for future clinical trials of curcumin. It also indicates a potential effect of curcumin in suppressing angiogenesis in the conversion of pre-malignant to malignant lesions. Binding of FGFs to FGFRs activates Extracellular Regulated Kinase (ERK) and PI3K/AKT pathways. This promotes proliferation and survival of tumor cells and stimulates angiogenesis (9, 29, 30). In an earlier study we found up-regulation of FGF-2 expression ($p<0.001$) with increasing grades of dysplasia that correlated with increase in mean vessel density (28). Acquiring the angiogenic phenotype by pre-malignant cells is the most critical step in carcinogenesis and FGF-2 is one of the most important angiogenic markers (9, 29, 30). Oral dysplasias are characterized by de-regulations (DNA amplification and homozygous deletion) of multiple components of the FGF signaling network (9). Other serum biomarkers found to be significantly inhibited by curcumin in our study are also known to be implicated in the regulation of angiogenesis and cancer cell invasion. GM-CSF promotes proliferation of endothelial progenitor cells (31), induces endothelial capillary formation *via* stimulation of MMP expression (32), and activates Janus kinase 2/STAT3 pathway (33). IL-17, besides its function as immune marker, is also implicated in stimulating angiogenesis mainly *via* its effects on stromal cells (34). Anti-angiogenic properties of curcumin are well-documented (35-37). Furthermore, Chakravarti *et al.* have shown that curcumin treatment is highly effective in inhibiting the growth of not only malignant oral cells, but also premalignant leukoplakia cells (38) further supporting the development of curcumin as a chemopreventive agent.

The limitations of the present study include relatively small sample size and short dosing duration. This could be a reason we have not detected a statistically significant effect of curcumin consumption on the levels of certain serum biomarkers despite the substantial numerical changes observed.

Conclusion

Curcumin is a beneficial nutraceutical agent that is gaining popularity because of its safety profile and promising anticancer efficacy. We showed that the problem of poor bioavailability can be overcome by oral transmucosal administration of curcumin that greatly improves systemic bioavailability of the compound. We demonstrated that improved bioavailability of microgranular curcumin was associated with a significant decrease in FGF-2 and other factors implicated in the regulation of angiogenesis and cell invasion. This shows that curcumin is a potential angiogenic inhibitor in HNSCC and can potentially prevent progression of pre-neoplastic lesions to invasive cancer. This pilot trial provides the basis for a direct comparison of the microgranular formulation of curcumin and the capsular formulation for patients with oral pre-malignant lesions.

Conflicts of Interest

No potential financial conflicts of interest to declare. Patent No. 14/602178 is pending. *Clinical Trial #NCT01160302 "Curcumin Biomarker Trial in Head and Neck Cancer"*.

Funding

The study was supported in part by grant # R21CA137545 from the National Cancer Institute to C.O. Nathan. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. The study was also supported in part by the Feist-Weiller Cancer Center Idea Award Grant "Pilot study testing microgranular curcumin in head and neck cancer patients".

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Received September 2, 2015
Revised September 15, 2015
Accepted September 24, 2015