ORIGINAL RESEARCH

Intake consumption of ginsenoside Rg3, profiling of selected cytokines, and development of rectal polyps

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Background: Rectal polyps is a major risk factor for rectal cancer. There is a need to explore a panel of preventive measures, as well as reliable biomarkers for screening of rectal polyps.

Patients and methods: We conducted a case control study which aimed to explore the effects of regular consumption of ginsenoside Rg3, profiling of selected cytokines, and development of rectal polyps in a Chinese population.

Results: Significantly higher levels of IL-4, MIP-1β, FasL, TGF-β1, and RANTES were detected in rectal polyp cases. Further, we found significant dose-response relationships between quartile-categorized levels of IL-4, MIP-1β, FasL, and TGF-β1, and risk of rectal polyps. The strongest associations for IL-4, MIP-1β, FasL, and TGF-β1 were observed for the highest quartile vs the lowest quartile with an OR of 1.78, 2.70, 1.49, and 2.36, respectively. Compared with non-Rg3 consumers, regular Rg3 consumers had a significantly lower risk of rectal polyps (OR =0.71; 95% CI: 0.55–0.92; *P*=0.009). We also found that Rg3 consumers had significantly lower levels of IL-4, MIP-1β, FasL, and TGF-β1 than non-Rg3 consumers, in both rectal polyp cases and healthy controls.

Conclusion: These results indicate that regular consumption of Rg3 might prevent the occurrence of rectal polyps through decreasing the serum level of selected cytokines, including IL-4, MIP-1β, FasL, and TGF-β1. Further clinical trials and prospective cohort studies with larger sample sizes are warranted to validate the anti-inflammatory activity and the anti-tumorigenic role of Rg3.

Keywords: cytokine, Rg3, rectal polyps, IL-4, MIP-1β, FasL, TGF-β1

Introduction

Rectal polyps occur in 7%–50% of all people, and can be either benign or malignant.[1,2] Epidemiological studies have proven that rectal polyps are a major risk factor for rectal cancer and have raised severe public concern.[3–5] Thus, there is a need to develop a panel of preventive measures, as well as reliable biomarkers for screening rectal polyps.

Many kinds of cytokines, which act as cell signaling proteins, are involved in the physiologic and pathophysiologic mechanisms of immunity, inflammation, and hematopoiesis of tumorigenesis and carcinogenesis.[6,7] Previously, Johdi et al[8] explored the profiles of key inflammatory cytokines, chemokines, and other soluble proteins using multiplexing technology in small samples, and found that colorectal polyp patients had high IL-4, MIP-1β, FasL, and TGF-β1 levels, but lower levels of RANTES, compared with healthy controls. However, further validation of their findings with a larger sample size is needed to produce a panel of serum biomarkers for colorectal polyps.

Ginsenoside Rg3, the major active component of ginseng, has been shown to have various therapeutic effects including anti-inflammatory and anti-tumorigenic activity, however, its relationship with level of IL-4, MIP-1β, FasL, TGF-β1, and RANTES remains unexplored.[9–12] Multiple experimental studies revealed the inhibitory effect of Rg3 on growth and angiogenesis of tumors, including colorectal cancer, ovarian cancer, gastric cancer, lung cancer, intestinal adenocarcinomas, melanoma, breast cancer, and so on.[13–21] Clinical trials have also proven that Rg3 could improve the prognosis of non-small-cell lung cancer and hepatocellular carcinoma, although the possible mechanism and the regulatory network were unclear.[22–24] However, the possible beneficial effects of Rg3 consumption on the occurrence of rectal polyps still remain unknown. Considering the fact that Rg3 is widely used and popular in Asian populations for the prevention of many diseases, evaluation of association of regular consumption of Rg3 with serum levels of selected cytokines, and risk of rectal polyps is warranted. Thus, we conducted this case control study which aimed to explore consumption of ginsenoside Rg3, the profiling of selected cytokines (IL-4, MIP-1β, FasL, TGF-β1, and RANTES), and risk of rectal polyps in a Chinese population.

Patients and methods
Study subjects
To improve the reporting quality of our research, we followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The current study included a total of 600 cases of rectal polyps and 600 frequency-matched healthy controls by age and gender. Both the cases and controls were recruited since January 2014. The cases were diagnosed by two senior gastrointestinal pathologists, respectively. Controls were randomly selected from the volunteers who underwent endoscopy procedures and were diagnosed as healthy. Demographic data and information about the regular consumption of Rg3 were collected face to face using a uniform questionnaire, while body mass index (BMI) was measured at the same time. The frequency of regular consumption of Rg3 was classified as 1–3 times/week, 4–7 times/week, and 7–10 times/week. Ten milliliters of heparinized blood were taken from each participant at the interview and centrifuged at 3,000 g for 10 minutes. Serum samples were stored at −80°C and thawed immediately prior to any laboratory determination. Written informed consent was obtained from all individual participants, and

the study was approved by the institutional Ethics Committee of the second affiliated Hospital of Kunming Medical University (IRB-014023). This study was conducted in accordance with the Declaration of Helsinki.

Cytokine analysis
As reported previously, Luminex cytokine bead array technology was utilized for this study using an EMD Millipore (Billerica, MA, USA) HCTYOMAG-60K kit on a BioPlex analyzer (Bio-Rad Laboratories Inc., Hercules, CA, USA).[25] Data were acquired using the Bioplex analyzer, and the contents of each well were examined using Luminex xPonent software.

Statistical analysis
All statistical analyses were conducted with STATA (version 13.1). $P<0.05$ was considered significant. Descriptive statistics were presented as means, SDs, and percentages. Student's t-tests were used for comparison of continuous variables and chi-squared tests (Fisher's exact tests) for comparison of categorical variables. To explore the possible dose-response relationship between level of selected cytokines and risk of rectal polyps, we categorized the level of selected cytokines using their interquartile range distributions among the healthy controls. ORs and 95% CIs using logistic regression model were calculated to estimate the relative risks related to the quartile distribution of selected cytokines, regular consumption of Rg3, and risk of rectal polyps.

Results
Characteristics of the study population
As shown in Table 1, 600 cases of rectal polyps and 600 frequency-matched healthy controls by age and gender were included in the current study. No significant differences in the distribution of age, gender, BMI, and smoking status between the cases and controls were observed ($P>0.05$). However, more subjects with family history of cancer, alcohol status, and regular consumption of Rg3 were found in the rectal polyp cases ($P<0.05$). The frequency of regular consumption of Rg3 was also presented, which showed that rectal polyp cases had lower consumption of Rg3 as well asless high-frequency consumption. For the selected cytokines, we found that rectal polyp cases had higher serum levels of IL-4, MIP-1β, FasL, TGF-β1, and RANTES.

Table 1 Characteristics of rectal polyp cases and healthy controls

	Cases (n=600)	Controls (n=600)	*P*-value
Age at diagnosis (years)			
≥60	288 (48.0%)	293 (48.8%)	0.773
<60	312 (52.0%)	307 (51.2%)	
Gender			
Male	327 (54.5%)	322 (53.7%)	0.772
Female	273 (45.5%)	278 (46.3%)	
BMI (kg/m²)	26.1±4.8	25.8±4.5	0.264
Family history of cancer			
Yes	87 (14.5%)	31 (5.2%)	P<0.001
No	513 (85.5%)	569 (94.8%)	
Alcohol status			
Drinkers	175 (29.1%)	122 (20.4%)	P<0.001
Non-drinkers	425 (70.9%)	478 (79.6%)	
Smoking			
Smokers	152 (25.3%)	127 (21.2%)	0.088
Non-smokers	448 (74.7%)	473 (78.8%)	
Regular consumption of Rg3			
No	483 (80.5%)	447 (74.5%)	0.013
Yes	117 (19.5%)	153 (25.5%)	
1–3 times/week	46 (7.67%)	57 (9.50%)	
4–7 times/week	39 (6.50%)	51 (8.50%)	
7–10 times/week	32 (5.33%)	45 (7.60%)	
IL-4 (pg/mL)	8.4±6.3	2.0±1.6	P<0.001
MIP-1β (pg/mL)	98.4±44.8	14.9±7.8	P<0.001
FasL (ng/mL)	1.48±0.94	0.24±0.18	P<0.001
TGF-β1 (ng/mL)	16.6±6.1	14.2±5.4	P<0.001
RANTES (ng/mL)	23.0±9.3	20.7±10.5	0.0005

Abbreviation: BMI, body mass index.

Table 2 ORs for rectal polyp cases by quartile distribution of selected cytokines by logistic regression analysis

Quartiles	Cases	Controls	OR (95% CIs)*	*P*-value
IL-4				
Quartile 1	113	167	Reference	0.001
Quartile 2	156	142	1.62 (1.17–2.25)	
Quartile 3	161	150	1.59 (1.15–2.20)	
Quartile 4	170	141	1.78 (1.29–2.47)	
MIP-1β				
Quartile 1	91	173	Reference	4.3×10^{-7}
Quartile 2	155	139	2.12 (1.51–2.98)	
Quartile 3	165	155	2.02 (1.45–2.83)	
Quartile 4	189	133	2.70 (1.93–3.78)	
FasL				
Quartile 1	108	150	Reference	0.009
Quartile 2	152	150	1.41 (1.01–1.97)	
Quartile 3	167	150	1.55 (1.11–2.15)	
Quartile 4	173	150	1.49 (1.03–2.15)	
TGF-β1				
Quartile 1	79	149	Reference	7.7×10^{-7}
Quartile 2	156	150	1.96 (1.38–2.79)	
Quartile 3	177	151	2.21 (1.56–3.13)	
Quartile 4	188	150	2.36 (1.67–3.35)	
RANTES				
Quartile 1	133	150	Reference	0.194
Quartile 2	147	151	1.10 (0.79–1.52)	
Quartile 3	155	151	1.16 (0.84–1.60)	
Quartile 4	150	148	1.26 (0.91–1.74)	

Note: *Adjusted for family history of cancer, alcohol and smoking status, and regular consumption of Rg3.

Quartile distribution of selected cytokines and risk of rectal polyps

To explore the possible dose-response relationship between level of selected cytokines and risk of rectal polyps, the levels of selected cytokines were categorized using their interquartile range distributions among the healthy controls. Overall, there were statistically significant dose-response relationships between IL-4, MIP-1β, FasL, TGF-β1, and risk of rectal polyps (Table 2, $P<0.05$). The strongest associations for IL-4, MIP-1β, FasL, and TGF-β1 were observed for the highest vs the lowest quartile with an OR of 1.78, 2.70, 1.49, and 2.36, respectively. However, we did not detect a significant dose-response relationship for the quartile distribution of RANTES.

Association between the consumption of Rg3 and risk of rectal polyps

As shown in Table 3, we evaluated the association between the consumption of Rg3 with risk of rectal polyps in both qualitative and quantitative models. Compared with non-Rg3 consumers, those who consumed Rg3 had significantly lower risk of rectal polyps (OR =0.71; 95% CI: 0.55–0.92; $P=0.009$). Further, we found a reversed dose-response relationship between frequency of Rg3 consumption and risk of rectal polyps (P for trend =0.015). Those who consumed Rg3 7–10 times/week had a 0.66-fold risk of rectal polyps

Table 3 Adjusted association between the consumption of Rg3 with susceptibility of rectal polyps

Regular consumption of Rg3	Cases	Controls	OR (95% CIs)*	P-value
Qualitative				
No	483	447	Reference	
Yes	117	153	0.71 (0.55–0.92)	0.009
Quantitative				
No	483	447	Reference	0.015
1–3 times/week	46	57	0.75 (0.50–1.13)	
4–7 times/week	39	51	0.71 (0.46–1.10)	
7–10 times/week	32	45	0.66 (0.41–1.05)	

Note: *Adjusted for family history of cancer, alcohol and smoking status.

(OR =0.66; 95% CI: 0.41–1.05), compared with non-Rg3 consumers.

Comparisons of selected cytokines between Rg3 consumers and non-Rg3 consumers in rectal polyp cases and healthy controls

Further, we also evaluated the effect of regular consumption of Rg3 on serum levels of IL-4, MIP-1β, FasL, TGF-β1, and RANTES. As shown in Table 4, we found that Rg3 consumers had significantly lower levels of IL-4, MIP-1β, FasL, and TGF-β1 than non-Rg3 consumers, in both rectal polyp cases and healthy controls.

Discussion

Based on the preliminary results identified by Johdi,[8] we evaluated the associations of profiling of selected cytokines, together with the regular consumption of ginsenoside Rg3 with risk of rectal polyps in a Chinese population. Significantly higher levels of IL-4, MIP-1β, FasL, TGF-β1, and RANTES were detected in rectal polyp cases. We also found significant dose-response relationships between quartile-categorized levels of IL-4, MIP-1β, FasL, TGF-β1, and

risk of rectal polyps. Compared with non-Rg3 consumers, Rg3 consumers had significantly lower risk of rectal polyps. We also found that Rg3 consumers had significantly lower levels of IL-4, MIP-1β, FasL, and TGF-β1 than non-Rg3 consumers, in both rectal polyp cases and healthy controls. These results indicate that regular consumption of Rg3 might prevent the occurrence of rectal polyps through decreasing the serum level of selected cytokines, including IL-4, MIP-1β, FasL, and TGF-β1.

Rg3 has a number of pharmacological effects, including inducing the apoptosis of tumor cells, promoting T lymphocyte mitosis and NK cell activity.[26] Wang et al[26] detected 43 differentially expressed genes, consisting of ten upregulated genes and 33 downregulated genes, in Rg3-consuming diabetic nephropathy patients. Saba et al[27] reported the anti-inflammatory activity of Rg3 in a murine model of sepsis through the NF-κB and MAPK pathways. Clinical benefit from EGFR-TKI plus Rg3 in patients with advanced non-small-cell lung cancer harboring EGFR active mutation was also identified.[22] Besides, Rg3 was also found to benefit the progression and prognosis of lung cancer, colorectal cancer, and hepatocellular carcinoma.[9,23,24,28] Consistent with these findings, we found that regular consumption of Rg3 could significantly reduce the risk of rectal

Table 4 Comparison of selected cytokines between Rg3 consumers and non-Rg3 consumers

	Rectal polyps cases (n=600)			Controls (n=600)		
	Rg3 consumers (n=117)	Non-Rg3 consumers (n=483)	P-value	Consumption of Rg3 (n=153)	No consumption of Rg3 (n=447)	P-value
IL-4 (pg/mL)	6.3±5.1	8.9±6.6	P<0.001	1.6±1.2	2.1±1.7	P<0.001
MIP-1β (pg/mL)	89.6±41.7	100.5±45.6	0.019	12.1±5.4	15.9±8.6	P<0.001
FasL (ng/mL)	1.23±0.87	1.54±0.96	0.001	0.20±0.17	0.25±0.18	0.003
TGF-β1 (ng/mL)	15.5±5.8	16.9±6.2	0.027	13.2±5.0	14.5±5.6	0.011
RANTES (ng/mL)	22.1±8.9	23.2±9.4	0.252	20.5±11.2	20.8±10.2	0.760

polyps. Furthermore, we also detected a reversed dose-response relationship between the quantity of regularly consumed Rg3 and risk of rectal polyps.

IL-4, MIP-1β, FasL, TGF-β1, and RANTES are important cytokines and are involved in the pathogenesis of many diseases, including cancers.[8,29,30] Our results validated the preliminary results identified by Johdi et al,[8] and found significantly higher levels of IL-4, MIP-1β, FasL, TGF-β1, and RANTES in rectal polyp cases, although we did not find a significant dose-response relationship between quartile-categorized level of RANTES and risk of rectal polyps. Eissa et al[31] found that RANTES was significantly increased in breast cancer cases with no metastasis compared to the control group ($p<0.05$) and a highly significant increase in metastatic patients compared to controls ($p<0.001$). Serum FasL level was also found to be associated with esophageal squamous cell carcinoma and follicular thyroid cancer.[32,33] Besides, we also found that Rg3 could significantly reduce the levels of IL-4, MIP-1β, FasL, and TGF-β1 in both rectal polyp cases and healthy controls. This also validated the anti-inflammatory activity of Rg3.

In conclusion, our findings indicate that aberrant expression of IL-4, MIP-1β, FasL, and TGF-β1 could contribute to the risk of rectal polyps, while regular consumption of Rg3 could significantly reduce the risk of rectal polyps with a reversed dose-response relationship in a Chinese population. Rg3 could also significantly reduce the levels of IL-4, MIP-1β, FasL, and TGF-β1 in both rectal polyp cases and healthy controls, which validated the anti-inflammatory activity of Rg3. Further clinical trials (for example, randomized controlled trials about the effect of Rg3 consumption on the level of selected cytokines and development of rectal polyps) and prospective cohort studies (comparing the changes in levels of selected cytokines and incidence of rectal polyps between the regular Rg3 consumption group and non-consumption group respectively) with larger sample sizes are warranted to validate the anti-inflammatory activity and the anti-tumorigenic role of Rg3.

Disclosure

The authors report no conflicts of interest in this work.

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