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Original Article / Özgün Araştırma

Effect of Tartrazine and Curcumin Intake on Serum Carcinoembryonic Antigen (CEA) and Stomach Histopathology in Rats

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Abstract

Objective: Food colorants are known to induce physiological and biochemical changes in tissues, raising concerns about their potential health effects. The purpose of this study was to assess tartrazine's effects and curcumin supplementation on stomach tissue and serum carcinoembryonic antigen (CEA) levels in rats.

Methods: Thirty-five male rats were randomly divided into five groups (n=7 per group) and treated via oral gavage for three weeks: Group 1 consisted of a control group, Group 2 of low-dose tartrazine, Group 3 of high-dose tartrazine, Group 4 of low-dose tartrazine + curcumin, and Group 5 of high-dose tartrazine + curcumin. Serum CEA levels were measured and stomach tissues were subjected to histopathological examination.

Results: Following tartrazine treatment, serum CEA levels were higher than in the control group; however, this difference was not of statistical significance ($p > 0.05$). CEA levels were somewhat lowered by co-administration of curcumin. When compared to the control, histopathological investigation showed that all tartrazine-treated groups had degenerated stomach tissues. Hyperkeratosis was notably increased in all experimental groups relative to the control group, with the most pronounced effect observed in Group 5 ($p < 0.001$). While hyperplasia in Group 2 did not differ significantly from the control ($p > 0.05$), Groups 3, 4, and 5 exhibited a statistically notable rise ($p < 0.05$).

Conclusion: These results show that tartrazine may induce dose-dependent histopathological alterations in stomach tissue, and curcumin may exert a modest protective effect.

Keywords: Carcinoembryonic antigen, stomach, tartrazine, curcumin, histopathology

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Ratlarda Tartrazin ve Kurkumin Alımının Serum Karsinoembriyonik Antijen (CEA) ve Mide Histopatolojisi Üzerine Etkisi

Öz

Amaç: Gıda renklendiricilerinin dokularda fizyolojik ve biyokimyasal değişikliklere neden olduğu bilinmekte olup, potansiyel sağlık etkileri konusunda endişelere yol açmaktadır. Bu çalışma, tartrazin ve kurkumin takviyesinin sıçanlarda mide dokusu ve serum karsinoembriyonik antijen (CEA) düzeyleri üzerindeki etkisini değerlendirmeyi amaçlamaktadır.

Yöntemler: Otuz beş erkek sıçan rastgele beş gruba ayrıldı (grup başına n=7) ve üç hafta boyunca oral gavaj yoluyla tedavi edildi: Grup 1 (kontrol), Grup 2 (düşük doz tartrazin), Grup 3 (yüksek doz tartrazin), Grup 4 (düşük doz tartrazin + kurkumin) ve Grup 5 (yüksek doz tartrazin + kurkumin). Serum CEA düzeyleri ölçüldü ve mide dokuları histopatolojik incelemeye tabi tutuldu.

Bulgular: Tartrazin uygulaması, kontrol grubuna kıyasla serum CEA seviyelerinin yükselmesine rağmen önemli bir istatistiksel fark tespit edilmedi ($p > 0,05$). Kurkumin ile birlikte uygulanması, CEA seviyelerinde kısmi bir azalmaya yol açtı. Histopatolojik analiz, tartrazin ile tedavi edilen tüm gruplarda kontrol grubuna kıyasla mide dokularında dejenerasyon olduğunu ortaya koydu. Hiperkeratoz, kontrol grubuna kıyasla tüm deney gruplarında anlamlı şekilde arttı ve en belirgin etki Grup 5'te gözlendi ($p < 0,001$). Grup 2'deki hiperplazi kontrolden anlamlı şekilde farklı olmasa da ($p > 0,05$), Grup 3, 4 ve 5 istatistiksel olarak anlamlı bir yükselme gösterdi ($p < 0,05$).

Sonuç: Bu bulgular tartrazinin mide dokusunda doza bağlı histopatolojik değişikliklere neden olabileceğini, kurkuminin ise orta düzeyde koruyucu etki gösterebileceğini düşündürmektedir.

Anahtar kelimeler: Karsinoembriyonik antijen, mide, tartrazin, kurkumin, histopatoloji.

INTRODUCTION

Tartrazine, sunset yellow, and carmoisine are examples of azo dyes frequently added to food products to boost the color, despite offering no nutritional value, preservative function, or health benefits. Synthetic azo dyes are frequently preferred by the food industry over natural colorants because of their broad availability, affordability, chemical stability, and capacity to produce vibrant hue without changing flavor profiles[1]. Among these, tartrazine is one of the most extensively used synthetic food dyes[2]. Its safety was last assessed by the European Food Safety Authority (EFSA) in 2009, which confirmed the previously established acceptable daily intake (ADI) of 0–7.5 mg/kg body weight per day. However, current data indicate that daily intake levels in children often exceed this threshold[3]. Studies have shown that excessive consumption of tartrazine may negatively impact digestive processes and disrupt enzymatic activity. While intake within the ADI range appears to pose no significant risk, high consumption—particularly among children—warrants careful regulation[4].

Numerous studies have reported severe toxic effects at doses not representative of typical human exposure through food. Nonetheless, such experimental approaches are necessary to support the design of robust clinical research and future trials[5].

Many experimental investigations have been carried out to lessen tartrazine's negative effects. In this context, the protective effects of various bioactive agents are being explored. Researchers have reported that curcumin alleviates the detrimental effects of tartrazine on chicken embryo development[6], riboflavin promotes the healing of gastric mucosa[7], onion juice reduces tartrazine-induced damage[8], and crocin counteracts tissue injury caused by tartrazine through its antioxidant and free radical scavenging properties[9]. In a number of studies, including those involving tartrazine-induced toxicity, curcumin, a polyphenolic

molecule produced from turmeric, has shown anti-inflammatory, antioxidant, and anti-apoptotic properties.

A non-specific serum biomarker called carcinoembryonic antigen (CEA) is raised in a number of cancer types, such as colorectal, medullary thyroid, breast, and mucinous ovarian tumors[10]. The biological activity and progression of stomach cancer are frequently evaluated using CEA and a number of other biomarkers[11]. The effects induced by tartrazine can be evaluated through histopathological analyses[12].

The study's hypothesis is to identify the food coloring tartrazine's potentially harmful effects on stomach tissue, assess curcumin's potential protective impact against these effects, and ascertain tartrazine's toxicity.

METHOD

This investigation was carried out using 35 mature Wistar albino male rats that weighed an average of 300–350 g. Experimental animals were kept in cages with temperature set at 22±2 °C, 37% relative humidity, and a 12-h light-dark cycle. A week was spent acclimating each group prior to the start of the trial. Figure I shows 5 experimental groups (seven rats/group). The control group (without any treatment) received 0.25 ml distilled water by gavage. Tartrazine (Sigma-Aldrich, CAS number 1934-21-0, Cl 19140, USA) and Curcumin (Sigma-Aldrich Chemie GmbH Curcuma longa, CAS Number: 458-37-7, USA) are two examples of similar products that are used in reference materials[13,14]. In our study, the experimental groups were organized as follows: Group 1: Control (0.25 mL distilled water); Group 2: 10 mg/kg/day tartrazine; Group 3: 100 mg/kg/day tartrazine; Group 4: 10 mg/kg/day tartrazine + 20 mg/kg/day curcumin; Group 5: 100 mg/kg/day tartrazine + 20 mg/kg/day curcumin. Oral gavage was used for all administrations, and the experimental protocol was followed for 21 days.

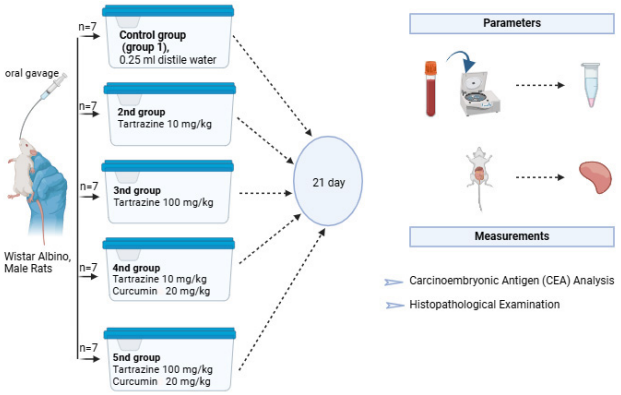

Figure I. The experimental protocol. Created with https://www.biorender.com/.

Biochemical parameters

Serum was extracted from intracardiac blood samples acquired under anesthesia.

Serums were stored under appropriate conditions until the time of analysis.

Carcinoembryonic antigen (CEA)

The serum samples obtained were tested by the Elisa method. BT-Lab (Shanghai, China), Cat No: E1625Ra kit was used. The microeliza method was used in the Biobase-BK-EL10C device.

Histopathological examination

Paraffin blocks were prepared from the stomach specimens after formalin fixation. 5 micron thick sections were obtained to be evaluated under light microscope. Hematoxylin and Eosin were used to stain the sections. To view sections of dyed stomach tissue, a binocular Olympus Cx43 light microscope (Olympus Inc.) was used. the parameters evaluated with their relevant scores in glandular and nonglandular stomachs were; nonglandular stomach hyperkeratosis (0=absent, 1=mild, 2=moderate, 3=severe), nonglandular stomach parakeratosis (0=absent, 1=focal, 2=extensive), nonglandular stomach hyperplasia (0=absent, 1=present, focal), presence of inflammation in nonglandular

stomach (0=absent, 1=present), interstitial inflammatory infiltration in nonglandular stomach (0=absent, 1=mild, 2=moderate, 3=extensive), nonglandular stomach metaplasia (0=absent, 1=focal, 2=extensive). Additionally, glandular stomach hyperplasia (0=absent, 1=present, focal), glandular stomach inflammation (0=absent, 1=present), glandular stomach interstitial inflammatory infiltration (0=absent, 1=mild, 2=moderate, 3=intense), glandular stomach atrophy (0=absent, 1=present), glandular stomach intestinal metaplasia (0=absent, 1=present), dysplastic lesions (0=absent, 1=mild dysplasia, 2=moderate dysplasia, 3=severe dysplasia), glandular dilatation (0=absent, 1=focal, 2=extensive), vascular congestion (0=absent, 1=focal, 2=extensive) were rated[15,16].

Statistical Analysis

Normality was assessed using the Shapiro-Wilk test. Tukey's post hoc analysis was performed after a one-way ANOVA. The obtained values were displayed as mean±SD. ANOVA was used in the statistical analysis, and the Student t-test was used to compare the paired groups. The significance threshold was established at $P<0.05$ using SPSS software 26.0.

RESULTS

Serum CEA measurement findings

The effect of curcumin on tartrazine exposure was designed in vivo. When the serum carcinoembryonic antigen level was contrasted with the control group, it was found to be low except in group 5. When the tartrazine groups were contrasted with the control group, it was determined that the serum carcinoembryonic antigen level increased, and when curcumin was added, the serum carcinoembryonic antigen level decreased. Table I shows that there was no discernible difference between the groups ($p>0.05$).

Table I: Serum carcinoembryonic antigen (CEA) levels of experimental groups

	Group 1	Group 2	Group 3	Group 4	Group 5	ANOVA
CEA (ng/mL)	1.36 ± 0.37	1.55 ± 0.39	1.47 ± 0.24	1.53 ± 0.30	1.34 ± 0.34	*Df: 4, F* = 0,585 *p= 0.676*

Anova variance analysis test was performed in statistical analysis (p > 0.05). (Mean ±SD).

Histopathological findings

Histological evaluation was performed for all groups. Histological evaluations are presented in Figure II. In Group 1 (a), findings compatible with normal stomach tissue (H&Ex40). In Group 2 (b), there is hyperkeratosis in the nonglandular gastric mucosa, hyperplasia and inflammation in the epithelium, and inflammation in the glandular gastric mucosa (H&Ex10). In Group 3 (c), there is glandular dilation and inflammation, and hyperkeratosis in the nonglandular gastric mucosa, with epithelial hyperplasia (H&Ex10). Group 4 (d) showed severe inflammation in the glandular gastric mucosa and moderate inflammation in the glandular gastric mucosa (H&Ex10). In Group 5 (e), severe inflammation and glandular dilation (H&Ex20) were observed in the glandular gastric mucosa. The "☆" symbol represents changes in the groups.

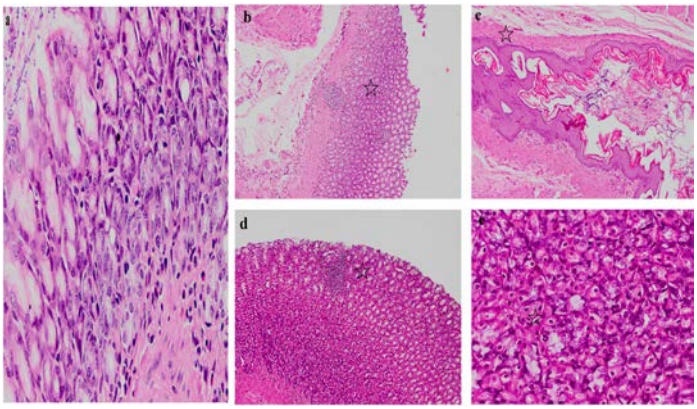

Figure II. Histomorphological evaluation of the study groups

Scoring analyses of parameters in the glandular stomach (hyperkeratosis, parakeratosis, hyperplasia, presence of inflammation, interstitial inflammatory infiltration, metaplasia) and nonglandular stomach (hyperplasia, presence of inflammation, interstitial inflammatory infiltration, atrophy, intestinal metaplasia, dysplastic lesion, glandular dilatation and vascular congestion) were performed for all groups. Statistical analysis was not performed because the parameters of parakeratosis, metaplasia, presence of inflammation, atrophy, intestinal metaplasia and dysplastic lesion did not have sufficient scoring in all groups. Among the remaining groups, a statistically significant score was found (p<0.001). As the tartrazine dose increased, hyperkeratosis, hyperplasia, presence of inflammation and interstitial inflammatory infiltration parameters were observed to increase degeneration in contrast to the control group. Table II shows the histopathological scoring findings of the stomach tissue.

Table II: Histopathological scoring of stomach tissue (mean±SD)

	Groups	Group 1	Group 2	Group 3	Group 4	Group 5	P*
Nonglandular Stomach	Hyperkeratosis	0.0±0,00^{a}	0.57±0,54^{b}	1.0±0,00^{b}	1.0±0,00^{b}	1.71±0,49^{c}	<0.001
	Hyperplasia	0.0±0,00^{a}	0.29±0,49^{a}	1.0±0,00^{b}	1.0±0,58^{b}	1.57±0,54^{b}	<0.001
	Presence of Inflammation	0.0±0,00^{a}	0.29±0,49^{a}	1.0±0,00^{b}	1.0±0,00^{b}	1.00±0,00^{b}	<0.001
	Interstitial Inflammatory Infiltration	0.0±0,00^{a}	0.29±0,49^{a}	1.0±0,00^{b}	1.29±0,49^{b}	1.00±0,00^{b}	<0.001
In the Glandular	Hyperplasia	0.0±0,00^{a}	0.00±0,00^{a}	0.0±0,00^{a}	0.86±0,38^{b}	1.43±0,54^{c}	<0.001
	Interstitial Inflammatory Infiltration	0.0±0,00^{a}	1.0±0,00^{b}	1.33±0,52^{b}	2.0±0,82^{b}	3.0±0,00^{c}	<0.001
	Glandular Dilatation	0.0±0,00^{a}	0.0±0,00^{a}	0.43±0,54^{a}	1.0±0,58^{b}	1.14±0,38^{b}	<0.001
	Vascular Congestion	0.0±0,00^{a}	0.0±0,00^{a}	0.33±0,52^{a}	0.86±0,38^{b}	1.0±0,00^{b}	<0.001

**: Anova variance analysis was performed in statistical analysis.*

A statistically important difference (P<0.05) is shown by distinct letters, while the same letters in the same row imply no statistically important difference.

DISCUSSION

The safety and effectiveness of artificial food additives, as well as their impacts on organisms, have been the subject of an increasing number of scientific research in recent years. However, an increasing incidence of symptoms such as diarrhea, skin irritation, gastrointestinal discomfort, vomiting, and elevated body temperature has been reported following exposure to food additives[17].

In comparison to the control group, the subjects who received low doses (10 mg/kg) and high doses (100 mg/kg) of tartrazine for 30 and 60 days had smaller organ weights, greater body weights, and higher levels of biochemical markers such as AST and ALT. However, when 50 mg/kg of curcumin was added to the same dose group, the serum levels decreased, and curcumin was found to have a protective effect[18]. It was observed that some biochemical parameters (ALT, AST, ALP etc.) were increased in rats administered tartrazine compared to the control group. Researchers have stated that tartrazine may affect biochemical markers in vital organs[19]. Carcinoembryonic antigen (CEA) is used in the diagnosis and follow-up of stomach cancer. This marker is frequently used in the detection of epithelial-based malignancies associated with the gastrointestinal system[20,21]. When literature findings were examined, studies conducted with tartrazine were examined. In studies analyzing the effect of tartrazine as a method, no studies were found measuring the carcinoembryonic antigen (CEA) parameter. In

addition, CEA is seen to be preferred more, especially in terms of cancer biomarkers. Our study investigates the effect of food colorants on stomach tissue in this respect. According to the results of our investigation, serum CEA levels rose in the low-dose (10 mg/kg) and high-dose (100 mg/kg) groups based on the dose when compared to the control group. This increase was somewhat mitigated by curcumin supplementation. These results suggest that stomach tissue may be significantly impacted by tartrazine exposure.

Rats given tartrazine at doses of 7.5 mg/kg, 15 mg/kg, and 100 mg/kg body weight for 30 days were compared to the control group. It was highlighted that tartrazine may lead to cytoarchitecture degradation in the kidneys, submandibular glands, and cerebellum, which could result in abnormalities in the organs' functional characteristics[22]. However, it was reported that it caused some histopathological changes in the liver and kidney tissue at lower tartrazine exposure for 90 days. As the tartrazine dose increased, the weight of the stomach tissue decreased compared to the control group. No significant change was detected in the sections taken from the stomach tissue[23]. In another study, it was observed that it caused DNA damage in the glandular stomach in a dose-dependent manner[24]. In rats that were orally administered 200 mg/kg/day of tartrazine for 60 days, the stomach tissue was affected, and riboflavin supplementation was associated with improvement in the stomach mucosa[7]. In a study investigating the effects of long-term use of tartrazine on the gastric mucosa of Wistar rats, it was reported that long-term exposure could inflame the stomach lining of rats and caused a significant increase in the number of lymphocytes and eosinophils in the gastric antrum mucosa[25]. It was reported that tartrazine (10 mg/kg) for eight weeks caused atrophy in the gastric glands with ulceration areas in the stomach tissue of rats in the experimental group[26]. Curcumin can reduce the number of apoptotic cells in the early stages with its anti-apoptotic properties[27]. Some studies have reported that curcumin reduces tartrazine-induced neurotoxic effects due to its antioxidant, anti-neuroinflammatory, and anti-apoptotic properties[28]. It has been observed that studies on the gastric dose of tartrazine are rare in the literature and that there are some contradictory reports. In the histopathological evaluations of our study, glandular and non-glandular inflammations, were observed in the sections of the gastric tissue. Scoring analyses were performed for many parameters in our study. Hyperkeratosis, hyperplasia, inflammation and interstitial inflammatory infiltration were detected with the increase in the tartrazine dose. However, contrary to the literature, it was observed that curcumin could not repair the damage caused by tartrazine in both our histopathological and scoring data.

CONCLUSION

In our study, the effect of tartrazine exposure on stomach tissue and histopathology was investigated. CEA, a cancer biomarker associated with gastric and other tissues, was also evaluated. To our knowledge, no prior studies have specifically examined whether tartrazine alters CEA levels, indicating a gap in the current literature. Our findings suggest that the dose-dependent increase in carcinoembryonic antigen (CEA) levels following tartrazine exposure may be indicative of adverse effects on stomach tissue and overall health. Although curcumin, known for its protective properties, was observed to mitigate these effects to some extent, its protective impact was relatively limited. It is particularly important to raise awareness among young individuals about the potential long-term consequences of frequent consumption of food products containing additives and synthetic colorants, as these may negatively affect gastric and other tissues. Further studies with more

detailed findings are warranted to better understand the possible effects of tartrazine on the stomach and the gastrointestinal system.

Ethics Committee Approval: All groups included in the study were conducted in accordance with the NIH general guidelines for the care and use of laboratory animals and with ethical permission from the Dicle University Health Sciences Research and Application Center Animal Experiments Local Ethics Committee (25/09/2024, Decision no: 03, Meeting no: 12).

Conflict of Interest: The authors declared no conflicts of interest.

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