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Investigating the potential effects of thymoquinone on cisplatin-induced nausea and vomiting

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ABSTRACT

Cisplatin is a powerful chemotherapy drug used to treat certain types of cancer. The effects of this drug, nausea and vomiting, can reduce patients' quality of life and make it difficult to continue treatment. Thymoquinone is known to act on the gastrointestinal system. However, its effect on nausea is not clear. This study investigated the effects of thymoquinone on cisplatin-induced nausea. Animals were divided into four groups (control, cisplatin, thymoquinone, and cisplatin+thymoquinone). Cisplatin was administered intraperitoneally and thymoquinone by gavage. The amount of food consumed by the animals was recorded. In addition, gastrointestinal tissues were examined by hematoxylin and eosin (H&E) staining. The data obtained suggest that cisplatin causes damage to the gastrointestinal tract. However, it is possible that thymoquinone may contribute to the healing of this damage. Therefore, the addition of thymoquinone to patients undergoing chemotherapy has the potential to increase the effectiveness of the treatment process.

Keywords: cisplatin, gastrointestinal system, pica, thymoquinone

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INTRODUCTION

Cisplatin (cis-dichlorodiammineplatinum) is a heavy metal compound that has shown antineoplastic activity in clinical and preclinical studies[1]. It is used in the clinic as an effective chemotherapeutic agent in many cancer treatments[2]. However, acute kidney injury, gastrointestinal problems, bleeding and a reduced immune response to infection are among the most common side effects observed[3]. Chemotherapy-induced nausea and vomiting (CINV) can cause a variety of adverse physical effects and significantly reduce the quality of life of patients undergoing chemotherapy. Persistent nausea and vomiting associated with CINV leads to serious physical complications such as dehydration, anorexia and unwanted weight loss[4]. Antiemetic agents are widely used to relieve this discomfort. Dopamine D2, histamine H1, serotonin 5HT3 (serotonin receptor), tachykinin NK1 receptor antagonists and corticosteroids among these agents are used as antiemetic prophylaxis and therapeutic in clinic[5,6].

Nigella sativa L. (Black cumin), a member of the Ranunculaceae family, is a fragrant herbaceous plant that blooms between April and August with blue and green flowers and grows to a height of about 60 cm[7,8]. Black cumin seeds are rich and diverse in chemical components; they contain amino acids, protein, carbohydrate, mixed and essential oils[7].This plant has been used by patients for gastrointestinal disorders such as abdominal pain, diarrhoea and flatulence[9] as an anti-carcinogenic[10,11] anti-inflammatory[12] and antioxidant[13]. In addition, black cumin oil has been reported to have various pharmacological effects such as antihistamine[14], antioxytocic[15], liver protector[16] and immune enhancer[17].

Most of the pharmacological activity in black cumin seed has been associated with the 'quinone' component. Chopra et al. (1956) discovered that Thymoquinone (TQ) is the main active component of the essential oil in black cumin[18]. Later, Houghton et al. (1995) reported that thymoquinone (TQ) is the main component of the essential oil[19]. TQ has attracted considerable scientific interest due to its high biological activity and low systemic toxicity, making it a promising alternative to classical therapeutic drugs[20]. Recent studies on TQ have shown that it has a protective effect against several free radical-generating compounds such as doxorubicin and carcinogenesis caused by different chemical compounds, diabetic neuropathy and membrane lipid peroxidation, and has anti-inflammatory and analgesic effects[21,22,23,24].

The gastro-protective mechanisms of TQ are to inhibit proton pumps, acid secretion and neutrophil infiltration while increasing mucus secretion and nitric oxide products[25]. Black cumin essential oil and TQ have been shown to have gastro-protective effects in relation with the maintenance of the redox

state in the gastric mucosa[26,27,28].

In this study, in order to evaluate the effect of TQ on cisplatin-induced nausea and vomiting in rats, the amount of kaolin consumption and animal weights were evaluated by applying the pica method. Gastrointestinal system tissues were also examined histologically.

METHODOLOGY

This study was conducted at Necmettin Erbakan University KONÜDAM Experimental Medicine Research and Application Centre and KTO Karatay University Faculty of Medicine Histology/Pathology Laboratory. The study protocol was approved by Necmettin Erbakan University KONÜDAM Experimental Medicine Research and Application Centre Animal Experiments Ethics Committee (2021-040) and adult female *Wistar albino* rats weighing 180-220 g obtained from the same unit were used.

Rats were housed under standard laboratory conditions (22-23°C ambient temperature, 50% humidity and 12-hour light/dark cycle). Water and food were provided during the experiment. The rats were kept in standard cages until the day of application, and after the experimental groups were formed and the applications were performed, they were taken to individual cages, and the experimental procedure was carried out.

Preparation of kaolin

Kaolin was prepared according to a previously described method[29]. Kaolin (ZAG Kimya, Cas No: 1332-58-7) was mixed with acacia gum (Sigma-Aldrich, Cas No: 9000-01-5) in a ratio of 99:1. It was then mixed with distilled water to form a paste and allowed to dry at room temperature for 72 hours.

Experimental procedure

All animals were subjected to a 3-day adaptation period before the start of the experiment. During this period, animals were housed in separate cages to provide access to both normal food and kaolin and experimental groups were formed. A total of 28 rats were used, 7 animals in each group.

Group 1; Control: No treatment was given to the animals in this group.

Group 2; Cisplatin (CIS): In this group, cisplatin [Koçak Farma (50mg/100mL concentrated solution for infusion)] was administered intraperitoneally (i.p) at a dose of 6mg/kg[30].

Group 3; Thymoquinone (TQ): Thymoquinone (Sigma-Aldrich) at a dose of 1.5 mg/kg was administered to the animals in this group by gavage[31].

Group 4; Cisplatin + Thymoquinone (CIS + TQ): In this group, 6 mg/kg dose of cisplatin was administered intraperitoneally and then 1.5 mg/kg dose of Thymoquinone was given by gavage[30,31].

No irritation, restlessness or other adverse effects (e.g. respiratory distress, abnormal movement or catalepsy) were detected in rats following i.p. administration. The amount of kaolin consumption was noted 12-24 h after administration to the animals in accordance with experimental groups[32]. To measure kaolin and food intake, the remaining kaolin and food, including those spilled out of the containers, were collected and kaolin intake, food intake and body weight of the animals were noted on each experimental day. After administration, animals were decapitated, and gastrointestinal tract tissues were placed in 10% buffered formalin solution for histopathological evaluation.

Histopathological examination

After fixation in 10% formalin solution for 48 hours, the tissues were passed through graded alcohol (70, 80, 90, 100%) and xylol (Xylene I, II) series for one hour and routine tissue follow-up procedures were performed. Then, 3µm thick sections were taken from the paraffin blocked samples on slides using a rotary microtome (Leica DSC2). The sections were freed from paraffin. The sections were stained with hematoxylin and eosin (H&E). H&E-stained slides were examined under a light microscope (Olympus SC50) and images were taken.

Statistical analysis

Statistical interpretation of the results was performed using the SPSS 22.0 computer package program, and arithmetic means and standard errors of all parameters were calculated. “The Shapiro-Wilk test was performed to determine the homogeneity of the data and it was found that the data had a normal distribution.” One-way analysis of variance (ANOVA) test was used to determine the difference between groups, and Tukey’s test, one of the multiple comparison tests, was used to determine which group the differences originated from. Differences at the $p<0.05$ level was considered significant.

RESULTS and DISCUSSION

Animal weight and kaolin consumption results

According to statistical analyses of animal weights taken at the beginning and end of the experiment, there was no change in the weights of the control and thymoquinone groups. However, CIS and Animal weights decreased in the CIS+TQ group, and this decrease was the highest in the CIS group and significant differences were observed between the groups ($p\leq0.05$) (Figure 1).

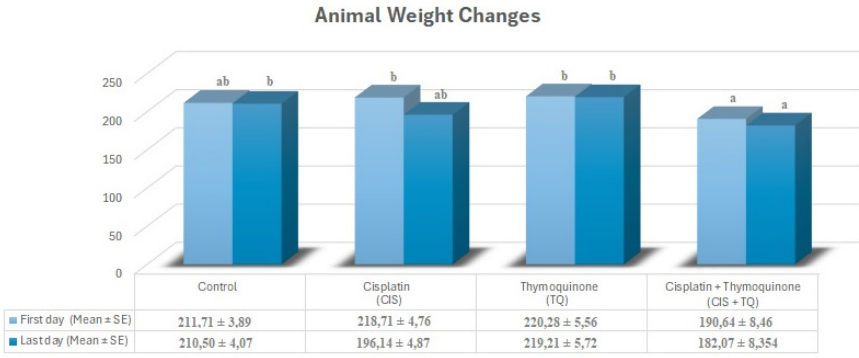

Figure 1. Animal weight changes (there was a significant difference between groups in the same column and carrying different letters [p<0.05]).

After application, the kaolin was left in the cages and the total amount of kaolin consumed was determined. According to the data obtained as a result of statistical analyses, it was determined that the highest kaolin consumption among the experimental groups was in the CIS group. The difference between the groups was found to be significant (p≤0.05) (Figure 2).

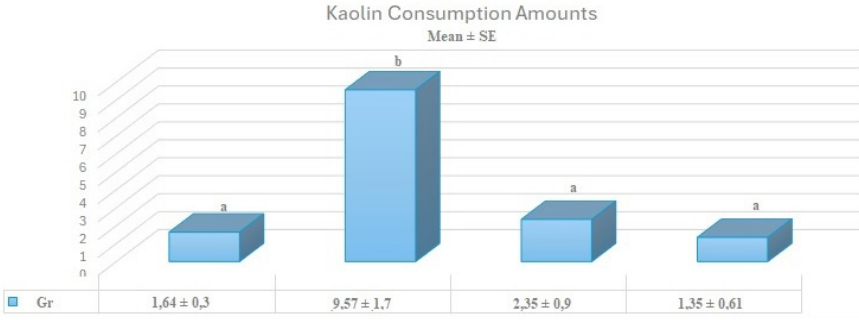

Figure 2. Kaolin consumption amounts (there was a significant difference between groups in the same column and carrying different letters [p<0.05]).

Histopathological results

The gastrointestinal tract tissues obtained after decapitation were histopathologically evaluated by H&E staining. In the control group and TQ group rats, the oesophagus showed normal histological structure; the mucosa, submucosa, which is the layer under the mucosa, and muscularis layer showed normal structure. In the CIS group, cisplatin caused damage in the oesophagus. Hyperkeratisation, degeneration and desquamation were observed in the mucosa. No significant difference was observed in the submucosa and muscularis layer. In the CIS+TQ group, no significant reduction in cisplatin-induced mucosal damage was observed (Figure 3).

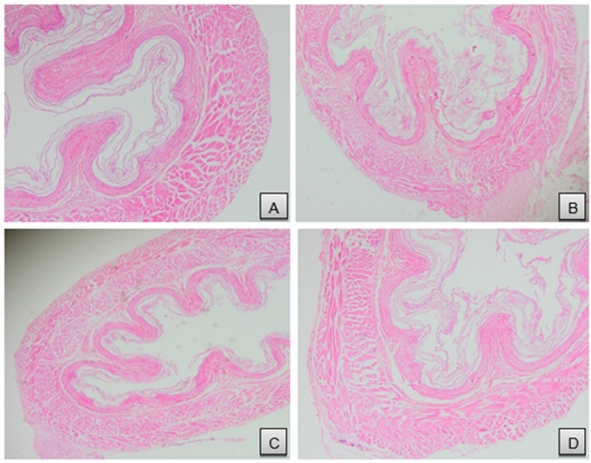

Figure 3. Esophageal histopathology x4. A: Control, B: CIS, C: TQ, D: CIS+TQ

When the histological structure of non-glandular anterior stomach was evaluated in control group rats, muscularis, submucosa and mucosa showed normal histological structure. Mucosa epithelium showed normal keratinisation. In rats given CIS, there was damage similar to the oesophagus structure. Hyperkeratosis, which is a thickening of the multilayered keratinized epithelial layer of the mucosa, was observed to be increased. Only in TQ group, keratinisation similar to the control group was observed. In CIS+TQ, there was no significant decrease in the hyperkeratosis caused by CIS (Figure 4).

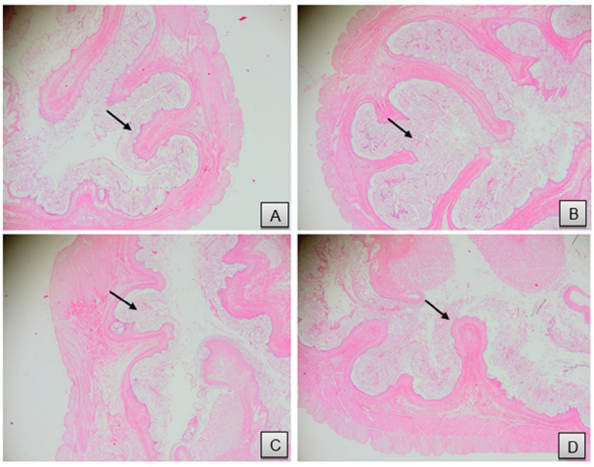

Figure 4. Histopathology of the stomach (non-glandular anterior stomach). Arrows point to squamous keratinized epithelium x4. A: Control, B: CIS, C: TQ, D: CIS+TQ H&E.

In control group rats, the stomach showed normal histological structure. The epithelium forming the mucosa of the fundic stomach and the gastric (fundic) glands in the lamina propria underneath showed normal histological structure. Submucosa and muscularis layer showed normal structure. The most prominent difference in the CIS group rats was cellular infiltration in the submucosa layer of the mucosa. There are also degenerations in the mucosal epithelial cells. The structure of the fundic glands shows a histological structure similar to the control group. TQ group showed normal histopathological structure. In the treatment group CIS+TQ, cellular infiltration and epithelial degeneration decreased (Figure 5).

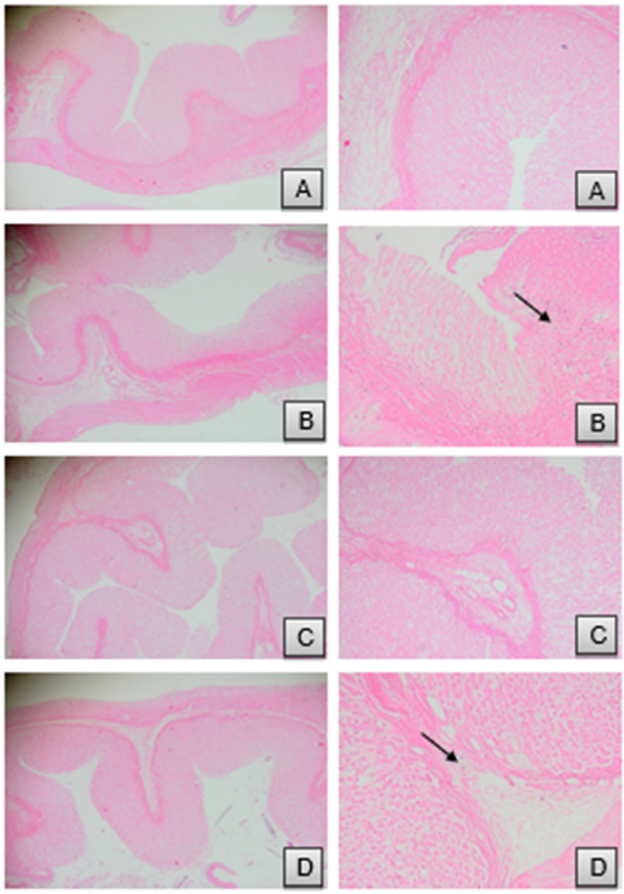

Figure 5. Histopathology of the stomach (fundus) x10. A: Control, B: CIS, C: TQ, D: CIS+TQ. (Arrows point to inflammatory cells). General image x4, close-up, H&E.

Small intestine of control rats showed normal histological structure. No histopathological changes were observed in the TQ group. Damage to the normal mucosa architecture was evident in rats given CIS. Degeneration and desquamation were observed at the ends of intestinal villi. Atrophic villi, wide cell spaces and cell atrophy were observed in the lamina propria. There was decreased fibrous content in the muscularis mucosa layer. In TQ+CIS group, thymoquinone decreased cisplatin-induced mucosal damage in the intestine, although it had no significant effect. In the muscularis mucosa, CIS-induced damage was significantly improved (Figure 6).

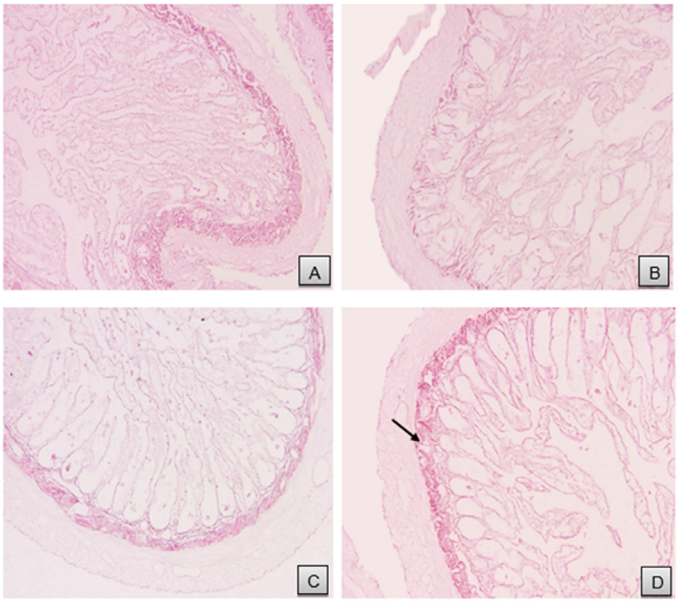

Figure 6. Small bowel histopathology x10. A: Control, B: CIS, C: TQ, D: CIS+TQ.

In control rats, the cecum showed normal histological structure. No adverse histopathological changes were observed in the TQ group. Cisplatin slightly damaged the cecal architecture. Thinning (decreased fibrous content) was observed in the muscularis externa layer. In the TQ+CIS group, mild damage to the cecal architecture continued, but the muscularis layer showed normal histological structure (Figure 7).

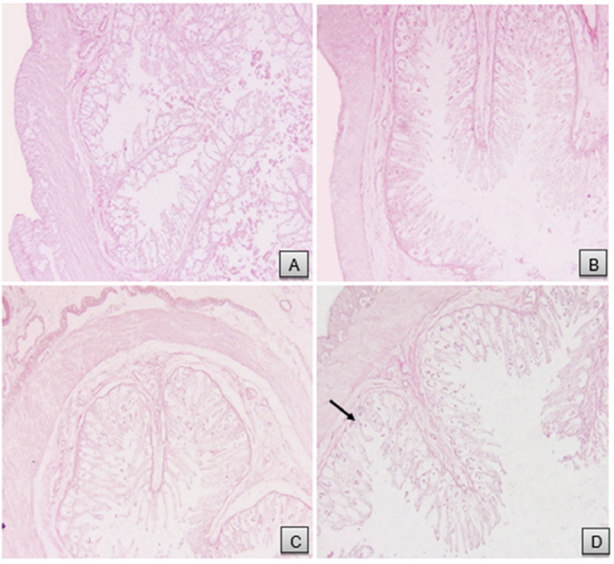

Figure 7. Histopathology of cecum x10. A: Control, B: CIS, C: TQ, D: CIS+TQ.

Histopathological evaluation revealed no severe degenerative changes in the architecture of the large intestine in the CIS group compared to the control group and the TQ group. This was the same in the CIS+TQ group (Figure 8).

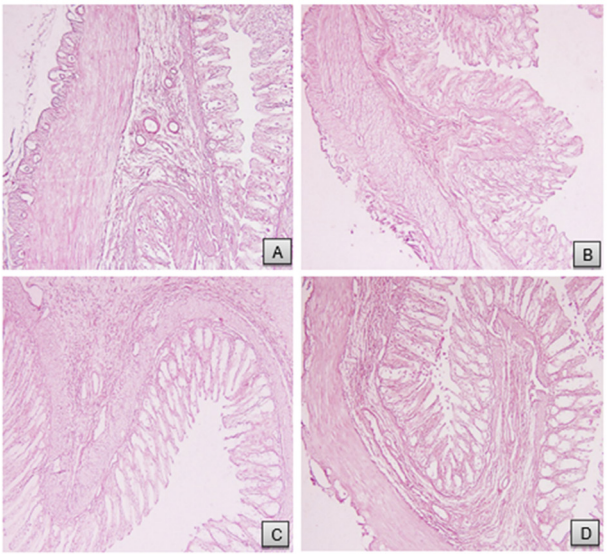

Figure 8. Large intestine histopathology x10. A: Control, B: CIS, C: TQ, D: CIS+TQ.

RESULTS and DISCUSSION

In this study, we observed that TQ reduced kaolin intake (pica) in cisplatin-treated rats and may partially contribute to gastrointestinal tract damage.

Various animal models have been used to evaluate emetic and antiemetic compounds[33,34,35]. Although these models have advantages such as cost and ease of animal handling, they also have limiting factors such as the absence of an emesis centre and the inability to demonstrate the vomiting reflex[36]. Although not through vomiting, the rat model responds to the effects of various stimuli that cause vomiting such as cisplatin, morphine, simulated motion sickness and radiation in a manner consistent with pica[37-39]. Cabezos et al. (2010) found that gastric motility was exacerbated in parallel with the increase in pica with chronic administration of cisplatin in mice. In addition, these researchers found that one week after the end of the treatment, no signs of gastric motility disorder remained, but basal kaolin intake was still higher than rats in control group[40]. Another study to investigate the effect of Xiao-Ban-Xia decoction (XBXD) on chemotherapy-induced nausea and vomiting (CINV) using rat pica model, parameters such as kaolin consumption, food intake and body weight were monitored after cisplatin administration and suggested that XBXD could be considered as a potential therapeutic agent in the treatment of CINV[41].

In this study, induction of pica in the first 24 hours following cisplatin (6 mg/kg, i.p.) in rats is consistent with previous studies using doses in the same range[37,40,41,42]. In addition, we concluded that the decrease in pica and simultaneous improvement in food intake in the group treated with CIS and then treated with TQ, and the reflection of this situation on animal weights showed the anti-nausea/antiemetic effect of TQ.

Low doses (≤3.5 mg/kg bwt) of CP treatment have been reported to cause villus atrophy but not affect crypt depth, thus reducing the villus-to-crypt ratio by approximately 47%. However, studies performed at higher doses (≥6 mg/kgwt) also revealed that CP caused disruption of mucosal glandular architecture, cryptablation, intense inflammatory cell infiltration in mucosal and submucosal layers, formation of crypt abscess, villus degeneration, decrease in villous density (rarefaction) and reduced villous height, enterocyte damage, nuclear crowding, cytoplasmic vacuolation[43-45]. Sathyanath et al. (2013) administered saponin and non-saponin obtained from the fractions of red ginseng before a single dose of intraperitoneal cisplatin (6 mg/kg) injection (-48, -24 and 0 h) and showed that it caused degenerative changes in the stomach (glandular region) and small intestine, mainly in the mucus-secreting cells and intestinal epithelium on the villi, with enlargement of intercellular spaces and disruption

of the epithelial structure[45]. The results of this study report that both red ginseng saponin and non-saponin improve feeding behavior against CP-induced pica in rats. Another group of investigators evaluated cisplatin-induced pathological changes in the GI tract using H&E staining and showed that Xiao-Ban-Xia-Tang decoction (XBXT), an antiemetic formula, can improve cisplatin-induced gastrointestinal tract damage and inflammatory response after 72 hours of model creation[46]. In parallel with the above-mentioned studies, in this study, we showed that cisplatin caused inflammatory damage in the GI tract, but TQ administration helped to ameliorate this damage.

In conclusion, this is the first study in which the effects of TQ on nausea and vomiting were investigated by pica method and histopathological examination of the gastrointestinal tract. The obtained findings contribute to the elucidation of the comprehensive mechanisms of TQ effect in CIS-induced pica, but further investigations are needed.

STATEMENT OF ETHICS

The study protocol was approved by Konya Necmettin Erbakan University Experimental Medicine Research and Application Center Laboratory Animals Ethics Board (No: 2021-040).

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Motivation / Concept: Elif Gulbahce-Mutlu, Ayse Nur Yildiz,

Design: Elif Gulbahce-Mutlu, Ayse Nur Yildiz,

Control/Supervision: Elif Gulbahce-Mutlu, Serife Alpa,

Data Collection and/or Processing: Elif Gulbahce-Mutlu, Ayse Nur Yildiz, Serife Alpa, Fatma Nur Türkoglu, Hatice Nur Seflek,

Analysis and/or Interpretation: Elif Gulbahce-Mutlu, Serife Alpa, Hatice Nur Seflek,

Literature Review: Elif Gulbahce-Mutlu, Ayse Nur Yildiz, Fatma Nur Türkoglu, Zeynep Nur Akyar,

Writing the Article: Elif Gulbahce-Mutlu, Serife Alpa, Fatma Nur Türkoglu, Hatice Nur Seflek,

Critical Review: Elif Gulbahce-Mutlu, Ayse Nur Yildiz, Serife Alpa, Fatma Nur Türkoglu, Hatice Nur Seflek, Zeynep Nur Akyar.

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