EXPERIMENTAL STUDY

Co-administration of cisplatin and curcumin does not alter mood-associated behaviors

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ABSTRACT

OBJECTIVES: Cisplatin (cis-diamminedichloroplatinum (II)) is a widely-used platinum-based chemotherapeutic agent which has dose-limiting side-effects. Also, the drug resistance is another instance that decreases treatment success in cisplatin chemotherapy. The growing body of evidence suggests that curcumin, a polyphenolic compound extracted from the spice turmeric, may exert synergistic effects and sensitize malign cells to cisplatin, while alleviating cytotoxicity-related side-effects. The present study was aimed to investigate mood-associated interactions between cisplatin and curcumin.

MATERIALS AND METHODS: Thirty-four adult male Wistar albino rats were randomly assigned to four groups as control, curcumin (300 mg/kg/day, p.o. for 5 weeks), cisplatin (5 mg/kg/week, i.p. for 5 weeks), and curcumin plus cisplatin (same doses as above). The open field, elevated plus maze, and forced swim tests were engaged to evaluate mood-associated behaviors.

RESULTS: We demonstrated that depression- and anxiety-like behaviors were not altered by the administration of curcumin along with the chronic cisplatin treatment.

CONCLUSION: According to the results of the present study, we concluded that curcumin might be regarded as a safe adjuvant in cisplatin chemotherapy in terms of the mood-associated behaviors *(Fig. 4, Ref. 41)*. Text in PDF *www.elis.sk*.

KEY WORDS: cisplatin, curcumin, depression, anxiety; locomotion, exploration.

Introduction

Chemotherapy is the prominent strategy against numerous malignancies. Cisplatin (cis-diamminedichloroplatinum (II)) is an alkylating platinum-based chemotherapeutic agent which is used in patients with solid tumors, including lung, ovary, testis, bladder, endometrium, and head and neck (Albers et al, 2007). Cisplatin interacts with intracellular structures such as proteins, DNA, RNA, membrane phospholipids, cytoskeletal filaments, and thiol-containing molecules. Hence, its antineoplastic activity emerges from the suspension of the cell cycle, induction of apoptosis and necrosis, destabilization of the biological membranes, disruption of the energy metabolism, and generation of reactive oxygen molecules (Macciò and Madeddu 2013). As a result of its target width, it has several side-effects, particularly nephrotoxicity, ototoxicity, and neurotoxicity, that can hinder reaching the effec-

tive dosage and indeed, lead to cessation of the therapy. Cisplatin is predominantly excreted by glomerular filtration and renal accumulation of the drug drives nephrotoxicity (Peres and da Cunha, Jr 2013; Yilmaz et al, 2004; Ozyurt et al, 2004). Although pathogenesis of neurotoxicity is more obscure, oxidative stress (Pace et al, 2003; Bhadri et al, 2013), and mitochondrial (Podratz et al, 2011) and nuclear DNA damage (McDonald et al, 2005; Ta et al, 2006) are entwined factors, which are attributed to the peripheral neurotoxic effects of cisplatin.

There is a long effort to discover adjuvant treatments to limit side-effects of chemotherapeutics, and emerging evidences suggest that curcumin, a polyphenolic antioxidant compound, alleviates abovementioned side-effects of cisplatin (Mendonça et al, 2013; Ueki et al, 2013; Fetoni et al, 2014; Salehi et al, 2014). Curcumin is the active ingredient of the spice turmeric and is used in traditional Eastern medicine for centuries (Noorafshan and Ashkani-Esfahani 2013). Previous studies have shown that it has also health-beneficial effects against stroke (Jiang et al, 2007), neurodegeneration (Cole et al, 2007), inflammation (Chainani-Wu 2003), and autoimmunity (Srivastava et al, 2011). In terms of chemotherapy, curcumin attenuates morphological and biochemical alterations such as peripheral nerve demyelination (Al Moundhri et al, 2013), neurite outgrowth inhibition (Mendonça et al, 2013), and oxidative stress (Waseem and Parvez 2013), which are seen in cisplatin chemotherapy. Additionally, several authors reported that this polyphenolic compound sensitizes malign cells to cispla-

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tin and exerts a synergistic role with it (Duarte et al, 2010; Tsai et al, 2011; Nessa et al, 2012; Chen et al, 2014; Roy and Mukherjee 2014; Wang et al, 2014).

Despite the additive features of curcumin in cisplatin chemotherapy, we are not aware of any study about their compatibility regarding mood-associated behaviors, and thus, in the present study, we aimed to investigate effects of the chronic co-administration of cisplatin and curcumin in a rat model to anticipate behavioral consequences of future curcumin containing cisplatin regimens.

Materials and methods

Animals

Thirty-four adult male rats (10–12 weeks old, 330±20 g) were obtained from the Necmettin Erbakan University Experimental Medicine and Administration Center (Konya, Turkey). The animals were housed in climate-controlled rooms (20±2 °C temperature, 50±10 % humidity) with '12-hour' light/dark cycle and had free access to tap water and rat chow. All experimental procedures were conducted with the approval of the Local Ethics and Animal Care Committee of Necmettin Erbakan University (2013/14-177/030), in accordance with the National Institute of Health Guide for Care and Use of Laboratory Animals (Publication No. 86-23, revised 1996)

Experimental procedure

Cisplatin (St. Louis, MO, USA), dissolved in 0.9 % saline, was intraperitoneally injected in a dose of 5 mg/kg/week for 5 weeks and curcumin (St. Louis, MO, USA), suspended in corn oil, was orally administered in a dose of 300 mg/kg/day for 5 weeks. Both were prepared freshly before usage. The animals were randomly divided into four groups as follow: Control (n = 7; received 0.9 % saline once per week intraperitoneally and oral corn oil once a day), Curcumin (n = 7; received 300 mg/kg/day, p.o. curcumin), Cisplatin (n = 10; received 5 mg/kg/week, i.p. cisplatin), and Curcumin plus Cisplatin (n = 10; received 5 mg/kg/week, i.p. cisplatin and 300 mg/kg/day, p.o. curcumin) groups. The animal care was undertaken by the researcher, who carried on the behavioral experiments. All behavioral experiments were performed between 0900–1500 h.

Forced Swim Test

The test was done similarly to the method described by Caletti et al (2012) with minor modifications. The forced swim test (FST) consisted of a training session (15 min), followed 24-h later by a test session (5 min). Briefly, the rats were placed into cylindrical Plexiglas pools (25 x 60 cm) containing 35 cm of water at 25 ± 1 °C temperature. In the training session, the animals were left to swim freely, while in the test session, behaviors of the rats were video-recorded for ethological analyses. A highly-trained observer, who was blind to the experimental groups, evaluated immobility, swimming, climbing, diving, and head-shaking behaviors. Immobility was defined as movements necessary to keep the head above water. Active swimming movements in an attempt to escape were accepted as swimming. Climbing was considered as upward

movements with forepaws directed against the wall. Diving was defined as movements of swimming submerged. The twitching movements of the head were noted as head-shaking. The cylinders were emptied and carefully cleaned between animals. Movement scoring was done from recorded videos by using computer software (BORIS v.1.64, Life Sciences and Systems Biology Via dell'Accademia Albertina, Torino, Italy). Intra-rater reliability was found to be ICC = 0.91 (95 % CI: 0.58 – 0.98).

Open Field Test

Locomotion, exploratory activity, and anxiety-like behaviors were assessed with the open field test (OFT). Briefly, each animal was placed to the center of a black-painted open field apparatus (80 x 80 x 40 cm) and allowed to explore it for 5 min. The total distance traveled, velocity, and time spent at the center were automatically quantified by using a computer software (EthoVision XT v.8.0, Noldus Information Tech., Wageningen, Netherlands). The numbers of rearing, grooming, and defecations were manually scored by the researcher during test. The apparatus was carefully cleaned between animals to exclude odor-related behavioral effects.

Elevated Plus Maze Test

The elevated plus maze test (EPM) was performed immediately after the OFT in a cross-shaped maze with an open top, which is consisted of two open arms (50 x 10 cm), two closed arms (50 x
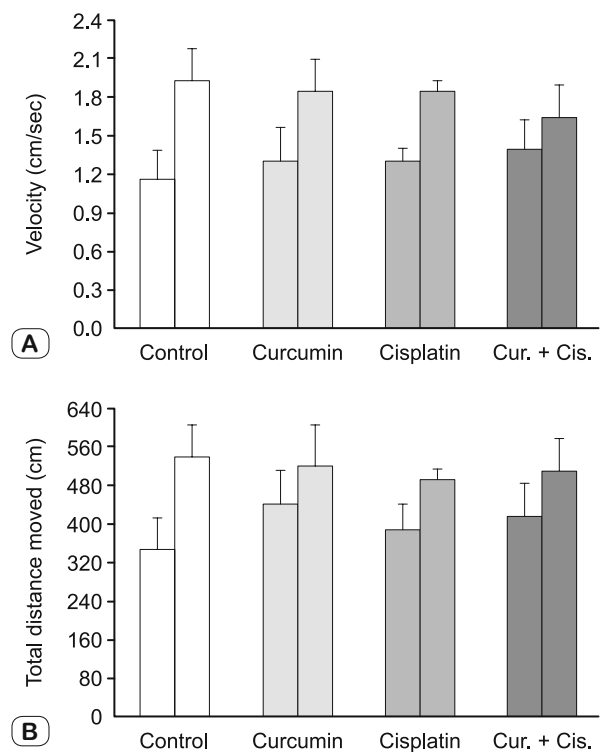
Fig. 1. Locomotion-related behaviors in the EPM (left bars) and OFT (right bars). The administration of cisplatin, curcumin, or curcumin plus cisplatin did not change the velocity (A) and total distance moved (B) in both tests. Data represented as the mean ± SEM. Cur. + Cis.; curcumin plus cisplatin.
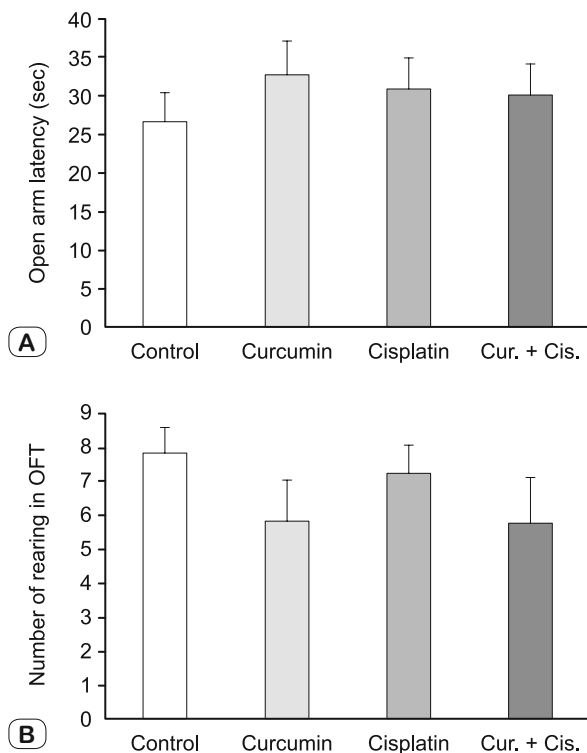
Fig. 2. Explorative behaviors in the EPM and OFT. None of the treatments altered the open arm latency (A) and number of rearing (B). Data represented as the mean ± SEM. Cur. + Cis.; curcumin plus cisplatin.

Fig. 3. Depression-like behaviors in the FST. The number of head-shaking (A), climbing time (B), and immobility time (C) were affected by neither treatment. Data represented as the mean ± SEM. Cur. + Cis.; curcumin plus cisplatin.

10 cm), and a central square (10 x 10 cm). The maze was elevated 50 cm from the floor. Each rat was placed on the central square facing an open arm and allowed to freely explore the maze for 5 min. The total distance traveled, velocity, latency to enter the open arms, and time spent in the closed arms were automatically evaluated by using the computer software (EthoVision XT v.8.0, Noldus Information Tech., Wageningen, Netherlands).
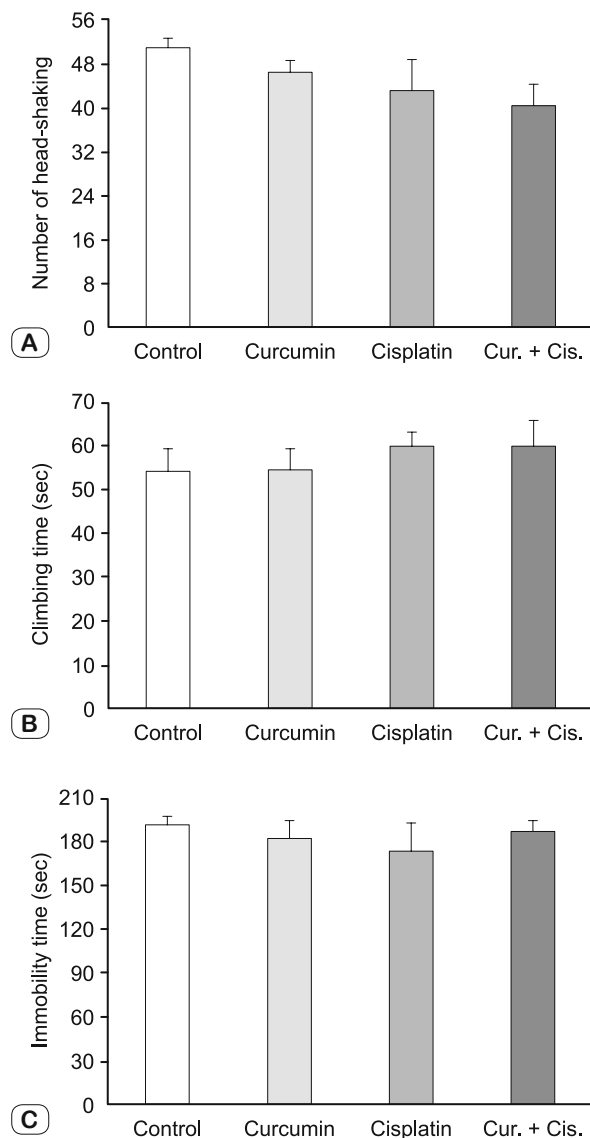
Statistical analyses

The data were analyzed by the one-way ANOVA test for inter-group comparisons and two-tailed Student's t-test for comparisons with the controls. The statistical significance was set to $p < 0.05$. The analyses were performed using the GraphPad Prism v.6.0 (GraphPad software Inc, California, USA).

Results

Locomotion-related behavior

As indicated in the Figure 1A and B, the velocity and total distance moved, measured in the EPM, were significantly different in neither cisplatin- nor curcumin-treated animals as compared to the controls ($p = 0.55$ and $p = 0.36$; Student's t-test), similarly to that in the OFT ($p = 0.76$ and $p = 0.46$; Student's t-test). Nor did the co-administration of cisplatin and curcumin change the locomotion-related behaviors in the EPM and OFT ($p > 0.05$;

one-way ANOVA). There was no difference between the animals that were treated with only cisplatin and curcumin plus cisplatin in both behavioral tests ($p > 0.05$; one-way ANOVA).

Exploratory behavior

The administration of curcumin or cisplatin did not change the latency to enter open arms in the EPM ($p = 0.35$ and $p = 0.51$; Student's t-test) and the number of rearings in the OFT ($p = 0.18$ and $p = 0.63$; Student's t-test). Although the co-administration of cisplatin and curcumin decreased the rearing behavior in the OFT, and not the latency to enter open arms in the EPM ($p = 0.60$; Student's t-test), it did not reach a statistically significant level ($p = 0.24$; Student's t-test) (Fig. 2A). As shown in the Figure 2B, the

animals which received curcumin plus cisplatin displayed the number of rearings similar to the ones that were treated only with curcumin (p > 0.05; one-way ANOVA).

Depression-like behavior

As represented in the Figure 3A, the animals with curcumin plus cisplatin showed the lowest number of head-shaking behavior; however, the differences between the groups were not in the boundary of the statistical significance (p > 0.05; one-way ANOVA). The diving behavior had a rare occurrence in all groups and neither treatment did change it (data not showed). The cisplatin and cisplatin plus curcumin groups exhibited a slightly longer climbing behavior which was not significant as compared to the controls (p = 0.36 and p = 0.48; Student's t-test) (Fig. 3B). The total time spent in an immobile posture was determined and the results showed that there was no difference between the experimental groups (p > 0.05; one-way ANOVA) (Fig. 3C).
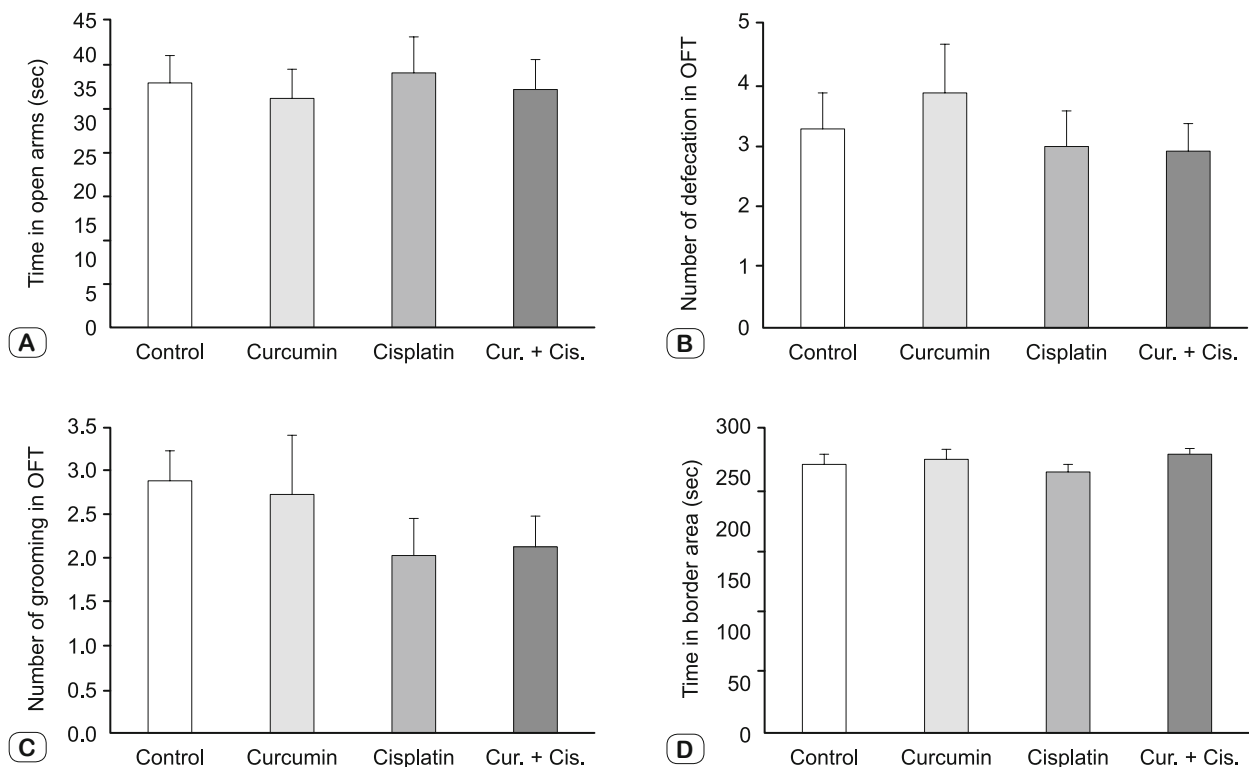
Anxiety-like behavior

The cisplatin group passed time akin to that in animals with curcumin plus cisplatin in the open arms of the EPM (Fig. 4A) and the results of the experimental groups were not statistically different (p > 0.05; one-way ANOVA). The curcumin group had the highest number of defecations (Fig. 4B), although the parameter did not reach to the level of significance with any of the

treatments (p > 0.05; one-way ANOVA). The administration of cisplatin or curcumin plus cisplatin produced similar numbers of the grooming behavior during the OFT (Fig. 4C) and there was no difference between the curcumin, cisplatin, or curcumin plus cisplatin groups and controls (p = 0.84, p = 0.16, and p = 0.15; Student's t-test). As denoted in the Figure 4D, the time spent in the border area was quite similar in all groups and no change was found with curcumin, cisplatin, or curcumin plus cisplatin treatments (p > 0.05; one-way ANOVA).

Discussion

Chemotherapeutics generally bear neurological side effects that range from moderate to severe. Among the chemotherapeutics, which are used against solid tumors, cisplatin is a widely preferred alkylating agent. Although the action mechanism is not definitely apparent, cisplatin chemotherapy is strongly associated with neurotoxicity, especially on the peripheral nerves, which is one of the main limiting factor for treatment adherence (Friesland et al, 2014). The dorsal root ganglion occurs out of the blood-brain barrier (BBB), and hence, it is highly vulnerable to the neurotoxic effects of cisplatin. On the other side, the brain is protected by the BBB against hydrophilic molecules such as cisplatin. Even though cisplatin cannot readily pass across the BBB, the medical literature suggests somewhat penetration in certain

Fig. 4. Anxiety-like behaviors in the EPM and OFT. The administration of cisplatin, curcumin, or curcumin plus cisplatin did not change the time spent in open arms of the EPM (A), number of defecations (B), number of grooming (C), and time spent in border area of the OFT (D). Data represented as the mean ± SEM. Cur. + Cis.; curcumin plus cisplatin.

circumstances. The abnormal vascularization of brain tumors permits cisplatin to pass the BBB and to accumulate in peritumoral tissue (Stewart et al, 1982). Also, cisplatin has been identified in several brain areas such as cortex, thalamus, hypothalamus, and olfactory bulbus under hypoxic conditions whereas only in olfactory bulbus in normoxic atmosphere (Minami et al, 1996). Additionally, several authors reported some neurochemical disturbances with cisplatin treatment in the brain of healthy animals which did not carry any secondary pathologies such as tumor, sepsis, hypoxia, hyperthermia, *et cetera*. To illustrate, Turan et al (2014) showed an alteration of the redox balance in favor of oxidation, while Gulec et al (2013) demonstrated that cisplatin triggers the oxidative stress in the brain tissue of adult rats. Likewise, Özyurt et al (2006) stated that the enzymatic activities in the brain, including hexokinase, glucose-6-phosphate dehydrogenase, lactate dehydrogenase, and malate dehydrogenase, were disturbed following the cisplatin treatment. Nevertheless, it can be assumed that the systemic adverse effects of cisplatin, as being a highly potent cytotoxic agent, can easily generate reactive oxygen species which pass across the BBB to impair the brain physiology, and hence, cisplatin should not necessarily penetrate to the brain tissue to create mentioned alterations.

In patients with malignancies, depression and anxiety are common affective disorders that can decrease adherence to treatment and impair the life quality in patients with malignancies (Jadoon et al, 2010). Nearly one-fifth of the patients suffers from depression, while it is almost one-fourth for anxiety (Zabora et al, 2001). However, distinguishing whether chemotherapy, burden of the disease, or psychosocial environment creates these problems is impossible most of times. In recent years, researchers had reported numerous strategies for coping with chemotherapy-induced depression and anxiety, and concurrently, curcumin has gained prominence as an adjuvant to cisplatin treatment to sensitize cells to the chemotherapy and limit the side-effects. Nevertheless, to our best awareness, no published researches had dealt with the compatibility of curcumin with cisplatin for the mood-associated behaviors.

Recently, Ali et al (2014) highlighted that acute cisplatin therapy, in a dose to provoke the renal failure, is associated with the depression-like behavior in mice. However, it is not clear by this study whether single high-dose cisplatin or renal failure created the mood alteration. In the present study, we used three diverse rodent models to investigate depression- and anxiety-like behaviors as well as locomotion and exploratory behaviors in animals which were chronically treated with curcumin, cisplatin, or curcumin plus cisplatin in a dose that was akin to the therapeutic usage. Regarding the anxiety-like behaviors, our results were in accordance with the study by Shabani et al (2012) which stated that the treatment with 5 mg/kg/week cisplatin for 5 weeks did not provoke an increase in anxiety parameters in the open field test. Also, a change of the locomotion and number of the rearings was reported in the mentioned study. However, we found that the treatment with cisplatin in a similar dose did not alter the number of the rearing, as a component of the exploratory behavior, and locomotion-related behaviors. It may be useful to note that our study was dissimilar in terms of the animals' age, which can influence the locomotion and exploratory behaviors (Pardon et al, 2000; Cao et al, 2010; Arrant et al, 2013). Our results demonstrated that the administration of curcumin alongside cisplatin did not change anxiety levels of the animals, which means no interactions between cisplatin and curcumin. Considering the cisplatin-induced depression-like behaviors, we showed that the chronic treatment with cisplatin (5 mg/kg/week for 5 weeks) did not develop any undesired effects. Additionally, supplementing the cisplatin-treated animals with curcumin did not disturb investigated depression-like parameters, which indicates no drug interactions. Bearing the fact in mind that curcumin is unintrusive to the antitumoral activity of cisplatin (Mendonça et al, 2013), we deduced that it is safe to include curcumin as an additive in cisplatin chemotherapy regimens with regard to mood-associated behaviors.

Conclusively, in our present study, we found that curcumin does not interact with cisplatin to alter anxiety- and depression-like behaviors. With the previously shown synergistic features in cisplatin chemotherapy, curcumin may be seen as a promising adjuvant.

Learning points

Curcumin, the active ingredient of the spice turmeric, does not alter anxiety- and depression-like behaviors in cisplatin-treated rats.

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