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Liposomal Curcumin Enhances the Effect of Naproxen in a Rat Model of Migraine

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABEF 1 Adriana E. Bulboacă
CDE 2 Sorana D. Bolboacă
ADE 3 Angelo C. Bulboacă
AEF 4 Alina S. Porfire
BEF 4 Lucia R. Tefas
ADF 5 Șoimița M. Suciu
BEF 6 Gabriela Dogaru
DEF 3 Ioana C. Stănescu

1 Department of Pathophysiology, Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Romania
2 Department of Medical Informatics and Biostatistics, Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Romania
3 Department of Neurology and Pediatric Neurology, Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Romania
4 Department of Pharmaceutical Technology and Biopharmaceutics, Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Romania
5 Department of Physiology, Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Romania
6 Department of Physical Medicine and Rehabilitation, Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Romania

Corresponding Author: Sorana D. Bolboacă, e-mail: sbolboaca@umfcluj.ro
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Background: Curcumin is an antioxidant that reduces inflammation and pain. This study aimed to assess the effect of pretreatment with naproxen and liposomal curcumin compared with naproxen and curcumin solution on oxidative stress parameters and pain in a rat model of migraine.

Material/Methods: Sixty-three male Wistar rats included a control group (n=9) and a rat model of migraine (n=54) induced by intraperitoneal injection of nitroglycerin (1 mg/0.1 kg). The rat model group was divided into an untreated control group (n=9), a group pretreated with naproxen alone (2.8 mg/kg) (n=9), a group pretreated with naproxen (2.8 mg/kg) combined with curcumin solution (1 mg/0.1 kg) (n=9), a group pretreated with naproxen (2.8 mg/kg) combined with curcumin solution (2 mg/0.1 kg) (n=9), a group pretreated with naproxen (2.8 mg/kg) combined with liposomal curcumin solution (1 mg/0.1 kg) (n=9) a group pretreated with naproxen (2.8 mg/kg) combined with liposomal curcumin solution (2 mg/0.1 kg) (n=9). Spectroscopy measured biomarkers of total oxidative status and nociception was tested using an injection of 1% of formalin into the rat paw.

Results: Expression of biomarkers of oxidative stress and enhanced nociception were significantly increased following pretreatment with combined naproxen and liposomal curcumin compared with curcumin solution or naproxen alone (P<0.001). Combined curcumin solution and naproxen were more effective at a concentration of 2 mg/0.1 kg for the first nociceptive phase (P<0.005).

Conclusions: In a rat model of migraine, combined therapy with liposomal curcumin and naproxen showed an improved antioxidant effect and anti-nociceptive effect.

MeSH Keywords: Curcumin • Migraine Disorders • Naproxen • Oxidative Stress • Pain Measurement • Rat

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Background

Migraine is a common neurovascular disorder, ranked as the sixth cause of disability in the world, that still has unknown mechanisms [1]. Currently, treatments for acute migraine attacks and chronic forms of migraine remain unsatisfactory due to lack of understanding of pathophysiological mechanisms. The oxidative stress-induced acute inflammatory response is an important mechanism in the pathogenesis of pain associated with migraine [2,3]. The migraine threshold depends on the stimulation of central nervous system by the reactive oxygen species, including hydroxyl (OH) radicals, superoxide anions, hydrogen peroxide, and nitric oxide (NO), which disrupt antioxidant defense systems. Increased NO production has a vasodilator effect that contributes to migraine pathophysiology. In experimental migraine, treatment with nitroglycerin induces an increase of nitric oxide concentration in the blood due to its proprieties to release NO, mimicking in this way one of the most crucial pathophysiological mechanism associated with migraine [4].

Nitroglycerin as a NO donor represents a trigger for migraine attack by inducing cortical spreading depression, a phenomenon which is electrophysiologically correlated with migraine with aura [5]. Cortical spreading depression is also associated with increased cerebral blood flow due to arteriolar vasodilatation, mainly mediated by NO [6]. The underlying mechanism of the nociception evoked by nitroglycerin is unknown. The pro-algesic receptors (TRPA1) expressed by trigeminal ganglions are sensitive to oxidative stress and are the target for NO or its products [7]. Two hours after administration of nitroglycerin, a significant increase of mast cell degranulation occurs, by an unknown mechanism [8]. By rapid degranulation of mast cells, a high concentration of tumor necrosis factor-alpha (TNF-alpha) is released, which mediates the inflammatory response in migraine [9,10]. The release of the calcitonin-gene-related peptide (CGRP) by activation of trigeminal fibers or the trigeminal ganglion and interaction with NO can substantially contribute to vasodilation and peripheral sensitization of perivascular afferent fibers [3].

Serotonin receptor agonists result in vasoconstriction and are widely used as medications for migraine attacks [11]. Nonsteroidal anti-inflammatory drugs (NSAIDs) including naproxen, a non-selective inhibitor of cyclooxygenase (COX) [12], are used as alternative treatments for migraine attacks that aim to reduce inflammation associated with nociception.

The treatment strategies for migraine attacks that mainly modulate pain mechanisms have several limitations. Because the use of serotonin receptor agonists is limited by their side effects in patients with cardiovascular and cerebrovascular diseases [13,14], and rebound headache following long-term use [15], NSAIDs remain an alternative treatment for migraine attacks [16]. Also, current studies have supported a more favorable cardiovascular risk profile for naproxen treatment compared with other NSAIDs [17]. However, the use of NSAIDs, including naproxen, can be useful to treat pain in patients who also suffer from other types of pain, including osteoarthritis or rheumatoid disorders [18,19]. In migraine, NSAIDs have an analgesic effect that relieves pain, while their anti-inflammatory effect reduces inflammation involving the trigeminal ganglion, reducing pain transmission through ascending pain pathways, which has been hypothesized as the mechanism that prevents the development of central sensitization [6,20]. Naproxen has been shown to block the sensitization of central trigeminovascular neurons in the medullary dorsal horn [21]. Naproxen also has analgesic and anti-inflammatory properties by decreasing the formation of prostaglandins, as a result of reversible inhibition of COX-1 [20]. Naproxen has been successfully used for menstrual migraine [22], pediatric migraine [23], and migraine associated with breastfeeding [24], supporting both its analgesic and anti-inflammatory effect.

Curcumin, a component of turmeric plant (*Curcuma longa*), has been reported to be associated with analgesia by reducing inflammation and oxidative stress associated with migraine attacks [25]. However, curcumin has poor bioavailability, poor absorption, rapid metabolism and elimination, which are the main issues that limit its use [26]. The therapeutic availability and efficacy of curcumin can be increased by combination with other molecules, such as piperine [27], or by its formulation as nanoparticles [28]. Curcumin nanoformulations, including curcumin-loaded liposomes, can be developed using high-performance liquid chromatography (HPLC), and have been shown to cross the blood-brain barrier and to reach the central nervous system following intravenous route administration [29]. Liposomal curcumin, when administered intravenously, preferentially accumulates in the hippocampus, which is involved in pain during a migraine attack [29,30]. The antioxidant effects and analgesic properties of curcumin have been previously described [31]. The enhanced efficiency of sumatriptan has previously been reported by adding liposomal curcumin [32].

This study aimed to assess the effect of pretreatment with naproxen and liposomal curcumin compared with naproxen and curcumin solution on oxidative stress parameters and pain in a rat model of migraine.

Material and Methods

Animals and housing

Healthy male adult albino Wistar rats weighing between 200–250 g were purchased from the Centre of Experimental Medicine and Practical Skills, Iuliu Haţieganu University of Medicine and

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Table 1. Design of the experimental migraine: naproxen and curcumin pre-treatment.

Group (abbreviation)	Administration route | dose (ref)
Control (C)	1 ml i.p. saline solution (0.9%)
M Control (M-C)	1 ml i.p. NTG | 1 mg/100 g bw [31–33]
M with NP pre-treatment (NTG+NP)	1 ml i.p. NTG | 1 mg/100 g bw 1 ml i.p. NP | 2.8 mg/kg bw [12]
M with NP and curcumin	1 ml i.p. NTG | 1 mg/100 g bw 1 ml i.p. NP | 2.8 mg/kg bw
$CC_{(1)}$ (M+NP+$CC_{(1)}$)	1 ml i.v. Curcumin solution | 1 mg/0.1 kg bw
$CC_{(2)}$ (M+NP+$CC_{(2)}$)	1 ml i.v. Curcumin solution | 2 mg/0.1 kg bw
$CCl_{(1)}$ (M+NP+$CCl_{(1)}$)	1 ml i.v. liposomal Curcumin | 1 mg/0.1 kg bw
$CCl_{(2)}$ (M+NP+$CCl_{(2)}$)	1 ml i.v. liposomal Curcumin | 2 mg/0.1 kg bw

M – migraine; bw – body weight; i.p. – intraperitoneal; i.v. – intravenous.

Pharmacy, Cluj-Napoca. For the duration of the experiment, the rats were housed in polypropylene cages, with a constant environmental temperature (24±2°C), humidity (60±5%), and alternating 12-hour light and 12-hour dark cycles. Free access to water and standard pellets (Cantacuzino Institute, Bucharest, Romania) was given to all rats during the experiment. The experimental design and the development of the rat model used in this study have been previously described [32].

Ethical approval

The study had ethical approval from the University of Medicine and Pharmacy, Cluj-Napoca, Romania, (372/16.10.2018) and was approved by the National Sanitary Veterinary and Food Safety Authority, Cluj Branch (135/13.11.2018). All animals were treated according to the European Council recommendations (63/2010) regarding the use and care of animal during experimental studies.

Chemicals

Chemicals were obtained from Sigma-Aldrich Co (St Louis, MO, USA) and Lipoid GmbH (Ludwigshafen, Germany).

Experimental design

Sixty-three male Wistar rats included a control group (n=9) and a rat model of migraine (n=54) induced by intraperitoneal injection of nitroglycerin (1 mg/0.1 kg). The rat model group (n=54) was divided into an untreated control group (n=9), a group pretreated with naproxen (2.8 mg/kg) (n=9), a group pretreated with naproxen (2.8 mg/kg) and curcumin solution (1 mg/0.1 kg) (n=9), a group pretreated with naproxen (2.8 mg/kg) and curcumin solution (2 mg/0.1 kg) (n=9), a group pretreated with naproxen (2.8 mg/kg) and liposomal curcumin solution (1 mg/0.1 kg) (n=9) a group pretreated with naproxen (2.8 mg/kg) and liposomal curcumin solution (2 mg/0.1 kg) (n=9). The experimental design is detailed in Table 1.

In the experimental rat model, migraine was induced by intraperitoneal administration of nitroglycerin at a dose of 1 mg/0.1 kg. In the migraine model treated with naproxen (M+NP), naproxen (2.8 mg/kg) was administrated by intraperitoneal injection, 60 minutes before administration of nitroglycerin, to allow the absorption of the drug, following the method described by Vause et al. [12]. Curcumin was administered intravenously immediately after treatment with naproxen, following the protocol described by Chiu et al. [29]. Intravenous injections were made by puncturing the rat lateral tail vein.

Preparation of liposomal curcumin

Curcumin was encapsulated in long circulation liposomes (LCL) at a concentration of 4.7 mg/ml, using the film hydration method with a lipid molar ratio 9.5: 0.5: 1 (DPPC: PEG-2000-DSPE: CHO) as previously described [33,34]. Briefly, curcumin and the lipid components were dissolved in ethanol, and the solvent was removed by rotary evaporation (Heidolph, Schwabach, Germany). For size reduction, the liposomal dispersion was sequentially extruded through polycarbonate membranes with a pore size of 100 nm, using a LiposoFast LF-50 extruder (Avestin Europe GmbH, Mannheim, Germany). The liposomal size and polydispersion were determined using dynamic light scattering, and the zeta potential was measured by laser Doppler electrophoresis, using a Zetasizer Nano ZS (Malvern Instruments, Malvern, UK). The proposed formulation had appropriate quality attributes for intravenous administration, including the monodispersion size of 140 nm and zeta

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potential of –50 mV. To determine whether liposomal encapsulation increased the therapeutic efficacy of curcumin, curcumin solutions of the same concentration were prepared by dilution in ethanol 96% (v/v) and by dilution in saline solution.

Assessment of oxidative stress parameters and the formalin nociception test

Orbital sinus blood samples were collected under intraperitoneal ketamine anesthesia (5 mg/kg) from each animal at the end of the experiment [35]. The animals were euthanized under anesthesia after the collection of the blood samples. Spectroscopy measured the parameters for oxidative stress, including total oxidative status and malondialdehyde (MDA) [36], and an indirect indicator of nitric oxide (NO) synthesis [37]. Spectroscopy measured the parameters for the antioxidant status in plasma, including total antioxidant capacity [37] and thiol [38].

The formalin nociception test used formalin (1%) injected subcutaneously in the right paw, as previously described [39], which was used to evaluate nociception four hours after administration of nitroglycerin [31,32]. Rat behavior was evaluated by counting the number of rapid and brief withdraws or flexion of the injected paw in two distinct phases after formalin administration. The first phase of observation was done in the first 1–5 min after administration by counting the number of specific movements. The specific movements for one-minute periods, at five-minute intervals, was performed in the second phase from 10–60 minutes after the injection of formalin. The first phase was dominated to vasodilatation induced by the nociceptive effect of formalin injection, whereas the second phase was dominated by inflammation [32,40,41].

Statistical analysis

Data were analyzed using the Statistica 8.1 program (StatSoft Inc., Tulsa, OK, USA). Differences between the groups were compared for the degree of oxidative stress, antioxidant capacity, and the outcomes of the formalin test, using the Mann-Whitney test. The quantitative data were reported as the mean ± standard deviation (SD), and median and interquartile range (IQR), respectively. Statistical significance was defined as $P<0.05$.

Results

Oxidative stress parameters

All rats included in the study were assessed and no animals were lost during the experiment. The rats in the migraine model had significantly increased values of all metrics that quantified the oxidative stress intensity (Table 2). The increase in concentration for the curcumin solution had no significant effect on the oxidative stress intensity ($P>0.05$). A significant decrease in the concentration of malondialdehyde (MDA) was observed for the group pretreated with a higher concentration of liposomal curcumin (2.8 mg/kg) (Table 2, Figure 1). Compared with curcumin solution, liposomal curcumin combined with naproxen pretreatment resulted in a significant decrease in all measured oxidative stress intensity parameters ($P<0.001$) (Table 2, Figure 1). The induction of migraine was associated with a significant decrease in both the thiol concentration and the total antioxidant capacity (Table 3). The total antioxidant capacity values significantly increased with treatment using the curcumin solution and naproxen combination compared with naproxen pretreatment alone (Table 3, Figure 2). A similar result was also found for the liposomal formulation of curcumin (Table 3). The increase in liposomal curcumin concentration did not significantly affect thiol or total antioxidant capacity ($P>0.1$) (Table 3).

The formalin test

A significantly increased number of flinches and shakes was observed in the migraine rat model group when compared with the normal control rat group without a migraine for both phases of the formalin test (Mann-Whitney test, $P<0.001$). Pretreatment with naproxen significantly decreased the response to nociceptive stimulus in the first phase of the formalin test (Table 4, Figure 3). An increase in the concentration of curcumin reduced the number of flinches and shakes, but this reduction was statistically significant only for the second phase ($P<0.001$). The number of flinches and shakes were similar for the two doses of liposomal curcumin, with significant differences just in the second phase ($P<0.001$). The biphasic response to the nociceptive stimulus was significantly reduced in both groups treated with liposomal curcumin compared with groups treated with curcumin solution ($P<0.001$) (Table 4, Figure 3).

Discussion

In a rat model of migraine, combined treatment with liposomal curcumin and naproxen had a beneficial therapeutic effect on the nociception phase (the first phase) and also on inflammation (the second phase) induced by the formalin test. The study aimed to investigate the effects of the combination of curcumin, as a liposomal formula, and naproxen on oxidative stress and nociception. Pretreatment with liposomal curcumin in the experimental rat model of migraine rats showed its effectiveness on both oxidative stress, by reducing the levels of malondialdehyde (MDA), nitric oxide (NO), and total oxidative status, and nociception. Schwartz et al. showed a positive association between the oxidative stress molecules, MDA, NO, and total oxidative status, and central sensitization

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Table 2. Quantification of oxidative stress intensity by groups (values expressed as mean (standard deviation)).

Group abb.	MDA (pmol/L)		NOx (µmol/L)		TOS (µmol/L)	
C	2.6	(0.06)	14.9	(2.03)	26.6	(1.67)
M-C	4.7	(0.13)	37.9	(2.67)	46.0	(2.24)
M+NP	4.1	(0.10)	32.2	(2.17)	38.9	(2.93)
M+NP+$CC_{(1)}$	4.0	(0.21)	30.6	(1.67)	33.6	(2.79)
M+NP+$CC_{(2)}$	4.0	(0.20)	29.7	(2.24)	34.7	(2.35)
M+NP+$CCl_{(1)}$	3.2	(0.11)	21.7	(1.32)	22.4	(2.24)
M+NP+$CCL_{(2)}$	3.0	(0.14)	20.2	(1.86)	21.3	(1.66)

MDA – malondialdehyde; NOx – the indirect assessment of NOx synthesis; TOS – total oxidative status; C – control; M – migraine; NP – naproxen; $CC_{(1)/(2)}$ – Curcumin solution 1 mg/0.1 kg bw (1) respectively 2 mg/0.1 kg bw (2); $CCl_{(1)/(2)}$ – liposomal Curcumin 1 mg/0.1 kg bw (1), respectively 2 mg/0.1 kg bw.

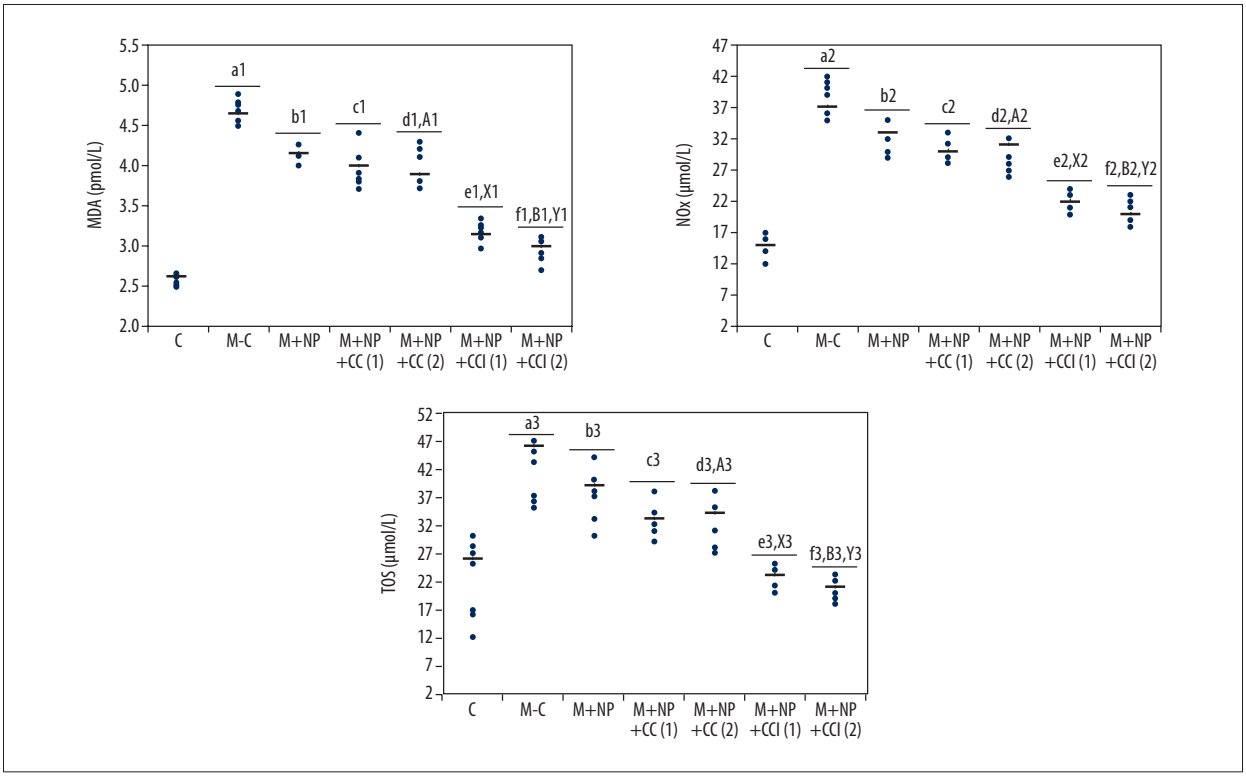

Figure 1. The patterns of expression of the oxidative stress biomarkers malondialdehyde (MDA), nitric oxide (NO), and total oxidative status (TOS) in the pretreated groups in a rat model of migraine. The line represents the median, and the circles represent the individual values. The rat model of migraine (M) (n=54), was induced by intraperitoneal injection of nitroglycerin (1 mg/0.1 kg). The groups include the untreated control group (M-C) (n=9), a group pretreated with naproxen (2.8 mg/kg) (M+NP) (n=9), a group pretreated with naproxen (2.8 mg/kg) and curcumin solution (1 mg/0.1 kg) (M +NP+$CC_{(1)}$) (n=9), a group pretreated with naproxen (2.8 mg/kg) and curcumin solution (2 mg/0.1 kg) (M +NP+$CC_{(2)}$) (n=9), a group pretreated with naproxen (2.8 mg/kg) and liposomal curcumin solution (1 mg/0.1 kg) (M+NP+$CCl_{(1)}$) (n=9) a group pretreated with naproxen (2.8 mg/kg) and liposomal curcumin solution (2 mg/0.1 kg) (M+NP+$CCl_{(2)}$) (n=9). The letters and numbers correspond to the P-values, as follows in the M-C compared with C: $^{a1–a3}$ 0.0003; M+NP compared with M-C: ^{b1} 0.0003, ^{b2} 0.0007, ^{b3} 0.0006; M+NP+$CC_{(1)}$ compared with M+NP: ^{c1} 0.0423, ^{c2} 0.1333, ^{c3} 0.0027; M+NP+$CC_{(2)}$ compared with M+NP: ^{d1}0.0703, ^{d2} 0.0341, ^{d3}0.0071; M+NP+$CCl_{(1)}$ compared with M+NP: $^{e1-e3}$0.0003; M+NP+$CCl_{(2)}$ compared with M+NP: $^{f1-f3}$ 0.0003; M+NP+$CC_{(1)}$ compared with M+NP+$CC_{(2)}$: ^{A1} 0.9296, ^{A2} 0.5660; ^{A3} 0.3772; M+NP+$CCl_{(1)}$ compared with M+NP+$CCl_{(2)}$: ^{B1}0.0047, ^{B2}0.1120; ^{B3}0.2510; NTG+NP+$CC_{(1)}$ compared with NTG+NP+$CCl_{(1)}$: $^{X1–X3}$ 0.0003; NTG+NP+$CC_{(2)}$ compared with NTG+NP+$CCl_{(2)}$: $^{Y1–Y3}$ 0.0003.

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in hyperalgesia in mice [42]. The assessment of the antioxidant status, by assessment of plasma thiol and total antioxidant capacity, was also useful to establish the effects of liposomal curcumin when combined with naproxen. The thiol level after curcumin administration may be partly explained by its ability to maintain the thiol pool due to the protection of -SH groups from oxidation [43].

Table 3. Quantification of antioxidant capacity by groups.

Group abb.	Thiol (mg%)	TAC (Eq/L)
C	208.0 (3.84)	1.23 (0.03)
M-C	182.6 (5.61)	1.08 (0.04)
M+NP	225.6 (5.29)	1.24 (0.06)
M+NP+$CC_{(1)}$	221.7 (6.71)	1.35 (0.09)
M+NP+$CC_{(2)}$	231.7 (5.61)	1.42 (0.07)
M+NP+$CCl_{(1)}$	244.8 (3.99)	1.61 (0.07)
M+NP+$CCL_{(2)}$	241.8 (4.12)	1.59 (0.07)

TAC – total antioxidant capacity; C – control; M – migraine; NP – naproxen; $CC_{(1)/(2)}$ – Curcumin solution 1 mg/0.1 kg bw (1) respectively 2 mg/0.1 kg bw (2); $CCl_{(1)/(2)}$ – liposomal Curcumin 1 mg/0.1 kg bw (1), respectively 2 mg/0.1 kg bw.

The findings of the present study showed that treatment with nitroglycerin resulted in a significant increase in oxidative stress and decreased plasma antioxidant capacity (Tables 2 and 3, Figures 1 and 2). Nitroglycerin induces hyperalgesia by acting as a NO donor [44], and the findings of this study showed significant changes in the rat behavior after the formalin test, in both phases of experimental migraine. In response to noxious stimuli, pro-inflammatory molecules that promote peripheral and central sensitization are released [45].

The release of pro-inflammatory molecules can be enhanced by reactive oxygen species (ROS) [46]. NO can also generate ROS, which plays a central role in the inflammatory response, and increased NO production can amplify ROS production [47]. In this study, the significant increase in NO production after treatment with nitroglycerin influenced the production of ROS, resulting in central and peripheral sensitization [12]. Consequently, the nociceptive stimulus led to an increase in the levels of oxidative stress molecules, MDA and NO, and also increased total oxidative status. A connection between these oxidative stress molecules may also exist, in that NO synthesis can influence the level of MDA.

While chronic migraine is associated with the risk of stroke [48], increased NO synthesis and inflammatory mechanisms can contribute to post-stroke cerebral cortical atrophy and cognitive decline [49–51]. However, a migraine attack, with or without

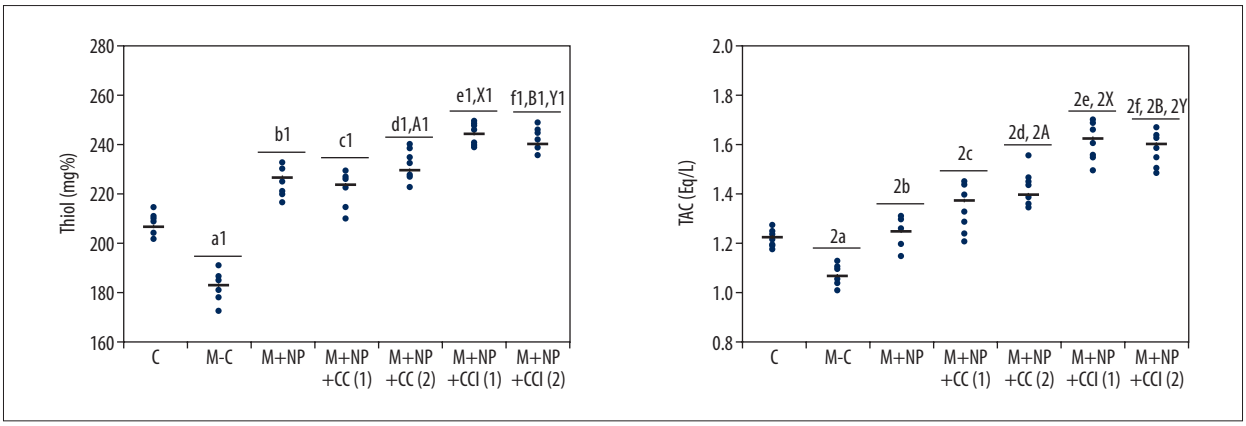

Figure 2. Distribution of antioxidant status in the plasma, including the thiol and total antioxidative capacity (TAC), in the pretreated groups in a rat model of migraine. The line is given by the median, and the circles represent the individual values. The rat model of migraine (M) (n=54), was induced by intraperitoneal injection of nitroglycerin (1 mg/0.1 kg). The groups include the untreated control group (M-C) (n=9), a group pretreated with naproxen (2.8 mg/kg) (M+NP) (n=9), a group pretreated with naproxen (2.8 mg/kg) and curcumin solution (1 mg/0.1 kg) (M+NP+$CC_{(1)}$) (n=9), a group pretreated with naproxen (2.8 mg/kg) and curcumin solution (2 mg/0.1 kg) (M +NP+$CC_{(2)}$) (n=9), a group pretreated with naproxen (2.8 mg/kg) and liposomal curcumin solution (1 mg/0.1 kg) (M+NP+$CCl_{(1)}$) (n=9) a group pretreated with naproxen (2.8 mg/kg) and liposomal curcumin solution (2 mg/0.1 kg) (M+NP+$CCl_{(2)}$) (n=9). The letters and numbers correspond to the P-values, as follows in the M-C compared with C: $^{1a–2a}$ 0.0003; M+NP compared with M: $^{1b-2b}$ 0.0003; M+NP+$CC_{(1)}$ compared with M+NP: ^{1c}0.1853, ^{2c}0.0193; M+NP+$CC_{(2)}$ compared with M+NP: ^{1d}0.0423, ^{2d}0.0003; M+NP+$CCl_{(1)}$ compared with M+NP: $^{e1–e2}$ 0.0003; M+NP+$CCl_{(2)}$ compared with M+NP: $^{1f–2fr}$ 0.0003; M+NP+$CC_{(1)}$ compared with M+NP+$CC_{(2)}$: ^{1A}0.0054, ^{2A}0.1223; M+NP+$CCl_{(1)}$ compared with M+NP+$CCl_{(2)}$: ^{1B}0.1451, ^{2B}0.5365; M+NP+$CC_{(1)}$ compared with M+NP+$CCl_{(1)}$: $^{1X–2X}$ 0.0003; M+NP+$CC_{(2)}$ compared with M+NP+$CCl_{(2)}$: ^{1Y} 0.0023, ^{2Y}0.0009.

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aura, may cause an increase in plasma serotonin released by activated platelets. High concentrations of serotonin may cause signs of aura due to vasoconstriction, whereas at low concentrations of serotonin may stimulate perivascular pain fibers and cause vasodilatation due to the local formation of NO, prostaglandins, and neuropeptides [52]. Evidence of serotonin release by activated platelets due to nitroglycerin-induced migraine attacks have been previously reported [53].

The antioxidant properties of curcumin that mediate its anti-inflammatory effects include its effects on blocking the production of ROS and tumor necrosis factor-α (TNF-α) that will reduce the activation of nuclear factor-κB (NF-κB), which has a central role in the inflammatory response [54,55]. NF-κB can lead to the expression of cytosolic phospholipase A_2 ($cPLA_2$), cyclooxygenase-2 (COX-2) and membrane-bound prostaglandin E synthase 1 (PGES-1), leading to the increased release of arachidonic acid and production of prostaglandins [55]. The activity of these enzymes and the quantity of released arachidonic acid metabolites depend on the cell type and also on the intensity of the oxidative stress [56]. Naproxen has been shown to inhibit the prostaglandin synthesis by non-selective inhibition of COX, and the role of curcumin in prostaglandin synthesis inhibition has also been reported [57]. Curcumin may act as a natural free radical scavenger due to its chemical structure [47], as well as a NO scavenger by its conversion to nitrite or nitrate [58]. Curcumin levels can decrease through its scavenging and chelating activities, lipid peroxidation, and glutathione depletion, and also can reduce alterations in antioxidant enzymes [59]. The reduction in the total oxidative status and the increase in total antioxidant capacity has previously been shown to be due to the antioxidant and free radical scavenging activity of curcumin [60].

Table 4. Results for the formalin test by groups: number of flinches and shakes in the first and second phase.

Group abb.	No. flinches and shakes	
	First phase	Second phase
C	20.1 (1.76)	114.1 (2.93)
M-C	42.2 (2.68)	146.4 (9.86)
M+NP	30.4 (2.30)	140.6 (1.88)
M+NP+$CC_{(1)}$	28.3 (2.78)	134.9 (3.82)
M+NP+$CC_{(2)}$	26.1 (2.03)	125.6 (2.60)
M+NP+$CCl_{(1)}$	20.4 (1.59)	119.9 (2.85)
M+NP+$CCL_{(2)}$	20.1 (2.47)	113.8 (2.54)

C – control; M – migraine; NP – naproxen; $CC_{(1)/(2)}$ – Curcumin solution 1 mg/0.1 kg bw (1) respectively 2 mg/0.1 kg bw (2); $CCl_{(1)/(2)}$ – liposomal Curcumin 1 mg/0.1 kg bw (1), respectively 2 mg/0.1 kg bw.

The combination of NSAIDs, such as celecoxib, and curcumin-loaded nanosystems has previously been shown to have synergistic anti-inflammatory (NSAIDs, curcumin) and antioxidant effects (curcumin) [61]. There is some evidence that suggests a beneficial synergic effect when curcumin is combined with steroidal anti-inflammatory agents, including methylprednisolone sodium succinate, in reducing the inflammatory process

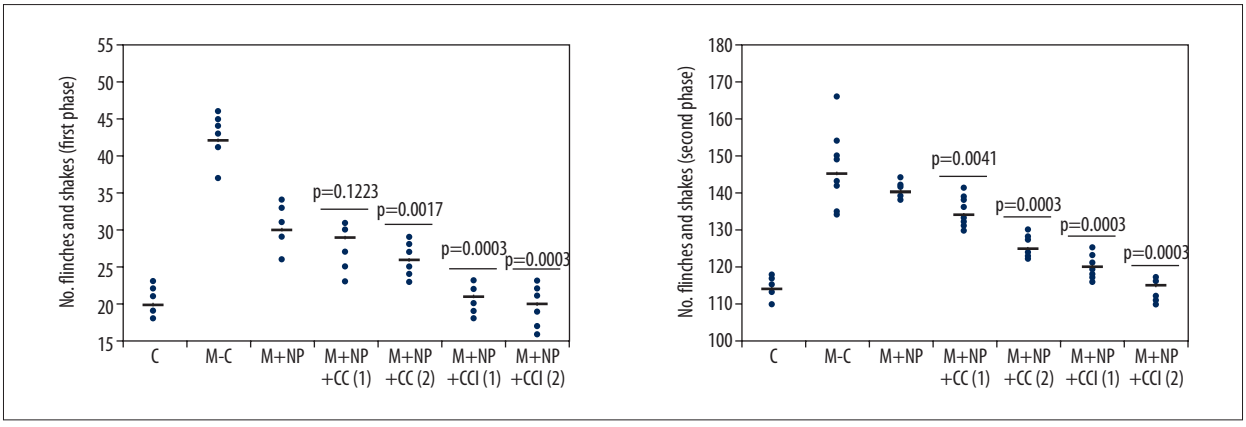

Figure 3. The distribution of the number of flinches and shakes by groups as a test of nociception following the injection of 1% of formalin subcutaneously in the right paw of the rats. The first phase (left-hand graph), and the second phase (right-hand graph). The line represents the median, and the circles represent the individual values. C is the rat control group (no medication) (n=9). The rat model of migraine (M) (n=54), was induced by intraperitoneal injection of nitroglycerin (1 mg/0.1 kg). The groups include the untreated control group (M-C) (n=9), a group pretreated with naproxen (2.8 mg/kg) (M+NP) (n=9), a group pretreated with naproxen (2.8 mg/kg) and curcumin solution (1 mg/0.1 kg) (M +NP+$CC_{(1)}$) (n=9), a group pretreated with naproxen (2.8 mg/kg) and curcumin solution (2 mg/0.1 kg) (M +NP+$CC_{(2)}$) (n=9), a group pretreated with naproxen (2.8 mg/kg) and liposomal curcumin solution (1 mg/0.1 kg) (M+NP+$CCl_{(1)}$) (n=9) a group pretreated with naproxen (2.8 mg/kg) and liposomal curcumin solution (2 mg/0.1 kg) (M+NP+$CCl_{(2)}$) (n=9). The P-values represent comparison with the M+NP group.

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more than each treatment alone [62]. Curcumin has been previously shown to exert a synergic effect in myocardial protection when combined with the NSAID, celecoxib, the immunosuppressant tacrolimus, and selective estrogen receptor modulators, raloxifene, and tamoxifen [63].

The findings of the present study showed a significant difference in oxidative stress parameters, MDA, NO, and total oxidative status, and increased antioxidative mechanisms, including thiol and total antioxidant capacity, for combined treatment with curcumin and naproxen, when compared with naproxen alone. There was one exception, as the thiol level was reduced after treatment with curcumin solution (1 mg/0.1 kg), but was not significantly reduced when compared with naproxen treatment alone). The liposomal curcumin formula had a higher efficacy when compared with curcumin solution (Tables 2 and 3, Figures 1 and 2). Improved bioavailability of liposomal curcumin might explain the higher effectiveness of the liposomal curcumin compared with the curcumin solution [32]. However, with one exception, neither of the two forms of curcumin (solution and liposomes) had a dose-dependent effect on the oxidative stress parameters (Table 2). The level of MDA represents the exception, as its levels were significantly reduced by the increased concentration of liposomal curcumin (Table 2). MDA, which results from oxidative stress-induced lipid peroxidation, can contribute to DNA damage and mutation. Therefore, MDA is an important biomarker for damage due to oxidative stress [64].

Several previously published studies have reported the neuroprotective effect of the systemic administration of curcumin, including the combination of curcumin with stem cells and progenitor cells that enhance neuroprotection, increase axonal growth and improve functional recovery in experimental acute central nervous system injury [65]. Migraine, like ischemic stroke, can produce neuronal dysfunction, increased cellular vulnerability, neurodegeneration and cell death due to a common pathophysiological mechanism represented by endothelial dysfunction [66]. Intravascular thrombosis may be favored by inflammatory responses caused by the release of vasoactive peptides, including NO [67]. Curcumin can also reduce neuronal death induced by oxidative stress, excitotoxicity, and glucose starvation [68]. Also, white matter microstructural differences have been observed in patients suffering from migraine with aura, when compared with the controls, which is a result that can be explained by the presence of degenerative and maladaptive mechanisms [69]. Therefore, curcumin combined with NSAIDs can contribute to neuroprotective mechanisms against the oxidative stress that is associated with migraine attacks. Several studies have shown that the outcome of acute cerebral hemorrhage is related to inflammatory and oxidative stress processes, being accompanied by changes in the neutrophil-to-lymphocytes ratio and increase in C-reactive protein (CRP) in the acute phase response reaction [70–72]. Due to its anti-inflammatory and anti-oxidant proprieties, curcumin may be effective in brain tissue neuroprotection in the acute phase of a cerebral hemorrhage. Therefore, the liposomal formulation of curcumin might have therapeutic potential to improve patient outcome due to its rapid absorption and ability to cross the brain-blood barrier [73].

In the present study, except for the effect of the curcumin solution on the first phase treatment group, both the curcumin solution and the curcumin liposomes and both concentrations of curcumin had a significant effect on the rat experimental migraine model, when associated with naproxen treatment (Table 4, Figure 3). These findings showed that combining liposomal curcumin with naproxen had an effect on vasodilatation induced by nociception processes (specific for the first phase) and inflammation induced by noxious stimuli (specific for the second phase). Acute nociception (first phase) is followed by the facilitated state (second phase). In the first phase, the acute pain (induced by the formalin test) is caused by a prompt and intensive increase in the activity of primary afferent fibers, while in the second phase, the response is the result of the activation of wide dynamic range neurons in the dorsal horn [74]. The intrathecal administration of curcumin solution in different doses has previously been shown to have a significant effect on the second phase in the formalin test, suggesting a possible central nervous system component of the mechanism of its analgesic effect [75]. Previous studies have shown an analgesic effect of curcumin, after systemic administration, in experimental models of diabetic neuropathic pain [76], formalin-induced orofacial pain [77], capsaicin-induced thermal hyperalgesia [78], and nitroglycerin-induced experimental migraine [31]. The mechanisms underlying the analgesic action of curcumin consists of suppressing the production of oxidative stress parameters, including MDA and NO synthesis [31], suppressing inflammatory molecules such as TNF-α [76], and involves the descending mechanism of pain modulation associated with the activation of the monoamine system and delta-opioid and mu-opioid receptors [79]. Qin et al. showed that curcumin could also reduce monocyte chemoattractant protein-1 (MCP-1) expression and activity *in vitro*, as well as superoxide dismutase-2 (SOD2) expression, which might contribute to a reduction in neuropathic pain [80].

The use of oral curcumin can require several doses needed to be used, due to its poor absorption, low bioavailability, rapid systemic elimination and high metabolism, which reduces its therapeutic efficiency [26]. Liposomal curcumin combined with naproxen therapy improved its efficacy in this study, proving an increased effect on the nociceptive process than curcumin solution (Table 4). Ghalandarlaki et al. showed that curcumin encapsulated in liposomes had enhanced solubility, was safe, and was transported without rapid degradation, had better

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absorption, and higher stability in the blood and tissues [81]. Curcumin-loaded solid lipid nanoparticles effectively reduced levels of IL-1β expression, decreased the expression of serum pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β) and suppressed NF-κB activation, reducing inflammation [82]. In an experimental model of hepatic injury induced by carbon tetrachloride in rats, curcumin-loaded solid nanoparticles reduced inflammation by reducing the level of TNF-α in the blood as well as oxidative stress quantified by specific markers, MDA, superoxide dismutase, and reduced glutathione [83]. In a rat model of rheumatoid arthritis, characterized by chronic inflammation, curcumin-loaded nanoparticles also demonstrated an anti-inflammatory effect by reducing the level of TNF-α and CRP and reduced oxidative-nitrosative stress [84]. The synergistic action of the combination of the NSAID, celecoxib, and a curcumin nanoformulation was achieved in a rat model of ulcerative colitis [61]. Also, the anti-inflammatory and antioxidant properties of curcumin may be useful as an adjuvant therapy combined with novel drug treatments in migraine, such as erenumab, a human monoclonal antibody against calcitonin gene-related peptide (CGRP) [85,86].

Conclusions

In a rat model of migraine, combined therapy with liposomal curcumin and naproxen showed an improved antioxidant effect and anti-nociceptive effect. The findings from the present study require support from future clinical studies to determine the possible role for curcumin as a safe adjuvant therapy for migraine.

Conflict of interest

None.

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