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Therapeutic Potential of 2,5-Dimethoxy-p-Cymene and Thymol methyl ether from Arnica montana Essential Oils: Neuro-protection and Stress Mitigation

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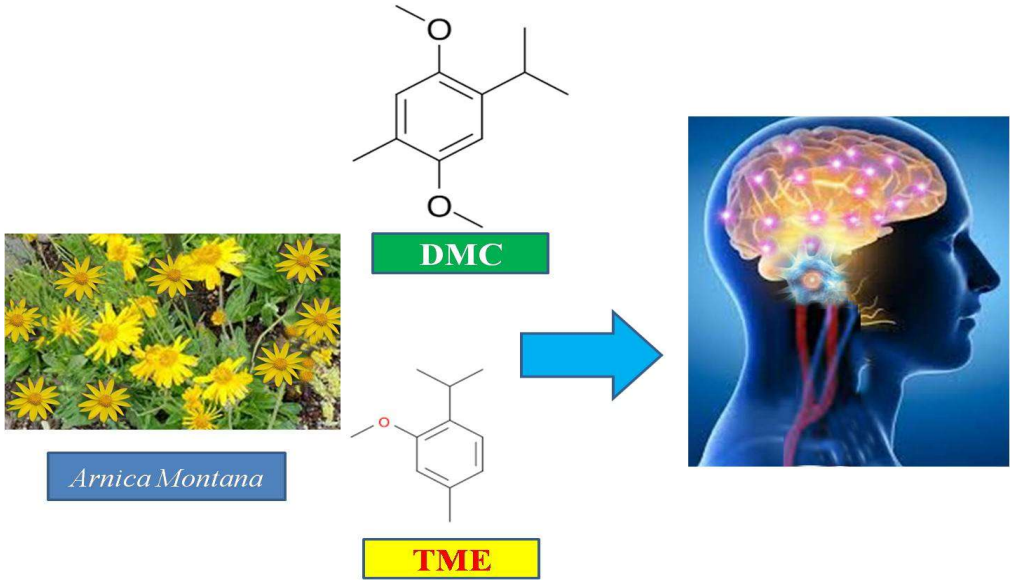
Graphical Abstract:



Abstract

Arnica Montana (AM), a medicinal plant traditionally used in India for stress-related conditions, has been studied for its bioactive compounds. In this study, two isolated AM compounds, 2,5-dimethoxy-p-cymene (DMC) and thymol-methyl ether (TME), were evaluated for their impact on different stress induced models to access the oxidant and neurotransmitters level in the different brain regions. CUS exposure (two daily stressors over seven days) significantly altered the monoamines levels, which were normalized by pretreatment with DMC and TME (50 mg/kg p.o.). CUS also reduced the levels of different neurotransmitters levels like noradrenaline, serotonin and dopamine. Additionally, stress also affects the glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) levels. Moreover, it is increasing the lipid peroxidation (MDA). Treatment with DMC and TME attenuated these CUS-induced changes, similar to the effects of Panax quinquefolium as reference. In this study we are focusing on the potential of DMC and TME in managing

stress-related disorders.

Keywords: *Arnica Montana;* dimethoxy-p-cymene (DMC); thymol methyl ether (TME); Panax quinquefolium; chronic unpredictable stress (CUS)

Introduction

Stress plays a critical role in triggering various clinical conditions. Moreover, it's not only activate the hypothalamic-pituitary-adrenal (HPA) axis but also actively affected the damage induced by oxidation which disrupting the balance between pro-oxidants and antioxidants in the body [1]. To assess this, chronic unpredictable stress (CUS) was used as a model to evaluate the anti-stress potential of various medicinal plants and their active compounds. In this model, animals were exposed to different stressors, ranging in intensity from mild to severe, over a 7-day period. The unpredictability of CUS prevents the anticipation of stress and adaptation that may occur with repeated exposure, making it a relevant model for human stress conditions [2]. After the stress regimen, rats were decapitated, and blood plasma and brain tissues were collected to measure monoamine levels and brain antioxidant status. Therefore, it is important to evaluate the anti-stress properties of medicinal plants or their active constituents.

Arnica montana L. is a perennial herb widely utilized in herbal medicine and homeopathy for centuries for their therapeutic use such as reducing inflammation, boosting the immune system, and in promoting wound healing [3]. ***Arnica montana*** contains various bioactive compounds, including essential oils, glucosides, terpenoids, flavonoids, and acids of phenols [4], known for their anti-microbial, anti-inflammatory, antiseptic, anti-cancer, and antioxidant effects [5]. Moreover ***Arnica montana*** also renowned for their essential oils contents extracted from different parts of the plant mainly include sesquiterpene hydrocarbons, monoterpenoids linalool & 1,8-cineole, and phenyl derivatives (such as thymol methyl ether) [6]. These variations in chemical composition across flower, buds, rhizomes, roots, and roots hair allow for diverse applications of secondary metabolites. This study aimed to identify new molecules from *A. Montana* also we analyzed the constituents of arnica's essential oil by Gas Chromatography Mass Spectrometry (GC-MS). In addition, 18 components were found from the *A. Montana* plants. Major compounds included 2, 5-dimethoxy--p cymene (DMC; 44.65%), cumene (10.71-13.24%), thymol methyl ether (TME; 8.63-8.66%), and others.

Whereas, DMC and TME (50 mg/kg body p.o.) have been evaluated in frontal cortex (FC), striatum (ST) and hippocampus (HI) against CUS induced stress models in SD rats. CUS exhibited increase level of MDA and reduction in superoxide dismutase, glutathione and catalase. Moreover, monoaminergic system interlinked with different brain parts like FC, ST and HI and involved in CUS [7-8]. Furthermore, DCM and TME also impact the levels of DA, 5HT and NA. Hence, an effort has been made to understand the *in vivo* alterations on antioxidant due to CUS. In addition, DCM and TME from *A. Montana* altered the antioxidant parameters in the above mentioned specific brain region. Whereas, for reference *Panax quinquefolium* (100mg/kg p.o. PQ) was used.

Methodology

Animals used in study

Institutional Ethical and Usage Committee of Teerthanker Mahaveer Medical College & Research Centre (TMMC & RC), Moradabad approved our research protocols, in accordance with Committee for the Purpose of Control and Supervision of Experiments (1205/PO/Re/S/08/CPCSEA). Whereas, Sprague–Dawley male rats (160–200 g), were used in this study. Also we kept the rats in air conditioned room at 24 ± 3 ◦C and day night cycles were sustained. Additionally, rats were deprived of food before 18hr of experiments.

Chemicals

Dopamine (DA), epinephrine, nor-adrenaline (NA), reduced glutathione (GSH) enzymes, thio-barbituric acid, 1,3,3-

tetraethoxypropane, 5-hydroxy tryptamine (5-HT) and 5, 5–dithiobis-2-nitrobenzoic acid (DTNB), as well as root of *Panax quinquefolium* (PQ) were used as reference procured from Sigma Aldrich, whereas, other were procured from locally.

Protocol for Chronic Unpredictable Stress (CUS)

CUS were induced by stressors given daily for 7 days. To avoid habituation the minimal repetition of stressors were used. Also, the stressors encompass pinching of tail (with steel clips for 5min), fasting (18hr), restraint (120 min in restrain cages), cold-restraint (rats were kept for 120min at 4 ◦C in cold chamber), in cold exposure animals were subjected at 4 ◦C, overnight wet cage bedding, isolation (kept alone for a period of 12 hr), forced swimming (for a period of 30 min), reversal of light cycle (during the dark period animals were kept at 3hr in dark and then 12hr in increased light), deprivation of water (18hr), Furthermore, animals were kept in agressometer for 20 min to give foot-shock, in detail 2mA for 2s is treated as one shock in an (Techno electronics, India).

Selection of Dose

Initially we examination the ethanolic extract of AM (100 to 400 mg/kg.), along with DMC and TME from AM (10 to 50 mg/ kg) in different stress models [14]. The dose chosen for the present study (50 mg/kg p.o.) that found effective on CUS induced brain monoamine levels was based on this prior research [14]. Moreover, *Panax quinquefolium* administered at 100 mg/kg p.o. and used as reference. Although, 1% sodium carboxy methyl cellulose was used to prepare suspension of DMC, TME, and PQ.

Groups of Animal

All rats were acclimated to laboratory conditions before the experiment began.
Group I: Non-stress control group (NS).
Group II: Chronic unpredictable stress (CUS).
Groups III and IV (Per-se): In this group animals were treated with DMC and TME (50 mg/kg p.o.).
Groups V, and VI (Treatment group): DMC and TME (50 mg/kg.).
Groups VII (Reference group): *Panax* at 100 mg/kg p.o.).

Preparation of tissue sample for analysis

To analyze monoamines, antioxidants and MDA in brain samples, rats were sacrificed using conscious cervical dislocation, and isolate their different brain parts [13]. The brain regions were weighed, and for neurotransmitter analysis add (DHBA, 25 ng/mL) as an internal standard. Further to prepare the samples add 0.17 M perchloric acid to homogenize it with the help of Ultra-T homogenizer (Model T-25, Germany). After that for monoamines analysis tissues were centrifuged at 35,000 g and for antioxidants and MDA analysis centrifuged at 1000 g at 4°C for 15 minutes (Sigma Centrifuge, Model 3K30). As well as, to avoid any contamination supernatants were filtered by using 0.22 µm sieve membrane.

Monoamines Estimation in brain region

Neurotransmitter dopamine, serotonin, nor adrenaline and serotonin metabolite 5-HIAA were analyzed by binary gradient Waters HPLC (Model-1525, USA). In addition, C18 Spherisorb RP column (particle size of 5 µm, 4.6 mm i.d. × 250 mm,) sustained at 30°C temperature and linked to a Waters electrochemical detector (Model 2465, USA). Whereas, the mobile phase comprised 1.4 mM sodium octyl sulfonate, 12.5 mM disodium hydrogen orthophosphate, 32 mM citric acid, 0.05 mM EDTA, and 16% methanol (v/v), with the pH adjusted to 4.05. 1.2 mL/min was the flow rate for separation and by using Breeze 3.2, neurotransmitter levels were quantified in ng/gm of brain tissue by comparing sample peak

heights to standard curves [12].

Superoxide dismutase estimation

As described by Mishra and Fridovich in 1972, SOD was analyzed [11]. The samples were observed at 480 nm over a duration of 4 minutes. Enzyme activity was quantified in terms of U/mg at 30°C. A single unit (U) of enzyme was defined as the enzyme quantity required to achieve a 50% inhibition of epinephrine autoxidation.

Catalase estimation

To measure CAT activity, used H_2O_2 as substrate according to Aebi et al 1984 [10]. Also, Enzyme activity was quantified in terms of U/mg at 25 ◦C, whereas for estimation 1U equivalent to deprivation of 1 mol H_2O_2.

Reduced Glutathione estimation

Glutathione levels were considered through, Ellman's reagent (DTNB) and enzyme interaction, which produces a yellow-colored compound. Moreover, the optical density of this compound was recorded spectrophotometrically at 412 nm within 15 minutes, following the method by Garima Sharma et al 2021,Sedlak and Lindsay 1968 [9, 15]. The GSH concentration was determined from a reference curve and articulated as micromoles per milligram of protein (μM/mg protein).

Malondialdehyde estimation

Malondialdehyde (MDA) was assessed as a thiobarbituric acid reactive substance (TBARS) using standard 1,1,3,3-tetraethoxypropan, following the methodology by Ohkawa et al. (1979). Moreover, the optical density of this compound was recorded spectrophotometrically at 532 nm. Overall, in this sample content of protein was analyzed by the Lowry method (1951) [16].

Statistical analysis

ANOVA was used to analysed the data and if the sample found significance then scored it as $p < 0.05$. Moreover, Comparisons between the Chronic Unpredictable, oxidative stress (OS) compound groups and the normal saline, vehicle control, DMC and TME treated groups were performed.

Results

Brain monoamine level

Frontal cortex

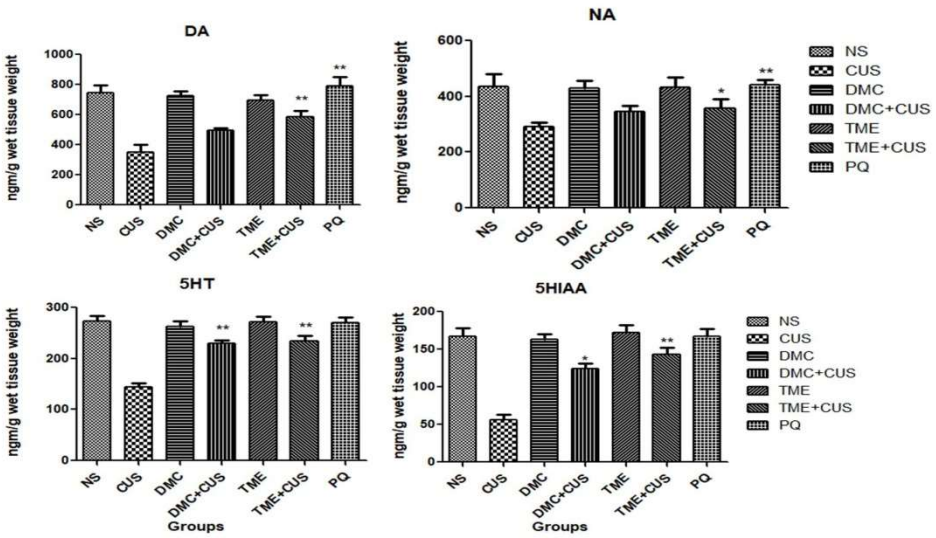


Figure 1. This image depicts NA, DA, 5HT and 5HT metabolite 5HIAA I; control NS, groups II; CUS, groups III; treatment groups DMC and TME, and groups VII reference drug PQ on CUS-induced animal model.

Figure 1 illustrates the impact of oxidative stress DMC and TME on the changes in monoamine levels induced by CUS in the frontal cortex. CUS significantly reduced the levels of dopamine, nor-adrenaline, serotonin, and 5HT metabolites 5HIAA with to the normal saline (NS) control group. Treatment with DMC, TME, and *Panax quinquefolium* (PQ) significantly restored these alterations ($p < 0.05–0.001$) in comparison to the group II; CUS.

Striatum

Exposure to CUS significantly decreased the levels of dopamine, noradrenaline, serotonin, and 5hydroxyindole acetic acid in the striatum ($p < 0.05–0.001$) Figures 3(A) and (B). However, DMC and TME significantly restored the altered levels of monoamine and 5HIAA to the respective CUS group. Whereas treatment with *Panax quinquefolium* (PQ) as reference normalized the CUS-induced changes significantly (Figure 2).

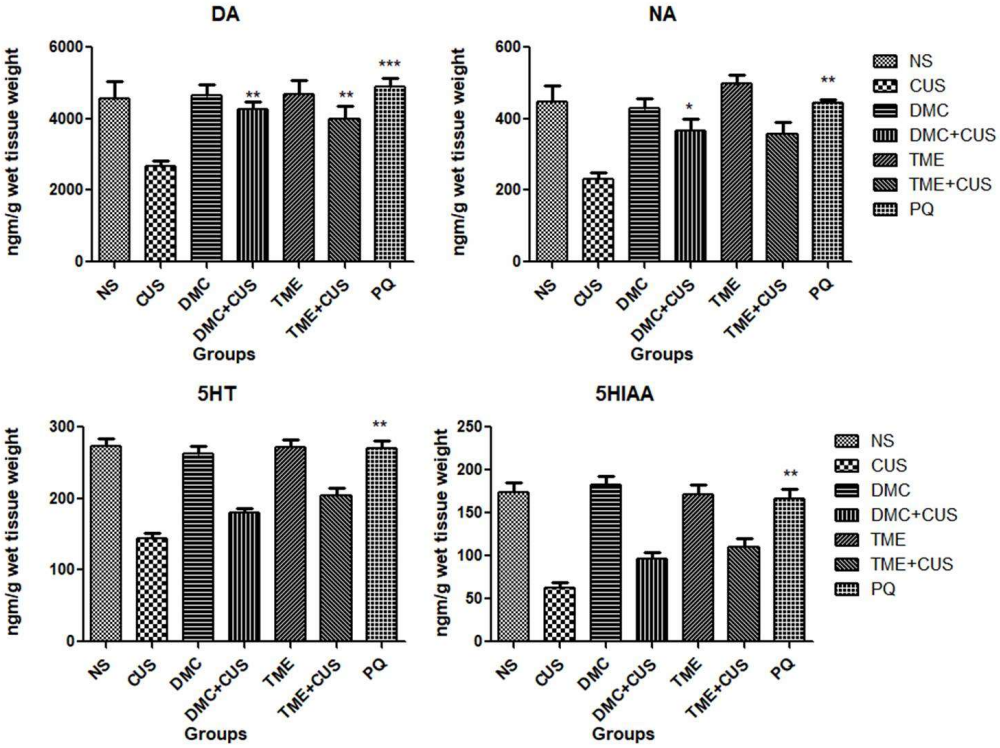


Figure 2. This image depicts NA, DA, 5HT and 5HT metabolite 5HIAA I; control NS, groups II; CUS, groups III; treatment groups DMC and TME, and groups VII reference drug PQ on CUS-induced animal model.

Hippocampus

CUS significantly reduced the monoamine that equated to the others group (NS). Moreover, after the treatment of DMC, TME and *Panax quinquefolium* (PQ) significantly restored the levels of NA and 5HT compared to the respective CUS group (Figure 3).

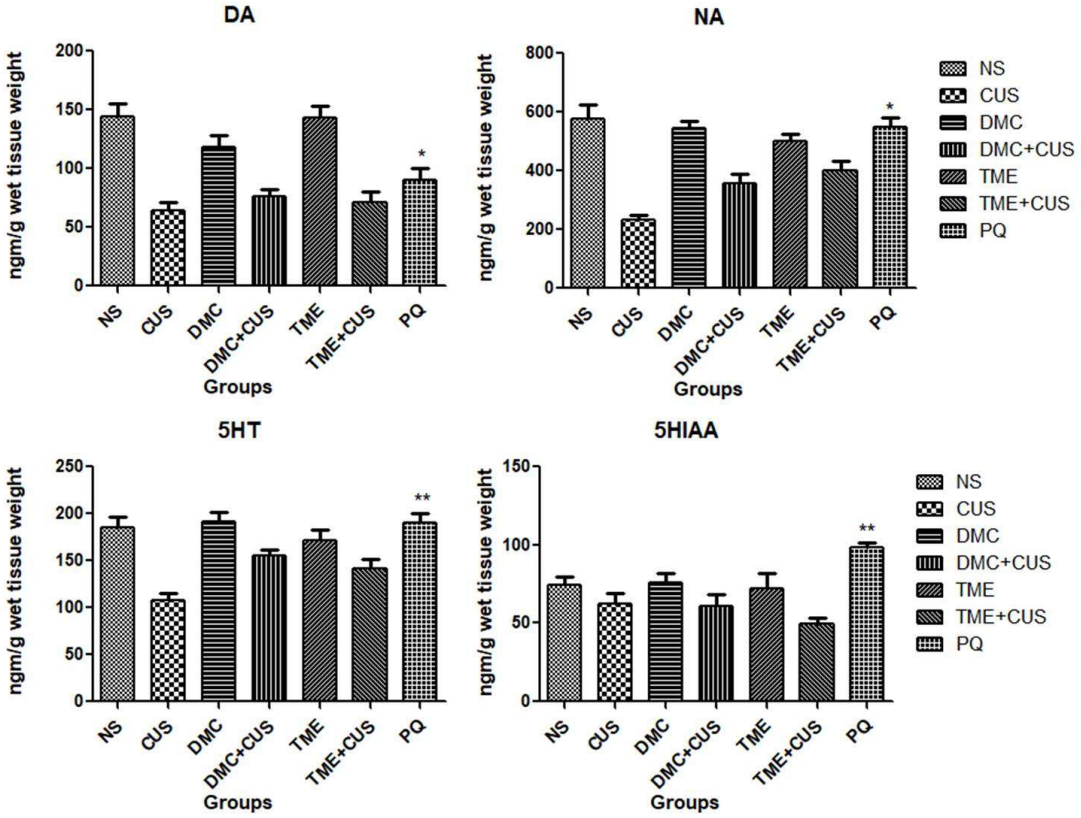


Figure 3. This image depicts NA, DA, 5HT and 5HT metabolite 5HIAA I; control NS, groups II; CUS, groups III; treatment groups DMC and TME, and groups VII reference drug PQ on CUS-induced animal model.

Antioxidant system and lipid peroxidation

DMC and TME changes antioxidant and lipid peroxidation levels caused by CUS in the frontal, striatum, and another brain region hippocampus. Furthermore, CUS potentially dropped in SOD, CAT and glutathione (GSH) levels ($p < 0.01$) across all the samples equated to the group normal saline (NS). In contrast, the levels of malondialdehyde (MDA) significantly increased ($p < 0.01$ and $p < 0.001$, respectively). However, DMC and TME pretreatments significantly ($p < 0.05$–0.001) restored. Whereas the stress affected the LPO and oxidant system.

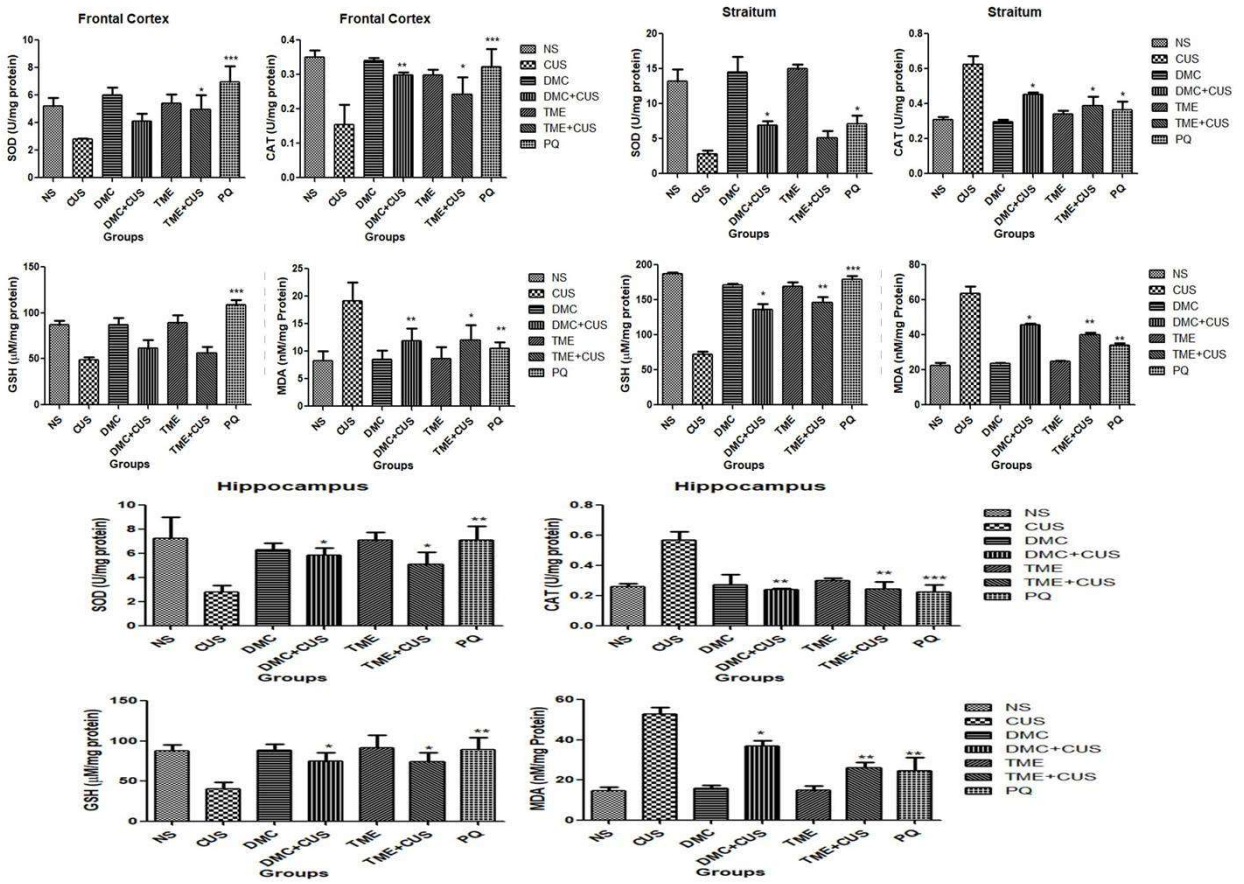


Figure 3. Effect of DMC and TME on antioxidant and MDA in the different brain region like FC, ST and HI. Significant difference of values of in the group I; control NS, groups II; CUS, groups III; treatment groups DMC and TME, and groups VII reference drug PQ on CUS-induced animal model.

Discussion

The monoamine and antioxidant systems in the brain are intricately connected with the hypothalamic-pituitary-adrenal (HPA) axis and are crucial in initiating and sustaining both mental and physical responses to stress [17]. Chronic unpredictable stress (CUS) disrupts the body's ability to adapt to stress and serves as a model comparable to human stress conditions. This study demonstrated that DMC and TME, administered orally at 50 mg/kg body weight, had restorative effects on CUS-induced disruptions in central monoamine levels, which were also linked to enhanced brain antioxidant defense systems. Similar to chronic stress exposure over several days, CUS led to reduced dopamine (DA) levels across all brain regions [18]. The lowered monoamine levels were associated with increased stress sensitivity and heightened utilization [19]. The reduced DA levels in the hippocampus could also be due to decreased cholinesterase activity [20]. However, pretreatment with DMC and TME restored these altered DA levels in both the frontal cortex and striatum. Since impaired monoamine function significantly contributes to stress-related disorders such as anxiety and depression [21], various antidepressants and anxiolytics work by improving monoamine synthesis, release, and availability in the synapse [21]. Our findings suggest that DMC and TME's ability to restore stress-altered DA levels align with these therapeutic mechanisms. The effects of PQ may be associated with its main component, ginsenosides Rb1, recognized for enhancing cholinergic activity and impacting DA responses in the cortex and hippocampus [22]. However, our findings do not entirely clarify why AM compounds were unable to counteract the CUS-induced decrease in hippocampal DA levels, suggesting that additional, complex DA regulatory mechanisms could be involved.

The activation of the nor-epinephrine (NA) system by stress generally occurs briefly [23], which could explain the lowered NA levels during chronic unpredictable stress (CUS), as stressors in this study were applied over a week. Treatment with DMC and TME effectively counteracted the NA decrease induced by CUS. PQ's effect on NA levels might be attributed to ginsenosides, its main component, known for corticosteroid-like effects [24]. Regional variations in monoamine synthesis, distribution, and degradation may also influence monoaminergic responses. The CUS-related reduction in 5-HT and its metabolite aligns with findings indicating reduced brain 5-HT can alter chronic stress responses, implicating 5-HT in stress adaptation [25]. The hippocampus, rich in corticosteroid receptors and diverse 5-HT receptors [26], may link elevated corticosterone and altered serotonergic activity through the HPA-axis feedback mechanism during CUS. DMC and TME normalized depleted 5-HT and 5-HIAA in the frontal cortex, while TME and PQ restored 5-HT in the hippocampus, showing region-specific serotonergic effects potentially due to microenvironmental differences. PQ was also found to normalize serotonergic changes across all brain regions, consistent with prior research showing PQ's ability to reverse stress-induced 5-HT changes [27]. The ginsenosides in PQ may modulate nerve transmission by affecting neurotransmitter availability [22].

Chronic unpredictable stress (CUS) was shown to reduce the activities of superoxide dismutase (SOD) and catalase (CAT) across three brain regions, likely due to the influence of glucocorticoids (GCs) weakening the antioxidant defense system [21]. The decrease in glutathione (GSH) levels can be attributed to its higher consumption during oxidative stress. Treatment with DMC and TME over seven days successfully reversed these CUS-induced disturbances, restoring antioxidant enzyme activity, GSH content, and lipid peroxidation levels to near normal. The differential effects observed between brain regions may result from variations in antioxidant capacity or susceptibility to oxidative stress. Stress-induced GCs are known to damage the oxidative defense system [21], and free radicals produced during catecholamine metabolism may further contribute to this damage [28].

Conclusion – The disrupted monoamine response in the brain likely amplifies oxidative stress during CUS. The ability of DMC and TME to restore the redox balance in different brain regions can be attributed to their role in modulating brain monoamine levels. Adaptogens, such as DMC and TME, provide adaptive defense through various metabolites, whose biological activity depends on the stress context and associated chemical structure. These findings emphasize the potential of pharmacological interventions using active compounds from AM to prevent stress-related neurological and associated disorders.

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