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Decaffeinated Tea Extract and its Fractions attenuate Clonidine- induced Aggressive Behavior in Mice

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ABSTRACT

Introduction: Considerable data have been generated on anti-aggressive drugs of different pharmacological profiles. Present study was based on research findings that caffeine produced inverted 'U' shaped aggressive behavior in mice, lower and very higher doses reducing aggressive behavior and moderate doses increasing aggressive behavior. Therefore, we studied effect of decaffeinated tea and its fractions on clonidine- induced aggression in mice. **Objective:** Objective was to evaluate the effect of polyphenol rich Decaffeinated Tea Extract (DTE) and its fractions namely chloroform fraction (DTCf), ethyl acetate fraction (DTEa), diethyl ether fraction (DTDe) and acetone- water fraction (DTAw) against clonidine- induced aggressive behavior in mice. **Methods:** Mice were pretreated with caffeine (10 mg/Kg, i.p.), DTE (100- 300 mg/kg) or its fractions (100, 200 mg/kg) and clonidine (30 mg/Kg, i.p.) was administered after 30 min. Diazepam (2.5 mg/kg, i.p.) was used as reference standard. Aggressive behaviour viz: latency to first attack and total no. of attacks were observed in transparent activity chamber for1hr duration. **Results:** DTE 300 mg/Kg, i.p. increased latency to first attack and decreased total no. of attacks significantly (P< 0.0001) as compared to control group. DTCf, DTDe and DTAw at doses 100 & 200 mg/kg significantly decreased number of attacks (P<0.0001) while DTEa in doses of 100 and 200 mg/kg, significantly increased latency to first attack (*P*<0.0001) as compared to control group.

Keywords: Decaffeinated tea, Clonidine, Aggression, Polyphenols.

INTRODUCTION

Aggressiveness and anxiety are the normal behavioral response features of animals including humans when exposed to unaccustomed conditions; needs treatment if occurs in excess and repeatedly. Aggressive behaviour is an acute symptom rather than chronic disorder. Impact of neurotransmitter modulation decides the degree and/ or severity of this bizarre social behavior. Various lesions of the CNS are associated with aggressiveness pattern and forebrain to be a region probably involved in the aggression built- up (Baker *et al*. 1980) [2]. The Scientific evidences for the involvement of noradrenaline (NA) in aggression have been reported. In support of vital role of central NA system function, one study suggests low basal presynaptic output of NA while the sensitivity of post- synaptic NA receptors is high, as a function of aggression (Coccaro *et al*. 2003) [4].

Clonidine is non- selective α_2 agonist and partial α_1 adrenergic agonist; it stimulates pre- synaptic α_2 adrenoceptors at lower doses and postsynaptic α_1 adrenoceptors at higher doses (Ushijima *et al*. 1984) [30] indicating a distinct dose-response relationship. Therapeutically, it is used as an antihypertensive drug in the management of surgical procedures in patients (Ghingone *et al*., 1986) [10]. An acute administration of clonidine at higher dose exhibited aggressive behavior in mice characterized by fighting, biting and attacking each other, when placed in pairs (Morpurgo 1968) [18] and self-injurious behavior when placed alone (Razzak *et al*. 1975; Mueller and Nyhan 1983; Katsuragi *et al*. 1984) [22, 19, 13]. Clonidine- induced aggressive behaviour is mediated through stimulation of α_1 adrenoceptors. This is confirmed by the evidences for reduced clonidine aggression by administration of α_1 the selective antagonist- prazosin (Bourin *et al*. 1996) [3]. Aggressive behaviour induced by high doses of clonidine was inhibited by adenosine but conversely potentiated by methylxanthines such as theophylline (Ushijima *et al*. 1984) [30]. This supports the research finding that clonidine- induced aggressive behaviour involved blockage of central adenosine receptor which modulates noradrenergic transmission (Katsuragi *et al*. 1985) [14].

Adenosine triphosphate and adenosine acts as co-transmitter and neuromodulator; co-released with classical neurotransmitter that inhibits spontaneous neuronal firing and the release of excitatory neurotransmitter as well. Adenosine A_1 receptor is high affinity receptor that decreases cyclic AMP and mediate inhibitory effect; A_2 adenosine receptor is low affinity receptor that increases cyclic AMP and mediates stimulatory effect (Van Calker *et al*. 1979) [31]. Methylxanthines, such as theophylline and

caffeine are antagonists of adenosine at both of this receptor (Fujiwara *et al*. 1988) [8]. Caffeine is reported to have an inverted 'U' shaped dose response curve in animal model of aggressive behavior; low (2.5 mg/kg) and very high doses (above 30 mg/kg) suppressing aggression and moderate doses increasing aggression (Wilson *et al*., 2000) [33].

There exists a number of inbred strains of mice that are genetically homogenous are known for particular behavioral patterns, ranging from various levels of the spontaneous activity to diverse responses to clonidine administration (Hano *et al*. 1978) [11]. One hypothesis has put forward that dopaminergic transmission is necessary for the occurrence of clonidine- induced aggressiveness (Maj *et al*. 1981) [16]. In animal models, indices of increased NA function in brain correlate directly with the number of shock- induced aggressive episodes in rodents (Stolk *et al*. 1974) [26]. However, patients with a tendency towards impulsive aggressive behavior, such as borderline personality disorder, have been reported increased agitation during treatment with tricyclic and monoamine oxidase inhibitor antidepressant agents (Soloff *et al*. 1986) [25] that ultimately leads to more NA availability. Interplay between NA and growth hormone (GH) is well studied, decreased activity of pre-synaptic NA neurons has been associated with an amplification of the GH response to clonidine (Eriksson *et al*. 1982) [6].

Caffeine has been a subject of research in many laboratories. Considerable data have been collected on anti-aggressive drugs of different pharmacological profiles. Petkov and Rousseva (1984) [21] have suggested role of brain dopaminergic system in the isolated aggressive rats. Though physiological effects of caffeine are reversible and do not cause a lasting effects on health, however, in patients with anxiety and aggressive behavior, caffeine may cause untoward effects. The trend of using decaffeinated tea is increasing gradually. Henry and Larson (1984) [12] suggested that Polyphenols (bioflavonoids) of tea may have a beneficial sedative action. Sen *et al*., (2020) [24] have shown that decaffeinated tea contain large amount of polyphenols without the unwanted side effects of caffeine.

Since caffeine potentiates clonidine- induced aggression in experimental animals (Wilson *et al*., 2000) [33], the objective of our study was to investigate the effect of acute treatment of decaffeinated tea extract (DTE) and its fractions on clonidine- induced aggressive behaviour in mice. In the present study, we investigated the effect of decaffeinated tea extract and its fractions on latency to first attack and total no. of attacks in mice treated with clonidine.

MATERIALS AND METHODS

Animals

Albino mice were obtained from Global Bioresearch Solutions Pvt. Ltd. Tal-Bhor, Dist. Pune. Mice weighing 22- 25 g were housed in groups of five under standard laboratory conditions at ambient temperature of 25± 1°C and relative humidity 45-55%. 12:12 h light/dark cycle was strictly maintained during the experiment. The animals were fed *ad libitum* with standard feed and water. They were deprived of food 12 h before testing but had free access to water. All the experiments were carried out between 08:00 and 14:00 h.

The protocol of animal experiments was approved by Institutional Animal Ethical Committee (IAEC) (Approval No. SIOP/IAEC/2019/10). The animal house facility of STES's Sinhgad Institute of Pharmacy, Narhe, Pune (SIOP) is registered under the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA) with Reg. No. 1139/a/07/CPCSEA.

Drugs/ chemicals

The decaffeinated tea extract (DTE), its fractions in various solvents, clonidine hydrochloride (Neon Laboratories, Mumbai), caffeine (Sigma, USA) and Calmpose (diazepam) (Ranbaxy, India) were used for the study. Solvents viz: chloroform, ethyl acetate, diethyl ether, acetone (Research-Lab Fine Chem Industries, Mumbai) were used for obtaining respective fractions.

Extraction/ fractionation

The test sample used in the present study i.e. decaffeinated tea powder- "Tetley tea" was purchased from Dorabji, MG Road Camp, Pune. Decaffeinated tea (500 g) was extracted using acetone- water solvent system (80:20) by standard maceration method of extraction (Druzynska *et al*., 2007) [5] as it extracts most of the polyphenols. The decaffeinated tea extract (DTE) was concentrated in rotating evaporator under reduced pressure followed by lyophilizer until dry residue was obtained. DTE was further fractioned using various solvents with increasing polarity and the fractions were evaporated to dryness as stated earlier for DTE. DTE fractions obtained included chloroform fraction (DTCf), ethyl acetate fraction (DTEa), diethyl ether fraction (DTDe) and acetone-water fraction (DTAw) (Babbar *et al*. 2014) [1]. Detailed procedure of extraction and fractionation is given in the flow sheet (Fig.1).

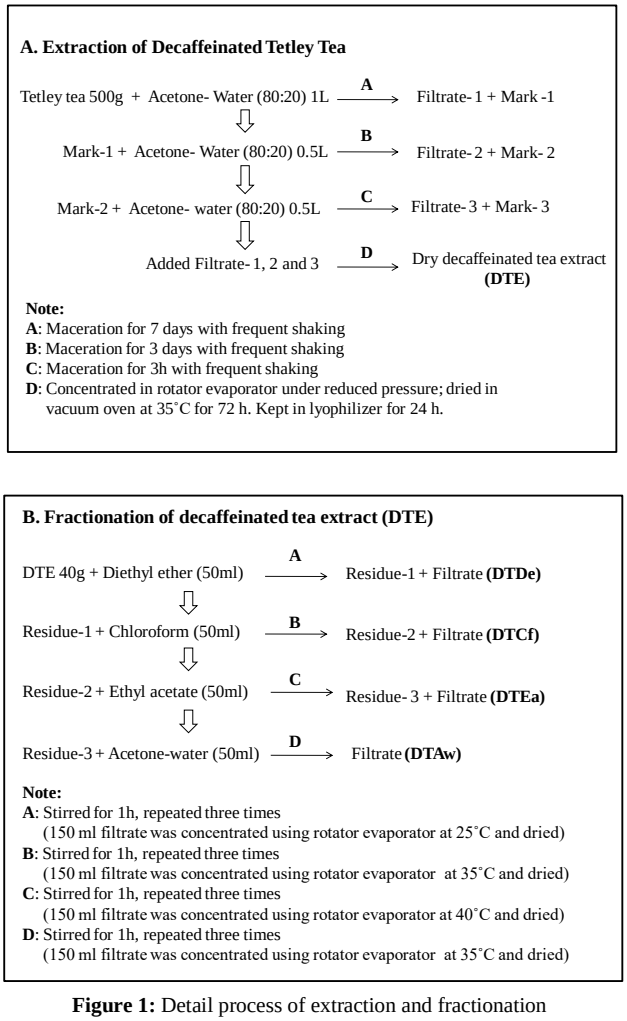

Figure 1: Detail process of extraction and fractionation

Dosage preparation

Clonidine (30mg/Kg, i.p.), caffeine (10mg/Kg, i.p.), DTE (100, 200 and 300mg/Kg, i.p.), DTE fractions (DTCf, DTEa, DTDe and DTAw; 100 and 200 mg/Kg, i.p. each) and Calmpose (diazepam) (2.5 mg/kg, i.p.) were used. All the drug solutions were prepared in pyrogen- free glass wares which were heated for 5 h at 180°C before use. Drugs, test samples were dissolved in distilled water immediately before the use and administered intraperitoneally to mice in a volume of 1 ml/kg.

Assessment of aggressive behaviour

During quarantine period, mice were observed for abnormal aggressive behaviour viz: vocalization, self-biting, attacking and inflicting wounds. Mice with abnormal signs were replaced. Aggression in mice was induced by clonidine administered at the dose of 30 mg/kg, i.p. All drugs, test samples were administered 30 min before clonidine challenge. Immediately after clonidine injection; groups of five mice from the same home cage were placed together in transparent plastic box (20 x 20 x 15) and observed for1 h. The aggressiveness was recorded on the basis of two parameters i.e. latency for first attack and total no. of attacks in 1h duration (Fujiwara *et al*. 1988; Georgieva 1989) [8, 9].

Statistical Analysis

The mean ± SEM in groups was calculated, statistical significance of differences between the means of group analyzed by a one way analysis of variance (ANOVA). An analysis of individual between group comparisons was carried out using Tukey's multiple comparison tests; $P< 0.05$ is considered to be statistically significant.

RESULTS

Extraction and Fractionation

The 500 g of Decaffeinated Tea produced 50 g of extract (DTE), which tested positive for polyphenols. The DTE (40 g) when fractionated with Diethyl ether produced 4.2 g of DTDe fraction. The marc fractionated with chloroform produced 2.5 g of DTCf, on subsequent fractionation with ethyl acetate 8.5 g of DTEa was obtained and finally fractionation with acetone water 18.5 g of DTAw was obtained. These extracts and fractions were soluble in water.

Assessment of Aggressive behavior

Aggression was assessed as latency to first attack and number of biting attacks among mice within 1h duration. Here, after clonidine challenge, aggressive responses began within 5-10 min with marked tremors and piloerection, causing bleeding wounds mainly on the region of tail and the back; and frequency of attack was highest at 15-20 min; diminishing within 35-40 min. Self-biting behaviour was noticed which was preceded by abnormal grooming, nibbing the surface and preening.

DTE (200 & 300 mg/Kg, i.p.) has significantly increased latency to first attack as compared to control group ($P< 0.05$) (Fig.2). DTE 100, 200 and 300 significantly decreased total no. of attacks as compared to control group ($P< 0.0001$) (Fig.3). Among the DTE fractions tested, DTEa in doses of 100 and 200 mg/kg, significantly increased latency to first attack ($P<0.0001$) as compared to control group (Fig.4). All the fractions DTCf, DTEa, DTDe and DTAw at 100 and 200 mg doses caused significant decrease in total no. of attacks as compared to control group ($P<0.001$) (Fig.5). Caffeine exhibited stimulatory effect that deceased latency for first attack and increased no. of attacks. However, the effect of caffeine given with clonidine was not significantly different from the control group.

Effect of DTE on clonidine- induced aggression

A. Latency for first attack

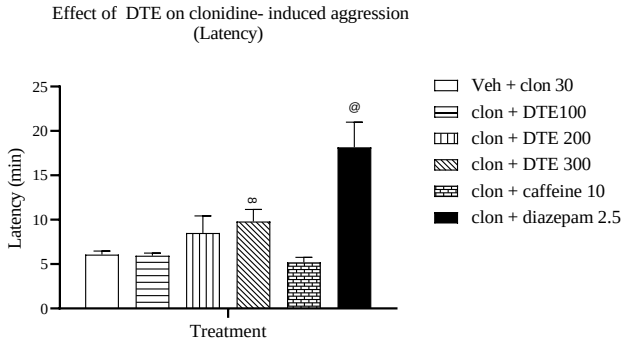

Figure 2: Effect of DTE on clonidine -induced aggression (Latency for first attack)

Data was expressed as mean ± SEM., statistical significance were determined by one way analysis of variance (ANOVA) followed by Tukey's multiple comparison test; $^{@}P<0.0001$, $^{\propto}P<0.05$ as compared to vehicle + clonidine group.

B. Number of attacks

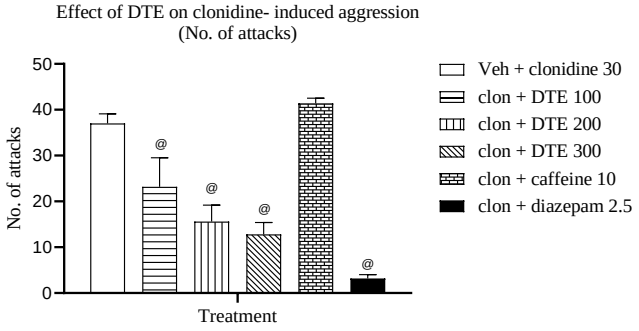

Figure 3: Effect of DTE on clonidine- induced aggression (Number of attacks)

Data was expressed as mean ± SEM., statistical significance were determined by one way analysis of variance (ANOVA) followed by Tukey's multiple comparison test; $^{@}P<0.0001$, as compared to vehicle + clonidine group.

Effect of DTE fractions on clonidine- induced aggression

A. Latency for first attack

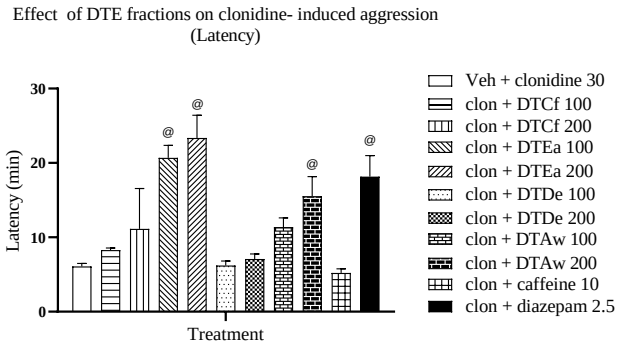

Figure 4: Effect of DTE fractions on clonidine- induced aggression (Latency for first attack)

Data was expressed as mean ± SEM., statistical significance were determined by one way analysis of variance (ANOVA) followed by Tukey's multiple comparison test; $^{@}P<0.0001$, as compared to vehicle + clonidine group.

B. Number of attacks

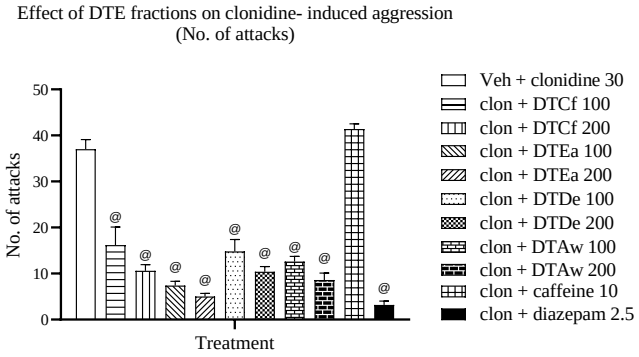

Figure 5: Effect of DTE fractions on clonidine -induced aggression (Number of attacks)

Data was expressed as mean ± SEM., statistical significance were determined by one way analysis of variance (ANOVA) followed by Tukey's multiple comparison test; $^{@}P<0.0001$, as compared to vehicle + clonidine group.

DISCUSSION

Aggressive behavior is considered as an acute symptom rather than a chronic disorder. An ideal anti-aggressive drug must be effective against acute episodes of aggressiveness. Isolated mice show more aggressive behavior than mice housed in group. Social isolation and food deprivation together, potentiate aggressive behavior induced by clonidine (Ushijima *et al*. 1984) [30]. Because of multiple interactions of clonidine with different neurotransmitters and biochemical, the mechanisms involved in clonidine-induced aggression are difficult to understand. Clonidine activates presynaptic $\alpha_2$adrenoceptors resulting in an inhibition of noradrenaline release, while higher doses stimulate postsynaptic α_1 adrenergic receptors. Aggression is mediated through α_1 adrenergic receptors; as prazosin, the α_1 selective antagonist, reduced clonidine aggression (Mogilnicka and Zazula 1986) [17].

Clonidine- produced aggression was strongly reduced by diazepam. Benzodiazepines have been known to exert their actions via activation of GABAergic neurons and release of GABA. However, the inhibitory effect of diazepam on aggressive behavior was not affected by $GABA_A$ receptor antagonist bicuculline. Current evidence symbolizes that benzodiazepine may exert some of their therapeutic actions by potentiating the effects of endogenously released adenosine (Ushijima *et al*. 1984) [30]. Benzodiazepine has been shown to inhibit adenosine uptake into brain slices of rat (Mah and Daly 1976) [15]. In this study diazepam was most effective in suppressing clonidine-induced aggression.

Caffeine at the dose of 20 mg/kg stimulated clonidine- induced aggressive behaviour (Fujiwara *et al*. 1986) [7]. We also observed similar effect of caffeine on clonidine- induced aggression. Same study indicated that haloperidol, a neuroleptic and carbamazepine, an anti-epileptic, significantly decreased aggressive behaviour. Haloperidol induces catalepsy, thereby decreases spontaneous motor activity and reduces degree of aggression. Presence of dopaminergic transmission is necessary for occurrence of aggressiveness. Interaction between dopamine and NA containing neurons in the CNS was described by Baker *et al*., (1980) [2]. In an animal strain specific study, Nikulina & Klimek (1993) [20], in support of this assumption has shown that apomorphine, an agonist of both dopamine receptors D_1 and D_2 potentiated the clonidine- induced aggressiveness in C57BL/6J and DD strain of mice.

In the present study, the polyphenol rich extract of decaffeinated tea (DTE) in a dose of 300 mg/kg, significantly attenuated clonidine-induced aggressive behaviour in mice. These effects of might be explained mainly by its interactions with adenylate cyclase (stimulation of catalytic subunit) and perhaps with other neurotransmitter systems in the CNS. Another possibility is that DTE could have resulted in decreased responsiveness of central postsynaptic α_1 NA receptors; it seems to be the cause of attenuation of clonidine- induced aggression (Fig 2 and 3). Fraction DTEa200 has significantly increased latency for first attack. Flavonoids content in said fractions might be responsible for decrease in aggression. However, total no. of attacks in 1h observation period was significantly decreased by all the DTE fractions; $P<0.0001$ compare to control group. Caffeine, as reported in previous studies, has shown stimulant effect on aggression caused by clonidine. It has decreased latency for first attack. Total no. of attacks were increased the number of attacks, but insignificantly, as compare to control and (Fig. 4 and 5).

These observations are in line with several reports published earlier. Polyphenols, which contain multiple phenol structural units, are abundantly present in tea and have multiple benefits for human health including anti-obesity, anti-hyperglycemic and anti- hyperlipidemic effects. Additionally, polyphenols also have anti-stress effects (Sakakibara and Shimoi, 2020) [23]. Low caffeine tea exhibited antistress effect in mice (Unno *et al*. 2016) [29]. Polyphenols from green tea inhibited oxidative stress caused by haloperidol indicating beneficial effects in treating serious side effects associated with administration of neuroleptics to patients suffering from schizophrenia (Trebaticka and Durackova, 2015) [28]. Suresh and Raju (2013) [27] have reported that polyphenols inhibit foot shock- induced aggression and show anti-dopaminergic effects on schizophrenic rat models.

The outcome of the present study strengthens the hypothesis of effect of DTE and its fractions might be in favour of adenosine, attenuating

clonidine- induced aggressive response. In addition to this, involvement of brain GABA, dopamine etc. and other co-transmitters in realization of inhibitory effect of DTE and its fractions on clonidine-induced aggressive behavior should also be considered. Vignes *et al*. (2006) [32] have reported anxiolytic activity of green tea polyphenol and they attributed this effect to interaction with $GABA_A$ receptors.

CONCLUSION

In conclusion, decaffeinated tea extract (DTE) and its ethyl acetate fraction (DTEa) exerted pronounced inhibitory effects on aggressive responses induced by clonidine. It has been confirmed that caffeine stimulates aggressive behavior. The study suggests that replacing regular tea with decaffeinated tea might be beneficial for patients with impulsive aggressive behavior like borderline personality disorder.

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Conflicts of Interest

All the listed authors do not have conflict of interest.

Declaration

This manuscript/data has not been published or currently under review for publication elsewhere.

REFERENCES

1. Babbar N, Oberoi HS, Sandhu SK, Bhargav VK. Influence of different solvents in extraction of phenolic compounds from vegetable residues and their evaluation as natural sources of antioxidants. J Food. Sci. Technol. 2014; 51(10):2568–75.
2. Baker H, John TH, Reis DJ. Genetic control of numbers of midbrain dopaminergic neurons in inbred mouse strain: Relationship to size and neuronal density of striatum. Proc. Natl. Acad. Sci. USA. 1980; 77:4367-3.
3. Bourin M, Hascoet M, Colombel MC, Redrobe JP, Baker GB. Differential effects of clonidine, lithium and quinine in the forced swimming test in mice for antidepressants: possible roles of serotoninergic systems. Eur. Neuropsychopharmacol. 1996; 6(3):231-6.
4. Coccaro EF, Lee R, McCloskey M. Norepinephrine function in personality disorder: plasma MHPG correlates with Life History of Aggression. CNS. Spectr. 2003; 8(10):731-6.
5. Druzynska B, Stępniewska A, Wolosiak R. The influence of time and type of solvent on efficiency of the extraction of polyphenols from green tea and antioxidant properties obtained extracts. Acta Sci. Pol., Technol. Aliment. 2007; 6(1):27-6.
6. Eriksson E, Eden S, Modigh K. Up- and down regulation of central postsynaptic alpha 2 receptors reflected in the growth hormone response to clonidine in reserpine pretreated rats. Psychopharmacology (Berl) 1982; 77(4):327-31.
7. Fujiwara Y, Sato M, Otsuki S. Interaction of carbamazepine and other drugs with adenosine (A-1 and A-2) receptors. Psychopharmacology. (Berl) 1986; 90(3):332-5.
8. Fujiwara Y, Takeda T, Kazahaya Y, Otsuki S. Inhibitory effects of carbamazepine on clonidine- induced aggressive behavior in mice. Int J Neurosci 1988; (42):77-4.
9. Georgieva JV. Diterpene sclareol glycol inhibits clonidine-induced aggressive responses in mice. Pharmacol. Biochem. Behav. 1989; 34(3):503-5.
10. Ghingone M, Quintin L, Duck PC, Kehler CH, Calvillo O. Effect of clonidine on narcotic requirement and hemodynamics response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology. 1986; 64(1): 36-2.
11. Hano J, Vetulani J, Sansone M, Oliverio A. Effect of clonidine, amphetamine and their combinations on the locomotor activity of CD-I C57BL/6 mice. Pharmacol. Biochem. Behav. 1978; 9(6):741-6.
12. Henry JP, Larson PS. Reduction of chronic psychosocial hypertension in mice by decaffeinated tea. Hypertension. 1984; 6(3):437-4.
13. Katsuragi T, Ushijima I, Furukawa T. The clonidine-induced self-injurious behavior of mice involves purinergic mechanisms. Pharmacol. Biochem. Behav. 1984; 20(6):943-6.
14. Katsuragi, T. & Furukawa, T. Novel, selective purinoceptor antagonists: Investigation of ATP as a neurotransmitter. Trends in Pharmacological Sciences Volume 6, Cell Press 1985, Pages 337-9.
15. Mah HD, Daly JW. Adenosine-dependent formation of cyclic AMP in brain slices. Pharmacol. Res. Commun. 1976; 8(1):65-79.
16. Maj J, Mogilnicka E, Klimek V, Kordecka- Magiera A. Chronic Treatment with Antidepressants: Potentiation of Clonidine-Induced Aggression in Mice via Noradrenergic Mechanism. J. Neural. Transm. 1981; 52(3):189-7.
17. Mogilnicka E, Zazula M. Interaction between β-adrenoceptor agonists and α_1 adrenergic system. A behavioral study with the clonidine-induced aggression test. Pol. J. Pharmacol. Pharm. 1986; 38(5-6):529-34.
18. Morpurgo C. Aggressive behaviour induced by large doses of 2-(2,6-dichloro phenylamine- 2- Imidazoline hydrochloride (ST115) in mice. Eur. J. Pharmacol. 1968; 3(4):374-7.
19. Mueller K, Nyhan WL. Clonidine potentiates drug induced self-injurious behavior in rats. Pharmacol. Biochem. Behav. 1983; 18(6):891-4.
20. Nikulina EM, Klimek V. Strain Differences in Clonidine-Induced Aggressiveness in Mice and its Interaction with the Dopamine System. Pharmacol. Biochem. Behav. 1993; 44(4):821-5.
21. Petkov VV, Rousseva S. Effects of caffeine on aggressive behavior and avoidance learning of rats with isolation syndrome. Exp. Clin. Pharmacol. 1984; 6(8):433-6.
22. Razzak A, Fujiwara, M, Ueki S. Automutilation induced by clonidine in mice. Eur J Pharmacol 1975; 30(2):356-9.
23. Sakakibara H, Shimoi K. Anti-stress effects of polyphenols: animal models and human trials. Food. Funct. 2020; 11:5702-17.
24. Sen G, Sarkar N, Nath M, Maity S. Bioactive components of tea. Arch Food Nutr Sci. 2020; 4:1-9.
25. Soloff PH, George A, Nathan RS, Schulz PM, Perel JM. Paradoxical effects of amitriptyline on borderline patients. Am. J. Psychiatry. 1986; 143(12):1603-5.
26. Stolk JM, Conner RL, Levine S, Barchas JD. Brain norepinephrine metabolism and shock-induced fighting behavior in rats: differential effects of shock and fighting on the neurochemical response to a common footshock stimulus. J. Pharmacol. Exp. Ther. 1974; 90(2):193-209.
27. Suresh P, Raju AB. Antidopaminergic effects of leucine and genistein on shizophrenic rat models. Neurosciences (Riyadh). 2013; 18(3):235-41.
28. Trebaticka J, Durackova Z. Psychiatric Disorders and Polyphenols: Can They Be Helpful in Therapy? Oxid. Med. Cell. Longev. 2015; 2015:248529.
29. Unno K, Hara A, Nakagawa A, Iguchi K, Ohshio M, Morita A, *et al*. Anti-stress effects of drinking green tea with lowered caffeine and enriched theanine, epigallocatechin and arginine on psychosocial stress induced adrenal hypertrophy in mice. Phytomedicine. 2016; 23(12):1365-74.
30. Ushijima I, Katsuragi T, Furukawa T. Involvement of adenosine receptor activities in aggressive responses produced by clonidine in mice. Psychopharmacology. 1984; 83(4):335-9.
31. Van Calker D, Muller M, Hamprecht B. Adenosine regulates via two different types of receptors: The accumulation of cyclic AMP in cultured brain cells. J. Neurochem. 1979; 33(5):999-1005.

32. Vignes M, Maurice T, Lante F, Nedjar M, Thethi K, Guiramand J, Recasens M. Anxiolytic properties of green tea polyphenol (-)-epigallocatechin gallate (EGCG). Brain. Res. 2006; 1110(1):102-15.
33. Wilson JF, Nugent NR, Baltes J, Tokunaga S, Canic T, Young B, el al. Effects of low doses of caffeine on aggressive behavior of male rats. Psychological Reports. 2000; 86(3 Pt1);941-6.

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