Original article

Potential benefits of gallic acid as skeletal muscle relaxant in animal experimental models

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ABSTRACT

Background and Objective: Many natural bioactive chemicals have been shown to have functional activity, suggesting that they could be useful in the treatment and management of a wide range of chronic conditions. Flavonoids, which include gallic acid (GA), are the most abundant polyphenols found in nature. Skeletal muscle relaxants are drugs that reduce undesired spasms while maintaining awareness and reflexes unaffected. The purpose of this investigation was to determine if GA has any skeletal muscle relaxant properties in experimental animal models.
Materials and Methods: The muscle relaxant activity of three dosages of GA (5, 10, and 20 mg/kg) was compared to that of normal diazepam (5 mg/kg) utilizing climbing, chimney, and modified Kondziela's inverted tests. An analysis of variance (ANOVA) and a post-ANOVA Tukey multiple comparisons test were used to assess the data.
Results: Animals given 10 and 20 mg/kg of GA had a great deal of trouble climbing up the chain, presumably because their muscles were relaxed. Similarly, rats given a high dose of GA (20 mg/kg) had a significantly ($P < 0.05$) longer response time in the chimney test, indicating a lack of attention and slowed muscle tone, resulting in problems with motor coordination. In inverted testing, animals given a high dose of GA had a significantly ($P < 0.01$) reduced holding capacity on the mesh for a longer period of time. A decrease in holding time is caused by a decrease in muscular contraction. The low dose of GA, on the other hand, failed to show muscle relaxant effect in any of the three models.
Conclusions: As a conclusion, our data show that GA has a dose-dependent skeletal muscle relaxant effect when administered orally to mice.

1. Introduction

Skeletal muscle relaxants are drugs that reduce unwanted spasms or spasticity without affecting wakefulness or reflexes. They can help with a wide range of neurological and painful mus-culoskeletal issues (Naidu and Rani, 2019). Muscle relaxant drugs have been used since the sixteenth century. By 1943, neuromuscular blocking drugs were routinely employed as muscle relaxants in anaesthesia and surgery (Veena et al., 2015). According to a World Health Organization estimate, over 450 million people suffer from a neurological or behavioral disorder (WHO, Geneva; 2001). This accounts for 12.3% of the global disease burden (George et al., 2012). Drugs that affect skeletal muscle function are used to treat muscle spasms, pain, and hyperreflexia. The two main components of this category of medicine are neuromuscular blockers and spasmolytics. The first is more commonly employed during surgical procedures, whereas the second is used to relieve musculoskeletal pain (Craig and Stitzel, 2003). Nonetheless, spasmolytics are not recommended as a first-line treatment for acute low back pain since they are no more effective than paracetamol or NSAIDs,

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and their efficacy in fibromyalgia is lower than antidepressants (Chou et al., 2007, Van Tulder et al., 2003). The risk of addiction and drug interactions, as well as the chance of dizziness and sleepiness, all add to the reasons for their restricted use. Additionally, an increased risk of falling has been associated with currently available skeletal muscle relaxants. These medicines are incorrectly used as a substitute for standard pain therapies in the elderly population, and they can be just as dangerous as opioids (Trueman et al., 2020). As a result, it is critical to support reputable research into developing a muscle relaxant that is free of misuse and other undesirable consequences associated with current muscle relaxants, as well as having high efficacy in reducing muscular pain and other neuromuscular abnormalities (Soprano et al., 2020). A number of recent studies have investigated the use of natural substances to treat a variety of diseases (Asdaq et al., 2020). The presence of phytoconstituents in medicinal plants makes them extremely beneficial to human health. Alkaloids, glycosides, tannins, flavonoids, and phenolic compounds are the most important of these components. The phenolic acids, which comprise hydroxybenzoic and hydroxycinnamic acids, are a varied category. Ferulic acid, ellagic acid, synergic acid, caffeic acid, and other phenolic acids have been reported from plants. They are also being studied as alternatives for synthetic antioxidants in the food, cosmetics, and pharmaceutical industries. Gallic acid, which can be found in a range of vegetables, fruits, tea, coffee, and wine, is one of the most well-known phenolic acids. It can be found in free acids, esters, catechin derivatives, and hydrolysable tannins in plants (Soong and Barlow, 2004). Gallic acid (GA) is a kind of phenol and 3. 4, 5-trihydroxybenzoic acid is its chemical name. Gallic acid's structure contains phenolic groups, which act as a source of easily available hydrogen atoms, allowing radicals to be delocalized over the phenolic structure (Nayeem et al., 2016).

Gallic acid (GA) and its derivatives have been reported to have a variety of pharmacological effects. It has been shown to have hepatoprotective properties (Tang et al., 2003, Kanai and Okano, 1998) as well as the ability to prevent mouse lung adenomas (Seyed et al., 2013). It is also said to have anti-oxidant properties (Gichner et al., 1987, Franziska et al., 2007). GA exhibits antimicrobial action against methicillin-resistant Staphylococcus aureus and Helicobacter pylori (Borges et al., 2013, Roberto et al., 2013). Antidepressant (Ritu and Dinesh, 2013), antiparkinson (Chen, 2003), anti diabetic (Vishnu Prasad et al., 2010), anti malarial (Griffith et al., 2002), diuretic (Ramya et al., 2014), cardioprotective (Snehal and Ramesh, 2011), antiviral (Kratz et al., 2008), antifungal (Ana et al., 2014), wound healing (Nayeem and Karvekar, 2011), anthelmintic (Ndjonka et al., 2014), and anxiolytic (Dhingra et al., 2012) are some of the other described properties.

As previously stated, a more effective and safer muscle relaxant that may be prescribed broadly without the risk of addiction is required. It's worth looking at GA's potential as a skeletal muscle relaxant in intact animal models because it's been connected to anxiolytic properties (Dhingra et al., 2012). Therefore, the goal of this study was to explore the involvement of gallic acid as a skeletal muscle relaxant in animal experimental models.

2. Materials and methods

2.1. Chemicals and drugs

For the experiment, Al-Majharia international trading establishment in Saudi Arabia provided methylcellulose and sodium chloride, while Gulf Scientific Glass Industry Limited in Saudi Arabia and Scientific Equipment Trading Establishment in Saudi Arabia provided glasswares and other required equipment, respectively. All other chemicals needed for this investigation were purchased from well-known companies, and the specifications were saved for future reference.

2.2. Experimental animals

Wistar albino mice weighing 16–25 g, housed at 25 °C in an air-conditioned animal room under regular conditions, were employed in this experiment (total 90, 30 for each model). The mice were given free access to regular laboratory feed and water, and they were acclimatized to laboratory settings 48 h prior to the experiment to reduce non-specific stress. The Research Committee at AlMaarefa University's College of Pharmacy in Riyadh, Saudi Arabia, approved the study protocol (**MCST (AU)-COP 1940/RC**).

2.3. Experimental protocol

The animals were split into five groups, each with six animals. Groups I and II received distilled water and diazepam 5 mg/kg [29] (p.o), respectively, as the control and standard groups. Low (5 mg/kg p.o), medium (10 mg/kg p.o), and high (20 mg/kg p.o) doses of GA (Shoubaky et al., 2016) were given to Group III, IV, and V, respectively.

2.4. Climbing test

Yemitan and Adeyemi (2003) were the ones who first proposed this test. Mice were taught to use their forepaws to climb a 50-centimetre chain by placing them on the chain's free end. The chain is suspended using a clamp-on from a laboratory table (90 cm from the ground). A normal mouse grabs the chain with its forepaws and, once free, climbs the chain with its two feet until it reaches a marked spot 2 cm from the top. Prior to the trial, mice were given a day of training. The 50-centimetre chain was given to each mouse three times. Mice who arrived at the goal in under 30 s were chosen for further testing. Muscle relaxation was measured by the amount of time it took to ascend a chain. After 30 min, 60 min, 120 min, and 240 min, muscle relaxant action was measured.

2.5. Chimney test

This is one of the most used tests for determining the action of tranquilizers and muscle relaxants (Ahmad et al., 2019, Adeyemi et al., 2006). The cylinders were Pyrex glass cylinders with a length of 30 cm. Mice measuring 16 to 18 g had a 22 mm internal diameter, mice weighing 18 to 20 g had a 25 mm internal diameter, and mice weighing 20 to 22 g had a 28 mm internal diameter. Each tube has a mark 20 cm from the bottom. Initially, the tube was kept in a horizontal posture. Near the end of the tube, near the mark, a mouse with its head forward was introduced. When the mouse reaches the other end of the tube, which it may be pushed towards with a rod if necessary, the tube is moved to a vertical position. It was timed how long it took the mouse to climb backwards out of the cylinder at the top. Prior to the trial, mice were given a day of training. Each mouse had three attempts at climbing backwards, each with a one-minute pause in between. Mice were utilized in the experiment who climbed backwards in 30 s. The inability of the mice to climb backwards out of the tube in 30 s served as the endpoint for determining muscle relaxant action. Mice that had previously been investigated were uniformly divided into groups (Groups I-V) and treated accordingly. After 30 min, 1 h, 2 h, and 4 h of medication administration, muscle relaxant activity was measured.

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Table 1
Descriptive statistics of Climbing test.

Time (minutes) post-administration	Treatment	Distance travelled (cm)	Time is taken to travel (sec)
30	Control	41.1 ± 9.28	18.3 ± 3.22
	Diazepam	24.1 ± 3.22***	30.0 ± 0.00
	GA 5 mg/kg	50.0 ± 0.00	12.0 ± 2.3
	GA 10 mg/kg	50.0 ± 0.00	15.8 ± 5.22
	GA 20 mg/kg	41.0 ± 4.39	21.4 ± 12.5
60	Control	50.0 ± 0.00	18.9 ± 4.44
	Diazepam	07.3 ± 1.98***	30.0 ± 0.00
	GA 5 mg/kg	50.0 ± 0.00	15.9 ± 3.75
	GA 10 mg/kg	44.2 ± 10.56	24.5 ± 5.76
	GA 20 mg/kg	32.0 ± 6.57*	21.80 ± 4.33
120	Control	46.0 ± 4.47	18.8 ± 7.13
	Diazepam	12.3 ± 5.21***	30.0 ± 0.00
	GA 5 mg/kg	50.0 ± 0.00	16.12 ± 1.47
	GA 10 mg/kg	35.2 ± 0.20*	16.60 ± 2.94
	GA 20 mg/kg	23.25 ± 3.59**	19.65 ± 5.23
240	Control	48.0 ± 6.7	19.0 ± 4.4
	Diazepam	14.8 ± 3.49***	30.0 ± 0.00
	GA 5 mg/kg	41.3 ± 9.87	23.47 ± 3.32*
	GA 10 mg/kg	26.2 ± 3.08**	23.40 ± 4.22*
	GA 20 mg/kg	23.2 ± 4.45**	21.80 ± 4.01*

Values are given as mean ± SEM, n = 6, GA:Gallic acid; $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$ when compared to the control group (Chi-Square test).

2.6. Modified Kondziela's inverted screen test

The inverted screen is a 43-centimetre-square wire mesh (Vogel and Drug, 2002, Deacon, 2013, Bawazeer et al., 2020) made up of 12-remillimetre squares of 1 mm-diameter wire. It is surrounded by a 4 cm deep wooden bead (which pre-vents the occasional mouse which attempts to climb onto the other side). The Mouse was placed in the center of a reversed (180°) wire mesh screen, and a stopped clock was started, with the mouse's head descending first. The experiment used mice that were held upside down for 60 s. The inability to hang upside-down for 60 s was described as muscle relaxation. Animals that fell from the mesh within 10 s were given a score of '1,' while those that fell between 11 and 25 s and 26 to 59 s were given scores of '2' and '3,' respectively. Those who fell after 60 s were given a 4. Following 30 min, 1 h, 2 h, and 4 h after medication administration, muscle relaxant activity was assessed in each group of animals.

2.7. Statistical analysis

The climbing test employed a two-way multivariate analysis of variance (two-way MANOVA) to investigate if the two independent factors of drug treatment and recording time, as well as the two dependent variables of distance traveled and time spent to cross that distance, had any effect on each other. Wilks' Lambda (), a multivariate statistic, was used to interpret the impact of independent variables on dependent variables. To examine the influence of treatment and time of recording response on a single dependent variable, the chimney and modified Kondziela's inverted screen tests used Univariate Analysis of Variance. To determine the level of significance, Post-ANOVA Tukey multiple comparisons were used. SPSS IBM 25 was used for the study, and P 0.05 was considered statistically significant.

3. Results

3.1. Effect of GA using climbing test

Previously, trained mice were expected to climb the chain for a maximum of 30 s over a 50-centimeter distance. Animals that

quickly ascend the chain are a sign that the medication has no muscle relaxant properties. When comparing animals treated with either of three dosages of GA to the usual control group 30 min later, the distance traveled in a given period was not significantly different (Table 1). Furthermore, the time taken by these three groups is not significantly different from the time taken by the normal control group, demonstrating that GA has no muscular relaxant effect 30 min after administration.

A high dose (20 mg/kg) of GA resulted in a significant reduction in the distance traveled in a given period when compared to control group animals after 60 min of treatment, but other doses of GA showed no significant difference. When animals were assessed for their climbing abilities on the chain after 2 h and 4 h, both medium and high doses (10 and 20 mg/kg) showed considerably less travelled distance in 30 s than the control group.

When compared to the control group, the diazepam group demonstrated a significant reduction in the distance travelled in 30 s at all recording times (30, 60, 120, and 24 min), indicating their ability to promote muscular relaxation (Table 1). However, by the end of two hours, there was a modest improvement in travel distance, which stayed nearly constant until the end of four hours. Because these animals had poor muscular coordination, they were labeled as potent muscle relaxants.

Treatment had a significant impact on the dependent variable, according to a two-way multivariate analysis of variance (two-way MANOVA). The impact of independent factors (drug administered) on dependent variables was examined in all four major multivariate tests (distance travelled and time taken to travel). Pillali's trace test, Hotelling's trace, Wilk's Lambda, and Roy's Largest root test were the four tests employed.

The P-value was 0.001 based on the results of all four tests, indicating that there is a statistically significant effect of animal treatment on both the dependent and independent variables. To put it another way, some of the treatments in the research groups were able to reduce the chain's transit time. Furthermore, the effect of treatment on travel time varies depending on when the reaction is recorded. Pillali's trace test (P = 0.001), Hotelling's trace (P = 0.000), and Roy's Largest root (P = 0.000) tests all revealed a significantinfluence of treatment at different recording times. Wilks' Lambda (Λ) was the most widely suggested test. On the

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Table 2
Descriptive statistics of Chimney test.

Time (minutes) post-administration	Treatment	Response time (sec)	Significance (P Value)
30	Control	3.88 ± 2.03	
	Diazepam	11.11 ± 4.13***	0.001
	GA 5 mg/kg	3.9 ± 1.01	0.265
	GA 10 mg/kg	4.9 ± 1.00	0.594
	GA 20 mg/kg	4.8 ± 1.02	0.487
60	Control	4.7 ± 1.25	
	Diazepam	15.0 ± 0.00***	0.001
	GA 5 mg/kg	6.3 ± 0.98	0.589
	GA 10 mg/kg	6.1 ± 1.06	0.398
	GA 20 mg/kg	7.5 ± 1.10	0.234
120	Control	4.5 ± 0.88	
	Diazepam	15.0 ± 0.00***	0.001
	GA 5 mg/kg	4.4 ± 0.54	0.523
	GA 10 mg/kg	7.4 ± 1.02	0.442
	GA 20 mg/kg	8.2 ± 1.59	0.081
240	Control	5.6 ± 1.02	
	Diazepam	15.0 ± 0.00***	0.001
	GA 5 mg/kg	6.1 ± 0.87	0.542
	GA 10 mg/kg	7.7 ± 0.98	0.312
	GA 20 mg/kg	11.7 ± 1.45*	0.034

Values are given as mean ± SEM, n = 6, GA:Gallic acid; *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ when compared to the control group (Chi-Square test).

Table 3
Descriptive statistics of Modified Inverted test.

Time (minutes) post administration	Treatment	Response time (sec)	Significance (P value)
30	Control	48.20 ± 2.03	
	Diazepam	24.09 ± 4.13***	0.001
	GA 5 mg/kg	48.66 ± 1.01	0.876
	GA 10 mg/kg	45.40 ± 1.00	0.532
	GA 20 mg/kg	38.98 ± 1.02	0.082
60	Control	44.00 ± 1.25	
	Diazepam	10.87 ± 0.00***	0.000
	GA 5 mg/kg	44.3 ± 0.98	0.893
	GA 10 mg/kg	43.2 ± 1.06	0.675
	GA 20 mg/kg	27.1 ± 1.10	0.058
120	Control	43 ± 0.88	
	Diazepam	5.88 ± 0.00***	0.001
	GA 5 mg/kg	51.4 ± 0.54	0.887
	GA 10 mg/kg	31.1 ± 1.02	0.054
	GA 20 mg/kg	16.2 ± 1.59*	0.021
240	Control	50.87 ± 1.02	
	Diazepam	2.78 ± 0.00***	0.001
	GA 5 mg/kg	51.9 ± 0.87	0.876
	GA 10 mg/kg	22.8 ± 0.98*	0.058
	GA 20 mg/kg	10.65 ± 1.45**	0.009

Values are given as mean ± SEM, n = 6, GA:Gallic acid; *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ when compared to the control group (Chi-Square test).

combined dependent variables, it also revealed a statistically significant interaction effect between the type of treatment administered and the recording duration.

3.2. Effect of GA using chimney test

Table 2 shows that at all recording times, the response time of diazepam-treated rats was considerably longer than the control group. At 30 and 60 min recordings, no significant difference was seen in groups given GA 5 mg, 10 mg, and 20 mg/kg. At 120 min, animals given a high dose of GA (20 mg/kg) showed a trend of muscular relaxant activity, although it was not significant. The

response time of rats given a high dose of GA (20 mg/kg) was significantly increased at 240 min recording.

3.3. Effect of GA using inverted test

When compared to control animals, diazepam-treated animals cling on to mesh for significantly less time. The animals given a low amount of GA (10 mg/kg) held the mesh for an extended period of time, practically identical to the control groups (Table 3). When compared to the control, animals given a modest dose (25 mg/kg) showed a tendency of activity from 120 to 240 min.

At 120 min and 240 min, animals given a high dose of GA showed a considerably reduced holding capacity on the mesh.

4. Discussion

The study used standardized animal experimental settings to investigate the role of one of the naturally occurring chemicals, gallic acid (GA), as a muscle relaxant.

The current investigation found a dose-dependent pharmacological effect on diminishing muscle strength and decreasing muscle tone. The experimental models used in our investigation have been established and verified as models to assess muscular tone, alertness, and muscle strength in the literature.

The Climbing test is used to evaluate motor balance and coordination (Luong et al., 2011). Animals with extremely relaxed muscles had a tough time ascending the chain, while others were able to do so but took longer than the control animals. The Chimney test is a measure of an animal's alertness. Animals having retarted muscle tone had trouble with muscle coordination, which was similar to a previous study (Muhammad et al., 2013). Our findings are consistent with those of an earlier study that used an inverted test in which animals were unable to hold on to the mesh in the inverted posture after being treated with muscle relaxant drugs, and a decrease in muscular contraction decreased the holding period (García-Campos et al., 2020).

Diazepam, a centrally acting muscle relaxant, was employed as a control in our study to examine the effects of GA. GA exhibits a competitive kind of inhibition in brain synaptosomal membranes by binding to the central BDZ-R with a Ki in the low micromolar range. In our investigation, a high dose of GA caused muscle incoordination, similar to an earlier work (Dhingra et al., 2012) in which GA was demonstrated to have anxiolytic activity through its competitive activity in the brain. We think that GA may have a centrally acting muscle relaxant effect. Low dosages of GA failed to produce equivalent effects in this investigation, implying that only a lower concentration of GA was available to penetrate the blood brain barrier that was not sufficient enough to elicit the therapeutic response seen with higher doses.

In climbing and chimney testing, GA's muscle relaxant efficacy was found to be high four hours after ingestion. In the inverted test, a high dose of GA showed a rather early beginning of action (from 2 hrs), and even a moderate dose of GA showed a positive tendency toward muscle relaxant potential. In contrast, classic BDZs result in a considerable reduction in these parameters, indicating high-intensity muscle relaxation. The effect of BDZs is also spontaneous and visible from the moment the reaction is recorded, while the effects of the large dose of GA are delayed. Reduced solubility, slow absorption, or delayed distribution of GA for central effects could all contribute to GA's delayed onset of action. In order to better target tissues and organs and increase therapeutic efficacy, micro- and nanodelivery for medicinal formulations containing GA should be explored and implemented (Huang et al., 2019).

5. Conclusion

In conclusion, our findings demonstrate that GA possesses dose-dependent skeletal muscle relaxant characteristics when given orally to mice. Moreover, because the muscle relaxant function was delayed, it would be beneficial to optimize the formulation to promote better absorption and distribution, which would improve the formulation's pharmacokinetic profile and give a desirable pharmacological impact. GA must also be examined in direct centrally acting models and compared to in-vitro experiments in order to determine the exact mechanism of action.

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