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EFFECT OF iNTERACTION BETWEEN TWO CALCIMIMETIC DRUGS; NIFEDIPINE AND gENTAMICIN ON SOME CARDIOVASCULAR PREPARATIONS IN EXPERIMENTAL ANIMALS

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Abstract
This study examines the effects of CaSR agonists, specifically nifedipine and gentamicin, on different cardiovascular parameters using both in-vitro and in-vivo trials. Gentamicin demonstrated a dose-dependent decrease in myocardial contraction amplitudes in isolated perfused rabbit hearts. Additionally, it suppressed basal tone and lowered NE-precontracted strip amplitudes in aortic strips. Gentamicin enhanced the cholinomimetic impact of acetylcholine, while suppressing the sympathomimetic impact of isoprenaline and norepinephrine, as well as the stimulating effects of histamine, serotonin, and Ca2+-gluconate.
The interaction trials between gentamicin and nifedipine demonstrated a notable decrease in the amplitudes of cardiac contractions as compared to the use of gentamicin alone. In in-vivo trials on anaesthetized rats, gentamicin elicited a dose-dependent drop in arterial blood pressure and an increase in heart rate. The coadministration of gentamicin with nifedipine led to a more significant decrease in blood pressure and heart rate, accompanied by cardiac ischemia alterations in electrocardiograms.
The results em
phasize the cardiac inhibitory, vasorelaxant, and hypotensive properties of gentamicin, as well as its ability to potentially cause heart ischemic alterations. The combination of nifedipine and gentamicin led to acute cardiovascular failure and widespread ischemia alterations. Exercise caution when administering them together, with particular emphasis on the necessity for meticulous dosage modification and ongoing monitoring of blood pressure and electrocardiogram (ECG). This study emphasizes the necessity for more research to gain a deeper comprehension of the function of calcimimetics in the cardiovascular system and guarantee their secure implementation in the treatment of heart disease.

Keywords: CaSR agonists, Nifedipine, Gentamicin, Cardiovascular parameters, Dose-dependent response.

Introduction

Cardiovascular disorders continue to be a major source of illness and death worldwide, requiring ongoing investigation into pharmaceutical treatments[1]. Calcimimetic medicines, which control cellular reactions to calcium signaling, are among the fascinating candidates[2].

Calcimimetics, such as nifedipine and gentamicin, affect the calcium-sensing receptor (CaSR) and are believed to influence cardiovascular functions[3]. Nifedipine, a widely recognized calcium channel antagonist, predominantly impacts the smooth muscle cells, resulting in vasodilation and reduced cardiac contractility[4]. Conversely, gentamicin, an antibiotic, has been acknowledged for its potential impact on several physiological systems, including cardiovascular parameters.

The mutation of CaSR elucidates the underlying mechanisms of various disorders and has revolutionized the understanding of cell signaling[5]. Subsequently, extracellular calcium (Ca2+)0 was recognized as an initial signaling molecule capable of activating CaSR[6]. Elevated extracellular calcium levels induce the release of intracellular calcium, a well-established phenomenon recognized as a second messenger[7]. In 1995, Brown et al. provided a definition of CaSR as a receptor that binds to an inorganic chemical rather than a hormone[8]. They also identified this receptor as a seven transmembrane domain G-protein coupled receptor, belonging to the group II family C of metabotropic glutamate receptors[9]. In 1996, Brown et al. discovered that the calcium receptor was initially identified on the parathyroid chief cells and thyroid C-cells[10, 11]. They also noted that these cells are responsible for detecting calcium levels and maintaining calcium balance in the body.

The present study aims at investigating the potential impact of CaSR agonists, specifically nifedipine and gentamicin, on various cardiovascular parameters. The study involved conducting experiments on cardiovascular preparations in experimental animals, both in-vitro and in-vivo, to investigate the impact of the interaction between the calcimimetics nifedipine and gentamicin.

Methods

Study settings

The study was conducted at the department of Pharmacology, Faculty of Medicine for Girls, Al-Azhar university, Egypt

Study design

A total of thirty-six male albino rats, weighing on average between 200-250 grams, were selected for a study examining the impact of gentamicin and its combination with nifedipine on arterial blood pressure (specifically systolic, diastolic, and mean arterial blood pressure) as well as the electrocardiogram (ECG) of fully anesthetized rats.

- The rats were separated into two groups, with each group consisting of 18 rats (Group I and Group II).
- The groups were divided into three subgroups, each consisting of six rats: Group I (Ia, Ib, Ic) and Group II (IIa, IIb, IIc).

-Medication delivery:

-Administration method: intravenously (IV).

-Dosing: - Group I: was utilized to investigate the impact of gentamicin at the subsequent dosage levels:

I received a dosage of gentamicin at a rate of 2.5 milligrams per kilogram of body weight.

I was administered gentamicin at a dosage of 5 mg per kilogram.

I received a dose of gentamicin at a rate of 10 milligrams per kilogram.

-Group II: Investigated the impact of the interaction between gentamicin and nifedipine at the specified doses:

IIa: administered gentamicin at a dosage of 2.5 mg per kilogram and nifedipine at a dosage of 0.42 mg per kilogram.

IIb: administered gentamicin at a dosage of 5 mg per kilogram and nifedipine at a dosage of 0.42 mg per kilogram.
IIc: administered gentamicin at a dosage of 10 mg per kilogram and nifedipine at a dosage of 0.42 mg per kilogram.
Simultaneous recordings of arterial blood pressure (ABP) and electrocardiogram (ECG) were obtained. The ABP and ECG patterns were taken both before (as the control parameter) and after the administration of drug(s).

In-Vitro Experiments: Isolated Perfused Rabbit Heart and Aortic Strips
The study employed a comprehensive in-vitro approach to investigate the impact of calcimimetics on cardiovascular preparations. Isolated perfused rabbit hearts and aortic strips were utilized to assess the individual and combined effects of gentamicin and nifedipine.

1. Isolated Perfused Rabbit Heart Experiments:
- To evaluate the impact of gentamicin on myocardial contraction amplitudes and explore its interaction with nifedipine. Hearts isolated from rabbits were perfused, and the amplitude of myocardial contractions was measured in response to different doses of gentamicin (15, 30, 60, 120, and 240 μg/ml). Additionally, the interaction between gentamicin (30, 60, and 120 μg/ml) and a fixed dose of nifedipine (4.5 μg/ml) was investigated.

2. Isolated Rabbit Aortic Spiral Strips Experiments:
- To assess the impact of gentamicin on basal tone and NE-precontracted aortic strips and to study its interaction with nifedipine. Aortic strips isolated from rabbits were subjected to different concentrations of gentamicin (15, 30, 60, 120, and 240 μg/ml) to measure their effect on basal tone. NE-precontracted strips were used to study the dose-response effect, impact on acetylcholine-induced relaxation, and the interaction with nifedipine (4.5 μg/ml).

In-Vivo Experiments: Arterial Blood Pressure and Electrocardiogram in Anaesthetized Rats
The study extended to in-vivo experiments involving intact anaesthetized male albino rats to assess the cardiovascular effects of gentamicin and its interaction with nifedipine.

1. Arterial Blood Pressure (ABP) Measurements:
The thirty-six rats were divided into two groups (Group I and Group II), with subgroups receiving varying doses of gentamicin in Group I and the interaction of gentamicin with nifedipine in Group II. ABP measurements were recorded.

2. Electrocardiogram (ECG) Measurements:
ECG recordings were obtained, and heart rate, T-wave, ST-segment, P-R interval, QRS complex, and QT interval were analyzed. The impact of both gentamicin and its interaction with nifedipine on ECG parameters was evaluated.

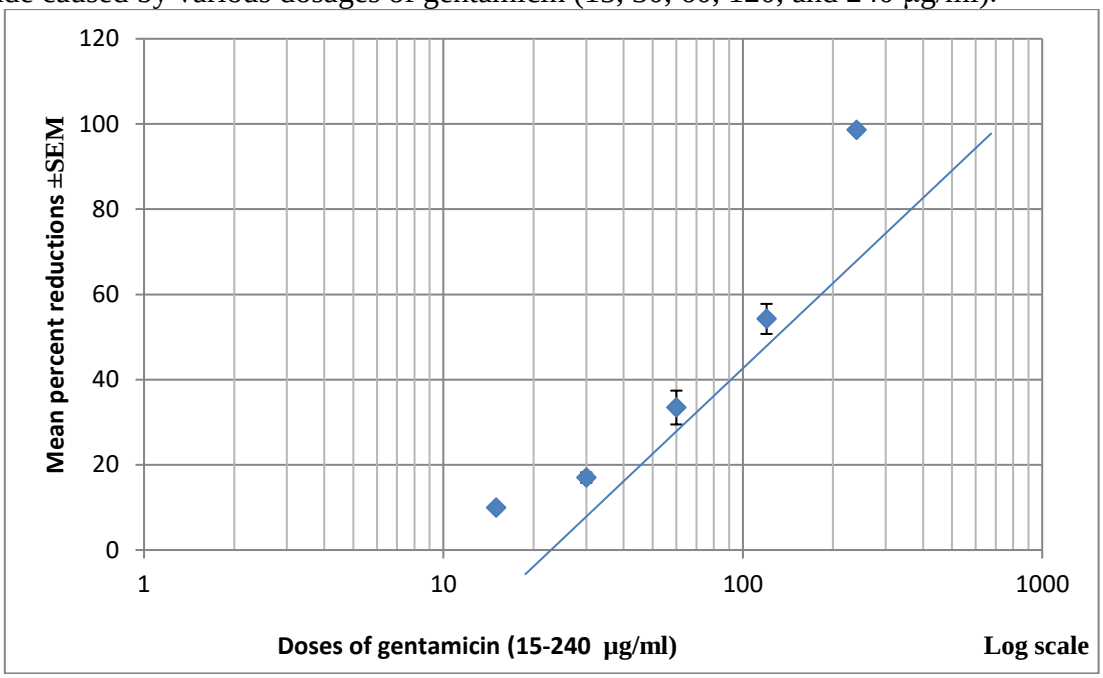
Statistical analysis
The study used the Student t-test, specifically for comparing means and determining significance.

Results
1. In-Vitro experiment
The administration of Gentamicin at concentrations of 15, 30, 60, 120, and 240 μg/ml resulted in a decrease in the strength of cardiac contractions. This effect was observed within 20 seconds of administration and lasted for 1-2 minutes. The average percentage decrease ± standard error of the mean (SEM) varied from 9.93 ± 0.39 to 98.60 ± 0.11 and was determined to be statistically significant. (Table 1 and Graph1).

Table (1): The isolated perfused rabbit heart experiment measured the average percentage decrease ± standard error of the amplitude of myocardial contractions induced by various dosages of gentamicin (15, 30, 60, 120, and 240 µg/ml).

Exp. No.	Contractions (cm)		% Red	Contractions (cm)		% Red	Contractions (cm)		% Red	Contractions (cm)		% Red	Contractions (cm)		% Red		
	cont	genta 15µg/ml		cont	genta 30µg/ml		cont	genta 60µg/ml		cont	genta 120µg/ml		cont	genta 240µg/ml			
1	9.8	8.8	**10.20**	9.9	8.3	**16.16**	9.7	6.2	**36.08**	9.2	2.8	**69.56**	8.1	0.1	**98.76**		
2	9.9	8.9	**10.10**	9.8	8.4	**14.28**	9.8	7.8	**20.40**	9.5	4.6	**51.57**	9.8	0.1	**98.97**		
3	8.0	7.2	**10.00**	7.6	6.1	**19.73**	7.3	4.6	**36.98**	7.0	3.8	**45.71**	6.7	0.1	**98.50**		
4	7.4	6.8	**8.10**	7.4	6.4	**13.51**	7.2	5.5	**23.61**	7.3	3.1	**57.53**	7.2	0.1	**98.61**		
5	6.4	5.7	**10.93**	6.3	5.2	**17.46**	6.5	4.1	**36.92**	5.3	2.8	**47.16**	5.3	0.1	**98.11**		
6	6.8	6.1	**10.29**	6.7	5.3	**20.89**	7.5	4.0	**46.66**	7.6	3.5	**53.94**	7.7	0.1	**98.70**		
Mean	**8.05**	**7.25**	**9.93**	**7.95**	**6.61**	**17.00**	**8.00**	**5.36**	**33.44**	**7.65**	**3.43**	**54.24**	**7.46**	**0.1**	**98.60**		
±SEM	**0.61**	**0.54**	**0.39**	**0.63**	**0.57**	**1.19**	**0.57**	**0.59**	**3.97**	**0.62**	**0.28**	**3.53**	**0.61**	**0.1**	**0.11**		
P			**<0.001**			**<0.001**			**<0.001**			**<0.001**			**<0.001**		

Graph (1): Isolated perfused rabbit heart: Mean percent reduction ±SEM of myocardial contraction amplitude caused by various dosages of gentamicin (15, 30, 60, 120, and 240 µg/ml).



The study found that gentamicin, when combined with acetylcholine, enhanced the inhibitory activity of acetylcholine on cardiac contraction amplitude (figure 1). Even after blocking cholinergic receptors, gentamicin suppressed its inhibitory impact, eliminating the possibility of cholinomimetic activity. It also decreased the strength of myocardial contractions caused by positive inotropics like isoprenaline, histamine, serotonin, and calcium gluconate (figure 2)

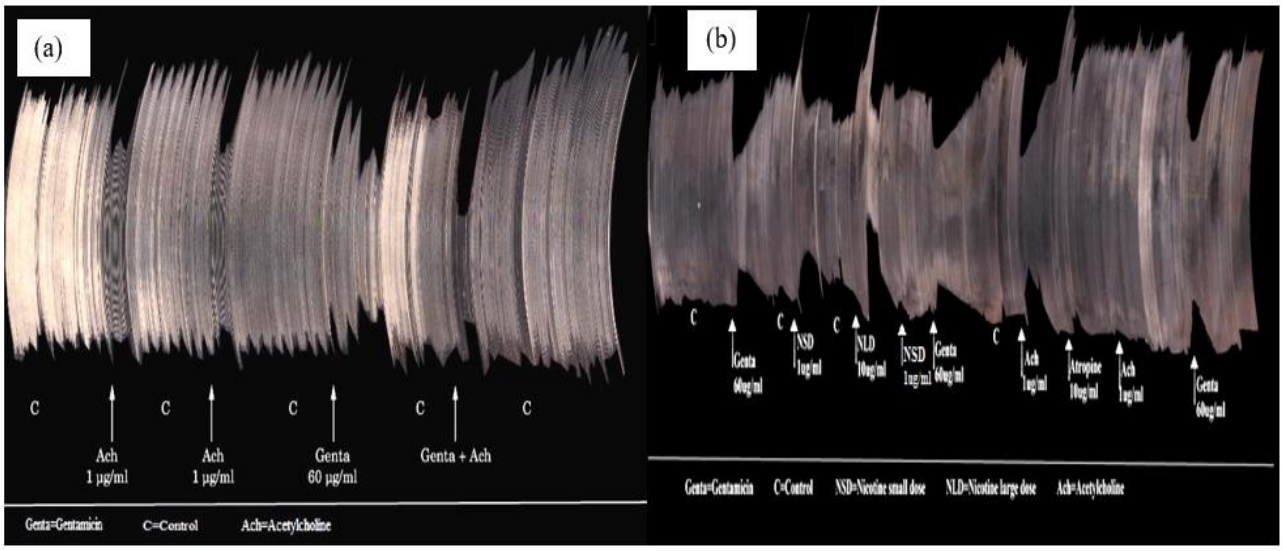


Figure 1: (a) The impact of the concurrent introduction of gentamicin (60 µg/ml) and acetylcholine (1 µg/ml) on the magnitude of cardiac contractions in an isolated perfused rabbit heart. (b) The impact of gentamicin (60 µg/ml) on the strength of myocardial contractions in an isolated perfused rabbit heart, both before and after blocking nicotinic and muscarinic receptors, was examined.

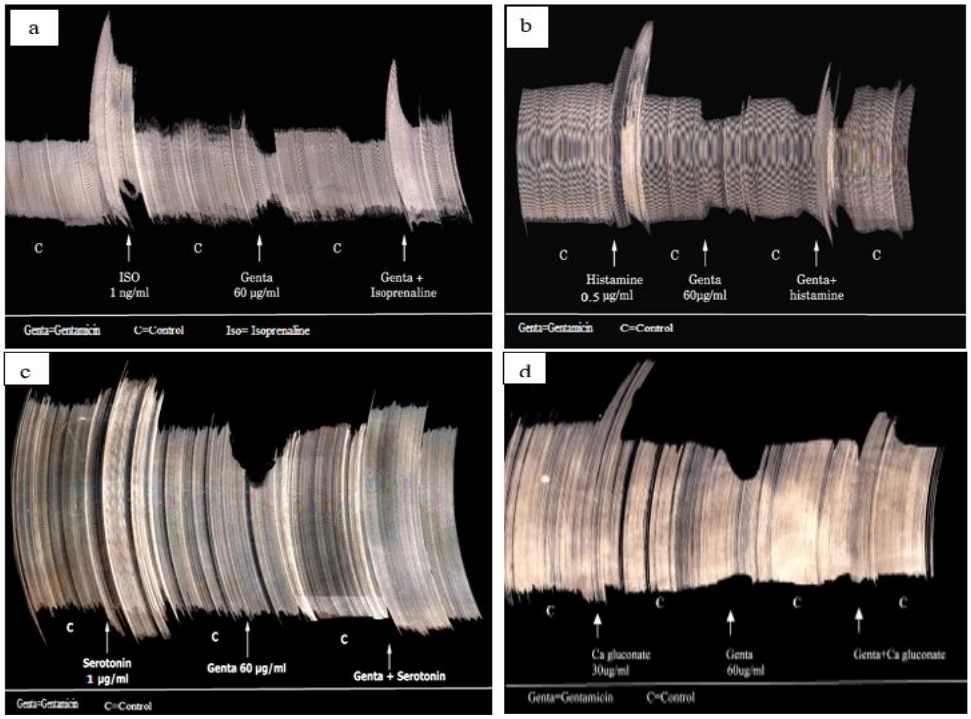
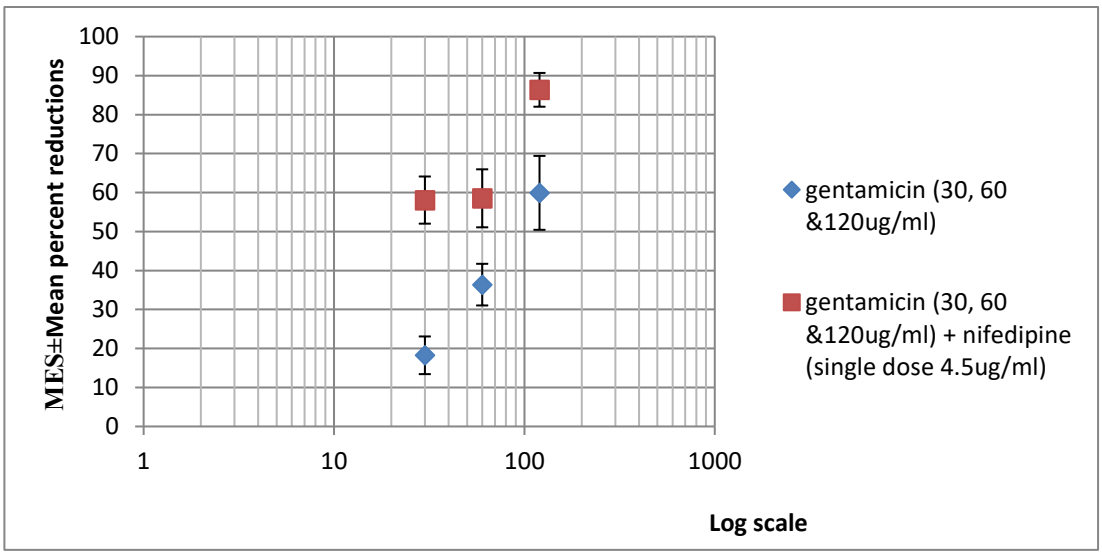


Figure 2: (a) **Isolated perfused rabbit heart:** Effect of gentamicin (60 µg/ml) on the isoprenaline (1 ng/ml) induced myocardial contractions. (b) **Isolated perfused rabbit heart:** Effect of gentamicin (60 µg/ml) on the histamine (0.5 µg/ml) induced myocardial contractions. (c) **Isolated perfused rabbit heart:** Effect of gentamicin (60 µg/ml) on the serotonin (1 µg/ml) induced myocardial contractions. (d) **Isolated perfused rabbit heart:** Effect of gentamicin (60 µg/ml) on the calcium gluconate (30 µg/ml) induced myocardial contractions.

The combination of gentamicin at concentrations of 30, 60, and 120 µg/ml with a single dose of nifedipine at 4.5 µg/ml resulted in a decrease in the magnitude of cardiac contractions, as shown in Figure 14. The average percentage reduction ± standard error of the mean (SEM) varied from 58.07 ± 6.05 to 86.35 ± 4.33 and were determined to have statistical significance, as shown in Table 2**.**
The analysis comparing the average percentage decrease generated by gentamicin alone to that caused by its combination with nifedipine demonstrated that the interaction resulted in a much greater reduction in the magnitude of cardiac contractions.



Graph (2): illustrates the leftward shift of the dosage response curve of gentamicin caused by its interaction with nifedipine**.**

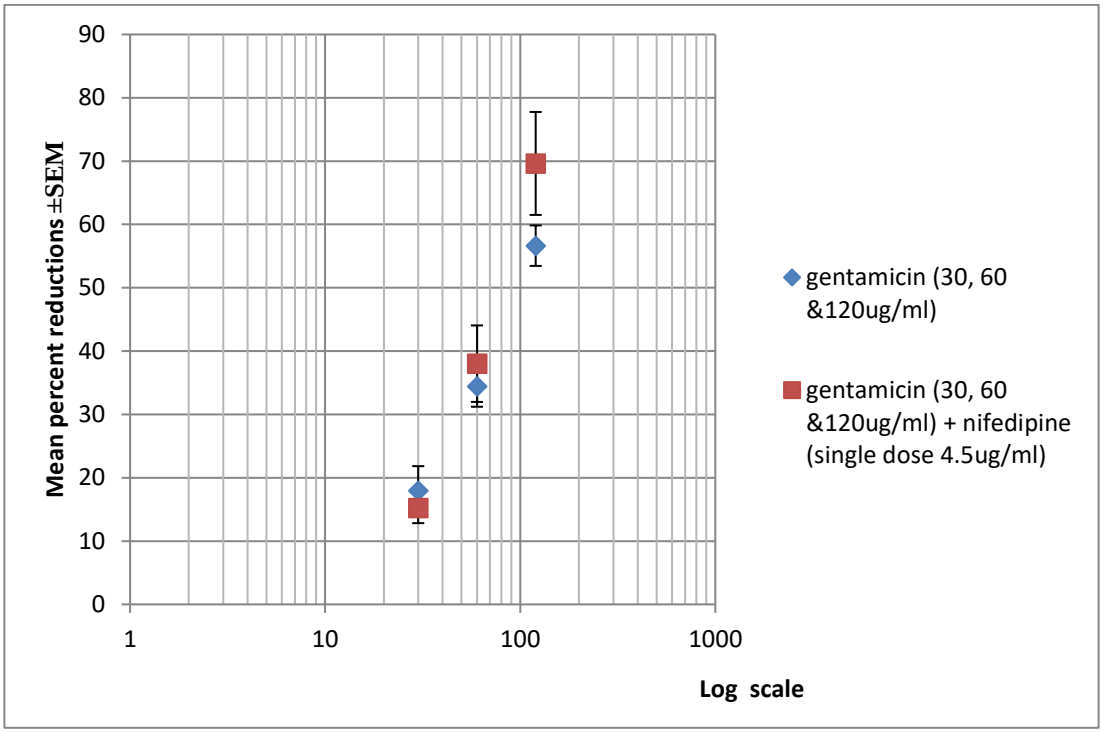
Table (2): Mean percent reduction ±SEM of the myocardial contraction amplitude in an isolated perfused rabbit heart due to gentamicin (30, 60, & 120 µg/ml) and its combination with nifedipine (single dosage 4.5 µg/ml).

Exp. No.	Contractions (cm) genta 30µg/ml cont	Contractions (cm) genta 30µg/ml+nif cont	% Red	Contractions (cm) genta 60µg/ml cont	Contractions (cm) genta 60µg/ml+nif cont	% Red	Contractions (cm) genta 120µg/ml cont	Contractions (cm) genta 120µg/ml +nif cont	% Red	Mean	± SEM	P
1	6.2	5.3	6.45	5.0	5.7	18.00	6.7	6.0	38.80	5.48	0.44	
2	7.0	7.1	38.57	7.2	7.4	40.27	7.1	7.2	45.07	5.30	0.40	
3	5.9	5.6	8.47	5.4	5.4	42.59	5.0	4.8	36.00	5.35	0.50	
4	4.0	4.5	20.00	6.3	6.9	22.22	6.9	6.9	85.50	5.68	0.52	
5	4.6	4.8	13.04	4.2	4.7	45.23	4.0	4.1	87.5	5.70	0.55	
6	5.2	4.5	23.07	4.0	4.0	50.00	4.5	5.2	66.66	5.70	0.49	
Mean	5.48	5.30	18.26	5.35	5.68	36.38	5.70	5.70	59.92	5.45	0.39	
± SEM	0.44	0.40	4.83	0.50	0.52	5.34	0.55	0.49	9.48	0.33	0.27	
P			<0.01			<0.01			<0.01			<0.001
1	5.8	2.7	53.44	5.0	3.3	42.10	6.7	1.6	73.33			
2	4.3	2.2	69.01	7.2	4.0	45.45	7.1	1.5	79.16			
3	5.4	3.6	35.71	5.4	3.3	38.88	5.0	1.0	79.16			
4	3.2	2.0	55.55	6.3	2.0	71.01	6.9	0.1	98.55			
5	4.0	1.0	79.16	4.2	1.0	78.72	4.0	0.1	97.56			
6	4.0	2.0	55.55	4.0	1.0	75.00	4.5	0.5	90.38			
Mean	4.45	2.25	58.07	5.35	2.43	58.52	5.70	0.8	86.35			
± SEM	0.39	0.35	6.05	0.50	0.52	7.44	0.55	0.27	4.33			
P			<0.001			<0.001			<0.001			

The co-administration of gentamicin (at concentrations of 30, 60, and 120 µg/ml) and a single dosage of nifedipine (at a concentration of 4.5 µg/ml) resulted in a decrease in the strength of contraction in NE-precontracted aortic strips. This effect was observed through the simultaneous addition of the drugs in a cumulative response manner.

The average percentage decrease ± standard error of the mean varied from 15.22 ± 2.39 to 69.63 ± 8.13 and was determined to have statistical significance, as shown in Table 3.

The comparison of the mean percent reduction generated by gentamicin alone and its interaction with nifedipine showed no significant difference, as seen in Table 4 and Graph 3.



Graph 3: Comparison of the mean percent reduction caused by gentamicin alone with that caused by its interaction with nifedipine revealed insignificant difference.

Table (3): Isolated aortic spiral strips precontracted with NE (norepinephrine) in rabbits: The mean percentage reduction ± standard error of the mean (SEM) generated by increasing doses of gentamicin (G: 30, 60, and 120 µg/ml) in the presence of nifedipine (N: 4.5 µg/ml).

Exp. No.	Height of contraction(cm)	Gentamicin (G) + nifedipine (N: 4.5 µg/ml)					
		G30 +N		G60 +N		G120 +N	
		cm	%Red	cm	%Red	cm	%Red
1	3.7	3.0	18.91	1.7	54.05	0.2	94.59
2	5.2	4.6	11.53	3.6	30.76	1.8	65.38
3	4.5	3.7	17.77	2.7	40.00	1.7	62.22
4	3.7	3.0	18.91	2.0	45.94	0.8	78.37
5	3.1	2.5	19.35	1.7	45.16	0.6	80.64
6	4.1	3.9	4.87	3.6	12.19	2.6	36.58
Mean	4.05	3.45	15.22	2.55	38.01	1.28	69.63
±SEM	0.21	0.31	2.39	0.36	6.04	0.36	8.13
P			<0.001		<0.001		<0.001

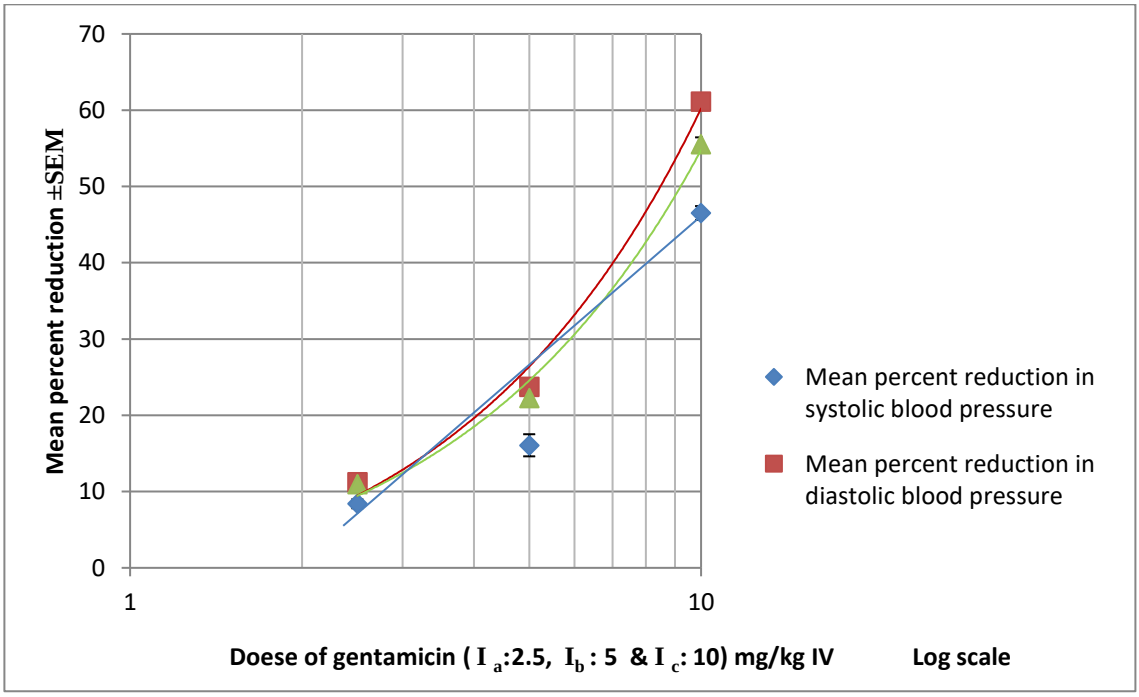
Table (4): The comparison between the mean percent reduction ±SEM generated by cumulative dosages of gentamicin (30, 60, and 120 µg/ml) alone and that caused by its interaction with nifedipine (4.5 µg/ml) is shown by NE-precontracted isolated (rabbit) aorta spiral strips**.**

	Gentamicin (µg/ml)					
	30		**60**		**120**	
	alone	**+nif**	**alone**	**+nif**	**alone**	**+nif**
Mean	**17.98**	**15.22**	**34.46**	**38.01**	**56.65**	**69.63**
±SEM	**3.85**	**2.39**	**3.25**	**6.04**	**3.20**	**8.13**
P	**>0.05**		**>0.05**		**>0.05**	

3. In-vivo Experiments

Gentamicin induced hypotension. The observed effect is dependent on the dosage. The initial administration resulted in a fast onset (within 1-2 minutes), brief duration (lasting 25-30 minutes), and a reversible decrease in blood pressure. The second dose resulted in a rapid beginning of action within 1-2 minutes, a longer duration of impact lasting 35-40 minutes, and a reversible increase in hypotensive effect. It has been observed that the ABP did not attain the level of control. The third dose resulted in a permanent decrease in ABP levels and led to the animal's demise.

Measurements of systolic, diastolic, and mean arterial blood pressure were taken prior to the administration of the drugs. Group I: Investigation of the impact of gentamicin on the systolic, diastolic, and mean arterial blood pressure (measured in mmHg) in fully anesthetized rats. Group Ia (administered intravenously at a dose of 2.5 mg/kg), Group Ib (administered intravenously at a dose of 5 mg/kg), and Group Ic (administered intravenously at a dose of 10 mg/kg). Decreases in arterial blood pressure were measured in systolic, diastolic, and mean arterial blood pressure. The statistical significance of the mean percent reduction ±SEM was determined through calculation. This information is presented in Table 5 and Graph 4.



Graph 4: The intact anaesthetized rats experienced a mean percent drop ±SEM in systolic (S), diastolic (D), and mean arterial blood pressure (MAP) (mmHg) due to the administration of gentamicin.

Table (5): The effect of gentamicin on systolic (S), diastolic (D), and mean arterial blood pressure (MAP) in intact anaesthetized rats was measured as the mean percent reduction ±SEM (standard error of the mean) in millimeters of mercury (mmHg).

Group **I_a**

Number of rats Group **I_a**	**Control (mmHg)**			**gentamicin** 2.5 mg/kg			**%Red S**	**%Red D**	**%Red MAP**
	S	**D**	**MAP**	**S (mmHg)**	**D (mmHg)**	**MAP (mmHg)**			
1	136	80	99	126	73	90	7.35	8.75	9.09
2	139	82	103	129	72	91	7.19	12.19	11.65
3	140	79	99	130	72	91	7.14	8.86	8.79
4	114	74	92	102	64	79	10.52	13.51	14.13
5	142	94	110	130	82	97	8.45	12.76	11.81
6	123	70	87	111	62	78	9.75	11.42	10.34
Mean	**132.3**	**79.8**	**98.3**	**121.3**	**70.83**	**87.6**	**8.4**	**11.24**	**10.96**
±SEM	**4.5**	**3.3**	**3.3**	**4.8**	**2.9**	**3.07**	**0.59**	**0.82**	**0.81**
P							**<0.001**	**<0.001**	**<0.001**

Group I_b

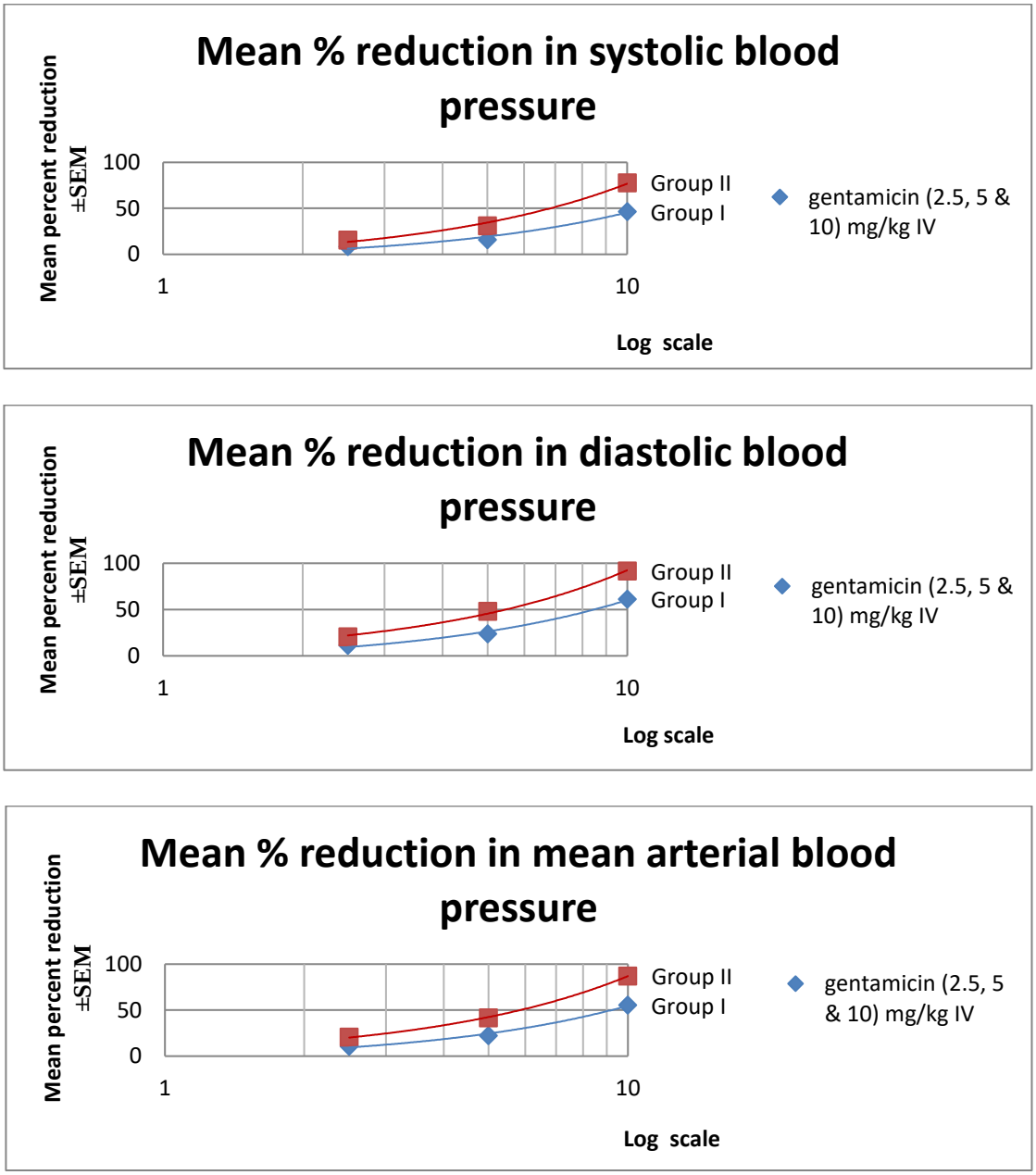
Number of rats Group I_b	**Control (mmHg)**			**gentamicin** 5 mg/kg			**%Red S**	**%Red D**	**%Red MAP**
	S	**D**	**MAP**	**S (mmHg)**	**D (mmHg)**	**MAP (mmHg)**			
1	140	110	123	117	88	97	16.42	20	21.13
2	139	116	125	115	85	95	17.26	26.74	24
3	128	99	112	105	73	83	17.96	26.26	25.89
4	130	108	117	103	83	91	20.76	23.14	22.22
5	112	92	98	100	70	80	10.71	23.91	18.36
6	150	116	132	130	90	103	13.33	22.41	21.96
Mean	**133.1**	**106.8**	**117.8**	**111.6**	**81.5**	**91.5**	**16.07**	**23.74**	**22.26**
±SEM	**5.3**	**3.9**	**4.8**	**4.5**	**3.3**	**3.5**	**1.45**	**1.02**	**1.04**
P							**<0.001**	**<0.001**	**<0.001**

Group Ic

Number of rats Group Ic	**Control (mmHg)**			**gentamicin** 10 mg/kg			**%Red S**	**%Red D**	**%Red MAP**
	S	**D**	**MAP**	**S (mmHg)**	**D (mmHg)**	**MAP (mmHg)**			
1	136	98	110	76	35	49	44.11	64.28	55.45
2	131	80	100	72	34	46	45.03	57.5	54
3	155	92	115	80	36	50	48.38	60.86	56.52
4	133	96	108	70	39	49	47.36	59.37	54.62
5	141	88	105	78	35	49	44.68	60.22	53.33
6	123	90	101	62	32	41	49.59	64.44	59.40
Mean	**136.5**	**90.6**	**106.5**	**73**	**35.2**	**47.3**	**46.52**	**61.11**	**55.55**
±SEM	**4.4**	**2.6**	**2.3**	**2.6**	**0.9**	**1.4**	**0.91**	**1.12**	**0.89**
P							**<0.001**	**<0.001**	**<0.001**

The impact of the interaction between gentamicin and nifedipine on the systolic, diastolic, and MAP in fully anesthetized rats was examined.

A decrease in arterial blood pressure was measured in systolic, diastolic, and mean arterial blood pressure. The statistical significance of the mean percent reduction ±SEM was determined through calculations (Table 6). It may be inferred that gentamicin led to a substantial decrease in arterial blood pressure, whether administered alone (Group I) or in conjunction with nifedipine (Group II). Table 9 displays the comparison of the average percentage decrease, together with the standard error of the mean (SEM), in systolic, diastolic, and mean arterial blood pressure for Group I and Group II. It was discovered that the combination of gentamicin and nifedipine resulted in a substantial decrease in arterial blood pressure, as shown in Graph (5).



Graph (5): The presented data shows the average percentage decrease, together with the standard error of the mean, in systolic (S), diastolic (D), and mean arterial blood pressure (MAP) measured in millimeters of mercury (mmHg) in fully anesthetized rats. Group I represent the impact of gentamicin. Group II: Depicts the interaction between gentamicin and nifedipine.

The impact of gentamicin on the electrocardiogram (ECG) of fully anesthetized rats:

Group I: Gentamicin administration resulted in a notable and proportional rise in heart rate. In Group Ic, there was a notable increase in the T-wave and ST-segment, which suggests the presence of primary ischemia alterations.
Group II: - The combination of gentamicin and nifedipine resulted in a notable elevation in heart rate in Group IIa and Group IIb, surpassing the rise generated by gentamicin alone in Group Ia and Group Ib. In contrast, Group IIc had bradycardia.
- Group IIb exhibited primary ischemia alterations, specifically increased T-wave and ST-segment. In contrast, Group IIc had significant ischemia alterations, characterized by depressed T-waves and ST-segments, longer P-R and QT intervals, and enlargement of the QRS complex.

Discussion

Cardiovascular health is an essential component of total wellness, and it is crucial to comprehend the impact of pharmaceutical substances on the cardiovascular system [12]. The latest study, which examined the effects of gentamicin alone and its interaction with nifedipine on experimental animals, offers valuable insights into the intricate dynamics of cardiac and vascular responses.
Administering gentamicin at different concentrations resulted in a reduction in the intensity of cardiac contractions that was dependent on the dose [13]. The observed phenomenon, occurring within a time frame of 20 seconds and enduring for a duration of 1-2 minutes, indicated a swift and reversible reaction.
These findings agree with the study of Çakmak T.[14] who found that Gentamicin can cause heart injury by increasing PTX-3 levels, although this damage can be reversed with treatment with Pycnogenol.
Gentamicin induced a substantial negative inotropic impact on the isolated perfused rabbit heart, which was depending on the dosage administered. Adams[15] previously investigated the impact of gentamicin on the performance of the heart muscle. It was shown that this antibiotic belonging to the aminoglycoside class caused a sustained and dose-dependent decrease in the tension of the heart muscle's contractions. The author stated that the negative inotropic response was counteracted by calcium (Ca2+) through competitive-like means, while it was counteracted by norepinephrine through non-competitive-like means. Gotanda et al.[16] conducted a study where they found that gentamicin suppressed the automaticity of the right atrium and ventricular septum in separated mongrel dogs. Hashimoto et al.[17] found that gentamicin has a suppressive impact on the heart muscle, known as myocardium. This action is caused by gentamicin competing with calcium ions (Ca2+) at the entrance of calcium channels in the outer layer of the heart muscle membrane, also known as the cardiac sarcolemma.[18]
Furthermore, the research examined the interaction between gentamicin and acetylcholine as well as positive inotropics. The findings demonstrated an augmentation of acetylcholine's inhibitory function and a decrease in the intensity of contractions caused by isoprenaline, histamine, serotonin, and calcium gluconate. The coadministration of gentamicin and nifedipine resulted in a heightened decrease in the amplitudes of cardiac contractions, highlighting a synergistic impact.[19]
The increased suppression of heart muscle activity by acetylcholine due to the presence of gentamicin can be related to its ability to mimic the effects of calcium [20]. According to a report, the activation of ventricular myocytes CaSR leads to an increase in cytosolic calcium levels, which subsequently triggers the activation of inward rectifier potassium-channels, resulting in membrane hyperpolarization[21]
Furthermore, acetylcholine's inhibitory impact as a muscarinic agonist is also achieved by activating its selective inward-rectifying potassium channels (I K,Ach), leading to membrane hyperpolarization and shortening of the action potential[22]
Hence, the potentiation of the suppressive impact of acetylcholine on the heart muscle is likely due to the combined influence of gentamicin and their cumulative impact on the inward rectifying potassium channels[23]. Despite their varying receptor affinities (CaSR and M2-receptor, respectively), gentamicin and acetylcholine both utilize the same subcellular route.

The present study conducted trials to investigate the impact of gentamicin on several excitatory agonists. The findings consistently demonstrated that gentamicin functions as an inhibitory medication. It effectively decreased the excitatory effects of isoprenaline, histamine, serotonin, and Ca2+gluconate.

The positive inotropic action of isoprenaline is attributed to the enhanced likelihood of Ca2+-channels opening, resulting in an increase in the inward Ca2+-current.[24] Conversely, gentamicin impacts either the transport mechanism accountable for the movement of Ca2+ in its channels, the accessibility of Ca2+ for transportation to these locations, or both.[25] The suppressive impact of gentamicin can be related to its likelihood of competing with calcium ions for the identical binding sites at the outer opening of Ca2+-channels in the cardiac sarcolemma.

The administration of gentamicin caused a decrease in blood pressure, and the extent of this impact was depending on the dosage [26]. The prompt initiation, short duration, and reversible decline in blood pressure reported are consistent with prior research on the cardiovascular effects of gentamicin [27]. The study rigorously assessed systolic, diastolic, and mean arterial blood pressure, providing comprehensive data for various dosages of gentamicin. The observed decline in arterial blood pressure (ABP), especially after the third dose, which results in a lasting reduction and mortality, highlights the possible hazards linked to elevated doses of gentamicin.

The study's findings provide a detailed and subtle comprehension of the cardiovascular impacts of gentamicin and its interplay with nifedipine. The decrease in cardiac contractions, along with the lowering of blood pressure, emphasizes the importance of cautious evaluation in clinical environments. The combined effect of gentamicin and nifedipine on cardiac parameters gives rise to worries regarding potential negative consequences, highlighting the significance of closely monitoring and modifying drug dosages.

Although the present investigation offers in-depth knowledge about the cardiovascular impacts of gentamicin and its combination with nifedipine, it is crucial to compare these findings with previous literature in order to gain a thorough picture. Previous research has also documented the blood pressure-lowering impact of gentamicin, which is consistent with the observed relationship between dosage and response in the current investigation. Nevertheless, it is necessary to do additional investigation into the precise interplay between nifedipine and its effect on cardiac contractions, particularly in relation to the current body of research.

Ultimately, the study provides a comprehensive examination of the cardiovascular impacts of gentamicin and its interplay with nifedipine, thereby adding significant insights to the current pool of information. The observed results highlight the significance of prudent drug administration and surveillance in clinical practice, stressing the safeguarding of patient well-being in cardiovascular treatments.

Conclusion

Gentamicin exhibits cardiac inhibitory and vasorelaxant properties, enhancing the cholinomimetic effects of acetylcholine, isoprenaline, nor-epinephrine, histamine, serotonin, and Ca2+-gluconate. Additionally, it possesses a hypotensive impact and has the potential to induce heart ischemia alterations. Concomitant administration of nifedipine and gentamicin may result in profound circulatory collapse and extensive ischemia alterations, necessitating meticulous dosage modification and close monitoring of blood pressure and electrocardiogram (ECG). Additional research is required to comprehend the role of calcimimetics in the cardiovascular system.

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References

1. Pickersgill SJ, Msemburi WT, Cobb L, Ide N, Moran AE, Su Y, Xu X, Watkins DA. Modeling global 80-80-80 blood pressure targets and cardiovascular outcomes. Nat. Med 2022 8:1693-9.
2. Striessnig J, Ortner NJ. Ca2+ channel blockers. In Encyclopedia of Molecular Pharmacology. Cham: Springer International Publishing, 2022.
3. DiVall MV, Woolley AB. CHAPTER Pharmacologic Agents. Acute Care Handbook for Physical Therapists E-Book. 2019.
4. Wang J, McDonagh DL, Meng L. Calcium channel blockers in acute care: the links and missing links between hemodynamic effects and outcome evidence. AM J CARDIOVASC DRUG 2021; 21:35-49.
5. Larson RC, Maus MV. Recent advances and discoveries in the mechanisms and functions of CAR T cells. Nat. Rev. Cancer2021;3:145-61.
6. An S. The emerging role of extracellular Ca2+ in osteo/odontogenic differentiation and the involvement of intracellular Ca 2+ signaling: from osteoblastic cells to dental pulp cells and odontoblasts. J. Cell. Physiol 2019;3:2169-93.
7. Zhou DR, Eid R, Miller KA, Boucher E, Mandato CA, Greenwood MT. Intracellular second messengers mediate stress inducible hormesis and Programmed Cell Death: A review. Biochim Biophys Acta Mol Cell Res BBA-MOL CELL RES 2019;5:773-92.
8. Foster JR, Tinwell H, Melching-Kollmuss S. A review of species differences in the control of, and response to, chemical-induced thyroid hormone perturbations leading to thyroid cancer. Arch. Toxicol 2021; 3:807-36.
9. Kim DH, Lee YH, Sayed AE, Choi IY, Lee JS. Genome-wide identification of 194 G protein-coupled receptor (GPCR) genes from the water flea Daphnia magna. Comparative Biochemistry and Physiology Part D: Genom. Proteom 2022;42:100983.
10. Cianferotti L, Romagnoli C, Brandi ML. Sensing Calcium Levels: The Biology of the Parathyroid Cells. InCellular Endocrinology in Health and Disease.Academic Press. 2021.
11. Brown AJ, Zhong M, Finch J, Ritter C, McCracken R, Morrissey J, Slatopolsky E. Rat calcium-sensing receptor is regulated by vitamin D but not by calcium. Am. J. Physiol. Renal Physiol 1996; 3:F454-60.
12. Zakir M, Ahuja N, Surksha MA, Sachdev R, Kalariya Y, Nasir M, Kashif M, Shahzeen F, Tayyab A, moazzam Khan MS, Junejo M. Cardiovascular complications of diabetes: from microvascular to macrovascular pathways. Cureus. 2023;15(9).
13. Simões LO, Alves QL, Camargo SB, Araújo FA, Hora VR, Jesus RL, Barreto BC, Macambira SG, Soares MB, Meira CS, Aguiar MC. Cardiac effect induced by Crotalus durissus cascavella venom: Morphofunctional evidence and mechanism of action. Toxicol. Lett. 2021;337:121-33.
14. Çakmak T. Exploring the impacts of pycnogenol on pentraxin-3 levels in the heart tissue of rats administered with gentamicin. Anatolian Current Medical Journal 2023;4:317-22.
15. Adams HR. Cardiovascular depressant effects of neomycin and gentamicin in rhesus monkeys. Br. J. Pharmacol. 1975;4:453.
16. Gotanda K, Yanagisawa T, Satoh K, Taira N. Are the cardiovascular effects of gentamicin similar to those of calcium antagonists?. JPN J PHARMACOL 1988;3:217-27.
17. Hashimoto H, Yanagisawa T, Taira N. Differential antagonism of the negative inotropic effect of gentamicin by calcium ions, Bay K 8644 and isoprenaline in canine ventricular muscle: comparison with cobalt ions. Br. J. Pharmacol. 1989; 4:906-12.
18. Man KN, Bartels P, Henderson PB, Kim K, Shi M, Zhang M, Ho SY, Nieves-Cintron M, Navedo MF, Horne MC, Hell JW. α1-Adrenergic receptor–PKC–Pyk2–Src signaling boosts L-type Ca2+ channel CaV1. 2 activity and long-term potentiation in rodents. eLife. 2023;12.
19. SESSION AP. XXXI ANNUAL CONFERENCE OF INDIAN PHARMACOLOGICAL SOCIETY DECEMBER 18-20, 1998, LUCKNOW. Indian Journal of Pharmacologyo 1999;31:41-80.

20. Krenn M, Grisold A, Wohlfarth P, Rath J, Cetin H, Koneczny I, Zimprich F. Pathomechanisms and clinical implications of myasthenic syndromes exacerbated and induced by medical treatments. Front. Mol. Neurosci. 2020 Aug 14;13:156.
21. Schreckenberg R, Schlüter KD. Calcium sensing receptor expression and signalling in cardiovascular physiology and disease. Vascul. Pharmacol 2018;107:35-42.
22. Magyar T, Árpádffy-Lovas T, Pászti B, Tóth N, Szlovák J, Gazdag P, Kohajda Z, Gyökeres A, Györe B, Gurabi Z, Jost N. Muscarinic agonists inhibit the ATP-dependent potassium current and suppress the ventricle–Purkinje action potential dispersion. Can. J. Physiol. Pharmacol 2021;2:247-53.
23. Martinou JC, Wollheim MP. The role of glutamate synthesis and release mechanisms in hormone secretion of pancreatic islet cells.
24. Liu M, Xue Y, Liang Y, Xue Y, Han X, Li Z, Chu L. Mechanisms underlying the cardioprotection of YangXinDingJi capsule against myocardial ischemia in rats. eCAM. 2020;1-6.
25. Jomova K, Makova M, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Rhodes CJ, Valko M. Essential metals in health and disease. Chem. Biol. Interact 2022; 22:110173.
26. Mousavinasab SR, Akhoundi-Meybodi Z, Mahmoudi L, Karimzadeh I. A randomized double-blinded placebo-controlled clinical trial on protective effects of pentoxifylline on gentamicin nephrotoxicity in infectious patients. Clin. Exp. Nephrol 2021;25:844-53.
27. Kozuch PL, Brandt LJ. diagnosis and management of mesenteric ischaemia with an emphasis on pharmacotherapy. AP&T 2005; 3:201-15.