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PREFACE

Dear scientist,

I am happy to announce that Volume VI - Issue I of the Eastern Anatolian Journal of Science (EAJS) has been published. This issue is composed of 5 papers that possess some of the leading and advanced techniques of natural and applied sciences. On behalf of the owner of EAJS, I would like to thank all authors, referees, our editorial board members and section editors that provide valuable contributions for the publication of the issue.

EAJS will publish original and high-quality articles covering a wide range of topics in scientific research, dedicated to promoting high standards and excellence in the creation and dissemination of scientific knowledge. EAJS published in English is open access journal and abstracting and indexing by various international index services.

Authors are solicited to contribute to the EAJS by submitting articles that illustrate research results, projects, surveying works and industrial experiences that describe significant advances in the following areas, but are not limited to:

- Biology
- Chemistry
- Engineering
- Mathematics
- Nanoscience and Nanotechnology
- Physics

Our previous issues have an attraction in terms of scientific quality and impact factor of articles by favorable feedbacks of readers. Our editorial team lend wings to be an internationally reputable and pioneer journal of science by their outstanding scientific personality. I am hoping to work effectively with our editorial team in the future.

I'd like to express my gratitude to all authors, members of editorial board and contributing reviewers. My sincere thanks go to Prof. Dr. Abdulhalik KARABULUT, the rector of Ağrı İbrahim Çeçen University, sets the goal of being also a top-ranking university in scientific sense, for supporting and motivating us in every respect. I express my gratitude to the members of technical staff of the journal for the design and proofreading of the articles. Last but not least, my special thanks go to the respectable businessman Mr. İbrahim ÇEÇEN who unsparingly supports our university financially and emotionally, to his team and to the director and staff of IC foundation.

I invite scientists from all branches of science to contribute our journal by sending papers for publication in EAJS.

Prof. Dr. İbrahim HAN

Editor-in-Chief

CONTENTS

Investigation of Mechanical Properties of E-Waste Added Concrete after Exposure to High Temperatures

Ali Serkan SAVAŞ[1*] and Ahmet Ferhat BİNGÖL[1]

[1] *Atatürk University, Civil Engineering Department, 25240, ERZURUM*
aliserkansavas@hotmail.com
afbingol@atauni.edu.tr

Abstract

In this study, certain mechanical behaviors of concretes that were added e-waste instead of fine aggregates under high temperature were investigated. The total binder was kept constant at 340 kg / m3 and the water / binder ratio was 0.51 in all mixtures. Concrete samples in which e-waste were substituted for fine aggregate in the ratios of 5%, 10%, 15% and 20% by weight were produced as well as control samples that do not contain e-waste so that a comparison could be performed. Cube concrete samples produced with the dimensions of 15x15x15 cm were subjected to standard water curing for 28 days, and then each sample was weighed for unit weight. After the samples were exposed to different temperatures, compressive strengths, bending tensile strengths were measured water and water absorption tests were performed. The samples produced were subjected to 100 ° C and 500 ° C temperature effects including the room temperature (25 ° C). As E-Waste ratio increases, compressive strength decreases. The observed decrease in strength increases with increasing temperature. Tensile strength increases as the E-Waste ratio increases, Although the tensile strength increased with increasing E-Waste ratio, the ratio of compressive strength to tensile strength increased with increasing E-waste ratio.This shows that E-Waste increases the ductility even if the material compressive strenght decreases.

Unit weights are measured each time E-Waste ratio increases and unit weights decrease. Water absorption rates by weight and volume were measured according to the TS 12390-7. Water absorption by volume and weight increases with the e-waste ratio.

Keywords: E-Waste, High Temperature, Concrete

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[*]Corresponding author: Ali Serkan SAVAŞ,
Atatürk Üniversitity Civil Engineering Department
E-mail:aliserkansavas@hotmail.com
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1. Introduction

Concrete is the most frequently used as construction material in civil engineering. Changing concrete components to improve certain characteristics of concrete and improving concrete performance by using different materials as well as using various waste materials to produce economic concretes have been part of the concrete technology for a long time.

The increasing use of electronic devices in today's world, the need for constant renewal with the common use of electronic devices and the increasing electronic waste amount is an environmental problem that is faced today. From this perspective, research on using e-waste in concretes has received a growing attention lately. With this approach, both e-waste would be eliminated and its damaging effects to the environment would be eliminated, and the amount of aggregate used in concrete would be decreased which would result in more economical productions as well as preserving the limited aggregate resources.

As it is known that there can be changes in both the mechanical and physical characteristics of the concrete exposed to high temperatures. High temperature which is one of the main physical effects that may cause durability problems in structures can lead to permanent damages and malfunctions which would cause loss of life and property.

High temperatures cause impairments in concrete structure. Available water in capillary and gel-spaces evaporates at 100-150°C. When the temperature reaches 150-250°C, capillary cracks occur in concrete due to contraction and the tensile strength of the concrete decreases. With the removal of the water that is chemically bound at 300°C, the extent of damage increases and the compression strength decreases. At temperatures above 400°C, disruptions in the C-S-H structure being and at 900°C the C-S-H

structure is completely disrupted which lead to significant losses (Baradan 2010).

Concretes with e-waste added rather than the coarse aggregate were produced in studies conducted by Lakshima and Nagan (2011). It was reported that e-plastic waste can be used as aggregate in the coarse aggregate up to 15% of the weight and in concrete with fly ash 10% of the weight instead of cement.

In a study conducted by A. Muthadhi (2017) on concrete containing e-plastic waste, concrete was produced using 0%, 10%, and 20% with a grain diameter of maximum 20mm of e-waste as coarse aggregate. They reported that e-waste can be used as a substitute for coarse aggregate with a ratio of 10% and this would not affect processability. At the same time, it was reported that the splitting tensile of concrete may have been affected by the characteristics of the interfacial transition area in the tensile splitting strength experiement and therefore, the free water accumulated on the surfaces of plastic particules and plastic surfaces could lead to a weaker adhesion between the aggregate, cement mortar and E-waste.

In a study conducted by Khalid Iqbal , e-waster was added instead of coarse aggregate at a ratio of between 0 and 50%. It was reported that it is possible to use e-waste up to 24% of the coarse aggregate, and that savings could be achieved in the production costs of concrete (3%).

In another study conducted by J Junak, N Junakova1 and V Csiszar (2019) in which e-waste was used instead of aggregate as filling material at the ratios of 5%, 10%, and 20%. Compressive strength and bending tension experiments were performed. It was reported that the compressive strength decreases as e-waste increases while bending tension decreases as the ratio of e-waste increases. With the increase of e-waste ratio, the bending beam fracture is delayed and therefore, provides a partial reinforcement for bending tension.

Senthil Kumar and Baskar(2015) conducted an experimental study on structural concrete in which they used e-plastic waste instead of coarse aggregate. They reported that the processability of the mixture decreases as the ratio of e-plastic waste increases. Also, compressive strength, tensile splitting strength and bending tensile strength decreased and the unit weights decreased in comparison to the control group. It was stated that such concrete can be used in light elements that are non-bearing.

According to a study by Dhanraj & Selvamony (2015) in which fine aggregate was partially replaced by e-waste, e-waste aggregate can be used up to 5% of weight of fine aggregate.

Asha (2015) conducted a study to examine the strength characteristics of concrete with e-waste and used e-waste instead of fine aggregate at the ratios of 10%, 20% and 30%. They showed that compressive, tensile splitting and bending tensile strength decrease with the increase in the amount of e-waste. This decrease in strength causes a weak bond force between cement mortar and e-waste and the decrease in density due to an increase in matrix gaps causes the reduction in strength.

In the current study, mechanical characteristics of e-waste added concrete instead of fine aggregate following high temperature impact were examined. Concrete mixes were produced by mixing fine aggregates and e-waste in different ratios and the samples were kept in curing for 28 days. Within this scope, compressive strengths, bending tension strength, unit weights before and after high temperature, and water absorption rates by weigth and volume according to TSE 12390-7 were compared following an exposure to 100oC and 500oC temperatures.

2. Experimental Study

2.1. Materials Used

In the study, crushed stones with a grain dimeter of 31.5 mm maximum and crushed sand were used. The saturated surface dry specific gravity, the absorption rates and moisture components of aggregates are presented in Table 1.

INFORMATION ON AGGREGATE						
Type of Aggregate	Source of Aggregate	Specific Gravity	Percentage of Aggregate Mix	% Humidity Content	% of Absorption	Fineness Modulus
0--5	İSPİR	2,6	58	6	1,8	2,74
5--12	İSPİR	2,64	16	5	1,3	5,43
12-31,5	İSPİR	2,67	26	1,5	1,1	6,54

Table 1 Aggregate Properties

CEM I 42.5 R type cement obtained from Askale Cement factory was used. The chemical and mechanical characteristics of the cement used are presented in Table 2.

E-waste with a specific weight of 1.3 gr/ cm3 obtained from Izmit Exitcom recycling facility were granulated and screened in E-waste

Chemical Analysis	
SiO2(%)	18,59
AlO3(%)	4,75
Fe2O3(%)	3,41
CaO(%)	63,59
MgO(%)	1,11
Na2O(%)	0,49
K2O(%)	0,77
SO3(%)	3,39
Cl(%)	0,016
Ignition Loss	3,03
Free CaO(%)	1,56
Mechanical Characteristics	
Initial Set (Minute)	160
Final Set (Minute)	203
Density (gr/cm3)	3,15
Volumetric Expansion (cm)	1,1
Specific Surface (blaine cm2/gr)	3740

Table 2 Chemical composition of cement, and certain physical and mechanical characteristics

2.2. Concrete Designs

The mixture ratios of concrete samples are provided in Table 3. The cement dosage amount in all concrete mixtures was 340 kg/m3 and water amounts was 175 kg/m3. These ratios were kept stable. In each group, 18 cubical samples with the dimensions of 150x150x150 mm and 3 beam samples with the dimensions of 100x100x400 mm were produced. First, a mixture calculation was performed for C25/30 and a sample was poured to identify the 7-day compressive strength. After determining that the mixture would provide the targeted compressive strength, the E-waste containing groups were produced based on the calculations performed previously. The concrete designs were completed to contain E-waste at the ratios of 5% (E5N95), 10% (E10N90), 15% (E15N85) and 20 % (E20N80) of the fine aggregate. Samples were removed from the molds at the end of 24 hours and subjected to standard water treatment for 28 days. The experiments were performed following these procedures.

2.3 Experiments Performed

Following the treatment, compressive strength experiments were completed on the samples that were kept in room temperature, and the samples that were exposed to 100°C and 500°C temperatures. The oven used for high temperature application is shown in Figure 1.

Figure 1 Interior of a High Temperature Oven

The concrete compression machine used to identify the compressive strength of cubical samples according to TS EB 12390-3 is shown in Figure 2. The 23°C, 100°C and 500°C used in the graphs refer to compressive strength values respectively. The compression machine used for bending tension strength is shown in Figure 2.

Figure 2 Concrete Compression Machine and Bending tension

MATERIALS	VOLUME(dm3)	DKY Specific Gravity	Amount in 1 m3 of Concrete (kg)	Surface Moisture Correction	Corrected Amount in 1 m3 of Concrete (kg)
CEMENT	109	3,11	340	-	340
MIXING WATER	175	1,00	175	56,63	118,37
AIR %2	20	-	-	-	-
WATER REDUCING ADMIXTURE	3	1,18	3,4	-	3,4
0--5 aggregate	402	2,6	1045	43,88	1088,88
5--12 aggregate	111	2,64	293	10,83	303,83
12-19 aggregate	180	2,67	481	1,92	482,92
TOTAL	1000 dm3		2337,4		2337,4

Table 3. Mixture Ratio of Concrete Samples

3. Experiment Results And Discussion

3.1. Saturated Dry Surface Unit Weight

The samples stored in the treatment pool for 28 days were removed from the pool and dried with a towel to obtain a saturated dry surface and their weigths were measured. The samples prepared for 23°C, 100°C and 500°C were weighed both before and after the baking. The unit weights obtained are presented in Table 4.

It was found that the unit weights of all the groups with e-waste added were lower than the control group. We can attribute the decrease in unit weights compared to the control sample, respectively, for two reasons. The first is that E-waste has less specific weight, and the second is that as the percentage of E-waste increases, the unit weight decreases.

The unit weights of the E5N95, E10N90, E15N85 and E20N80 groups in room temperature (23°C) were 3.37%, 7.17%, 9.28%. and 13.50% respectively, which are lower than the control group. After the exposure to 100°C, the loss in unit weights for all the groups was between 0.5% and 3%. The loss in the unit weight may be due to the evaporation of the water in the capillary spaces. After the exposure to 500°C, unit weights for each concrete sample showed a decrease in comparison to the previous temperature. The main reason for this is the melting of the e-waste, the decrease in the unit specific gravity, and the evaporation of the gel absorption water.

	UNIT WEIGHT gr/cm3 (dry surface , saturated)					UNIT WEIGHT gr/cm3 after heat				
	E0N100	E5N95	E10N90	E15N85	E20N80	E0N100	E5N95	E10N90	E15N85	E20N80
	2,37	2,28	2,19	2,16	2,06					
	2,38	2,29	2,19	2,13	2,02					
	2,38	2,29	2,20	2,14	2,07					
	2,37	2,29	2,21	2,15	2,06					
		2,30			2,03					
23C Average	2,37	2,29	2,20	2,15	2,05					
	2,36	2,30	2,21	2,16	2,02	2,33	2,26	2,17	2,12	1,97
	2,37	2,29	2,21	2,14	2,03	2,34	2,25	2,17	2,10	1,98
	2,37	2,29	2,19	2,15	2,04	2,34	2,26	2,16	2,11	1,99
	2,37	2,27	2,18	2,15	2,03	2,34	2,23	2,14	2,11	1,99
100C Average	2,37	2,28	2,20	2,15	2,03	2,34	2,25	2,16	2,11	1,98
	2,39	2,29	2,21	2,14	2,05	2,19	2,09	2,10	2,05	1,80
	2,37	2,29	2,18	2,15	2,04	2,20	2,11	2,11	2,00	1,79
	2,37	2,30	2,19	2,14	2,01	2,19	2,11	2,03	1,86	1,69
	2,36	2,28	2,20	2,13	2,02	2,19	2,09	2,07	1,89	1,71
500 C Average	2,37	2,29	2,19	2,14	2,03	2,19	2,10	2,08	1,95	1,75

Table 4. Unit Weight of Samples by Temperature

3.2. Water absorption by weight and volume

The samples were kept in 1000C three times with 24-hour intervals until the weight loss was 0.2% according to TS 12390-7 and measurements were taken every 24 hours. The water absorption rates by weight and volume are presented in Table 5 and the results are presented in Table 6.

The water absorption rates by weight and volume increase as the amount of e-waste increases. The water absorption rate by weight in the E20N80 group that contains 20% e-waste showed an increase up to 4.15%. This increase can be explained by the strength of adherence of plastic waste with cement mortar. It is thought that the strength is affected by formation of aerated concrete due to e-waste use. The water absorption values by weight and volume are presented in Figure 3.

	Sample weights measured after the first 24 hours (gr)				
	E0N100	E5N95	E10N90	E15N85	E20N80
	7864	7632	7314	7156	6637
	7890	7607	7318	7102	6684
	7898	7629	7287	7137	6710
	7898	7532	7221	7122	6710
AVERAGE	7887,5	7600	7285	7129,25	6685,25
	SECOND WEIGHING				
	E0N100	E5N95	E10N90	E15N85	E20N80
	7836	7601	7284	7129	6603
	7863	7572	7283	7071	6653
	7864	7591	7255	7110	6686
	7870	7504	7192	7098	6681
AVERAGE	7858,25	7567	7253,5	7102	6655,75
	THIRD WEIGHING				
	E0N100	E5N95	E10N90	E15N85	E20N80
	7754	7523	7206	7063	6537
	7786	7496	7215	7006	6581
	7791	7511	7197	7053	6611
	7794	7433	7134	7043	6619
AVERAGE	7781,25	7490,75	7188	7041,25	6587
	FOURTH WEIGHING				
	E0N100	E5N95	E10N90	E15N85	E20N80
	7743,14	7510,21	7196,63	7050,99	6525,23
	7775,10	7486,26	7205,62	6994,09	6569,15
	7780,09	7501,24	7187,64	7041,01	6599,10
	7783,09	7423,34	7124,73	7031,03	6607,09
AVERAGE	7770,36	7481,01	7178,66	7029,28	6575,14

Table 5 Unit Weights of Samples that are Saturated and Dried in Incubator

	Water absorption rate by wieght ((wet-dry)/dry*100)					Water absorption rate by volume ((wet-dry)/15^3)				
	E0N100	E5N95	E10N90	E15N85	E20N80	E0N100	E5N95	E10N90	E15N85	E20N80
	2,99	3,19	3,41	3,40	4,36	6,87	7,10	7,27	7,11	8,44
	2,83	3,07	3,31	3,46	4,34	6,52	6,81	7,06	7,17	8,44
	2,83	2,89	2,94	3,22	4,11	6,52	6,42	6,26	6,73	8,03
	2,68	3,12	3,15	3,23	3,81	6,19	6,86	6,65	6,73	7,46
Average %	2,83	3,06	3,20	3,33	4,15	6,52	6,78	6,81	6,93	8,09

Table 6 Water Absorption Rates by Weight and Volume According to TS 12390-7

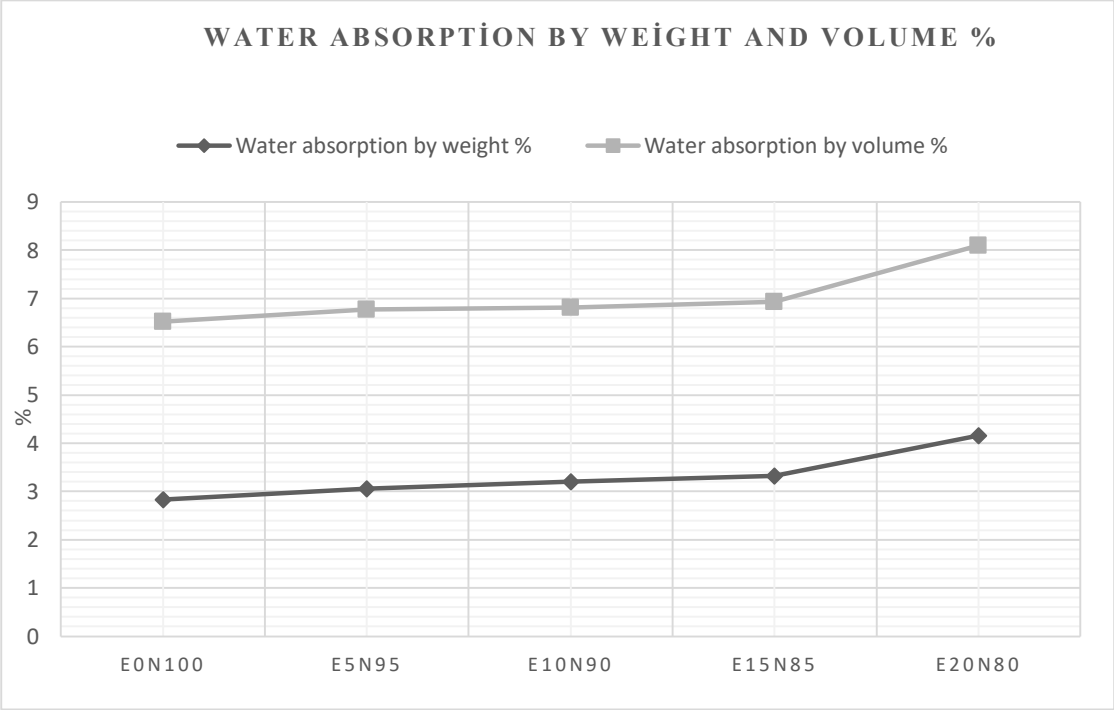

Figure 3. Change in Water Absorption by Weight and Volume

3.3. Compressive Strength

4 samples from each group were kept in the oven at 100°C and 500°C temperature for 3 hours, and then cooled down to room temperature. Compressive strength tests were then performed on these samples. The results of the compressive strength tests on samples exposed to high temperatures and the results of the control group kept in room temperature are provided in Table 7. A graphic representation is presented in Figure 4.

The results in Table 7 shows a systematic decrease in compressive strength with an increase in the amount of e-waste for all temperatures. The 28-day compressive strength of E5N95, E10N90, E15N85 and E20N80 that were not exposed to high temperatures are 7%, 21.65%, 34.5%, and 60% lower respectively, in comparison to the control group. These results show similarity with the study conducted by Lakshima(2011) on strength of concrete containing e-waste. Similar results are also reported in Senthil Kumar's (2015) study. The compressive strength results of the same group following an exposure to 1000C were 12.25%, 25.59%, 34.84%, and 61.68% lower, respectively, in comparison to the control group. The decrease rates in the compressive strength

results following the exposure to 5000C were 7.12%, 30.08%, 48.88%, and 75.52%, respectively. The lower compressive strength in concrete containing e-waste may be due to two reasons. First reason may be the decrease of strength due to the weak bond between e-waste particules and the cement mortar while the second reason may be low strength because of the increase in spaces. These results show similarity with the study conducted by Asha (2015) on examining the strength characteristics of concrete containing e-waste. Considering the relationship between the water absorption rates by weight and volume, and the compressive strength, the main reason for the decrease in strength may be an increase in space.

When the temperature effect is examined, although the control sample not containing e-waste showed a little increase at 1000C, the compressive strengths in all other samples decreased as the temperature increased. The reason for this can be said to stem from, as stated by Asha, the decrease in strength due to the weak bond between e-waste particles and the cement mortar, and the increase in spaces due to low strength (Figure 5).

	E0N100	E5N95	E10N90	E15N85	E20N80
Compressive Strength 23ºC	33,3	33,8	24,3	21,6	10,7
	31,5	34,1	28,5	21,3	14,2
	34,2	28,8	27	24,1	15,3
	36,1	29,7	26	21,4	11,9
	-	30,8	-	-	14,1
23 ºC Average	33,775	31,44	26,45	22,1	13,025
	E0N100	E5N95	E10N90	E15N85	E20N80
Strength results 100 ºC	35,3	28,9	25,9	21,8	12
	32,7	33,2	25,6	22,5	13,6
	34,8	28,1	25	22,7	13,8
	34,4	33,9	19,5	19	12,4
100 ºC Average	34,27	30,07	25,50	22,33	13,13
Strength Results 500 ºC	28,6	30,3	22,2	18,5	10,5
	32,1	28	20,8	20,4	8,8
	33,8	28,8	21,3	11,2	6
	30,5	29	23,1	13,8	5,3
500 ºC Average	31,25	29,025	21,85	15,975	7,65

Table 7. Compressive Strength Test Results

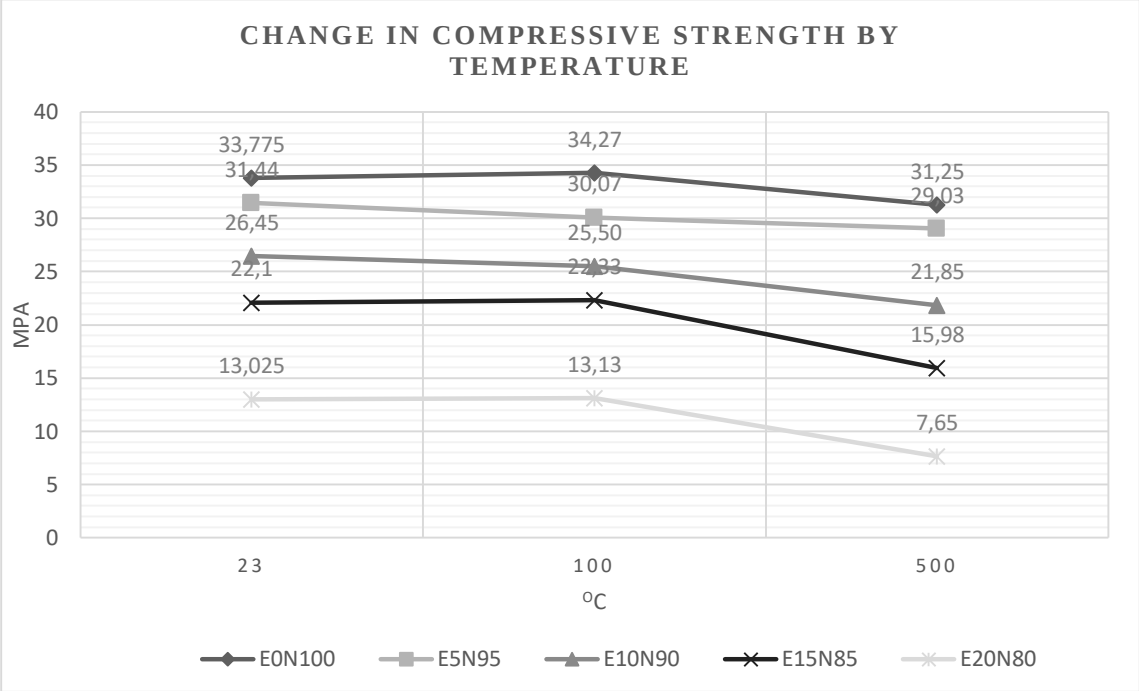

Figure 4. Change in Compressive Strength by Temperature

3.4 Single Point Bending Tension

The bending tension strength of the control mixture, E5N95, E10N90, E15N85 and E20N80 are presented in Table 8. The bending tension strengths of the E5N95, E10N90, E15N85 and E20N80 concrete were 18%, 25%, 34%, and 40% lower than the control group, respectively (Figure 5). The decrease in the bending tension can be explained with the decrease in compressive strength.

On the other hand, the ratio of tensile strength to compressive strength for E5N95, E10N90, E15N85 and E20N80 were 18.6%, 16.4%, 17.84%, 18.93%, and 29.10%, respectively (Figure 6). This ratio is thought to increase as the e-waste amount increases. The ratio of tensile strength to compressive strength being 29.10% for the E20N80 sample is due to the ductile behavior of the material. This is explained by the shift from brittle fracture to ductile fracture as the bending tension fractures increase with the plastic amount. J Junak, N Junakoval, and V Csiszar performed bending tension experiments in their study.

They reported that the bending tension strength decreased as the e-waste amount increased. These results are similar to the results of this study. It was reported that the bending beam fracture is delayed with the increase in the amount of e-waste which provides partial strengthening for bending tension.

The decrease in bending tension is thought to be impacted by the characteristics of the interfacial transition area and therefore, the free water accumulated on the surface of plastic particles and the plastic surface cause a weaker adhesion between the aggregate, cement mortar and the e-waste. Same results were provided in a study conducted by Muthadhi , A. Mohamed Basid , R. Madivarma , J.Satheesh Kumar , R. Raghuvarman (2017) on concrete containing e-plastic waste.

	DIMENSIONS			MAX FRACTURE FORCE N	BENDING STRENGTH N/mm2 (σe= 3PL/2bd2)	BENDING STRENGTH average N/mm2	COMPRESSIVE STRENGTH	STRENGTH/ COMPRESSİVE RATIO %
	Base (b, mm)	Height (h, mm)	Span (L, mm)					
E0N100	100,00	100,00	350,00	10898,91	1,48	1,63	33,78	0,05
				12497,94	1,70			
				12566,61	1,71			
E5N95	100,00	100,00	350,00	9535,32	1,30	1,34	31,44	0,04
				10035,63	1,37			
				9957,15	1,35			
E10N90	100,00	100,00	350,00	8829,00	1,20	1,22	26,45	0,05
				8976,15	1,22			
				9172,35	1,25			
E15N85	100,00	100,00	350,00	8220,78	1,12	1,08	22,10	0,05
				7671,42	1,04			
				8024,58	1,09			
E20N80	100,00	100,00	350,00	7808,76	1,06	0,98	13,03	0,08
				7180,92	0,98			
				6670,80	0,91			

Table 8 Calculated Values of Bending Tension Strength

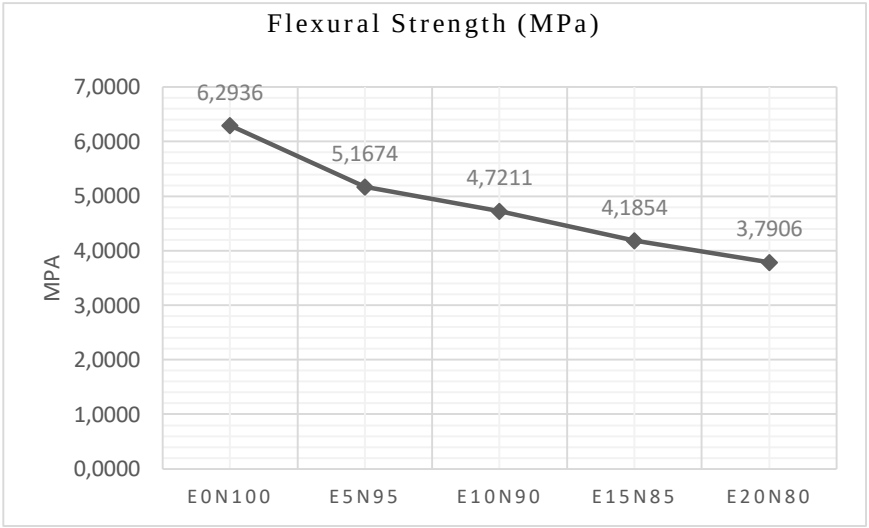

Figure 5. The results of the bending tension strength experiment

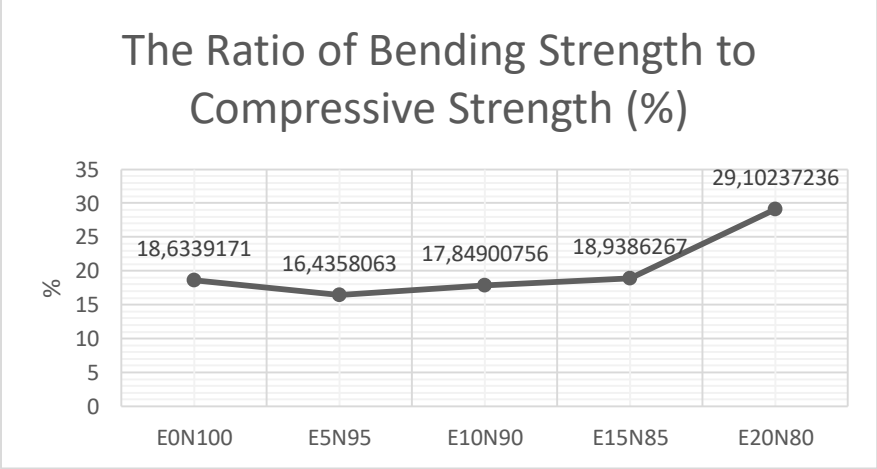

Figure 6. Bending Tension Strength/Compressive Strength Ratio

4. Conclusion

The results of this experimental study showed that it is possible to use e-waste in certain amounts, particularly in non-structural applications, as a substitute for fine aggregate and that the e-waste can be an alternative material as aggregates. The results of the study are summarized below.

- The weight of the concrete decreases as the e-waste percentage increases. Thus, e-waste added concrete can be used in light concrete effectively.

- The compressive strength of samples with e-waste were 7%, 21.65%, 34.5%, and 60% lower than the control mix. At 1000C, they were 12.25%, 25.59%, 34.84%, and 61.68% lower than the control sample while at 5000C, they were 7.12%, 30.08%, 48.88%, and 75.52% lower. Due to the weak adhesion between e-waste particles and the cement mortar, the strength decreases. Due to the increase in porosity which decreases density, the compressive strength decreases. When the water absorption ratios by weight and volume are compared to compressive strength, the reason for a decrease is the increase in spacing. Particularly, the concrete containing 5% e-waste can be used with different mixture calculations in areas where strength is needed

- The water absorption rate increased as the amount of e-waste used increased. At the same time, the ductility of the material increased. The use of e-waste at a certain ratio increases the space ratio and ductility which increases the material's ability of fatigue. Therefore, the resistance to freeze and thaw should be researched with freeze-thaw tests.

- As the e-waste ratio increases, it can be used in concrete that do not require strength.

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Analysis of a Fractional Plant-Nectar-Pollinator Model with the Exponential Kernel

Mustafa Ali DOKUYUCU[1*]

[1] *Ağrı İbrahim Çeçen University, Faculty of Science and Letters, Department of Mathematics, Ağrı, Turkey,*
mustafaalidokuyucu@gmail.com

Abstract

This paper extends the plant-nectar-pollination model to the Caputo-Fabrizio fractional derivative, following which the existence and singularity resolutions of the new model are studies with the Picard-Lindelöf method. Afterwards Hyers-Ulam stability is utilized to analyse the stability of the PNP model. Lastly, Adams-Bashforth numerical approach is used for numerical resolutions.

Keywords: PNP model, Caputo-Fabrizio fractional derivative, Adams-Bashforth numerical method, Picard-Lindelöf method.

1. Introduction

Many natural and flowering plants survive thanks to the accessibility of appropriate actors that pollenate or disperse seeds. Flowering plants require mechanisms, which will introduce pollen to their roots that will enable them to breed. In this respect, pollen transposition is termed pollination. The occurrence of pollination and the appropriateness of pollen and stigma lead to the formation of a pollen tube from a particle of pollen and this pollen tube transmits sperm into the ovule in the ovary. The life of the species necessitates the existence of seeds in most seed plants.

In this respect, a mathematical model has been brought forth. One can list the crucial studies in the literature as follows:

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**Corresponding author:* Mustafa Ali Dokuyucu, *PhD*
Agri Ibrahim Cecen University, Faculty of Science and Letters, Department of Mathematics, Agrı Turkey
E-mail: mustafaalidokuyucu@gmail.com
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Wang (2019) made use of pollination-mutuality in his analysis of the impact of nectar. He showed the mechanism through which the pollinator can lead to nectar consumption ratio, nectar degeneration ratio and through which the nectar production ratio can result in the perpetuity/demolition of pollination-mutuality in his examination of the model.

Wang (2018) has examined the global dynamics of plant-pollinator-robber systems, which comprise two opponent consumers being pollinator and nectar robber. In this example, whereas the nectar robber is a plant parasite pollinator is reciprocity. Vanbergen et al. (2017) examined the hardiness of insect flower visitor networks, the impacts of terrain disruption among species and the degree of mutuality among species. They were found to be in accord with the network structure in the integral and troubled terrain. In addition, they patterned whether the internal dependency of species on reciprocity affects the inclination of extinction cascades in the network. Khan et al. (2020) have popularized a PNP model that comprises Atangana-Baleanu gradual order differentials. They have acquired crucial data regarding the variables used in the complex system thanks to this new differential type. The presence and singularity of the Atangana-Baleanu differential were examined with the PL method and the stability analysis was conducted with Picard's stability technique for the fractional-order plant-nectar-pollinator model. The model brought forth also revealed different schemes of the plant-nectar-pollinator (PNP) model with numerical examples. In addition, there are many studies in the literature on the expansion of new fractional derivative operators to mathematical models (Dokuyucu et al. 2018a; Dokuyucu et al. 2018b; Dokuyucu 2020a; Dokuyucu and Dutta 2020; Dokuyucu 2020b; Rashid et al. 2019a; Nie et al. 2019; Rashid et al 2019b, Ekinci and Ozdemir 2019).

There are five chapters in this article. The first part presents general information concerning the plant-nectar-pollinator (PNP) model. The second part offers essential definitions and theorems concerning the new Caputo differential. The third part comprises the analysis of the existence and singularity of the mathematical model. The Picard- Lindelöf theorem helped in revealing the existence of the model. In the fourth part, the stability of the model is studied with Hyers-Ulam stability theorem. In the last part, the model's numerical solution is performed by integrating Adams-Bashforth's numerical approach into the Caputo-Fabrizio fractional differential. Simulations were also performed and the model was examined thoroughly.

2. Preliminaries

Descriptions and theorems regarding the non-singular fractional Caputo-Fabrizio operator are presented in this part. Please see (Caputo 1967; Caputo and Fabrizio 2015; Losada and Nieto 2015) articles for more detailed information.

Definition 2.1. The well-known fractional order Caputo derivative is defined as follows (Caputo 1967), let $f \in H^1(a,b)$

$$ {}_a^C D_t^\rho f(t) = \frac{1}{\Gamma(n-\rho)} \int_a^t \frac{f^{(n)}(r)}{(t-r)^{\rho+1-n}}, \qquad (1) $$

where $n-1 < \rho < n \in N$.

Definition 2.2. Let $f \in H^1(a,b), 0 < \rho < 1$. The new Caputo fractional derivative is defined as follows (Caputo and Fabrizio 2015),

$$ {}_a^{CF} D_t^\rho f(t) = \frac{\rho M(\rho)}{1-\rho} \int_a^t \frac{df(x)}{dx}\, exp\left[\rho \frac{x-t}{1-\rho}\right] dx, \quad (2) $$

Here $M(\rho)$ is a normalization constant. Also $M(0)$ and $M(1)$ are equal to 1. Further it can be written below, if the f does not belong to $H^1(a,b)$.

$$ {}_a^{CF} D_t^\rho f(t) = \frac{\rho M(\rho)}{1-\rho} \int_a^t \frac{\big(f(t)-f(x)\big)}{} \times exp\left[\rho \frac{x-t}{1-\rho}\right] dx, \qquad (3) $$

Definition 2.3. Let $f \in H^1(a,b),\ 0 < \rho < 1$. The Caputo-Fabrizio fractional derivative of order f is as follows (Losada and Nieto 2015),

$$ {}^{CF} D_\star^\rho f(t) = \frac{1}{1-\rho} \int_a^t f'(x) exp\left[\rho \frac{x-t}{1-\rho}\right] dx. \qquad (4) $$

Definition 2.4. Let $0 < \rho < 1$. The fractional integral order ρ of a function f is defined by (Losada and Nieto 2015),

$$ I^\rho f(t) = \frac{2(1-\rho)}{(2-\rho)M(\rho)} u(t) + \frac{2\rho}{(2-\rho)M(\rho)} \int_a^t u(s) ds \qquad (5) $$

3. Analysis of the existence and uniqueness of the new system

3.1. Existence Solution for the Plant-Nectar-Pollinator Model

Our system of equations comprises two types, one being the first plant and the other, a pollinator that interacts with the plant. As Revilla (2015) puts forth, one can describe the dynamic equations generated for these two types as follows.

$$ \begin{aligned} (\mathcal{N}_1)_t &= \mathcal{G}_1(.)\mathcal{N}_1 + \sigma_1\beta_0\mathcal{F}\mathcal{N}_0 + \sigma_1\beta_2\mathcal{F}\mathcal{N}_2, \\ (\mathcal{N}_2)_t &= \mathcal{G}_2(.)\mathcal{N}_2 + \sigma_2\beta_2\mathcal{F}\mathcal{N}_2, \\ \mathcal{F}_t &= \alpha\mathcal{N}_1 - (\omega + \beta_0\mathcal{N}_0 + \beta_2\mathcal{N}_2)\mathcal{F}. \end{aligned} \qquad (6) $$

The term "$\sigma_1\beta_0\mathcal{N}_0$" in the first equation indicates that pollination can be accomplished by abiotic factors. We can give the wind flow at the very beginning of the abiotic factors. For convenience, let's assume that $\mathcal{G}_1\mathcal{N}_1 = b_1N_1, \mathcal{G}_2\mathcal{N}_2 = -b_2$. Here, the r_1 parameter represents the plant's internal growth rate, and c_1 indicates the intraspecific competition level of r_1, while r_2 indicates the pollinator's mortality rate. Also, all parameters are positive in the system (6).

In the equation system (6), N_1 indicates the plant population density, while N_2 indicates the population density of the pollinator. Also, F represents the number of fruit or flowers produced by the plant. In addition, the explanation of each parameter is given in the table below.

Parameter	Explanation
$G_i(.)$	Percentage change of species i per person when it does not interact with j species by mutualism
σ_1	Parameter of plant conversion rate from a flower or fruit to new adult plants
σ_2	Conversion rate to biomass
β_1	Pollination rate by pollinator or nectar consumption rate by pollinator
α	Per capita rate of plants in nectar production
ω	Rate of loss or deterioration of nectar

Now let $N_1 = A$, $\beta_2 N_2 = B$, $\alpha = a$, $\sigma_1 = d_1$, $\sigma_2\beta_2 = d_2$, $\beta_0 N_0 = e_1$ and $\omega + \beta_0 N_0 = e_2$. this case, if the system (6) is regulated, the following system is obtained.

$$\begin{aligned} A_t &= A(t)\big(b_1 - c_1 A(t)\big) + d_1(e_1 + B(t))C(t), \\ B_t &= B(t)(-b_2 + d_2 C(t)), \\ C_t &= aA(t) - (e_2 + B(t))C(t), \end{aligned} \tag{7}$$

with initial conditions

$$A(0) \geq 0,\ B(0) \geq 0,\ C(0) \geq 0.$$

When the equation system (7) is extended to the Caputo-Fabrizio fractional derivative obtained using the exponential kernel, the following system is obtained.

$$\begin{aligned} {}^{CF}_{a}D^{\rho}_{t}\, A(t) &= A(t)\big(b_1 - c_1 A(t)\big) \\ &\quad + d_1(e_1 + B(t))C(t), \\ {}^{CF}_{a}D^{\rho}_{t}\, B(t) &= B(t)(-b_2 + d_2 C(t)), \\ {}^{CF}_{a}D^{\rho}_{t}\, C(t) &= aA(t) - \big(e_2 + B(t)\big)C(t). \end{aligned} \tag{8}$$

It is crucial to verify the existence and singularity of the solution for the equation or system of equations in derivative calculations. Hence, this part initially aims to demonstrate the presence of the system (8) of equations. System A, B and C are created and the constants used are just the same as Wang (2019). In the light of the integral form acquired with the help of Laplace transform of the new Caputo fractional differential, we can initially write the following theorem.

Theorem 3.1. Fractional differential equation below,

$${}^{CF}_{a}D^{\rho}_{t}\, f(t) = u(t) - u(0),$$

has a unique solution that takes the inverse Laplace transform and uses the following convolution theorem.

$$\begin{aligned} f(t) - f(0) &= \frac{2(1-\rho)}{(2-\rho)M(\rho)}u(t) \\ &\quad + \frac{2\rho}{(2-\rho)M(\rho)}\int_a^t u(s)ds \end{aligned} \tag{9}$$

With the help of the above theorem, the following system of equations can be obtained.

$$\begin{aligned} &A(t) - g_1(t) \\ &= \frac{2(1-\rho)}{(2-\rho)M(\rho)}\Big(A(t)\big(b_1 - c_1 A(t)\big) + d_1\big(e_1 \\ &\qquad + B(t)\big)C(t)\Big) \\ &+ \frac{2\rho}{(2-\rho)M(\rho)}\int_0^t \big(A(s)\big(b_1 - c_1 A(s)\big) \\ &\qquad + d_1(e_1 + B(s))C(s)\big)ds \\ &B(t) - g_2(t) \\ &= \frac{2(1-\rho)}{(2-\rho)M(\rho)}\Big(B(t)\big(-b_2 + d_2 C(t)\big)\Big) \\ &+ \frac{2\rho}{(2-\rho)M(\rho)}\int_0^t \Big(B(s)\big(-b_2 + d_2 C(s)\big)\Big)\, ds \end{aligned} \tag{10}$$

$$C(t) - g_3(t) = \frac{2(1-\rho)}{(2-\rho)M(\rho)}\big(aA(t) - \big(e_2 + B(t)\big)C(t)\big) + \frac{2\rho}{(2-\rho)M(\rho)}\int_0^t (aA(s) - (e_2 + B(s))C(s))\,ds$$

If it is taken as follows for iteration application for the system (10), we have

$$\begin{aligned} A_0(t) &= g_1(t) \\ B_0(t) &= g_2(t) \\ C_0(t) &= g_3(t) \end{aligned} \tag{11}$$

and

$$\begin{aligned} &A_{n+1}(t) \\ &= \frac{2(1-\rho)}{(2-\rho)M(\rho)}\Big(A_n(t)\big(b_1 - c_1A_n(t)\big) + d_1\big(e_1 + B_n(t)\big)C_n(t)\Big) \\ &+ \frac{2\rho}{(2-\rho)M(\rho)}\int_0^t \big(A_n(s)\big(b_1 - c_1A_n(s)\big) + d_1\big(e_1 + B_n(s)\big)C_n(s)\big)ds \\ &B_{n+1}(t) \\ &= \frac{2(1-\rho)}{(2-\rho)M(\rho)}\Big(B_n(t)\big(-b_2 + d_2C_n(t)\big)\Big) \\ &+ \frac{2\rho}{(2-\rho)M(\rho)}\int_0^t \Big(B_n(s)\big(-b_2 + d_2C_n(s)\big)\Big)\,ds \\ &C_{n+1}(t) \\ &= \frac{2(1-\rho)}{(2-\rho)M(\rho)}\Big(aA_n(t) - \big(e_2 + B_n(t)\big)C_n(t)\Big) \\ &+ \frac{2\rho}{(2-\rho)M(\rho)}\int_0^t \big(aA_n(s) - \big(e_2 + B_n(s)\big)C_n(s)\big)\,ds \end{aligned} \tag{12}$$

We will try to find the exact solution by limiting a large enough n value.

$$\begin{aligned} g_1(t,x) &= A(t)\big(b_1 - c_1A(t)\big) + d_1\big(e_1 + B(t)\big)C(t), \\ g_2(t,x) &= B(t)\big(-b_2 + d_2C(t)\big), \\ g_3(t,x) &= aA(t) - \big(e_2 + B(t)\big)C(t), \end{aligned} \tag{13}$$

If the kernels are taken as above, it is clear that the g_1, g_2 and g_3 functions have a contraction of p, r and s, respectively. Let

$$\begin{aligned} C_1 &= \sup_{N_{y,z_1}} \big||g_1(t,p)|\big|, \\ C_2 &= \sup_{N_{y,z_2}} \big||g_2(t,r)|\big|, \\ C_3 &= \sup_{N_{y,z_3}} \big||g_3(t,s)|\big|, \end{aligned} \tag{14}$$

where

$$\begin{aligned} N_{y,z_i} &= [t-y, t+y] \times [x - z_i, x + z_i] \\ &= Y_i \times Z_i, \quad i = 1,2,3. \end{aligned} \tag{15}$$

The equation system can also be used together with the metric in Banach space by means of the fixed-point theorem.

$$\|g(t)\|_\infty = \sup_{t\in[t-y,t+y]} |f(t)|. \tag{16}$$

Another operator is described among uninterrupted functions and is identified by the Picard operator.

$$T: N(Y_1, Z_1, Z_2, Z_3) \to N(Y_1, Z_1, Z_2, Z_3) \tag{17}$$

Defined as follows

$$T\Phi(t) = \Phi_0(t) + \frac{2(1-\rho)}{(2-\rho)M(\rho)}X(t) + \frac{2\rho}{(2-\rho)M(\rho)}\int_0^t F\big(s, X(s)\big)ds, \tag{18}$$

where Φ is the given matrix

$$\Phi(t) = \begin{cases} A(t) \\ B(t) \\ C(t) \end{cases} \qquad \Phi_0(t) = \begin{cases} g_1(t) \\ g_2(t) \\ g_3(t) \end{cases} \tag{19}$$

$$\mathrm{G}(t, \Phi(t)) = \begin{cases} g_1(t,x) \\ g_2(t,x) \\ g_3(t,x) \end{cases} \tag{20}$$

Since all plants are unlikely to be pollinated, the solutions can be considered to be limited in a time frame.

$$\|x(t)\|_\infty \leq \max\{b_1, b_2, b_3\}, \tag{21}$$

$$
\begin{aligned}
&\|T\Phi(t)-\Phi_0(t)\| \\
&=\left\|\frac{2(1-\rho)}{(2-\rho)M(\rho)}F(t,\Phi(t))\right\| \\
&+\left\|\frac{2\rho}{(2-\rho)M(\rho)}\int_0^t F(s,\Phi(s))ds\right\| \\
&\le \frac{2(1-\rho)}{(2-\rho)M(\rho)}\|F(t,\Phi(t))\| \\
&+\frac{2\rho}{(2-\rho)M(\rho)}\left\|\int_0^t F(s,\Phi(s))ds\right\| \\
&\le \frac{2(1-\rho)}{(2-\rho)M(\rho)}M+\frac{2\rho}{(2-\rho)M(\rho)}M \\
&\le aM \le b = max\{b_1,b_2,b_3\},
\end{aligned} \tag{22}
$$

where $M=\max\{M_1,M_2,M_3\}$. As a result,

$$a<\frac{b}{M}$$

In addition to the above, the following inequality can be found.

$$\|T\Phi_1-T\Phi_2\|_\infty = \sup_{t\in A}|\Phi_1-\Phi_2| \tag{23}$$

With the definition of the defined operator in hand, we produce the following

$$
\begin{aligned}
&\|T\Phi_1-T\Phi_2\| \\
&=\left\|\frac{2(1-\rho)}{(2-\rho)M(\rho)}\big(F(t,\Phi_1(t))\right. \\
&\left.-F(t,\Phi_2(t))\big)\right. \\
&+\frac{2\rho}{(2-\rho)M(\rho)}\int_0^t\big(F(s,\Phi_1(s))\right. \\
&\left.-F(s,\Phi_2(s))\big)ds\right\| \\
&\le \frac{2(1-\rho)}{(2-\rho)M(\rho)}\left\|\big(F(t,\Phi_1(t))\right. \\
&\left.-F(t,\Phi_2(t))\big)\right\| \\
&+\frac{2\rho}{(2-\rho)M(\rho)}\int_0^t\|\big(F(s,\Phi_1(s))\right. \\
&\left.-F(s,\Phi_2(s))\big)\|ds \\
&\le \frac{2(1-\rho)}{(2-\rho)M(\rho)}q+\frac{2\rho q}{(2-\rho)M(\rho)}\|\Phi_1(t)-\Phi_2(t)\| \\
&\le aq\|\Phi_1(t)-\Phi_2(t)\|.
\end{aligned} \tag{24}
$$

According to the last inequality, q less than 1. Namely, G has a contraction. At the same time, T has a contraction since $aq<1$. This result shows us that there is a unique solution set.

3.2. Uniqueness Solution for the Plant-Nectar-Pollinator Model

In this section we will show you the unique solution of Plant-Nectar-Pollinator mathematical model.

Theorem 3.2. The Plant-Nectar-Pollinator mathematical model shown in system (10) will have a unique solution if the following inequality hold true:

$$\left(\frac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}+\frac{2\rho}{2M(\rho)-\rho\,M(\rho)}\right)\Xi_i \le 1 \tag{25}$$

where $i=1,2,3$.

Proof Let us assume that the system (10) has solutions $A(t),B(t),C(t)$, as well as $\bar{A}(t),\bar{B}(t),\bar{C}(t)$. that, the following system can be written,

$$
\begin{aligned}
\bar{A}(t) &= \frac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Im_1\big(t,\bar{A}(t)\big) \\
&+\frac{2\rho}{2M(\rho)-\rho\,M(\rho)}\int_0^t\Im_1\big(y,\bar{A}(y)\big)\,dy \\
\bar{B}(t) &= \frac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Im_1\big(t,\bar{B}(t)\big) \\
&+\frac{2\rho}{2M(\rho)-\rho\,M(\rho)}\int_0^t\Im_1\big(y,\bar{B}(y)\big)\,dy \\
\bar{C}(t) &= \frac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Im_1\big(t,\bar{C}(t)\big) \\
&+\frac{2\rho}{2M(\rho)-\rho\,M(\rho)}\int_0^t\Im_1\big(y,\bar{C}(y)\big)\,dy
\end{aligned} \tag{26}
$$

When the norm is taken from both sides of the system of equations above, firstly

$$
\begin{aligned}
&\|A(t)-\bar{A}(t)\| \\
&\le \tfrac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\|\Im_1(t,A(t))-\Im_1(t,\bar{A}(t))\|+ \\
&\tfrac{2\rho}{2M(\rho)-\rho\,M(\rho)}\int_0^t\|\Im_1(y,A(y))-\Im_1(y,\bar{A}(y))\|dy \\
&\le \tfrac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Xi_1\|A-\bar{A}\|+\tfrac{2\rho\Xi_1}{2M(\rho)-\rho\,M(\rho)}\|A-\bar{A}\|
\end{aligned} \tag{27}
$$

The following inequality can be written,

$$\left(\begin{array}{l}\dfrac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Xi_1\|A-\bar{A}\| \\ +\dfrac{2\rho\Xi_1}{2M(\rho)-\rho\,M(\rho)}\|A-\bar{A}\|\end{array}\right)\geq 0 \tag{28}$$

Thus $\|A-\bar{A}\|=0$. This implies $A(t)=\bar{A}(t)$. When the same method is applied that $B(t)=\bar{B}(t)$, $C(t)=\bar{C}(t)$. According to these results, the model has a unique solution.

4. Stability Analysis

Exploring the stability of a mathematical model is as crucial as discovering resolutions. The stability of the Plant-Nectar-Pollinator model will be studied in this part. The following description should initially be provided.

Definition 4.1. The system (30) Hyers-Ulam stable if exists constants $\Theta_i, i=1,2,3$ satisfying for every $\varsigma_i>0, i=1,2,3$.

$$\begin{array}{l}\left|A(t)-\dfrac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Im_1\big(t,A(t)\big)\right. \\ \left.+\dfrac{2\rho}{2M(\rho)-\rho\,M(\rho)}\displaystyle\int_0^t\Im_1\big(y,A(y)\big)dy\right|\leq\varsigma_1, \\ \left|B(t)-\dfrac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Im_2\big(t,B(t)\big)\right. \\ \left.+\dfrac{2\rho}{2M(\rho)-\rho\,M(\rho)}\displaystyle\int_0^t\Im_2\big(y,B(y)\big)dy\right|\leq\varsigma_2, \\ \left|C(t)-\dfrac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Im_3\big(t,C(t)\big)\right. \\ \left.+\dfrac{2\rho}{2M(\rho)-\rho\,M(\rho)}\displaystyle\int_0^t\Im_3\big(y,C(y)\big)dy\right|\leq\varsigma_3.\end{array} \tag{29}$$

There exist $\bar{A}(t),\bar{B}(t),\bar{C}(t)$ are satisfying,

$$\begin{array}{l}\left|\bar{A}(t)-\dfrac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Im_1\big(t,\bar{A}(t)\big)\right. \\ \left.+\dfrac{2\rho}{2M(\rho)-\rho\,M(\rho)}\displaystyle\int_0^t\Im_1\big(y,\bar{A}(y)\big)dy\right|\leq\varsigma_1, \\ \left|\bar{B}(t)-\dfrac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Im_2\big(t,\bar{B}(t)\big)\right. \\ \left.+\dfrac{2\rho}{2M(\rho)-\rho\,M(\rho)}\displaystyle\int_0^t\Im_2\big(y,\bar{B}(y)\big)dy\right|\leq\varsigma_2, \\ \left|\bar{C}(t)-\dfrac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Im_3\big(t,\bar{C}(t)\big)\right. \\ \left.+\dfrac{2\rho}{2M(\rho)-\rho\,M(\rho)}\displaystyle\int_0^t\Im_3\big(y,\bar{C}(y)\big)dy\right|\leq\varsigma_3,\end{array} \tag{30}$$

such that,

$$\begin{array}{l}|A(t)-\bar{A}(t)|\leq\Theta_1\varsigma_1 \\ |B(t)-\bar{B}(t)|\leq\Theta_2\varsigma_2 \\ |C(t)-\bar{C}(t)|\leq\Theta_3\varsigma_3\end{array} \tag{31}$$

Theorem 4.2. The fractional system (8) is Hyers-Ulam stable with assumption H.

Proof. In theorem (3.2) $A(t),B(t),C(t)$, were shown to have a unique solution. Let $\bar{A}(t),\bar{B}(t),\bar{C}(t)$ be an approximate solution of system (8) satisfying system (25). After, we can say that

$$\begin{array}{l}\|A(t)-\bar{A}(t)\| \\ \leq\frac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\|\Im_1\big(t,A(t)\big)-\Im_1\big(t,\bar{A}(t)\big)\|+ \\ \frac{2\rho}{2M(\rho)-\rho\,M(\rho)}\int_0^t\|\Im_1\big(y,A(y)\big)-\Im_1\big(y,\bar{A}(y)\big)\|dy \\ \leq\frac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}\Xi_1\|A-\bar{A}\|+\frac{2\rho\Xi_1}{2M(\rho)-\rho\,M(\rho)}\|A-\bar{A}\|.\end{array} \tag{32}$$

When we take $\varsigma_1=\Xi_1$ and $\Theta_1=\frac{2(1-\rho)}{2M(\rho)-\rho\,M(\rho)}+\frac{2\rho}{2M(\rho)-\rho\,M(\rho)}$, we have,

$$\|A(t)-\bar{A}(t)\|\leq\varsigma_1\Theta_1. \tag{33}$$

In this way, the following inequalities can be easily written.

$$\begin{aligned}\|B(t)-\bar{B}(t)\| &\le \varsigma_2\Theta_2\\ \|C(t)-\bar{C}(t)\| &\le \varsigma_3\Theta_3\end{aligned} \tag{34}$$

With the help of inequalities (33) and (34), the system (18) Hyers-Ulam is stable. Thus, the theorem is proved.

5. Numerical Simulations

Atangana and Owolabi (2018) resorted to the Adams-Bashforth numeric approach to distinguish fractional differential equations, utilized the new Caputo fractional derivative and acquired a new numeric approach.

$${}^{CF}_{0}D_t^{\rho}x(t) = f\big(t,x(t)\big), \tag{35}$$

or

$$f\big(t,x(t)\big) = \frac{M(\rho)}{1-\rho}\int_0^t x'(\tau)exp\left[-\rho\frac{t-\tau}{1-\rho}\right]d\tau. \tag{36}$$

When the above equation is edited with the help of basic analysis theorem, we have,

$$\begin{aligned}x(t)-x(0) = &\frac{1-\rho}{M(\rho)}f\big(t,x(t)\big)\\ &+\frac{\rho}{M(\rho)}\int_0^t f\big(\tau,x(\tau)\big)d\tau,\end{aligned} \tag{37}$$

consequently,

$$\begin{aligned}x(t_{n+1})-x(0) = &\frac{1-\rho}{M(\rho)}f\big(t_n,x(t_n)\big)\\ &+\frac{\rho}{M(\rho)}\int_0^{t_{n+1}} f\big(t,x(t)\big)dt,\end{aligned} \tag{38}$$

and

$$\begin{aligned}x(t_n)-x(0) = &\frac{1-\rho}{M(\rho)}f\big(t_{n-1},x(t_{n-1})\big)\\ &+\frac{\rho}{M(\rho)}\int_0^{t_n} f\big(t,x(t)\big)dt,\end{aligned} \tag{39}$$

using the equations (38) and (39),

$$\begin{aligned}x(t_{n+1})-x(t_n) = &\frac{1-\rho}{M(\rho)}\big\{f\big(t_n,x(t_n)\big)\\ &-f\big(t_{n-1},x(t_{n-1})\big)\big\}\\ &+\frac{\rho}{M(\rho)}\int_0^{t_n} f\big(t,x(t)\big)dt,\end{aligned} \tag{40}$$

where

$$\begin{aligned}&\int_{t_n}^{t_{n+1}} f\big(t,x(t)\big)dt\\ &=\int_{t_n}^{t_{n+1}}\left\{\begin{matrix}\frac{f(t_n,x_n)}{h}(t-t_{n-1})\\ -\frac{f(t_{n-1},x_{n-1})}{h}(t-t_n)\end{matrix}\right\}dt\\ &=\frac{3h}{2}f(t_n,x_n)-\frac{h}{2}f(t_{n-1},x_{n-1}).\end{aligned} \tag{41}$$

Thus,

$$\begin{aligned}&x(t_{n+1})-x(t_n) = \tfrac{1-\rho}{M(\rho)}\big\{f\big(t_n,x(t_n)\big)-\\ &f\big(t_{n-1},x(t_{n-1})\big)\big\}+\tfrac{3\rho h}{2M(\rho)}f(t_n,x_n)-\\ &\tfrac{\rho h}{2M(\rho)}f(t_{n-1},x_{n-1}),\end{aligned} \tag{42}$$

which implies that

$$\begin{aligned}x(t_{n+1})-x(t_n) = &\left(\frac{1-\rho}{M(\rho)}\right.\\ &\left.+\frac{3\rho h}{2M(\rho)}\right)\big\{f\big(t_n,x(t_n)\big)\\ &+\left(\frac{1-\rho}{M(\rho)}\right.\\ &\left.+\frac{3\rho h}{2M(\rho)}\right)f\big(t_{n-1},x(t_{n-1})\big)\big\}\end{aligned} \tag{43}$$

Hence,

$$\begin{aligned}x(t_{n+1}) = x(t_n)+&\left(\frac{1-\rho}{M(\rho)}\right.\\ &\left.+\frac{3\rho h}{2M(\rho)}\right)\big\{f\big(t_n,x(t_n)\big)\\ &+\left(\frac{1-\rho}{M(\rho)}\right.\\ &\left.+\frac{3\rho h}{2M(\rho)}\right)f\big(t_{n-1},x(t_{n-1})\big)\big\}\end{aligned} \tag{44}$$

Theorem 5.1. Let f is a continuous function and $x(t)$ be a solution of

$$ {}^{CF}_{0}D^{\rho}_{t}x(t) = f\big(t, x(t)\big) $$

for the Caputo-Fabrizio fractional derivative (Atangana and Owolabi 2018).

$$ \begin{aligned} x(t_{n+1}) = x(t_n) &+ \Big(\frac{1-\rho}{M(\rho)} \\ &+ \frac{3\rho h}{2M(\rho)}\Big)\Big\{f\big(t_n, x(t_n)\big) \\ &+ \Big(\frac{1-\rho}{M(\rho)} \\ &+ \frac{3\rho h}{2M(\rho)}\Big) f\big(t_{n-1}, x(t_{n-1})\big)\Big\} \\ &+ R^{n}_{\rho} \end{aligned} \tag{45} $$

where $\|R^{n}_{\rho}\| \leq M$.

5.1. Numerical Simulations

The extended Plant-Nectar-Pollinator model for the new Caputo fractional differential was brought in the system (8). The next system of equations is acquired for $\Upsilon_i, i = 1,2,3$.

$$ \begin{aligned} A(t) - A(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_1\big(t, A(t)\big) \\ &\quad + \frac{\rho}{M(\rho)}\int_0^t \Upsilon_1\big(\tau, A(\tau)\big)\, d\tau, \\ B(t) - B(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_2\big(t, B(t)\big) \\ &\quad + \frac{\rho}{M(\rho)}\int_0^t \Upsilon_2\big(\tau, B(\tau)\big)\, d\tau, \\ C(t) - C(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_3\big(t, C(t)\big) \\ &\quad + \frac{\rho}{M(\rho)}\int_0^t \Upsilon_3\big(\tau, C(\tau)\big)\, d\tau. \end{aligned} \tag{46} $$

Thus,

$$ \begin{aligned} A(t_{n+1}) - A(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_1\big(t_n, A(t_n)\big) \\ &\quad + \frac{\rho}{M(\rho)}\int_0^{t_{n+1}} \Upsilon_1\big(t, A(t)\big)\, dt, \\ B(t_{n+1}) - B(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_2\big(t_n, B(t_n)\big) \\ &\quad + \frac{\rho}{M(\rho)}\int_0^{t_{n+1}} \Upsilon_2\big(t, B(t)\big)\, dt, \\ C(t_{n+1}) - C(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_3\big(t_n, C(t_n)\big) \\ &\quad + \frac{\rho}{M(\rho)}\int_0^{t_{n+1}} \Upsilon_3\big(t, C(t)\big)\, dt, \end{aligned} \tag{47} $$

and

$$ \begin{aligned} A(t_n) - A(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_1\big(t_{n-1}, A(t_{n-1})\big) \\ &\quad + \frac{\rho}{M(\rho)}\int_0^{t_n} \Upsilon_1\big(t, A(t)\big)\, dt, \\ B(t_n) - B(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_2\big(t_{n-1}, B(t_{n-1})\big) \\ &\quad + \frac{\rho}{M(\rho)}\int_0^{t_n} \Upsilon_2\big(t, B(t)\big)\, dt, \\ C(t_n) - C(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_3\big(t_{n-1}, C(t_{n-1})\big) \\ &\quad + \frac{\rho}{M(\rho)}\int_0^{t_n} \Upsilon_3\big(t, C(t)\big)\, dt. \end{aligned} \tag{48} $$

When we removing (48) from (47), the following equation system is obtained.

$$ \begin{aligned} A(t_{n+1}) - A(0) &= \frac{1-\rho}{M(\rho)}\big\{\Upsilon_1\big(t_n, A(t_n)\big) \\ &\quad - \Upsilon_1\big(t_{n-1}, A(t_{n-1})\big)\big\} \\ &\quad + \frac{\rho}{M(\rho)}\int_{t_n}^{t_{n+1}} \Upsilon_1\big(t, A(t)\big)\, dt, \\ B(t_{n+1}) - B(0) &= \frac{1-\rho}{M(\rho)}\big\{\Upsilon_2\big(t_n, B(t_n)\big) \\ &\quad - \Upsilon_2\big(t_{n-1}, B(t_{n-1})\big)\big\} \\ &\quad + \frac{\rho}{M(\rho)}\int_{t_n}^{t_{n+1}} \Upsilon_2\big(t, B(t)\big)dt, \\ C(t_{n+1}) - C(0) &= \frac{1-\rho}{M(\rho)}\big\{\Upsilon_3\big(t_n, C(t_n)\big) \\ &\quad - \Upsilon_3\big(t_{n-1}, C(t_{n-1})\big)\big\} \\ &\quad + \frac{\rho}{M(\rho)}\int_{t_n}^{t_{n+1}} \Upsilon_3\big(t, C(t)\big)dt, \end{aligned} \tag{49} $$

where

$$ \int_{t_n}^{t_{n+1}} \Upsilon_1(t, A(t))dt = \int_{t_n}^{t_{n+1}} \Big\{\frac{\Upsilon_1(t_n, A_n)}{h}(t - $$

$$
\begin{aligned}
&t_{n-1}) - \tfrac{\Upsilon_1(t_{n-1},A_{n-1})}{h}(t-t_n)\Big\}\,dt \\
&\quad = \frac{3h}{2}\Upsilon_1(t_n,A_n) - \frac{h}{2}\Upsilon_1(t_{n-1},A_{n-1}),\\
&\int_{t_n}^{t_{n+1}}\Upsilon_2(t,B(t))dt = \int_{t_n}^{t_{n+1}}\Big\{\tfrac{\Upsilon_2(t_n,B_n)}{h}(t- \\
&t_{n-1}) - \tfrac{\Upsilon_2(t_{n-1},B_{n-1})}{h}(t-t_n)\Big\}\,dt \\
&\quad = \frac{3h}{2}\Upsilon_2(t_n,B_n) - \frac{h}{2}\Upsilon_2(t_{n-1},B_{n-1}),\\
&\int_{t_n}^{t_{n+1}}\Upsilon_3(t,C(t))dt = \int_{t_n}^{t_{n+1}}\Big\{\tfrac{\Upsilon_3(t_n,C_n)}{h}(t- \\
&t_{n-1}) - \tfrac{\Upsilon_3(t_{n-1},C_{n-1})}{h}(t-t_n)\Big\}\,dt \\
&\quad = \frac{3h}{2}\Upsilon_3(t_n,C_n) - \frac{h}{2}\Upsilon_3(t_{n-1},C_{n-1}),
\end{aligned}
\tag{50}
$$

Therefore,

$$
\begin{aligned}
A(t_{n+1}) - A(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_1\big(t_n,A(t_n)\big) \\
&\quad + \frac{\rho}{M(\rho)}\int_0^{t_{n+1}}\Upsilon_1\big(t,A(t)\big)\,dt,\\
B(t_{n+1}) - B(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_2\big(t_n,B(t_n)\big) \\
&\quad + \frac{\rho}{M(\rho)}\int_0^{t_{n+1}}\Upsilon_2\big(t,B(t)\big)\,dt,\\
C(t_{n+1}) - C(0) &= \frac{1-\rho}{M(\rho)}\Upsilon_3\big(t_n,C(t_n)\big) \\
&\quad + \frac{\rho}{M(\rho)}\int_0^{t_{n+1}}\Upsilon_3\big(t,C(t)\big)\,dt,
\end{aligned}
\tag{51}
$$

which implies that,

$$
\begin{aligned}
A_{n+1} &= A_n + \Big(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)}\Big)\Upsilon_1(t_n,A_n) \\
&\quad + \Big(\frac{1-\rho}{M(\rho)} \\
&\quad + \frac{\rho h}{2M(\rho)}\Big)\Upsilon_1(t_{n-1},A_{n-1}),\\
B_{n+1} &= B_n + \Big(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)}\Big)\Upsilon_2(t_n,B_n) \\
&\quad + \Big(\frac{1-\rho}{M(\rho)} \\
&\quad + \frac{\rho h}{2M(\rho)}\Big)\Upsilon_2(t_{n-1},B_{n-1}),\\
C_{n+1} &= C_n + \Big(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)}\Big)\Upsilon_3(t_n,C_n) \\
&\quad + \Big(\frac{1-\rho}{M(\rho)} \\
&\quad + \frac{\rho h}{2M(\rho)}\Big)\Upsilon_3(t_{n-1},C_{n-1}).
\end{aligned}
\tag{52}
$$

According to theorem (5.1), we get,

$$
\begin{aligned}
A_{n+1} &= A_n + \Big(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)}\Big)\Upsilon_1(t_n,A_n) \\
&\quad + \Big(\frac{1-\rho}{M(\rho)} \\
&\quad + \frac{\rho h}{2M(\rho)}\Big)\Upsilon_1(t_{n-1},A_{n-1}) \\
&\quad + {}^1R_\rho^n,\\
B_{n+1} &= B_n + \Big(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)}\Big)\Upsilon_2(t_n,B_n) \\
&\quad + \Big(\frac{1-\rho}{M(\rho)} \\
&\quad + \frac{\rho h}{2M(\rho)}\Big)\Upsilon_2(t_{n-1},B_{n-1}) \\
&\quad + {}^2R_\rho^n,\\
C_{n+1} &= C_n + \Big(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)}\Big)\Upsilon_3(t_n,C_n) \\
&\quad + \Big(\frac{1-\rho}{M(\rho)} \\
&\quad + \frac{\rho h}{2M(\rho)}\Big)\Upsilon_3(t_{n-1},C_{n-1}) \\
&\quad + {}^3R_\rho^n.
\end{aligned}
\tag{53}
$$

where

$$
\left\| {}^iR_\rho^n \right\|_\infty < \frac{\rho}{M(\rho)}(n+1)!\,h^{n+1},\ \ i = 1,2,3. \tag{54}
$$

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The Biological Importance of Curcumin

Merve ARLI [1], Hülya ÇELİK[2*]

[1] *Ağrı İbrahim Çeçen University, Faculty of Pharmacy, Ağrı, Turkey*

mervearli42@gmail.com

[2] *Ağrı İbrahim Çeçen University, Faculty of Pharmacy, Pharmacy Technology Department, Ağrı, Turkey,*
hycelik@agri.edu.tr

Abstract

Turmeric (*Curcuma longa*); In India, China and South East Asia, spices are widely used as aromatic stimulants, food preservatives and coloring materials. Among the people as "castor saffron, turmeric, turmeric, saffron root"; Turmeric as the commonly used name is a yellow-orange colored polyphenolic natural substance derived from *C. longa* rhizomes. In traditional medicine for inflammation and tumors, biliary disorders, anorexia, cough, topical wounds, diabetic wounds, hepatic disorders, rheumatism and sinusitis. It was used as a medicine. In recent years, extensive studies have been conducted to determine the biological activities and pharmacological effects of turmeric and its extracts. Curcumin, which is the main yellow bioactive component of turmeric, is known to have a wide bioactivity such as anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antifibrotic, immunomodulator and antiulcer. Safety assessment studies show that curcumin is well tolerated without toxic effects when used in very high doses. Therefore, curcumin is a substance of high biological importance with the development potential of modern medicine for the treatment of various diseases. For this reason, more scientific studies on curcumin should be done and all the dark sides about this important compound should be illuminated.

Keywords*: Biological activity, Curcumin, Turmeric, C. longa rhizomes, natural*

1. Introduction

Turmeric (*Curcuma longa L.*) belonging to the Zingiberaceae family, is a perennial herbaceous plant with yellow flowers. It grows in the tropical and subtropical regions of Asia, especially in India, China, Indonesia, Jamaica, Peru and Pakistan. The main roots of the plant under the ground are in the form of eggs and pears, and the side roots are in the form of tuber (rhizome). These tubers contain yellow pigments. The plant originating from the tubers of the *Curcuma longa L.* plant is called turmeric (Akbay and Pekcan 2016).

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[*]*Corresponding author:* Hülya ÇELİK *PhD*
Agri Ibrahim Cecen University, Faculty of Pharmacy, Pharmacy Technology Department, Agrı Turkey
E-mail: hycelik@agri.edu.tr
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Figure 1. *Curcuma longa L.* (*Turmeric*) Plant

History of *Turmeric* (*Curcuma longa*) When looking at ancient scriptures, especially Indian sources, the most important plant encountered is turmeric. Turmeric, also known as "Indian saffron", BC. It was used until 4000. Its name and use is frequently mentioned in the ancient Indian medicine system, Ayurveda. In fact, the use of turmeric; It has spread to many purposes as paint, condiment and medicine. In Sanskrit, turmeric is called "Haridara", a word consisting of two parts. Turmeric has been put into various uses as a flavoring agent with digestive properties as a coloring in India. In fact, no Indian preparation is complete without turmeric as an ingredient. Turmeric is highly respected by Hindus and interestingly given in some temples as "Prasad" (a benevolent material) in powder form. Characa and Susruta, the great ancient Indian physicians who systemized Ayurvedic medicine, recorded various uses of turmeric.

Dioscorides, a Greek doctor in the Roman Army, also mentioned turmeric. European explorers traveling to the Asian continent brought turmeric to the Western world in the fourteenth century. For over 20,000 years, it has been crushed and powdered turmeric rhizome has been widely used in Asian cuisine, medicines, cosmetics, and fabric dyeing. About 40 species of the Curcuma genus are native to India, which indicates their Indian origin. Approximately 70-110 species of species have been reported in Tropical Asia. The species in India, Myanmar and Thailand show the greatest variety. Some species are seen as far away as China, Australia and the South Pacific, while some other popular species are grown in all tropical regions (Nair 2013).

Curcumin was first isolated from turmeric in 1815 and the structure Illuminated in 1910 was defined as diferuloylmethane (curcumin). The most curcumin preparations currently available include approximately 77% diferuloylmethane (curcumin), 18% demethoxycurcumin and 5% bismethoxycurcumin.

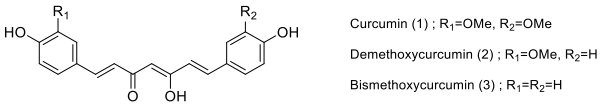

Figure 2. Curcuminoid structures

Turmeric consists of 3-5% Curcuminoid. Curcumin is the most important fraction responsible for the biological activities of turmeric (Çikrikçi et al. 2008). Curcumin is found in the rhizome of *Curcuma longa L.* and other *Curcuma spp* species. Commercially, curcumin is found in the plant at approximately 77%, as well as two other related compounds (bimethoxycurcumin and demethoxycurcumin). These compounds belong to the diarylheptanoid group. These three compounds are

called Curcuminoid. Curcumin appears as a bright orange-yellow crystalline compound. Curcumin is widely used as a coloring and food additive. Curcumin is almost insoluble in water at acidic and neutral pH, but it is soluble in polar and non-polar organic solvents, as well as in highly acidic solvents such as alkali or glacial acetic acid. Curcumin has a melting point of 183 °C. The curcumin molecular formula is $C_{21}H_{20}O_6$, with a molecular weight of 368.38 Dalton. Most studies on curcuminoid compounds have been performed on animals (mice, rats, or dogs), and studies on humans have reported in very few publications. Clinical studies have shown that curcumin is safe for humans even at high doses, but its therapeutic use is very low since its bioavailability is limited. Preclinical studies have reported that curcumin concentrations in plasma and target tissue are very low due to its widespread metabolism (Lestari and Indrayanto 2014; Celik et al.2008).

Uses of Curcumin; Curcumin has been used in traditional Indian and Chinese medicine for centuries, especially as an anti-inflammatory agent. In recent years, several studies of curcumin have been anticarcinogenic, antioxidant, immunomodulatory, antiangiogenic, etc. showed that it has various biological and pharmacological activities. However, preclinical and clinical studies have found that the potentially beneficial effects of curcumin on the prevention and treatment of various diseases are limited to poor pharmacokinetic properties due to its imbalance under physiological conditions that hinder its therapeutic benefit. Curcumin's main structural problem; physiological conditions are the presence of active methylene group and p-diketone fragment, causing curcumin instability under poor absorption and rapid metabolism (Wiggers et al. 2017).

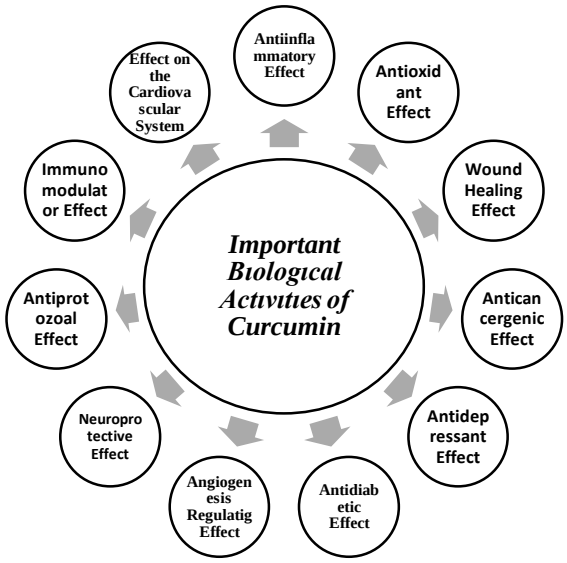

Figure 3. Schematic of the multiple biological activities of turmeric / curcumin

In various scientific studies, curcumin, a polyphenol, has been shown to target multiple signal molecules and also to act at the cellular level, helping to support multiple health benefits. It benefits inflammatory conditions, metabolic syndrome, pain; It has also been shown to assist in the treatment of inflammatory and degenerative eye conditions. It has also been shown to benefit the kidneys. Although there are numerous therapeutic benefits to curcumin supplements, most of these benefits are due to their antioxidant and anti-inflammatory effects. Despite its reported benefits through inflammatory and antioxidant mechanisms, one of the biggest problems in curcumin ingestion by itself is its poor bioavailability, which appears to be mainly due to poor absorption, rapid metabolism and rapid elimination. By addressing these various mechanisms, various substances have been tested to improve the bioavailability of curcumin. Many have been developed to block the metabolic pathway of curcumin to increase its bioavailability. For example, piperine, a known bioavailability enhancer, is the main active

ingredient of black pepper and is associated with a 2000% increase in curcumin bioavailability. Therefore, the problem of poor bioavailability appears to be solved by adding agents such as piperine that increase bioavailability and creating a curcumin complex (Hewlings and Kalman 2017).

Synthesis of synthetic analogues can be shown as one of the studies to increase the biological activity of curcumin. In addition to synthetic analogues, other strategies have been considered to increase the biological activity of curcumin. These strategies include adjuvants, nanoparticles, liposomes, micelles and phospholipid complexes. The adjuvants were selected on the basis of their ability to prevent the rapid metabolism of curcumin by interfering with enzymes that catalyze curcumin metabolism. All other formulations mentioned are primarily designed to increase the absorption of curcumin into tissues. Nanoparticles can provide greater penetration into membrane barriers due to their small size. Besides their size, their modification potentials targeting specific organs make them excellent drug carriers. Liposomes, micelles and phospholipid complexes can reduce the hydrophobicity of curcumin; these carriers can also interact with the membrane components to increase the permeability of the membrane barriers. Recently, it has been reported that the water solubility of curcumin can be 12 times with the use of heat (Kurien et al 2007).

Curcumin is recognized and used worldwide for many potential health benefits. For example, turmeric containing curcumin in India has been used in curries, served as tea in Japan, used in cosmetics in Thailand, used as a colorant in China, served in drinks in Korea, used as an antiseptic in Malaysia, a in Pakistan used as an anti-inflammatory agent and in the United States in mustard sauce, cheese, butter and chips; It is used in addition to capsules and powder forms as a preservative and coloring agent. Curcumin capsule, tablet, ointment, energy drink, soap, cosmetics, etc. various forms are available. Curcuminoids have been approved by the U.S. Food and Drug Administration (FDA) as GRAS (Generally Recognized as Safe), and good tolerability and safety profiles have been demonstrated by clinical studies even at doses from 4000 to 8000 mg / dose (Hewlings and Kalman 2017).

In this research study, curcumin, which is the main active ingredient of turmeric, which has a wide range of uses, is aimed to illuminate a few of its important biological activities.

Figure 4. Turmeric (Curcuma longa)

Anticancergenic Activity

Curcumin has attracted attention in cancer researches in recent years due to its cancer suppressor feature. It has been shown in many cancer types as an anticancer effective agent in studies that suppress tumor formation. Curcumin obtained from turmeric; It has been used for centuries to treat various inflammatory diseases. The turmeric; cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and reduction of receptors in antiapoptotic genes), proliferation (HER-2, EGFR, AP-1), survival (PI3K / AKT pathway), spread (MMP-9 and adhesion molecules), new blood vessel network formation (VEGF), metastasis (CXCR-4), inflammation (NF-

KB, TNF, IL-6, IL-1, COX-2, VE 5-LOX) and their multiple cells signal is thought to act by interfering on the path. Curcumin has been reported to suppress tumor formation in leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous (flat) carcinoma, lung cancer, melanoma and neurological cancers (Anand et al. 2008). Although traditional herbal medicines are thought to be safe, it is not known exactly what their active principles are and how they mediate cancer. Phenolic compounds; It exhibits antioxidant and anticancer activity thanks to its free radical scavenger properties. Curcumin has excellent antioxidant activity due to its phenolic and enolic functional groups (Sharma et al. 2005). Studies have confirmed that aromatic rings with curcumin and their analogs show cytostatic activity. Curcumin has antineoplastic activity, low molecular weight and no toxicity. makes it the ideal precursor molecule in the development of potential chemotherapeutic drugs. Based on the chemical structure of curcumin, various analogues are synthesized and their effects are tested (Youssef et al 2007; Tomeh et al.2019; Vallianou et al. 2015).

Anti-inflammatory and Antioxidant Activity

Numerous studies have been conducted on curcumin, especially in respiratory diseases. Curcumin is used in Eastern medicine for the treatment of various chronic inflammatory diseases, including respiratory diseases. Curcumin has been shown to reduce inducible nitric oxide synthase activity in aspiration induced airway damage in rats. Sharma (1976) reported that the antioxidant property of curcumin is due to its phenolic structure and prevents apoptosis by restoring growth-inhibited cells. Turmeric increases the duration of protection by preventing the formation of peroxide in foods. Turmeric has been reported to be more effective than vitamin E in preventing lipid oxidation. It has been determined that the components isolated from Curcuma longa have a strong antioxidant effect and are very important on lipid oxidation (Jayaprakasha et al. 2005; Wright 2002).

Curcumin also inhibits neural activation, mixed lymphatic reaction, and platelet development by eliminating mitogens that cause rapid growth of mononuclear blood cells (Huang 1992). It also partially inhibits the protein kinase enzyme (Liu 1993). Oxidative stress is known to play an important role in the pathogenesis of many diseases, including myocardial ischemia, brain ischemia-reperfusion injury, bleeding, shock, nervous cell damage, and cancer. Curcumin has proven anti-inflammatory and antioxidant properties. Curcumin has been reported to remove different types of reactive oxygen, including hydroxyl radicals (Reddy and Lokesh 1994) and nitrogen dioxide radicals (Unnikrishnan and Rao 1995, Sreejayan and Rao 1997). Khanna (2009) stated that the antioxidant capacity of curcuminoids is equivalent to ascorbic acid. Curcumin is a powerful hydroxyl radical scavenger as well as capturing superoxide radicals. It protects DNA from oxidative damage due to its ability to retain free radicals (Pandya et al 2000). When curcumin is taken orally, it turns into tetrahydrokurumin by hydrogenation in the intestines. It is absorbed from the intestines, distributed into the blood and thus tissues, and is excreted in bile. Davis et al. (2007) showed that curcumin supplementation reduced muscle damage caused by excentric exercise in rats (Boz 2013; Aggarwal 2009).

Local application of turmeric is used in skin diseases, insect bites and chickenpox in India. It has been used as an alternative medical support for wound

healing for many years. Wound contraction is faster in myofibroblasts treated with curcumin. As a result of curcumin treatment, fibronectin and collagen expression increases. In addition, the formation of granulation tissue, neovascularization re-epithelialization increases in mouse wound models formed with diabetic and hydrocortisone. Curcumin has been shown to reduce hydrogen peroxide-induced damage in yellow keratinocytes and fibroblasts. Jagetia looked at wound healing in Swedish albino mice by willing the body half in multiple fractionated doses; evaluated dose-dependent wound contractions and wound healing in animals examined on days 4, 8, and 12 after radiation exposure. It has been shown that curcumin administered before treatment significantly reduces wound contraction and average wound healing time. With curcumin treatment, collagen, hexosamine, DNA, nitrate, and nitrite synthesis increased before the radiation, and collagen accumulation, fibroblast and vascular densities also increased. In the acute ulcer model created in mice, it also shows antiulcer effect by decreasing lipid peroxidation and protein oxidation. Epithelial cell damage in the gastic lumen is reversible by providing reepithelialization with curcumin (Uzer 2007).

As a result, curcumin has been found to have powerful modulating effects on wound healing. Studies have shown that curcumin does this by acting in the inflammatory, proliferative and remodeling stages of the wound healing process, and by doing so it reduces the time required for wound healing. Unfortunately, curcumin is limited by its low bioavailability, rapid metabolism, poor solubility and light sensitivity. In order to minimize these effects and to use curcumin to its maximum capacity, new formulations such as nanoparticles should be investigated (Akbik et al. 2014; Jurenka 2009).

Angiogenesis Activity

Angiogenesis is a physiological process characterized by the formation of new vascular capillary canals. These steps extend from embryonic development, production processes, wound healing to bone healing. On the other hand, there are many pathological conditions related to uncontrolled angiogenesis. Tumor growth, Rheumatoid Arthritis, Diabetic Retinopathy and hemangiomas can be counted. In the last 30 years, intensive studies have been conducted on the growth of primary tumor and its role in angiogenesis in distant metastases. Curcumin has been beneficial in many models as a regulator of uncontrolled angiogenesis. In laboratory conditions, angiogenic differentiation with curcumin in human umbilical vein endothelial cells, mouse oral mucosa cells and chicken chorioallantoic membrane cells was inhibited. In a different study, corneal neovascularization was inhibited in the mouse cornea with a basic fibroblast growth factor (bFGF) stimulus. This effect can be explained by the fact that curcumin analogs reduce over-expression of genes associated with angiogenesis. Curcumin and its analogs inhibit metalloproteinases and reduce angiogenesis in tumor tissues (Uzer 2007; Wang and Chen 2019).

Antineuroprotective Activity

Curcumin (*Curcuma longa*), a biologically active component of turmeric, is used as a curry spice and herbal remedy for the treatment of inflammatory conditions, cancer, AIDS and other diseases. Epicchemical studies in India, where turmeric is routinely used, show that the incidence of AD between the ages of 70 and 79 is 4.4 times less than in the USA. The researchers used transgenic mouse APPSw to investigate curcumin therapeutic effect. The results

show that low-dose curcumin significantly suppresses inflammatory cytokine IL-1 and astrocytic marker GFAP, reduces oxidative damage and plaque burden, and reduces the amount of insoluble amyloid. Compared to other antioxidant drugs such as NSAID or ibuprofen, curcumin has less side effects. Evidence shows that metals are concentrated in the AD brain and curcumin is a chelating agent that can bind iron and copper (not zinc) onto beta amyloid, which could potentially contribute to amyloid reduction. In vivo, curcumin can protect cells from beta amyloid attack and subsequently damage from oxidative stress in the antioxidant pathway.

Curcumin significantly improved the memory ability of AD mice in step test testing, as indicated by reduced number of step-by-step errors and extended step-by-step latency. Curcumin also relieved neuropathological changes in the hippocampus and inhibited apoptosis with an increase in Bcl-2 level, but Bax activity did not change. Curcumin increased cell viability in the presence of ALCL. The rate of apoptosis decreased significantly in the curcumin group, when measured by flow cytometric analysis. Curcumin preserved cells by increasing the Bcl-2 level, but the Bax level has not changed. In this study, curcumin was found to increase the memory ability of AD mice (Pan et al. 2008; Amalraj et al.2017)

Antidepressant Activity

Several traditional Chinese herbal medicines such as Xiaoyao-san and Jieyu-wan, which were prescribed by the famous Chinese folk doctor Zhong-jing Zhang thousands of years ago; It has been used in the treatment of mental stress, hypochondriac intense pain, hysteria and manic. Various findings in recent preclinical studies have supported the therapeutic value of herbal medicines in a clinical setting. In laboratory studies of animals, Xiaoyao-san has been shown to have antidepressive-like effects using tail suspension and forced swimming tests. In the study of Ying et al., The effects of curcumin on depressive-like behaviors in mice were analyzed using two animal depression models. The results showed that curcumin treatment at 5 and 10 mg / kg (po) significantly reduced inactivity. In both tail suspension and forced swimming tests. These doses that affect the inactive response did not affect locomotor activity. In addition, neurochemical analysis showed that curcumin produced a marked increase in serotonin and noradrenaline levels at 10 mg / kg in both the frontal cortex and hippocampus. Dopamine levels also increased in the frontal cortex and striatum. In addition, curcumin has been found to inhibit monoaminoxidase activity in the mouse brain. These findings suggest that the antidepressant-like effects of curcumin may include central monoaminergic neurotransmitter systems. Therefore, the results of the study show that curcumin has antidepressant properties in behavioral hopelessness tests and the effects may be related to monoaminergic systems. These studies may contribute to understanding the mechanisms of curcumin antidepressant effects. The modified amine theory suggests that an acute increase in monoamine levels in synapse can only be an early step in a potentially complex sequence of events that ultimately leads to antidepressant activity. Given that chronic antidepressant effects are frequently seen after chronic treatment, the long-term effects of curcumin should be evaluated and further studies should focus on receptors and signal transduction to explain the detailed mechanisms of the curcumin antidepressant effect (Ying et al. 2005; Kulkarni 2009).

Antiprotozoal Activity

The antiprotozoal activities of curcumin have been extensively studied in the past decade. Turmeric (1% raw extract), as well as its functional and medicinal ingredient, curcumin (0.05%), seems to be effective in reducing upper and middle-small bowel infections caused by Eimeria acervulina and E. maxima. It is useful in E. tenella infections. However, in vitro incubation of E. tenella sporozoites with curcumin showed significant effects on sporozoite morphology and viability, leading to reduced invasion of MDBK cells. The curcumin alcohol extract has been found to have antiprotozoal activity. Against Entamoeba histolytica. Curcumin antiprotozoal activities have also been reported for Plasmodium, Leishmania, Trypanosoma and Giardia lamblia both in vitro and in vivo. Curcumin reduced parasitemia by 80% to 90% in mice infected with Plasmodium berghei. In another study, curcumin was found to be effective against Cryptosporidium parvum in cell culture. *C.parvum* has been found to be more sensitive to curcumin than Plasmodium, Giardia and Leishmania. Synergistic antiprotozoal effects have been shown when curcumin is administered in combination with other drugs. For example, the combination of artemicin and curcumin exhibited additional activity in the culture killing of Plasmodium falciparum and allowed survival of mice infected with P. berghei. Drug resistance of plasmodium strains is a major threat to malaria control. However, chloroquine-resistant P. falciparum and artemisinin-resistant Plasmodium chabaudi were found susceptible to curcumin in cultures and mice, respectively. These are promising data that can open alternative options for malaria control, especially where drug resistance has become a relevant issue.

Curcumin's antiparasitic activities are obtained by effects on the transcription of genes. Recent studies have shown that histone acetylation plays an important role in eukaryotic gene expression and antiparasitic therapy. The balance between acetylation and deacetylation of histones is correctly maintained by histone acetyltransferase (HAT) and histone deacetylase balance. Curcumin induces histone hypoacetylation mainly in vivo through HAT inhibition and simultaneous effects of curcumin with ROS production, it also contributes to the inhibition of HAT activity. Curcumin inhibits intracellular adhesion molecules that contribute to the sequestration and formation of Toxoplasma and has been associated with a glutathione transferase (PfGST) chloroquine resistance isolated from Plasmodium P. falciparum. Curcumin is a powerful PfGST inhibitor that can open alternative perspectives for the management of drug resistance in malaria. It inhibits metalloproteinase activity comparable to classical matrix metalloproteinase inhibitors such as curcumin, EDTA, EGTA, phenanthroline and also trypanosoma brucei infection, such as tetracycline. Survivin's curcumin-mediated downregulation induces apoptosis in tumor cells and can likewise increase the apoptosis of C. parvum. Infected cells. Curcumin can effectively regulate NF-kB, thereby inhibiting IkappaBalpha kinase and reducing IkappaBalpha phosphorylation, leading to cell cycle arrest, apoptosis and proliferation of parasitically infected cells. Inhibition of thioredoxin reductase by curcumin may reduce parasite proliferation, which is attractive for control strategies (Parasuraman 2017; Rasmussen et al.2000)

Antidiabetes Activity

Curcumin is used in ayurveda and traditional Chinese medicine for the treatment of diabetes. It is thought to be a potential treatment for diabetes and its complications as it is a relatively safe and inexpensive

drug that reduces glycemia and hyperlipidemia in diabetes models (Zhang et al 2013). In a study, the effects of curcumin with antioxidant and anti-inflammatory properties on diabetic oxidative stress and inflammation in the retina of mice were investigated. One group of diabetic mice induced with streptozotokin was given a powder diet supplemented with 0.05 curcumin (w/w) and a diet without curcumin was applied to the other group. Mice were sacrificed 6 weeks after induction of diabetes. The retina has been used to identify oxidative stress and proinflammatory signs. At the end of the study; antioxidant capacity and intracellular antioxidant levels, GSH levels decreased about 30-35%. Application of curcumin prevented a decrease in antioxidant capacity from diabetes. Curcumin effects were achieved without correction of severe hyperglycemia. In this case, curcumin has been suggested to have beneficial effects on metabolic abnormalities (Kowluru and Kanvar 2007).

In a study on the anti-inflammatory, antioxidant, hypoglycemic and lipid-lowering effects of turmeric extract; live subjects induced by high fat diet were divided into two groups and extract was given to one of these groups at determined doses. In the extract group, turmeric showed a strong inhibitory effect against the oxidation of LDL (low density lipoprotein) and glycation caused by fructose due to the high radical scavenging effect caused by the antioxidant activity. As a result, turmeric extract has been declared to prevent glycation due to its strong antioxidant activity, decreases LDL (low density lipoprotein) and thus reduces the risk of atherosclerosis (vascular stiffness) (Kubra et al. 2010).

In a study on the effect of Curcuma longa extract on plasma glucose and insulin; Research has been conducted on 14 healthy volunteers (7 men, 7 women). Orally 6 g Curcuma longa extract was given on certain days and insulin levels were checked at certain time intervals. It was observed that satiety insulin levels increased in these groups of people given Curcuma longa extract. As a result, it has been scientifically explained that *C. Longa* extract has positive effects on insulin release in humans (Wickenberg et al. 2010).

Anticardiovascular Activity

The protective effects of turmeric on the cardiovascular system include lowering cholesterol and triglyceride levels, lowering the sensitivity of low-density lipoprotein (LDL) to lipid peroxidation and inhibiting platelet aggregation. These effects are noted even with a low dose of turmeric. In a study of 18 atherosclerotic rabbits given a low dose of turmeric extract (1.6-3.2 mg / kg body weight per day), LDL's sensitivity to lipid peroxidation in addition to low plasma cholesterol and triglyceride levels has been shown to decrease. The higher dose did not reduce the lipid peroxidation of LDL, but to a lesser extent than the low dose, the level of cholesterol and triglycerides decreased. The effect of turmeric extract on cholesterol levels may be due to decreased cholesterol intake in the intestines and increased conversion of cholesterol to bile acids in the liver. Inhibition of platelet aggregation by C. longa components is thought to be by enhancing prostacyclin synthesis and inhibition of thromboxane synthesis (Akram et al. 2010; Gupta et al. 2012).

Anti-AIDS Activity

There are several reports showing that curcumin may have potential against AIDS. These effects of curcumin are mediated by inhibition of HIV long terminal repeat and HIV protease and inhibition of human immunodeficiency virus (HIV) replication, inhibit HIV-1 integration, p300 / CREB binding

protein specific acetyltransferase and chromatin dependent of histone / non histone proteins and histone acetyltransferase. Suppresses the acetylation of its transcription. For this reason, curcumin also has great potential against AIDS (Jagetia and Aggarwal 2007; Mazumdar et al. 1995).

Antigastrointestinal Activity

Curcuma longa components are known to exert various protective effects on the gastrointestinal tract. Sodium curcuminate has been shown to inhibit intestinal spasm and turmeric component p tolmethylcarbinol, increased gastrin, secretin, bicarbonate and pancreatic enzyme secretion. Turmeric has also been shown to inhibit the formation of stress, alcohol, indomethacin, pyloric ligation and ulcer-induced ulcer, and significantly increase gastric wall mucus in rats exposed to these gastrointestinal insults (Akram et al. 2010; Kwiecien et al. 2019).

Antiimmunomodulator Activity

The immune system has evolved to protect the host from microbial infection; However, a disruption in the immune system often results in infection, cancer, and autoimmune diseases. Multiple sclerosis, rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, myocarditis, thyroiditis, uveitis, systemic lupus erythromatosis, and myasthenia are organ-specific autoimmune diseases that affect more than 5% of the population worldwide. Although its etiology is not known but still requires a treatment, the use of herbal and dietary supplements is increasing in patients with autoimmune diseases, as they are mainly effective, inexpensive and relatively safe. Recent studies have shown that curcumin improves multiple sclerosis, rheumatoid arthritis, psoriasis and inflammatory bowel disease in human or animal models. Curcumin inhibits these autoimmune diseases by regulating inflammatory cytokines in immune cells such as IL-1β, IL-6, IL-12, TNF-a and IFN-y and associated JAK-STAT, AP-1 and NF-kB signaling pathways. Although the beneficial effects of nutraceuticals have traditionally been achieved with low levels of dietary consumption for a long time, the use of purified active compounds such as curcumin for therapeutic purposes requires extreme caution (Bright 2007).

According to many studies, curcumin increases immunity. Curcumin can also help the body fight cancer if some cells escape apoptosis. The researchers found that when they looked at the lining of the intestine after curcumin intake, the number of CD4 + T helper and B-type immune cells was higher. In addition to this localized immune stimulation, curcumin also increases immunity in general. Researchers in India have documented increased antibodies and greater immune action in mice given curcumin (Akram et al. 2010; Srivastava et al. 2011).

Antiviral Activity

In the study of Joe et al. Olarak In vitro, curcumin (0.32 mg / ml) partially inhibited the activity of the human simplex virus-2 (Bourne et al. 1999). Curcumin provided significant protection in a mouse model of the intravaginal human simplex virus-2 threat (Bourne et al. 1999). Curcumin is also highly effective in inhibiting Type I Human Immunodeficiency Virus (HIV) long terminal repeat directed gene expression and viral replication (Jiang et al. 1996; Li et al. 1993). Curcumin inhibited the production of p24 antigen in acute or chronically infected cells with HIV-1 (Li et al. 1993). However, curcumin was unable to inhibit HIV-

1 proliferation in acute infected MT-4 cells (Artico et al. 1998). However, curcumin specifically inhibited enzymatic reactions associated with HIV-1 integrase, but other viral (HIV-1 reverse transcriptase) and cellular (RNA polymerase II) nucleic acid processing enzymes (Artico et al., 1998; Burke et al., 1995). Mazumder et al. (1997) synthesized and tested curcumin analogs to examine the structure-activity relationships and mechanism of action of this family of compounds in more detail. The two curcumin analogues, dichopeoylmethane and rosmarinic acid inhibited the integrase activity with IC50 values below 10 μM. The two curcumin analogues showed lysine 136 (required for viral DNA binding) and equivalent potencies in wild-type integrase. Curcumin binding site and substrate binding site may not overlap (Mazumder et al. 1997). Combination of a curcumin analog with the recently described integrase inhibitor NSC 158393 resulted in synergistic or reflective integrase inhibition of drug binding sites that may not match. They also determined that these analogs could prevent the enzyme from binding to viral DNA, but this inhibition was independent of the divalent metal ion. In addition, kinetic studies of these analogs suggest that they bind slowly to the enzyme (Mazumder et al. 1997; Joe et al 2004).

Use in Ischemia

Neuronal energy metabolism is dependent on oxygen and glucose and cannot cope with hypoxic or hypoglycemic periods. A decrease in oxygen or glucose concentrations in the brain inevitably leads to loss of neuronal function. Ischemia is caused by a deficiency in blood flow to the brain or areas of the brain, as in stroke. The results of ischemia are an increase in intracellular Ca2 + levels through excessive mitochondrial production of reactive oxygen species, activation of the NMDA receptor, stimulation of astrocytes, and neuronal death. Evidence from animal models shows that curcumin can protect against ischemic damage. In addition to keeping the injured area in the brain, curcumin can reduce oxidative damage and mitochondrial dysfunction, as well as inhibit neuronal apoptosis and microglial activation. During and after ischemia, other inflammatory agents are produced, such as leukotriene and cytokine, which facilitate infiltration of leukocytes. Proteolytic enzymes from recruited leukocytes disperse the blood-brain barrier, resulting in edema in damaged brain tissue. Application of curcumin to laboratory rodents can prevent edema and maintain the integrity of the blood-brain barrier. Their significant improvement in cognitive performance is now observed in curcumin-treated animals as compared to untreated ischemic controls. Interestingly, curcumin can provide significant protection from the harmful effects of ischemia, regardless of the route of administration (intraperitoneal injection, gavage or dietary supplement). Despite the large available data on the anti-ischemic effects of curcumin in animal models, studies in humans are scarce. In fact, a possible therapeutic application of curcumin in cases of stroke and ischemia is controversial. On the one hand, curcumin and its synthetic derivatives (CNB - 001) are considered potential neuroprotectants based on epidemiological observations and preclinical data. However, in order to achieve levels comparable to those used in animal models, high concentrations of curcumin will be required daily (Esatbeyoğlu et al. 2012; Bavarsad et al. 2018).

2. Discussion

Turmeric (curcumin) is known to give positive results in the treatment of many diseases such as

neurological diseases, indigestion, urinary system infections, liver diseases, rheumatoid arthritis, respiratory system diseases, obesity, diabetes, cancer. Curcumin is the most important active ingredient responsible for the biological activities of turmeric. Curcumin has been used for centuries due to its non-toxic and potential therapeutic effects. As a result of the studies, the tolerability and safety of this polyphenol (curcumin) at doses not exceeding 8 mg per day revealed that it is non-toxic. In addition to the use of sweeteners and colorants in nutrition, curcumin antioxidant, antimutagenic, antidiabetic, antibacterial, antiviral, anti-inflammatory, antinociceptive anti-inflammatory, anticancer, antioxidant, anti-protozoal, anti-microbial, antimalarial, antiinflammatory, antiproliferative, anti-inflammatory, anti-inflammatory, antiproliferative, antiproliferative, antiproliferative, antiproliferative, anti-inflammatory It has. With its reliability, low cost and proven efficacy, turmeric is a promising natural medicine for diseases. It is seen that more comprehensive studies are needed since there are not enough studies in terms of drug interactions. Turmeric must be present in our daily diet.

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Peripheral Adropin Application Regulates Nutritional Behavior and Fat Tissue-mediated Energy Metabolism

Ersen ERASLAN[1*], Tuncer NACAR[2], Ayhan TANYELİ[2], Mustafa Can GÜLER[2], Elif POLAT[3], Ali Sefa MENDİL[4], Elif POLAT[5] and Mustafa ÖZKARACA[6]

[1*] Yozgat Bozok University, Faculty of Medicine, Department of Physiology, Yozgat, Turkey
ersen.eraslan@yobu.edu.tr
[2] Atatürk University, Faculty of Medicine, Department of Physiology, Erzurum, Turkey
tnacar@atauni.edu.tr
ayhan.tanyeli@atauni.edu.tr
mustafacan.guler@atauni.edu.tr
[3]Atatürk University, Faculty of Medicine, Department of Biochemistry, Erzurum, Turkey
elif_2577@hotmail.com
[4] Erciyes University, Faculty of Veterinary Medicine, Department of Pathology, Kayseri, Turkey
sefaali5252@gmail.com
[5]Namık Kemal University, Faculty of Medicine, Department of Histology and Embryology, Tekirdağ, Turkey
epolat@nku.edu.tr
[6] Atatürk University, Faculty of Veterinary Medicine, Department of Pathology, Erzurum, Turkey
mustafa.ozkaraca@atauni.*edu.tr*

Abstract

Adropin is a peptide hormone that is involved in food and energy homeostasis and has many metabolic roles. Although previous studies attempted to explain the relation between adropin and nutritional behavior, there is no strong evidence. In the present study, the effects of peripheral adropin administration on various signals related to nutritional behavior were investigated in rats at doses of 4 µg/kg and 40 µg/kg by using biochemical and histopathological analyses.

It was shown that adropin reduces feed and water consumption in rats. It was also shown that these effects occur through various neuron groups in the central area by affecting many peripheral signals. Adropin modulates many signals contributing to nutritional behavior.

Keywords: Adropin, Food intake, Feeding behaviour, Hypothalamus

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[*]Corresponding author:Ersen ERASLAN PhD
Department of Physiology, Faculty of Medicine, Yozgat Bozok University, Yozgat 66900, Turkey
E-mail: ersen.eraslan@bozok.edu.tr
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1. Introduction

The hypothalamus has critical roles in regulating many homeostatic processes like nutrition, thermoregulation, energy use and reproduction (Elmquist, Elias, & Saper, 1999; Hall et al., 2012). The Arcuate Nucleus (ARC), paraventricular nucleus (PVN), and different nuclei that include ventromedial and dorsomedial hypothalamus and hypothalamic area share neuronal interconnections and maintain body homeostasis

together (Schwartz, Woods, Porte, Seeley, & Baskin, 2000). ARC neurons are regulated with metabolic peripheral signals, which contain hormones and gastrointestinal peptides [e.g. leptin, adiponectin, glucagon-like peptide-1 (GLP-1) and thyroid hormones (Krashes et al., 2014; Rohner-Jeanrenaud & Nogueiras, 2015; Schwartz et al., 2000). ARC neurons produce orexigenic neuropeptides like agouti-related peptide (AgRP) and neuropeptide Y (NPY), and anorexigenic neuropeptides like proopiomelanocortin (POMC) and cocaine and amphetamine-related transcripts (CART). These neuropeptide signals are transmitted to the melancholine neurons in other parts of the hypothalamus where they are integrated with information coming from the rising fibers of the nucleus tractus solitarius (NTS) (Kim, Leyva, & Diano, 2014). These neuron groups are involved in the protection of the homeostatic system.

Adropin (Adr) is a peptide hormone consisting of 76 amino acids that are encoded by the gene (Enho) that is associated with the energy homeostasis organized by the diet. This peptide is expressed in many tissues particularly in the liver and the brain. Adr plays roles in maintaining the energy homeostasis and insulin resistance (Aydin et al., 2013; Kumar et al., 2008). The relations between Adr and obesity were analyzed in animal and human studies. It was been determined that Adr is a hormone that fights fat tissue, brings positive contributions to food intake and insulin resistance (Akcilar et al., 2016; Kumar et al., 2008; Sayin, Tokgoz, & Arslan, 2014) and has relations with cardiovascular diseases (Altamimi et al., 2019; Wu, Fang, Yuan, Xiong, & Chen, 2019).

In this study, the effects of Adr peptide on adipose tissue with peripheral and central signals controlling the feeding behavior were investigated.

2. Material And Methods

2.1 Ethical Consideration and the Animals

The permission for all applications to rats was obtained from the Local Ethics Committee of Atatürk University, Experimental Animals (Protocol no: 30.06.2017/65). In the present study, a total of 40 Wistar albino male rats with average weights of 304 ± 11 g were used. The animals were divided into four groups to include the closest to each other in terms of body weight averages as the Control, Sham, 4 µg/kg Adr, and 40 µg/kg Adr groups (n=10). The animals were kept at 21±1°C in a light/dark cycle for 12 h during the experiment. The rats were fed with standard rat feed *ad libitum* and drank regular tap water. The Adr peptide was obtained from Phoenix Pharmaceuticals (CA, USA), dissolved in pure water, and then injected intraperitoneally to rats.

After 10 days of the injections, the animals were decapitated, and their blood, hypothalamus, liver, thyroid gland, white adipose tissue (WAT) and brown adipose tissue (BAT) were collected. The blood samples were centrifuged at 5000 rpm for 10 minutes, the serums were separated, and stored at -80°C until the analyses with ELISA kits. The hypothalamus, liver, thyroid gland, white and brown fat tissue samples were stored at 10 % formaldehyde for histopathological studies.

2.2 Biochemical Analyses

The ELISA kits used in the study were supplied by Elabscience (E-EL) (Wuhan, China). Adiponectin (E-EL-R0329), Ghrelin (E-EL-R0842), Leptin (E-EL-R0582), Insulin (E-EL-R2466), Peptide YY (PYY) (E-EL-R0720), GLP-1 (E-EL-R0059), oxyntomodulin (OXM) (E-EL-R1130), Triiodothyronine (T3) (E-EL-R1097), Thyroxin (T4) (E-EL-R0390) and Thyroid-stimulating Hormone (TSH) (E-EL-R0976) were analyzed in line with the usage protocol in the ELISA kits in the ELISA Device (BioTEK Powerwawe XS Winooski, UK).

The TG, LDL, HDL, cholesterol and glucose levels were determined with Cobas Integra 1600 Fully-Automated Biochemistry Analyzer (Roche Diagnostics, Mannheim, Germany) by using the Photometric Method.

2.3 Histopathological Procedures

The hypothalamus, liver, thyroid, and the white and brown fat tissue samples that were taken from the animals were taken to 10% formalin solution for 72 hours for fixation, and were then subjected to tissue monitoring procedures. For this purpose, the tissue samples were taped according to groups, and the monitoring process was started by placing them on an automatic monitoring device.

The rats were sacrificed and the hypothalamus and white and brown adipose tissues were detected in 10% neutral formalin solution. The tissues were processed through routine alcohol-xylol, and taken into paraffin blocks. The 5-µm sections that were taken into polylysine slides were passed through xylol and alcohol series, and after washing with PBS, endogenous peroxidase inactivation was achieved by keeping them in 3% H_2O_2 for 10 minutes. The sections were then treated at antigen retrieval solution for 2x5 mins in 500 watts to reveal the antigen in the tissues. The tissues that were washed with PBS were then left for incubation at room temperature for 20 mins with AgRP (sc-517457), CART (sc-293241), NPY, POMC (sc-20148) and uncoupling protein 1(UCP1) (sc-6529) primary antibodies (SantaCruz (Sc) Texas, USA). Secondarily, the LSAB2 kit (Dako, K0679) was done as instructed by the company. DAB (3,3′-Diaminobenzidine) was used as chromogen. After counter-staining with Mayer's Hematoxylin, they were closed with an entellan, and their images were photographed in the same light setting under the light microscope and then evaluated.

2.4 Statistical Analysis

Statistical analysis of the data was made with the IBM SPSS Statistics 20v. (Chicago, USA) program. The normality of the data was tested by using the Kolmogorov-Smirnov Test. Parametric values were determined with the One-Way Variance Analysis with Bonferroni Correction, nonparametric values were determined with the Kruskal Wallis, and the group that created the difference was determined with the Mann Whitney U-test ($p<0.05$). The values were given as mean ± standart error mean (SEM).

3. Results

3.1 Metabolic parameters

The biochemical results are given in Table 1. Although Adr 4 µg/kg administration only caused changes in glucose levels, Adr 40 µg/kg administration decreased glucose and TG levels, and increased HDL levels. It was found that Adr administrations had no effect on cholesterol and LDL levels.

3.2 Food and Water Intake, and Body Weight

The change in daily body weight changes with Adr administration at different doses (Figure 1a), feed consumption (Figure 1b), and total water consumption (Figure 1c) were evaluated, and are given in Figure 1. The changes in feed consumption and body weight showed their effects as of the 6th day in the group to which Adr 40 µg/kg was administered, and the administration decreased the weight gain and feed consumption as of the 7th day in the Adr 4 µg/kg group. In addition, when the total amount of water consumed by animals was evaluated on the last day of the study, it was determined that the Adr treatment decreased water consumption.

Figure 1. The effects of Adr on nutritional behavior. (a) the changes in body weight showed effects as of

the 6th day (b) similarly, food intake decreased daily on the 6th day (c) water consumption decreased in Adr groups *p<0.05 compared to the control group (mean ± SEM, n=10).

3.3 Hormonal Parameters

The levels of adiponectin and leptin, which are the fat tissue hormones, decreased. The gastrointestinal tract hormones, ghrelin and GLP-1 levels, increased; while PYY levels decreased. The OXM levels did not change. There was a slight decrease in insulin levels; however, this change was not significant. Although the TSH and T4 levels remained unchanged, it was determined that there was an increase in T3 levels.

Figure 2. The effects of 10-day intraperitoneal Adr administratin on peripheral signals. (a and b) fat tissue hormones, (c) insulin, (d, e, f and g) gastrointestinal system hormones and (h, i and j) TSH and thyroid hormones. *p<0.05 compared to the control group (mean ± SEM, n=10).

3.4 Histological Evaluation

The liver and thyroid tissues were evaluated with hematoxylin eosin, and in the group to which 40 µg/kg Adr was administrated, an increase was detected in the number of double-nuclei hepatocytes and hyperplasia in thyroid follicles (As shown in Figure 3).

Figure 3. A photomicrograph of hematoxylin and eosin sections in thyroid gland and liver tissue. (A) control group, (B) sham group, (C) 4 µg/kg Adr and (D) 40 µg/kg Adr groups.

3.5 Immunohistochemical Evaluation

Orexigenic NPY, AgRP and anorexigenic POMC and CART neurons in the ARC (Figure 4a) and UCP 1 expressions, WAT and BAT (Figure 4b) were evaluated. The Adr administration increased AGRP and NPY expression. POMC expressions decreased and no changes were determined in CART expression. Although Adr administration did not cause any changes in WAT, 40 µg/kg Adr administration raised the expression of UCP 1 in BAT. Images are given in Figure 4, and scoring is given in Figure 5.

Figure 4a and 4b. The orexigenic and anorexigenic neurons in the ARC and UCP 1 in adipose tissues immunoreactivity. (A) control group, (B) sham group, (C) 4 µg/kg Adr and (D) 40 µg/kg Adr groups.

Figure 5. It represents their density in percentage of IHC obtained from histological images of ARC and fat tissues. **(a)** AgRP, **(b)** NPY, **(c)** CART, **(d)** POMC, **(e)** WAT and **(f)** BAT. *p<0.05 compared to control group.

4. Discussion

In the present study, the influence of Adr on nutritional behaviour and its effects on the central nervous system and some peripheral signals that are involved in regulating energy homeostasis were explained. Our objectives were to explain how Adr administration affects UCP 1 expressions in fat tissue hormones, thyroid hormones, gastrointestinal hormones, various neuron groups in the ARC nucleus and fat tissues. It is necessary to apply the Adr to the central or peripheral areas to evaluate these variables. As a matter of fact, some evidence (the molecular size and lipophobic structure of Adr) show that the Adr cannot cross the blood brain barrier (BBB). However, we administered peripheral Adr, considering that the Adr affects various peripheral signals and will pass the weakened BBB around the ARC nucleus. Spencer et al. conducted a study and reported that the central administration of Adr caused depolarization in hypothalamic nuclei (Loewen & Ferguson, 2017). These data show us

that Adr can play a number of roles on hypothalamic neuron groups directly or via peripheral signal exchange.

The triglycerides (TGs) in circulation represent the main lipid source for metabolically active tissues like the heart and the muscles (Ruge et al., 2009). The accumulation of TGs causes the formation of fat tissue. The two important hormones of fat tissue, i.e. leptin and adiponectin, play roles in blood TG modulation. Both hormones decrease lipogenesis in various tissues and increase triglyceride hydrolysis by increasing fat oxidation (Minokoshi et al., 2002; Stefan et al., 2002; William, Ceddia, & Curi, 2002). The levels of leptin and insulin, which are among the best known and studied environmental signals, are associated with total body fat mass. Leptin, which is an adipokine, is secreted positively by WAT with the total amount of body fat. Insulin is secreted by pancreatic β cells, which are linked to blood glucose level in the short term, and to the adiposity level in the long term. Both peripheral signals show strong anorexic effects (Woods & Seeley, 2000). It inhibits the AgRP and NPY neurons in the ARC nucleus by performing the effects of both molecules in central area on receptors (Konner et al., 2007; Schwartz et al., 1992). Although these results contradict the results of some previous studies, it was reported that Adr causes fat tissue oxidation and decreases tissue fat mass. In the present study, it was shown that this is the result of the oxidation of adiponectin and leptin levels.

BAT stores more energy in TGs, and contributes to thermogenesis by burning the lipids via UCP 1 particularly in BAT. In this way, it also reduces plasma levels of TGs and glucose by fighting against hypothermia and obesity (Bartelt et al., 2011; Geerling et al., 2014). Based on the environmental effects of Adr on glucose and lipid homeostasis, it is possible that Adr affects TRH-secreting neuroendocrine neurons, because TRH plays important roles in energy homeostasis (Lechan & Fekete, 2006). The GPR19-mediated response of the Adr administered to PVN might cause TRH modulation. This increase in TRH may be the main reason for the suppression of water intake as we determined (Ishihara, Mori, Kobayashi, & Kobayashi, 1985). It was reported in similar studies that Adr suppresses water intake (Stein, Yosten, & Samson, 2016). In addition, thyroid hormones [i.e. T4 and T3] control important biological processes including metabolism and energy balance (Lopez, Alvarez, Nogueiras, & Dieguez, 2013). In the study that was conducted by Crespo et al., it was found that central T3 injection causes UCP1 expression in BAT in addition to its effects on the body weight and nutrient intake (Alvarez-Crespo et al., 2016). In the first study that was conducted by Kumar et al. describing the Adr, it was reported that there were no changes in UCP1 expression in BAT in the diet-induced obesity model in transgenic mice with Adr overexpression, which was associated with leptin levels (Kumar et al., 2008). Our results show that UCP1 expressions do not show any changes in WAT, but increase in BAT, which is because of the effects of possible thyroid hormones.

Gastrointestinal tract hormones play roles in nutritional behavior control. The effects of these hormones occur through various neuron groups in the ARC. At the same time, it was determined that some of these hormones are expressed in various parts of the brain, including the hypothalamus. Although the ghrelin hormone investigated in the present study increases appetite, PYY, GLP-1 and OXM suppress food intake (Dakin et al., 2004; Date et al., 2000; Date et al., 2002; Halatchev & Cone, 2005). Ghrelin shows orexigenic effects on nutrition by stimulating NPY/AgRP-expressing neurons in ARC nucleus. The PYY, GLP-1 and OXM hormones show their effects by changing the expressions of various neuron groups in the ARC

nucleus like AgRP/NPY and POMC/CART (Batterham et al., 2002; Cohen et al., 2003; Dakin et al., 2004; Halatchev & Cone, 2005).

The results of the present study show that Adr is related directly to food intake, regulates central and peripheral signals that control nutritional behavior, and also contributes to UCP1-mediated energy homeostasis.

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Table 1. Metabolic parameters.

Parameters/Groups	Glucose (mg/dl)	HDL (mg/dl)	TG (mg/dl)	Cholesterol (mg/dl)	LDL (mg/dl)
Control	157 ± 5,1	37,40 ± 6,4	34 ± 5,1	67 ± 7,1	11,85 ± 2,3
Sham	161 ± 4,4	38,30 ± 7,1	33 ± 2,9	71 ± 4,9	11,25 ± 1,9
Adr 4 µg/kg	133 ± 7,1[a]	34,15 ± 6,5	27 ± 6,3	63 ± 2,6	11,00 ± 2,3
Adr 40 µg/kg	126 ± 4,6[a]	42,55 ± 6,6[a]	24 ± 2,4[a]	61 ± 4,8	10,00 ± 1,1

HDL: High Density Lipoprotein, LDL; Low Density Lipoprotein, TG; Triglyceride. [a]$p < 0.05$ versus control group.

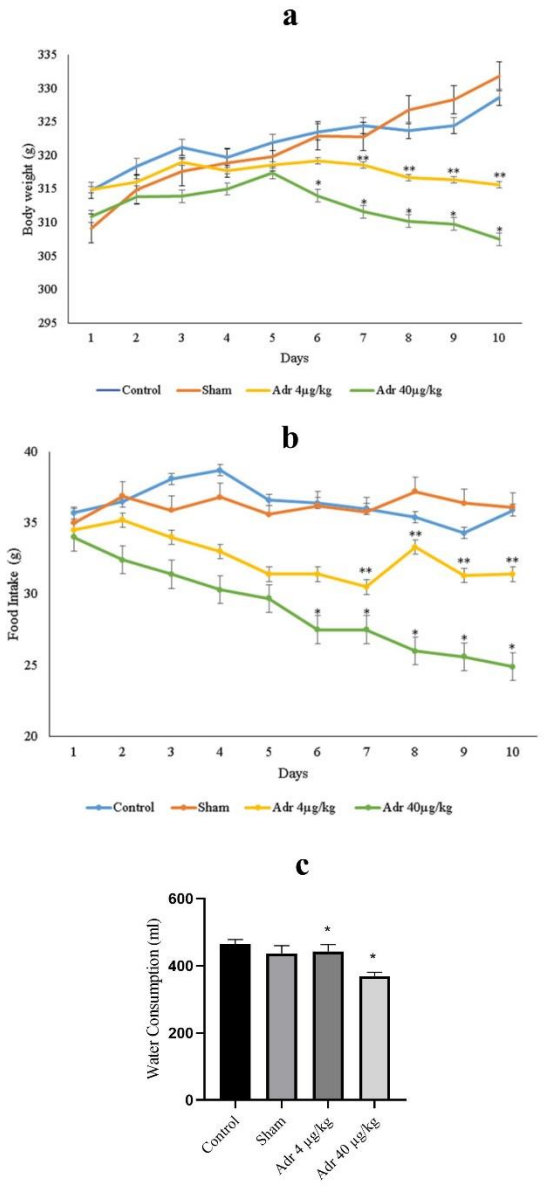

Figure 1

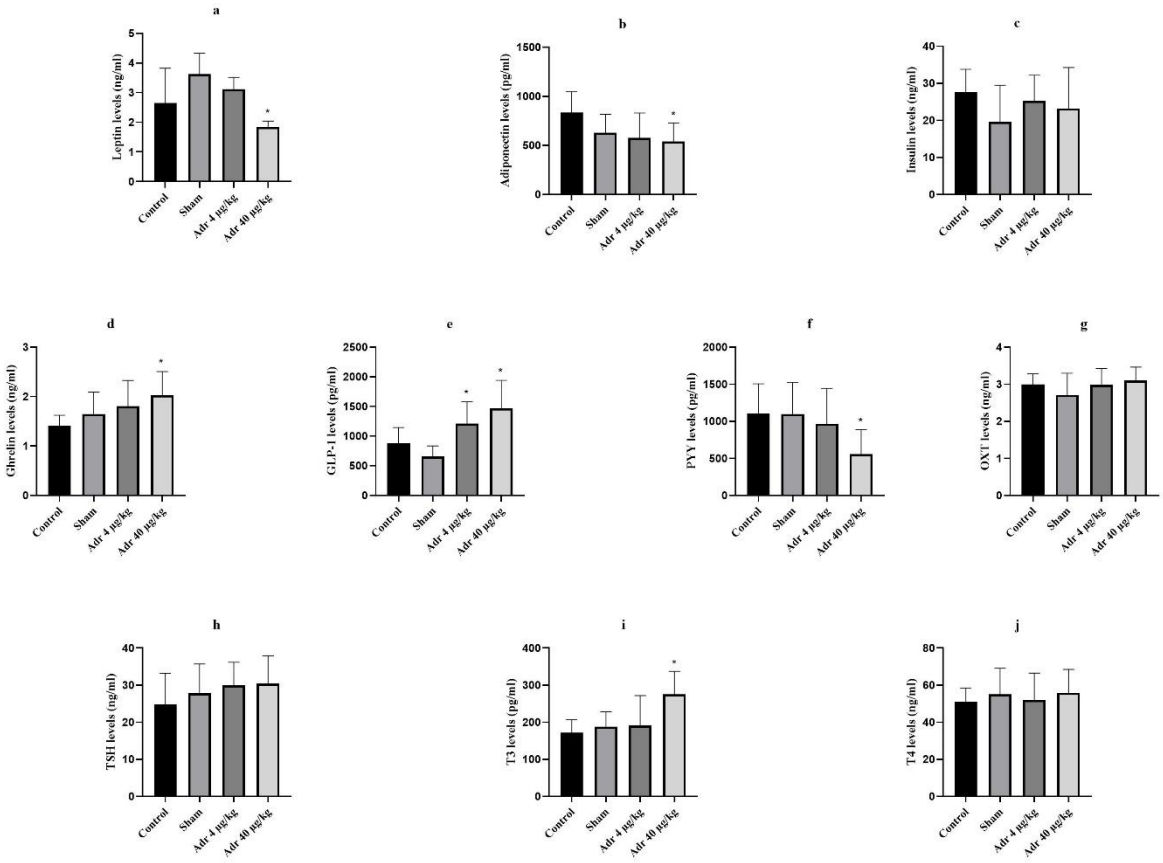

Figure 2

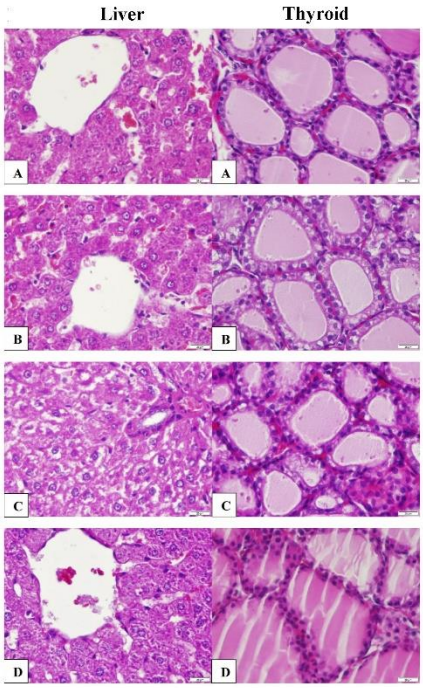

Figure 3

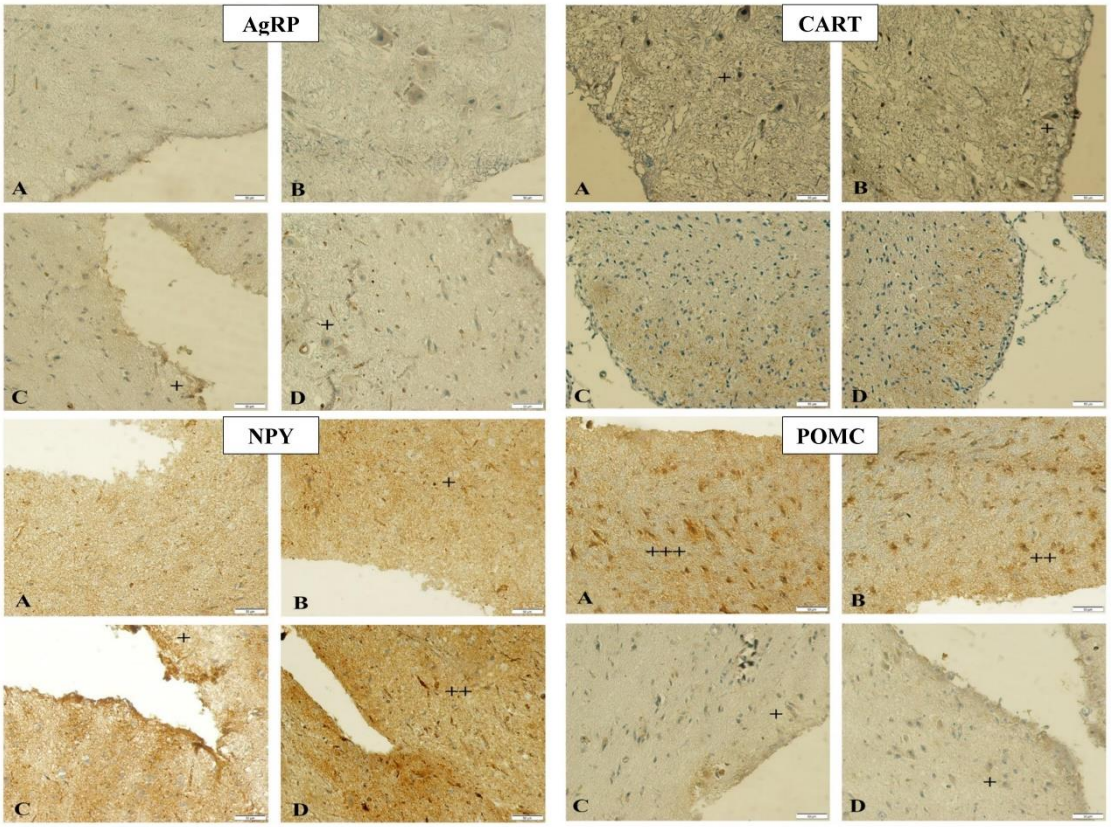

Figure 4.a

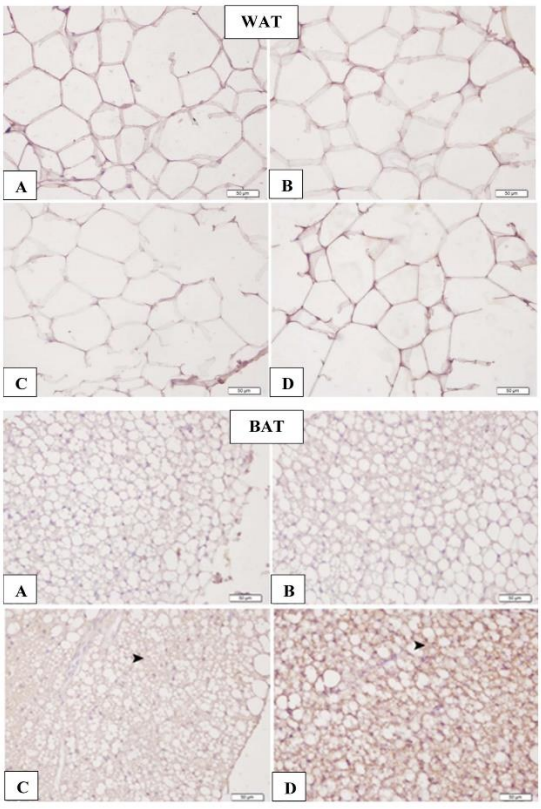

Figure 4.b

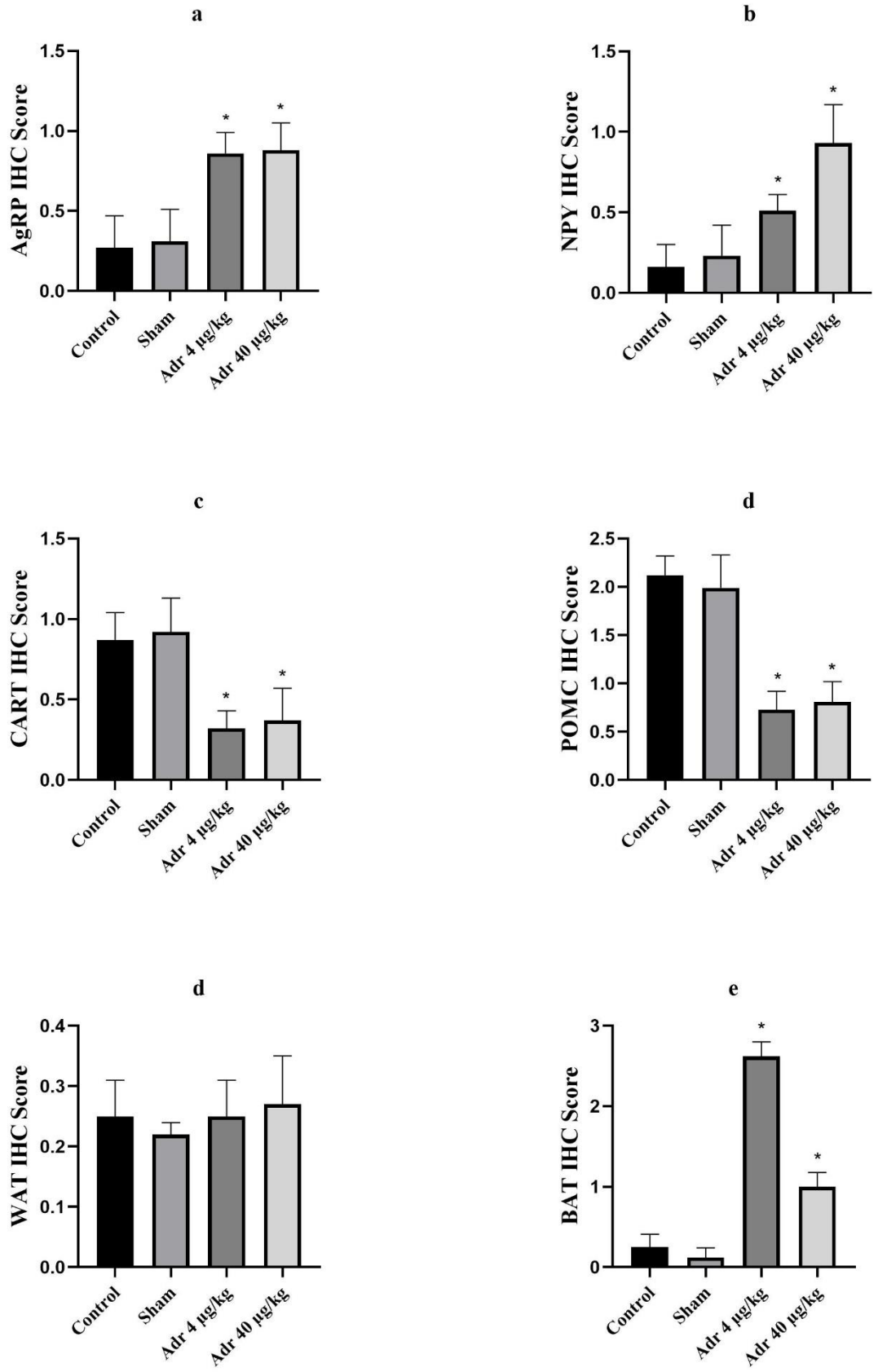
a
AgRP IHC Score
1.5
1.0
0.5
0.0
Control
Sham
Adr 4 µg/kg
Adr 40 µg/kg
b
NPY IHC Score
c
CART IHC Score
d
POMC IHC Score
2.5
2.0
d
WAT IHC Score
0.4
0.3
0.2
0.1
e
BAT IHC Score
3
2
1
0

Figure 5

The Possible Beneficial Effects of Lazaroid U-74389G on Ovarian Torsion Detorsion Injury

Mustafa Can GÜLER[1], Ayhan TANYELİ[1]*

[1] *Department of Physiology, Faculty of Medicine, Atatürk University, Erzurum, Turkey,*
mcanguler@yahoo.com
ayhan.tanyeli@atauni.edu.tr

Abstract

It was planned to search the possible beneficial effects of Lazaroid U-74389G (Laz) on ovarian tissue injury caused by bilateral ovarian torsion detorsion (T/D) in the experimental rat model. Wistar type female rats were randomly allocated to 3 groups. Groups of this research were designed as sham, T/D, and T/D+Laz groups. In sham group, the abdomen was incised and sutured but no intervention was performed. In T/D group, following the incision, ovarian T/D model was carried out and the incision was sutured. In treatment group, Laz was administered intraperitoneally at 20 mg/kg dose just before detorsion. After the detorsion period, rats were sacrificed and ovarian tissues were excised. Oxidant parameters elevated and antioxidant activity declined significantly in T/D group compared to sham group in ovarian tissues. Laz treatment reversed the oxidant and antioxidant parameters. Thereby, Laz protected against T/D-induced ovarian tissue injury in experimental rats.

Keywords: Lazaroid U-74389G, Ovarian Torsion Detorsion, Ovary, Rat..

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**Corresponding author:* Ayhan TANYELİ, *PhD*
Department of Physiology, Faculty of Medicine, Atatürk University, Erzurum, Turkey
E-mail: ayhan.tanyeli@atauni.edu.tr
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1. Introduction

Ovarian torsion detorsion (T/D) is among gynecological emergencies and it is widely observed in reproductive age (1). Ischemia reperfusion (I/R) injury induces oxidative stress and inflammation leading to tissue injury (2; 3). I/R injury enhances the generation of reactive oxygen species (ROS) and malondialdehyde (MDA) production (4). ROS acts on membrane lipids and elevates MDA level (5). MDA is a lipid peroxidation metabolite and used for oxidative stress determination (6). During detorsion, ROS production increases and plays role in ovarian injury (7). Antioxidant enzymes including superoxide dismutase (SOD) prevent oxidative injury (8). The levels of ROS and antioxidant activity determine the rate of oxidative stress (9). Interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) exist in the beginning of inflammatory respond and induce the release of free radicals (10; 11).

Different agents have been studied to alleviate or eliminate I/R injuries in various organs (12-16). Lazaroid U-74389G (Laz), a lazaroid family member, blocks lipid peroxidation through removing free radicals (17; 18). Laz has been examined in various I/R injury models including renal I/R injury (19). Laz eased I/R-induced intestinal injury in a previous study (20). Laz declined lipid peroxidation through reduction in MDA level (21).

Current study was planned to investigate the protective effect of Laz against ovarian oxidative damage induced by T/D.

2. Materials and Methods

2.1. Experimental Animals and Ethical Approval

Animals were procured from Atatürk University Experimental Animal Research and Application Center and also experimental steps were carried out at same place. The rats were housed in laboratory conditions such as polypropylene cages, appropriate humidity, temperature, etc. They could reach both food

and water but fasted 12 hours prior to experiment. Atatürk University Experimental Animals Local Ethics Committee permitted the study (07.11.2019/203).

2.2. Groups and Torsion/Detorsion Model

Prior to experiment, animals were fixed in supine position. Abdominal region was shaved, cleaned. Anesthesia was applied to animals before surgical process. Povidone-iodine was used for disinfection. 10 mg/kg i.p. xylazine hydrochloride (Rompun®, Bayer, Istanbul) and 60 mg/kg intraperitoneally (i.p.) ketamine (Ketalar®, Pfizer, Istanbul) were preferred for anesthesia as described before (22). Laz purchased from Sigma Aldrich Co.

18 Wistar Albino female rats, weighing 230-240 g, were randomly divided into 3 groups. Group I (sham group), the abdominal area applied 1-2 cm incision and repaired with 3/0 silk suture and no additional intervention was done. Group II (T/D group), following incision as described in group I, the ovaries, fallopian tubes, ovarian veins and arteria were rotated in clockwise 720 degrees and fixed with clamps for 3 hours. Then, clamps were removed and blood flow restarted for 3 hours (23; 24). Group III (T/D+Laz group), same steps in group II were done and 10 mg/kg Laz was administered i.p. to the rats just before detorsion. Finally, at the end of the experiment, the ovarian tissues were removed, cleaned and held frozen the analysis.

3. Biochemical assessments

Total antioxidant status (TAS) and total oxidant status (TOS) values were evaluated via appropriate kits (Rel Assay Diagnostics). TOS to TAS ratio, the oxidative stress index (OSI), was gauged as: OSI=[(TOS, μmol H_2O_2 equivalent L)/(TAS, mmol Trolox equivalent/L)×10]. Evaluation of SOD activity depends on formazan dye level (25). Lipid peroxidation was measured by determining MDA level through thiobarbituric acid test (26). Myeloperoxidase (MPO) activity was gauged according to method described previously (27). IL-1β and TNF-α levels were evaluated via appropriate kits (Elabscience, Wuhan, China).

4. Statistical analysis

Data were analyzed with One-Way ANOVA and Tukey test using statistical package program, SPSS. All results were presented in table 1 and figure 1 as Mean±SD. P value was considered significant when $p<0.05$.

5. Results

TNF-α and IL-1β values, MDA, TAS, TOS, OSI levels, MPO and SOD activities in ovarian tissues were demonstrated in table 1 and figure 1. Oxidative parameters (MDA, TOS, OSI, MPO) and inflammatory mediators (TNF-α, IL-1β) elevated significantly in T/D group compared to sham group. In Laz treatment group, these parameters declined significantly. Moreover, antioxidant activity (TAS and SOD) diminished in T/D group, whereas Laz treatment elevated TAS and SOD levels (Table 1; Figure 1, $p<0.001$).

Table 1: Results of biochemical parameters among all the experimental groups.

Experimental Groups (n=6)	TAS (mmol/L)	TOS (μmol/L)	OSI (arbitrary unit)	SOD (U/mg protein)	MPO (U/g protein)	MDA (μmol/g tissue)
Sham	0.86 ± 0.04	6.62 ± 0.89	0.76 ± 0.10	437.02 ± 16.57	259471.94 ± 302466.65	64.64 ± 5.71
T/D	0.22 ± 0.03[a]	11.64 ± 1.08[a]	5.20 ± 0.97[a]	174.32 ± 7.05[a]	77222.10 ± 42575.30[a]	141.64 ± 11.83[a]
T/D+Laz	0.82 ± 0.11[b]	6.99 ± 0.37[b]	0.84 ± 0.09[b]	407.85 ± 20.51[b]	284813.46 ± 24588.28[b]	68.60 ± 5.33[b]

[a]$p<0.001$ compared to sham group. [b]$p<0.001$ compared to T/D group.

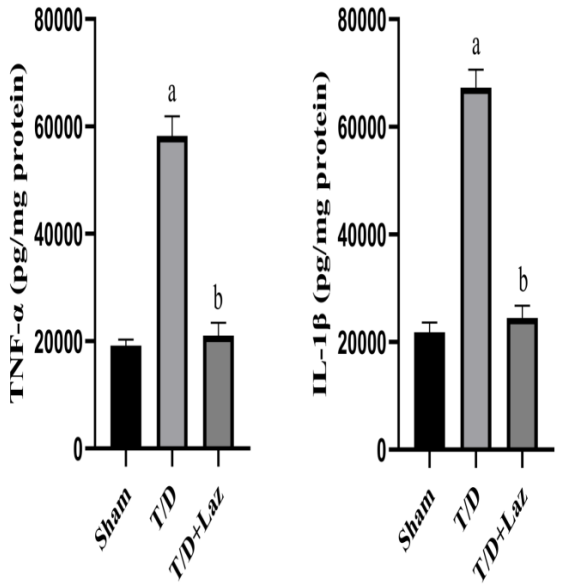

Figure 1: Results of IL-1β and TNF-α among all the experimental groups.

6. Discussion

Ovarian torsion (O/T) mostly occurs during reproductive period (28). Ischemic tissue injury is based on insufficient materials for energy supply. Ovarian detorsion means the recovery of blood flow. But replenishment of blood flow results in ovarian tissue injury (29). O/T is an emergency situation with a 3% prevalence (30; 31).

During ovarian T/D, blood reflow elevates in lactic acid, proinflammatory cytokine and lipid peroxide levels (7; 32; 33). Increased ROS damages cells via lipid peroxidation (34). MDA is a lipid peroxidation product and harmful for tissues. It reflects oxidative stress (6). It is created by ROS during I/R (35). It has been proven that oxidative stress causes tissue damage in various animal models (36-39). Neutrophil infiltration also leads to I/R injury besides oxidative stress. MPO activity represents neutrophil activation and infiltration (40). Neutrophil infiltration, TNF-α, IL-1β and several proinflammatory cytokine production accompany I/R (41). IL-1β plays role in apoptosis and inflammation (10; 42).

Besides ischemic injury, reperfusion also leads to injury in tissues (43). Antioxidant enzymes like SOD compose cellular defense system against oxidative injury (44). SOD is a crucial antioxidant enzyme and SOD activity declined during ovarian T/D in previous studies (45; 46). Oxidative stress is the surpass of oxidant activity against antioxidant system. OSI is the ratio of TOS to TAS. It is preferred for the determination of oxidative stress (47; 48). TOS and TAS play role in I/R injury assessment (49).

Laz has been studied in various I/R injury models including renal I/R injury (19), intestinal I/R injury in rats (50). Different agents with feature anti-inflammatory, antioxidant and radical scavengers have beneficial effects have been reported in alleviation or elimination of I/R injuries (51-56). In the current study, we thought that Laz could minimize T/D damage with its antioxidant and anti-inflammatory effects. Therefore, current study was planned to investigate possible protective effects of Laz on ovarian tissue by using an ovarian T/D model.

Here, several inflammatory mediators and oxidative stress biomarkers were diminished and antioxidant activity was enhanced by Laz treatment in ovarian T/D injury model.

7. Conclusions

Laz alleviated T/D-induced ovarian injury in experimental rat model through declining oxidative mediators and elevating antioxidant parameters. This is a hope-inspiring result in order to evaluate for T/D pathologies.

8. Acknowledgement

None.

9. Conflict of interest statement

None.

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