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Increased Atherogenic Indices and Basal Cell Carcinoma

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Abstract: Atherosclerosis and cancer are chronic diseases that are considered to be two of the most common causes of death. Given that both diseases are chronic multifactorial, they may also share many etiological and mechanistic processes. Inflammatory processes and oxidative stress are also important factors in the development of both atherosclerosis and cancer. The aim of this study is to provide new evidence, not included in the literature, between calculable atherogenicity risk indices and basal cell carcinoma (BCC) formation, and to encourage the identification of closer molecular links between these two pathologies. Atherogenic plasma index (AIP), atherogenic index (AI) and Lipoprotein combined index (LCI) were calculated using mathematical formulas and routine lipid values. The routine lipid parametres and atherogenic index values of the BCC patients (n: 39) were compared with the controls (n: 44). Unpaired t-test were used for parameters with normal distribution and Mann-Whitney test were used for non-normally distributed parameters. Among the serum lipid parameters, only low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) were significantly increased in the patient group. However, all atherogenic indices (AIP, AI and LCI) were found to be statistically significantly higher in the patient group (p<0.0001). Atherosclerosis is associated with a variety of comorbidities; this preliminary study showed an increase in atherogenic risk indices in elderly patients with BCC. There is no doubt that index calculations such as AIP, AI and LCI will increasingly be included in cancer research. Future studies with large participation may better show the clinical importance of serum lipid values and atherogenic risk index calculations. ©2024 NTMS.

Keywords: Basal cell carcinoma; Cancer; Atherogenic Index; Lipid.

1. Introduction

Currently, atherosclerosis and cancer are chronic diseases that are accepted as the top two causes of death all over the world. Many factors that play a role in the development of atherosclerosis are also involved in the development and progression of cancer, especially in skin cancers. Genetic changes, inflammatory processes, uncontrolled cell proliferation and increased oxidative stress can be given as examples among the most important risk factors for both atherosclerosis and cancer [1].

Basal cell carcinoma (BCC) is a malignant skin tumor originating from the basal cell layer of the epidermis and its appendages. BCC, which is responsible for 90% of all cutaneous malignancies of the skin, is one of the

most common malignancies in the world and its incidence is increasing [2]. Because the skin is the largest body organ that protects it from external factors, which is very important for homeostasis. Many environmental influences such as ultraviolet (UV) from the Sun are oxidant and directly or indirectly catalyze the production of reactive oxygen species (ROS). ROS can damage the skin, largely by directing several key molecular pathways that play important roles in a variety of pathological processes, including atherosclerosis and inflammatory responses. Unfortunately, these cutaneous homeostatic defenses, although highly effective, have limited capacity and can be overloaded and thus lead to increased ROS in the skin, which can promote the development of dermatological diseases [3]. In addition, changes in serum lipid profile and lipoprotein levels have been reported in the pathogenesis of BCC and other skin cancers in previous studies [4, 5]. It may be considered useful to measure atherosclerotic risk indices to predict different types of skin diseases and the progression of these cancers [6-8].

 Of course, the main reason why changes in lipid profile have long been associated with cancer is that lipids play a key role in maintaining cell integrity and vascular endothelium. Lipid metabolism has been recognized as one of the major metabolic pathways involved in many aspects of cancer cell developmental function, including signaling processes related to cell transformation and tumor growth [9, 10]. Although serum lipid levels have been investigated in different types of cancer to date, they have revealed conflicting results of the relationship between serum lipid biomarkers and BCC [4, 5]. However, serum proatherogenic lipid profile and atherogenic indices in BCC patients are not yet included in the literature.

Currently, new "atherogenic indices" from various lipoprotein ratios have been defined to optimize the predictive capacity of the lipid profile. These indexes are a simple calculation with no extra cost. Atherogenic plasma index (AIP), atherogenic index (AI) and lipoprotein combined index (LCI) are some of the new indices created [11]. These atherogenic indices are increasingly associated with diseases and are widely used as indicators of dyslipidemia and related diseases [12, 13]. Although they are used as powerful biomarkers to determine the prognostic value of atherogenicity and cardiovascular diseases, they have also been associated with obesity and cancer risk [7, 14].

Studies have shown a correlation between atherogenic indices (AIP, AI) and markers of oxidative stress [15]. It is known that oxidative stress plays an important role in the initiation of carcinogenesis events. The role of atherosclerosis-related oxidative stress in the pathogenesis of many cancers, including BCC, has also been reported by different researchers [15, 16]. Therefore, it is very valuable to investigate the relationship between atherogenic indices and cancers. Since possible lipid metabolism changes in BCC have not

been clarified yet, we aimed to examine the relationship between atherogenic indices and BCC in our study.

2.   Material and Methods
2.1. Subjects
This study was carried out in a single center at Antalya Training and Research Hospital between September 2019 and February 2021. The patient group included in the study consisted of 39 (18 men and 21 women) patients who applied with a suspicious BCC lesion(s) and were subsequently diagnosed with histopathological BCC. The control group consisted of 44 people (23 men and 21 women) who applied to different clinics of the hospital and were not diagnosed with BCC. All participants of the study were randomly selected in the same process. The number of study subjects was calculated from the prevalence of the disease using the www.Raosoft.com calculator.

People with antioxidant drug use, herbal supplement use, statin-derived drug use, and any of the cancer types other than BCC were excluded from the study. Our study is a retrospective cohort study. This study was approved by the local ethics committee in accordance with the principles of the 2008 Declaration of Helsinki. Written and informed consent forms were obtained from the participants.

2.2. Methods
Blood samples from all participants included in the study were taken into vacuumed yellow capped tubes after 12 hours of night fasting. Then, the blood samples were centrifuged for 10 minutes with a refrigerated centrifuge device, and the serum samples were obtained. TC analysis by cholesterol oxidase enzymatic method (Beckman® coulter total cholesterol kit), TG analysis by Glycerophosphate Oxidase enzymatic method (Beckman® coulter triglyceride kit), HDL-C analysis by Cholesterol Oxidase enzymatic method (Beckman® coulter HDL cholesterol kit) were measured in autoanalyzer. LDL-C results were calculated using the Friedewald formula, as fasting serum TG values of all participants were <400 mg/dl. Also, VLDL results were obtained by calculating (VLDL=TG/5). Thereafter each patient's atherogenic indices were calculated from mathematical formulations and various lipoprotein ratios.

For example, AIP was first calculated as the logarithmic transformation of the ratio of TG level to HDL-C level. AIP = log10 (TG/HDL-C)

AI is defined as the ratio of non-HDL-C to HDL-C and is calculated using the formula: AI=non-HDL-C/HDL-C (non-HDL-C=TC - HDL-C).

LCI is calculated using the formula: LCI= (TC x TG x LDL)/HDL-C.

2.3. Statistical Analysis
Statistical analysis of the calculated lipid index data was performed using MedCalc® Version 19.3 program. Kolmogorov-Smirnov test was used to

determine the distribution of the collected data for each variable considered in the study.

Unpaired sample t-test was used for countable data with normal distribution, and Mann-Whitney U test was used for countable data without normal distribution.

In the comparisons made between the groups created, descriptive statistics showing for the continuous variables with normal distribution at the 95% confidence interval, the mean and standard deviation (SD); for the continuous variables that do not fit the normal distribution at the 95% confidence interval, the median and interquantile range (IQR) has been done. Descriptive statistics results were used for categorical variables such as gender, known disease, number (frequency) and percentage.

A 95% confidence level [error (α)=0.05] was used to identify differences in analyzes. A probability level of P<0.05 was considered statistically significant.

3. Results

There were 39 patients in the study, 21 women (53.8%) and 18 men (46.2%), who were diagnosed with definitive BCC by biopsy. Also, 44 non-BCC (21 women (47.7%) and 23 men (52.3%)) were in the control group. The mean age of the participants was 71±10.6 years in the patient group and 68±7.5 years in the control group. Statistically, the age distribution was found normally distributed in both groups and no significant difference was found between the mean ages of the two groups (p=0.219).

However, the clinical findings of the patient group include type 2 diabetes (DM) in 11 (28.2%), hypertension (HT) in 23 (58.9%), cardiovascular disease (CVD) in 7 (17.9%), and cerebrovascular disease (CVd) in 2 (5.1%). In the control group, 14 (31.8%) people had type 2 DM, 17 (38.6%) people had HT, 2 (4.5%) people had CVd, 4 (9.0%) subjects had CVD. Comparison of clinical and demographic data of both groups is shown in Table 1.

Table 1: Demographic characteristics of the patient and control groups.

Parameters	Patient	Control
Age (years)	71±10.6 *	68±7.5 *
Female Gender	21 (53.8%)	21 (47.7%)
Male Gender	18 (46.2%)	23 (52. %3)
DM	11 (28.2%)	14 (31.8%)
HT	23 (58.9%)	17 (38.6%)
CVD	7 (17.9%)	4 (9. %0)
CVd	2 (5.1%)	2 (4. %5)

DM: Type 2 diabetes, HT: Hypertension, CVD: Cardiovascular disease, CVd: Cerebrovascular disease. * Mean ± SD / Unpaired t test.

As a result of the statistical analysis of routine laboratory parameters and serum lipid profile analysis values, no statistically significant difference was found between patient and control group individuals in total cholesterol, TG, HDL-C and VLDL-C values. However, when the serum LDL-C results of the two groups were evaluated, the LDL-C values of the patient group diagnosed with BCC were higher than the control group, and this elevation was found to be statistically significantly different compared to the control group (P=0.003). Similarly, serum non-HDL-C values were higher in the BCC patient group compared to the control group, and there was a statistically significant difference between them. (P=0.006). The serum lipid profile values of the groups are presented in Table 2.

Table 2: Serum routine lipid profile values of the patient and control groups.

Parameters	Patient	Control	P
Total Cholesterol (mg/dL)	209.2±42.15 * (n:34)	185.5±38.71 * (n:44)	0.594
Triglyceride (mg/dL)	146.2±62.5 * (n:33)	127.2±56.5 * (n:44)	0.176
LDL Cholesterol (mg/dL)	132.5±33.86 * (n:32)	109.9±29.78 * (n:44)	0.003
HDL Cholesterol (mg/dL)	50.5±14.3 * (n:34)	50.8±13.85 * (n:44)	0.920
VLDL Cholesterol (mg/dL)	26 (19.0-40.75) ** (n:21)	22 (17.5-29.0) ** (n:37)	0.145
Non-HDL Cholesterol (mg/dL)	158.6±40.17 * (n:34)	134.6±33.37 * (n:44)	0.006

HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, VLDL-C: Very low-density lipoprotein cholesterol. n: Number of individuals, * Mean±SD/Unpaired t test, ** Median (IQR: Interquantile Range)/Mann-Whitney U test.

In our study, atherogenic plasma indices were calculated over routine serum lipid concentrations. AIP, AI and LPCI values of the patient and control groups were compared statistically. The median AIP value in the patient group was 1.02 (IQR: 1.01-1.03) and 0.31 (IQR: 0.30-0.33) in the control group. The median AI values were 3.13 (IQR: 3.12-3.14) in the patient group and 2.65 (IQR: 2.64-2.65) in the control group. The median LPCI values were 23.3 (IQR: 23.22-23.23) in the patient group and 14.67 (IQR: 14.65-14.67) in the control group. When the median values of AIP, AI and LPCI were compared between the groups, respectively, a statistically significant difference was observed in all three values (P<0.001) (Table 3).

Table 3: Atherogenic plasma indices of patient and control group.

Parameters	Patient	Control	p
AIP**	1.02 (1.01-1.03)* (n=15)	0.31 (0.30-0.33)* (n=16)	<0.001
AI	3.13 (3.12-3.14)* (n=15)	2.65 (2.64-2.65)* (n=18)	<0.001
LCI	23.23 (23.22-23.23)* (n=16)	14.66 (14.65-14.67)* (n=16)	<0.001

AIP: Atherogenic plasma index, AI: atherogenic index, LCI: lipoprotein combined index n: Number of individuals. *Median (IQR: Interquantile Range)/Mann-Whitney U test, **It has been suggested that AIP values between -0.3 and 0.1 are associated with low risk, 0.1 and 0.24 are associated with moderate risk, and values above 0.24 are associated with high atherogenic risk.

4. Discussion

One of the most important findings of our study is that API, AI and LCI values, which are atherogenic index markers, were all found to be significantly higher in the BCC patients when the BCC patients group were compared with the control group. In addition, the higher LDL-C and non-HDL-C levels in BCC patients support the possible role of lipid metabolism in the development of cancer. Although there was no significant difference in routinely measured total cholesterol, TG and HDL-C levels in our study between BCC patients and control group individuals, the fact that atherogenic indices were significantly higher in cancer patients suggests that atherogenicity and atherogenic indices may play a role in BCC disease. It can be expected that the results of the study, which have not yet been adequately covered in the literature, will be preliminary and make a significant contribution to the literature.

Because many studies have been conducted that show that lipids and lipoproteins may be associated with the risk of developing cancer in various types of cancer, and it has been reported that there is a direct relationship for some lipids [17]. Meanwhile, the relationship between lipid biomarkers in serum and plasma and BCC has conflicting results, suggesting that the mechanism of lipid metabolism in BCC is still unclear and requires further investigation. In one of the studies on this subject, the lipid profile of BCC patients and healthy adults was compared; however, no significant difference was observed between the groups in cholesterol, TG, LDL-C and HDL-C levels [5]. In a recent study, an increase was found in the levels of all lipid markers (TG, cholesterol, HDL-C) except LDL-C in patients with BCC, and this increase was statistically significant for HDL-C and cholesterol values [4].

Lipid metabolism has been recognized as one of the major metabolic pathways in cancer cell developmental. Related to this, it was investigated whether exposure to systemic environment enriched with LDL-C promotes breast cancer progression. As a result of the study, it was observed that exposure to LDL-C in breast cancer cell lines induces cell proliferation, migration, and loss of adhesion, which are hallmarks of the epithelial-to-mesenchymal transition process [18]. In another study conducted in patients with breast and prostate cancer, although a significant relationship could not be shown between increased cancer risk and LDL-C, LDL-C/HDL-C ratio was found to be associated with an increased risk of general cancer [19].

Non-HDL-C represents the portion of blood cholesterol that is not considered good cholesterol. Calculation of the non-HDL-C concentration allows to measure the total amount of proatherogenic lipoproteins containing Apolipoprotein B [20]. Non-HDL-C is a more comprehensive measure of atherogenic particles than LDL-C, and non-HDL-C may be superior to LDL-C in its ability to predict cardiovascular events. There are studies investigating the role of non-HDL-C in cancer as well as cardiovascular events. In a study parallel to the results of our study, the lipid profile of women with benign and malignant breast cancer was evaluated and a positive correlation was shown between non-HDL-C levels and breast cancer patients [21]. In studies conducted in patients with lung and endometrial cancer, no significant relationship was found between non-HDL-C and cancer risk [22, 23].

Atherogenic indices and lipid ratios, which are new to the literature and are being used frequently, gain importance especially in the evaluation of CVD risk. These indices have been a strong indicator of the risk of atherogenicity by expressing the imbalance between atherogenic and anti-atherogenic lipoproteins, which routine lipid parameters cannot show [24]. AIP was defined as a predictive marker for plasma atherogenicity and it was stated that it showed the risk of atherosclerosis according to the values obtained. It has been suggested that AIP values between -0.3 and 0.1 are associated with low risk, 0.1 and 0.24 are associated with moderate risk, and values above 0.24 are associated with high atherogenic risk [25]. Accordingly, a large study has shown that there is a significant relationship between AIP and CVD risk factors. In addition, there was a significant positive correlation between AIP and total cholesterol, LDL-C and TG, while a significant negative correlation was observed between AIP and HDL-C [24]. In our study, while the mean AIP values of the patients with BCC were at high risk, the mean AIP values of the control group were found to be lower.

We have not yet come across a study evaluating new atherogenic indices in BCC patients in the literature. However, there are studies showing the relationship of new atherogenic indices with cancer risk in different cancer types. For example, in a study conducted in breast cancer patients, high AIP levels were observed in cancer patients [7]. In a study evaluating lipid derivatives for postoperative gastric cancer mortality, it was shown that preoperative lipid derivatives, especially AI and LDL-C/HDL-C ratio, were strong

predictors of gastric cancer mortality [26]. Different investigators have also conducted studies evaluating AIP to predict malignant renal masses in the preoperative period. In a study, the AIP value of malignant cases was found to be significantly higher than benign cases. In conclusion, it has been stated that AIP can be used as a predictive tool in the suspicion of malignant renal mass [27].

The role of oxidative stress in the pathogenesis of human skin cancers, including BCC, has been reported by many researchers [28, 29]. It has been suggested that the decrease in plasma antioxidant levels in patients with BCC is due to prolonged exposure to UV radiation [29]. The relationship between atherogenic indices AIP and AI and oxidative stress markers has been examined in different studies and a positive correlation has been shown between [15]. The fact that atherogenic indices were found to be significantly higher in cancer patients in our study suggests that atherogenicity and indices showing it may play a role in BCC disease.

One of the limitations of our study is the limited number of participants included in the groups. In addition, since BCC is a type of cancer that occurs at an advanced age, the average age of the control group was kept high. It is inevitable that both the patient group and the control group have comorbid diseases related to advanced age. Not surprisingly, these diseases are associated with atherogenicity, which may have been reflected in the results of the study.

5. Conclusions

The main finding of this study is the high atherogenic indices in BCC disease, which is increasingly seen in the community. Considering the relationship between atherogenicity and BCC, it should be considered that atherogenic indices can be used as an additional tool for predicting malignancy in BCC disease, since it is easy and inexpensive to calculate.

Of course, the findings of our study are preliminary and need to be supported by larger-scale clinical studies.

Limitations of the Study

The limitations of the study are small sample size, retrospective design and potential population bias (represents only patients in our institution). Also, homogenization could not be achieved in terms of other parameters that will affect the indexes.

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RESEARCH ARTICLE

Evaluation of Women's Knowledge Levels About Folic Acid; An Example of a University Hospital

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Abstract: Folic acid decreases physiologically during pregnancy and this situation predisposes to congenital anomalies such as neural tube defects and spina bifida. The aim of our study was to measure the level of knowledge of women of reproductive age and female health care workers about the use of folic acid in the preconceptional period, to draw attention to the correct timing and adequate dose of folic acid to prevent neural tube defects, and to identify problems related to reducing the incidence of neural tube defects and to develop solutions. In this study, we conducted a questionnaire study questioning the level of knowledge about folic acid among women aged 18-49 years and female health care workers who applied to Van Yüzüncü Yıl Dursun Odabaş Medical Center Family Medicine outpatient clinics and statistical analyses were evaluated in SPSS (Version 20) program. Of the 400 women who participated in our study, 47% were health workers and 53% were patients. To the question "Have you heard of folic acid before?" 78.3% of the participants answered "Yes" and 21.9% answered "No". In the study, it was observed that the level of knowledge about folic acid and folic acid use was higher in younger age groups, healthcare workers, single women, university graduates, those with higher income levels and those with fewer parities. It was concluded that the level of knowledge and awareness of folic acid is not at an adequate level and folic acid awareness of women of reproductive age should be increased. ©2024 NTMS.

Keywords: Folic acid; Pregnancy; Neural Tube Defect.

1. Introduction

Neural tube defects (NTDs) are congenital malformations that result from the failure of the fetal spinal canal to close after conception for a number of reasons [2]. If the neural tube does not close in the intrauterine period until the end of the 4th week, conditions such as meningocele, meningomyelocele, myeloschisis, anencephaly, encephalocele, which are generally called Neural Tube Defects (NTD), occur. Hereditary and environmental factors play a role in the etiology of NTDs. Folate deficiency is one of the most important preventable causes of NTDs [3]. Folic acid

supplementation alone has been shown to reduce the recurrence of NTDs by up to 71% in pregnant women [4]. Folic acid should be started 2 months before conception and folic acid supplementation should continue until the end of the first trimester of pregnancy [5]. Folic acid intake of 400 µg/day during the preconceptional period reduces the likelihood of neural tube defects by 50-70% by assisting DNA synthesis and repair during organogenesis [6].

NTDs are one of the most common congenital anomalies. They increase the likelihood of a pregnancy

ending in miscarriage. They also cause infant mortality, severe congenital anomalies and disability. NTDs account for 10% of all neonatal deaths and are responsible for 41.000 deaths and 2.3 million disabilities annually. Worldwide, NTDs occur in 0.5-2 per 1000 pregnancies and in approximately 2-3% of live births. It has been reported that the incidence of NTDs in developing countries is up to four times higher than in developed countries due to low standard of living, poor pregnancy follow-up and low number of terminations [7].

The prevalence of NTD is 0.7-1 per 1000 live births in the United States of America (USA) and 0.4-1.6 per 1000 live births in European countries. Considering that the prevalence rate in Turkey is 3 per 1000 live births, it is seen that the prevalence rate is higher in Turkey compared to other western countries [2].

Rehabilitation and treatment of NTDs is both difficult and costly. It imposes a heavy financial and moral burden on families and society. The mortality and morbidity of surgical treatment of NTDs is also very high. Relatives also face many psychosocial and economic difficulties during treatment. Therefore, it is clear that it would be wiser to conduct studies for the prevention of NTDs rather than the diagnosis and treatment of NTDs [8].

In this study, it was aimed to determine the level of knowledge of women of reproductive age about the use of folic acid in the preconceptional period, to increase awareness, to draw attention to the success of folic acid in preventing neural tube defects when used at the right time and at the right dose, to emphasize the importance of physicians and other health professionals in informing women, to identify problems, to develop solutions and to contribute to the formation of healthier generations.

2. Material and Methods

The study was conducted on 400 women of reproductive age (18-49 years) and female healthcare workers who applied to the Medical Center Family Medicine Outpatient Clinics between February 2021 and May 2021 and volunteered to participate in the study. The questionnaires used in previous studies on similar topics in the literature were examined and the 11-question questionnaire form was applied to the participants by face-to-face interview technique. This study was conducted after the approval of Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee. Permission was also obtained from the relevant department to conduct a survey in the outpatient clinic (Date: 10.12.2021, Decision No: 2021/13-09). After the data were collected, the SPSS program was used in the calculations and the level considered statistically significant was taken as 5% (p=0.05).

3. Results

44% (n=176) of the participants were in the 18-25 age group, 41.8% (n=167) in the 26-35 age group, and 14.3% (n=57) in the 36-49 age group. 56.8% (n=227) of the participants were married and 43.3% (n=173) were single. 61% (n=244) of the participants were university graduates, 14.3% (n=57) were high school graduates, 9% (n=36) were middle school graduates, 9.3% (n=37) were primary school graduates, and 6.5% (n=26) were illiterate. 78.5% (n=314) of the participants earn TL 10000 or less, 21.5% (n=86) earn TL 10000 or more. The sociodemographic characteristics of the participating in the study is given in Table 1.

Table 1: The sociodemographic characteristics of the participating in the study.

Features	Categories	N=400	%
Age	18-25 Age	176	44.0
	26-35 Age	167	41.8
	36-49 Age	57	14.3
Marital Status	Married	227	56.8
	Single	173	43.3
Education Status	Illiterate	26	6.5
	Primary School	37	9.3
	Middle School	36	9.0
	High school	57	14.3
	University	244	61.0
Monthly Income	TL 10000 or less	314	78.5
	TL 10000 or more	86	21.5
Participant Type	Patient	212	53.0
	Health workers	188	47. 0

While 47% (n=188) of the participants were health workers, 53% (n=212) were patients. The occupational distribution of the participants in the patient category is as follows; housewife 69.3% (n=147), civil servant 10.8% (n=23), insured worker 6.1% (n=13), other occupational group 13.7% (n=29). The occupational distribution of the participants in the health worker category is as follows; doctor 42% (n=79), intern doctor 25.5% (n=48), midwife/nurse 18.6% (n=35), janitorial staff 3.2% (n=6) data entry staff 5.9% (n=11), other occupational group 4.8% (n=9).

Of the participants, 78.3% (n=313) answered the question "Have you heard of folic acid before?" as "Yes". Of those who had heard of folic acid, 51.1% (n=160) learned about it during their education, 8.6% (n=27) from family physicians, 24.9% (n=78) from gynecologists and obstetricians, 9.3% (n=29) from family/friends and 6.1% (n=19) from TV/radio/news/internet. The rate of hearing about folic acid and the source of hearing about folic acid among the participants in the study are given in Table 2 and Table 3.

Table 2: Hearing of folic acid among study participants.

Features	Categories	N=400	%
Hearing of Vitamin	No	87	21.8
Folic Acid	Yes	313	78.3

Table 3: Study participants' source of hearıng folic acid.

Features	Categories	N=313	%
Folic Acid Hearing Source	My Education Life	160	51.1
	My Family Physician	27	8.6
	From my Obstetrics and Gynecology Specialist	78	24.9
	Family/Friends	29	9.3
	TV/Radio/Newspaper /Internet	19	6.1

To the question "Did you use a folic acid-containing preparation in your previous/current pregnancy?", 51.9% (n=107) of 206 individuals with a history of pregnancy answered "Yes" and 48.1% (n=99) answered "No". When the reasons for not using folic acid were asked to the 99 people who answered "No" to this question, 75.8% (n=75) answered because they did not know, 6.1% (n=6) because no one recommended it, 7.1% (n=7) because I had an unplanned pregnancy, 5.1% (n=5) because it caused nausea and vomiting/I did not like using tablets and 6.1% (n=6) because I believed that the need for folic acid was met with a balanced diet. Table 4 shows the folic acid use status of the participants during pregnancy. The reasons for not using folic acid during pregnancy are given in Table 5.

Table 4: Use of folic acid during pregnancy among the participants in the study.

Features	Categories	N=206	%
Folic Acid Use	No	99	48.1
in Pregnancy	Yes	107	51.9

Table 5: Reasons for not using folic acid during pregnancy among study participants.

Features	Categories	N=99	%
Reasons not to use folic acid during pregnancy	Because I don't know	75	75.8
	Since no one suggested it	6	6.1
	Because of my unplanned conception	7	7.1
	Because it causes nausea and vomiting / because I don't like using tablets	5	5.1
	Because I believe that folic acid needs are met with a balanced diet	6	6.1

Of the 107 participants who answered "Yes" to the question "Did you use a preparation containing folic acid vitamin in your previous/current pregnancy?", 60.7% (n=65) answered the question "When did you start using folic acid in your pregnancy?" as "I started after I learned that I was pregnant", while 39.3% (n=42) answered "I started when I planned to become pregnant". Of the 107 participants who used folic acid during pregnancy, 84.1% (n=90) answered "Yes" and 15.9% (n=17) answered "No" to the question "Did/do you use it regularly?".

To the question "How much dose should folic acid be taken before pregnancy?" 9.5% (n=38) of the participants answered "All pregnant women should take 400 mcg", 29.5% (n=118) answered "Pregnant women with risk factors should take 4 mg, the rest should take 400 mcg", 2.5% (n=10) answered "I think the need is met by diet" and 58.5% (n=234) answered "I do not know".

Of those who answered "Yes" to the question "Have you heard of folic acid vitamin before?", 45.4% (n=142) were in the 18-25 age group, 44.7% (n=140) were in the 26-35 age group, and 9.9% (n=31) were in the 36-49 age group. Of those who answered "Yes" to the question "Can neural tube defects (anencephaly, spina bifida, etc.) seen in newborn babies be prevented with folic acid vitamin used before pregnancy?" 46.2% (n=115) were in the 18-25 age group, 46.2% (n=115) in the 26-35 age group and 7.6% (n=19) in the 36-49 age group. Of those who answered the question "How much dose of folic acid should be taken before pregnancy?" as "Pregnant women with risk factors should take 4 mg, the rest should take 400 mcg", 54.2% (n=64) were aged 18-25 years, 41.5% (n=49) were aged 26-35 years, and 4.2% (n=5) were aged 36-49 years.

Of those who answered "Yes" to the question "Have you heard of folic acid vitamin before?" 85% (n=147) were single. 71.2% (n=84) of the respondents who answered "Pregnant women with risk factors should take 4 mg and the rest should take 400 mcg" to the question "What dose of folic acid should be taken before pregnancy?" were single. Among university graduates, 71.9% (n=225) had heard of folic acid before. The comparıson of the educatıonal status of the study participants and the use of folic acid during pregnancy is given in Tablo 6.

Of those who knew how much folic acid should be taken before pregnancy, 97.5% (n=115) were university graduates. 83.1% (n=207) of those who answered "Yes" to the question "Can neural tube defects (anencephaly, spina bifida, etc.) seen in newborn babies be prevented with folic acid vitamin used before pregnancy?" were university graduates. In response to the question "When should folic acid be started and how long should it be used to prevent congenital anomalies?", 91.1% (n=185) of those who answered "It should be started at least 1 month before fertilization and used in the first 3 months of pregnancy" were university graduates. Among those who used folic acid during pregnancy, 53.3% (n=57) were university graduates. 78.6% (n=33) of those who started to use folic acid in the preconceptional period were university graduates. The comparison of the educational status of the participants with their folic acid use in the preconceptional period is given in Table 7.

Table 6: The comparison of the educational status of the study participants and the use of folic acid during pregnancy.

Education Level		Did you use a preparation containing folic acid during your previous/current pregnancy?		P
		Hayır	Evet	P=0.001
Illiterate	N	23	2	
	%	23.2%	1.9%	
Primary School	N	23	13	
	%	23.2%	12.1%	
Middle School	N	23	11	
	%	23.2%	10.3%	
High school	N	17	24	
	%	17.2%	22.4%	
University	N	13	57	
	%	13.1%	53.3%	

Table 7: The comparison of the educational status of the study participants and the use of folic acid in the preconseptional period of pregnancy.

Education Level		When did you start taking folic acid during your pregnancy?		P
		I started after I found out I was pregnant	I started when I was planning to conceive	P=0.001
Illiterate	N	2	0	
	%	3.1%	0%	
Primary School	N	11	2	
	%	16.9%	4.8%	
Middle School	N	10	1	
	%	15.4%	2.4%	
High school	N	18	6	
	%	27.7%	14.3%	
University	N	24	33	
	%	36.9%	78.6%	

Of those who had heard of folic acid vitamin before, 57.2% (n=179) were healthcare workers. In response to the question "From whom/where did you learn about folic acid?", 90.6% (n=145) of those who answered "During my education" were healthcare workers. Most of the respondents who answered "From my family physician/ Gynecologist/ Family/ Friends/ TV/Radio/Newspaper/Internet" to this question were from the "patient" group. 67.9% (n=169) of the respondents who answered "Yes" to the question "Can neural tube defects (anencephaly, spina bifida, etc.) in newborn babies be prevented with folic acid vitamin used before pregnancy?" were healthcare professionals. In response to the question "When should folic acid be started and how long should it be used to prevent congenital anomalies?", 73.9% (n=150) of the healthcare workers answered "It should be started at least 1 month before fertilization and used in the first 3 months of pregnancy". Among healthcare workers who had been pregnant before, 85.7% (n=36) had used folic acid during pregnancy. However, 43.3% (n=93) of the patients who had ever been pregnant used folic acid during pregnancy. Among patients who did not use folic acid during pregnancy, 97.3% (n=73) did not use folic acid because they did not know. While 52.4% (n=22) of those who started using folic acid in the preconceptional period were healthcare professionals, 78.5% (n=51) of those who started using folic acid after learning that they were pregnant were from the patient group. Table 8 shows the comparison of folic acid use in the preconceptional period of pregnancy between healthcare professionals and patients who participated in the study.

While 79.7% (n=63) of physicians and 52.1% (n=25) of trainee physicians answered the question "How much dose should folic acid be taken before pregnancy?" as "Pregnant women with risk factors should take 4 mg and the rest should take 400 mcg", 48.6% (n=17) of midwives/nurses, 66.7% (n=4) of janitorial staff and 81.8% (n=9) of data entry staff answered as "I don't know". When the income level of the participants in our study was compared with their level of knowledge about folic acid, 86% (n=74) of those with an income of TL 10000 and above answered "Yes" to the question "Have you heard of folic acid vitamin before?". 59.3% (N=16) of those with an income of TL 10000 and above started to use folic acid in the preconceptional period.

Table 8: The comparison of the use of folic acid in the preconceptional period of pregnancy with health workers and patients who participated in the study.

		When did you start taking folic acid during pregnancy?		P
Participant Type		I started after I found out I was pregnant	I started when I was planning to conceive	P=0.001
Patient	N	51	20	
	%	78.5%	47.6%	
Health Worker	N	14	22	
	%	21.5%	52.4%	

Of the pregnant women who participated in our study, 64.5% (n=62) answered "No" and 35.5% (n=44) answered "Yes" to the question "Did you use a preparation containing folic acid vitamin in your previous/current pregnancy?". However, 79.5% (n=35) of the pregnant women who used folic acid started to use folic acid after they learned that they were pregnant. It was observed that the rate of folic acid use during pregnancy decreased as the number of live births increased among the women who participated in our study.

4. Discussion

Worldwide, knowledge and awareness of folic acid varies by country. The rates of knowledge and awareness of women about folic acid are 95% in the UK, 80% in Switzerland, 79% in Spain, 64% in Norway, 50% in Ukraine, 49% in Portugal and 84% in the USA. Although this rate was found to be 71% in studies on the level of folic acid knowledge in our country, it varies between 18% and 46% from study to study. In our study, we found that the rate of hearing about folic acid in women of reproductive age in our region was 78.3%. However, considering that 57.2% of those who had heard about folic acid before were healthcare workers, it can be said that social awareness is low. This shows that the awareness of folic acid in our country is lower compared to women living in the UK, Switzerland, Spain and the USA.

In a study conducted by Somunkıran et al. in our country, it was found that 10.9% of women with planned pregnancies started to use folic acid in the preconceptional period. It was found that most of the women (78.6%) who used folic acid in the preconceptional period were healthcare workers. In our study, most of the women who were healthcare workers stated that they learned about folic acid during their education, while most of the other participants learned about folic acid from gynecologists and obstetricians. At the same time, the level of knowledge about folic acid among the women who participated in our study who were health care workers was found to be higher than the other occupational groups. In addition, most of the women who did not use folic acid during pregnancy stated that they did not use it because they did not know.

In a study conducted by Jihyun Kim et al. on pregnant women in Korea, folic acid awareness was found to be higher in pregnant women with higher education level. According to the results of our study, 71.9% of those who had heard of folic acid before were university

graduates. The group with the highest rate of folic acid use during pregnancy was university graduates with 53.3%. In addition, 83.1% of those who knew that neural tube defects (anencephaly, spina bifida, etc.) seen in newborn babies could be prevented with folic acid vitamin used before pregnancy and 97.5% of those who knew how much dose of folic acid should be taken before pregnancy were university graduates.

D. A. Forster et al. found that the rate of folic acid supplementation during pregnancy was 84.8% in the group with high socioeconomic status and 65.8% in the group with low socioeconomic status. In our study, it was observed that the rate of hearing about folic acid vitamin, the rate of starting to use folic acid in the preconceptional period and the rate of those who knew how much dose of folic acid should be taken before pregnancy were higher in those who received 10000 TL and above.

In a study conducted by Hedyeh Riazi et al. in Iran, awareness of folic acid was found to be very low in women aged 35 years and older, while the level of knowledge was found to be higher in women aged 20-24 years compared to other age groups. In our study, the rate of having heard of folic acid before, the rate of knowing that neural tube defects (anencephaly, spina bifida, etc.) seen in newborn babies can be prevented with folic acid vitamin used before pregnancy and the rate of knowing how much dose of folic acid should be taken before pregnancy were found to be higher in the 18-25 age group compared to other age groups, while the lowest knowledge rate was found in the 36-49 age group.

In a study conducted by Jihyun Kim et al. on pregnant women in Korea, 65.6% of pregnant women had heard of folic acid, but only 26.4% of these pregnant women used folic acid in the preconceptional period. Mark Maher et al. found that only 40% of women took folic acid in the preconceptional period in a study conducted in London, England. In a study conducted in Ethiopia, Dessie et al. found that approximately 48.4% of women took folic acid supplements at different periods of pregnancy, but only 1.92% took folic acid supplements in the preconceptional period. In our study, 51.9% of women with a history of previous pregnancy used folic acid during their pregnancies. However, only 20.3% of these women took folic acid supplements in the preconceptional period. In addition, it was found that the rate of folic acid use in pregnancy decreased as the number of births of these women increased.

5. Conclusions

In our study, the rates of folic acid use in the preconceptional period were found to be in parallel with other studies in our country and below the rates in western countries.

Among the women who participated in our study, most of those who did not use folic acid during pregnancy did not use it because they did not know, suggesting that the reason for women not using folic acid in the preconceptional period is more likely to be the lack of information and guidance. Moreover, the fact that most of the women who started taking folic acid in the preconceptional period were health workers suggests that if women are counseled to use folic acid in the prenatal period, the rate of folic acid use in the preconceptional period will increase. The fact that most of the women who did not take folic acid during pregnancy were housewives may be due to the fact that these women did not consult a doctor before pregnancy due to their lack of social security or economic freedom. Among the women who participated in our study, the rate of application to family physicians for pre-pregnancy counseling was found to be quite low. When the folic acid knowledge levels of healthcare professionals were compared, it was found that the knowledge level of physicians, intern doctors was higher than that of midwives, nurses, janitorial staff, data entry personnel and other healthcare personnel. This shows that physicians should train allied health personnel.

Increasing awareness and knowledge of folic acid in women of reproductive age can be possible through public health and preventive medicine practices. In order to increase this awareness at the social level, the health personnel that the public will reach in the first place, primarily family physicians, midwives and nurses, should inform the patients. At the same time, regardless of the reason for hospitalization of women of reproductive age, awareness of folic acid should be increased by explaining the importance of folic acid use in the preconsensual period to women and distributing brochures on this subject. Healthcare personnel should be provided with seminars on folic acid to keep their knowledge up to date, women of reproductive age should be counseled about folic acid during home visits or in hospital wards, folic acid levels in the blood should be checked during the follow-up of women who are planning to become pregnant, 4 mg folic acid should be prescribed to women in the risk group who are planning to become pregnant and 400 mcg folic acid should be prescribed to women who are not in the risk group. In addition, the fact that most multivitamin preparations containing folic acid are not covered by the state reduces the rate of folic acid use. Therefore, folic acid should be distributed free of charge by the government to women planning to conceive. Campaigns and promotions should be organized through media organizations and social media to raise public awareness by explaining that the use of folic acid

in the preconceptional period prevents congenital anomalies such as neural tube defects.

Limitations of the Study

The limitations of the study are that no sample calculation was made for the study, the questionnaire questions were not a questionnaire for which validity and reliability studies were conducted, but were created by ourselves from the relevant literature, and the samples were collected from a center.

Since the study is based on voluntary participation, it may lead to sampling bias. Because participants who volunteered may have more knowledge about folic acid than those who did not volunteer.

As the study was conducted in a specific medical center, the results of the study may not be generalizable to a wider population. Therefore, they may not generalize to women outside this geographical or health care context.

In the study, participants are asked about their past experiences of folic acid use in previous pregnancies. This raises the possibility of recall bias as participants may not be able to recall past events accurately.

The study relied mostly on self-reported information, including information on educational status, occupation and folic acid use. This increases the likelihood of inadvertent or deliberate misreporting of information.

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RESEARCH ARTICLE

A Newly Defined Electromagnetic Dural Armor Functioned as a Brain Protecting Cerebrosphere: A Preliminary Theoretical Analysis

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Abstract: Electric and magnetic field-generating systems must be insulated in order to maintain their balance. It is certain that the brain, which has a very intense electric and magnetic field, is insulated by the dura mater and cerebrospinal fluid (CSF) that surround it. In this article, the electrophysical properties of these structures will be postulated in accordance with the laws of mathematics and physics. In human samples, on the other hand, the morphological features of EEG waves were examined with parameters such as the number of scalp hairs and scalp thickness, conductivity, skull thickness, ratios between cra nnial and brain volumes, and the thickness of the subarachnoid space where CSF circulates, and ventricular volumes. Since this study is postulative, the data were not detailed by statistical evaluation. With the geometric shapes of EEG waves; scalp thickness and number of hairs, skull thickness, depth of subarachnoid space, ventricular volumes, thickness of dura mater. EEG artifacts were excessive in pediatric cases with closed fontanelles or in adults with bone defects. There were statistically varying safety limits between $0.05 < p < 0.0001$ values between neuron density in the sensory ganglion of the trigeminal nerve, which innervates the dura mater intensely, especially.

The morphological structure of the skull and brain is fundamental in determining the nature of the EEG waves. The artifact of EEG waves in infants with open fontanelles and individuals with cranial bone defects may result from the rupture of the cerebrospheric armor formed by the dura. ©2024 NTMS.

Keywords: Cerebrospher; Durospher; Electroencephalography; Wave Interferences.

1. Introduction

The anterior cranial dura is innervated by trigeminal nerves [1]. Upper cervical dorsal root ganglions, superior cervical ganglions, facial, trigeminal, hypoglossal, glossopharyngeal, and vagus nerves innervate the medial and posterior cranial fossa dura mater [2].

Intracranial nociceptive innervation is managed by trigeminal system [3]. Dura mater has an excellent magnetic field generating power because it has good electrical conductivity [4]. Along with the dura mater, the scalp, bones, cerecrospinal fluid (CSF), and cranial

vessels [5], create an electrical field [6]. Neurons are also electrically charged bodies [7]. Their vibrations create a magnetic field [8], and a vibrating electric field creates a magnetic field around them [9]. As a result, a unified electromagnetic field occurs [10] as described by Einstein. The brain resembles two parallel electric-loaded plates and the corpus callosum is an interconnection band between these two plates and equalizes the capacitance of the two cerebral hemispheres [7]. According to the moment, these electromagnetic fields charge the brain. Otherwise, the brain will not find enough ATP to ignite many synaptic circuits. Suppose the dura mater loses its electromagnetic properties. In that case, the brain is deprived of this electromagnetic shield, and its surroundings may suffer severe damage that has not yet been described. Here, we have defined the layers that protect the brain as the cerebrosphere, just like the Earth. We have denoted its layers from outside to inside: vibrisosphere, scalposphere, ososphere, durosphere, vesselospher, and hydrosphere. The durosphere will be discussed in this article.

2. Material and Methods

The data used in this study were obtained from a large number of rabbits subjected to the subarachnoid hemorrhage experiment. Atatürk University Local Ethics Council of Animal Experiments approved the study (25.06.2010/22). The EEG findings of the subjects who had seizures after subarachnoid hemorrhage and the neuro-degeneration relationships determined in the local hemispheres causing these EEG disorders formed the basis of the research.

3. Results

The epileptiform feature of EEG waves was found to be proportional to the number of ischemic neurons exploding like mines in the brain. Again, the ischemia of the cervical dorsal root ganglia, nodose-petrous and otic ganglia innervating the dura mater, probably caused dural innervation weakness and changed the EEG patterns by causing a decrease in magnetic power in the durosphere.

In the light of these data, the EEGs of babies whose fontanelles are not closed, adults with cranial surgical bone defects, people with different sizes of cranium and dura thickness, those with a wide subarachnoid distance, those with large ventricles, and those with hair loss or thick hair were evaluated quantitatively. Statistical analysis has confirmed that our thinking may be correct to varying degrees.

Especially in patients with subarachnoid hemorrhage, if there is ischemic damage to the neural structures that we think innervate the dura, the durospheric weakness is also more pronounced.

Ferromagnetic minerals in the blood flowing through the blood vessels can also act as coils and form a separate magnetosphere.
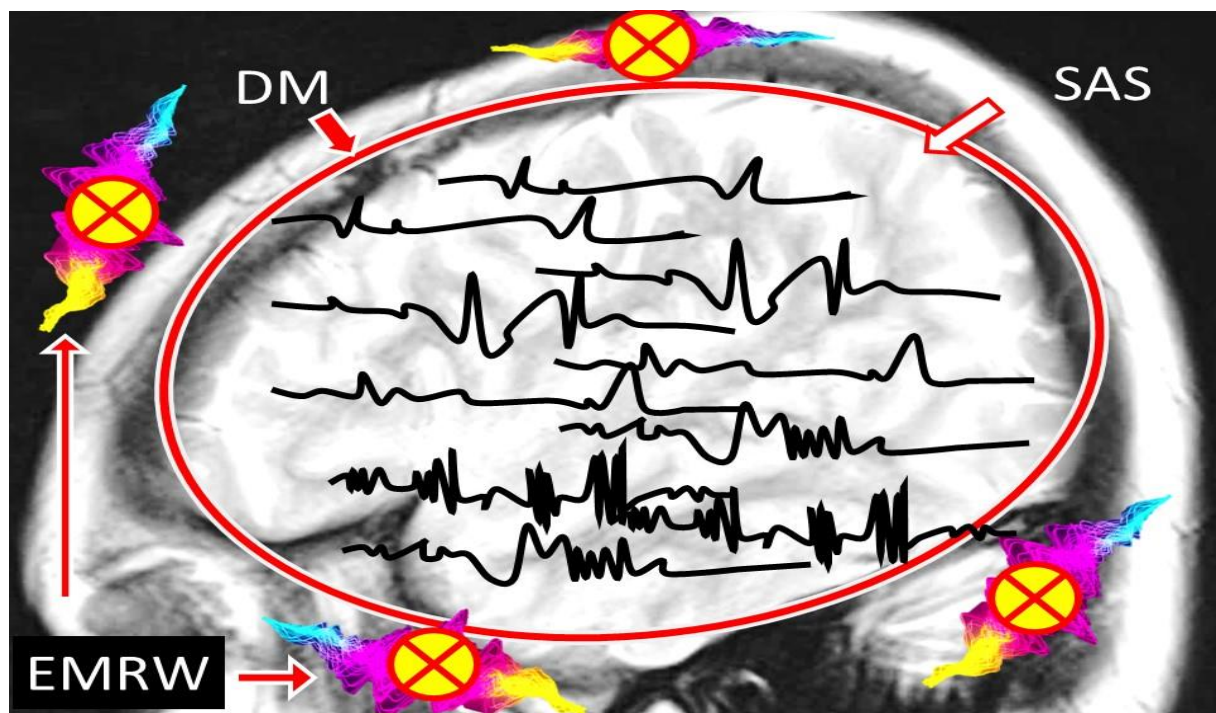
Figure 1: Dura mater is an electromagnetic shield, acting like the ionosphere with the CSF, protecting the brain. Due to these two strong armors (red-white ellipse), the electrical, magnetic and thermodynamic balances of the brain are preserved. These armors prohibit external magnetic resonance waves (EMRW) transmitted to brain.

$$X(f) = \int\limits_{-\infty}^{+\infty} x(t)\, e^{-j2\pi ft}\, dt$$

$$\int_{1}^{n} f\left(\frac{Sin\,(x^2+y^2)}{a+r^2} + (x^2+by^2)\right)dx$$
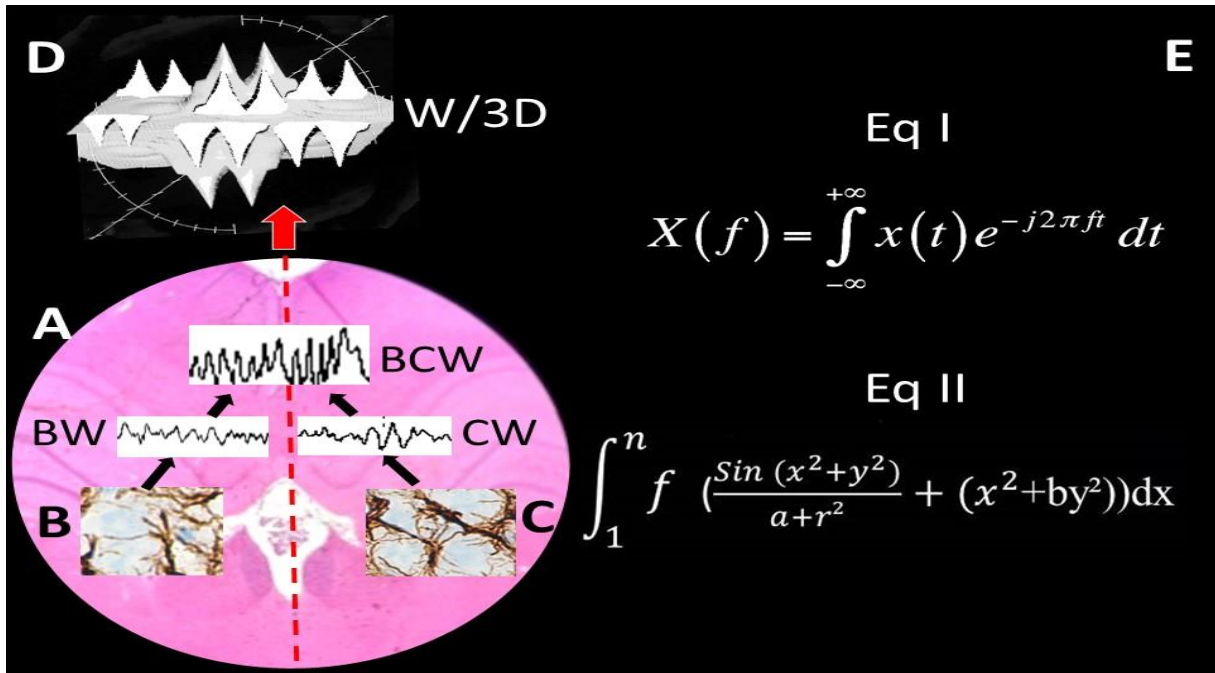
Figure 2: In a normal subject brain (A), neurons producing electroencephalography (EEG) waves and surrounding glia cells are observed (B) d (LM, H&E, x4/A; GFAP, x20/B, C). Integral formulas for how these cell groups produce EEG waves and how the waves interfere to produce resultant waves are given in EI and EII, respectively (Grapher Program of Apple Computer makes Figure D).
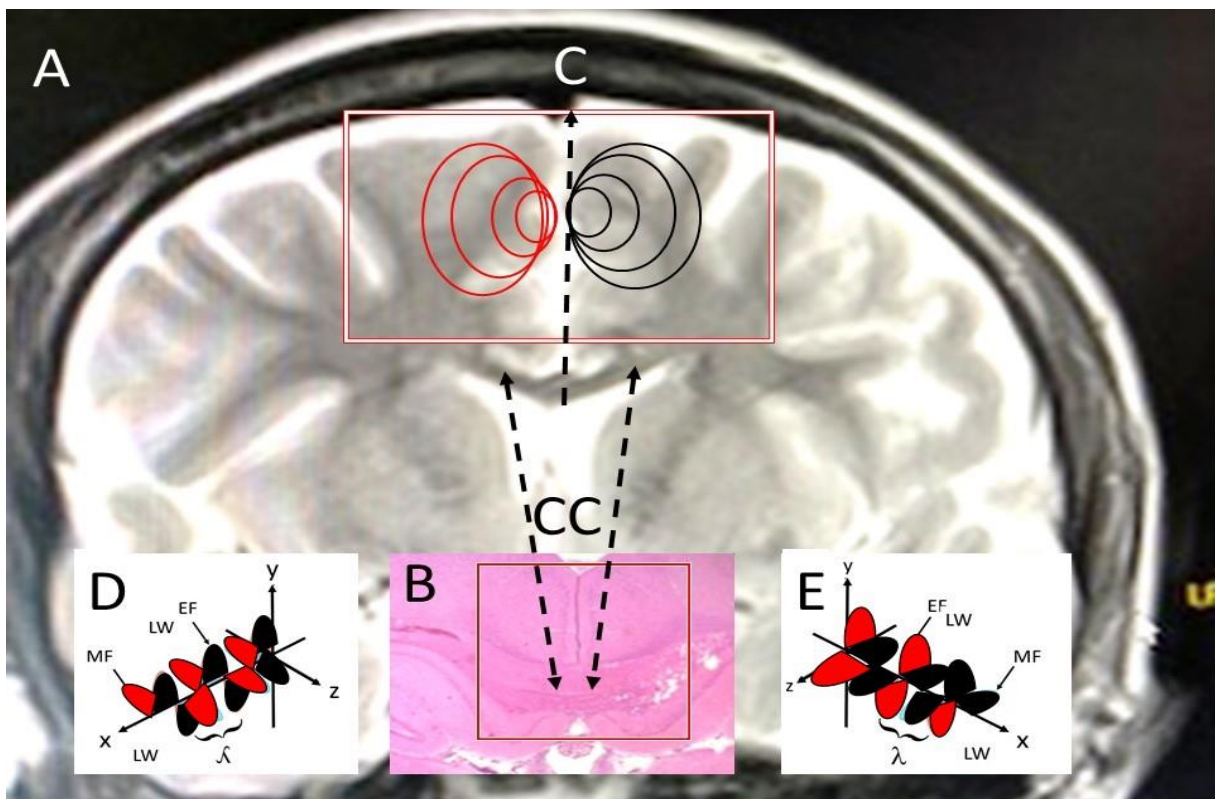
Figure 3: Regarding electrical engineering, the brain is two parallel plates that generate and charge energy. The corpus callosum (CC) is an intermediate link that balances the load between these two plates. Since both brain hemispheres are designed like the north-south hemispheres, their electromagnetic fields are in opposite directions and have different intensities according to the brain time.
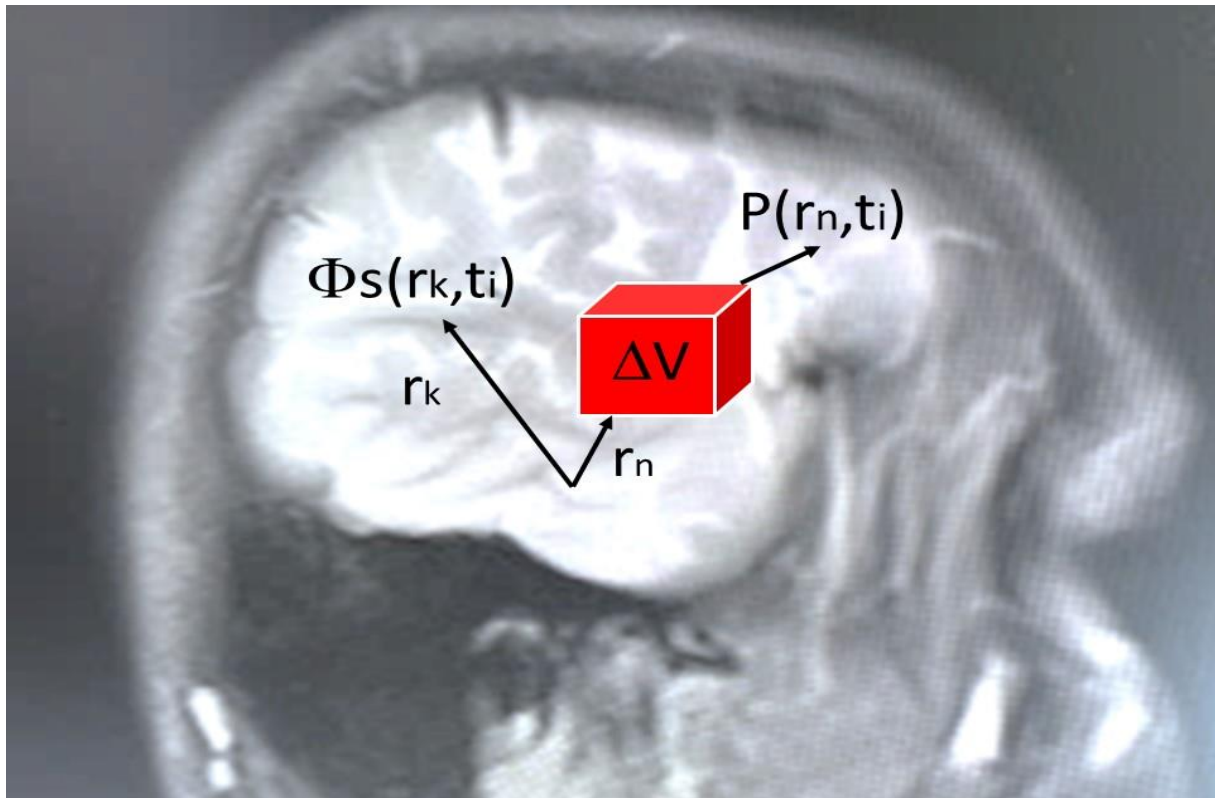
Figure 4: Brain volume conductor is indicated in which surface potentials Φs (rk, ti) are recorded at discrete surface lokations rk and time ti. The surface potentials are generated by dipole moments p (rn, ti) in tissue masses (voxels) ΔV located at rn. All volume conductor properties are included in the Green function G (rk, rn). Resources are defined as dipole moments per unit volume p (rn, ti) / ΔV. $\Phi(r,t) = \iiint_{Brain} G(r,r').P(r',t)dV(r')$.
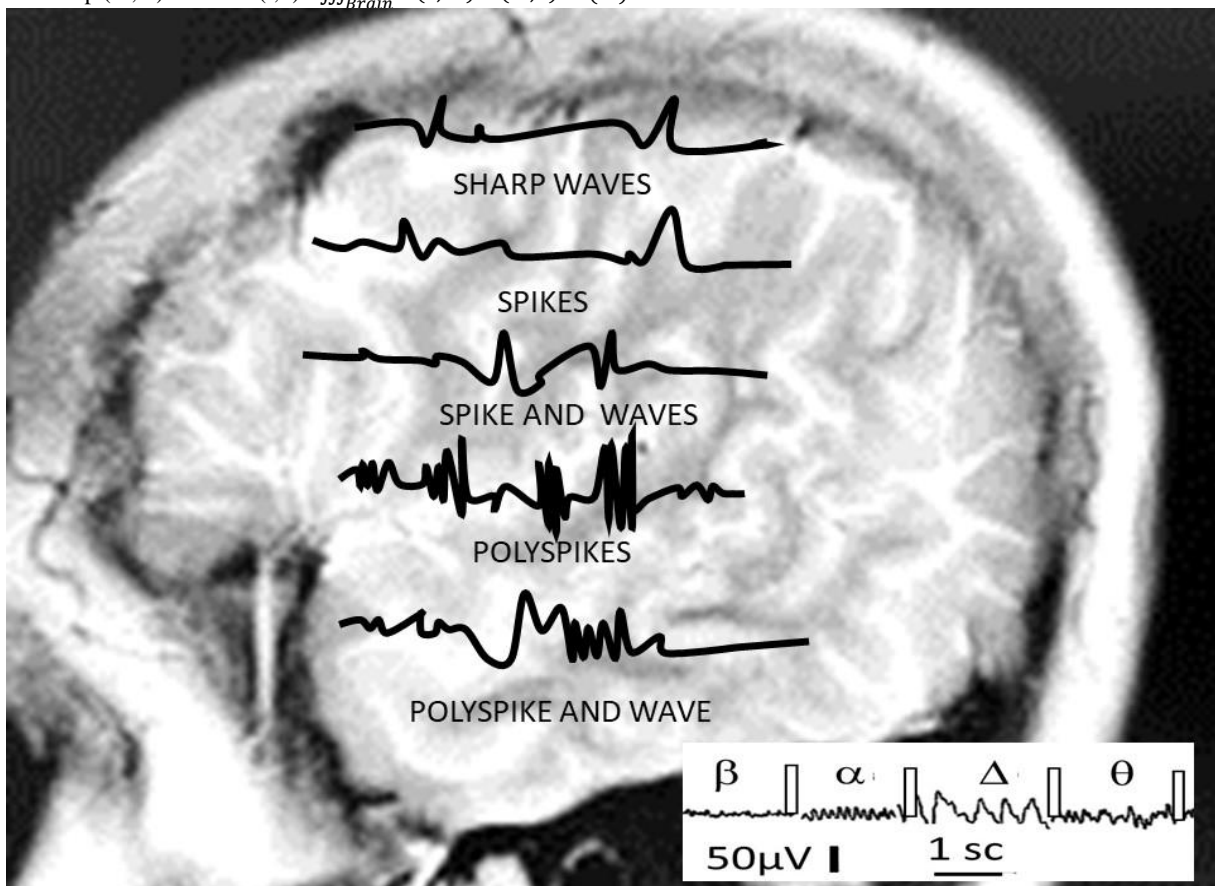
Figure 5: Cortical surface regions where alpha rhythms were recorded in a large population of epilepsy surgery patients are indicated by abnormal waves. Dotted regions near the central motor strip exhibited beta activity. ECoG activity was

characterized by counting zero crossing s before Fourier transforms were used in EEG 15. In the picture, normal EEG waves are in A; abnormal EEG waves are also observed in B-F.
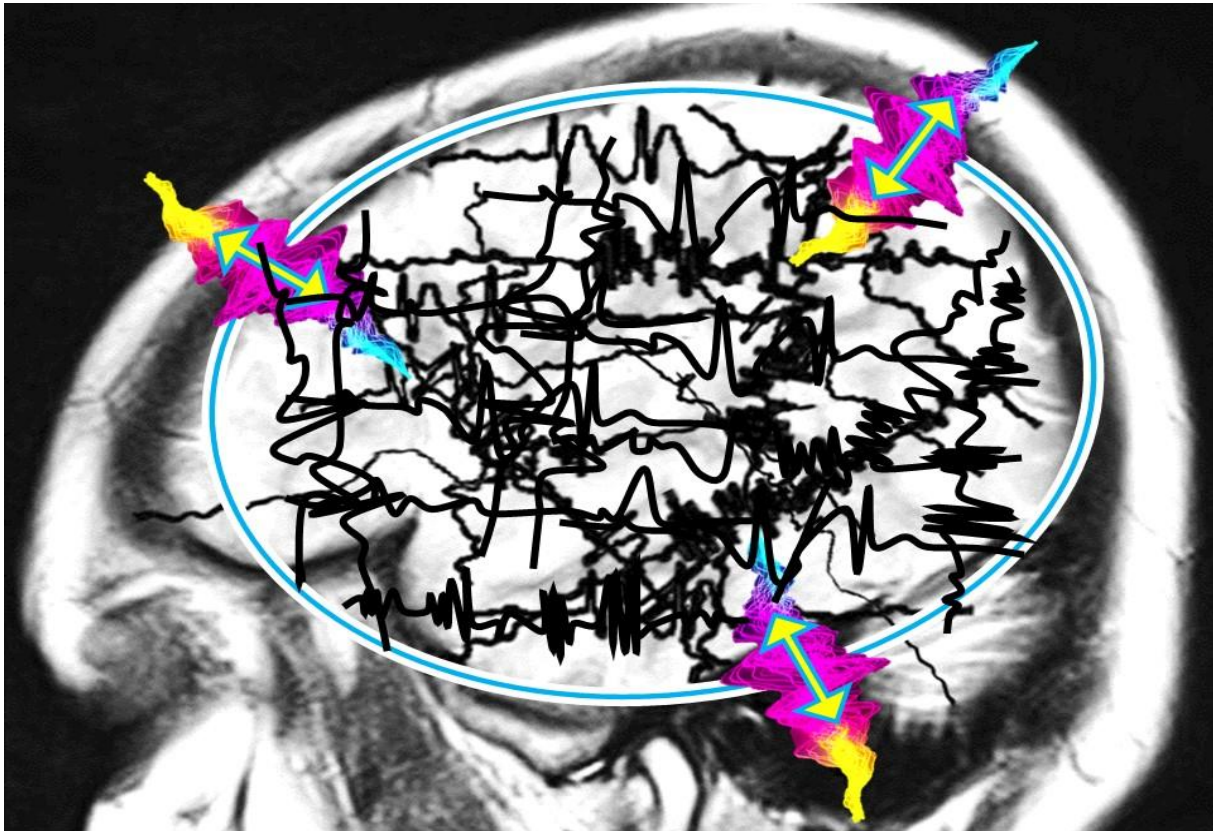
Figure 6: If the dura mater surrounding the brain cannot be adequately innervated by the trigeminal, facial, glossopharyngeal, vagal, and upper cervical nerves, and if the brain is deprived of this electromagnetic shield, both itself and its surroundings may suffer severe damage that has not yet been described. If the dura mater and CSF, which are the armors of the brain, cannot function, the electromagnetic, thermodynamic, and many other unknown functions of the brain will be disrupted. Due to these two weak armors (blue-white ellipse), the electrical, magnetic, and thermodynamic balances of the brain are not preserved. These armors do not prohibit external magnetic resonance waves (EMRW) from transmitting to the brain. In that situation, chaotic interferences occur among EEG waves, and various neuropsychiatrimlems can be developed.

4. Discussion

Just like the layers of the atmosphere surrounding the galaxies, the solar system, the planets, and the Earth. It is not against the laws of physics and reason to have an armor that covers the brain, which we can call the cerebrosphere.

4.1. Innervations of Cranial Dura Mater

Since the dura mater has a vibrant neural network, is conductive, and is vibrating, it can be predicted that it will create a magnetic field, an electric field, and ultimately an electromagnetic field, which will insulate the brain, thanks to the charged neuroparticles it contains (Figure 1). The temporomedial dura is innervated by trigeminal nerve fibers [1]. The posterior cranial fossa dura mater is innervated by upper cervical dorsal root ganglions, superior cervical ganglion, vagus nerve, trigeminal nerve, hypoglossal nerve, and glossopharyngeal nerve [2]. Intracranial nociceptive innervation is managed by trigeminal system [3]. The dura mater, which surrounds the brain and is intensely innervated by the trigeminal, facial, glossopharyngeal, vagal, and upper cervical nerves, forms a strong electromagnetic shield. While this armor protects me from external factors, it also protects the brain, electrically charged objects, and even other environmental organs from the dangers of this intense and dangerous electromagnetic field. The cerebrospinal fluid also acts as the ionosphere, protecting the brain with the same activities. Spherical shell is formed by the Earth's surface and the inner surface of the ionosphere. Due to these mechanisms, the brain's static and kinetic, electromagnetic, and thermodynamic balances are preserved.

4.2. The Electrophysical Properties of the Dura Mater and its Mysterious Role in the Formation of Electromagnetic Armor that We Think it Makes Around the Brain

Transcranial electrical stimulation and transcranial magnetic stimulation suggest that the dura mater may also have good magnetic field-generating power since it has good electrical conductivity. Because the dura mater, which has numerous electrically charged and conductive cells, is also in vibration, it can create a hemispherical magnetic field in terms of its shape and

a combined electromagnetic field with the electric field [4]. Head tissues have a measurable electrical impedance that mathematical methods can express. Every cranial tissue exhibits dielectric properties. The dura mater can be excited with inductive currents with frequencies greater than 200 Hz. The internal current source density for currents is negligible.

Along with the dura mater, the scalp, bones, CSF, and cranial vessels are also sensitive to electric current [5]. Cranial skin, bones, and dural layers create an electrical field with the placement of electrodes [6]. Since the dura mater conducts electrical current well, it can also damage the distant nerves and organs to which it is connected [11].

4.3. Biophysical Properties of Neurons

Neurons are -70mV electrically charged bodies [7]. When neurons vibrate like electrically charged bodies, they create a magnetic field around them [8]. While neurons vibrate synchronously with the brain, creating a magnetic field around them, this vibrating magnetic field creates an electric field [9]. Vibrating electrically charged objects create a magnetic field around them, an electric field around them when magnetic masses vibrate, and an intertwined common electromagnetic field if the two vibrate simultaneously [10].

Electromagnetic waves created by multiple ongoing lighting strikes cause waves traveling away from each epicenter with the velocity of light v=c, like earthquake waves or thunderstorms. Wave interference and periodic boundary conditions in the shell result in discrete preferred frequencies of field oscillations, the Schwann resonances, given by the expression of the wave energy of the total brain. The brain-like structures result from mentally inflating the folded cortical surface of one hemisphere. The characteristic velocity corresponds to the peak in the velocity distribution function for corticocortical transmission, roughly 6-9 m/s [12].

4.4. Neurophysical Properties of Neurons and Their Role in the Design of Differential-Integral Equations of EEG Waves

Regarding electrical engineering, the brain is two parallel plates that generate and load energy, and the corpus callosum is an interconnection that balances the load between these two plates. At large distances, the field is that of a monopole because the total local charge or current does not add to zero. If the current is a conductor, it must flow to distant sinks. Billions of neurons in the brain charged with -70 mV electrical current generate electrical current [7]. Since the brain is in a state of vibration, these neurons vibrate simultaneously with the brain, creating a magnetic field around them. As this magnetic field vibrates, it creates an electric field around it [9]. Thus, these two fields combine to form a unified electromagnetic field. In Figures C and D, combined electromagnetic fields running in opposite directions in both cerebral hemispheres are representatively drawn (Figure 2).

According to the moment, these electromagnetic fields charge the brain. Otherwise, the brain will not find enough ATP to ignite so many synaptic circuits, and even if it does, the heat released turns the brain into ashes.

Regarding electrical engineering, the brain is two parallel plates that generate and load energy, and the corpus callosum is an interconnection that balances the load between these two plates (Figure 3). At large distances, the field is that of a monopole because the total local charge or current does not add to zero.

In the Figure 4, brain volume conductor is indicated in which surface potentials Φs (r_k, t_i) are recorded at discrete surface locations rk and time ti. The surface potentials are generated by dipole moments p (rn, ti) in tissue masses (voxels) ΔV located at rn. All volume conductor properties are included in the Green function G (rk, rn). Resources are defined as dipole moments per unit volume p (rn, ti) / ΔV. Φ (r, t) $= \iiint_{Brain} G(r, r') . P(r', t) dV(r')$ [8, 13, 14].

Here, P (r, t) is the tissue dipole moment per unit volume, that is, resource strenght at location r and time t. Resource strenght in terms of the membrane current sources. The integral is weighted by the Green's function G (r, r'), which accounts for all geometric and conductive properties of the volume conductor. Generally, G (r, r') is large when the ''electrical distance'' between recording location r and source location r' is small. In an infinite, homogenous and isotropic medium, the electrical distance equals the actual distance, this idealisation is not accurate for the head volume conductor [14].

In the Figure 5, the cortical surface regions where alpha rhythms were recorded in a large population of epilepsy surgery patients are indicated by abnormal waves. Dotted regions near the central motor strip exihbited beta activity. ECoG activity was characterized by counting zero crossing s before Fourier transforms used in EEG [8, 13, 14]. If the dura mater surrounding the brain cannot be adequately innervated by the trigeminal, facial, glossopharyngeal, vagal and upper cervical nerves, and if the brain is deprived of this electromagnetic shield, both itself and its surroundings may suffer serious damage that has not yet been described (Figure 6).

5. Conclusion

Insufficient dura mater activity may cause many neuropsychiatric diseases of unknown origin, which result from congenital or acquired causes that damage these circuits. The same results are inevitable if the cerebrospinal fluid cannot function as the ionosphere for similar reasons.

Limitations of the Study

This theoretical study is devoid of rational data.

Conflict of Interests

The authors declare no competing interests.

Author Contributions
MDA and AA designed the study. MDA, MCG, AA, MHŞ, ECÇ, and ONK contributed to data collection and data analysis. MDA, MCG, AA, MHŞ, ECÇ, and ONK read the draft and approved the final scenario.

Ethical Approval
Atatürk University Local Ethics Council of Animal Experiments approved the study (25.06.2010/22).

Data sharing statement
None.

Consent to participate
None.

Informed Statement
None.

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Postnatal Hospitalization Rates and Short-term Follow-up Results of Late Preterm, Early Term and Term Newborns

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Abstract: Late preterm newborns are infants delivered between 34 and 36 weeks of gestation, and early term newborns are born between 37 and 38 weeks. Infants born between the late preterm and early term stages are more susceptible to morbidity and mortality as compared to infants delivered at full term. This study aimed to examine the factors contributing to illness and death among newborns delivered between 34 and 37 weeks gestation, as well as those born at full term. This study included a group of 1000 newborns delivered within a gestational age range of 34 to 42 weeks in our hospital. The assessment of these cases was based on factors such as the mother's age, the weight of the baby at birth, the APGAR score, the method of delivery, the requirement for postnatal resuscitation, the family's income, the rate of hospitalization, and the necessity for mechanical ventilation. Out of the 1000 babies examined in the study, respiratory issues were more prevalent among male newborns. With the rise in income levels, there was a corresponding increase in the rate of births occurring closer to the expected delivery date. Late preterm babies exhibited a greater hospitalization rate in comparison to both early term and term newborns, accompanied with poorer APGAR scores. Ultimately, the demand for mechanical ventilation was greater among late preterm babies. When assessing late preterm and early term newborns, it is important to take into account their physiological immaturity and the fact that they are at a greater risk of experiencing health problems and death. Delivery should be scheduled after the 39th week of gestation only if there is a medical reason. ©2024 NTMS.
Keywords: Late preterm; Early Term; Morbidity.

1. Introduction

Prematurity, as defined by the World Health Organization, refers to newborns with a gestational age between 22 weeks (beyond the limit of viability) and 37 weeks. It is a significant contributor to both morbidity and mortality [1-4]. A more extensive categorization was formed due to the fact that the occurrence of morbidity and mortality differs based on the exact week of birth, resulting in variations in terms of financial impact. As per this categorization, "late preterm" newborns are defined as those that are born between 34+0/7 and 36+6/7 weeks of gestation [1]. "Early term" infants are born between 37+0/7 and 38+6/7 weeks, and "term" infants are born between 39+0/7 and 41+6/7 weeks [2]. The incidence of late preterm and early term births has been on the rise in recent years, with a noteworthy increase in late preterm births during the past two

decades [3, 4]. The primary factors contributing to this phenomenon are the escalating prevalence of elective cesarean deliveries and the rising incidence of multiple pregnancies resulting from assisted reproductive technologies. Due to their physiological and metabolic immaturity, late preterm newborns have increased morbidity and mortality rates compared to term newborns. The prevalent short-term morbidities observed in this population are hypothermia, hypoglycemia, respiratory complications, apnea, hyperbilirubinemia, nutritional abnormalities, and, to a lesser degree, necrotizing enterocolitis and intraventricular hemorrhage [5]. Early term infants are more prone to respiratory difficulties, sepsis, jaundice, hypoglycemia, and hospital readmissions compared to term newborns [6-10]. Research has additionally demonstrated that there is a higher prevalence of chronic development difficulties, cognitive impairments, and mental health issues after deliveries that occur during the late preterm and early term periods [11, 12]. The mortality rates of late preterm and early term newborns have been found to be higher compared to term births [13-15].

The current study aimed to investigate the causes of neonatal morbidity and mortality in late preterm and early term newborns with reference to term births.

2. Material and Methods

This retrospective study investigated the rates of hospitalization and short-term outcomes of newborns with gestational ages ranging from 34 to 42 weeks who were born at Atatürk University Research Hospital over the period from 1 January 2016 to 31 December 2017. The study commenced with the authorization of the Atatürk University Faculty of Medicine Ethics Committee (Decision No. 12/5, dated 28.09.2017), and all research was carried out in conformity with the principles outlined in the Declaration of Helsinki.

The study assessed newborns in three distinct groups: late preterm newborns born between 34+0/6 and 36+6/7 weeks of gestation, early term newborns born between 37+0/7 and 38+6/7 weeks of gestation, and term newborns born between 39+0/6 and 41+6/7 weeks of gestation. All newborns included in the study were assessed for mother's age, birth weight, APGAR score, mode of delivery, the requirement for postnatal resuscitation, family's income level, rate of hospitalization, and need for mechanical ventilation. The gestational age of the newborn was ascertained based on the mother's most recent menstrual cycle. If this information was not available, it was established using ultrasonography and the new Ballard scoring system. The mode of delivery was classified into two categories: normal spontaneous vaginal birth and caesarean section. The assessment of the necessity for postnatal resuscitation was conducted by evaluating the application of positive pressure breathing and following appropriate measures. Hospitalized babies requiring mechanical ventilation were categorized into subgroups based on whether they received invasive or

noninvasive ventilation. Continuous positive airway pressure (CPAP) is recognized as a form of noninvasive ventilation, whereas endotracheal intubation is recognized as a form of intrusive ventilation. Family income levels were assessed based on the hunger and poverty line thresholds for the period of 2017-2018.

2.1. Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics 24.0. The analysis was conducted to assess how the data was distributed among the different groups. Mean and standard deviation were used to convey continuous data, while percentages were used to express frequency data. The chi-square test was employed to compare frequency data and ascertain risk factors for dependent variables, with risk analysis also conducted for the data. The analysis of variance (ANOVA) was conducted to examine parametric data in a unidirectional manner. The Duncan test was used to compare many variables. The significance level was deemed acceptable at a p-value of less than 0.05.

3. Results

This study included a group of 1000 babies, consisting of 274 late preterm, 370 early term, and 356 term births. No statistically significant difference was observed in the study of mother age between the groups. The average birth weight of the late preterm neonates was 2352 g, whereas the early term and term newborns had average birth weights of 3053 g and 3736 g, respectively. The weights of the babies included in the study were assessed as suitable based on their gestational age. Table 1 displays the comparisons of the babies based on maternal age, birth weight, and sex.

Upon analyzing the income levels of the families of the newborns during the study, we observed a correlation between approaching the poverty line and an increase in the rate of preterm births (p<0.001). Regarding late preterm births, 45.8% of the families had income levels that fell at or below the poverty line. 46.5% of households with early term newborns and 53.4% of families with term newborns had incomes above the poverty line (p<0.001).

When newborns were analyzed based on their method of delivery, it was shown that the rate of natural spontaneous vaginal birth increased as the gestational age advanced. The rate of caesarean section was highest among deliveries that occurred during the late preterm period, as indicated in Table 2.

The average APGAR scores for late preterm babies were 7.6 at the 1st minute and 9 at the 5th minute, based on the weeks of gestation. The average APGAR scores for early term newborns were 7.9 at the 1st minute and 9.2 at the 5th minute. In comparison, term newborns had scores of 8.5 at the 1st minute and 9.4 at the 5th minute. Hence, the APGAR scores of late preterm infants were seen to be markedly inferior to those of early term and term infants (p<0.001). The APGAR scores of early term neonates were seen to be significantly lower than those of term newborns

(p<0.001). Compared to term newborns, late preterm newborns had a 5.7 times higher requirement for postnatal resuscitation, whereas early term newborns had a 3.9 times higher demand (p<0.001). The

requirement for resuscitation escalated in proportion to the decrease in birth weight, as indicated in Table 3. Figure 1 displays the techniques employed for neonates necessitating postnatal resuscitation.

Table 1: Demographic characteristics of late preterm, early term, and term newborns.

	Group 1 n=274	Group 2 n=370	Group 3 n=356	p
Maternal age	31.04±5.9	30.69±5.6	30.58±5.4	0.584
Birth weight	2352±319 g	3053±246 g	3736±175 g	<0.001
Male/female ratio	133/141	188/182	166/190	0.529

Table 2: Rates of cesarean and normal spontaneous vaginal birth according to groups.

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	p
Cesarean	246 (89.7)	325 (88.5)	225 (63.1)	<0.001
Vaginal	29 (10.3)	43 (11.5)	132 (36.9)	<0.001

Table 3: Average APGAR scores and postnatal resuscitation needs according to groups.

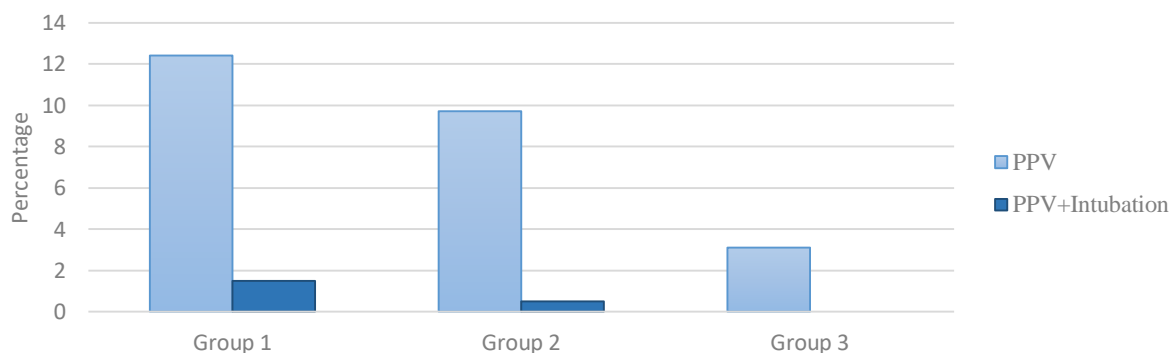|	Group 1	Group 2	Group 3	p
APGAR, 1st minute	7.59±1.45	7.89±1.2	8.49±1	<0.001
APGAR, 5th minute	8.97±1.1	9.20±0.8	9.42±0.6	<0.001
Need for resuscitation after birth	42 (15.3%)	41 (11.1%)	11 (3.1%)	<0.001

Figure 1: Resuscitation methods according to groups. PPV: Positive pressure ventilation.

Out of the 1000 newborns examined in this study, 260 needed to be admitted to the hospital. This group included 122 (47%) babies born at a later preterm stage, 105 (40%) babies born at an early term stage, and 33 (13%) babies born at a full-term stage. Consequently, late preterm neonates exhibited a considerably higher rate of hospitalization compared to early term and term newborns (p<0.001). The hospitalization rate of early term neonates was determined to be significantly greater than that of term newborns (p<0.001). Respiratory problems were the most common cause of hospitalization for late preterm and early term newborns, whereas term newborns were hospitalized for conditions such as neonatal hyperbilirubinemia, urinary tract infections, malnutrition, and congenital anomalies. Respiratory issues were discovered to be 5.9 times more prevalent in early term babies compared to term newborns, and 33.9 times more prevalent in late preterm newborns compared to term newborns (p<0.001). The incidence of respiratory issues was considerably higher in late preterm newborns compared to early term and term newborns (p<0.001). Respiratory distress syndrome (RDS) was the primary

cause of hospitalization in the majority of this category, accounting for 28.1% of cases. Among early term newborns, the most frequent reason for hospitalization was Transient tachypnea of the newborn (TTN), which accounted for 39% of cases. The incidence of respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN) was 33.9 and 3.6 times greater, respectively, for late preterm babies compared to term newborns. Similarly, early-term newborns had a 5.9- and 3.9-times higher risk of developing RDS and TTN, respectively, compared to term newborns. These findings were statistically significant (p<0.001).

In this study, respiratory problems were found to be more common among male newborns, being observed in 82/405 of the male infants and 56/457 of the female infants (p=0.007). Taking term newborns as a reference, statistical analysis of the hospitalized patients revealed that the need for mechanical ventilation was 2.9 and 1.6 times higher among late preterm and early term newborns, respectively. Late preterm newborns in neonatal intensive care had a higher need for mechanical ventilation (p=0.012); 63

(23%) patients in this group required noninvasive ventilation, while invasive ventilation was applied for 9 (3.2%) patients. In contrast, 47 (44.8%) of the early term newborns in the neonatal intensive care unit needed mechanical ventilation during hospitalization. While 42 (89%) of those infants improved with noninvasive ventilation, 5 (11%) needed invasive ventilation. Finally, 11 (33.3%) of the term newborns in the neonatal intensive care unit required mechanical ventilation and all of them improved with noninvasive ventilation.

Three late preterm newborns, four early term newborns, and one term newborn followed in the intensive care unit died. When mortality rates were calculated, the mortality rate was found to be 3.8% for early term and 2.5% for late preterm newborns. The mortality rate for term newborns was 3%. Thus, in this study, the mortality rate of late preterm newborns was lower than that of early term births. Causes of mortality included non-immune hydrops fetalis, perinatal asphyxia, anencephaly, Crouzon syndrome, congenital multiple anomalies, double outlet right ventricle, and congenital diaphragmatic hernia.

4. Discussion

The rates of premature birth and early term birth are steadily increasing in the world in general and in Turkey [16, 17]. These globally increasing rates of early births are attributed to pregnancy complications, the increase in multiple pregnancies achieved with assisted reproductive techniques, and the increase in elective cesarean sections. Studies conducted in recent years have shown that late preterm and early term newborns have higher risks of morbidity and mortality than term newborns [18-20]. The treatments provided in these cases are also important in terms of economic burden as the hospitalization of these infants is prolonged and postnatal problems such as hypoglycemia, hyperbilirubinemia, RDS, and TTN occur.

In our study, it was found that late preterm newborns had more respiratory problems than term newborns. In a study conducted with 90 term and 95 late preterm newborns, Wang et al. reported that respiratory problems were 9 times more common in the late preterm group compared to term newborns [19]. In another recent study, it was reported that respiratory problems were more common among early term infants compared to term infants [21]. Our research yielded similar results. In our study, the risks of RDS and TTN were higher in the late preterm and early term groups, respectively, when term newborns were taken as a reference and Thomas et al. found that the incidence of RDS and TTN was higher in late preterm and early term infants than in term infants [22]. Data on lung maturation in late preterm infants and the application of antenatal steroids before 34 weeks are based on studies evaluating lung maturation with amniotic fluid measurements. More specifically, it is reported that the maturation of surfactant production in the lungs is completed at about 35 weeks based on measurements of the lectin/sphingomyelin ratio and lamellar bodies in the amniotic fluid [23]. However, it is obvious that alveolarization continues in these infants [23]. As the production of fetal lung fluid and therefore its passage into the amniotic fluid decreases due to the intrauterine stress the fetuses are exposed to, which also causes premature birth, fetal markers of surfactant production are misleading and previously published information on surfactant maturation has become controversial [23]. Considering this information and the frequency of respiratory problems in late preterm newborns, complete lung maturation cannot be discussed for these infants. In a study conducted with early term newborns, Tita et al. found that respiratory problems increased in this population as a result of elective cesarean sections compared to term newborns [24]. Ghartey et al. found that the rates of respiratory problems such as RDS, TTN, and pneumonia in early term newborns were two times higher compared to term newborns[25]. When differences between the sexes were evaluated, we found that respiratory problems were more common in male infants in our study. Similarly, some studies reported that respiratory problems were more common in male infants at 37, 38, and 39 weeks [25, 26]. Differences in hormonal regulation of lung development provide candidate mechanisms to account for an increased risk of RDS associated with male sex. The increased incidence breathing problems in males may be due to the increased levels of fetal androgens. Fetal androgens delay lung maturation and PG production (by approximately a week) through direct action on lung fibroblasts [27].

Our hospital is a reference hospital, and for that reason, the number of high-risk pregnancies being followed was high. The resulting increase in cesarean section rates was an expected result. We found that the rate of births by normal spontaneous vaginal delivery increased as gestational age increased. Some previous studies similarly reported that the rate of cesarean sections decreased as the weeks of gestation increased [12, 28].

In our study, as expected, we found that early term and late preterm newborns had lower APGAR scores than term newborns, supporting the literature. In a previous study, it was reported that 48 late preterm newborns (17.5%) required resuscitation procedures of any type, and 37 of those 48 late preterm newborns (13.5%) required ventilation [29]. In the same study, it was found that the rate of 5-minute APGAR scores of <7 was higher in the 34th week than in the 35th and 36th weeks [29]. In another recent study, APGAR scores were lower among late preterm and early term newborns [30].

When hospitalization rates were evaluated, it was determined in our study that 122 late preterm (47%), 105 early term (40%), and 33 term newborns (13%) were hospitalized. In another study, it was determined that 88% of infants born at 34 weeks, 12% of infants born at 37 weeks, and 2.6% of infants born between 38 and 40 weeks were hospitalized[31]. In a study conducted in 2021, it was found that the hospital stays of early

term newborns were longer than those of term newborns[22]. When mechanical ventilation and CPAP support rates were examined, it was seen that they were also higher among late preterm and early term newborns. It was determined that 59% of late preterm newborns, 44.8% of early term newborns, and 33.3% of term newborns in intensive care needed mechanical ventilation. In our study, we found that the need for mechanical ventilation decreased as weeks of gestation increased. Hibbard et al. determined that the need for mechanical ventilation decreased in evaluations performed from the 34th week to the 40th week [9]. Thomas et al. determined that 1.2% of early term newborns and 0.8% of term newborns needed invasive ventilation among the hospitalized infants included in their study[22]. In our study, supporting the literature, we found that late preterm newborns needed CPAP more often than early term and term newborns, and early term newborns need CPAP more often than term newborns. In the study conducted by Ghartey et al., 39 weeks was taken as a reference point and the need for CPAP was found to be 2.2 times higher in the 37th week, 1.7 times higher in the 38th week, and 1.9 times higher when the 37th and 38th weeks were evaluated together [25].

In our study, which was conducted taking into account the 2016-2017 minimum wage and poverty and hunger thresholds, it was found that the rate of premature birth increased as income levels decreased. It has been observed that as income levels decrease, malnutrition during pregnancy and inadequate pregnancy follow-up due to sociocultural factors are more likely to occur, and these are associated with preterm birth. Previous studies showed that socioeconomic level is associated with preterm birth [32] and that lower socioeconomic levels were linked to increased preterm birth rates [33].

In our study, the neonatal mortality rate was found to be 2.5% (three patients) among the late preterm newborns in intensive care, 3.8% (four patients) among the early term newborns, and 3% (one patient) among the term newborns. Looking at studies in the literature, mortality rates were found by some researchers to be higher among early term infants [34, 35], in contrast to our study. In a study conducted in 2007, Engle et al. reported that the mortality rate in the first week of life was 9.5 times for births that occurred in the 34th week, 6.4 times in the 35th week, and 3.7 times in the 36th week per 1000 live births in comparison to births in the 39th week[36]. In the same study, the neonatal mortality rate was found to be 2.3 times higher in the first week of life for those born in the 37th week and 1.4 times higher in the 38th week [36]. However, when the causes of mortality were examined in the current study for late preterm newborns, there was one death each due to Crouzon syndrome, congenital diaphragmatic hernia, and perinatal asphyxia. Among the early term newborns, the causes of death were non-immune hydrops fetalis in one case, anencephaly in one case, and complex congenital heart disease in two cases. The single death recorded among the term newborns was

due to perinatal asphyxia. Looking at these etiologies, it is noteworthy that all of them carry inherently high risks of mortality.

One of the limitations of our study since our center is a reference hospital, the relatively high mortality rate observed in term newborns in this study may not statistically generalizable.

5. Conclusion

Early term newborns, like late preterm newborns, should be evaluated considering their physiological immaturity, and obstetricians should work in consensus with pediatricians to prevent unnecessarily early births. Ensuring frequent monitoring after birth, making the right discharge decisions and delaying discharge if necessary, and providing adequate education to families will also help prevent possible complications.

Limitations of the Study

One of the limitations of our study since our center is a reference hospital, the relatively high mortality rate observed in term newborns in this study may not statistically generalizable.

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Investigation of the Protective Effects of *Capparis Spinosa* Extract in Indomethacin Induced Ulcer Model in Rats

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Abstract: Capparis spinosa is a genus of the Capparaceae family. In the literature, it has been found that the main components of Capparis buds, quercetin and kaempferol were found to be effective in many diseases. In this study, the protective effects of Capparis spinosa on damaged rat stomach tissue induced by indomethacin and some antioxidant parameters were investigated. A total of 36 female Sprague Dawley rats weighing 200-220 grams were used in the study and six groups were formed. Groups were: healthy group; positive control group (famotidine 20 mg/kg+indomethacin 25 mg/kg); negative control group (distilled water+indomethacin); low-dose study group (125 mg/kg Capparis spinosa+indomethacin); medium dose group (250 mg/kg Capparis spinosa+indomethacin); and high dose group (500 mg/kg Capparis spinosa+indomethacin). Six hours after indomethacin was given to the groups by gastric lavage, all rats were killed under general anesthesia. The stomachs of all rats were removed, the ulcerated areas on the stomach surface were evaluated macroscopically, and the ulcer areas were measured on mm2 paper. In addition, blood and stomach tissues of all rats were biochemically examined, and malondialdehyde, superoxide dismutase and glutathione parameters were measured. The antiulcer activity of CS was compared with all groups. When the ulcer area and histopathological evaluation were examined, it was determined that the group applied 250 mg/kg Capparis spinosa had an appearance close to the healthy group. It was also found that plant extracts at all concentrations decreased the level of MDA in rat gastric tissue and increased SOD activity and GSH levels statistically. It was obtained that Capparis spinosa has antiulcer activity. ©2024 NTMS.

Keywords: Capparis spinosa; Indomethacin; Antiulcer; Antioxidant.

1. Introduction

It is known that peptic ulcer is a polyethiological chronic disease [1]. Disruption of the balance between protective and aggressive factors, trauma, stress, sepsis, hemorrhagic shock, pulmonary and liver diseases,

smoking, alcohol, steroid and nonsteroidal drug use have been shown in the etiopathogenesis of gastric ulcer [2-6]. Although the aggressive factors that because ulcers are different, there is an increase in the amount of reactive oxygen species (ROS) in the mechanism of gastric damage caused by all of them. This supports that ROS are closely related with ulcer pathogenesis [7]. The significance of the difference between oxidant and antioxidant levels in damaged tissue and undamaged tissue [8] shows the importance of these parameters in the development and treatment of ulcers. Although there are many antiulcer drugs used in the treatment of peptic ulcer, a complete cure cannot be achieved with these drugs. Therefore, researches that can provide permanent treatment of the ulcer are still ongoing.

Capparis, which grows in natural environment in the west of Azerbaijan, is a thorny plant with a bushy structure. As a plant that loves clay soils rich in phosphorus, calcium and potassium and enjoys the sun, it grows spontaneously in sunny areas. The buds of *Capparis spinosa* flower are very rich in mineral substances. In 100 g of edible dry matter: 65 mg of phosphorus, 67 mg of calcium, 9 mg of iron, and 24 g of protein were found. Being from the Capparaceae family, the plant has varieties such as *Capparis spinosa*, *Capparis ovata*, *Capparis scula* and *Capparis orientalis*. The buds and fruits of plants belonging to the Capparidaceae family are used partially as flavoring in meals. In addition, their anti-inflammatory, expectorant and anti–hepatotoxic usage in alternative medicine has also been reported [9].

In a study conducted on Capparis buds, it was determined that the main constituents were quercetin–3–rutinoside, kaempherol–3–rutinoside and kaempferol–3–rhamnosyl-rutinoside. In that study, it was also stated that 10 grams of capparis buds contain 65 mg of flavonoid glycoside, and this antioxidant content can make a significant contribution to human nutrition [9].

In our literature review, there is no study investigating the effectiveness of *Capparis spinosa* in protection from gastric ulcers. In this study; by investigating the protective effect of *Capparis spinosa* against stomach ulcers caused by indomethacin, we examined its connection with oxidant-antioxidant parameters in the stomach tissue.

2.   Material and Methods

2.1. Ethical Approval
The experiments adhered to ethical standards approved by the Ethics Committee of the Experimental Animal Teaching and Research Center (E.1800039863). Rats were procured from the Medicinal and Experimental Application and Research Center in Erzurum, Turkey (ATADEM).

2.2. Animals
For this study, a total of 36 female Sprague Dawley rats weighing between 200-220 grams were sourced from the experimental animal laboratory at the Atatürk University Experimental Research and Application Center (ATADEM). Throughout the experiment, the rats were provided with ad libitum access to both water and standard rat chow and were accommodated in a laboratory environment maintained at a regular room temperature of 22°C. The rats were randomly allocated into six groups, each consisting of six animals. The experimental groups were established as follows:

Group 1: Healthy
Group 2: Famotidine (20 mg/kg)+Indomethacin (25 mg/kg) (positive control group)
Group 3: Distilled water+Indomethacin (25 mg/kg) (negative control group)
Group 4: Low dose *Capparis spinosa* (125 mg/kg)+Indomethacin (25 mg/kg)
Group 5: Medium dose Capparis spinosa (250 mg/kg)+Indomethacin (25 mg/kg)
Group 6: High dose *Capparis spinosa* (500 mg/kg)+Indomethacin (25 mg/kg)

Capparis spinosa 125, 250, 500 mg/kg and famotidine 20 mg/kg were administered orally by gavage to the rat groups, after fasted for 24 hours. The same volume of distilled water was given to the control group. Five minutes after the drugs were administered, indomethacin was administered orally at a dose of 25 mg/kg to all rat groups by the same method. Six hours after indomethacin administration, all rat groups were euthanized by injection of high dose thiopental sodium (50 mg/kg). The rat stomachs were accessed through the greater curvature and rinsed with physiological saline. In this process, each stomach was immobilized on a flat surface, covered with a cellophane sheet, and the contours of both the stomach and the ulcerous regions were traced onto the cellophane. Subsequently, the stomach and ulcer areas were quantified by superimposing the cellophane sheet onto millimeter squared paper. The cumulative surface area of the ulcerous regions was then represented in terms of mm^2. Additionally, blood and stomach tissues were taken and oxidant and antioxidant parameters were biochemically measured. The antiulcer activity of *Capparis spinosa* was evaluated by comparing them with the results obtained from famotidine and the control group.

2.3. Biochemical Analysis
Following the macroscopic analysis of the stomach tissues taken from the rats after the experiments, the tissues were immediately frozen under liquid nitrogen and stored at -80 ° C until the experiments were carried out. For all biochemical analyzes, measurements were made according to the protocols suggested by the manufacturer companies, taking into account two different serum and tissue measurement protocols with Elisa test kits specially purchased for rats.

Superoxide dismutase (SOD), Malondialdehyde (MDA) and glutathione (GSH) levels and/or activities were determined in the stomach tissues. Measurements of SOD, GSH and MDA levels and/or activities in tissues were made in accordance with the protocols in the literature [10-13]. These measurement protocols are

generally similar. In principle, the levels of the relevant parameters were determined by comparing the color reactions that would occur with the standards. Tissue samples kept at -80 °C were pulverized one by one with a mortar under liquid nitrogen and stored at -20 °C. Then, approximately 100 mg of each tissue was weighed and homogenate buffer of the relevant parameter was added onto it. Then the mixture was homogenized for two minutes with a tissue lyser mixer and homogenizer. After the homogenized mixture was centrifuged at the relevant speed according to the measurement protocol included in each kit, the level of oxidant-antioxidant parameters in the supernatant section was determined by Elisa in two or three repetitions for each tissues. Then the amount of protein was determined according to the lowry method. Finally, statistical differences between groups were determined by one-way analysis of variance.

2.4. Histological Examination
Histological examinations were carried out in histology laboratory in Atatürk University Faculty of Medicine, Histology and Embryology Department. Stomach tissues taken from rats in all groups were given code numbers and left in bottles containing 4% formaldehyde. Then, tissue follow-up procedures were started. The tissues were then embedded in paraffin blocks and made ready for sectioning procedures. Staining process was carried out after 5 μm sections of paraffin blocks were taken on glass slides with microtome (Leica RM2125RT). The sections, which were ready to be examined, were examined under the Olympus BH 40 camera attached light microscope and photographs of all relevant groups were taken.

2.5. Preparation of Capparis Spinosa Extracts
Capparis spinosa buds samples collected from Azerbaijani Ganja region of Azerbaijan State Agricultural University, and after drying at room temperature in an environment without sunlight, were brought to Turkey. Then, they were ground with a grinder, pulverized and sieved using a 300 mm diameter 50 mesh sieve in the Department of Pharmacology of Atatürk University Faculty of Medicine. The capers powder sample obtained was extracted with ethanol at 50 °C. For this, 500 g powder sample was treated with 2 liters of ethyl alcohol for 3 days with back cooler, and the solvent was changed every 24 hours. By combining the filtrates, the ethanol in the total extract was removed in the evaporator at 40 °C. Then, the water in the extract was removed by means of a lyophilizer and the pure extract was obtained as a powder. Thus, the extract was dissolved in water and applied.

2.6. Statistical analysis
The statistical analyzes and comparisons were made by using SPSS Statistic 19.0 program (IBM, NY, USA). The experimental results were presented as Mean±Standard deviation (SD), and p-values less than 0.05 were regarded as statistically significant. To determine the significance of differences among the groups, Duncan's post-hoc multiple comparative test was employed in conjunction with the one-way ANOVA test. Each different letter shows that it is statistically different from the other group, and the same letters are meaningless.

3. Results
When we examined the ulcerated areas in the stomach tissues of rats sacrificed, it was observed that *Capparis spinosa* extract at a concentration of 250 mg/kg showed an antiulcer activity of 83% ($p < 0.05$) and the famotidine group showed an antiulcer activity at a rate of 88% ($p < 0.05$). The ulcer areas of *Capparis spinosa* extracts (125, 250, 500 mg/kg doses), famotidine (20 mg/kg dose) and control group are shown in Figure 1. It was observed that all Capparis spinosa extract doses had a significant anti-ulcer effects ($p < 0.05$).

Figure 1: Average gastric ulcer areas of the groups.
*Each value represents a Mean±SD. The different letters given on the bars show a significant difference ($P < 0.05$). Famotidine (FAM), Indomethacin (IND), Capparis Spinosa (CS).

3.1. Biochemical Analyzes Results
When the results of the biochemical analyzes performed within the scope of the study were evaluated, *Capparis spinosa* extract at all doses significantly increased SOD activity ($p < 0.05$) and GSH levels ($p < 0.05$) in the stomach tissues of rats. The extract at a concentration of 250 mg/kg increased the SOD activity and GSH levels at the highest rate. All extract doses significantly reduced MDA ($p < 0.05$). The most effective decrease was observed at a dose of 250 mg/kg. The SOD activity, GSH and MDA levels of all samples are shown in Figures 2, 3 and 4.

SOD (U/mg protein)

Figure 2: Superoxide dismutase (SOD) activities of the groups.
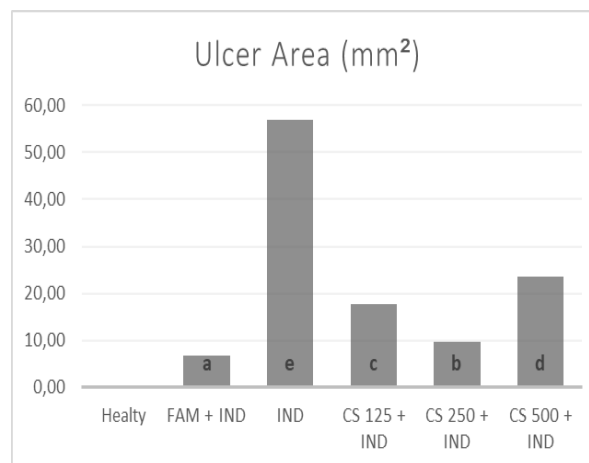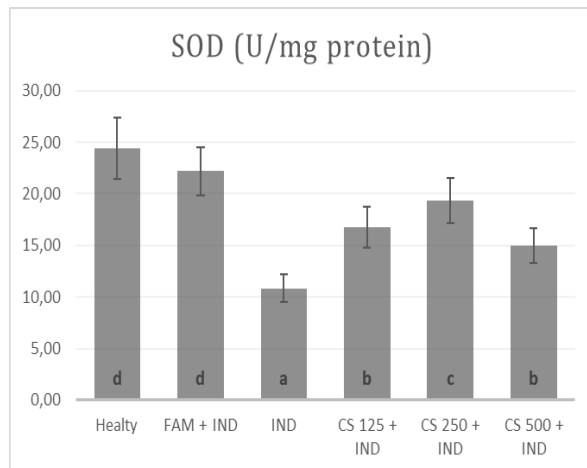*Each value represents a Mean±SD. The different letters given on the bars show a significant difference (P<0.05). Famotidine (FAM), Indomethacin (IND), Capparis spinosa (CS).
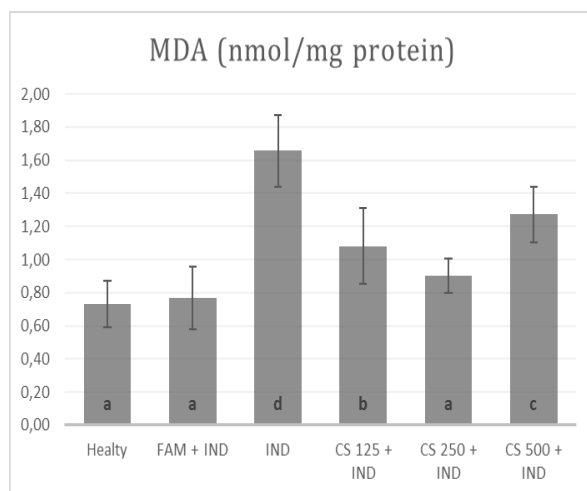
MDA (nmol/mg protein)

Figure 3: Malondialdehyde (MDA) levels of the groups.
Each value represents a Mean±SD. The different letters given on the bars show a significant difference (P<0.05). Famotidine (FAM), Indomethacin (IND), Capparis spinosa (CS).
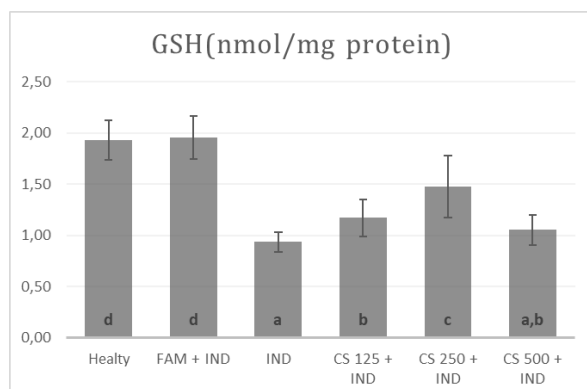
GSH(nmol/mg protein)

Figure 4: Glutathione (GSH) levels of the groups.
*Each value represents a Mean±SD. The different letters given on the bars show a significant difference (P<0.05). Famotidine (FAM), Indomethacin (IND), Capparis spinosa (CS).

3.2. Histopathological Results

The histopathological evaluation of our study performed with hematoxylin and eosin staining (H&E) was based on the gastric mucosa layer. As per the findings, in the healthy group, it was observed that the gastric cavities of the stomach exhibited a normal appearance, and both the parietal and mucous cells appeared healthy (Figure 5A).

The positive control group, consisting of famotidine+indomethacin (FAM+IND), exhibited a resemblance to the healthy group in terms of appearance. No necrotic alterations in the surface mucous cells were observed (Figure 5B).

In the negative control group, distilled water+indomethacin (IND), epithelial losses and irregular gastric pits were observed in the superficial mucosa, while especially surface mucous cells were observed to have necrotic appearances. However, the increase in lymphatic cells in the lamina propria was also remarkable. In addition, an increase in eosinophilia was observed in some parietal cells (Figure 5C).

In the low-dose *Capparis spinosa* group (125 mg/kg: CS 125), epithelial losses were severely reduced, but surface-facing mucous cells had necrotic appearances (Figure 5D).

In the medium dose *Capparis spinosa* group (250 mg/kg: CS 250), an appearance similar to the healthy group was dominant. However, spills were still observed in some epithelial cells (Figure 5E).

In the high-dose *Capparis spinosa* group (500 mg/kg: CS 500), in addition to necrotic-looking surface mucous cells, increased inflammatory cells in the near-surface lamina propria were remarkable. In addition, some parietal cells showed an increase in eosinophilia (Figure 5F).

In order to better understand histopathological evaluations, epithelial cell loss, histopathological damage based on the presence of hemorrhage and necrotic cells; they were scored as - (none), + (little damage), ++ (moderate damage), +++ (severe damage) (Table 1).

Table 1: Average histopathological damage score of all groups.

	Necrotic cell	Haemorrahage	Epithelial cell loss
Healty	-	-	-
FAM+IND	-	-	-
IND	+++	+	+++
CS 125+IND	+	-	-/+
CS 250+IND	-	-	-
CS 500+IND	+	+	+

4. Discussion

Peptic ulcers, characterized by mucosal erosions or ulcers in the stomach or duodenum, are significant gastrointestinal disorders that can lead to various complications if left untreated. A multitude of factors, including the use of nonsteroidal anti-inflammatory drugs like indomethacin, stress, and bacterial

infections, have been implicated in their pathogenesis [14-19]. The pathophysiology of peptic ulcers is complex, involving an intricate balance between aggressive factors such as acid secretion, pepsin activity, and oxidative stress, and protective mechanisms including mucus and bicarbonate secretion, mucosal blood flow, and antioxidant defenses [20].

The present study has shed light on the potential therapeutic utility of *Capparis spinosa* extract in countering the damaging effects of indomethacin-induced gastric ulcers. Indomethacin, a widely used nonsteroidal anti-inflammatory drugs, is known to disrupt the mucosal barrier and enhance oxidative stress within the gastric mucosa, leading to the development of ulcers [16, 17]. The observation that *Capparis spinosa* extract, particularly at a medium dose of 250 mg/kg, exhibited a substantial reduction (83%) in ulcer formation in the rat model suggests that this natural extract may hold promise as a protective agent against nonsteroidal anti-inflammatory drugs -induced gastric ulcers. These findings are consistent with the hypothesis that *Capparis spinosa* may exert its effects by bolstering the gastric mucosa's defenses against oxidative damage.
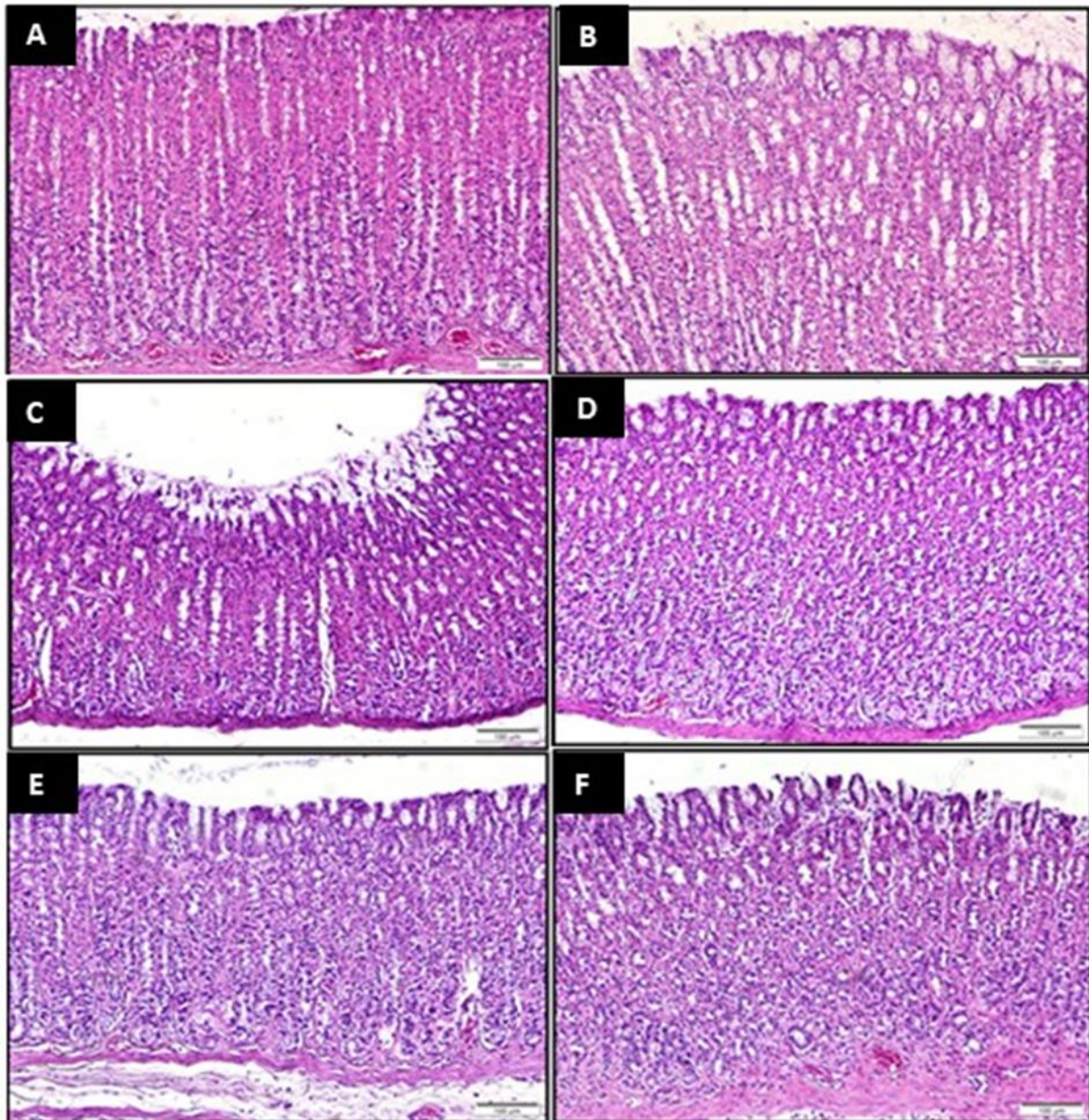
Figure 5. Histopathological results of rat stomach tissues (A: Healthy group; B: FAM+IND; C: IND; D: CS 125 mg/kg+IND; E: CS 250 mg/kg+IND; F: CS 500 mg/kg+IND).

The antioxidative properties of *Capparis spinosa* extract, as evidenced by the significant increases in SOD activity and GSH levels along with a reduction in MDA levels in the stomach tissues of rats, suggest that this extract has the capacity to counteract oxidative stress within the gastric mucosa. Oxidative stress is a pivotal contributor to mucosal damage in the stomach [21]. Excessive production of ROS overwhelms the

endogenous antioxidant defenses, leading to lipid peroxidation and cellular damage [21]. The ability of *Capparis spinosa* extract to enhance SOD and GSH levels while reducing MDA levels underscores its potential as an antioxidant agent. This is consistent with previous research demonstrating the antioxidant activity of *Capparis spinosa* and its flavonoid constituents, such as quercetin and kaempferol [22]. Flavonoids possess free radical-scavenging properties and can mitigate oxidative damage, making them relevant in the context of gastric ulcer prevention [23].

The mechanisms underlying the protective effects of *Capparis spinosa* extract warrant further investigation. It is plausible that the extract exerts its antiulcer and antioxidant actions through multiple pathways. Firstly, as an antioxidant, it likely scavenges ROS generated during the ulcer-inducing process, thereby reducing tissue damage. Moreover, *Capparis spinosa* may modulate inflammatory responses and support the repair of damaged gastric mucosa. Its anti-inflammatory and tissue-healing properties, reported in previous studies [22], may contribute to its overall efficacy in reducing ulcer formation. Additionally, the extract might enhance mucosal blood flow, stimulate mucus and bicarbonate secretion, or directly protect mucosal cells from nonsteroidal anti-inflammatory drugs-induced damage, as observed in some gastroprotective agents [15, 17].

While these findings are promising, it's crucial to recognize that this study was conducted in a rat model, and extrapolating the results to humans requires caution. Further research, including well-designed clinical trials, is needed to evaluate the safety and efficacy of *Capparis spinosa* extract in human subjects. These studies should consider optimal dosages, formulations, and potential adverse effects. Moreover, investigations into the long-term effects of *Capparis spinosa* extract and its comparative efficacy with established antiulcer medications are warranted to establish its clinical relevance.

5. Conclusions

In conclusion, this study provides valuable insights into the potential therapeutic utility of Capparis spinosa extract as a protective agent against NSAID-induced gastric ulcers. Its antioxidant properties, coupled with its significant reduction in ulcer formation in the rat model, suggest its promise as a natural remedy for peptic ulcers. However, further research is essential to validate these findings in human populations and elucidate the precise mechanisms responsible for its therapeutic effects.

Limitations of the Study

To definitively establish the anti-ulcer efficacy of *Capparis spinosa*, clinical studies involving humans are needed. The absence of research conducted on humans in this study represents a limitation.

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Hippophae rhamnoides L. Botanical, Medicinal, Traditional, and Current Use of Plant and Fruits: A Review

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Abstract: Scientific research on medicinal plants is increasing day by day. Hippophae rhamnoides L. is a medicinal plant, which belongs to the family of L. Elaeagnaceae, and is consumed as a medicinal and food at the same time. It is a type of plant in the form of a bush with thorny, nitrogen-fixing roots and fruit that grows in cold and arid regions. It is native to and widely found in cold temperate regions of Europe and Asia. The species differ in their phytochemical compositions, depending on the climate and the soil they grow in. Due to its rich chemical composition, it has been used in traditional medicine for centuries as herbal medicine, health promoter, and food additive. Hippophae rhamnoides L. plant; It has attracted worldwide attention due to the presence of different types of nutrients and bioactive compounds such as vitamins, amino acids, fatty acids, carotenoids, phenolic compounds, and micro and macro elements, including its leaves, fruits, and seeds. Hippophae rhamnoides L. contains phytochemicals besides reducing platelet aggregation, blood pressure, and blood sugar; It has been reported to have a wide range of activities ranging from anticarcinogen, antifungal, antibacterial, antioxidant, antihistaminic, antiviral, anti-inflammatory, spasmolytic, gastroprotective, cardioprotective and radioprotective potential. In addition, it is promising to be used as an alternative support for the treatment of diseases such as skin burns and atopic dermatitis, since it protects and regulates cell metabolism and has a protective effect on skin cells. Hippophae rhamnoides L., which has economic value with the rich components it contains, is used in the medical, food, and cosmetic industries, while at the same time, it is used as a feed additive for animals and to prevent the destruction of the field by flood waters for ecological purposes. Studies on the plant Hippophae rhamnoides L. are important due to the use of a wide spectrum. The aim of this review is to give information about the botanical, medicinal, traditional and current uses of the fruit and plant of Hippophae rhamnoides L. ©2024 NTMS.

Keywords: Hippophae rhamnoides; Sea buckthorn; Omega 7.

1. Introduction
1.1. Botanical Information

Section: Plantae
Branch: Magnoliophyta

Class: Magnoliopsida
Team: Rosales
Genus: Elaeagnaceae
Type: Hippophae L. 1
Genre and species characteristics
The Elaeagnaceae family is native to Australia, Asia, and Europe, as well as tropical North and South America, and has three genera, Hippophae, Shepherdia, and Elaeagnus, and about 70-80 subspecies [2, 3].

Hippophae rhamnoides L., on the other hand, is a flowering plant species with spiny shoot tips, orange fruits, deciduous at various heights, and shrub-shaped that can grow up to 10 m [4–6]. This shrub, which is generally described as a weed; is hard, woody, often multiparous, cylindrical, perennial, and waxy. Each branch of the stem develops into thorns and the spines are stiff and 1-5 cm 2 apart [7-9]. Hippophae rhamnoides L., which takes its name from the Latin word "Hippos" meaning "horse" and "Phaos" meaning "brightness", was used in Greece to feed horses with its leaves and branches, to gain weight and shine their feathers [10-12]. Hippophae rhamnoides L. is named differently in each geography. There are 23 different nomenclatures in Russian alone. in English Seabuckthorn in French Argousier in German Sanddorn is known as Havtorn in Danish, Tyrni in Finnish, Tindved in Norwegian, Havtorn in Swedish, Dzbidda in Uzbekistan, and Tea thistle in Azeri. It has been given different names such as sand willow, sea thistle, shore thistle, Rhine thistle, Haff thistle, grassland thistle, meadow thistle, painful thistle, fire thistle, coral bush, scarlet thistle, or pheasant fruit [12].

Fruit and seed properties
Depending on the height, flowering occurs in April-May, and fruit formation occurs in September-October. Ripe Hippophae rhamnoides L. fruit color is yellow-orange and its shape can be spherical or oval. The weight of the fruit is usually in the range of 4-60 g per 100 pieces and can be exceptionally heavier for some varieties grown in Russia [10]. The importance of the plant is due to the bioactive substances in its fruit and seed [13]. The plant contains many bioactive substances such as vitamins, carotenoids, flavonoids, sterols, organic acids, saturated and unsaturated fatty acids, and some essential [14–17].

Hippophae rhamnoides L., its fruit is the main component of herbal value 6. Its fruits have a unique composition that combines a cocktail of ingredients that are often found separately. Each fruit is surrounded by a cellular structure (pulp) filled with the juice of the fruit and consists of a single seed [18]. The fruit of Hippophae rhamnoides L. consists of 68% pulp, 23% seeds, and 7.75% peel 19. There are various bioactive substances in Hippophae rhamnoides L. fruits and seed oil [13]. Fruits contain carbohydrates, proteins, flavonoids, antioxidants, sugars, sugar alcohols, fat- or water-soluble vitamins, phytosterols, polyphenols, carotenoids, polyunsaturated fatty acids, amino acids, fruit acids, plant sterols, and minerals [6, 20, 21].

Natural growing geography and agricultural production

Hippophae rhamnoides L. It has a wide geographical distribution, peculiar to cold temperate regions ranging from latitudes and longitudes of 27°-69°, extending from Europe to China (Bulgaria, Caucasus, Northern Iran, Western Europe, Asia, Azerbaijan, Turkey) [22]. In our country, in the cities of Samsun, Ordu, Giresun, Trabzon, Çankırı, Nevşehir, Kayseri, Sivas, Kahramanmaraş, Erzincan, Ağrı, Van, Mersin, and Erzurum, mainly on the In our country, mainly on the North Anatolian line, in the cities of Samsun, Ordu, Giresun, Trabzon, Çankırı, Nevşehir, Kayseri, Sivas, Kahramanmaraş, Erzincan, Ağrı, Van, Mersin, and Erzurum, from -40°C to +40°C, from the sea coast to 5000 It has a natural distribution up to meters altitude [4, 6, 12, 22]. It grows naturally in mountainous areas, lake shores, wet areas to arid areas, cold tolerant, sandy, and stony areas, especially near rivers and streams. It can spread rapidly with its rhizome roots and because its requirements are low in growing conditions; When it is rooted in the soil by cutting a single branch in low humidity, alluvial gravel, wet landslides, and river banks, it acts invasively in the area where it is planted within two years [23].

Historical background and traditional uses and present
Used for centuries by the people of Northeast, Central, and Southeast Asia as an agent of traditional medicine, this plant appears to be widely used for the treatment of various ailments such as asthma, skin diseases, stomach ulcers, and lung ailments [24]. The medicinal pharmacological effects of Hippophae rhamnoides L. in Chinese sources can also be found in the 'RGyud Bzi' medical text, pharmacopeias, and various Chinese classical works written during the Tang Dynasty (618-907 AD) [12, 25, 26]. In the 8th century AD, in the work " Djud-shi " written by the famous doctor Yuthog Yontan Gonpo , more than 300 medicinal preparations of sea buckthorn are presented by processing, either alone or in combination with other herbs, minerals, and even foods [12]. The fruits of Hippophae rhamnoides L. have been used in Europe and Asia as a source of herbal medicine, nutritional supplement, and natural skin care. Every part of the plant, such as fruit, leaves, branches, roots, and bark, has been seen as a multidimensional and valuable bioresource for centuries. Some of the usage areas; food, fuel, feed, nutritional supplements, cosmetics, pharmaceuticals, veterinary, agricultural tools and timber, biofencing [12, 27–31]. Hippophae rhamnoides L. Various medicine in China, such as raw herbs (juice, fruit oil, seed oil, pigment, etc.), soft and alcoholic beverages, cosmetics, flavonoid tablets to treat ischemic cardiomyopathy disease, and capsules for ulcer and inflammation treatment and health products [32]. Used by local people in Central Asia (in the mountainous regions of Tajikistan and Afghanistan) for the treatment of hypertension, digestive system, and skin diseases, Tibetan and Mongolian people for liver diseases, gallstones, gynecological diseases, rheumatic pains and joint edema, expectorant, cough treatment, blood It has been used to support circulation and improve the function of the digestive system. Dsejchar

It is mentioned in the Tibetan book Migczan that it heals the way of the lungs and throat, and for this reason, it is called 'the blood of the king's heart'. The people of Russia and the Indian Himalayan regions used it in the treatment of skin diseases, jaundice, asthma, laxatives, and rheumatism [12, 33, 34]. Oils obtained from its fruits; It has been used for therapeutic purposes in gastritis, gastric ulcer, uterine necrosis, and inflammation of genital organs [12, 33]. In addition, the fruits of Hippophae rhamnoides L. have traditionally been used in Austrian medicine as tea, juice, or syrup for the treatment of infections [12, 21].

Today, Hippophae rhamnoides L. drugs have been developed due to the excess of bioactive substances it contains which used in the field of health with its increasing commercial importance in western countries and is used in different forms such as liquid, powder, cream, paste, ointment [6, 35, 36]. The highly acidic nature of the fruits and their exotic flavors are also valued in the food and cosmetics industry. Hippophae rhamnoides L. subsp sinensis and Hippophae rhamnoides L. subsp rhamnoides are the most used subspecies for commercial purposes [37]. Hippophae rhamnoides market products from L. range from oil, juice, and food additives to candies, instant beverages, pastes, purees, syrups, jams, pies, lotions, liqueurs, jellies, cosmetics, and shampoos [6, 21, 35, 38]. In Finland, the fruit of Hippophae rhamnoides L. is used as a nutrient in baby food, while India's Defense Research and Development Organization has set up a factory to produce a multi-vitamin herbal drink based on Hippophae rhamnoides L. juice for its military troops facing extremely low temperatures [39]. It is seen as a potential additive in the production of wheat bread [40].

In Ladakth, Hippophae rhamnoides L. thickets were cut during winter and placed on opposite banks of the river, and the thickets that turned into a long and thick ice cover over time were used as a bridge. Today, this bridge mastery has sunk into oblivion. It is preferred by blacksmiths as wood charcoal. Branches used as roofing material in building constructions are used for certain religious rites in Buddhism and are believed to drive away evil spirits [31].

Hippophae rhamnoides L., which usually harbors nitrogen-fixing actinomycetes in root nodules, is very useful for soil improvement [4, 5, 9, 34]. Its extensive root system is used for land reclamation and protection due to its tolerance to strongly eroded, nutrient-poor, and sometimes salty soils and drought, as well as being used as candara to prevent landslides and flooding. Hippophae rhamnoides L. is one of the most used species for afforestation of heavily degraded fields in Romania and is called 'the balm of degraded soils' [23]. Hippophae rhamnoides for the control of industrial dumps, soil erosion, and degraded soils, especially from coal mining, in Germany the use of L. began a long time ago. Apart from these, it can be planted around these areas to prevent the damage of stray animals and pedestrian movement to agriculture and planting areas [31].

Table 1: Pharmacological effects of Hippophae rhamnoides L.

Effect	References
Anti-inflammatory	24, 49
Antioxidant	50
Antibacterial	50,51
Cytoprotective	50
Antitumor	52–54
Anti-ulcerogenic effect	55
Hepatoprotective effect	56, 57
Improves alcoholic fatty liver disease	58, 59
Liver fibrosis treatment	60
Anti-atherogenic	61
Anti-hypertensive	51, 62
Cardiovascular protection	51
Regulating coagulation	51
Keratitis and dry eye treatment	63
Treatment of skin diseases (eczema, acne, psoriasis, dermatitis)	64
UV radiation shielding	65
Tissue regeneration, Burn, wound healing	66
Vaginal atrophy	67, 68
Antihyperglycemic	69
Treatment of acrylamide-induced neurotoxicity	70
Alzheimer's	71
Antidepressant	72
It prevents oxidative stress	73–75
Metabolic syndrome	76, 77

Hippophae rhamnoides L. has a positive effect on the health and development of newborn calves in nutrition [41]. It increases egg quality when used in the feeding of layer hens [42, 43]. Increases egg quality when used in the feeding of laying hens [43]. It has been observed that when used as a feed additive by reversing the low growth performances of broilers grown in severe climatic conditions and high altitude regions, it has been observed to increase live weight, and it has been reported that it reduces the death rate due to acidosis and coccidiosis [44]. The use of its oil for the treatment of gastric ulceration and erosions in dogs has resulted in positive results [45]. It is promising against gastrointestinal nematodes in small ruminants 46.

Hippophae rhamnoides L. contributed positively to aquaculture and production. Many formulations containing many additives have been developed to improve growth performance in aquaculture, but natural plant extracts and oils must promote growth and create strong immunity. For example; in Bayir, rainbow trout (Oncorhynchus mykiss), it was stated that the addition of 0.5% and 1% Hippophae rhamnoides L. to the diet revealed positive growth results [47].

Pharmacological effects

Hippophae rhamnoides L. has been scientifically analyzed and many of its traditional uses have been distinguished by pharmacological studies Table 1. No adverse effects were observed in acute toxicity studies with oral administration [48].

1.2. Chemical Content

Hippophae rhamnoides L may vary according to the plant's origin, climate, geographical location, plant

parts, fruit maturity, fruit size, harvest time, and extraction method 11, 28, 38, 78. Hippophae rhamnoides L. The fruit and leaves of mainly contain organic acids, vitamins, carotenoids, tocopherols, flavonoids, sterols, volatile compounds, oils, saturated and unsaturated fatty acids, sugar alcohols, minerals, amino acids, macro, and microelements Table 2 [14-17].

1.7.1. Vitamins
Hippophae rhamnoides L. fruits their high vitamin C content. The rate of vitamin C in fruits grown in the USA can reach up to 1550 mg/100g. It has a much higher vitamin C ratio than fruits that are considered high in vitamin C [85] *Hippophae rhamnoides* L. contains [86] Another vitamin found high in [86]. The amount of vitamin E in fruits reaches a maximum level of over 800 mg/kg from the 30th day to the 150th day after flowering and decreases over time in the following period [79]. Apart from these, it also contains vitamins A, B, and K [6].

1.7.2. Sugar
Glucose and fructose are the two main sugar groups found in *Hippophae rhamnoides* L. fruit. Fructose content varies between 0.2-3.5 g/100 mL and glucose content varies between 1.5-4.2 g/100 mL [87]. Apart from these sugars, it also contains sucrose, xylose, mannitol, ethyl β-D glucopyranose, sorbitol, xylitol, and methyl inositol sugars. The total amount of sugar in the species is between 9-25g/L [38].

1.7.3. Organic acids
The organic acids contained in it are; malic acid, quinic acid, citric acid, tartaric acid, and succinic acids. The malic acid content in fruit juice varies between 11-60 mg/L and quinic acid content varies between 7-49mg/L. Malic acid and quinic acid constitute approximately 98% of all fruit acids in fruit [87], [38].

1.7.4. Amino acids
It contains 18 of 22 known amino acids in *Hippophae rhamnoides* L. fruit. These; aspartic acid, serine, glutamine, glycine, alanine, cysteine, valine, tyrosine, isoleucine, methionine, proline, phenylalanine, histidine, lysine, threonine, and arginine [38].

1.7.5. Fatty acids
From a nutritional point of view, fatty acids have an important role in various metabolic and structural functions. The main component of cell membranes, they are responsible for the transport of vitamins and regulate the concentration of lipids in the plasma. It also produces compounds important for metabolisms such as fatty acids eicosanoids, eicosanoids, steroid hormones, and biliary acid [37].

From *Hippophae rhamnoides* L. 21-47% of saturated and 39-53% of unsaturated fatty acids are composed of fruits, especially in their seeds [21]. It is also rich in fatty acids including palmitic acid, oleic acid (omega-9), palmitoleic acid (omega-7), linoleic acid (omega-6), linolenic acid (omega-3), and phytosterols [4, 37]. *Hippophae rhamnoides* L.'s reputation is due to its seed oil enriched with essential fatty acids (omega-3 and 6) and high levels of omega-7 [37, 88]. Although the prevalence of fatty acids in different parts is well known, there may be differences depending on subspecies, harvest time, and isolation method [37]. *Hippophae rhamnoides* L. oil is the only oil that naturally provides a 1:1 ratio of omega-3:omega-6 (linolenic and linoleic acid, respectively). β-Sitosterol has been identified as the main component of phytosterols in the oil of *Hippophae rhamnoides L.* The β-carotene content in *Hippophae rhamnoides* L. oils acts as a quality indicator.

Seed oils contain high levels of unsaturated fatty acids. More than 73% of these unsaturated fatty acids are composed of linoleic and linolenic acids. Palmitic acid constitutes 38% and palmitoleic acid constitutes 14-59% of the pulp oil of the plant. *Hippophae rhamnoides* It is oleic acid, an important saturated fatty acid found in L. and it is found in approximately 13-19% of,, seed oil and 12-33% of pulp oil [21]. Oleic acid has an important place in the protection of cardiovascular diseases [37]. It is rich in *Hippophae rhamnoides* L oil and fatty acids and has various therapeutic benefits. There are prominent studies of *Hippophae rhamnoides* L. on vaginal atrophy, skin hyperpigmentation or sores, skin and mucus disorders, hypercholesterolemia, diabetes, and liver dysfunction [37]. It is a promising source of seed oil because of its high unsaturated fatty acid content, its seed, ultraviolet light absorption, and its emollient properties promoting healthy skin [21, 33, 68, 89]. Due to its high lipid content, the freezing point of unfiltered juice can be as low as -18.5 degrees. This juice is a very important advantage for storage, as it can maintain its liquid form even at sub-zero temperatures Table 3 [90].

1.7.6. Flavonoids
The flavonoids isolated from the orange-yellow to red fruit of *Hippophae rhamnoides* L. mainly contain various simple glycosides such as isorhamnetin, quercetin, kaempferol, myricetin, and syringin. Glucosides in its structure, rutinosides, sophorosides, α- rhamnosides, rutinosides, rhamnosides, quercetin other bioactive compounds such as cerebroside, oleanolic acid, ursolic acid, 19-alpha-hydroxyrimolic acid, succinic acid, 5-hydroxymethyl-2-furancarbox-aldehyde, cirsiumaldehyde, octacosanoic acid, isorhamnetin and 1-O hexadecanolenin are widely available [6, 16, 91-96].

Table 2: Major phytochemicals in *Hippophae rhamnoides* L. and their medicinal properties.

SBT phytoconstituents	Medicinal properties	References
Tocopherols	Acts as an antioxidant, minimizes lipid oxidation, helps relieve pain	[79]
Carotenoids	Acts as an antioxidant and aids collagen synthesis and epithelization	[80]
Vitamin K	Prevents bleeding, promotes wound healing, anti-ulcer effect	[81]
C vitamin	Acts as an antioxidant and maintains cell membrane integrity, accelerates collagen synthesis	[79]
Vitamin B complex	Stimulates cell repair and nerve regeneration	[81]
Phytosterols	Improves skin microcirculation, anti-ulcer, anti-atherogenic, and anti-cancer, regulates the inflammatory process	[82]
Polyphenolic compounds	Antioxidant, cytoprotective, cardioprotective, wound healing	[50]
Polyunsaturated fatty acids (PUFA)	Immunomodulatory, neuroprotective, anti-tumor	[19]
Organic acids	Reduce the risk of heart attack and stroke, anti-ulcer, wound healing, anti-arthritic	[19]
Coumarins and triterpenes	Control of appetite, sleep, memory, and learning	[83]
Zinc	It strengthens blood circulation, anti-tumor aids in cell proliferation, acts as a cofactor for enzymes, and increases the use of vitamin A.	[84]

Table 3: Fatty acid composition of *Hippophae rhamnoides L.* oil.

Common Name	Systematic Name	Amount (%)	Symbol	Omega family
Saturated fatty acids				
Palmitic acid	hexadecanoic acid	30–33	C16:0	-
Stearic acid	Octadecanoic acid	<1	C 18:0	
Unsaturated fatty acids				
Palmitoleic acid	(Z)-9-exadecenoic acid	30–35	16:1	7
oleic acid	(Z)-9-octadecenoic acid	14–18	18:1	9
Linoleic acid (LA)	(Z, Z)-9, 12-octadecadienoic acid	5–7	18:2	6
α-Linolenic acid (ALA)	(Z, Z, Z)-9, 12, 15- octadecatrienoic acid	30	18:3	3
γ-linolenic acid (GLA)	(Z, Z, Z)-6, 9, 12- octadecatrienoic acid	35	18:3	6
Gondoic acid	(Z)-11-eicosenoic acid	2	20:1	9

1.7.7. Micro and Macro Elements

Although the most abundant element in the fruit is potassium, nearly 30 macro and microelements such as iron, nitrogen, magnesium, copper, zinc, nitrogen, manganese, calcium, phosphorus, magnesium, and sodium have been detected [97]. The maturity of the plant also affects the number of elements [38].

The juice also contains an oil phase and is called pulp oil. In this phase, it contains in fruit carotenoids are beta-carotene, lutein, zeaxanthin, and lycopene. Alpha-tocopherol is the main vitamin E compound. The content of tocopherol and tocotrienol in the fruit varied between 100-300 mg/100g [28, 79]. The fruit is also rich in phytosterols (340-520 mg/kg), the main sterol as β-sitosterol makes up 57-83% of the total sterols compound.

The purpose of this review is to give information about the fruit and plant of *Hippophae rhamnoides* L.

especially to scientists who are interested in health and agriculture, about botany, chemical content, medicine, traditional and current use.

2. Discussion

Hippophae rhamnoides L. are rich in carbohydrates, protein, organic acids, amino acids, and vitamins, which have strong biological activity. It is also extremely important in that it contains a wide variety of substances such as intense carotenoids, vitamin E, dietary minerals, β- sitosterol, and polyphenolic acid. Although wild plant Hippophae rhamnoides Due to the nutritional, medical, and economic potential of L, it's scientific research and commercial importance are increasing day by day, and the excess of the substances it contains makes this plant not only used in the field of health but also agriculture, cosmetics, food, etc. sectors have also been evaluated. The use of Hippophae rhamnoides L. in various forms as a natural product has been increasing in recent years due to the shift of consumers' attention to natural products with functional properties. Hippophae rhamnoides L. prevents the issuance of a standard prescription about the nutritional value and chemical composition of bioactive substances, which vary according to the origin of the plant, climate, geographical location, plant parts, fruit maturity, fruit size, harvest time, and extraction method. For this reason, Hippophae rhamnoides L.'s nutritional value and chemical composition. The literature describing it is both scattered and limited. As a result, it is extremely important to standardize the products to be obtained with this plant. The mechanism of action of targeted studies with concentration, isolation of pure substances, further production by culture, lethal dose (although not reported), effective dose and bioavailability mechanisms need to be realized in the future.

3. Conclusions

Within the scope of our literature review, we think that the sustainable harvest and production potential of this species can increase the local economy and have a serious impact on the socio-economic and ecological balance. The fact that the sharp spines on the Hippophae rhamnoides L. bush are difficult to harvest increases the importance of breeding studies on the plant. The harvested fruit of Hippophae rhamnoides L. can be used to produce beverages and natural food ingredients, and can be used to produce seed oil, creams, shampoos, soaps, etc. can be used for cosmetic products such as Due to the high nutritional value and increasing demand of the fruits of Hippophae rhamnoides L. it can be recommended to investigate them for use in different food products with high added value. Hippophae rhamnoides L. leaf, fruit pulp, and seed residues from the juice and oil extraction of Hippophae rhamnoides L. can be turned into a large amount of "value-added waste" product. Its leaves have great potential to support the food industry and human health. However, due to the nutrients contained in the waste products, it can potentially be used as a feed additive for animals in livestock. It is recommended to increase medical and therapeutic R&D researches for reducing different types of acute and chronic diseases with components of Hippophae rhamnoides L. with strong biological activity.

Limitations of the Study
Bioaccessibility and potential applications in female reproduction.

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