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Aim and Scope

Quality of Life publishes original research papers and reviews and aims to provide a forum for the rapid dissemination of significant novel research in the various disciplines encompassing the Science and technology of food, Public health engineering, Sanitary inspection and control, Environmental and public health. Topics covered by the journal include:

- Dietetics; Nutrition principles applied to foods
- Food Technology; Production and preservation of foodstuffs; Food preservation technique
- Industrial microbiology; Science and technique of applied microbiology; Applied mycology
- Public Health, environment and hygiene
- Hygiene of air, water, soil; Pollution and its control
- Water; Sanitation; Water treatment
- Sewage; Treatment, disposal, utilization of sewage
- Urban hygiene; Wastes; Refuse; Rubbish; Garbage; Collection and disposal of town wastes
- Measures against industrial and other nuisances
- Occupational health hazards; Occupational health and hygiene
- Ecology; Environmental engineering, sustainability and health
- Related topics

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Dear readers,

it is my pleasure to present you the new issue of Quality of Life magazine and to thank you for your trust. In 2023, we continued to work to provide our readers with high-quality and interesting research papers in the various disciplines encompassing the Science and technology of food, Public health engineering, Sanitary inspection and control, Environmental and public health in our country, the region as well as at the international level. The topics covered in this issue of the Quality of Life magazine are diverse and address current issues in health, food technology, and environmental protection.

The journal Quality of Life was registered in the Register of Public Media in 2010 by the Decision of the RS Ministry of Education and Culture. Over the past years, this journal has published a large number of original scientific research papers, communications and review papers. Quality of Life is published twice a year by Pan-European University "Apeiron" Banja Luka. All the papers published so far have undergone a thorough review by the editorial board and the reviewers, made up of experts from both RS/B&H, the surrounding and other countries, from proven and recognized university and research institutions. As a result of a professional approach to selecting and reviewing papers, and raising the quality of the journal, Quality of Life was classified in the first category of journals in 2019 by the Ministry of Education and Culture. We are proud to say that Quality of Life has been well received by the scientific and the general public in a relatively short period, which gives the editorial board a strong motivation for further work. The editorial team would like to thank our many reviewers who helped to maintain the journal standard; our many authors who submitted their best work to the journal; and, most importantly, our readers for your continuing support. I assure all our readers that our consistent efforts will be aimed toward increasing the visibility, impact, editorial cycle time, citations and overall quality of our journal. We very much look forward to strengthening the reputation of our publications, and we want to attract more higher-quality submissions.

As always, I would like to thank the authors for their contributions to this issue of the magazine, and express great gratitude to all the reviewers who participated in the editorial process by providing valuable feedback to the editors and authors in a timely manner. We also extend our heartfelt thanks to the numerous authors who submitted their best papers to the magazine, and most importantly, to our readers for their continued support.

In the spirit of continuous improvement, any constructive input on streamlining our processes is very welcome. Please help us grow by citing articles that you read in Quality of Life. We look forward to receiving your contributions in the near future.

Editors

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Original scientific paper

Optimization of Oil Extraction Process from White Mustard Seeds Using Response Surface Methodology

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ABSTRACT: In this study, response surface methodology (*RSM*) was used for the determination of the effect of two process parameters (extraction temperature and extraction time) and their interaction on the yield of the total extract from white mustard seeds (*Sinapis alba l.*), as well as the creation of a mathematical model, 3D response surface, and the establishment of an optimal extraction region. Ethanol 96% as a green solvent was employed to separate biological compounds from white mustard (*Sinapis alba l.*) seeds by applying ultrasound-assisted extraction (*UAE*). *UAE* was performed at the temperature of 25, 30, and 35°C for a duration of 30, 60, and 90 min. *UAE* as a modern extraction technique showed great performance, while the ethanol solvent provided a high yield of compounds. The utilized *RSM* design adequately fit the experimental data with a high coefficient of determination (R^2=0.9365) and low mean absolute error (*MAE*=1.12242). Estimated effects for the yield of the total extract showed that the extraction time, the temperature, and the interaction between time and temperature influenced positively, while the time-squared and the temperature-squared influenced negativity on the yield of the total extract. Analysis of variance showed that 2 effects have *P*-values less than 0.05. The optimal yield of the total extracted oil was 15.19% at the temperature of 35°C for a duration of 70.3 min.

Keywords: white mustard seeds, extraction, *RSM* optimization, influence of process parameters, 3D response surface.

INTRODUCTION

Plants are sources of important bioactive compounds with diverse structures. Natural products strongly impact human culture and have been used as cosmetics, pigments, and pharmaceuticals (Alamgir, 2018). The extraction processes of natural products mainly have negative effects on the environment. The challenges launched by the competitiveness of the globalized market and environmental protection strongly require technological innovations. In this context, the development and use of green technologies for the separation of bioactive compounds from plant materials have essential meaning (Soquetta et al, 2018).

Different solid-liquid extraction techniques are used for the separation of biologically active compounds from white mustard (Barthet & Daun, 2002; Boscariol Rasera et al, 2019). The traditional solid-liquid extraction methods such as maceration (Swarcewicz et al, 2013) and Soxhlet extraction (Stamenković et al, 2018), have been associated with high consumption of organic solvents that limit the application of the extracts due to solvent toxicity. Additionally, these methods include high energy and time consumption (Picot-Allain et al, 2021). Ultrasound-assisted extraction (*UAE*) represents a sustainable alternative. *UAE* has certain advantages in terms of equipment cost, energy, and time consumption, application of green solvents, isolation of bioactive compounds under atmospheric pressure, etc (Wen et al, 2018). The application of ultrasound is relatively simple, flexible, and requires less investment compared to other extraction techniques. Therefore, this technique is characterized as green with low negative effects and impacts on the environment. *UAE* allows the use of all solvents, such as water or organic solvents (Chemat et al, 2017). However, according to the trends of green chemistry as solvents are used water, or a mixture of ethanol-water for the extraction of polar and oils for the extraction of non-polar compounds (Chemat et al, 2019). Ethanol (*EtOH*) is one of the most suitable solvents for green extraction. *EtOH* has a low vapor

pressure, which leads to uncomplicated evaporation, and consequently lower inhaled quantities. *EtOH* is also cheaper than other organic solvents which promotes its use for the extraction of large amounts of natural products (Dogan et al, 2020).

Optimization, analysis, and control of extraction processes of bioactive compounds from plant materials are unavoidable phases for reducing energy exhaustion and reducing the influence on the environment (Iglesias-Carres et al, 2019; Rezazi et al, 2017). In addition, the use of natural extracts is becoming more popular than the use of chemically synthesized drugs. Conventional optimization involves the one-factor-at-time testing effect of operating parameters, while the other parameters are kept constant (Abdel-Rahman et al, 2020). However, statistically designed experiments in which several factors are varying simultaneously are more efficient when studying two or more factors (Li et al, 2016). In the last decade, response surface methodology (*RSM*) has been often used for modeling and mostly for optimization of various extraction processes and food manufacturing processes. This methodology as a statistical technique is useful for the determination of the influence of independent process parameters on dependent parameters. However, it is not able to use outside of the studied regions (Kasapoğlu et al, 2023; Krongrawa et al, 2022; Milić et al, 2013).

In this study, in order to optimize the ultrasound-assisted extraction of the yield of total separated biological compounds from white mustard seed by using ethanol 96%, as well as to determine and statistically verify the influence of two extraction process parameters on the investigated dependent variable, response surface methodology was implemented.

MATERIALS AND METHODS

Materials

The white mustard (*Sinapis alba l.*) seeds used in this study as a raw material for isolating natural compounds were purchased from Natural Pharmacy & Healthy Food (Skopje, N. Macedonia). The dry raw material was treated with a manual mince machine through holes with a diameter of 0.5 mm (particle size<0.5 mm), to homogenize the raw material and increase the contact surface. The material was stored in a plastic closed container at the ambient temperature of 20°C.

Ultrasound-Assisted Extraction Process

Ultrasound-assisted extraction (*UAE*) was performed in an ultrasonic bath (Ei Niš OOUR-RC). Ethanol 96% as a green solvent was used for the separation of biological compounds from white mustard (*Sinapis alba l.*) seeds. *UAE* was performed at a constant ultrasound frequency of 40 kHz and a constant module of sample-to-solvent ratio (raw material [g]:solvent [mL]=1:30). The white mustard seeds 3.00 g and 90 ml of ethanol 96% were placed into an Erlenmeyer flask with a volume of 300 mL. The flask was placed in the center of the ultrasonic bath. After the extraction process, the mixture was immediately filtered through a laboratory filter paper (pore size of 25 μm) using a vacuum filtration technique. The solvent was evaporated by using a rotary vacuum evaporator (Büchi R-200) at the temperature of 40°C until the entire solvent was removed from the extract. The obtained extract was dried in a laboratory furnace (Instrumentaria ST-06) at the temperature of 60°C and ambient air to constant mass. The dry residue represented the total extract from white mustard (*Sinapis alba l.*) seeds. *UAE* was employed because it is an effective technique for the extraction of compounds from plant materials. The acoustic cavitation enables better penetration of the solvent into the sample, increasing the extraction yield of target compounds. The efficiency of *UAE* depends on operation parameters, such as solvent concentration, solvent-to-solid ratio, extraction

temperature, extraction time, and ultrasound frequency, as well as their interactions. Hence optimization is a very important phase in increasing product yield (Xu et al, 2016). Therefore in this study, the effects of extraction temperature and extraction time were investigated. *UAE* was carried out at the temperature of 25, 30, and 35°C for a duration of 30, 60, and 90 min.

The yield of the total extract was mathematically calculated by the equation:

$$Y_{total} = \frac{m_e}{m_s} 100 \quad (1)$$

where Y_{total} is the yield of the total extract [%], m_e is the mass of obtained extract [g], and m_s is the mass of raw material [g].

A non-linear equation was employed to develop the ultrasound-assisted extraction process kinetics model. The kinetics was mathematically defined by:

$$Y_{total} = \frac{at}{1 + bt} \quad (2)$$

where Y_{total} is the predicted yield of total extract, and a and b are regression coefficients. Regression coefficients were determined by using MATLAB-Curve Fitting.

RSM Design and Statistical Analysis

The response surface methodology (*RSM*) is a set of mathematical and statistical techniques useful for developing, improving, and optimizing processes. *RSM* is based on fitting experimental values using polynomial equations. This method is applied to investigate the influence of process parameters on one or more responses. *RSM* was employed to determine the effects of extraction time t and extraction temperature T and their interaction on the yield of the total extract Y_{total} from white mustard (*Sinapis alba l.*) seeds using ethanol 96%. The *RSM* model was developed using Statgraphics Centurion XV. The 3^2 full factorial design was employed for the optimization of the process. The experimental data for the yield of total extract was fitted using a second-order polynomial equation and the regression coefficients were calculated. The model was mathematically defined using the following equation:

$$Y_{total} = k_0 + k_1 t + k_2 T + k_3 t^2 + k_4 tT + k_5 T^2 \quad (3)$$

where Y_{total} is the response or the predicted yield of the total extract [%], t is extraction time [min] and T is extraction temperature [°C]. The adequacy of the applied method was determined by the coefficient of determination (R^2) and the mean absolute error (*MAE*) (Kuvendziev et al, 2014):

$$R^2 = 1 - \frac{\sum_{i=1}^{n} (Y_i - Y_{ai})^2}{\sum_{i=1}^{n} (Y_{ai} - Y_m)^2} \quad (4)$$

$$MAE = \frac{1}{n} \sum_{i=1}^{n} |Y_i - Y_{ai}| \quad (5)$$

where n is the number of points, Y_i is the predicted value, Y_{ai} is the experimental value, and Y_m is the average of the experimental values.

RESULTS AND DISCUSSION

Effect of Process Parameters

From several operating parameters to influence the yield of total extract, the temperature T and the extraction time t were determined as independent operating parameters for optimization of the ultrasound-assisted extraction of biological compounds from white mustard seeds using a green polar solvent.

In order to study the effect of the temperature (25-35°C) and extraction time (0-90 min) on the yield of total extract, other parameters were kept fixed. The modeled kinetics of the studied process is given in Figure 1. The regression coefficients of the kinetic models are given in Table 1.

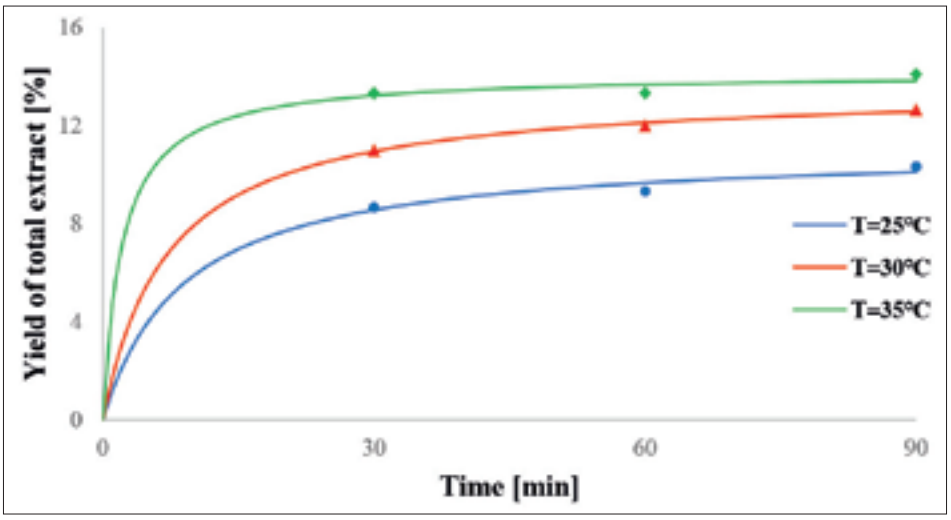

Figure 1. Kinetic of the yield of total extract from white mustard seeds

Table 1. Regression coefficients of developed kinetic models

T [°C]	*a*	*b*	R^2
25	1.2460	0.1122	0.9974
30	1.8950	0.1396	0.9998
35	6.7280	0.4750	0.9985

The experimental results suggested that the extraction time and extraction temperature have a greatly positive effect on the yield of biological compounds from white mustard (*Sinapis alba l.*) seeds. *RSM* was employed for creating the optimization model for the investigated system.

RSM Optimization

RSM was used for the determination of the influence of working parameters and their interaction on the yield of the total extract, as well as the creation of a mathematical model, 3D response surface, and the establishment of an optimum extraction region. The Pareto chart (significance level, α=0.05) of the importance and influence of the independent operating parameters (*t* and *T*) on the Y_{total} is presented in Figure 2. Each of the estimated effects is given in Table 2.

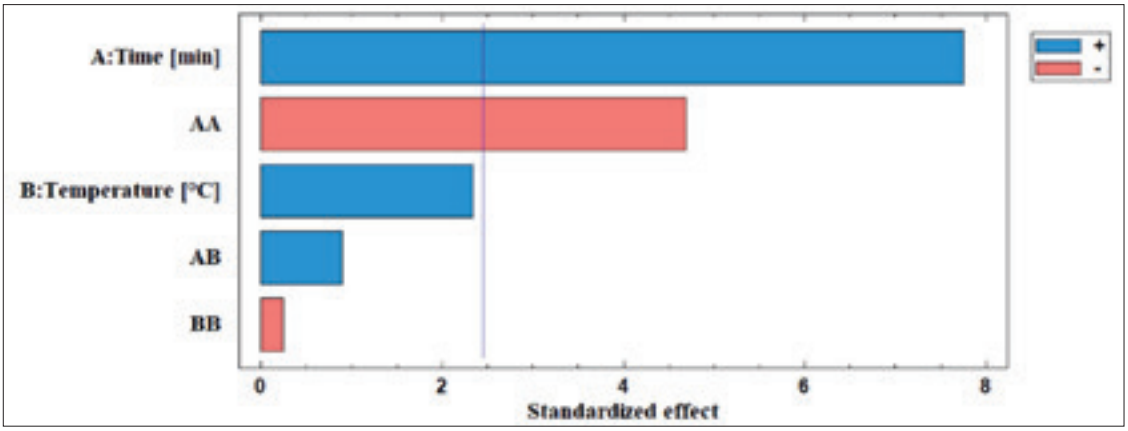

Figure 2. Pareto chart of standardized effect of studied experimental factors for ultrasound-assisted extraction, $Y_{total}=f(t,T)$

Table 2. Estimated influence of operating parameters on Y_{total} for *UAE*

Variables	Estimated effect
Average	12.1001
Time	11.2966
Temperature	3.10675
Time-squared	-11.46
Temperature-squared	-0.56025
Time x Temperature	1.59525

The Pareto chart showed that the extraction time (A), the temperature (B), and the interaction between extraction time and temperature (AB) influence positively, while the time-squared (AA) and the temperature-squared (BB) have a negative influence on the yield of the total extract. Analysis of variance (AVONA) which tests the statistical significance of each effect by comparing the mean square against an estimate of the experimental error, showed that 2 effects (A and AA) have *P*-values less than 0.05. The impacts of the extraction time and the temperature on the response of interest are given graphically in Figure 3.

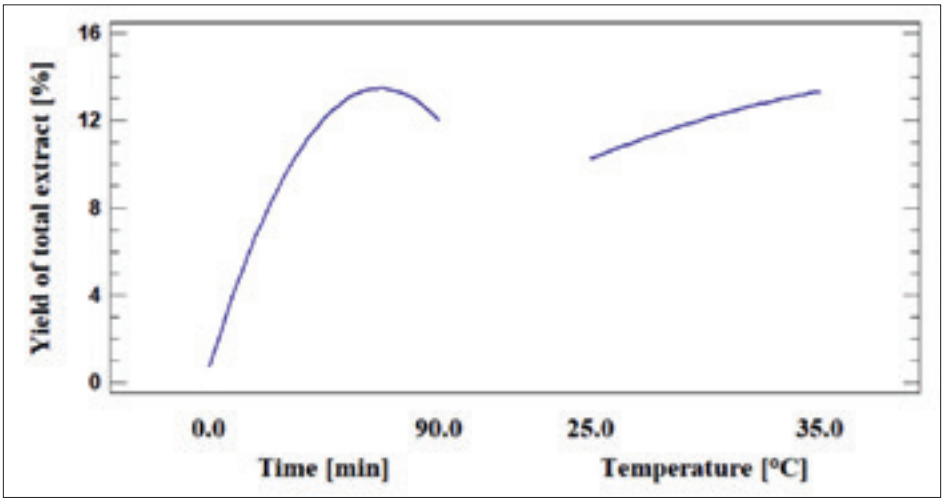

Figure 3. Main effects plot for the yield of total extract

The second-order empirical equation was utilized for the mathematical definition of the dependence of the yield of the total extract on the extraction time and extraction temperature according to Equation 3. The regression coefficients are given in Table 3.

Table 3. Regression coefficients of the *RSM* model

Coefficient	Value
k_0	-13.8972
k_1	0.273834
k_2	0.82345
k_3	-0.00282963
k_4	0.003545
k_5	-0.011205

The standard error of the estimate showed the standard deviation of the residuals was 1.88074, and the mean absolute error (*MAE*) was 1.12242. The *RSM* provided an adequate fitting of experimental data

with a high coefficient of determination (R^2) of 0.9365. In an aim to graphically demonstrate the influence of investigated process parameters on the yield of total extract, the 3D response surface was created (Figure 4).

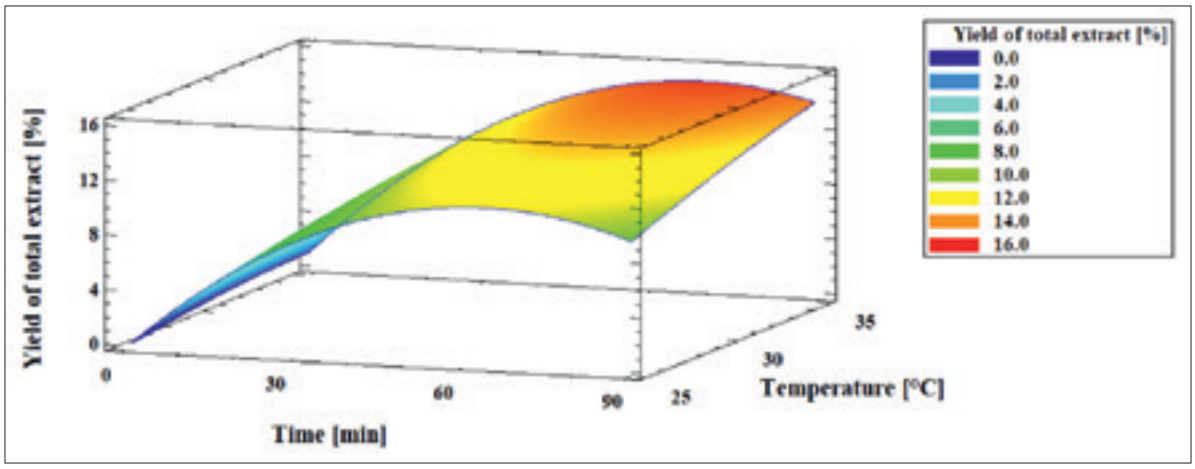

Figure 4. Estimated 3D response surface for the ultrasound-assisted extraction of the yield of total extract using ethanol 96%; $Y_{total}=f(t, T)$

The 3D response surface showed that in the observed ultrasound-assisted extraction system, the investigated operating parameters have significant effects on the total separated compounds from white mustard seeds, extracted by using green solvent. The developed 3D response surface showed that extraction time has a high effect on the yield of total extract in the first 30 minutes i.e. washing step. The generated response graph demonstrated that in the diffusion step, increasing the operating temperature in the range of 25–35°C results in a linear increase in the yield of the total extract. This phenomenon is not detected by the extraction time increasing.

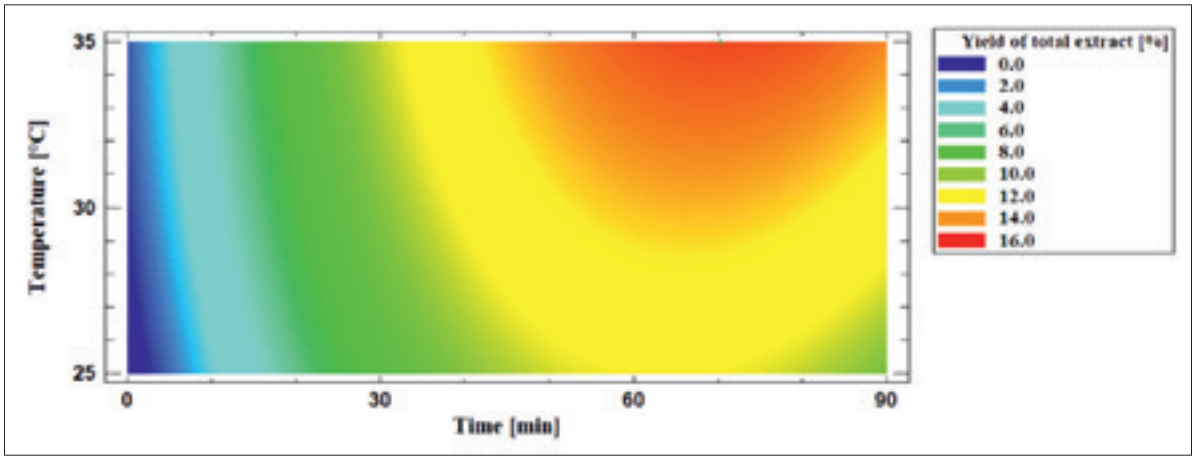

Figure 5. Contours of an estimated response surface for the *UAE*; $Y_{total}=f(t, T)$

The created contours of the estimated response surface (Figure 5) show that the optimum value of yield of the total extract is 15.19% at the temperature of 35°C and extraction time of 70.3 min.

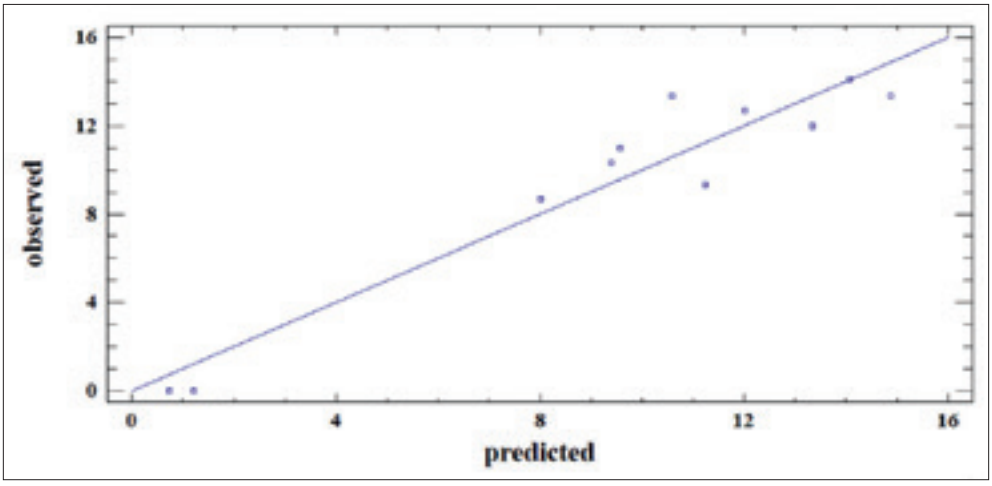

Figure 6. The plot of *RSM* predicted versus observed values for *UAE*; $Y_{total}=f(t, T)$

The *RSM* was applied for the prediction of the actual yield obtained from white mustard seed. The comparison is given in Figure 6.

CONCLUSION

The process of ultrasound-assisted extraction of biological compounds from white mustard seed using green solvent (ethanol 96%) was investigated and optimized by observing the effects of extraction time and temperature on the yield of the total extract. *UAE* as a modern extraction technique showed great performance, while the ethanol solvent provided a high yield of compounds. From a technological point of view, lower temperatures and shorter time of extraction were investigated. The *RSM* provided an adequate fitting of the experimental data with a high coefficient of determination (R^2=0.9365) and low mean absolute error (*MAE*= 1.12242). The model showed that the extraction time is more important than the extraction temperature. However, these parameters had a complex impact. The optimal yield of the total extracted oil was 15.19% at the temperature of 35°C for a duration of 70.3 min.

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Original scientific paper

Indoor Air Quality Monitoring in Akure, Ondo State, Nigeria

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ABSTRACT: Using the Canāree A1, a low-cost monitoring device made by Piera System, Canada, variations in Particle Count (PC) and Particulate Matter were observed in a building residence of five rooms in Akure, Nigeria (two living rooms, two bedrooms, and one kitchen) in both January and February 2022. The average $PM_{2.5}$ and PM_{10} levels in all rooms were above the World Health Organization (WHO) guidelines for 2021, which were: $PM_{2.5}$ - Annual (5 µg/m^3), 24 h (15 µg/m^3), and PM_{10} - Annual (15 µg/m^3), 24 h (45 µg/m^3). Rooms A (the first sitting room) and C (the kitchen) were found to have greater PC and PM values than the other rooms. Room A had the greatest $PC_{1.0}$ level, however, $PC_{5.0}$ was also discovered to be high. Based on the volume of activities, PM_{10}, $PM_{5.0}$, and $PM_{2.5}$ were the main air pollutants in Akure. These results indicate considerable effects from both indoor and outdoor activity, two key sources. During the duration of the study, certain residents of the building frequently complained of having a cough, a running nose, and other ailments. These results indicate considerable impacts from both indoor as well as outdoor activities. During the duration of the study, certain residents of the residence often reported having a cough, a running nose, and other ailments.

Keywords: PM10, PM2.5, PC1.0, Indoor, Kitchen, Low-cost sensor.

INTRODUCTION

According to the World Health Organization (WHO, 2021), access to clean air is a fundamental human right. But this seems to be a dream. Many factors make it unclean. Indoor Air pollution (IAP) is one of them. The biggest environmental health risk and a significant contributor to noncommunicable diseases (NCDs) like heart attacks and stroke, air pollution persists to pose a danger to individuals around the globe. Approximately 7 million individuals die prematurely every year as a consequence of outdoor and indoor air pollution, and millions more get sick from breathing it in, according to the WHO. In poor countries, much over half of these casualties take place. Large amounts of particulate matter (PM) of different sizes contribute to air pollution. Examples of particulate matter (airborne liquid or solid particles) include dust, pollen, mold, smoke, metals, bacteria, and viruses (Figure 1). When exposed for a short time or a long time, a few of these particles may be harmful to health. To protect individuals from poor air quality and pandemics like SARS-CoV-2, it is crucial to understand the size of these different types of particulate matter. PM, especially 'fine' PM, can penetrate the lungs and the bloodstream and cause problems with the organs. It causes cardiovascular and respiratory conditions, low moods, and childhood growth retardation (WHO, 2021). SARS-CoV-2, the virus that causes COVID-19, is a very tiny virus. It typically has a diameter between 0.06

and 0.14 microns. Viruses and ultra-fine dust, which range in size from $PM_{0.3}$ to $PM_{0.1}$, include the smallest particles (International Enviroguard, 2021)

Figure 1: Pictorial Diagram showing the diameter of the Particulate Matter

Due to the adverse effects of air pollution on health, the WHO recommended standards for specific pollutants to assist nations in constructing air quality that protects residents. In light of a review of the publications between 1987 and 2005, the 2021 standard was issued as an addendum to the earlier ones. Table 1 contains a list of the PM modifications.

Table 1: Update on the Particulate Guidelines of PM

Pollutant	Average time	2005 Guideline	2021 Guideline
$PM_{2.5}$ (µg/m^3)	Annual	10	5
	24 h	25	15
PM_{10} (µg/m^3)	Annual	20	15
	24 h	50	45

There is a good chance that human actions will have detrimental effects on human health and the environment (Trippetta et al., 2013). Research has shown that there is increased emission of different gaseous pollutants and particulate matter as a result of fast industrialized growth (Jain and Palwa, 2015).

Research has linked the escalating industrialization trend to the causes and sources of air pollution (Jain and Palwa, 2015). In some societies, the combustion of garbage, trash, and other solid waste is still a common trend. In all locations in Auckland, the most prevalent contributors of $PM_{2.5}$ are the burning of biomass and vehicular fumes (Davy et al., 2017; Bulto, 2020). In addition to these, brick kilns, rice and pulse (beans) grinding mills, dust from highways and building sites, dust from chicken farms, and harmful gases from industries are causes of air pollution, according to Huda et al. (2018). The study by Knight et al. (2021) on the Impact of Misting Systems on Local Particulate Matter concluded that misting systems in-

creased PM concentrations. Njoku et al. (2016) and Ibe et al. (2020) list increasing vehicle traffic, biomass fuels, the usage of electricity generators, and leaks from open burning and flare stacks as additional sources of air pollution. Other man-made sources include frying, using pesticides and insecticides, lighting candles, smoking cigarettes, vacuuming, and so on. Volcanic activity, wind-borne dust, suspended soils and dust, sea-salt spray, wildfires, and plant emissions of volatile organic compounds are examples of natural sources (Mackenzie and Turrentine, 2021).

The environment must be checked both inside and out to see if it is below WHO standard limits in order to reduce air pollution. In the past, complex technologies were employed to detect pollution levels, but wearable devices and citizen science projects employing inexpensive technology have rescued the day for individuals with little financial resources (Abulude, 2021). Air sensor networks, including WiFi-distributed networks of sensors, have been devised and developed employing phone apps to collect and make available real-time data on air quality (Jiao et al., 2016). Cell phones are widely used, making them an ideal alternative for monitoring personal exposure (Abulude et al., 2022a). Alternative methods used to measure air quality include mass spectrometry, various low-cost sensor types (which are sometimes combined to form electronic noses), and optical classification. Numerous quantitative networking based on mass spectrometry is typically sensitive and selective, however, despite the considerable effort being made to build portable systems, they are limited in mobility and expensive due to suction technology (Napier et al., 2021).

Nigeria's score of 152nd on the Global Climate Risk Index for Air Quality raises concerns for the country's environmental security (Abulude et al., 2022b). To monitor indoor pollution and its causes, Nigeria, unfortunately, lacks a national program of air quality monitoring stations. In order to do this, a CanreeTM low-cost Intelligent Particulate Sensors (IPS) network was set up in a four-bedroom cottage in Akure, the capital of Ondo State in Nigeria. IPS is precise, straightforward, affordable, and widely used. In contrast to previous inexpensive PM sensors, it detects "extremely fine particles" less than 1.0 microns and reports particle size, and counts in real-time at little power. It could be utilized in a variety of circumstances because it can assess up to seven particle sizes ($PM_{0.1}$, $PM_{0.3}$, $PM_{0.5}$, $PM_{1.0}$, $PM_{2.5}$, $PM_{5.0}$, and PM_{10}). Last but not least, the use of AI/ML algorithms makes it simple to identify sources of pollutants, for example, cooking, vaping, and cigarette smoke. In this region of the world, IPS is being utilized for the first time to track indoor air pollution. The purpose of this research is to present the results of an evaluation of a four-bedroom apartment over the course of one month, including particle counts, particulate matter, and sources of air pollution. As a result, the study's goals were to evaluate the concentrations of PC and PM, to ascertain the sources of PM to each room, to learn the connections between PC and PM, and to highlight the effects of each room's sources on PM.

MATERIALS AND METHODS

Nigeria, a West African nation with 36 states and the Federal Capital Territory, has Abuja as its capital. Africa's most populous nation is Nigeria. According to the World Bank (2020), Lagos is the nation's most significant commercial and industrial hub. Nigeria borders Niger to the north, Chad and Cameroon to the east, the Gulf of Guinea to the south, and Benin to the west. Nigeria's terrain is characterized by plateaus and hills in the middle and lowlands to the north and south. The Niger-Benue basin, Lake Chad basin, and Gulf of Guinea basin are Nigeria's three principal drainage basins. The Niger River inspired the naming of the nation. The two main rivers in the nation are the Niger River and the Benue River. The soil in Nigeria is not as good as soils elsewhere in the world. The Oji River, the Afam, Sapele, and Lagos thermal power plants, as well as the dams at Kainji, Shiroro (Niger State), and Jebba (Kwara State), provide hydroelectricity (firewood and charcoal). All of these support the nation's energy supply (Udo et al., 2021; Abulude et al., 2022b).

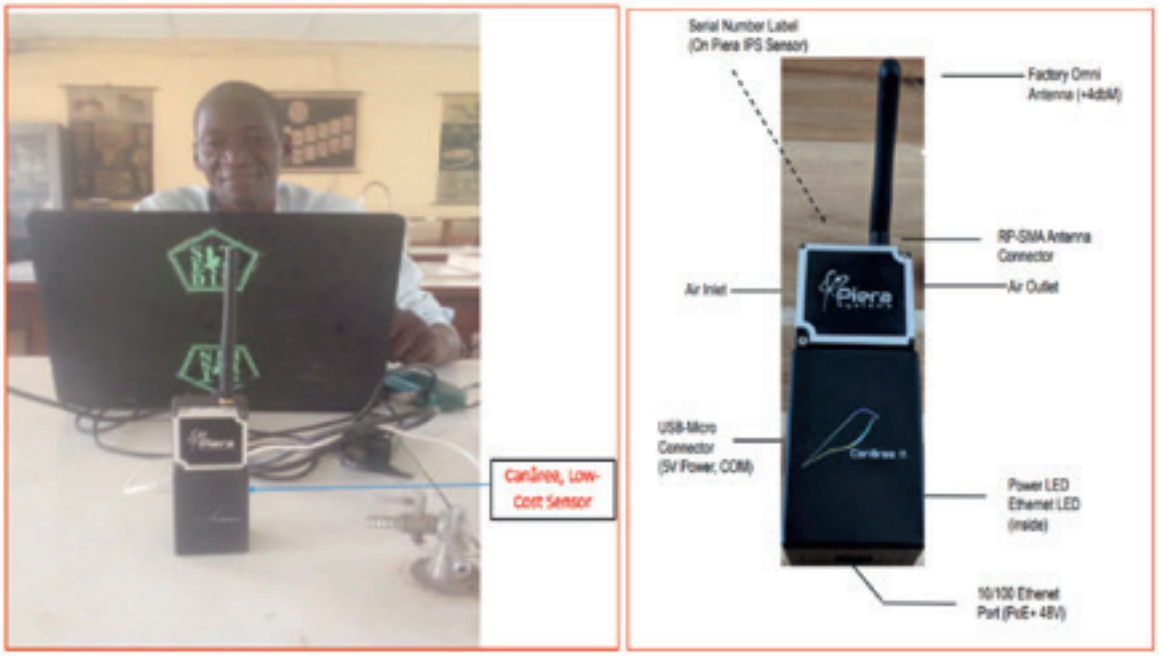
The nation has a tropical climate with distinct rainy and dry seasons according to the region. The southeast is generally warm and muggy, while the southwest and farther interior are dry. October to March, make up the dry season, while the rainy season is from March to September. The center region experiences rainfall totals between 1000 and 1500 mm (40 and 60 inches), exceeding 2000 mm (80 inches) in the south, and exceeding 3000 mm (120 inches) in the far southeast. Depending on the climatic zone, temperatures, which range from 12 to 40 degrees Celsius, vary significantly.

Nigeria is the most populated nation in Africa. Its population totals 211 million, and its total land area is 923,769 km^2. The city of Akure, the capital of Ondo State in southwest Nigeria, was the subject of this study.

The building chosen for the study is a four-bedroom, two-parlor bungalow apartment made of cement that is home to a five-person household. The household makes a middle-class living. The property's floors are tiled consistently. The building's perimeter is made up of unpaved roads and is 100 meters from a busy thoroughfare (8 m). During the entire period, the structure was exposed to outdoor air. A separate room in the building houses the kitchen and pantry (3 x 3 x 3 m^3). The kitchen is usually used for cooking by at least three people.

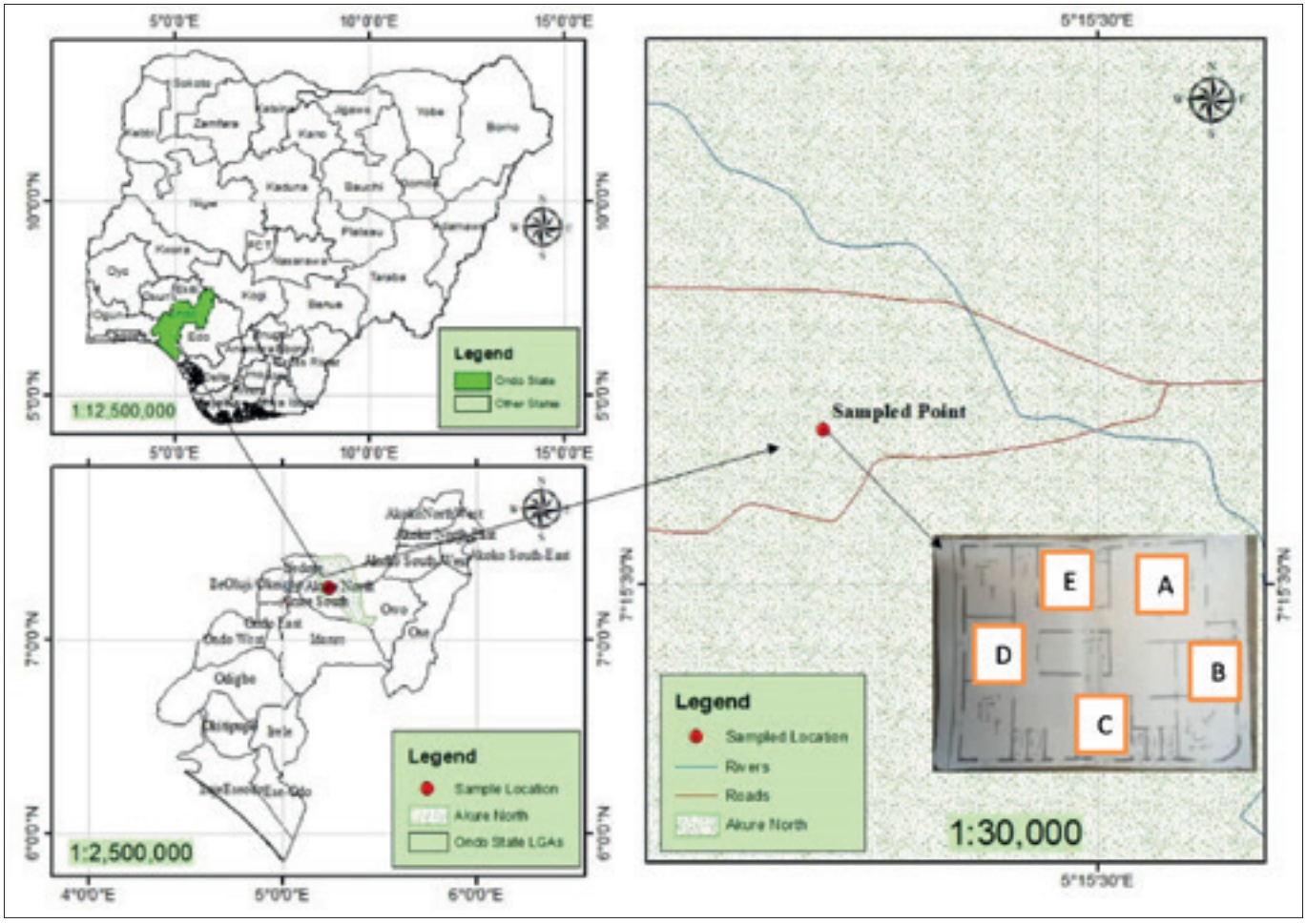
Every single kitchen window and the storeroom has three doors (two for the kitchen and one for the pantry). The windows and doors are typically left open while cooking. No room in the structure has a kitchen heaters system, and there is no air exhaust in the kitchen. Amongst cookware are gas cookers, stoves, and ovens that use gas, kerosene, or electricity. Every day, cooking activities like frying, grilling, boiling, and oven baking take place in the kitchen two to four times. In general, cooking approximately take place within 50 minutes.

The monitoring device (Canāree A1) utilized in this investigation is shown in Figure 2. The measurement took place at Akure, Ondo State, in a four-room house from January 5 to February 2 of 2022. Two living rooms, a kitchen, and two rooms were used for the research (Figure 3). There are various man-made activities that took place indoors, including candle combustion, cooking, sweeping, using insecticides (aerosol and coil), smoking cigarettes, and applying perfume. Within the study area, sweeping, burning of trash dumps and biomass, vehicle, pedestrian, and animal movements are a few examples of outdoor activities (Figure 4).



a) b) **Source:** This Study (2022)

Figure 2: a) Photograph Showing the Low-Cost Sensor during Monitoring of the Indoor Pollution b) Picture of the Sensor depicting the Parts



Source: This Study (2022)

Figure 3: Map Showing Nigeria, Ondo State, and the Sampling Point and the Sketch of the Building with Marked Rooms (A- 1st Living Room, B- 2nd Living Room, C- Kitchen, D- 1st Room, And E- 2nd Room).

When using the equipment, the manufacturer's procedures were meticulously followed. The device was initially set up with wireless networks before coming live. SenseiAQ Software Version 1.2.3 (Download: https://github.com/PieraSystems/SenseiAQ) was used to set up the device and register it with a SenseiAQ Cloud Account.

The USB cable was used to connect the device to the laptop, and then it was powered on. The SenseiAQ Software Version 1.2.3 (https://pierasystems.com/support/) and the Windows 10 installer were downloaded on the computer. The gadget (network) settings were set once the software detected the sensor while it was operating. The WiFi network's name and password were typed in and saved. To register the gadget with SenseiAQ Cloud, an account was made. Using SenseiAQ, the freshly made account was utilized to log into the device remotely (pierasystems.com).

The five sensors were mounted horizontally on a level surface after the previous stages were finished. Every second, the gadget downloaded data for Particle Counts ($PC_{0.1}$–PC_{10}) and Particulate Matter ($PM_{0.1}$–PM_{10}). A local CSV log file was created and used to view the obtained data in SenseiAQ. Hours instead of seconds were used to translate the data for this investigation. With Excel 2013's pie chart and basic description as well as Minitab 2020's t-test and 0.05 level of significance, the data was statistically evaluated.

RESULTS AND DISCUSSION

In the specified living rooms, kitchens, and rooms, the concentrations of Particle Counts ($PC_{0.1}$, $PC_{0.3}$, $PC_{0.5}$, $PC_{1.0}$, $PC_{2.5}$, $PC_{5.0}$, and PC_{10}) and Particulate Matter ($PM_{0.1}$, $PM_{0.3}$, $PM_{0.5}$, $PM_{1.0}$, $PM_{2.5}$, $PM_{5.0}$, and PM_{10}) were measured. It was anticipated that indoor air quality would differ because of the different conditions in the home areas. The validity of conducting a comparison examination between the living rooms, kitchen, and rooms is simultaneously supported by occupancy and internal sources of air pollution.

Table 2 displays the indoor PC levels and indoor PM levels recorded at every site (Table 3). The average level ranged from 522473 to 515529, 460491, 479130, and 388548 #/liter, while the minimum indoor levels for PC were 0.0 #/liter in all rooms A–E and the maximum values (#/liter) were 2920856 (A), 1829277 (C), 1489895 (D), 826443 (B), and 702683 (E). The significant changes in the initial and final results were the cause of the high variation in the outcomes in each of the apartments. Skewness values larger than one were found for $PC_{1.0}$, $PC_{2.5}$, and $PC_{5.0}$, indicating that the data sets had distortions or asymmetries that varied from the normal distribution. All of the data from sites A through E showed positively skewed distributions when the mean values were higher than the median.

Table 2: The Basic Description of the Particle Counts in the Different Monitoring Sites inside the Building

Statistics	PC 0.1	PC 0.3	PC 0.5	PC 1.0	PC 2.5	PC 5.0	PC 10
A							
Mean	522473	364491	570438	170866	37044	951	1.978
StDev	328498	24726	359160	422653	87660	1098	1.846
CoefVar	62.87	67.84	62.6	247.36	236.64	115.47	93.29
Skewness	4.64	4.93	3.92	8.36	8.28	4.41	1.76
Kurtosis	31.09	34.16	23.87	75.33	74.27	26.33	4.35
Minimum	209087	139082	186204	22466	5177	178	0.0
1st Quartile	333361	230268	35210	52277	11720	363	1.0
Median	439360	301843	491331	87760	19628	610	1.5
Maximum	2920856	2210458	3033271	3990283	826491	8589	10.0
B							
Mean	479130	273312	332470	110449	25034	932.3	0.97
StDev	166339	96992	131048	72165	16562	561.6	1.62
CoefVar	34.72	35.49	39.42	65.34	66.16	60.24	166.97
Skewness	0.31	0.33	.46	1.19	1.39	1.14	5.70
Kurtosis	-0.98	-0.89	-0.02	2.09	3.74	2.13	43.52
Minimum	215511	119317	124567	23440	3909	236.0	0.00
1st Quartile	339384	193398	225051	52532	12526	490.0	0.00
Median	455705	258214	305889	90961	19174	772.0	1.00
Maximum	826443	507505	791309	417123	103615	3345.0	14.00
C							
Mean	515529	326941	455985	115783	25292	817.1	1.121
StDev	218078	144796	240171	133981	29197	910.3	1.674
CoefVar	42.30	44.29	52.67	115.72	115.44	111.40	149.20

Skewness	2.60	2.56	2.36	5.29	5.30	5.18	2.78
Kurtosis	12.64	12.54	10.94	37.25	37.38	35.92	9.47
Minimum	238127	142923	152435	22002	4735	176.0	0.00
1st Quartile	354018	217284	265803	45369	10186	332.0	0.00
Median	488672	305711	410973	84280	18521	602.0	1.00
Maximum	1829277	1198785	1860805	1152693	251446	7796.0	10.00
D							
Mean	460491	277109	328310	86760	18142	202.5	0.376
StDev	254843	160727	198011	109871	22490	199.4	0.806
CoefVar	55.34	58.00	60.311	126.64	123.7	98.51	214.28
Skewness	2.02	2.06	1.84	3.22	3.17	2.33	4.29
Kurtosis	4.54	4.75	3.83	11.11	11.65	5.83	25.97
Minimum	200928	115035	119499	17448	2680	46.0	0.000
1st Quartile	297762	174747	200306	3129	6408	87.0	0.000
Median	364277	214938	265588	46490	9540	120.0	0.000
Maximum	1489895	931384	1124491	608299	137745	1016.0	6.000
E							
Mean	388548	268424	414200	83952	20648	503.3	16.2
StDev	126451	91513	163982	53046	13299	311.9	162.2
CoefVar	32.54	34.09	399.59	63.19	64.41	61.7	1000.30
Skewness	0.74	0.75	0.72	1.14	1.12	1.14	10.39
Kurtosis	-0.50	-0.50	-0.46	0.33	0.31	0.30	107.99
Minimum	226447	150254	177187	26533	5499	168.0	0.0
1st Quartile	290341	197447	282481	44723	11110	270.3	0.00
Median	357297	246354	378005	65445	16132	403.0	0.0
Maximum	702683	494819	799428	238650	59352	1388.0	1686.0

A- 1st Living Room, B- 2nd Living Room, C- Kitchen, D- 1st Room, and E- 2nd Room.

Table 3: The Basic Description of the Particulate Matter in the Different Monitoring Sites inside the Building

Statistics	PM 0.1	PM 0.3	PM 0.5	PM 1.0	PM 2.5	PM 5.0	PM 10
A							
Mean	0.437	8.66	68.24	-	695	794	797
StDev	0.28	5.85	43.30	-	1537	1642	1642
CoefVar	62.87	67.59	63.46	-	221.16	206.71	206.13
Skewness	4.64	4.92	4.05	-	8.22	8.00	7.99
Kurtosis	31.09	34.02	25.23	-	73.46	70.54	70.46
Minimum	0.18	3.31	22.76	-	109	128	128
1st Quartile	0.28	5.48	42.39	-	239	277	279
Median	0.37	7.18	58.41	-	389	453	455
Maximum	2.44	52.31	369.10	-	14497	15394	15395

B							
Mean	0.40	6.57	41.29	133.58	460.5	557.9	559.2
StDev	0.14	2.33	15.95	75.75	290.9	349.1	349.8
CoefVar	34.72	35.44	38.62	56.17	63.18	62.58	62.56
Skewness	0.31	0.33	0.41	1.01	1.29	1.27	1.27
Kurtosis	-0.98	-0.90	-0.24	1.51	3.11	2.95	2.96
Minimum	0.18	2.87	15.88	35.47	87.1	111.8	112.1
1st Quartile	0.28	4.65	27.80	72.22	232.8	279.0	279.8
Median	0.38	6.21	37.98	115.01	390.1	470.8	472.1
Maximum	0.69	12.14	94.78	443.32	176.5	2145.9	2151.8
C							
Mean	0.43	7.81	55.43	153.3	482.7	567.9	569.4
StDev	0.18	3.45	28.47	139.5	519.6	614.5	615.3
CoefVar	42.30	44.18	51.36	91.10	107.65	108.21	108.04
Skewness	2.60	2.57	2.39	4.63	5.15	5.16	5.14
Kurtosis	12.64	12.55	11.22	30.68	35.87	35.92	35.79
Minimum	0.20	3.42	19.34	37.7	9.6	118.1	118.4
1st Quartile	0.30	5.20	32.96	71.2	201.4	236.9	237.5
Median	0.41	7.31	50.37	121.0	363.1	425.3	427.4
Maximum	1.53	28.57	222.92	1186.1	4469.9	5283.9	5286.5
D							
Mean	0.39	6.64	40.93	113.4	350.3	371.5	372.2
StDev	0.21	3.84	24.49	115.3	408.0	428.5	428.6
CoefVar	55.35	57.85	59.84	101.62	116.49	115.36	115.16
Skewness	2.02	2.06	1.88	2.95	3.08	3.04	3.04
Kurtosis	4.54	4.74	3.97	9.51	10.79	10.49	10.47
Minimum	0.17	2.77	15.25	30.0	65.2	70.1	70.3
1st Quartile	0.25	4.19	25.17	51.3	135.8	144.7	145.2
Median	0.31	5.15	32.8	68.3	197.0	208.8	209.7
Maximum	1.25	22.26	139.70	648.0	2446.9	2552.9	2553.5
E							
Mean	0.32	6.38	49.64	124.83	390.6	442.0	443.1
StDev	0.11	2.17	19.29	92.44	240.5	269.2	270.0
CoefVar	32.53	34.01	38.86	74.06	61.59	60.92	60.94
Skewness	0.74	0.75	0.72	4.58	1.16	1.09	1.09
Kurtosis	-0.51	-0.50	-0.47	32.61	0.60	0.22	0.22
Minimum	0.19	3.58	22.08	44.67	117.7	135.3	135.6
1st Quartile	0.24	4.70	34.30	72.00	216.6	244.9	245.5
Median	0.30	5.86	45.50	100.45	311.5	353.8	354.7
Maximum	0.59	11.75	95.24	838.85	118.3	1200.2	1206.3

PM_{10}, which ranged in diameter from 0.1 to 10 µg/m^3, had the greatest concentration of all the particulate matter. Sites A, C, D, B, and E had minimum and maximum (g/m3) values of 128 and 15395 (mean

= 797) and 118.4, 5286.5 (mean = 569.4), 70.3, 2553.5 (mean = 372), 112.1, 2151.8 (mean = 559.2), and 135.6, 1206.3 (mean = 443.1), accordingly. The findings showed that the PM ranges had significant standard deviations. While a low standard deviation meant that the data points were closely clustered around the mean, a high standard deviation meant that the data points were distant from the mean. All measurements revealed a significant degree of kurtosis. It must be observed that the data has heavier tails than a normal distribution (more in the tails) if the kurtosis is larger than 3; conversely, the data has lighter tails than a normal distribution (less in the tails) if the kurtosis is less than 3. (less in the tails). According to the general principle for kurtosis, the dispersion is too peaked if the value is higher than +1. Similar to this, an excessively flat distribution is indicated by a kurtosis of less than -1. Skewness and/or kurtosis in non-normal distributions are above these limits (Hair et al., 2016).

The sites with the highest PM and PC values were the living room (Site A) and the kitchen (Site C), depicted in Figure 4. The reasons for the high PM and PC values were: Firstly, the living room was nearer to a dirt road, secondly, the windows and entry door have all been frequently left closed, implying low ventilation; thirdly, smoke from the kitchen during cooking moved into the living room through the passage within the building; the forth, cigarette smoking and vaping; and lastly, smoke from outside. The cooking, frying, baking, and grilling that's been done in the kitchen resulted in exceptionally high PM and PC levels. Additional sources of pollution in other rooms included cigarette smoking (Site B), pesticide and mosquito coils (Site D), and fragrance and candle burning (Site E). In general, the interior air quality might have been impacted by the cooking and outside activities. The results back up Tran et al. (2020)'s assertion that several pollution sources can be found in both indoor and outdoor settings, whereas others come from outside settings. Indoor air quality in residential neighborhoods or buildings is primarily influenced by three factors: (i) outdoor air quality, (ii) human activities in structures, and (iii) building and construction supplies, furnishings, and equipment (Mar et al., 2018; Peng et al., 2017). IAP is harmful to health whether exposed for a short time or a long time, according to WHO (2017). It's understandable why some of the people living in this building were sneezing, coughing, and had runny noses.

Source: This Study (2022)

Figure 4: Sources of Indoor Air Pollution from Indoor and Outdoor of the Building

For facility economy and human comfort, indoor air quality (IAQ) is essential. Since studies have connected poor interior air quality to enhanced COVID-19 transmission, the building's residents were at risk for COVID-19 because the particle counts and mass indoors were high in this study (Watson, 2021).

Table 4 displayed the PC and PM assessments of the rooms. Particle counts in Rooms A and C were greater than in the other rooms. The room with the least PC was Room E. The high PC indicated an increase in the particles produced by nearby man-made activities. Environmental pollution also had an effect on the higher PC. The results show that the PC values decrease as the particle count diameter increases. The high PC in the different rooms may be caused by stagnant air (lack of wind and air mixing), when particles are not removed by the wind, or when breezes carry dirty air in from outside sources. The t-test findings showed that there was no statistically significant difference between the PC results' means among the five rooms ($p > 0.05$). All of the rooms showed the similar patterns, with the exception of room D, which had low readings from $PM_{0.5}$ to PM_{10} compared to the others. The events that took place during the monitoring could be reason for this state. The results reported by Tittarelli et al. (2008) for the particle counts (13517 (minimum) - 507529 (maximum) at a location in Lingotto station, a residential area in Turin, were significantly lower than the PC mean values observed here. The discrepancies between the two places might be attributed to the temperature, population in the buildings, weather parameters, and circulation of the two places.

Table 4: Comparisons of the Mean Results of Rooms (A-E) Within the Building

Parameter	A (n=92)	B (n=99)	C (n=99)	D (n=93)	E (n=108)
PC 0.1	522473	479130	515529	460491	388548
PC 0.3	364491	273312	326941	277109	268424
PC 0.5	570438	332470	455985	328310	414200
PC 1.0	170866	110449	115783	86760	83952
PC 2.5	37044	25034	25292	18142	20648
PC 5.0	951	932.3	817.1	202.5	503.3
PC 10	1.978	0.970	1.121	0.3763	16.2
PM 0.1	0.4366	0.4.003	0.4308	0.3847	0.3246
PM 0.3	8.660	6.566	7.807	6.636	6.380
PM 0.5	68.24	41.29	55.43	40.93	49.64
PM 1.0	-	133.58	153.2	113.4	124.83
PM 2.5	695	460.5	482.7	350.3	390.6
PM 5.0	794	557.9	567.9	371.5	442.0
PM 10	797	559.2	569.4	372.2	443.1

The impacts of locations to each of the observed PCs as identified during tracking are shown in Figure 5(a-e). In every site, the sequence of impact was the same: $PC_{0.1} > PC_{0.3} > PC_{0.2} > PC_{0.5} > PC_{1.0}$. Rooms A, B, C, and D had the highest levels of $PC_{0.1}$, $PC_{0.3}$, and $PC_{0.2}$, respectively. The impacts of each location to the overall quantity in the surroundings are shown in Figure 6(a-e). The PC and PM values were influenced by the indoor activities that took place during the measurement times. The most abundant particles were PM_{10} and PM_5, which made up of rooms B (32%), C (31%), D (31%), and E (30%). These results are in line with those made by Al-Awadhi (2014) in Kuwait, who found that PM10 was the main contributor of air pollution, and Motesaddi et al. (2017) in Tehran, also made a similar discovery. In-room A, PM_5, and $PM_{2.5}$ had higher percentage, each contributing 34% to the air quality determination, followed by $PM_{1.0}$, which

accounted for 29%. This might be caused by interior ventilation issues, crowding, and indoor air pollution infiltration.

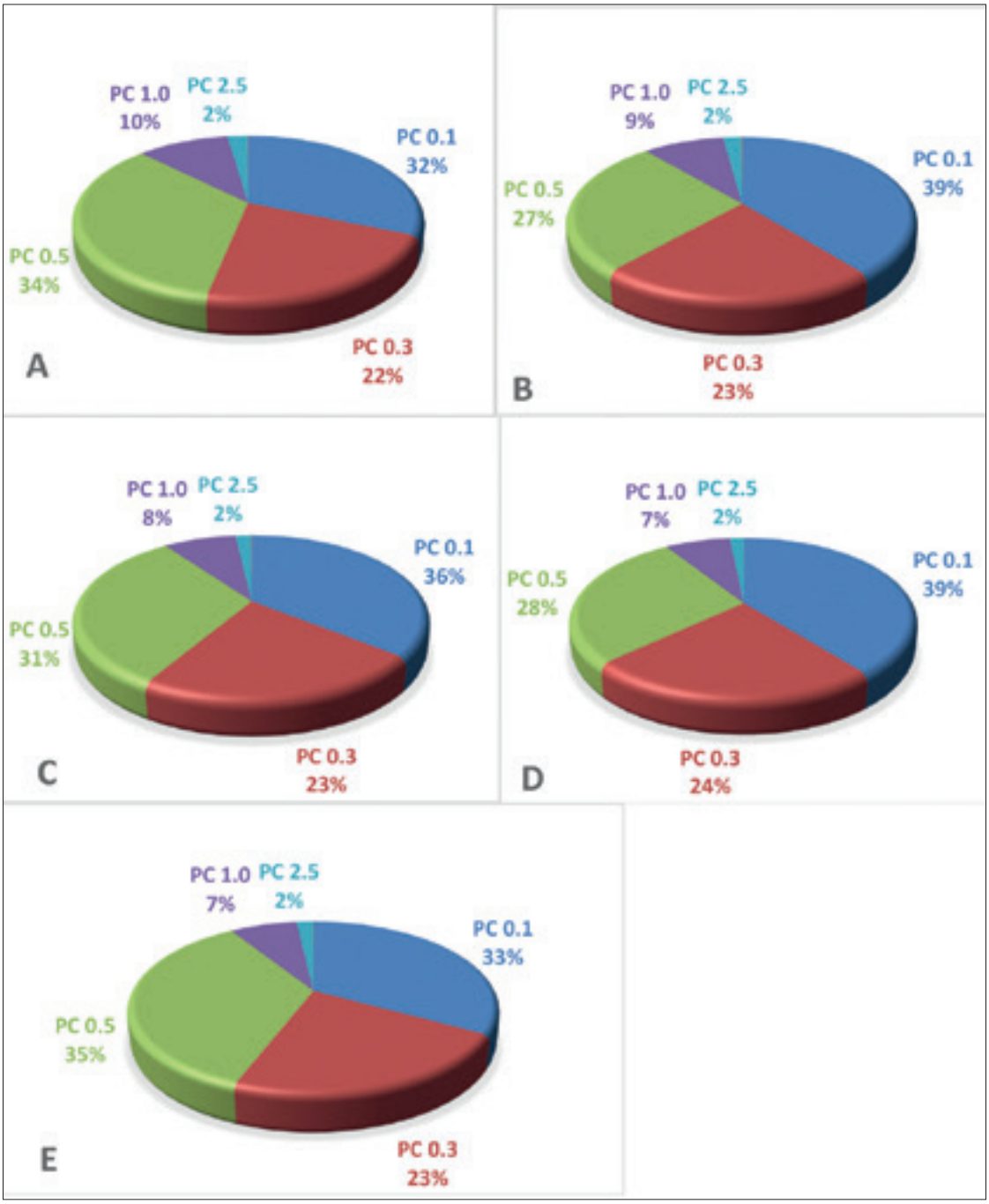


Figure 5: The Contributions of Particle Count to Each of the Rooms in the Building

The time series of PC and PM were plotted using the data that were gathered for this investigation. The average PC and PM concentrations are shown in Figure 7(a-e), and they generally follow a pattern of greater PC_{10} and PM_{10} concentrations in rooms A and C and lower values in room E. On the other hand, $PC_{0.5}$ concentrations were higher in Room E. If the atmosphere were more active, the pollutant dispersion processes would aid the emitted pollutants, explaining the lower PM_{10} concentration in room D. The time of monitoring and, most likely, weather conditions were the causes of the discrepancies found in this study. There are three fundamental elements of time series data: seasonality, trend, and residuals (Gerbing, 2016).

Understanding a time series' behavior requires deconstructing it. The time series' seasonality is consistent with seasonal swings in pollution levels. Seasonality has always had a defined and well-established period, typically several months (twelve). The trend component shows whether a pollutant's concentration is rising or falling over time and illustrates the time series' general long-term tendency. The part of the data that cannot be assigned to seasonality or trend is known as the residual or error component of a time series (Munir and Mayfield, 2021).

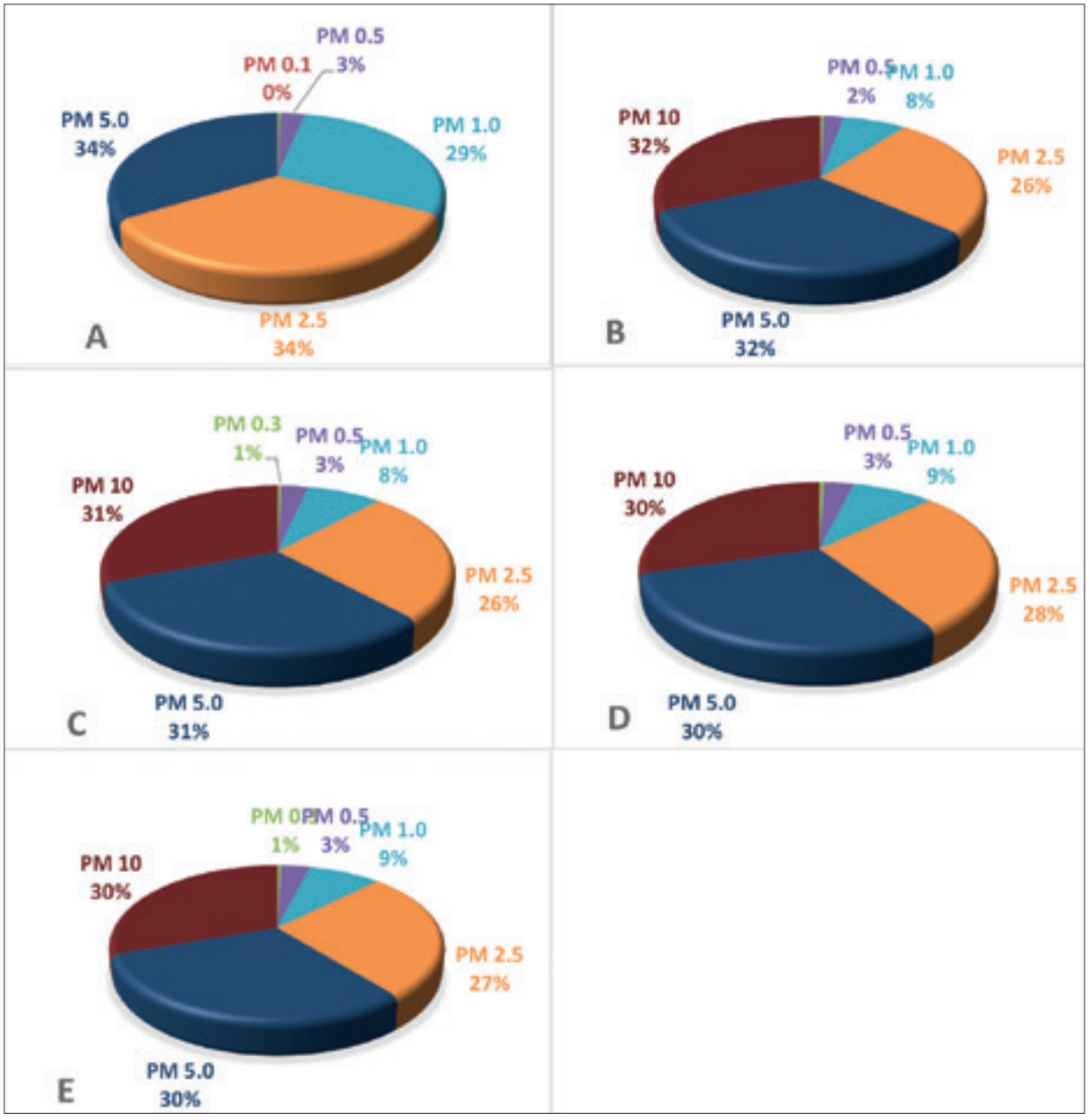
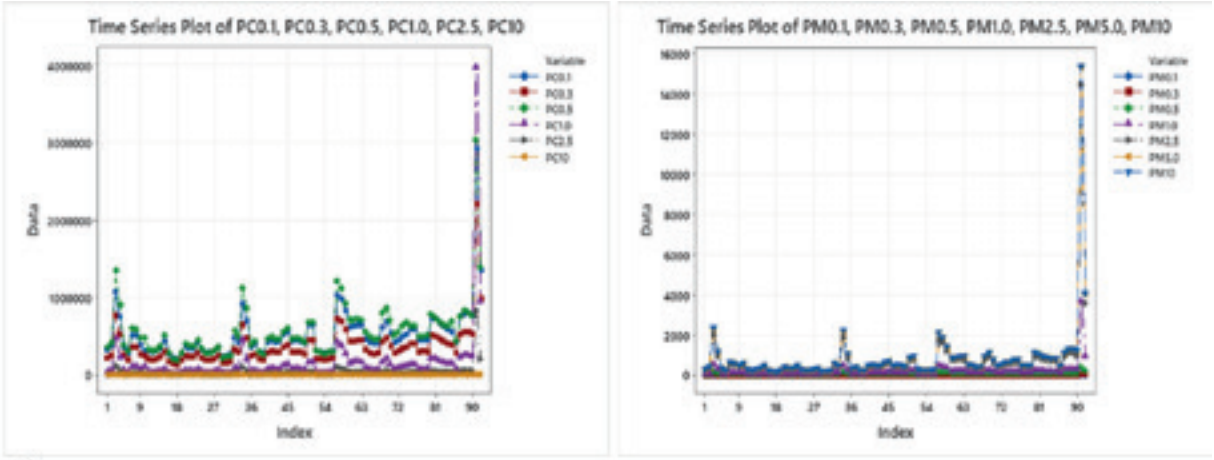
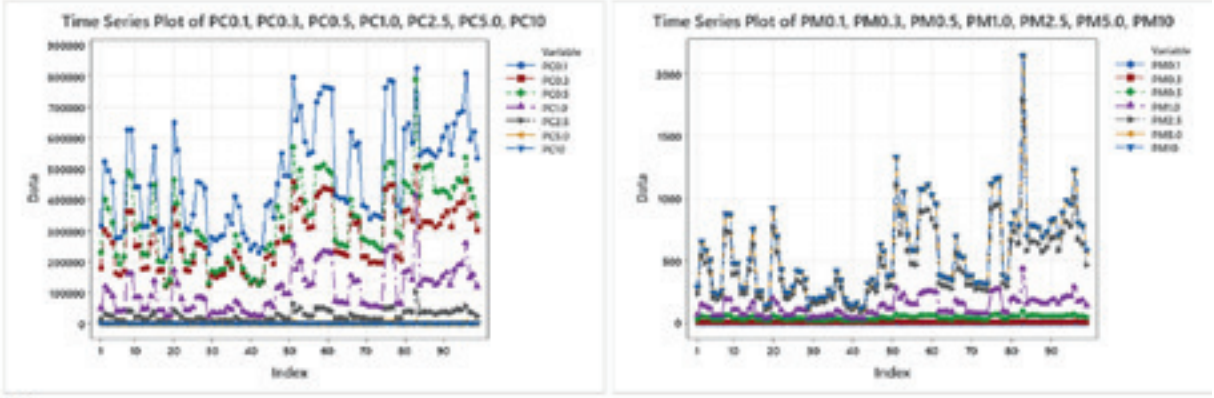


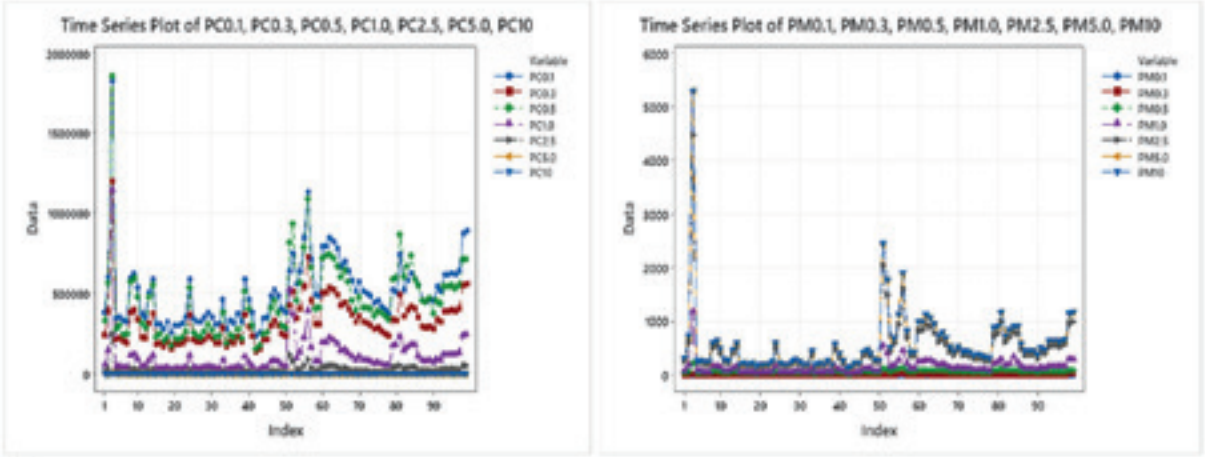
Figure 6: The Contributions of Particulate Matter to Each of the Rooms in the Building


Time Series Plot of PC0.1, PC0.3, PC0.5, PC1.0, PC2.5, PC10
Time Series Plot of PM0.1, PM0.3, PM0.5, PM1.0, PM2.5, PM5.0, PM10
Data
Index
Variable

a)


Time Series Plot of PC0.1, PC0.3, PC0.5, PC1.0, PC2.5, PC5.0, PC10
Time Series Plot of PM0.1, PM0.3, PM0.5, PM1.0, PM2.5, PM5.0, PM10
Data
Index
Variable

b)


Time Series Plot of PC0.1, PC0.3, PC0.5, PC1.0, PC2.5, PC5.0, PC10
Time Series Plot of PM0.1, PM0.3, PM0.5, PM1.0, PM2.5, PM5.0, PM10
Data
Index
Variable

c)

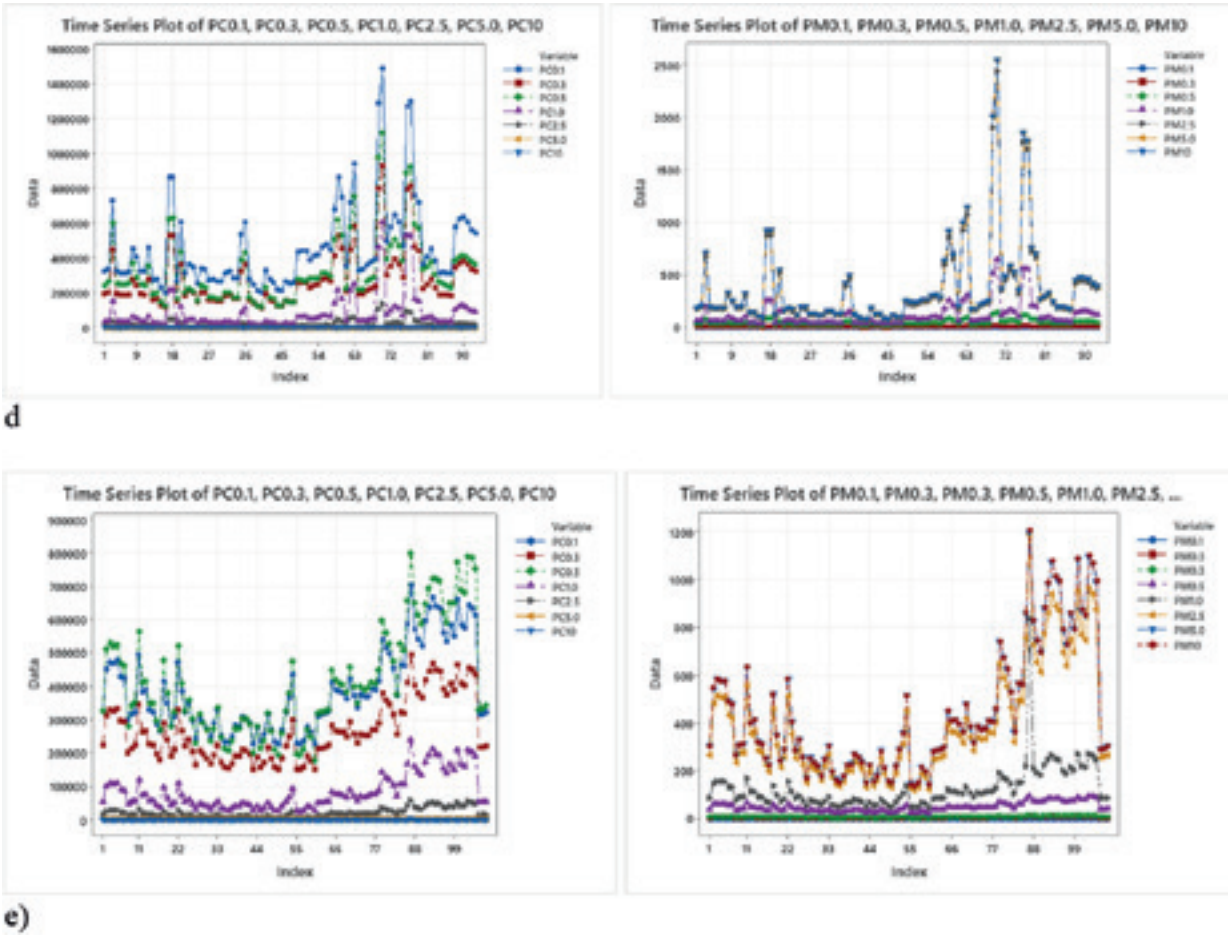


Figure 7 (a - e): The Time Series Plot Showing the Results of PC and PM in the Indoor Monitoring Location

CONCLUSION

In summary, PC and PM levels were high and surpassed WHO benchmark levels for different diameters (0.1, 0.3, 0.5, 1.0, 2.5, 5.0, and 10). One of the key advantages of Canāree, the low-cost particle counter model employed in this research, is its ability to identify particles with diameters as small as 0.3 µm, indicating an adequate evaluation of total particle number and a feasible evaluation of mass over the monitoring periods. The indoor air pollutant was notable for causing poor IAQ and, as a result, causing negative health consequences such as coughing, sneezing, and runny nose. The residents are prone to COVID-19 even though there were no incidences reported during the study. There were two primary sources of pollution in the building: i. human-induced activities in the building rooms, like combustion in the kitchen and candle burning, cleaning, smoking, using insecticide and mosquito coils, using perfume, and using specific materials and products when using electronic machines; and (ii) vehicular movements from outside sources, burning of waste and biomass, sweeping, and other factors. High amounts of this pollutant were discovered in the rooms, and prolonged exposure and poor ventilation can have detrimental effects on one's health. Implementing techniques and approaches for pollution control and reduction is necessary to lessen the effects of IAP in this apartment complex.

DECLARATIONS

Ethical Approval

The Ondo State Health Research Ethics Committee of the Ministry of Health gave the study approval with the given numbers NHREC/18/08/2016 and OSHREC 29/11/2021/403.

Consent to Publish
Not Applicable
Authors Contributions
Francis, Conceptualization and wrote the original draft; Vincent, Jay, Raj – All provided the sensors; Akinyinka, Yemisi, Kikelomo, Ademola, Lateef, writing, reviewed, and editing. All authors read and approved the final manuscript**.**
Funding
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Competing Interests
None
Availability of data and materials
On request, information are available.
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Original scientific paper

Modeling of Microwave-Assisted Extraction of Lycopene from Tomato Peels

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ABSTRACT: Dry tomato peels were investigated as a natural source of lycopene in this study. Microwave-assisted extraction (MAE) was used for the isolation of bioactive compound of interest. The MAE was performed at a microwave power of 120, 230, and 385 W for a duration of 2, 5, 8, and 10 min. The concentration of lycopene in the separated extract with n-hexane was quantified by UV/Vis spectrophotometer. The absorbance at 501 nm was selected for the determination of lycopene content and the calculation of lycopene yield (mg/100 g). An adequate feedforward artificial neural network (ANN) model with architecture 2-10-1, trained by the Levenberg-Marquardt (LM) back-propagation algorithm was developed for modeling the MAE process and for the prediction of the lycopene yield. The model predicted lycopene yield with a high coefficient of determination R^2=0.9957 and low mean squared error MSE=0.475. The response surface methodology (RSM) was successfully applied and combined with the ANN model to optimize the MAE process with R^2=0.9477 and a low mean absolute error MAE=1.84507. The analysis of variance showed that extraction time and time-squared have statistically significant effects on the lycopene yield. The created 3D response surface showed that the optimum lycopene yield was 27.25 mg/100g of tomato peels at the microwave power of 324 W and extraction time of 8.6 min.

Keywords: lycopene, tomato peels, microwave-assisted extraction, artificial neural network modeling.

INTRODUCTION

Industries based on the processing of agricultural products produce a tremendous amount of biowaste (industrial by-products) every year. Biomass is considered one of the most valuable energy and raw material sources (Sadh et al, 2018). Over the last few years, using waste materials from numerous industries has garnered considerable attention as a sustainable approach to resource management and environmental protection. Industrial by-products are cheap, renewable, abundant raw materials, rich in bioactive compounds, and can be used as alternative sources for obtaining new products, including biochemical products, biomaterials, biogas, etc (Babu et al, 2022; Messinese et al, 2023). Tomato processing industries generate significant amounts of waste by-products, including tomato peels, which are usually dumped and contribute to environmental pollution. However, tomato peels are also a natural source of biologically active compounds that contribute to their nutritional and potential healthy beneficial effects. Tomato peels contain lycopene, beta-carotene, vitamins C and E, phenolic compounds, flavonoids, fibers, minerals, etc (Laranjeira et al, 2022). Lycopene is highly concentrated in tomato peels, making them a rich source of this carotenoid pigment (Zuorro, 2020).

Lycopene or ψ,ψ-carotene is a red carotenoid pigment and is the most abundant carotenoid in ripe tomatoes (approximately 80-90% of the total pigments) (Cadoni et al, 1999), as well as in watermelon, apricot, pink grapefruit, guava, etc (Xi, 2006). This compound has an anti-inflammatory effect (Hazewindus et al, 2012) and it is a well-known powerful natural antioxidant that scavenges free radicals in the body (Imran et al, 2020), and in nature mainly exists in the all-*trans* form, but it can be degraded through the processes of *cis-trans* isomerization and oxidation, due to its high sensitivity to light, heat, and oxygen (Shi et al, 2002). Lycopene has many positive benefits on human health, including cancer prevention, skin protection, im-

proving eye health and cardiovascular system, and osteoporosis prevention (Khan et al, 2021; Walallawita et al, 2020). Hence it is widely applied in the food, cosmetics, pharmaceuticals, and textile industries. In recent years, there has been a growing interest in using waste by-products from the food industry to extract bioactive compounds, and tomato peels represent a valuable source for the extraction of lycopene, so its recovery from tomato peels represents a sustainable solution for both waste management and the production of a valuable natural pigment (Trombino et al, 2021). Various extraction techniques have been applied for lycopene separation from natural matrixes, such as maceration, ultrasound-assisted extraction, microwave-assisted extraction, enzyme-assisted extraction, and supercritical fluid extraction (Catalkaya & Kahveci, 2019; Kehili et al, 2019; Lianfu & Zelong, 2008; Rahimi & Mikani, 2019). Conventional extraction techniques are less efficient, time-consuming processes that are performed in several steps, using a larger amount of solvent. On the other hand, non-conventional extraction techniques, such as microwave-assisted extraction (MAE), are more efficient and selective, environmentally friendly, and provide the preservation of heat-sensitive compounds due to reduced extraction time (Bitwell et al, 2023).

Microwave-assisted extraction (MAE) is a modern extraction technique that is intensively employed for the isolation of compounds from plant material. MAE is a process of using electromagnetic radiation with a frequency of 0.3-300 GHz (Chan et al, 2011). Heat and mass transfer in MAE is different compared to conventional methods. In conventional solid-liquid extraction, heat transfer takes place from the liquid to the solid phase, while mass transfer occurs from the solid to the liquid phase. Contrarily in the MAE the heat and mass are transferred from the solid to the liquid. During the MAE, microwave energy penetrates the sample and generates heat internally. This results in the disruption of cell structures and provides extraction time reduction and better penetration of compounds from the matrix to the solvent (Sadeghi et al, 2017). Understanding these processes and proper control of microwave power, extraction time, and sample-solvent interactions is necessary to ensure effective heat and mass transfer during the MAE. In microwave-assisted extraction, several parameters affect on the efficiency and the yield of extracted compounds of interest such as extraction time, solvent type, microwave power, sample-solvent ratio, sample size, etc (Alara et al, 2018; Pengdee et al, 2020). Modeling the process is an essential step for achieving an efficient and selective extraction process, and obtaining high-quality extracts. Artificial neural networks (ANNs) are often used to model and predict complex processes such as microwave-assisted extraction (Simić et al, 2013; Sinha et al, 2013).

In this study, in order to model the microwave-assisted extraction process and predict the yield of lycopene extracted from tomato peels as a function of the extraction time and microwave power, an appropriate artificial neural network was created.

MATERIALS AND METHODS

Materials

Fresh ripe tomatoes (*Solanum lycopersicum*) used in this study as a raw material for obtaining tomato peels were purchased from a local market in Skopje, N. Macedonia. The tomato peels were separated by using a commercial electric peeling machine. Obtained tomato peels were immersed in the 1% potassium metabisulfite solution for 3 min to inhibit the growth of microorganisms and protect the material from molds. Pre-treated peels were dried at 30°C to moisture less than 10%. The average moisture content of the homogenized material was 8.24%. The particle size of the working raw material was in the range of 0.315-3.15 mm. The raw material was vacuumed in plastic bags and stored in a refrigerator at a temperature of 4°C. The prepared tomato peels were employed for the extraction of lycopene by using microwave-assisted extraction. n-Hexane (for analysis, Merck) was used for the isolation of lycopene from tomato peels.

Microwave-assisted extraction process

The microwave-assisted extraction process was done in a created system for microwave-assisted extraction by using a modified commercial microwave oven (Superior Technology, maximum power of 700 W). Tomato peels 2 g and 40 ml of n-hexane (1:20 sample to solvent ratio w/v) were placed into a 250 ml round bottom flask and fixed into the oven. The bottom flask was connected to a condenser. The microwave-assisted extraction system is illustrated in Figure 1. After finishing the extraction, the sample was immediately filtered through a filter paper with a pore size of 25 μm. Inert residues were separated on the filter paper. The n-hexane was vaporized from the extract in a rotary vacuum evaporator (Büchi R-200). The dried residue represented the total extract and the yield of the total extract was determined. Subsequently, the total extract was dissolved in the n-hexane, and the concentration of the lycopene was measured.

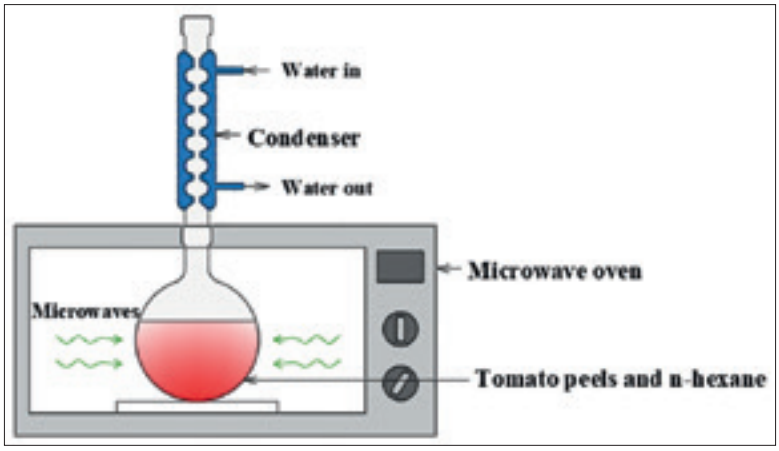

Figure 1. Schematic of the microwave-assisted extraction system for recovering lycopene from tomato peels

In this study, the influence of extraction time *t* and microwave power *P* on the yield of lycopene was investigated. MAE was performed at a microwave power of 120, 230, and 385 W for a duration of 2, 5, 8, and 10 min.

Determination of lycopene yield

The concentration of lycopene in the prepared solution was quantified by using a UV/Vis spectrophotometer (Spectroquant® Prove 600). The measurement was performed at 25°C in the wavelength range of 300-600 nm with a peak detection of 0.05 and $\Delta\lambda$=1 nm. A rectangular quartz glass cuvette with a 10 mm path length was used for analysis. n-Hexane as a blank solution was employed to automatically adjust the baseline.

The yield of lycopene y_L (mg/100 g of tomato peels) was calculated by:

$$y_L = \frac{0.00312\, A\, V_E\, D}{m_S} \quad (1)$$

where: A is the absorbance at 501 nm, V_E is the volume of extract (ml), D is the dilution coefficient, and m_S is the mass of the sample (kg).

ANN modeling of MAE

Artificial neural networks (ANNs) have often been used to model complex relations between independent input data and dependent output data. An artificial neural network is a statistical model of learning inspired by biological neural networks. ANN is a technique for generating a prediction of output variables such as the concentration of target compounds or extraction yield. The effectiveness of ANN modeling de-

pends on data quality, ANN architecture, hyperparameter tuning, activation functions, training, validation, and testing of the created model.

ANN model was created and developed to model and optimize the microwave-assisted extraction process of lycopene from tomato peels, i.e. for predicting the lycopene yield as a function of extraction time and microwave power. The ANN model was designed in MATLAB-Neural Network Toolbox. The extraction time and microwave power were used as input values so the ANN contained two neurons in the input layer. The yield of lycopene was employed as a target value hence the output layer contained one neuron. The optimal number of neurons in the hidden layer as a crucial parameter was verified by determining the minimum value of mean squared error (MSE). The MSE is mathematically calculated by:

$$MSE = \frac{1}{n}\sum_{i=1}^{n}(X_{pi} - X_{ai})^2 \quad (2)$$

where n is the number of all observations, X_{pi} is a predicted value generated from the model, and X_{ai} is an actual value obtained from the experiments. Response surface methodology (RSM) was applied and combined with the ANN model to optimize the MAE process, mathematical model fitting, graphical response surface representation, and analysis of the importance of investigated operating parameters. RSM model was developed in Statgraphics Centurion XV.

The evaluation of adequacy and efficiency of the model was determined by the MSE, the coefficient of determination (R^2), and the mean absolute error (MAE).

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(X_{pi} - X_{ai})^2}{\sum_{i=1}^{n}(X_{ai} - X_{m})^2} \quad (3)$$

$$MAE = \frac{1}{n}\sum_{i=1}^{n}\left|X_{pi} - X_{ai}\right| \quad (4)$$

where X_m is the average of the actual values.

RESULTS AND DISCUSSION

Microwave-assisted extraction of lycopene from tomato peels with n-hexane was performed at working conditions as described previously, in order to determine and model the influence of extraction time t and microwave power P on the lycopene yield. The UV/Vis absorption spectrum of each obtained extract contained three characteristic peaks of lycopene at 444, 470, and 501 nm (Figure 2). To avoid interference of other carotenoids, the absorbance at 501 nm was selected for the determination of lycopene content in the extract.

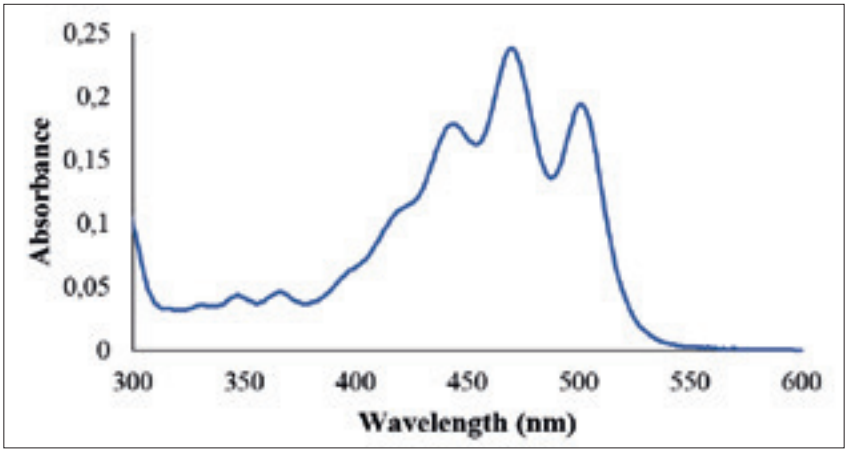

Figure 2. The UV/Vis absorption spectrum of the lycopene extracted with n-hexane from tomato peels by using MAE (t=2 min, P=120 W)

An adequate artificial neural network model was developed for modeling the microwave-assisted extraction process and for the prediction of the lycopene yield from tomato peels obtained by using n-hexane as a solvent. The development of the appropriate ANN model based on the experimental values involved several steps, from data collection and splitting to model training and evaluation. Choosing from the several types, a feedforward neural network (FNN) was built and trained by using the Levenberg-Marquardt (LM) algorithm to adjust the weights during the backpropagation process. The values of extraction time and microwave power were used as an input matrix in the ANN model. The experimentally obtained yields of lycopene were used as a target matrix in the model. The model was trained by using 60% of the data set and the training involved optimizing weights and calculating the error between the predicted and the actual target output. The performance and precision of the ANN were monitored through the validation and testing steps. The data set was split into training, validation, and test sets, containing 60% for training, 20% for validation, and 20% for testing. The optimal number of neurons in the hidden layer with nonlinear hyperbolic tangent activation function was determined at a minimum MSE. Different numbers of neurons in the range of 2-12 in the hidden layer were analyzed (Figure 3).

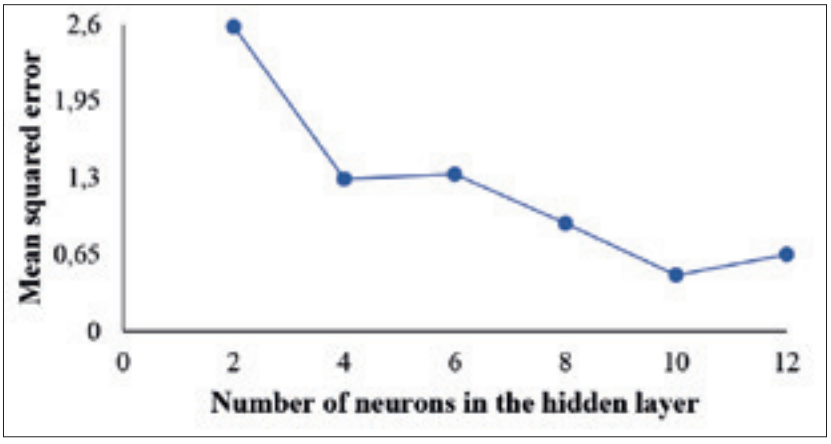

Figure 3. The relation between the number of neurons in the hidden layer and the mean squared error

The created ANN model with architecture 2-10-1 generated an output matrix of predicted lycopene yield y_{LANN} versus experimentally obtained actual lycopene yield y_L with a high coefficient of determination R^2=0.9957 and low mean squared error MSE=0.475. The visual relations between the predicted outputs of the model and the actual target for the training, validation, testing, and all are given in Figure 4. The scatter plots also show that the ANN model adequacy and efficiency predicted the actual data with high correlation coefficients of 1, 0.99821, and 0.997494 for training, validation, and testing, respectively.

The error histogram shown in Figure 5 provided additional verification of the network performance, where most data fall on the zero error line. It generally suggests that each pair of data is a good fit and the ANN model mathematically describes the MAE process well. The utilized ANN model adequately predicted the lycopene yield from tomato peels obtained in the operating range of 0-10 min and 120-385 W (Figure 6).

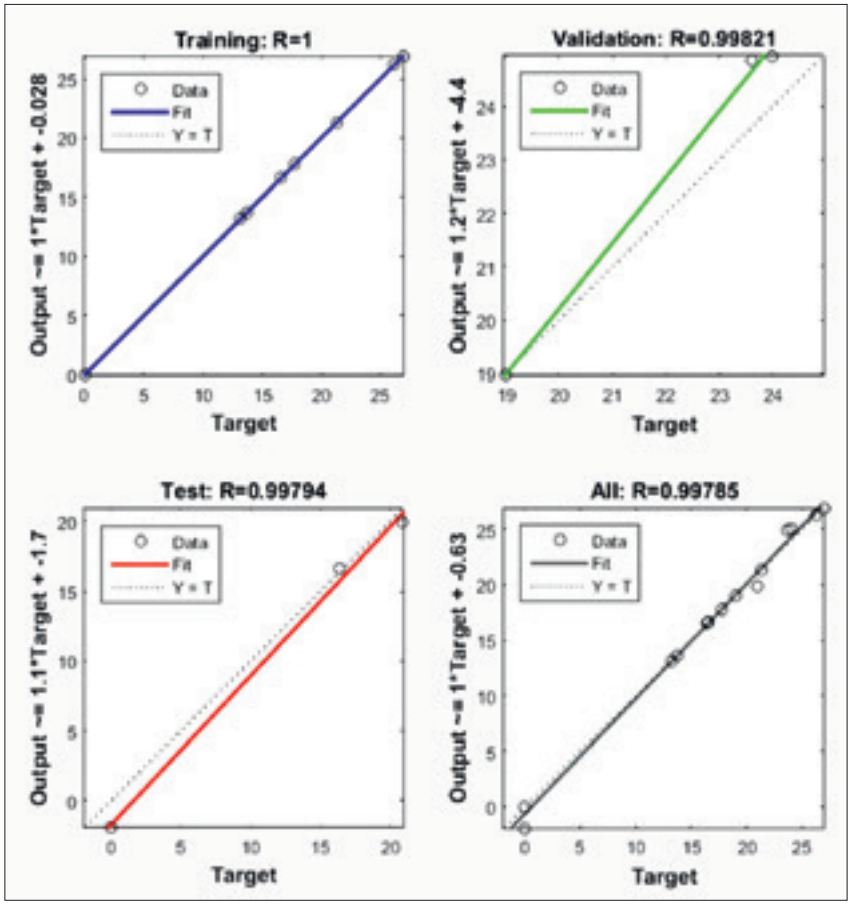

Figure 4. ANN regression plots for training, validation, testing, and all data sets

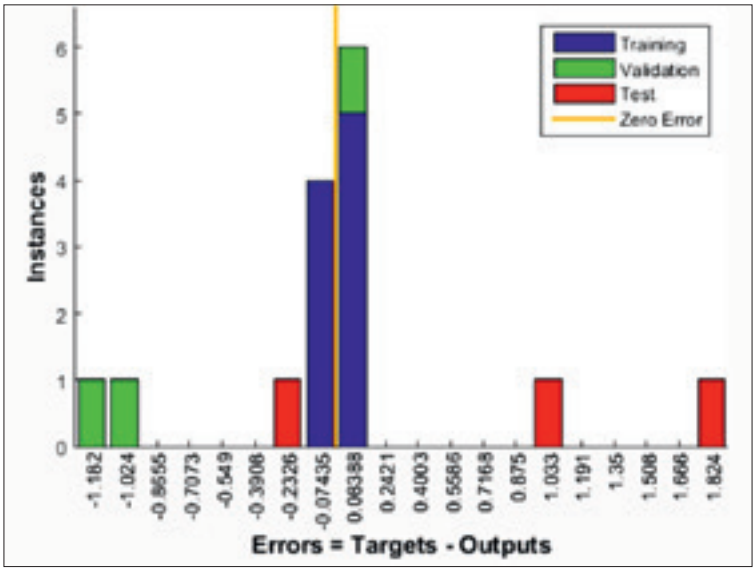

Figure 5. Plot error histogram for the ANN model

The RSM was used to optimize the ANN model and determine the effects of extraction time and microwave power on the lycopene yield, as well as to define the optimum MAE region. The RSM efficiently fitted the ANN predicted yield of lycopene y_{LANN} with a high coefficient of determination R^2=0.9477 and a low mean absolute error MAE=1.84507. The standardized Pareto chart (significance level, α=0.05) for the considered process is shown in Figure 7. The chart shows that the extraction time (A), the interaction between extraction time and microwave power (AB), and the microwave power (B) have a positive effect

on the lycopene yield, while the extraction time-squared (AA) and the microwave power-squared (BB) influence negatively. However, the extraction time and extraction time-squared have statistically significant effects on the lycopene yield.

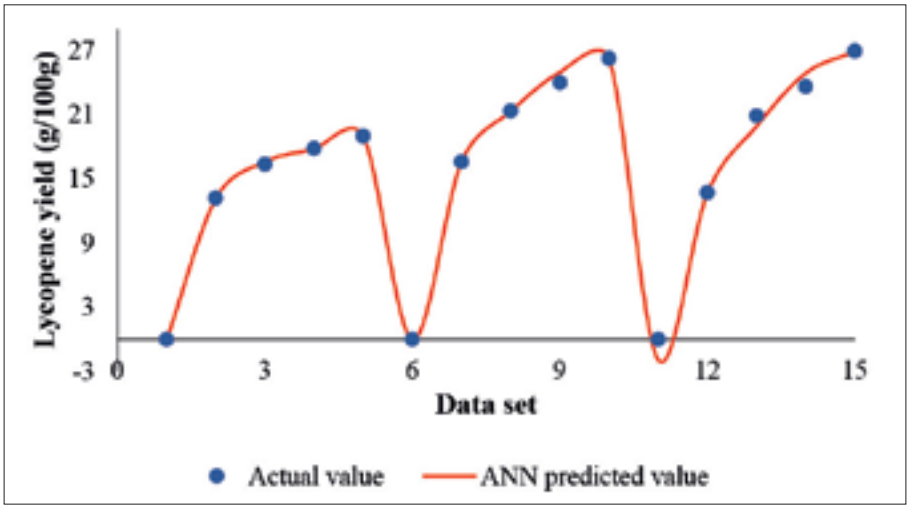

Figure 6. A comparative plot of ANN predicted lycopene yield and experimentally obtained lycopene yield

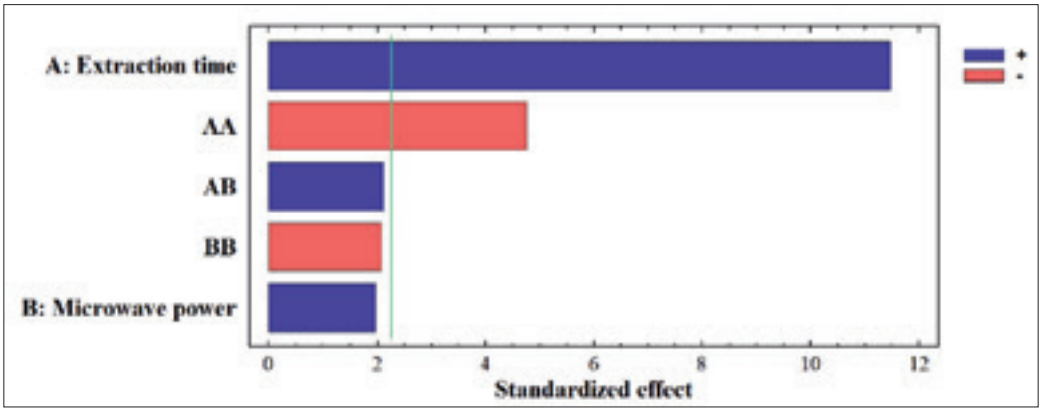

Figure 7. Pareto chart of relative importance and standardized influence of operating parameters on the lycopene yield

The regression equation was utilized to empirically describe the relation between the studied operating parameters and ANN-predicted lycopene yield. The relation was mathematically defined using the following equation:

$$y_{LANN} = -6.8851 + 4.6669\,t + 0.0866\,P - 0.3404\,t^2 + 0.0037\,t\,P - 0.0002\,P^2 \quad (5)$$

A 3D response surface was created to visually present the effects and interactions of independent factors on the response (y_{LANN}). The response surface is given in Figure 8, where the axes represent the levels of inputs (time and power), and the vertical axis represents the ANN-predicted lycopene yield.

The response surface shows that the increase of extraction time in the region of 0-8.5 min results in the lycopene yield increase, but in this interval the increase of microwave power does not significantly influence in lycopene yield increase. After approximately 8.5 min to 10 min, the effect of time on the lycopene yield is insignificant, however, the increase in microwave power leads to the lycopene yield increasing. The response surface and analysis of variance showed that the optimum lycopene yield is 27.25 mg/100g at the microwave power of 324 W and extraction time of 8.6 min.

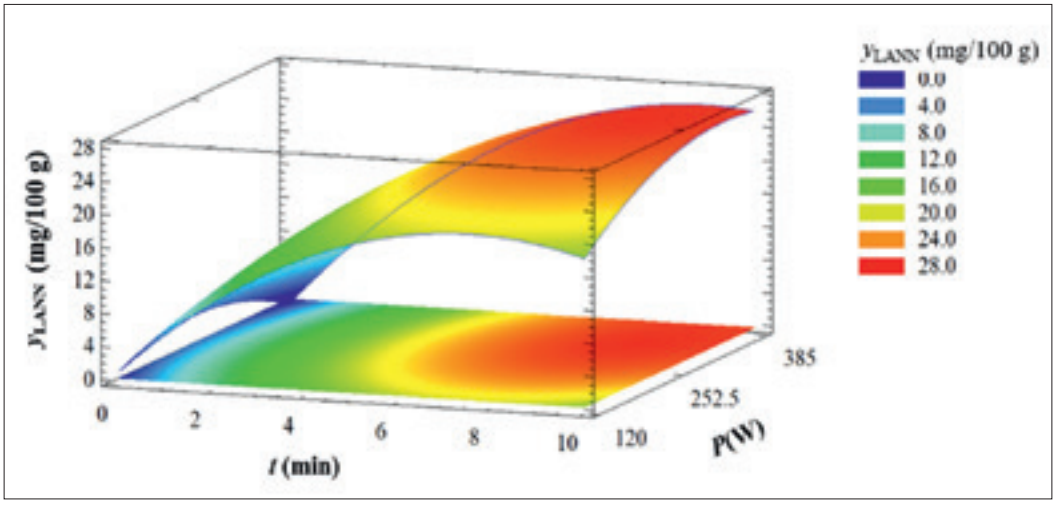

Figure 8. Response surface plot for the microwave-assisted extraction of lycopene from tomato peels

CONCLUSION

The recovery of lycopene from tomato peels with n-hexane by using microwave-assisted extraction was investigated in this study. The tomato peels were selected as a low-cost and renewable natural source of lycopene which usually has been generated by various industries as a waste by-product. The non-conventional microwave-assisted extraction technique provided a high lycopene yield in a short period of time. The artificial neural network model with architecture 2-10-1 was successfully developed and used to model the complex influence of extraction time and microwave power on the lycopene yield. The ANN model produced an output matrix of predicted lycopene yield versus experimentally obtained yield with R^2=0.9957 and MSE=0.475. The created model adequately predicted the lycopene yield from dry tomato peels in the operating range of 0-10 min and 120-385 W. The RSM with a high coefficient of determination R^2=0.9477 and a low mean absolute error MAE=1.84507, was applied and combined with the ANN model to optimize the MAE process. The statistical analysis showed that extraction time, microwave power, and their interaction influence positively, while time-squared and power-squared had a negative effect on the lycopene yield. The optimal yield of lycopene was achieved (27.25 mg/100g) at the microwave power of 324 W for a duration of 8.6 min.

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Original scientific paper

The Influence of Physical Activity on Body Mass Index Values in Adolescents

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ABSTRACT: Physical activity as an important factor of proper growth and development today, under the influence of modern technologies, is causing a decline in the interest of young people, which results in an increase in BMI and the development of obesity. **The goal**. The aim of the work was to examine the influence of physical activity on BMI values in adolescents. **Methods**. The respondents were students from the first to the third grade of the Bihać secondary medical school, of both sexes. The time of data collection is November 2022. There were a total of 120 respondents. They were divided into two groups, working and control, with 60 students each. The working group consisted of students who did not engage in any physical activity, while the control group consisted of students who engaged in physical activity 1x-3x a week. **Results**. The mean value of BMI in the working group of students was 29.14 kg/m² compared to the mean value of BMI of the control group, 21.75 kg/m² (p= 0.044). BMI values among students from the first to the third grade of the working group were equal, without statistical significance (p= 2.785). In the control group, the BMI values were also equal, but lower compared to the BMI values of the working group. According to gender, the boys of the working group had a mean BMI of 29.26 kg/m², compared to the boys of the control group, BMI of 21.71 kg/m² (p= 0.000). The same is true for girls, the mean BMI of the working group was 29.08 kg/m², while the BMI of the control group was 21.70 kg/m² (p=0.000). **Conclusion.** The absence of physical activity has a significant effect on the increase of BMI in adolescents and is a risk factor for obesity. The promotion of healthy lifestyle habits, proper nutrition and physical activity should be key features of the lives of children and adolescents.

Key words. Physical activity, body mass index, adolescents.

INTRODUCTION

The basic human need, looking through the history of civilization, in addition to nutrition, also represents movement as the simplest form of physical activity that contributes to better and better health of people, both in the physical and psychological aspects. In everyday life, children need to satisfy their instinctive and natural need for movement, which is achieved through various forms of play that positively affects proper growth and development. Regular physical activity in adolescents has numerous benefits for their health, including healthy growth and development of bones, muscular and cardiorespiratory systems, maintains energy balance, has a beneficial effect on mental health, greater possibility of social interaction, reduction of anxiety and stress (British Heart Foundation, 2004). In the last decades of the 20th century, there was a decrease in physical activity among children and adolescents and an increase in BMI (Body Mass Index), which numerous scientific studies have confirmed. The trend of increasing BMI among the young population continues in the new century and takes on an epidemic character in many parts of the world. According to data from the World Health Organization (WHO), obesity is highest in the countries of North America, Central and Eastern Europe, as well as in the countries of the Middle East. It is estimated that in 2016 worldwide, 124 million children and adolescents aged 5 to 19 years were obese (BMI ≥ 30 kg/m2), and 213 million were overweight (BMI 25.0 - 29, 9 kg/m2) (Spinelli et al, 2019). In the last three decades of the 21st century, there was a sudden increase in BMI in children aged 2 to 18 years in both devel-

oped and developing countries (Güngör, 2014; Lee et al, 2018). Literature data also indicate that children and adolescents in most countries have a low prevalence of the overall level of physical activity, a high prevalence of sedentary/sedentary behavior, which includes time spent awake, sitting or lying down with low energy expenditure (watching television, working on a computer, using smartphones telephone, etc.) and a serious increase in the prevalence of obesity (Zhu et al, 2017). It is considered that physical inactivity along with inadequate nutrition is the main cause of health problems in children and adolescents. The emergence of obesity can also be observed in the context of complex social environments in which children and adolescents grow up. Eating habits and physical activity must be connected and combined in order to have a good result in maintaining a normal body mass (Stanić, 2017). There are a number of expert recommendations to what extent adolescents should participate in physical activities of medium to high intensity - at least one hour a day, while in physical activities that involve strengthening the locomotor system - at least three times a week (Sever, 2019). The mutual influence of certain factors such as family, friends and peers from school and the social community can also be reflected in the way of eating, physical activity and sedentary/sedentary behavior of adolescents. Parents represent the primary social context and pattern of behavior in the approach to nutrition and physical activity that children adopt and develop as healthy or unhealthy lifestyles (Bogl, 2020). Considering the worrying increase in overweight and obesity among children and adolescents, WHO member states set an important goal until 2025 to stop this negative trend and approved a project under the slogan "No increase in overweight and obesity" (Baran, 2020; WHO, 2021).

Objective

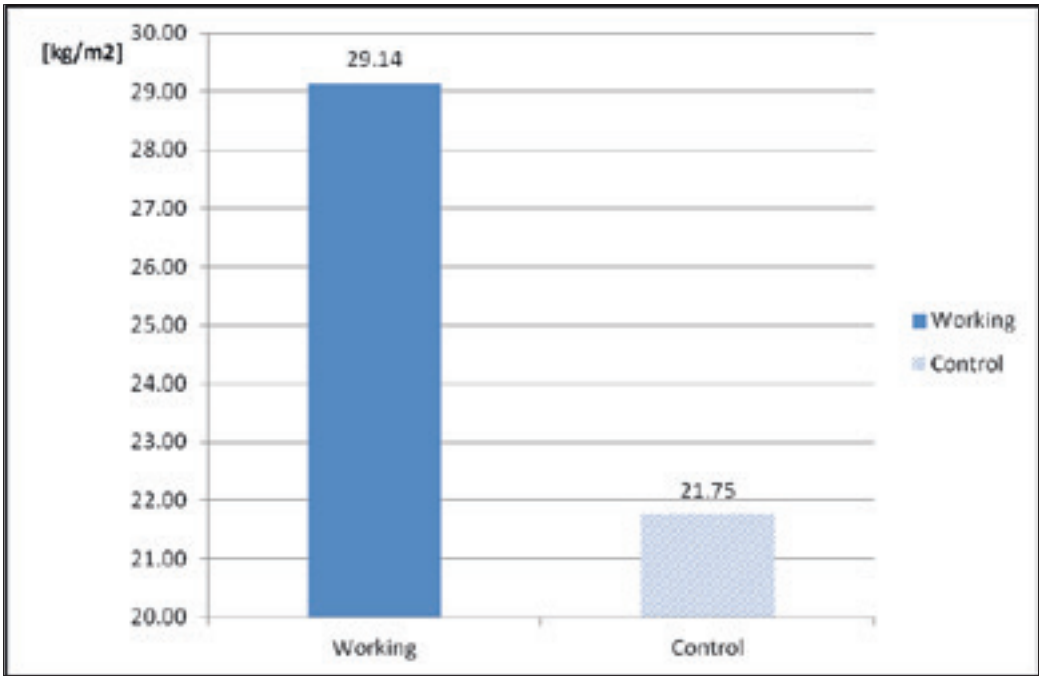
The main goal of this work is to examine the influence of physical activity on BMI values in adolescents from the secondary medical school in Bihać.

METHODS AND RESPONDENTS

The respondents were students from the first to the third grade of the secondary medical school in Bihać, aged 15 to 17, of both sexes. The total number of students in the research was 120. The time of data collection is the period from 04.11. - 29.11.2022. years. The respondents were divided into two groups, working and control, with 60 students in each group. The working group consisted of students from first to third grade who did not engage in any physical activity in their free time, while the control group consisted of students from first to third grade who engaged in physical activity 1x-3x a week, during their free time. Anthropometric measurements of body height and weight were performed on the subjects in order to calculate the BMI value, and were carried out on an Omron scale (BF 511/201-107-00214F/ 2018/Amsterdam). For the purpose of researching the connection between BMI and physical activity, a separate survey questionnaire was created in the form of a test with provided answers. For the purpose of data processing, the arithmetic mean method was applied, and the results were presented graphically. The data were processed in MS EXCEL to determine the arithmetic mean (AVERGE) and the statistical value p (STAT-p).

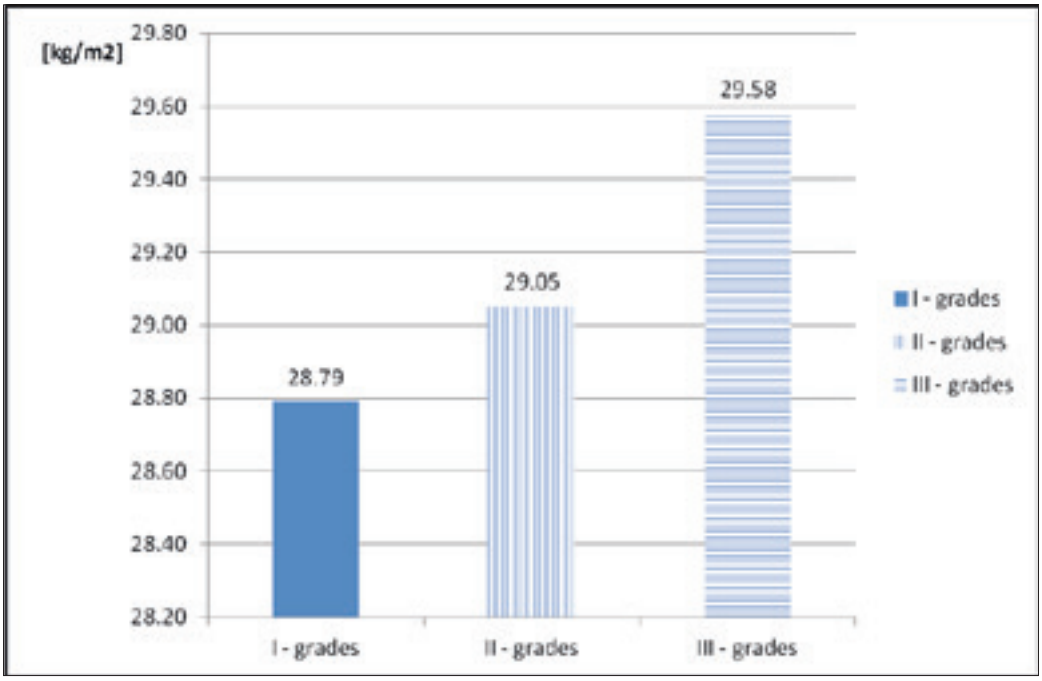
RESULTS

Out of the total number of respondents in our study (120 respondents), 29 male respondents (boys) and 31 female respondents (girls) were represented in the working group that was not physically active. In the control group that was physically active (1x-3x a week) there were 28 male respondents and 32 female respondents. The mean value of BMI in the subjects of the work group was 29.14 kg/m², while in the control group the value of BMI was 21.75 kg/m², which represents a statistically significant difference ($p=0.044$) (Graph 1).



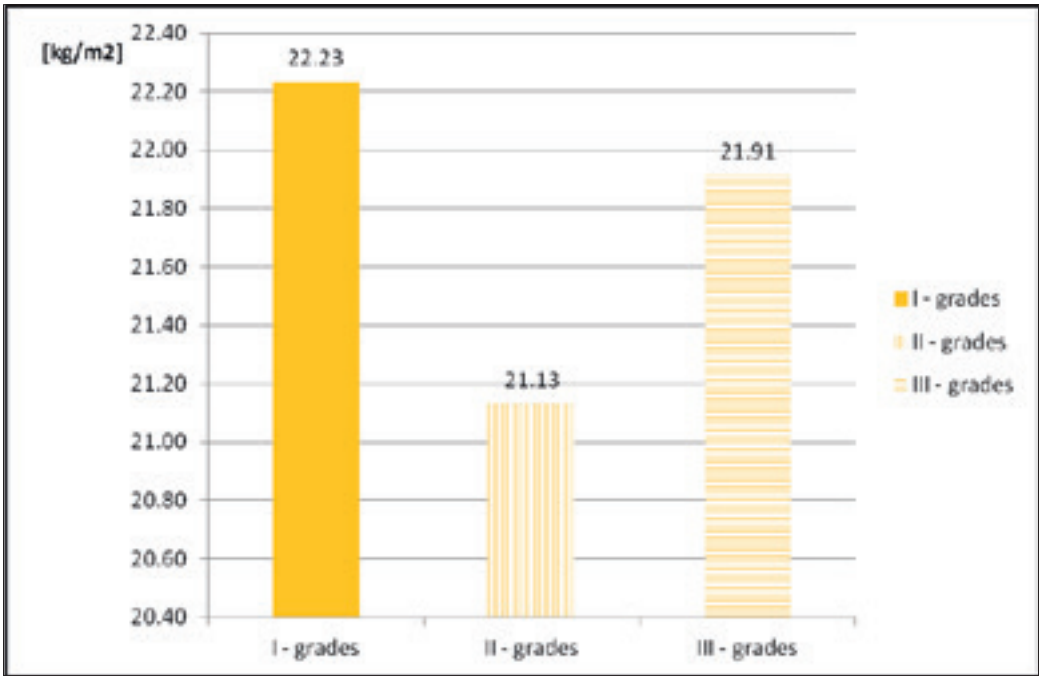
Graph 1. Mean value of BMI of the Working and Control groups

The BMI values of the working group of respondents from I to III grades are shown in Graph 2 and show that the mean BMI value for I grade was 28.79 kg/m^2, for II grade 29.05 kg/m^2, while the BMI values in III class amounted to 29.58 kg/m^2, which statistically does not represent a significant difference (p=2.785).



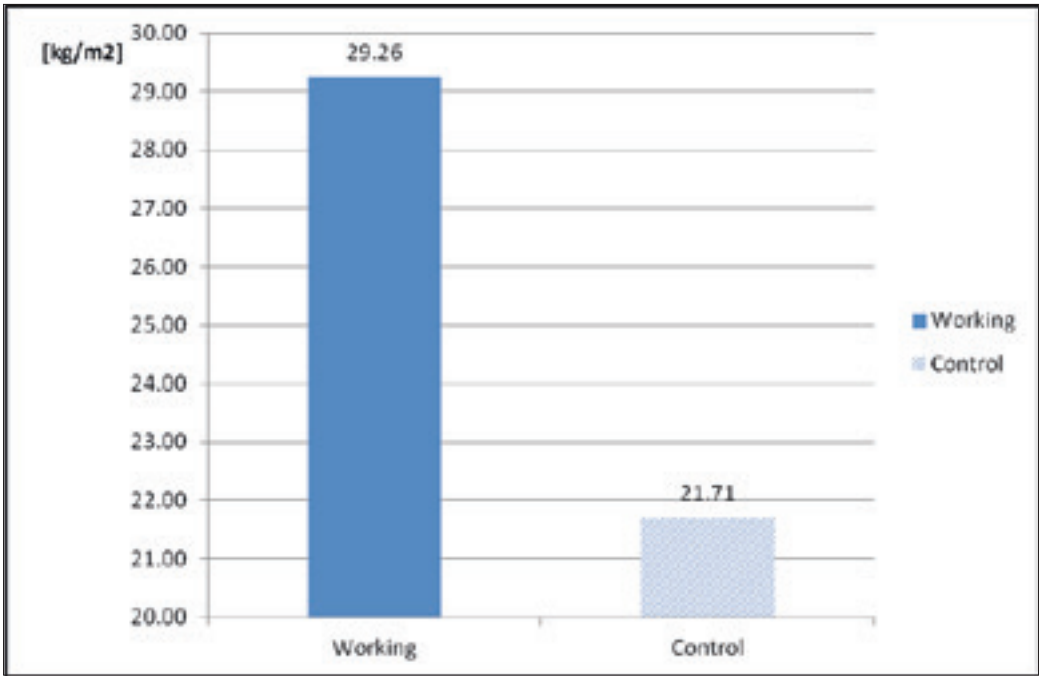
Graph 2. Mean values of BMI in the Working Group of subjects from I to III grades

The mean value of BMI in the Control group, by class, is shown in Graph 3. The mean value of BMI for the first class was 22.23 kg/m^2, for the second class 21.13 kg/m^2, while for the third class it was 21.91 kg. /m^2 which does not represent a statistically significant difference (p=2.281).



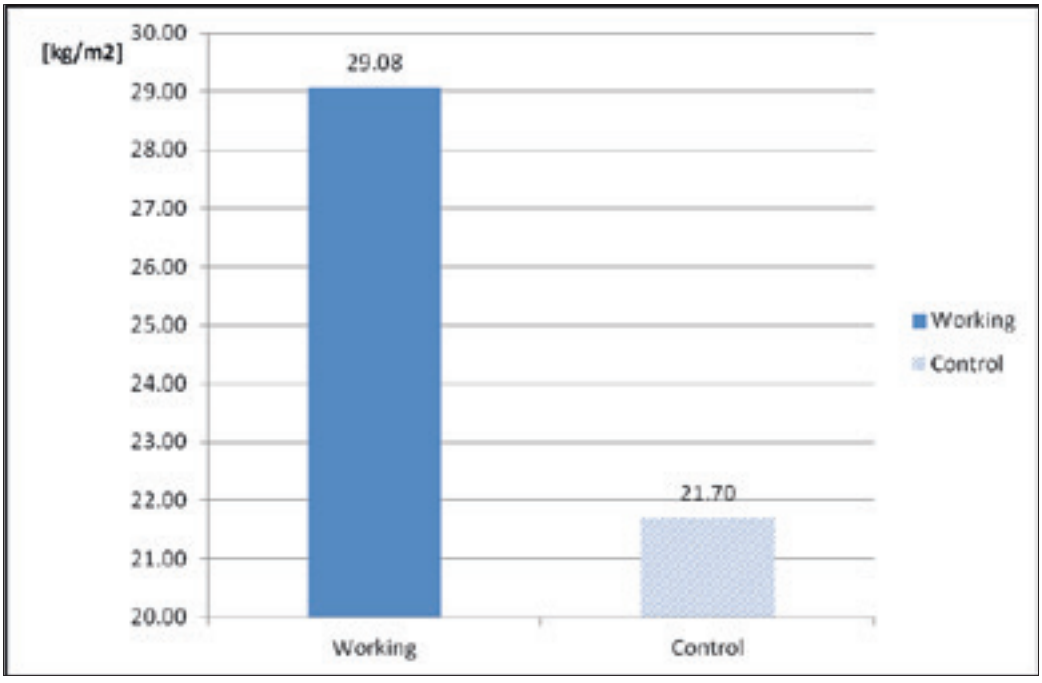
Graph 3. Mean values of BMI in the Control Group of subjects from I to III grades

Graph 4 shows the mean values of BMI in male subjects (boys) of the working group, which was 29.26 kg/m², while in male subjects of the control group, BMI was 21.71 kg/m², which represents a significant difference.



Graph 4. Mean value of BMI in boys of the Working and Control groups.

Graph 5 shows the mean value of BMI in female respondents (girls) in both groups. We can see that the mean value of BMI in the female subjects of the work group was 29.08 kg/m², while the BMI value in the female subjects of the control group was 21.70 kg/m², which represents a significant difference.



Graph 5. Mean value of BMI in girls of the Working and Control groups

DISCUSSION

Our research included 120 respondents, students of the Bihać High School of Medicine from the first to the third grade. The study showed that physical activity is an important factor that affects the nutritional status of adolescents, but also the BMI (body mass index). In the working group of respondents, who did not engage in any physical activity, in their free time, the mean value of BMI was much higher and amounted to 29.14 kg/m^2 compared to the control group who had physical activity once, twice or three times weekly for 90 minutes (in their free time they engaged in physical activity, aerobic exercises or team games) whose mean BMI was 21.75 kg/m^2, which represents a statistically significant difference (p=0.044) and is in line with other literature data.

Namely, the confirmation that physical activity has a positive effect on the reduction of BMI is proven by a study in Italy in a high school on a sample of 60 obese adolescent girls aged 15-17 years, who were divided into the Work (physically inactive) and Control (physically active) groups. The results of this study indicate that physical activity, program of moderate to vigorous aerobic exercises is effective in reducing body weight in adolescent girls and provides positive and significant effects on the behavior of girls who have obesity problems. It also indicates that physical activity has a strong potential in promoting a number of outcomes that are important for the quality growth of adolescents (Latino et al., 2021).

In accordance with our results, and according to the research of Hills et al. (2011) in many western countries, a large number of adolescents who did not adhere to the recommended guidelines for physical activity had elevated BMI values, i.e. the results of that study show that physically active respondents had lower BMI values and body fat percentage compared to respondents who did not engage in physical activity. Physical activity plays an important role in the prevention of obesity and obesity in childhood and adolescence and reduces the risk of developing obesity in adulthood.

Children are not born obese, but they certainly become obese. Most studies show that body weight increases with age (Singh et al. 2008). Also, weight gain in children causes many problems in early childhood and adolescence including, in more severe degrees of overweight, developmental abnormalities of the

locomotor system and weight-bearing limbs. Metabolic problems such as insulin resistance, the development of diabetes, and higher blood pressure and dyslipidemia are also evident in obese children even when they are young, and later in life cardiovascular complications and early death occur (Gunnell et al. 1998). The results of the study by Bukara-Radujkovic et al. (2019) also prove a positive correlation of reduced physical activity and a sedentary lifestyle, as significant determinants and risk factors in the development of moderate obesity and obesity in childhood.

Physical activity represents the most natural way of spending energy, which has become very limited in developed countries due to rapid technological progress. Research results regarding the impact of physical activity on body mass are different, but they all have in common that regular physical activity in both sexes is associated with a lower percentage of fat in the total body composition. However, some studies show that differences in body fat between physically active and physically inactive children are greater in girls than in boys (Krassas et al. 2001). When we compare the results of our study, by gender, in the boys of the work group, the BMI values were much higher compared to the BMI values of the boys of the control group ($p=0.000$) where physical activity of different intensity was represented once, twice or three times a week. Also, the BMI values of the girls of the work group compared to the BMI values of the girls of the control group were higher, which is in accordance with other literature data. According to research by Zvonar et al. (2019), which included adolescents aged 15 to 18 years who were physically active, the results showed that there are differences in BMI by gender as the classes get older. In fact, the results show that boys have a higher BMI, waist circumference and height compared to girls.

Other literature data also indicate a positive influence of intense and regular physical activity on normal body mass index in girls and boys ($p<0.05$) (Bukara-Radujkovic et al, 2019). Namely, girls who are often physically active had the lowest BMI values (that is normal body mass), and girls who do not engage in physical activity had the highest BMI values. Also, the results of this study show the positive impact of regular (at least 3 times a week for 1 hour) physical activity on the normal BMI of boys. Boys who were engaged in physical activity in addition to well-developed muscle mass had normal body mass values (BMI), which is in accordance with the results of our study. In a multiple study analysis, Elmesmari et al. (2018), which included respondents from Asia, Canada, the USA and Europe, and which included a sample of 12,601 adolescents (of which 3,045 were obese), compared the level of physical activity in obese and non-obese peers. The results of the research showed that daily physical activity is lower than recommended in children and adolescents with obesity, and more so in male obese subjects compared to female subjects. Also, scientific studies confirm the thesis that moderate to intense physical activity compared to low-intensity exercises leads to a reduction in body weight (Keane et al 2017). On the other hand, scientific research into the physical activity of European and North American children and youth shows that the physical activity of school children increases until early adolescence, when it begins to decrease intensively and that in the late adolescence phase it is more pronounced in boys than in girls, although boys physically more active than girls (Malina et al. 1991).

Prevention of obesity in children and adolescents should include children as early as possible. Also, the promotion of healthy lifestyle habits - proper nutrition (which includes a balanced intake of building materials, fruits and vegetables), physical activity and playing sports, should be the task not only of school programs, but should be the responsibility of the family and society as a whole. A nine-country analysis that included England, the United States, Sweden, China, Australia, the Netherlands and Switzerland reported promising reductions in obesity in children and adolescents aged 2 to 19 years (Rokholm et al, 2010). However, although the prevention of childhood obesity is politically attractive, it is not realistic to expect that some quick changes will bring long-term positive solutions in the health of the population and will not

affect the reduction of health costs in diabetes and hypertension that are caused by obesity, so that it has a negligible impact on the burden of disease in the next 40 years. Parents as adults should be positive role models for their children precisely in the promotion of health and healthy lifestyle habits (Rind et al, 2011).

CONCLUSION

The absence of physical activity among adolescents with a sedentary lifestyle results in a significant increase in BMI compared to peers who practice some of the aerobic exercises or team games one to three times a week in their free time. The development of obesity in children and adolescents can lead to the development of chronic non-communicable diseases and an increase in the rate of morbidity and mortality in adult life. The promotion of healthy lifestyle habits, above all proper nutrition and physical activity, should be the primary task of the family and society as a whole.

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Influence of Modified Diet and Low Grade Physical Activity on Serum Lipids in Patients With Type IIa and IIb dyslipoproteinaemia

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ABSTRACT: Dyslipoproteinaemia, a common name for different types of serum lipid disorders, plays one of the crucial roles in the etiology of atherosclerosis. Complications of atherosclerosis, primarily coronary heart disease (CHD), in early life lead to significant disability and are the worldwide leading cause of death. Treatment of dyslipoproteinaemia, as a separate disease, is carried out as a part of the treatment of CHD, and includes non-pharmacological and pharmacological measures. Recognizing an underestimated value and role of dietary modifications in everyday life of patients with hypercholesterolaemia, we decided to actualize our investigation from 2000, as we witness that lipid lowering drugs are prescribed almost as soon as elevated serum lipid levels are detected. The aim of our study was to evaluate the effects of a hypolipemic diet and low grade physical activity on serum lipid/lipoprotein levels in twenty patients with primary dyslipoproteinemia Type IIa and IIb, according to Fredrickson classification. All patients with Type IIa and IIb dyslipoproteinaemias were subjected to a hypolipemic diet that is a modification of Step I, Step II (NCEP) and the Mediterranean diet for a period of four weeks. The minimum physical activity involved a daily light walk lasting at least 1 hour. Complete lipid status has been done before and after the period of four weeks. The positive effects of our modified diet were shown as a decrease of all proatherogenic lipid/lipoprotein serum concentrations, except for β-lipoprotein. Serum concentrations of antiatherogenic α-lipoprotein increased.

Keywords: dyslipoproteinaemia, hypercholesterolemia, diet, exercise, serum lipids, lipoproteins.

INTRODUCTION

Dyslipoproteinaemia and its role in the development of atherosclerosis

Dyslipoproteinaemia - disorders of serum lipid/lipoprotein metabolism plays one of the crucial roles in the etiology of atherosclerosis, and results in clinical manifestations and complications of atherosclerosis such as coronary heart disease - CHD (angina pectoris, myocardial infarction), renal insufficiency, peripheral and central vascular diseases, dementia and pancreatitis. Complications of atherosclerosis, primarily CHD, in early life lead to significant disability and are the worldwide leading cause of death, both in total mortality and in mortality from cardiovascular diseases (Farnier et al. 1998; WHO, 2020). Although the disease has a multifactorial etiology, an increase in serum total cholesterol (TC), especially low-density lipoprotein cholesterol (LDL-C), is considered the most important risk factor in the development of atherosclerosis (Sloop, 1999; Zmysłowski and Szterk, 2017; Mortensen et al., 2023). Regardless of whether dyslipoproteinaemias are primary – genetic, or secondary (inadequate diet, poorly controlled diabetes, hypothyroidism, nephrotic syndrome, biliary obstruction, alcoholism, use of certain drugs), or combination of both, dyslipoproteinaemias represent a problem in managing patients with atherosclerosis and its complications. The need to lower serum cholesterol levels is increasingly emphasized, primarily by modifying the lifestyle, and if the target values are not achieved, then by drug therapy. Every 10% reduction in cholesterol is associated with approximately 20% to 30% reduction in the incidence of CHD (Drug Facts and Comparisons, 2000).

The recommendations of the Working Group of the Association of European Societies - European Society of Cardiology (ESC), European Atherosclerosis Society (EAS) and European Society of Hypertension (ESH) - were published in 1998 in the *European Heart Journal, Atherosclerosis and Journal of Hypertension* (Wood et al.,1998). Serum lipid target values in Europe differ from lipid target values in America. The new target values in Europe, based on *Recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention.* for cholesterol should be below 5.0 mmol/L (190 mg/dL), and for LDL cholesterol below 3.0 mmol/L (115 mg/dL). HDL cholesterol and triglyceride concentrations were not taken as a target values in hyperlipoproteinemia therapy, however HDL values below 1.0 mmol/L (40 mg/dL) and fasting triglyceride values greater than 2.0 mmol/L (180 mg/ dL) are set as markers of increased risk for CHD (Wood et al.,1998).

Disorders of lipoprotein metabolism were previously classified as hyperlipoproteinemias and were defined as an increase in lipoprotein levels above the values that are average for 95% of the population, that is, they were defined as values within two standard deviations (SD) above or below the mean value for the population (Steinberg and Gotto, 1999). Today, the classification according to Fredrickson and colleagues, recognized by the World Health Organization (WHO), is still in use (Beaumont, 1970; WHO 2021). This classification phenotypically categorizes 5, actually 6 types of hyperlipoproteinemias (Type I, IIa, IIb, III, IV and V) only according to which lipids and lipoproteins are elevated, regardless of etiology. WHO Fredrickson classification of lipid disorders is associated with clinical disorders (Table 1).

Table 1. Fredrickson classification of primary hyperlipidemias

Hyperlipoproteinemia	Name of disease	Elevated lipoprotein	Elevated lipid fraction
Type I	Hyperchylomicronemia	Chylomicrons	Triglycerides ++
Type IIa	Familial hypercholesterolemia	LDL	Cholesterol++
Type IIb	Familial combined hypercholesterolemia (hyperlipidemia)	LDL and VLDL	Cholesterol ++ and triglycerides +
Type III	Dysbetalipoproteinemia	IDL	Triglycerides + and cholesterol +
Type IV	Familial hypertriglyceridemia	VLDL	Triglycerides ++ Cholesterol N+
Type V	Familial lipoprotein lipase deficiency	VLDL and Chylomicrons	Triglycerides ++ and cholesterol +

+ = increased; ++ = greatly increased; N= normal; N+ = normal or increased (adapted from Chandra et al.,2014; WHO, 2021)

Cholesterol, triglycerides and phospholipids are the main lipids in the body. They are transported in the plasma bound to special proteins - apolipoproteins (apoproteins), forming hydrophilic lipoprotein complexes. They are classified into five main groups. Classification is made by size, density, electrophoretic mobility, as well as lipid and protein content (Table 2).

Table 2. Main lipoprotein characteristics

Lipoprotein	Density,g/dL	Mol. mass, kDa	Diameter, nm	Content of lipids, %		
				TG	C	PL
chylomicrons	0.95	400×10^3	75–1200	**80–95**	2–7	3–9
VLDL	0.95–1.006	$10–80 \times 10^3$	30–80	**55–80**	5–15	10–20

IDL	1.006–1.019	5–10 × 10^3	25–35	20–50	20–40	15–25
LDL	1.019–1.063	2.3 × 10^3	18–25	5–15	**40–50**	20–25
HDL	1.063–1.210	1.7–3.6 × 10^2	5–12	5–10	15–25	20–30

VLDL - very low-density lipoprotein
IDL – intermediate-density lipoprotein
LDL – low-density lipoproteins (with subgroups LDL_1,LDL_2)
HDL – high-density lipoproteins (with subgroups HDL_2, HDL_3iHDL-C)
TG - triglycerides
C – Sum of free and esterified cholesterol
PL, phospholipids (the rest of the percentage content of lipoproteins is made up of apoproteins).

Based on localization in relation to serum proteins in electrophoretic separation, lipoproteins are divided into α-lipoproteins, pre-β-lipoproteins, β-lipoproteins, while chylomicrons lag behind at the site of application.

Treatment of dyslipoproteinaemia

Treatment of dyslipoproteinaemia, as a separate disease, is carried out as a part of the treatment of CHD, and includes non-pharmacological and pharmacological measures.

Diet is the treatment of first choice in non-pharmacological treatment of elevated serum cholesterol values, both in patients suffering from primary, and in those suffering from secondary disorders of lipid metabolism. It is based on reducing the intake of saturated fatty acids from food of animal origin, increasing the intake of fruits, vegetables and fish (Dwyer, 1997; Diab, Dastmalchi, Gulati and Michos, 2023). The main goal of diet, as a therapy, is to reduce the elevated level of cholesterol in the serum, while at the same time, maintaining an adequate composition of food. According to NCEP *Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* (1994), diet therapy consists of two phases, Step I and Step II. Step I diet implies intake of saturated fatty acids in an amount that corresponds to 8 to 10% of total calories, 30% and fewer calories from total fats and cholesterol less than 300 mg/day. If the desired results are not achieved with the diet in Step I, it is switched to Step II, which implies intake of saturated fatty acids in an amount less than 7% of total calories and cholesterol less than 200 mg/day. In some patients, restriction of total fat intake causes a decrease in HDL-C and an increase in serum triglycerides (Knopp et al. 1997). A decrease in the concentration of HDL-C is undesirable, especially when the values in the serum are less than 0.9 mmol/L (35 mg/dl). This phenomenon is primarily a consequence of increased intake of carbohydrates and, most likely, increased intake of polyunsaturated fatty acids. Monounsaturated fatty acids lower the level of LDL-cholesterol without affecting the level of HDL-cholesterol.

An alternative strategy is the “Mediterranean diet”, which keeps the total fat intake at 35-40% of the total calorie intake, but replaces saturated fats with monounsaturated, such as those found in olives, peanuts, avocados and their oils. This diet is equally effective in lowering LDL-C but is less likely to reduce HDL-C (Lorgeril et al., 1999). Due to the significant fat intake, this diet does not lead to weight loss, so a low-fat diet is still recommended for overweight patients with dyslipoproteinaemia.

However, there are still contradictory views on which sources of certain types of fatty acids of plant origin (sunflower, soybean, olive or tropical oils) would satisfy the body’s needs, without having a harmful effect on the level of total cholesterol and triglycerides in the serum.

Adequate ***physical activity***, in addition to diet, is considered an essential element in the non-pharmacological treatment of elevated serum cholesterol concentrations. Both, weight reduction and physical activity, not only affects the reduction of LDL-cholesterol, but also causes a decrease in the level of triglyc-

erides, an increase in HDL-cholesterol, affects the reduction of high blood pressure, and reduces the risk of diabetes (Pescatello, Murphy and Costanzo, 2000; Williams and Thompson, 2013; Mann, Beedie, and Jimenez, 2014). Therefore, the risk of CHD is reduced in several ways.

Problem statement

Until the late 1990s, when hypolipemic drugs known as statins, were for the first time approved in Bosnia and Herzegovina, different types of hypolipemic diets were recommended to patients with dyslipoproteinaemias. Hypolipemic diet, which would be acceptable and understandable for all patients who need to adhere to this way of eating, has has not been developed. Recommendations such as "total cholesterol intake should be less than 300 mg per day" represent ambiguity for the patient, i.e. makes it difficult for them to be motivated to adhere to the recommendations within this diet. So, we made a new recommendations as a "modified diet" combining Step I, Step II and Mediterranean hypolipemic diet. The aim of our study was to evaluate the influence of modified Step I, Step II and Mediterranean diet, as well as low grade physical activity, on serum lipids in patients with Fredrickson Type IIa (Familial hypercholesterolemia) and IIb (Familial combined hyperlipidemia) primary dyslipoproteinaemia.

MATERIALS AND METHODS

Study design

The study was conducted as an open, prospective, longitudinal study during 2000, in the settings of real life, designed as two phase trial. Phase I (duration 4 weeks) was conducted in accordance to the rules of hypolipemic drug administration, which imply that every patient must undergo a hypolipemic diet in the settins of real life, for at least 4 weeks before starting the drug therapy. Guided by these rules, all patients with Type IIa and IIb dyslipoproteinaemia were subjected to a hypolipemic diet that is a modification of Step I, Step II (NCEP) and the Mediterranean diet, adapted to the habits and social status of the population. Within the recommended dietary measures, patients were not deprived of any type of food - cereals, pasta, milk and milk products, meat, fruits,vegetables and fats. All patients, apart from verbally, also received written recommendations for a modified diet in form of individualised dietary counselling. Direct phone number, in case of any ambiguities, was available all the time for consultations. The minimum physical activity involved a daily walk lasting at least 1 hour. After 4 weeks of modified diet, all patients underwent a control status of lipid metabolism. Patients whose cholesterol values in the control status were above the laboratory reference range and above target values recommended by the Working Group of the Association of European Societies, were included in Phase II which implied the use of statins in one daily dose, at the evening and this is part of separate duiscussion.

Subjects

After screening one hundred outpatients from the Clinic for Heart Diseases and Rheumatism of the University Clinical Centre Sarajevo, 20 drug-naïve patients with Type IIa and IIb disorders of lipid/lipoprotein metabolism, who met all inclusion criteria and none of the exclusion criteria, were included in the study. All patients voluntarily signed Informed Consent.

Parameters

Parameters for evaluation of diet effects on serum lipid levels were: total cholesterol (TC), low-density lipoprotein – cholesterol (LDL-C), high-density lipoprotein – cholesterol (HDL-C), triglycerides

(TG), ApoB as well as very low density lipoprotein – cholesterol (VLDL-C), ApoA1, phospholipids, total lipids, lipoprotein electrophoresis, index bata/alpha, degree of lipemia, appearance of serum, TC/HDL-C ratio, atherogenic index based on LDL/HDL cholesterol ratio.

Material and equipment

Blood samples, for analyzing serum lipid levels, were taken in the morning from the cubital vein, after overnight fasting period of at least 12 hours. Determination of lipid/lipoprotein status was performed in the Laboratory for Lipids of the Institute of Clinical Biochemistry, University Clinical Centre Sarajevo. Categorization, in accordance with Fredrickson classification, was also performed in this laboratory, by qualified specialist, in order to ensure maximum objectivity and reliability of test results. The *reference range* values in this study were the values of the Laboratory for Lipids, based on annually population statistic evaluation, while the *target values* were those recommended by European guideline form 1998. Total cholesterol, triglycerides, HDL-C, Apo AI and Apo B were determined by direct methods on the Dimension® clinical chemistry system with specific reagents. Phospholipids were also determined by the direct enzymatic method on the ABBOTT Spectrum Diagnostica apparatus. LDL-C was calculated by the Friedwald equation as follows: LDL-C mmol/L = total cholesterol –(triglycerides/2.2) – HDL-C. Lipoprotein electrophoresis was performed on cellulose acetate, while Index beta/alpha was calculated by the formula: (preβ +β)/ α. The atherogenic index was calculated as LDL/HDL cholesterol ratio.

Statistics

The baseline values before the beginning of the modified diet, were the initial values for evaluation of the diet effects after 4 weeks. At the same time, each patient served himself as a control, so the significance of the differences in mean values for the group, between two measurements, was calculated by Student's t-test for small dependent samples (paired t-test). The percentage reduction or increase of certain parameters in the test was calculated using basic mathematical operations.

RESULTS AND DISCUSSION

After screening one hundred patients from the Clinic for Heart Diseases and Rheumatism of the University Clinical Centre Sarajevo, 20 drug-naïve patients (11 mail and 9 femail, average age 55 years), with Type IIa (10 patients) and IIb (10 patients) dyslipidaemia were consecutively included in the study. The arrangement by type of dyslipidaemia was random. Comparations with results from other studies were intentionally done based on data from late 1990s and early 2000s, as that was the time period when our study was conducted and target values for serum lipids were published by American and European guidelines.

Analyzing the results obtained from this study, a significant decrease in total cholesterol (TC) can be observed after four weeks period of diet. The achieved TC reduction was 9.7% (P = 0.001), which correlates with the values of 7% to 16% described in young, healthy non-obese mail individuals (Jansen et al.,1998) and 8.5%, based on data from systemic overview od 19 randomised controlled trials, but achieved after 3 months of modified fat intake (Tang et al.,1998), instead after four weeks, as in our study. As our „modified diet" was a combination of Step I, Step II NCEP diet and Mediterranean diet, recorded decrease of total cholesterol values are in fact 10% what is in accordance with the data specified by Kris-Etherton and colleagues from 1988, but with difference is a quantity of cholesterol content in recommended diet. The fact is that Kris-Etherton and colleagues states that expected plasma total cholesterol (specifically low-density-lipoprotein cholesterol) reduction is approximately 10% to 20% when dietary saturated fatty acids

and cholesterol are decreased to less than or equal to 7% of calories, and less than or equal to 200 mg of cholesterol per day, while our patients received recommendations based on cholesterol intake less than 300 mg/day.

Although the reduction in triglyceride levels was calculated to be 15% (P = 0.125), it was not statistically significant. In the study conducted in 97 males and fimales, who dropped out from dietary weight management after 16-18 weeks of treatment, and after weight loss of 9-9.4 kg, when they rejoin to the program for a second time, the values of serum cholesterol and triglycerides were 15% and 26% less for females, and 17% and 24% less for males, compared to their respective values at the beginning the first attempt (Dhurandhar and Kulkarni, 1995). The above is important as it confirms the need for the longer duration of diet modification, as well as the possibility of longer duration of the effects achieved by diet.

Changes in serum lipid/lipoprotein concentrations after 4 weeks of modified diet and low grade physical activity

Lipids/lipoproteins	Mean baseline	Std. Error of Mean	Mean after 4 weeks	Std. Error of Mean	Refer-encerange after 4 weeks	t-test	P	%change	Significant
TC (3.1-6.5 mmol/L)	8.25	0.332	7.45	0.222	↓	3.772	0.001	-9.7%	+
TG (0.11-2.05 mmol/L)	2.58	0.3	2.18	0.155	↓	1.607	0.125	-15.5%	-
Apo B (0.54-1.47 g/L)	1.68	0.109	1.42	0.095	↓R	2.811	0.011	-15.5%	+
Apo AI (1.08-2.09 g/L)	1.56	0.056	1.42	0.0551	↓R	3.059	0.006	-9%	+
HDL-C (1.06-1.94 mmol/L)	1.29	0.11	1.23	0.0731	↓R	0.936	0.361	-4.7%	-
VLDLC (0.13-1.0 mmol/L)	1.10	0.1	0.97	0.0697	↓R	1.962	0.065	-11.8%	-
LDLC (2.88-4.87 mmol/L)	5.58	0.3	5.25	0.259	↓	1.228	0.234	-5.9%	-
TC/HDL-C ≤ 5	6.84	0.556	6.57	0.503	↓	0.556	0.585	-3.9%	-
Phospholipids 1.81-3.23 mmol/L	4.18	0.169	3.75	0.0863	↓	3.236	0.004	-10.3%	+
Total lipids (2.7-7.0 g/L)	8.77	0.352	7.79	0.187	↓	2.932	0.009	-11.1%	+
Alpha lp. (0.25-0.35)	0.198	0.0148	0.203	0.0153	↑	-0.368	0.717	+2.5%	-
Pre $Beta_1$ (0.08-0.22)	0.24	0.0275	0.21	0.0189	↓R	1.399	0.178	-12.5%	-
Beta (0.45-0.48)	0.56	0.0196	0.59	0.0136	↑	-1.461	0.160	+5.4%	-
Index beta/alpha (1.2-2.3)	4.7	0.453	4.4	0.368	↓	0.660	0.517	-6.4%	-
Degree of lipemia (10-35)	45	1.409	40.45	1.150	↓	2.705	0.014	-10.1%	+
Atherogenic index (LDL/HDL) (2.4-4.8)	5.8	0.499	5.6	0.503	↓	0.556	0.585	-3.4%	-

*R –values in reference range of laboratory

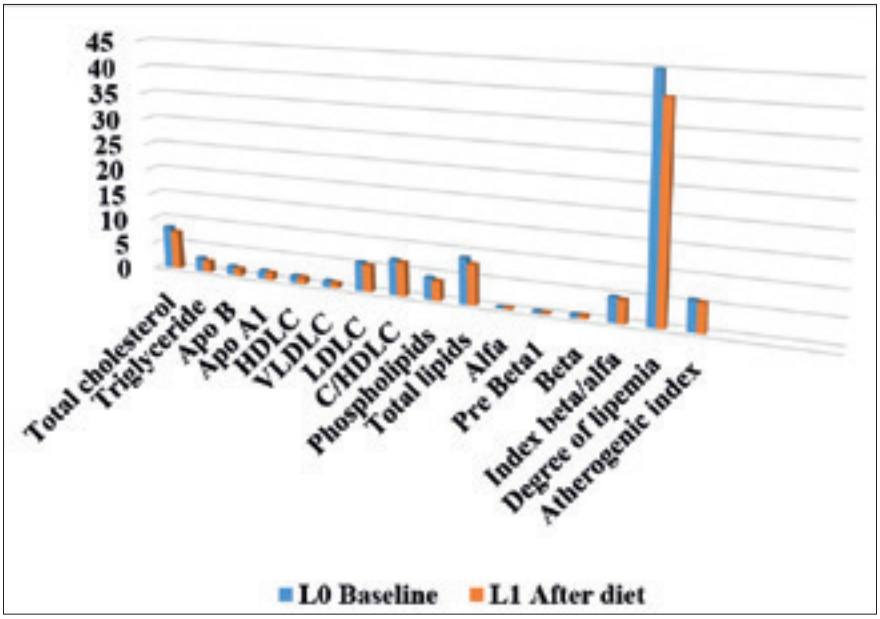

Chart 1. Changes in mean values of serum lipids/lipoproteins after 4 weeks of diet and physical activity

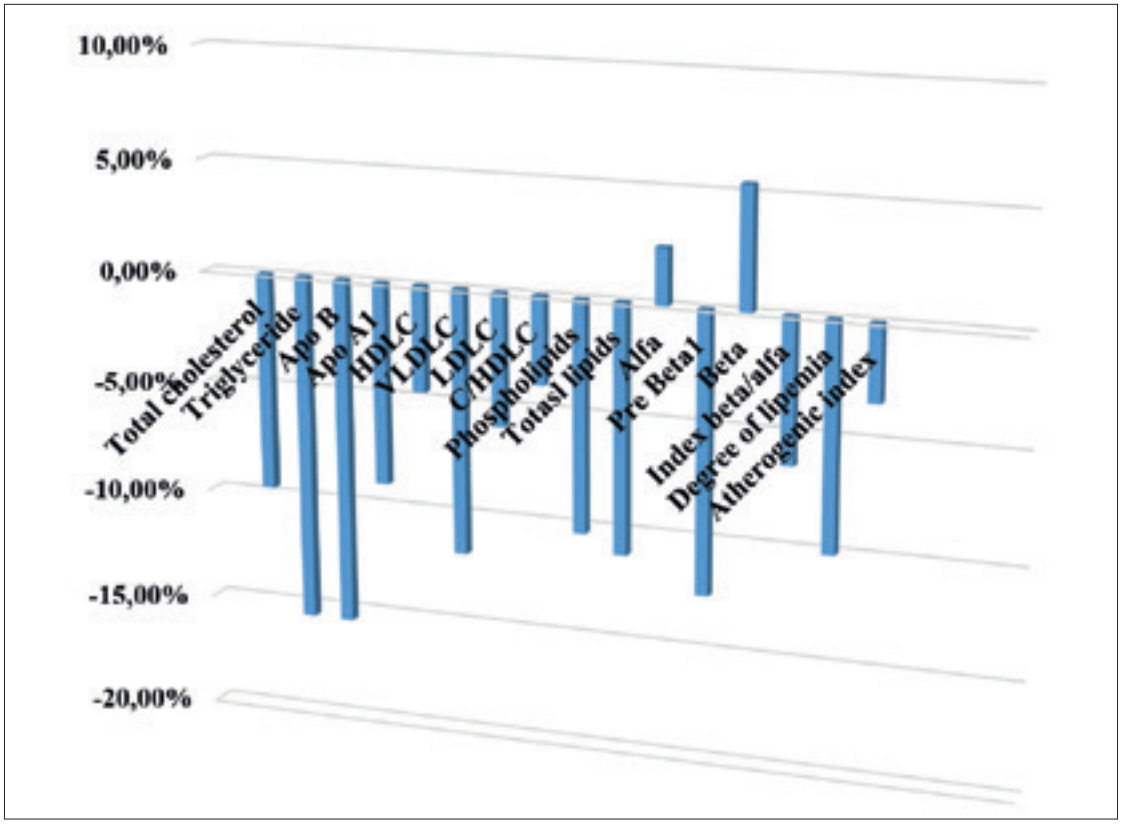

Chart 2. Percentual changes of serum lipids/lipoproteins after 4 weeks of diet and physical activity

In our study, a significant decrease in Apo B was recorded, with reduction of Apo B levels of -15.5% (P = 0.011) which was identical to that of triglycerides (–15.5%; P = 0.125), but unlike for triglycerides, this reduction for Apo B was statistically significant. But, if we consider that each VLDL and LDL particle contains one molecule of Apo B and that measuring Apo B accurately measures the total number of VLDL and LDL, of which 90% are LDL (Sniderman, Bergeron and Frohlich, 2001), than, if we add percentages of VLDL and LDL decrease (-11.8% and -5.9%), 90% of this total value is 15.93 what is approximately 15.5%, which in fact is the percent of Apo B reduction.

Analyzing the measurement of the level of Apo AI after period of the diet, a statistically significant decrease of 9% (P=0.006), compared to the baseline values was observed. All values were within a laboratory reference range. This significant decrease of Apo AI did not follow the decrease in HDL of - 4.7% (P = 0.361), which was not significant, but also within a laboratory reference range, although Apo AI is the major structural and functional protein component of HDL and it constitutes approximately 70% of HDL (Mangara, Nanda and Panda, 2016). Similar findings were reported by Lichtenstein and colleagues (1993) after 32-day study phase in which corn oil was replaced with cornoil margarine in stick form, as two thirds of the fat in the National Cholesterol Education Program (NCEP) Step II diet. The change in Step II NCEP diet also resulted in decrease of HDL-C and Apo AI levels, but in reverse manier as mean values for HDL-C decreased by 9% and Apo AI by 0.4% ($P < 0.01$ for HDL-C) on corn oil-enriched diet and 10% and 3% lower on margarine-enriched diet ($P < 0.01$ for HDL-C). These negative effects are attributed to hydrogenation present in margarine (Lichtenstein et al.,1993).

On the other hand, during our study, no statistically significant changes in the level of HDL-C were recorded, which correlates with data from the literature (Solov'eva, Rozhkova, Tvorogova and Kukharchuk, 1999). The percentage changes correlates with the data from literature, so recorded decrease in the level of HDL-C (-4.7%; P = 0.361) is a known negative effect of hypolipemic diets (Knopp et al. 1997, Oliver, 1998).

Our "modified diet" resulted in a non-significant reduction of VLDL-C (-11.8%; P = 0.065), and no significant changes in LDL-C values (- 5.9%; P = 0.234), which is in accordance with data from the literature (Knopp, 1997). However, the reduction achieved for VLDL-C resulted in the value returning to the laboratory reference values, while the LDL-C values all the time were above the upper limit of the laboratory reference values, what is less than 10% as Wadhera and colleagues states in their work from 2016, but after 5 weeks of pure Mediterranean diet.

Our modified diet did not lead to a significant decrease in TC/HDL-C ratio (-3.9%; P = 0.585), but still it was a decrease which is of clinical significance (Mensink, Zock, Kester and Katan, 2003). In his work from 2010, Kelly states that when two versions of a Mediterranean diet were compared with a low-fat diet, the Mediterranean diets lowered the total-to-HDL cholesterol ratio more than the low-fat diet, referring on data from randomized trial that was conducted in asymptomatic persons 55 to 80 years of age at high cardiovascular risk. There were no classification of dyslipidemia, primary or secondary, or even more by Fredrickson classification (Estruchet al., 2006). In this context, our combined "modified diet" (Step I, Step II and Mediterranean), can be considered as a low fat diet.

Taking into account that oxidation of phospholipids, containing polyunsaturated fatty acids present in plasma lipoproteins results in formation of a variety of reactive lipid aldehydes and oxidized phospholipids that convert these lipoproteins to atherogenic particles (Berliner, Leitinger ans Tsimikas, 2009; Linton et al., 2019), the significant decrease of phospholipids in our study (-10.3%; P = 0.004) is considered as an positive effect of our modified diet, as well as for lowering the total lipids concentration that was also statistically significant (-11,1%; P = 0.009).

Total plasma lipid levels in our study were significantly reduced by -11.1% (P = 0.009) what, together with other parameters, serves as a confirmation of adherence to the diet recommended.

As mentioned before, based on localization in relation to serum proteins, in electrophoretic separation lipoproteins are divided into α-lipoprotein, pre-β_1-lipoprotein, β-lipoprotein, corresponding to HDL, VLDL and LDL. One can assume that increase in α-lipoprotein of +2.5% (P = 0.717), and β-lipoprotein of +5.4% (P = 0.160) recorded in our study are inversly related to HDL or LDLvalues, but it should be kept in mind that values for HDL and LDL are in fact values for HDL-C and LDL-C. Back in 1964, De

Oliveira described in his work that in patients with coronary heart disease, serum β-lipoprotein and its cholesterol content are elevated, whereas levels of serum alpha cholesterol are diminished. Before De Oliveira, Barr and colleagues in 1951, suggested that patients who survived a coronary occlusion (acute myocardial infarction) or with other unequivocal evidence of atherosclerosis-related complications, had several abnormalities in plasma proteins, including a reduction in the alpha lipoprotein content (Ndrepepa, 2021). The baseline values of α-lipoprotein in our study were below lower reference limit (α-lp. = 0.198, reference range 0.25 – 0.35), almost reaching lower reference limit after four weeks of diet (α-lp. = 0.203). For β-lipoprotein, values were all the time above uper reference limit (baseline βlp. = 0.56; after diet βlp. = 0.59). Nevertheless, the increase in α-lipoprotein is a positive effect of our diet while increase in β-lipoprotein still needs to be explained. However, the proatherogenic index beta/alpha decreased by -6.4% (P = 0.517) and all changes were statistically not significant but were the result of adherence to the diet. Further, α-lipoprotein values increased close to the reference ones, pre-β_1-lipoprotein reached rerefence value after four weeks of diet (pre-$\beta_1$lp. = 0.21, reference values 0.08 - 0.22) and β-lipoprotein values remained above uper reference limit.

The degree of lipemia decreased significantly (-10.1%; P = 0.014) following decrease in triglycerides and lipoproteins which are the most common cause of turbidity (Kroll, 2004). Values of atherogenic index (LDL/HDL cholesterol), as a strong predictor of cardiaovascular events (Barter al, 2007), decreased for -3.4% (P = 0.585) in our study after four weeks of modified diet. Although these values were not statistically significant, the decrease is still evident.

After a period of adherence only to a diet, the subjective feeling characterized by “excellent” was recorded in all 20, or 100% of patients. The loss of body weight ranged from 1.5 to 4 kg, but since the measurement of body weight was not performed every time on the same measuring instrument and under the control of the medical staff, these data were not taken into statistical evaluation.

CONCLUSION

Recognizing an underestimated value and role of dietary modifications in everyday life of patients with hypercholesterolaemia, we decided to actualize our investigation from 2000, as we witnes that lipid lowering drugs are prescribed almost as soon as elevated serum lipid levels are detected. The reference range values in this study were the values of the Laboratory for Lipids, University Clinical Centre Sarajevo, which are higher than target values recommended by European guidelines. Compared to baseline values, decreased values were recorded for 14 out of 16 laboratory parameters from complete lipidogram. Two parameters, which values increased were antiproatherogenic α-lipoprotein (+2.5%) and proatherogenic β-lipoprotein (+5.4%), both statistically not significant. None of the target values, recommended by European guideline, were achieved. Based on the results from our study, lowering of serum lipid levels was achieved after four weeks of modified diet and low grade of physical activity, with positive effects on lowering serum proatherogenic lipids and on increase of antiproatherogenic α-lipoprotein. Larger number of drug-naïve patients with Type IIa and IIb dyslipoproteinaemia should be included in further investigations, physical activity should be more intense and for a longer duration of modified diet. Our study confirms that modified diet should precede the decision for hypolipemic drug use.

Limitations

Comparisons with results from other studies were intentionally done based on data from late 1990s and early 2000s, as our study was conducted during that period and target values for serum lipids were published in 1998 by American and European guidelines for the management of dyslipidaemias. In recent literature, the results of different statin drugs efficacy are presented, while there is a lack of data on the effectiveness of the diet itself.

Conflict of interest
There are no conflicts of interest.
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Review

Therapeutic Options for the Treatment of Community-Acquired Pneumonia Caused by Streptococcus Pneumoniae

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ABSTRACT: *Streptococcus pneumoniae* is the most common cause of community acquired pneumonia, acute otitis media, meningitis and other infections, asymptomatic colonizing nasopharynx of healthy children and adults. Since late 1970s there has been a steady decline in the susceptibility of *Streptococcus pneumoniae* to various groups of antibiotics.The number of antibiotic-resistant pneumococcal infections has decreased due to the success of the pneumococcal conjugate vaccine. In addition to vaccination, guidelines for treatment of pneumococcal disease are developed by various professional and scientific associations, intending to slow or reverse drug-resistant pneumococcal infections. The aim of this work is to provide a generated information about therapeutic options for the treatment of community-acquired pneumonia caused by *Streptococcus pneumoniae*, based on the recommendations and statements from various guidelines developed by different proffesional and scientific associations but limited on drugs available on the market in Bosnia and Herzegovina.

Keywords: pneumonia, *Streptococcus pneumoniae,* guidelines, antibiotics.

INTRODUCTION

In 1881, the microorganism, later known as *pneumococcus* due to its role in causing pneumonia, was first isolated simultaneously and independently by the American army physician George Sternberg and the French chemist Louis Pasteur.But, for the first time pneumococcus was described by German pathologist Edwin Klebs, who in 1875 observed the pneumonia bacterium under a microscopefrom the pleural fluid of patients with pneumonia (Tukbekova et al, 2019). That is what we now believe to be *Streptococcus pneumoniae*.

Streptococcus pneumoniae is a gram-positive, alpha-hemolytic, encapsulated bacteria that grows in chains or pairs (diplococci), with more than 100 known serotypes.It colonizes the nasopharynx of 5-10% healthy adults and 20-40% of healthy children on any single occasion (Fauci et al, 2009). The spread of, often asymptomatic colonized, bacteria from the nasopharynx causesotitis media and sinusitis,aspiration pneumonia andinvasion in normally sterile areas in the body can cause sepsis or meningitis.Other possible infections are endocarditis, septic arthritis, and, rarely, peritonitis.

Pneumonia is considered the most common clinical manifestation of pneumococcal disease in adults. *Streptococcus pneumoniae*(*pneumococcus*) historically hasbeen and still remains the most common cause of pneumonia. It is the most commonly identified bacterial cause of Community - acquired Pneumonia (CAP) requiring hospitalization andis the most common cause of death from pneumonia worldwide (Centers for Disease Control and Prevention - CDC, 2022).

Prevalence

Previously, in the United States, 5 to 15% of CAP cases were attributed to *pneumococcus*. However, recent quantitative molecular and bacteriological data indicate that this is an underestimate and suggest that nearly 22% of hospitalized cases may be caused by *pneumococcus*as well as in Europe (Musher et al.,

2020; Bjarnason et al., 2018), andeven more, to 30.5% in developing countries (Para et al., 2018).Morbidity and mortality from serious pneumococcal disease is highest in children and elderly people with chronic diseases.

Case fatality rates can be high for invasive pneumococcal disease, ranging up to 20% for sepsis and 50% for meningitis in developing countries (Worl Health Organization - WHO, 2018).Mortality associated with pneumococcal pneumonia in hospitalized patients is high, ranging from18% for adults aged < 65 years and 23% for the older than 65 years (Michelin et al, 2019).In 2008, an estimated 541,000 HIV-negative children under the age of 5 died from pneumococcal disease (WHO, 2018).

Therapeutic options in the treatment of pneumococcal disease are limited. *Streptococcus pneumoniae* was universally susceptible to penicillin until the late 1970s (O'Neill, Gillespie, and Whiting, 1999). Since then, there has been a steady decline in the susceptibility of *Streptococcus pneumoniae* to antibiotics. The bacteria has developed resistance to several antibiotics, including β-lactams, macrolides, tetracyclines, trimethoprim-sulfamethoxazole, vancomycin, and fluoroquinolones (Murphy et al., 2021).

According to the American CDC - *Centers for Disease Control and Prevention*, pneumococcal bacteria are resistant to one or more antibiotics in 3 out of every 10 cases.The number of antibiotic-resistant pneumococcal infections has decreased due to the success of the pneumococcal conjugate vaccine.

The use of the pneumococcal vaccines contributed to the reduction of resistance at least through the direct reduction of organisms and strains carrying resistance genes that are specifically targeted by the vaccine, andthrough a secondary effect thanks to the reduction of febrile illnesses that often lead to the use of antibiotics.Besides the vaccination, appropriate antibiotic use can also slow or reverse drug-resistant pneumococcal infections (CDC, 2022).There are different methods of antibiotic administration within the framework of rational (reasonable) administration.To understand the relationship between drug dose and efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics must be integrated (Jacobs, 2001).There are two main patterns of antimicrobial activity to distinguish:

a) concentration - dependent bactericidal activity which needs maximised antimicrobial concentration (aminoglycozides, quinolones and azalides)

b) time - dependent bactericidal activity which is characteristic of many classes of antibiotics, such as β-lactams and macrolides. By this way, an attempt is made to optimize the duration of exposure of the pathogen to the antimicrobial drug.

When *Streptococcus pneumoniae* is in question, **time - dependent bactericidal activity** is of the greatest interes and the main PK/PD parameter that correlates with the efficacy of time-dependent antimicrobials is the serum concentration present for 40-50% of the dosing interval. This concentration is the sensitivity limit or cut-off point for the dosing regimen used. The best two examples are given by Jacobs in his work from 2001 where he states the use of two different doses of amoxicillin, administered by different dosing shedule.

Example 1.

The serum concentration of amoxicillin when 500 mg of this drug is administered orally at 8-hour intervals over a 24-hour period indicates that amoxicillin has an elimination half-life of 30-45 minutes. With this dosing regimen, amoxicillin reaches a concentration of 2 mg/L in 3.3 h of each 8-hour dosing interval (or 9.9 h in a 24-hour day), which is 41% of the dosing interval. Therefore, this regimen achieves an amoxicillin concentration of 2 mg/L for more than 40% of the dosing interval, and should therefore be active against organisms with an MIC ≤2 mg/L (minimal inhibitory concentration).

Example 2.

If 875 mg is given at 12-hour intervals, the amoxicillin concentration exceeds 2 mg/L during 4.5 h of each dosing interval (9 h in a 24-hour day). Therefore, this regimen achieves an amoxicillin concentration exceeding 2 mg/L for approximately 40% of the dosing interval.

Thus, both dosing regimens achieve serum concentrations above 2 mg/L for about 40% of the dosing interval.

Mechanism of resistance

The mechanism of pneumococcal resistance to penicillin and cephalosporins is based on a change in the penicillin-binding protein (PBP). Mutations that alter PBP result in reduced binding affinity for these drugs, making them less effective.This type of resistance can be overcome if the concentration of the antibiotic at the site of infection exceeds the MIC of the organism by 40-50% of the dosing interval(Iyer, 2023). It is important to emphasise the two main virulence factors of *Streptococcus pneumoniae* that are polysaccharide capsule that surrounds the bacteria, and the toxin pneumolysin which is released during *Streptococcus pneumoniae* autolysis (Martner, Dahlgre, Paton & Wold, 2008).

Capsule is mainly composed of polysaccharides, with each capsule type having a different composition and linkage of sugars and other components, resulting in more than 100 different serotypes on the basis of antibody reactions with the capsule. For the pneumolysin it has been shown that it can stimulate the innate immune response including release of the inflammatory cytokine from the host's airway epithelial cells (Küng et al, 2014). In short, capsule inhibits antibody binding, directly inhibits phagocytosis, and prevents capture by neutrophiles, while pneumolysin inhibits neutrophil and oxidative burst, induces neutrophil lysis and inhibits neutrphil chemotaxis. So, these are numerous challenges for antibiotics to be effective against this bacteria, making these two virulence factors main therapeutic targets.

Mechanisms of action of antibiotics

Based on their *mechanism of action*, antibiotics can be classified in four major groups (Li F., Collins J.G. and Keene F.R., 2015).

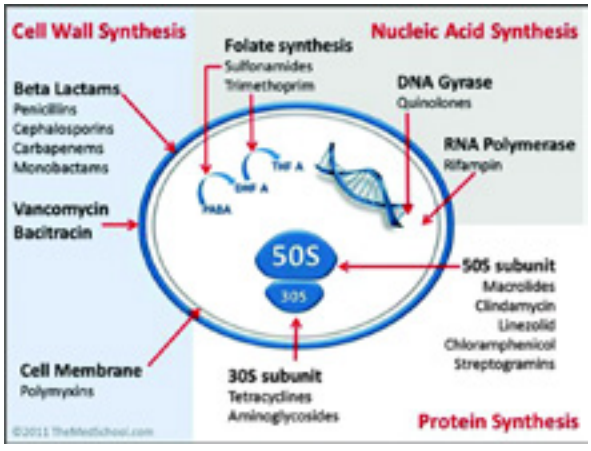

Figure 1. Classification of antibiotics by mechanism of action. (Image by Kendrick Johnson: Creative Commons Attribution-Share Alike 3.0 Unported license) in Li et al, 2015.

1. Inhibitors of cell wall synthesis (e.g. penicillins, cephalosporins, carbapenems, monobactams, glycopeptides)
2. Antibiotics that disrupt cell membrane (e.g. polymyxins)

3. Inhibitors of nucleic acid synthesis (e.g. quinolones, rifampicin)
4. Inhibitors of protein synthesis (e.g. tetracyclines, aminoglycosides, macrolides)

According to their mechanism of action antibiotics are classified based on the *effects* that they produce in two major groups:

a) bactericidal (killing the bacteria)

b) bacteriostatic (stopping bacterial growth)

Bactericidal antibiotics are those from group 1., 2. and 3. while bacteriostatic antibiotics are mainly from group 4. as well as inhibitors of folate synthesis. But, some bacteriostatis antibiotics can also act as a bactericidal, depending on their concentration(Fohner A.E., Sparreboom A., Altman R.B. and Klein T.E., 2017). Example is macrolide antibiotic erythromycin, which in low concentrations is classified as bacteriostatic but in high concentrations is classsified as a bactericidal.

Note:The above is of high importance for understanding the therapeutic options for pneumococcal disease, especially regarding dose levels and dosing regimens used.

Therapeutic options for the treatment of Community - acquired pneumonia

Various professional associations and various guidelines agree on therapeutic options for treatment of pneumococcal disease. Our intention is to present the main recommendations from different guidelines developed by respected scientists and professionals, available online *in extenso,* that can be used in Bosnia and Herzegovina, taking into account the drugs that are present on our market. Other drugs will not be included in this work.

In every guideline for the treatment of pneumococcal disease is stated that ***initial antibiotic therapy is empiric***. This empiric therapy varies depending on:disease severity, comorbidities, patient's history of recent antibiotic use, probability of infection with antibiotic-resistant pathogens, simultaneous infection with *Pseudomonas* or *Methicillin-resistant Staphylococcus aureus* (MRSA), allergies or drug intolerance.

Pneumonia (Comunity - acquired Pneumonia – CAP)

The main recommendations for treatment of ***Community Acquired Pneumonia (CAP)*** are summarized from following guidelines:

- "Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America" (Metlay etal, 2019)
- "ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia"- first international guidelines (Martin-Loeches et al, 2023)
- "Pneumonia (community-acquired): antimicrobial prescribing"(NICE guideline, 2019)
- "Updated Clinical Practice Guidelines for Community-Acquired Pneumonia"(Sucher, Knutsen, Falor & Mahin, 2020)

Considering empiric therapy for CAP, it has to be emphasized that there are different stages of disease severity as well as different patient populations regarding comorbidities, so the way of administration and the dose levels are different for different groups of patients, as follows:

1. Outpatients without comorbidities,
2. Outpatients with comorbidities
3. Hospitalized patients who are not in intensive care unit (ICU)

4. Hospitalized patients in the intensive care unit (ICU)
5. Patients allergic to penicillin

1. **Outpatients without comorbidities** are those with no comorbidities/previously healthy, age < 65 years, no recent use of antibiotics, no risk factors for MRSA or Pseudomonas aeruginosa. The drug of first choice is **amoxicillin 1 g peroral (PO) q8h** (every 8 hours, three times a day), OR, depending on patient's characteristics (allergies, intolerance) azithromycin 500 mg PO one dose, then 250 mg PO daily orclarithromycin 500 mg PO q12h (twice daily) OR clarithromycin extended release 1000 mg PO daily OR doxycycline 100 mg PO q12h.
2. **Outpatients with comorbidities**(e.g. alcoholism, chronic heart/liver/kidney disease, malignancy, asplenia, diabetes mellitus) and who have used antibiotics in the last 3 months. *Preferred*:β-**lactam combination** (**amoxicillin-clavulanate** 500 mg/125 mg PO q8hOR amoxicillin-clavulanate 875 mg/125 mg PO q12h PLUSmacrolides (azithromycin or clarithromycin) OR doxycycline (100 mg PO q12h). *Alternatively*:If there are no contraindications to the use of cephalosporins: cefpodoxime 200 mg PO q12hOR cefuroxime 500 mg PO q12hPLUS macrolide (azithromycin or clarithromycin) OR doxycycline (100 mg PO q12h).

If there are contraindications for β-lactam use: levofloxacin 750 mg PO q.d. (once daily) or moxifloxacin 400 mg PO q.d.

1. **Hospitalized patients who are *not* in intensive careunit** (ICU)

Therapy should be started as soon as CAP is suspected as a diagnosis, ideally within 4 hours of the patient's presentation.Factors determining the antibiotic regimen depend on the likelihood that MRSA or Pseudomonas is present. Risk factors for MRSA or Pseudomonas infection are:known colonization or previous infection with these organisms, especially from a respiratory tract specimen, andrecent hospitalization in the last 3 months, with intravenous (IV) antibiotics.

a) No suspicion on MRSA or Pseudomonas

Beta-**lactam combination** (**ampicillin-sulbactam** 1.5-3 g IV (intravenous) q6h (every 6 hours) OR ceftriaxone 1-2 g IV q24h OR cefotaxime 1-2g IV q8hPLUSazithromycin 500 mg IV/PO q24h OR doxycycline 100 mg PO q12h.

If there are contraindications for the above then levofloxacin 750 mg IV or PO q24h OR moxifloxacin 400 mg IV or PO q24h

Many observational studies indicate that macrolide regimens are associated with better clinical outcomes for patients with severe forms of CAP, possibly due to their immunomodulatory effects.

b) With known colonization or prior infection with ***Pseudomonas***, recent hospitalization with IV antibiotics, or other strong suspicion of *Pseudomonas* infection

Combination therapy, **antipseudomonal** β**-lactam (piperacillin/tazobactam** 4.5 g IV q6h OR cefepime 2g IV q8h OR ceftazidime 2g IV q8h OR meropenem 1 g IV q8h OR imipenem 500 mg IV q6h-PLUSone**antipseudomonal fluoroquinolone** (ciprofloxacin 400 mg IV q8h OR levofloxacin 750 mg IV q24h).

c) With known colonization or previous infection ***with Methicillin-resistant Staphylococcus aureus (MRSA)*** or another ***strong suspicion of MRSA*** infection**Initially add vancomycin** 15 to 20 mg/kg/dose IV q8h to q12h and adjust to therapeutic monitoring (TDM) OR linezolid 600 mg IV q12h.

If there are *contraindications* for macrolides and fluoroquinolones

Beta-**lactam combination** (**ampicillin-sulbactam** 1.5-3 g IV q6 h or ceftriaxone 1-2 g IV q24 h OR cefotaxime 1-2 g IV q8h) PLUSdoxycycline 100 mg q12h.

4. **Hospitalized patients *in the intensive care unit*** (ICU)

a) *No comorbidities*/previously healthy; age < 65 years; no recent use of antibiotics; *no risk factors for MRSA or Pseudomonas aeruginosa*

Beta-**lactam combination** (**ampicillin-sulbactam** 1.5-3 g IV q6h OR ceftriaxone 1-2 g IV q24h OR cefotaxime 1-2 g OR ertapenem 1 g IV q24h PLUS azithromycin 500 mg IV OR levofloxacin 750 mg IV or PO q24h OR moxifloxacin 400 mg IV or PO q24h.

b) *Present comorbidities* (eg alcoholism, chronic heart/liver/kidney disease, malignancy, asplenia, diabetes mellitus) and who have received antibiotics in the last 3 months *with* ***suspectedPseudomonas***:Combination of **antipseudomonal/antipneumococcal** β**-lactam** and **antipseudomonal fluoroquinolone**:**piperacillin-tazobactam** (4.5 g IV q6h) OR imipenem (500 mg IV q6h) OR meropenem (1 g IV q8h) OR cefepime (2 g IV q8h) OR ceftazidime (2 g q8h; activity against pneumococci is more limited than the above agents)PLUSciprofloxacin (400 mg IV q8h) OR levofloxacin (750 mg IV/PO q24h) The dose of levofloxacin is the same when given intravenously and orally, while the dose of ciprofloxacin is 750 mg orally q12h.

c) *Present comorbidities* (eg alcoholism, chronic heart/liver/kidney disease, malignancy,

asplenia, diabetes mellitus) and who have received antibiotics in the last 3 months with ***suspected MRSA***:**Initially add vancomycin** 15 to 20 mg/kg/dose IV q8h to q12hand adjust to therapeutic monitoring (TDM) OR linezolid 600 mg IV q12h.

Clindamycin 600 mg IV or PO q12his not empiric but directed therapy.

5. Patients allergic to penicillin

Approximately 10% of patients who received antibiotic therapy, report being allergic to penicillin, however, up to 90% of these patients do not have an actual allergy. The incidence of an anaphylactic reaction to penicillin is 0.02% to 0.04% and is mediated by a type 1 hypersensitivity reaction. The most commonly reported type of reactions are skin reactions.IgE antibodies decline over time so that,in patients who previously have been tested positive for penicillin allergy, in repeated tests an annual 10% reduction can be expected. Therefore, unless they receive penicillin, 80% to 100% of these patients will have a negative penicillin test 10 years after the first positive one (Patterson and Stankewicz, 2023).

Cross-sensitivity with other penicillin preparations, especially cephalosporins, resulted in the avoidance of its use.Earlier studies may have overestimated the cross-sensitivity between penicillins and cephalosporins, which was attributed to the β-lactam ring. This ring is present in the structure of both groups of these antibiotics.Later research showed that in determining immune reactions, the main determinant is the similarity between the R side chains of the first generation cephalosporins and penicillins, rather than their β-lactam structure(Patterson and Stankewicz, 2023).

Penicillins have one R side chain, while cephalosporins have two. If the penicillin side chain is similar to either of these two in cephalosporins, there is a higher risk of cross-sensitivity.This occurs more often with first and second generation cephalosporins than with third or fourth generation, making them a more attractive treatment choice for patients with proven penicillin allergy.

a) **Outpatients with comorbidities**

If there are *no contraindications for the use of cephalosporins*: cefpodoxime 200 mg PO q12hOR cefuroxime 500 mg q12hPLUS macrolide (azithromycin OR clarithromycin) OR doxycycline (100 mg PO

q12h)

If there are *contraindications for* β-lactam *use*: levofloxacin 750 mg PO q24h or moxifloxacin 400 mg PO q24h

b) **Hospitalized patients with comorbidities**

If there is *no contraindication for the use of cephalosporins:* cefpodoxime 200 mg PO q12hOR cefuroxime 500 mg q12h PLUS macrolide (azithromycin OR clarithromycin) OR doxycycline (100 mg PO q12h)

b) If there are *contraindications for* β-lactam *use*: levofloxacin 750 mg PO q24h OR moxifloxacin 400 mg PO q24h.

Note: Alternative antibiotics such as doxycycline (tetracycline), clarithromycin (macrolide) and erythromycin as an alternative macrolide in pregnancy, should be used only when there is a clinical reason not to use amoxicillin in patients with mild and moderate CAP.

These antibiotics have good activity against *Streptococcus pneumoniae*; however, because of their broader spectrum of activity and because some of them have additional safety warnings, the above notice should be kept in mind.

The committee of the first international guideline for the management of severe CAP (ERS/ESICM/ESCMID/ALAT , 2023)noted that there are no reasonable alternatives to dual therapy in adults who cannot receive penicillin, for example, because of penicillin allergy.The committee discussed the evidence that monotherapy with a fluoroquinolone (levofloxacin or moxifloxacin) was as effective as dual therapy with a β-lactam and a macrolide for people with moderate to severe CAP. However, they noted safety concerns with fluoroquinolones, such as tendon damage and aortic aneurysms. The Committee noted that the license was limited to CAP and agreed that ***fluroquinolones should only be used when other drugs cannot be prescribed or have been ineffective. As a recommendation N^{0}3 they also recommend the addition of macrolides, not fluoroquinolones, to beta-lactams as empiric antibiotic therapy in hospitalized patients with CAP*** (Martin-Loeches et al, 2023).

NEW ANTIMICROBIAL DRUGS FOR CAP

Tigecycline - glycylcycline class

Tigecycline is effective against multi-resistant strains of *streptococcus, vancomycin-resistant enterococcus (VRE), staphylococcus and methicillin-resistant staphylococcus (MRS), bacteroides, and enterobacteria.* It is also effective against *Acinetobacter,* which today is the cause of severe intrahospital infections. However, tigecycline does not work against *Pseudomonas*. Tigecycline is not the only new drug for CAP but, from this group of antibiotics, is the only one which is on market in Bosnia and Herzegovina.

America Food and Drug Administration - FDA, approved tigecycline in 2009 for adults with CAP caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteriemia. Data from various sources, including PubMed, the European Medicines Agency (EMEA) and the FDA, were evaluated. Tigecycline was found to be non-inferior to levofloxacin in the treatment of patients with bacterial CAP requiring hospitalization.Although tigecycline is indicated for CAP, data from clinical trials indicate a high incidence of adverse effects, especially gastrointestinal, which may limit its use (Ayoade, 2022).

Dosage (adults):Tigecycline 100 mg IV loading dose, then 50 mg IV q12h for 7-14 days

CORTICOSTEROIDS

The aim of this work is to provide a generated information about antibiotic treatment forCAP, but a short review on corticosteroid use is needed. As use of corticosteroids in patients with severe CAP is limited by their influence on patient's immune system and implies other adverse effects (e.g. hypeglycemia, secondary infections and other), with high doses administered for at least 7 days, and with limited data suggesting benefit in patients with severe CAP, the updated guidelines recommend the following:

- There are *no indications for the routine use* of corticosteroids in adults with mild and moderate CAP
- There are *no indications for the routine use* of corticosteroids in adults with severe CAP
- *May be considered* in patients with refractory septic shock.

TRANSITION FROM INTRAVENOUS TO ORAL ADMINISTRATION OF ANTIBIOTICS

Patients who initially received parenteral antibiotics can switch to oral administration if:

- are hemodynamically stable;
- are in clinical improvement;
- if they are able to swallow;
- if they have no problems with gastrointestinal tract;
- there is an oral form of antibiotic that they received parenterally or an oral antibiotic from the same group of antibiotics.

DURATION OF ANTIBIOTIC THERAPY

Before the decision to discontinue the further administration of antibiotics in patients suffering from CAP, it is necessary that the patient is afebrile for 48-72 hours, that there is no more signs of clinical instability for CAP: normalheart and respiratory rate, blood pressure, O_2% saturation, body temperature, appetite, mental status. Besides clinical signs, the laboratory findings, especially white blood cell count and C-reactive protein level are of great importance.

Proclacitonin values are useful only in severe cases in order to decide on shortening the duration of antibiotic therapy.

The minimum duration of therapy is 5 days, while, in relation to the degree of severity of the disease and comorbidities, this minimum period can be extended to 14 days. Patients with documented *MRSA* or *Pseudomonas aeruginosa* should receive therapy for at least 7 days. Pneumonia complicated by meningitis, endocarditis, or other deep-seated infection will require a longer duration of therapy.

CONCLUSION

Streptococcus pneumoniae(pneumococcus) still remains the most common cause of community-acquired pneumonia. Since late 1970s there has been a steady decline in the susceptibility of bacteria to various groups of antibiotics and this problem is recognized by professionals and scientist worldwide. Pneumococcal polyvalent vaccine was a great progress but it is used to prevent infection by pneumococcus. Once the patient is infected, antibiotics still remain the main option for the treatment of pneumonia. Various proffesional and scientific associations developed and updated guidelines for the management of adults with CAP, and in every of those guidelines the antibiotic of first choice is β-lactam antibiotic amoxicillin. Also available are combinations of β-lactam antibiotic ampicillin or piperacilin with β-lactamase inhibitors.

Second and third generation cephalosporins are stated as a second line antibiotics,with macrolides, fluoroquinolones, glycopeptide vancomycin for different groups of patients depending on their drug allergy, intolerance, possible or present infection with *Pseudomonas* or *MRSA.* Different antibiotic dose levels, different dosing shedules and different routs of administration are recommended for outpatients and for hospitalized ones. Bosnia and Herzegovina does not have a national treatment guideline for CAP caused by *Streptococcus pneumoniae*, and until one is developed, the recommendations from other guidelines can be used.

Conflict of interest
There are no conflicts of interest.

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Acknowledgements

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