CURRENT RESEARCH IN SCIENCE AND MATHEMATICS

MARCH 2023

Editor

Prof. Dr. Hasan AKGÜL

gece kitaplığı

İmtiyaz Sahibi / Publisher • Yaşar Hız
Genel Yayın Yönetmeni / Editor in Chief • Eda Altunel
Kapak & İç Tasarım / Cover & Interior Design • Gece Kitaplığı
Editörler / Edıtors • Prof. Dr. Hasan AKGÜL
Birinci Basım / First Edition • © Mart 2023
ISBN • 978-625-430-716-4

Gece Kitaplığı / Gece Publishing
Türkiye Adres / Turkey Address: Kızılay Mah. Fevzi Çakmak 1. Sokak
Ümit Apt. No: 22/A Çankaya / Ankara / TR
Telefon / Phone: +90 312 384 80 40
web: www.gecekitapligi.com
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Baskı & Cilt / Printing & Volume
Sertifika / Certificate No: 47083

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Chapter 1

METHODS FOR IDENTIFYING CHEMICAL RISKS IN THE FIELD OF OCCUPATIONAL HEALTH AND SAFETY

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INTRODUCTION

A chemical substance is the name given to any element, mixture or compound in its natural state, produced, used during any process, or emerged, including in waste, regardless of whether it is produced and whether there is a demand. In sectors such as agriculture, mining, furniture, construction, space, medicine, ceramics, cement It can find various uses such as paint, detergent, solvent, medicine, explosive, cosmetics. Today, chemical substances, which find more use with the developing technology, have become one of the indispensable elements of our lives. However, wastes generated as a result of unnecessary and excessive consumption can pose serious risks for both human health and ecology. Especially for those working in workplaces with high exposure levels, this can often cause serious occupational problems. Chemicals enter the body in the form of dust, vapor, smoke gas, solid or liquid. It can cause occupational diseases if the required personal protective equipment is not used above acceptable levels. For this reason, it is great important at this point to implement protective and preventive practices in workplaces whose exposure level poses a risk for employees. For example, in very dangerous areas, instant data can be obtained in integrated environments of systems where remote access can be used, such as RTLS (real-time monitoring systems). The most effective application in these areas is the risk assessment to be prepared with the participation of experts. While evaluating the risks, all kinds of risk factors that may come from the workplace or from outside are analyzed comprehensively. These analyzes are done through observation and measurement. Risks are scored according to their importance, taking into account the possibility of the hazard turning into a risk. The aim here is to classify the risks according to the danger dimension. Chemicals are substances that have the potential to cause serious injury or even death, even at very low concentrations. For this reason, the risk assessment to be implemented in these areas is important for the sustainability of both production and occupational health and safety. In the study, chemical risks, laws and regulations enacted in this context, occupational diseases and risk assessments applied in this field are discussed in detail.

Legal Regulations Regarding Occupational Health and Safety

The chemical sector is one of the most important areas that show the industrial development of a country. This sector is a sector that responds quickly and effectively to GDP changes in the world. In production, it is decisive in terms of security, social and economic development level. This development consists of five stages (1).

- Agricultural economy phase, industrial accidents are rare.

- Early industrialization phase, an increase in the number of accidents is experienced in this process.

- Mid-industrialization phase, fluctuations are seen in the number of accidents in this process.

- Advanced industrialization phase, a decrease in the number of accidents is observed in this process.

- Information society phase, the number of accidents is stable in this process.

Chemical sector, in all industrialized countries; Thanks to the added value and advanced technologies it provides to many fields such as health, transportation, food, electronics, textile, energy, agriculture, it is the locomotive of the industrial industry (2). Approximately 400 million tons of chemicals are produced in different sectors every year. It is known that between 5-7 thousand chemicals known in the world are harmful. About 3 thousands of this number has a carcinogenic effect, and 20-30 are defined as carcinogens (Safetyhealth.com.tr). Chemical factors causing occupational disease; metals and metals, gases, solvents, acids and alkalis, pesticides. For example, powders can be classified according to their chemical and biological properties; (27)

- Organic powders; fertilizer dust, cotton dust, poultry feathers, fungal spores are organic dusts.

- Inorganic powders: Coal, sand, asbestos, iron etc. is (3).

The most common elements in the workplace are chemicals. All of these substances are not risky for human health. The most frequently encountered substances in occupational diseases caused by chemical substances are; hydrogen cyanide, lead, mercury, toluene, benzene, hexane, solvents etc., is. Some of these substances can cause poisoning, some have behavioral disorders and some can have lethal effects (4;5). The most effective method of preventing occupational diseases in the workplace can be achieved by identifying potential risk factors and controlling these risks at their source. Occupational diseases are among the important dangers that we must protect our employees with the necessary protective practices beforehand. For eliminating these dangers; provided by employer/employer representative, occupational safety specialist and workplace doctor (6). According to the 4th article of the Occupational Health and Safety Law No. 6331, the employer;

- It works to prevent occupational risks, to take all kinds of measures, including training and information, to organize, to adapt tools and equipment, healthy and safety measures to changing conditions and to harmonize them with the current situation.

- It monitors and inspects whether the measures taken for occupational health and safety in the workplace are complied with, and ensures that non-compliance situations are eliminated.

- When assigning the employee, it takes into account the employee's suitability for the job.

- Takes all necessary precautions to prevent employees from entering places with life and special dangers, except those who are given sufficient instruction and information.

- Even if the employer purchases services from a specialist person or organization outside the workplace, this does not remove the employer's responsibility.

- The employer's obligations in the field of occupational health and safety in the workplace do not affect the employer's responsibilities.

- The employer makes or has the risk assessment done at the workplaces (7). According to Article 7 of the Regulation on Health and Safety Precautions in Working with Chemicals, dangerous chemicals and the precautions to be taken are listed as follows;

- Work organization is done with appropriate arrangement in the workplace.

- If it is necessary to work with dangerous substances, it is ensured that it is done with as few employees as possible.

- It is ensured that the amount of chemicals that the employees will be exposed to and the exposure time are at a minimum level.

- The minimum level of chemicals required to be kept in the workplaces is kept.

- Workplaces, buildings or annexes are kept clean and tidy.

- Appropriate and sufficient conditions are provided for the personal cleaning of the employees.

- Necessary arrangements are made for the processing, use, storage and transportation of hazardous chemicals, waste and residues according to standards.

- By using substitution methods, less dangerous and less hazardous materials are used for employee health and safety. If this is not possible, risks are reduced in order of priority by making a risk assessment and the following measures are taken;

o It is used in this field, including maintenance and repair works that pose a risk to the health and safety of employees. In addition, considering the technological developments, the most suitable engineering control systems are preferred and used.

o In cases where it is not possible for employees to be affected collectively by hazardous chemicals and their negative effects, these measures and personal protective measures are implemented together.

o In order to prevent the risk at its source; Collective protection methods such as the most ideal work organization and appropriate ventilation system are applied.

Risks Caused by Chemical Substances and Protection Methods

Chemicals are the locomotive of the industrial industry. While its use in many areas makes it indispensable, on the other hand, it can have serious negative effects as a result of excessive use, exceeding the limit values specified in laws and regulations, not implementing the necessary protective and preventive practices, and not disposing of wastes in accordance with the standards.

The determination of the risks arising from the chemicals used is important in terms of determining the protective and preventive practices to be taken in this area. The risks arising from chemical substances are mostly;

- Explosives
- Flammable substances
- Oxidizing agents
- Irritants

They show effects in the form of substances that react with each other. In some cases, harmful chemicals may occur in an integrated manner (toxic, suffocating or explosive). If the necessary occupational health and safety measures are not taken, it can cause workers to catch occupational diseases. For this reason, it is necessary to address the risks with a proactive approach to the chemical substance and its various effects. In this context, a safer working environment can be created by following the steps below for taking risks arising from chemicals (10).

- Conducting a comprehensive risk assessment
- Engineering precautions
- Administrative precautions

Risk assessment, according to the 4th article of the Occupational Health and Safety Risk Assessment Regulation; It is defined as the comprehensive studies carried out in order to identify the dangers that exist in the workplace or that may come from the outside, to analyze and rank the factors that cause these hazards to turn into risks, and to compare the control precautions. Risk assessment according to Article 8 of the same regulation; In all workplaces, hazards are determined during the design or establishment phase, risks are identified and analyzed. Risk control precautions are decided and updated if deemed appropriate, including the periods required by the legislation.

Employees are included in risk assessment processes, their opinions and suggestions are taken into account. In determining the risks;

All kinds of danger elements in the business ecosystem are determined separately. The probability of how often these hazards may turn into risks is evaluated. In addition, the people who will be adversely affected by this situation, what and how they will be harmed are taken into consideration.

- The risks identified in line with the data obtained are analyzed using one or more methods selected based on national or international standards.

If there is more than one department in the workplace, the first and second articles are applied separately for each department.

- Analyzed risks are taken into account according to their importance and risk levels.

The risk assessment is carried out by a team formed by the employer. This team consists of the following people;

- Employer or employer's representative
- Occupational safety specialist who carries out the services related to occupational health and safety in the workplace
- Workplace doctor
- Employee representative
- Support personnel (4)

In order to ensure coordination in the employer workplace, any of the team members can be assigned.

Risk assessments are updated every 2 years in highly hazardous workplaces, every 4 years in hazardous workplaces, and every 6 years in less hazardous workplaces (9). If the employer fulfills the conditions specified in the occupational safety law regarding occupational safety, the employer can either do it herself or assign one of the workers she employs at the workplace. If these two situations are not in question, it may choose to purchase a service. Engineering and administrative measures are applied to ensure that production is safely sustainable. Within the scope of engineering measures; Periodic maintenance-repair, control, replacement, cleaning, protective parts are taken into account. Within the scope of administrative precautions; Various practices can be implemented, such as increasing the number of employees and reducing working hours.

- Performing physical examination, analysis and other health examinations

- Health surveillance: These are the evaluations made to determine the negative effects of chemical or other harmful factors that employees are exposed to in the workplace.

Employees may be exposed to chemicals and their various phases. For this reason, regular health surveillance is a preventive practice in preventing occupational diseases by early diagnosis. It should not be forgotten that the sudden occurrence of occupational accidents and the unpredictability of 2% of them (earthquake, tornado, flood, etc.) can render all the measures taken to prevent occupational accidents inadequate. However, occupational diseases can be prevented if the necessary protective and preventive practices are implemented fully and completely. Taking into account the results obtained from the risk assessment, employees within the scope of risk are subject to appropriate health surveillance. Personal health and exposure records of each employee subjected to health surveillance are kept and updated (8).

According to sub-clause (c) of the second paragraph of article 9 of the Regulation on the Duties, Authorities, Responsibilities and Training of Workplace Physicians and Other Health Personnel; taking into account the risk assessment;

- At least once every five years in less hazardous workplaces
- At least once every three years in dangerous workplaces
- At least once a year in very dangerous workplaces

They are under health surveillance. However, in case of unexpected situations such as work accident or occupational disease, this situation may shorten the time of the workplace physician. Making chemical and physical environment measurements: The employer is obliged to make periodic measurements and controls of chemicals or other harmful elements in the workplace. Measurement of harmful chemicals to which workers are exposed; colored tubes, sensors, portable gas chromatographs, sampling pump etc. is done with. Considering these measurement results, new occupational health and safety practices are implemented if needed. Provision of personal protective equipment to employees (27).

The effects of harmful chemicals on health and safety have been mentioned in the previous sections. In this section, protective and preventive practices are decided by taking into account the results obtained from the risk assessment and checklists. Personal protective equipment is one of these applications.

PPE selection is made by taking into account the existing chemical substance and its phase form (solid, liquid and gas), exposure times and level of employees.

In particular, non-porous and impermeable PPE (glasses, helmet, gloves, mask, tyvek) should be preferred. Providing periodic trainings to employees;

Employees, general occupational health and safety training should be given periodically. General information is given about the machinery-equipment used, PPE, working environment and materials used. Employees are informed about the work they are doing or the risks they may be exposed to. These trainings are repeated regularly. Employees are obliged to act in line with the training they have received. According to Article 9 of the Regulation on Health and Safety Precautions in Working with Chemical Substances, the following points are considered in the training and informing of employees;

Results from the risk assessment,

Information on occupational exposure limit values of chemicals and other legal regulations,

Issues that employees should do in order not to endanger themselves and their colleagues,

Information about the material safety data sheet in Turkish from the supplier company for hazardous chemicals,

Information on labeling and locking in accordance with the legislation from the places where dangerous chemical substances are stored,

The trainings are given in written and visual form (12).

Another important issue to be considered in the workplaces of hazardous chemicals is ambient ventilation. Considering the possibility of chemicals in the environment in the form of gas, dust and steam, an effective ventilation system should be provided. Ventilation should be done in two ways, natural and mechanical. The main purpose here is to prevent harmful chemicals from reaching concentration properties such as explosion, poisoning and flammable. While the presence of oxygen in the range of 19.5%-20.8% is ensured in the study area, different precautions can be taken considering the characteristics and limit values of the existing chemicals.

Occupational Diseases Caused by Chemical Substances

In order for a disease to be considered an occupational disease, there must be a causal link between the disease and the work done classes and types of occupational diseases help to determine whether the disease is related to occupational disease (3).

Table 1. *Classification of occupational diseases (3).*

According to the organs damaged as a result of Occupational Diseases;	According to the factors that cause occupational disease;
Digestive system Respiratory system Hearing systems and organs Musculoskeletal system Hematopoietic system Multiple organ involvement	Physical elements Chemical elements Powders Biological elements,

In the classification and examination of occupational diseases, classification is made by considering the points of entry of the risk factor into the body (digestive, skin or respiratory), the effect of the disease (chronic and acute) and the region of the disease (systemic and local). In Turkey, there is a list of occupational diseases in the annex of the Social Insurance Law Health Transactions Regulation. According to the list of occupational diseases, occupational diseases consist of three parts. These; occupational disease and its symptoms, danger of disease, liability period. Chemical-related diseases and occupational poisonings, which have a very wide area, have an important place today. For example, occupational diseases caused by chemical substances are given below (15;27).

- Lead poisoning (eg: Accumulator construction)
- Arsenic (eg paint, artificial leather)
- Chrome, cadmium (eg: Metal plating)
- Carbontetra chloride benzol etc. (ex: Solvent)
- Mercury (eg mine, barometer)

Substances used in coating works such as nickel and chrome, machine oils, cement and coal distillation are considered as areas where occupational skin diseases are seen in business lines. When dust and other occupational respiratory system diseases are examined; Some of the areas in this risk group are coal mining, ceramic works, cement, asbestos, cotton, textiles. When occupational infectious diseases are examined; The diseases within this scope are diseases caused by living microorganisms.

In this area; tetanus, glanders, parasite named, sewage, wool works etc. exemplary (15).

Table 2. *Classification of occupational diseases in Turkey (11; 3).*

Groups	**Subgroup and Diseases**
Group A: Occupational diseases caused by chemicals	25 sub gr. 67 diseases
Group B: Occupational skin diseases	2 sub gr. Non-cancerous skin diseases and skin cancer
Group C: Pneumoconiosis and other occupational diseases	6 sub gr. 9 diseases
Grubu D: Infectious diseases	4 sub gr. 30 diseases
Group E: Physical	7 sub gr. 12 diseases

Table 3. *Precautions to be taken profitably against chemical risk factors(14;12;7;13).*

Preventive measures
Chemicals should not be used or mixed unconsciously.
Contact with chemicals should be minimized as much as possible by providing PPE. Employees related to the subject should be informed and supervised.
Necessary organization and emergency plans should be prepared against situations that require an emergency (flare, explosion, etc.).
Employees should be trained on the precautions to be applied in cases of exposure to chemicals that require emergency response and first aid, and on the safe use of them.

Risk Assessments Used in Safe Work with Chemicals

The Hazard and Operability Working Methodology (HAZOP) has been developed by the chemical industry in order to identify the risks that may arise in this area (26). The HAZOP method was used for the first time in the 1970s for the safety of chemical plants and was developed in the following years and became a risk analysis technique (16). In the HAZOP method, deviations from the system and the consequences of these deviations are discussed by brainstorming extensively by coming together with people from different fields of expertise. The issues that may be caused by these deviations are evaluated. The experience of the people who will participate in the study will also affect the success of the analysis. In this respect, it is important that the people to be included in HAZOP consist of competent people in their field. HAZOP studies consist of the following people.

- Employer

- Factory manager
- Job security specialist
- Process manager
- Automation and system manager
- Electrical engineer
- Civil engineer (if needed) (17).

The steps to be considered before and after the HAZOP analysis are listed below;

- The node selection of the factory where the analysis will be applied is determined,
- Examining work flow diagrams,
- Obtaining comprehensive information about the equipment and process used,

After this stage, the stages to be followed in the HAZOP analysis are carried out as follows;

Providing MSDS (material safety data sheet),

Lower and upper explosion limits of the substances to be used in the process,

Used in the process; examination of pressure, temperature, flow rate parameters,

Detecting hazards such as fire, explosion, exposure time,

Explaining the purpose of the analysis,

In order to determine the hazards, the work area is determined and examined by using guide words section-by-section (16).

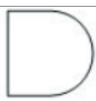
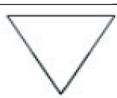
The keywords used in the methodology are as follows.

Table 4. *The words used in the HAZOP method and their meanings (26)*

Keywords	**Meaning**
(more)	Quantitative increase
(less)	Quantitative reduction
(none)	It’s out of the question,
(reverce)	Contrary to the predicted direction,
(part of)	One part of the system is different from the other parts,
…(as well as)	Equally,
…. (other than)	Totally different

Before applying the HAZOP method, the steps or process selection of the operation or the issues specified in the "Hazard and Operability Study Form" filled by the operation staff are used in the study. Before starting the work, the flow chart of the process ASME (American Society of Mechanical Engineer) is taken into account. The flow chart makes a serious contribution to the experts in increasing the success of the study. Symbols and their meanings prepared by taking into account ASME are given in Table 5. (26).

Table 5. *Process flowchart symbols according to ASME (26)*

Symbols	Activity	Mostly Result
	Operation	Final product, change step, execution progress in the process
	Check	Applied qualitatively or quantitatively
	Transport	
	Delay	Handling or shipping
	Storage	Obstacle, delay, warehousing

Accordingly, the purpose of the study is determined first at the beginning of the study. A variable of the operation or process is determined and a meaningful "Danger Deviation" is determined using the guiding words. The following steps are followed in the HAZOP application;

In case of a serious change in working conditions,

- Considering the health surveillance and ambient measurement results, if needed,
- In case of any accident caused by chemical substances in the operation or process,
- Once every five years,
- Before maintenance and repair operations,
- It is renewed in case of a new addition to the operation or process (26).

FMEA (Failure Mode and Effects Analysis), developed by the US military. This analysis method is a reliable method used to detect equipment and system errors and their effects. FMEA method finds widespread use in industries such as electronics, aerospace, automobile and chemistry (18;26). There are four commonly used types of FMEA. These; design, process, system and service is FMEA (19).

FEMA implementation;

- Identifies the factors and causes of each error,
- Identifies existing faults,
- Errors are prioritized by considering severity, probability and detectability,
- It ensures that the experienced problems are followed and corrective practices are implemented.

The team working in the execution of FMEA studies should try to determine the following points.

- The function of the part that is the subject of the analysis,
- Error status,
- Effects of error,
- Possible causes of the error,
- Detectability of the situation causing the error,
- Measures that can be taken to prevent this error.

FMEA (Failure Modes and Effects Analysis) solution consists of a total of nine stages. These stages consist of the next stages.

- FMEA planning to determine FMEA targets and levels,
- In order to apply FMEA, criteria, ground rules and special cases need to be defined.
- Analysis of the system (stages of activity, type of activity, etc.)
- Creation and analysis of reliability and mission phases
- Indication of existing error types,

Evaluation and classification of error types and effects,

- Determining methods to prevent and control errors,
- Evaluation of recommended measures,
- Documentation of results.

Possible damage mode: It refers to the random and natural events of any transaction that may occur in the system to cause damage.

Effects and consequences of damages: It refers to the determination of the effect that probable situations may have on the business.

The letters RÖS, D, S and P and their meanings are given below.

P: Probability of occurrence of damage mode,

S: The severity, severity and severity of the resulting harm,

D: Determining the situation that may cause the damage and grading the difficulty,

RÖS: It represents the risk priority number. The RÖS expression is obtained by multiplying the D, S and P values.

ROS: P (probability)x S (Severity)x D (noticeability)

In the evaluation process using FMEA, the system FMEA severity impact classification, the severity of the damage, the probability of being noticed, the possibility of being noticed, and finally the possible error types and effects analysis is filled in the risk assessment form and FMEA analysis is performed (26).

Fine-Kinney is a quantitative risk assessment method. In this method, numerical methods are used while calculating the risks. In the risk assessment made using the Fine Kinney method; The probability of occurrence of the risk is obtained by multiplying the numerical values given to its severity and frequency with each other. The most important point that distinguishes the quantitative method from the 5X5 Matrix method is the inclusion of the frequency element in the evaluation. In this method, the wide scale of risk is the most important factor that brings the method to the fore. The Fine Kinney method was developed by Kinney and Wiruth in 1976. It is a widely used risk assessment method in the field of Occupational Health and Safety (20).

In the Fine-Kinney method, the Risk: Probability x Frequency x Severity formula is used to calculate the Risk (R). Considering the results obtained in the calculation; acceptable risk, possible risk, significant risk, high risk and very high risk (22). Kinney and Wiruth base the method on the following idea;

- It is not possible to eliminate all risks in our lives,
- Risks can be reduced to acceptable levels (with care and due effort)
- To use labor and limited time to reduce risks and make maximum contribution instead of completely eliminating risks (21).

The probability, frequency and intensity values used in the Fine-Kinney method and their meanings are given (23).

Table 6. *Probability Value*

Probability	Meaning
0,2	Meaningless
0,5	low probability
1	Pretty low probability
3	Rare but can happen
6	Most likely
10	Very likely

Probability is graded on a scale of 0.2-10. Frequency is graded between 0.5-10 points (14).

Table 7. *Frequency Values*

Frequency	Meaning
0,5	Very rare
1	Quite rare
2	Rare
3	Now and again
6	Often
10	Continually

Violence is graded on a scale of 1 to 100 (14).

Table 8. *Violence*

Violence	Meaning
1	Should be considered
3	Important
7	Serious
15	So serious
40	Too bad
100	Disaster

Table 9. *Fine-Kinney Risk Assessment*

Risk Value	Conclusion
R <20	Acceptable Risk
20<R<70	Definite Risk
70<R<200	Significant Risk
200<R<400	High risk
R>400	Very High Risk

The Fine-Kinney method is a systematic analysis method. This method is a method that allows a very comprehensive analysis and its main purpose is to prevent accidents. It provides the opportunity to calculate the severity of the possible damage that may arise as a result of the danger and to evaluate the possible risks. The risks obtained from the analysis are classified according to their values (24).

The L-Type Matrix 5x5 method is a method used in the evaluation of cause-effect relationships. Because the method is simple, easy and understandable, it is one of the most ideal methods preferred by analysts. However, it is not sufficient in areas where there are different processes or works with various and many flow charts. It is used in such businesses as soon as possible or in urgent situations. In the L-Type Matrix 5x5 method, a situation is scored with the probability of its realization. The risk score is obtained by multiplying the probability with the degree of damage. The following formula is used in the calculation. Risk Score = Probability x Degree of Loss (26). In the tables below, the risk levels of the scores obtained as a result of probability, rating and calculation after the method are given (Table 10, Table 11 ve Table 12).

Table 10. *The probability of an event occurring (26)*

Possibility	**Occurrence Probability Rating Stages**
Very little	Hardly ever
Little	Very few, only in abnormal situations (once a year)
Middle	Few (more than once per year
High	Often (monthly)
Very High	Frequent, under normal operating conditions (almost every day)

Table 11. *Severity Rating (17)*

Definition	**Level Scale**
Requires first aid (no loss of working hours)	1 (So light)
Requires first aid, requires outpatient treatment (no lost workdays)	2 (Light)
Minor injury	3 (Middle)
Serious injury	4 (Serious)
Death	5 (So serious)

The score values in Table 12 are obtained by multiplying the values of Table 10 and Table 11. Then, the risks are prioritized by taking into account the score values as indicated in Table 12.

Table 12. *Risk Scores (26)*

	Violence				
Possibility	1 (Very Light)	2 (Light)	3 (Intermediate)	4 (Serious)	5 (Very Serious)
1 (Very small)	1	2	3	4	5
2 (Small)	2	4	6	8	10
3(Intermediate)	3	6	9	12	15
4 (High)	4	8	12	16	20
5(Very High)	5	10	15	20	25

In Table 12, the score values obtained as a result of the calculation of Risk = Probability x Impact (Severity) are given. According to this:

- A value of 1 is unimportant
- 2,3,4,5,6 values are bearable risks
- 8,9,10,11,12 Moderate risks,
- 15,16,20 Significant risks,
- 25 Unbearable risks

After the risk assessment process, control measures are determined. According to the risk assessment regulation, control measures are determined starting from the value with the highest score value. The studies are carried out until the risks are reduced to acceptable levels (25) continues. The main goal here is to make production and occupational safety sustainable. For this reason, all kinds of protective and preventive measures taken for risk factors are followed by using both observation and various measurement methods.

CONCLUSION

Chemicals have assumed the locomotive role of the industrial industry. In almost many sectors; It finds intensive use in many fields such as medicine, automotive, mining, construction, health, paint. However, there are also some negative effects. These; Occupational diseases can occur as different risk factors such as injury, explosion, burning and flashing. Especially in workplaces where chemicals are used as raw materials, it is vital to apply risk analyzes suitable for this area (HAZOP, FMEA, Fine-Kinney, L Type Matrix etc.). The fact that it acts in more than one way reveals the need for an integrated and proactive approach to the work being done. The effect of major industrial accidents in the past (Seveso-Italy 1976 Bhopal-India, 1984) has spread over a wide area, not just in one region. Therefore, it is of great importance at this point to comprehensively address the existing risks in the chemical industry. Another important issue is the regular and systematic implementation of preventive and preventive practices. PPE selection should be made by considering the risks of the substances used and suitable for the work done to the employees. The use of allocated PPE should be ensured. Employees should be informed about the possible risks of the substances used in the job. The risk assessment should be prepared not only for the operation, but also to prevent its spread during a possible accident and not to create an extra risk for the environment. It is known that human errors are a major factor in the occurrence of occupational accidents (88% people, 10% machines, 2% unpredictable situations). Especially in places such as factories, businesses or facilities with a high level of risk, remote access systems can be controlled by integrating technologies such as informatics, communication and internet, artificial intelligence, robot-cobot, and possible accidents and occupational diseases can be minimized.

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Chapter 2

SEYFERT GALAXIES

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History and General Information:

Seyfert galaxies are galaxies that have a variable and luminous core that is called nuclei (1). They seem like luminous stars covered by fainter surroundings. And this appearance makes them clearer to observe by telescopes. Even it is hard to distinguish them from a star in short-exposure photographs (2). Because of this property, a Seyfert galaxy is classified as a lower luminosity active galaxy. There are five types of active galaxies: Seyfert, Quasar, Blazar, Radio, and BL Lacertae objects (3). Seyfert and quasar galaxies are the largest ones of active galaxies. The main differences between them are distance and radiation amount they emit (4). Quasars are brighter and far away than Seyferts.

There are supermassive black holes at the center of them (5). This massive center causes a formation which is called an accretion disk. Materials (mostly diffuse) that turn around the mass are formed as a disc and spiral toward the mass. The main physical explanation is the instability that between quantities occurs in the orbital motion of the materials (6),(7). These forces are friction, uneven irradiance, magnetohydrodynamic effects, and some other forces (6). The main source of the radiation which is emitted from a Seyfert galaxy is an accretion disc. Accretion discs are so important subjects that help us to understand black holes too(8).

Image of NGC 1637, taken by Hubble S.T. (9).

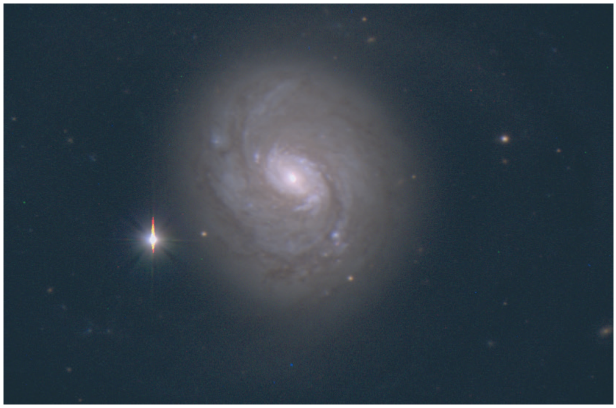


Image of NGC 1068, also known as Meisser 77(M77) (10).

NGC 1068 is the first Seyfert galaxy noted in 1908 by Edward Fath and Vesto Slipher. Since a Seyfert galaxy seems like a Spiral galaxy when it is observed under visible wavelengths, they thought they observed a spiral galaxy. But they realized that NGC 1068 has six bright emission lines on its spectra. This was not usual since the absorption spectrum is more way common among stars (11). These emission lines represent one of the important characteristics of Seyfert galaxies, they are broad and strong (12).

Line	λ_{vac} ()	Flux (10^{-13} ergs cm^{-2} s^{-1})	Δv^{a} (km s^{-1})	FWHM (km s^{-1})
C III	977.03	6.7 ± 0.4	−435 ± 51	1837 ± 129
N III	991.00	4.4 ± 0.4	−77 ± 81	2099 ± 213
Lyβ	1025.72	5.3 ± 0.4	−456 ± 49	1750 ± 87
O VI	1031.93	10.8 ± 0.4	−455 ± 49	1750 ± 87
O VI	1037.62	12.6 ± 0.5	−455 ± 49	1750 ± 87
He II	1085.15	3.4 ± 0.3	−678 ± 62	1557 ± 131
Ly α n	1215.67	45.6 ± 2.8	−86 ± 11	977 ± 37
Ly α b	1215.67	37.8 ± 4.4	−663 ± 61	3041 ± 120
N V	1240.15	23.9 ± 0.5	−511 ± 26	2588 ± 63
C II	1334.53	2.6 ± 0.2	−186 ± 48	1089 ± 120
Si IV+O IV]	1400.00	7.9 ± 0.4	−341 ± 84	3131 ± 165
N IV]	1486.50	3.3 ± 0.3	−928 ± 87	1767 ± 199
C IV n	1549.05	24.5 ± 1.4	−159 ± 16	1127 ± 47
C IV b	1549.05	22.3 ± 1.5	−736 ± 61	3041 ± 120
He II	1640.50	17.4 ± 0.6	−576 ± 31	1901 ± 63
O III]	1664.00	$<$ 1.7	−189 ± 350	1901 ± 63
N III]	1750.00	2.7 ± 0.4	−78 ± 81	2099 ± 213

[a]Velocities are relative to a systemic redshift of $z = 0.0038$ (Huchra et al. 1992).

Emissions line of NGC 1068(13).

After the detection of NGC 1068, Hubble classified it as extragalactic an object (14). Until 1943, there were no remarkable studies about galaxies like NGC 1068 since there were no important discoveries. But in 1943, the astronomer who is the reason why we called NGC 1068 type galaxies Seyfert galaxies discovered more galaxies like NGC 1068. This man was called Carl Keenan Seyfert. He realized that these galaxies have strong and large emission lines and very bright nuclei (15). In 1939, Cygnus A another important galaxy is discovered, it is not a Seyfert galaxy but it is a radio galaxy which is another type of active galaxy that helps us to understand their similar behavior (16). And it is observed at 160MHz in 1944. And by using interferometry, Cygnus A radio structure was observed. In the next years, astronomers discovered important structures like supernova remnants that are such good radio sources. After these and more discoveries and studies, the characteristics of Seyfert galaxies were understood in the 1950s. Three main properties are having compact nuclei of less than 100 pc, short nuclear emission durations, and high masses larger than nearly 109 M0(solar mass).

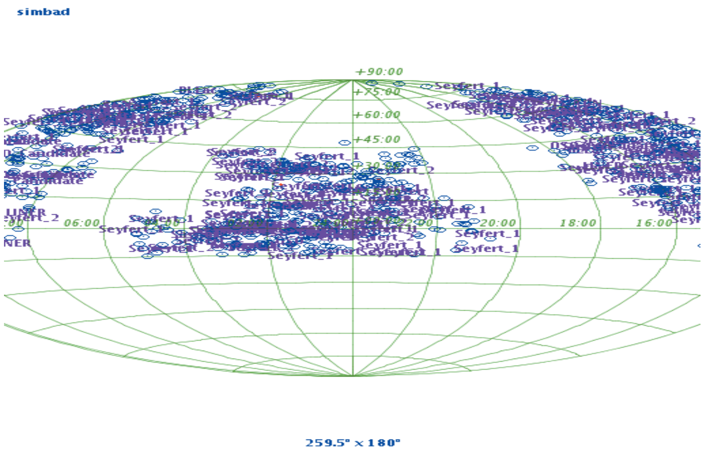
In the next decades, more studies have been done. It is determined that NGC 1068 emission lines spread from a region 500,000 light years in radius (17). Finding their age by using distance was not a proper way. Because their nuclei vary over a few years and this stops us to use the constant speed of light and distance for age calculations (18).

Object	Alternative name	RA [h m s]	DEC [d m s]	Hubble type	Redshift z	Velocity cz [km s^{-1}]	D_L [Mpc]	Ang.scale [pc/″]
Mrk 34	MCG +10-15-104	10 34 08.6	+60 01 52	Spiral	0.0505	15 140 ± 90	218	956
Mrk 622	UGC 04229	08 07 41.0	+39 00 15	S0	0.0232	6964 ± 11	99.6	461
Mrk 1066	UGC 02456	02 59 58.6	+36 49 14	(R)SB(s)0+	0.0120	3605 ± 22	47.3	224
NGC 262	Mrk 348	00 48 47.1	+31 57 25	SA(s)0/a	0.0150	4507 ± 4	58.2	274
NGC 449	Mrk 1	01 16 07.2	+33 05 22	(R')S?	0.0159	4780 ± 2	62.3	293
NGC 2273	Mrk 620	06 50 08.6	+60 50 45	SB(r)a:	0.0061	1840 ± 4	25.8	124
NGC 2992	MCG -02-25-014	09 45 42.0	−14 19 35	Sa pec	0.0077	2311 ± 4	36.6	175
NGC 3081	IC 2529	09 59 29.5	−22 49 35	(R_1)SAB(r)0/a	0.0080	2391 ± 3	37.7	180
NGC 4388	UGC 07520	12 25 46.7	+12 39 44	SA(s)b: sp	0.0084	2524 ± 1	16.7(*)	81(*)
NGC 5728	MCG -03-37-005	14 42 23.9	−17 15 11	(R_1)SAB(r)a	0.0094	2804 ± 20	41.9	199
NGC 5929	UGC 09851	15 26 06.1	+41 40 14	Sab: pec	0.0083	2492 ± 8	35.7	170

Adopted from the NASA/IPAC Extragalactic Database (NED). The cosmological scales assume $H_0 = 73\,km\,s^{-1}\,Mpc^{-1}$, $\Omega_M = 0.27$, $\Omega_\Lambda = 0.73$. D_L: luminosity distance; Ang.scale: angular scale. (*) Values from Yasuda et al. (1997), with NGC 4388 considered inside the Virgo cluster.

Data of some Seyfert galaxies(19) (this is a figure from 2009, OASIS integral-field spectroscopy of the central kpc in 11 Seyfert 2 galaxies: I put the website link in reference)

In 1963, Benjamin Markarian began to see a common property of some galaxies. And in 1967, Markarian published a list that contains these few hundred galaxies. The common property of these galaxies was having excessive ultraviolet emission which makes them different from other galaxies. These galaxies were called Markarian galaxies and in 1973 some galaxies were added to by other astronomers (20)(21).



Locations of Markarian galaxies due to the Milky Way.(22)

Until late the 1970s, it was not known that Seyfert galaxies are quite common, nearly 10% of all galaxies (23). They thought that they are only 1% of spiral galaxies at that time. Most of the Seyfert galaxies are spiral and barred spiral galaxies but few of them are elliptical galaxies (24). They realized that their spectra differ from each other and classified them as two classes according to their width emission lines. These classes are type 1 and type 2. Later, type 1 was subclassified into 1.2, 1.5, 1.8, and 1.9 (25). Unlike early time studies, the most recent ones show us that Seyfert galaxies can be low luminous and have obscured nuclei. These studies suggest that the Seyfert phenomena occur in between 11% and %20 of all galaxies (24)

Listing of Seyfert galaxies

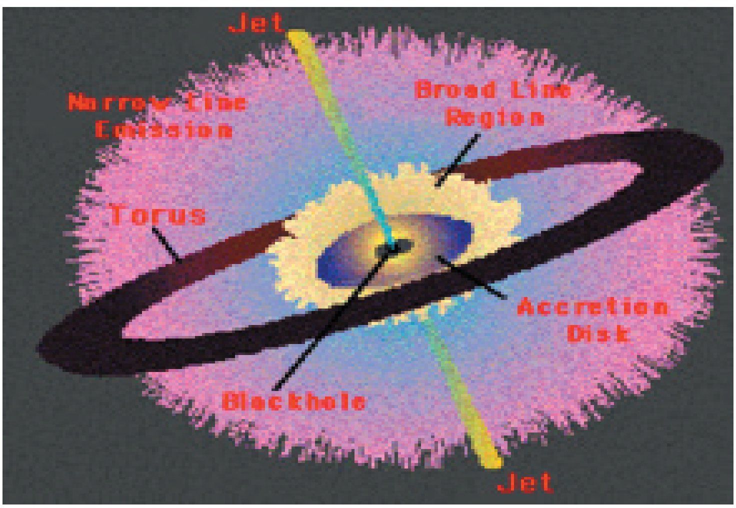
Object	RA (1950)	δ	Class	cz	θ″	Chart	(B–V)	(U–B)	UBV	Spectra	IR or Radio
Mkn 335	$00^{h}03^{m}45.1^{s}$	+19°55′27″	1^{a}	7500	16	1	0.41	−0.70	6	7, 5, 9, 23, 160	8
III Zw 2	00 08.0	+10 42	1	26930	12	2	0.52	−0.70	5, 135	2, 5, 73, 23, 160	161
Zwicky	00 39.5	+40 03	1	30780	8	3	—	—	136	3, 73	—
Mkn 348	00 46 04.4	+31 41 00	2	4200	77	1	0.95	+0.17	6	7, 5, 9, 162	8, 33, 47, 60, 155, 161
I Zw 1	00 51.0	+12 25	1	18280	22	4	0.36	−0.80	4, 5, 93, 135	10, 5, 11, 23, 73, 132, 160	8, 45, 51
Mkn 352	00 57 08.6	+31 33 27	1^{a}	4500	38	1	0.44	−0.66	6	7, 5, 9, 23, 160	8
Tololo	01 09	−38.3	2	3300	135	12	—	—	—	12	—
Mkn 1	01 13 19.5	+32 49 33	2^{a}	4800	34	13	0.90	+0.09	6	5, 14, 15, 30, 162	8, 30, 33, 45, 47, 155, 161
II Zw 1	01 19.5	−01 18	1	16240	15	4	0.57	−0.42	4, 5	4, 5, 23, 160	—
Akn 42	01 21.9	+31 55	1	10800	38	16	—	—	—	17	—
Mkn 358	01 23 45.1	+31 21 13	1	13750	42	1	0.79	−0.32	5	7, 18, 23, 160	—
4C 29.6	02 04 08.9	+29 16 40	1	32700		101	—	—	—	102	—
Mkn 590	02 12.0	−01 00	1	8100	55	20	—	—	—	19, 160	—
Akn 79	02 14.3	+38 11	1	6000	60	16	—	—	—	17	—
Akn 81	02 20.4	+31 58	1	10500	32	16	—	—	—	17	—
NGC 985	02 32.1	−08 59	1	12950	45	72	0.36	−0.95	21	21	—
NGC 1068	02 40.1	−00 14	2^{a}	1090	380	72	1.00	−0.01	22, 77, 26, 124	73, 52, 57, 96, 71, 128, 138, 118, 35, 94, 42, 49, 162	59, 48, 45, 34, 77, 107, 108, 110, 111, 127, 134, 125, 161
Mkn 372	02 46 30.9	+19 05 54	2	9300	23	1	1.05	−0.03	6	7, 5, 9, 162	8
NGC 1275	03 16.5	+41 20	?	5290	68	72	0.64	−0.23	22, 77, 124	89, 73, 71, 9, 5, 94, 79, 81	77, 45, 44, 8, 77, 112, 91, 137, 161
Mkn 609	03 22.9	−06 19	1	9600	17	24	—	—	—	19, 23	—
III Zw 55	03 38.7	−01 27	2	7380	13	4	0.84	+0.17	4	4, 5, 9, 162	8
NGC 1566	04 18.9	−55 04	1^{a}	1170	420	25	0.76	−0.04	26, 27, 133	25, 28, 73, 131	117, 133, 161
3C 120	04 30.0	+05 15	1	9900	42	2	0.58	−0.75	6, 77, 99, 124, 130	58, 56, 9, 73, 23, 106, 160	8, 45, 77, 41, 43, 140, 141, 161
Mkn 618	04 34.0	−10 28	1	10200	68	24	—	—	—	23, 160	—
Akn 120	05 13.6	−00 12	1	9900	60	16	—	—	—	17	—
Mkn 3	06 09 48.1	+71 03 00	2^{a}	4110	44	13	1.15	+0.15	6	5, 15, 14, 9, 30, 162	30, 33, 47, 155, 161
Mkn 6	06 45 43.4	+74 29 07	1^{a}	5290	52	13	0.97	+0.02	6	55, 9, 15, 30, 87, 88, 122, 162	30, 33, 47, 105, 161
Mkn 374	06 55 33.9	+54 15 53	1	13200	41	1	0.70	−0.38	6	7, 5, 9, 23, 160	8, 161
Mkn 376	07 10 35.8	+45 47 07	1	16800	18	1	0.55	−0.58	5	31, 9, 32, 23, 160	8
Mkn 9	07 32 42.0	+58 53 00	1	12040	22	13	0.54	−0.64	6	30, 14, 9, 23	30, 8, 45
Mkn 78	07 37 55.9	+65 17 43	2^{a}	11260	19	38	0.99	−0.31	6	36, 37, 9, 162	161
Mkn 79	07 38 46.9	+49 55 47	1	6580	86	38	0.47	−0.74	39, 6, 66	37, 30, 9, 23, 5, 115, 160	30, 8, 45, 51, 161
Mkn 10	07 43 07.4	+61 03 23	1	8790	95	13	0.67	−0.55	39, 6, 124	14, 30, 23, 160	30, 45
Mkn 382	07 52 03.2	+39 19 07	1	10200	42	1	0.51	−0.63	5	32, 23, 160	8
Mkn 110	09 21 44.4	+52 30 14	1^{a}	10800	47	38	0.76	−0.67	6	40, 5, 9, 160	8, 161
Zwicky	09 34.5	+01 20	1	15150	—	—	—	—	—	139	—
3C 227	09 45 06.3	+07 39 17	1^{a}	25600	8	29	0.98	−0.36	65	54, 23, 160	161
Mkn 124	09 45 24.3	+50 43 26	1	16970	18	38	0.61	−0.47	66	37, 30, 9, 160	30, 8, 161
Akn 223	09 54.7	+07 26	1	6600	21	16	—	—	—	67	—
Mkn 141	10 15 38.7	+64 13 14	1	11700	19	38	0.71	−0.32	6, 66	40, 9, 160	—
NGC 3227	10 20.7	+20 07	2^{a}	1000	330	72	0.82	−0.11	22, 77	69, 9, 71, 73, 5, 118, 160	45, 8, 77, 34, 125, 127, 126, 161
Mkn 142	10 22 23.1	+51 55 40	1	13500	24	38	0.44	−0.58	66	40, 160	8
Ton 524a	10 28.8	+29 06	1	18000	10	121	—	—	—	121	—
Mkn 34	10 30 52.2	+60 17 20	2^{a}	15300	39	13	1.06	+0.07	6	15, 9, 30, 162	30, 45, 161
Akn 253	10 41.4	−01 01	1	7800	34	16	—	—	—	67	—

(26)

General Properties:

As we mentioned before, a Seyfert galaxy has a very luminous core, it radiates a large amount of energy. We can compare the luminosity of its core to the luminosity of our Milk Way galaxy which is nearly amount of between 1035 and 1038 W. We can find total energy by mc2 (m: mass of gas) and radiating part is 10% of it. The mass loss rate is 0.1 (M0/year, M0:solar mass) and we calculate it from its luminosity (27). The radiation process occurs mostly because of the accretion disc nature, materials are compressed by friction and gravitational forces, temperature increases and which causes them to radiate (28).

Seyfert galaxies' emission lines are broad and bright. They have H, He, N, and O emission lines on infrared and visible spectra. Also, a few of them are radio bright: moderate lines in gamma rays and bright lines in X-rays (29). The gases that are the reason for these emissions move at very high speeds from 500 to 4000 (km/s) (we can look at the table of emission lines of NGC 1068 as an example, which is put on page 3)(27, 28). The speeds of gases are not the same for all regions of the accretion disc, they are getting faster when they get close to the supermassive black hole at the center. Since faster gas means broader emission lines, so we have broader emission lines when we move to near regions to a black hole from the surface of the accretion disc. The time scales of narrow and broad lines are so different. The time scale of narrow lines is so long but the time scale of broad lines is so short.



An explanatory active galactic nuclei model helps us to understand better (30).

There is a technique called as "Reverberation mapping" to measure broad line structure. Basically, it is a simple method to measure mass by using the motion of nearby galaxies. Since this motion occurs because of gravitational, we use Newton's Laws to write an equation. And this equation is taken from reference (31)

G x M = f x R(BLR) x (ΔV)2

f=[4(sin2i+(H(BLR)/R(BLR)2))]−1

for the second equation see (32).

(G: gravitational constant, M: mass of black hole, f: form factor (depends on the shape of the region), R(BLR): radius of broad line region, (ΔV)2: RMS velocity of gases are close to the black hole.)

Unless this method is simple, only less than 40 nuclei were mapped accurately using this way. Because finding R(BLR) is not easy (can be estimated by the time delay of light by travel from a continuous source to emitted gas(39)), the f value is not clear too, but ΔV is easier to find by using spectroscopy (33).

Another important characteristic is the Eddington limit. By this limit, we can find the minimum value of black hole mass. This limit comes from the relation between radiation pressure and gravitational forces. They must be equal since any non equality will cause expansion (34).

We must find radiational pressure force before. To find it:

$$\frac{dE}{dtdA} = \frac{L}{4\pi r^2};$$

Since E = pxc

$$\frac{dp}{dtdA} = \frac{L}{4\pi c r^2}.$$

then

$$\frac{dp}{dt} = \sigma_T \frac{dp}{dtdA} = \sigma_t \frac{L}{4\pi c r^2}.$$

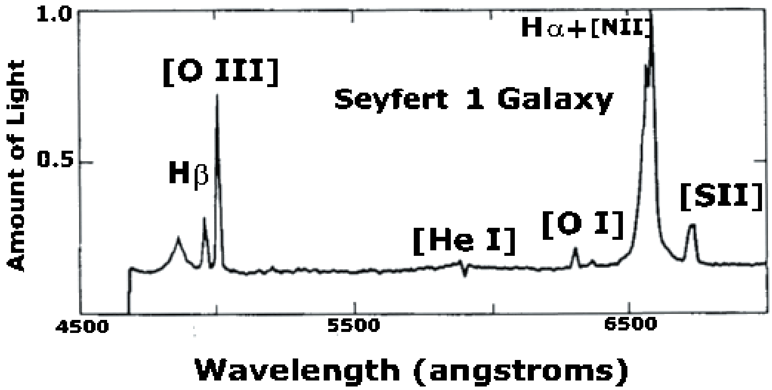
And gravitational force must be larger or equal to radiation pressure force:

$$\sigma_t \frac{L}{4\pi c r^2} \leq \frac{GMm_p}{r^2}$$

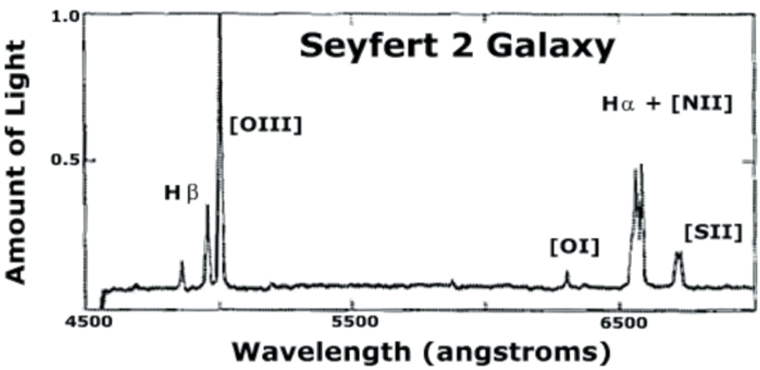
$$L \leq \frac{4\pi G m_p c}{\sigma_T} M \equiv L_{edd}. \qquad (35)$$

Types of Seyfert Galaxies:

The main difference between classes of Seyfert galaxies is the width of their emission lines. Mainly there are two classes, Type 1 and Type 2. Spectra of Type 1 has broad lines, it has narrow lines too. These narrow lines are still much larger than the narrow lines of normal galaxies. Spectra of Type 2 has no broad lines and has only narrow lines (not all narrows are permitted, there are some forbidden lines.) (36).



Spectra of Type 1 Seyfert. We can see that it has broad hydrogen emissions and narrow-line emissions. (37)



Spectra of a Type 2 Seyfert. It has narrower emissions than Type 1, especially H emission. (37)

Type 1:

Type 1 Seyfert galaxies emit high amounts of ultraviolet, X-rays, and visible light that come from their nuclei(38). So they are very bright. As we mentioned before, they have broad emission lines which indicate that the gas in the central regions moves with high velocities, almost 0.1 speed of light (37). A broad-line gas is very dense nearly 109 (g/cm3) or higher. So the nonelectric dipole transitions are reduced by collisions (38). They also have narrow lines which are less amount than the broader lines. The emission line gases are slower and less dense. Their velocities are several hundred (km/s) and densities are between 103-106 (g/cm3), these values are less for nonactive galaxies. Both emission and board gases are highly ionized (38, 39).

Type 2:

Type 2 Seyfert galaxies are observed very bright in infrared wavelengths (40). Unlike Type 1, broad lines are not permitted in Type 2 spectra. This gives them characteristic luminous nuclei. We can observe the nuclei of Type 2 by looking at light which is reflected by materials above and below the torus, this observation can be made when we look at the side view of the galaxy. Since the light is reflected by gas or dust, we will call it as polarized light. There is a method called spectropolarimetry to analyze some Type 2 galaxies by using this polarized light (41).

Type 1.2, 1.5, 1.8, 1.9:

There are some types of galaxies that show characteristics between Type 1 and Type 2. Their spectra have fewer broad lines when we compare them with their emission lines. So they can not be classified as Type 2 since they have broad lines but they can not be classified as Type 1 either since their narrow lines are more than broad lines. In 1981, Donald Osterbrock began to classify them by using fractional numbers like 1.5, 1.8…(39) Their Type 2 characteristics increase as they get closer to 2, so their Type 1 characteristic decreases. For example, Type 1.5 (middle point between 1 and 2) has nearly the same amount of narrow and broad lines, but in Type 1.9 there is only one broad line which is in the hydrogen alpha line (38)

Evolution:

We know that active galaxies were formed in the early times of the universe. They are moving away from Milky Way at high speeds, since the universe is expanding we can say they are very away from us. And this indicates that they are very old structures. And since they are far away and move fastly, their Doppler shifts are large (39,42).

Seyferts are at a distance of more than millions of light years, for example, the famous Seyfert galaxy the Circinus is 13 million light years away from us. Quasars are way more distant to us, like billions of light years. Realize that actually, we see them as they were billions of years ago and there is no active galaxy around our galaxy. So we can interpret that active galaxies may be one of the early stages of galactic evolution.

Some unified models have been designed to explain Active galaxies. Most of these models explain Seyfert galaxy types, quasars, and blazars very well. But these models can not explain why they are radio-loud or radio-quiet. Radio loud ones have high spin holes, and produce jets (source of loud). Radio quiet ones have low spin holes and they do not have jets (reason for their silence) (43).

Conclusions:

Seyfert galaxies are galaxies that have a massive and variable bright nucleus which are classified under active galaxies. They are quite common, and this was realized when astronomers began to observe them in infrared and ultraviolet wavelengths. They are hard to detect and seem quite normal in visible wavelengths. Observations show us, they are early-formed galaxies. They are far away from us and continue to move away from us at high speeds. They are subclassified under 2 main types Type 1 and Type 2. Other types of them show properties between them so they are called by fractional numbers between 1 and 2 like 1.2, 1.8. There are some unified models which explain the difference between these subclasses and the difference between Seyfert galaxies and other active galaxies.

I would like to thank Batuhan Alkan, my former undergraduate student who helped me in preparing this review.

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Chapter 3

PLANTS AS ACTIVE ANTIAGING INGREDIENTS IN COSMETIC PRODUCTS

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1. Introduction

1.1 Overview of the antiaging market

The anti-aging market is a rapidly growing industry, with an increasing demand for products and treatments that target the discernable traces attributed to aging. This includes wrinkles, fine lines, age spots, and other skin imperfections. Factors such as an aging population, increasing recognition of the benefits of anti-aging products, and the availability of a wide array of items catering to different skin types and concerns drive the market. The market is segmented into skincare, hair care, and anti-aging supplements, with skincare accounting for the largest share of the market. Within the skincare segment, the facial skincare sub-segment is the largest, driven by the increasing demand for anti-aging creams, lotions, and serums (Pandey, 2019).

1.2. Cosmeceutical products

Cosmeceuticals represent an emerging class of products that exist at the interface of conventional cosmetics and pharmaceuticals, offering therapeutic benefits in addition to their cosmetic effects. Indeed, cosmeceuticals are defined as cosmetic products incorporating biologically active ingredients that provide both cosmetic and pharmaceutical benefits. That includes vitamins, antioxidants, proteins, anti-inflammatory agents, etc. that claim to induce a more even skin tone, improve skin regeneration and decrease or prevent skin wrinkling and aging (Shin & Park, 2019). Cosmeceutical products containing natural active ingredients are the modern trend in the field of cosmetic. The popularity towards natural products in personal care is driven by consumer preferences for safer and more effective alternatives to synthetic chemicals, with a particular focus on products that are derived from plants and other natural sources. (Marchev & Georgiev, 2020).

1.3. Importance of natural compounds

The use of natural ingredients in cosmetics has gained increasing popularity in recent years. Natural ingredients are derived from plants, minerals, and other natural sources are considered to be healthier and pleasant on the skin than synthetic ingredients. Consumers are growing more conscious of the constituents of the products, and the demand for natural and organic cosmetics is on the rise.

Natural ingredients are often rich in active components such as vitamins, plant's phytochemicals, bioactive peptides, polyunsaturated fatty acids, oligosaccharides and carotenoids that can help to nourish and protect the skin via their special biological properties. These natural ingredients exhibit many biological futures such as; anti-oxidant, anti-microbial, anti-inflammation, anti-pigmentation, moisture holding capacity and elasticity retainment of the skin. All these biological properties synergically provide anti-aging benefits, such as reducing the appearance of wrinkles and fine lines. Furthermore, natural ingredients can be more sustainable and biodegradable than synthetic ingredients (Mohd-Nasir & Mohd-Setapar, 2018).

1.4. Plants as natural ingredients in cosmetics

Plants have been used for beauty and medicinal treatments for centuries in fact It is becoming increasingly popular to use plant extracts as the main ingredients in skin care products. Sometimes it is good to go bake to basics because nature hold the secret to beautiful skin. Natural ingredients incorporated to the cosmetic products because plant derived ingredients not only gentle yet effective in solving skincare woes in the same time they repair and rejuvenate skin.

Natural plants contain secondary metabolites, they have been recognized as cosmeceutical ingredients due to the existence of high value secondary metabolites namely phytochemicals such as phenolic acids, flavonoids, terpenes, therefor this metabolites are high value commercial products for cosmeceutical industries (Apone, Tito, Arciello, Carotenuto, & Colucci, 2020).

There are numerous studies are ranging and explore the effects of bioactive plant-based ingredients on having different use in cosmetic preparations for skincare such as antioxidant capacity, collagen synthesizing properties and modulation of enzymes involved in extracellular matrix restructuring (Udayakumar, Gurumallesh, & Ramakrishnan, 2020).

1.5. Purpose and scope of the chapter

The aim of this chapter is to provide an overview of the plant based natural resources that have been discovered and analyzed for their effectiveness as anti-aging ingredients in cosmetic products. The chapter will focus on highlighting the plant extracts in according to the scientific studies that have been found to be effective and safe for cosmeceutical targets. The goal is to present a comprehensive review of plant-based ingredients that have the potential to be utilized by cosmetic companies in the future. This will include a discussion of the scientific evidence supporting their effectiveness, as well as any challenges or limitations that may need to be addressed in order to make these ingredients viable options for use in commercial products.

2. Plant-based antiaging ingredients

The practice of utilizing plants for medicinal purposes is deeply rooted in human history, and in the upcoming years, plant-derived ingredients with anti-aging properties are anticipated to gain widespread acceptance in the cosmetic market. These ingredients are derived from a wide variety of plants, including fruits, vegetables, herbs, and flowers and contain within a wide range of phytochemicals that can help prevent the onset of degenerative skin conditions and improve appearance through the provision of essential micronutrients, crucial for the maintenance of healthy skin homeostasis. This leads to an enhancement in skin quality, with improvements in tone, texture, and radiance, alongside a reduction in the prominence of wrinkles. In addition, protect the skin from environmental damage so phytochemicals from plants are largely effective alternatives with less adverse effects (Chermahini, Majid, & Sarmidi, 2011).

2.1. Plant extract

The initial step to obtain the biologically active compound from plant resources are extraction, isolation and characterization of bioactive compounds followed by their pharmacological, toxicological, and clinical evaluations. As extraction is the most important stage in the analysis of constituents present in botanicals, use of suitable extraction techniques and solvent types gains much importance in this field. The most widely employed technique for isolating bioactive compounds from plant materials is solvent extraction; however, the composition and properties of the extracting solvent can significantly impact the yield and biological activity of the resulting extracts. Polar substances dissolve in polar solvents therefor polar solvents are regularly put to use for the retrieval of polyphenols from a plant matrix. Aqueous mixtures (hot or cold) containing ethanol, methanol, acetone, or ethyl acetate are the most suitable solvents (Ibrahim, Hassen, & Apostolides, 2022).

2.2. Plant secondary metabolites as active ingredients in cosmetic

Plant secondary metabolites are chemical compounds synthesized by plants that are not directly involved in primary life processes such as growth, reproduction, and response to the environment. Unlike primary metabolites, which are essential for plant survival and play a role in physiological processes, secondary metabolites have no known direct role in these processes. Instead, they often serve as defense mechanisms against herbivores, pathogens, and other environmental stressors, as well as attracting pollinators and seed dispersers (Zillich, Schweiggert-Weisz, Eisner, & Kerscher, 2015).

Examples of plant secondary metabolites include alkaloids, flavonoids, terpenoids, and phenolic compounds. These compounds demonstrate a broad spectrum of bioactive potential and are of significant interest to the pharmaceutical, cosmetic, and food industries due to their possible uses as drugs, cosmetics, and functional foods. Some secondary metabolites also have antimicrobial, antioxidant, anti-inflammatory, and photoprotective properties, which again encourages their use in cosmetic products (Chiocchio, Mandrone, Tomasi, Marincich, & Poli, 2021).

2.1.1. Classes of plants secondary metabolites

Secondary metabolites can be broadly categorized into distinct groups according to their chemical structure and biosynthetic pathways. The following are some of the major classes of plant secondary metabolites:

Alkaloids: A diverse class of nitrogen-containing compounds that are often toxic to herbivores and pathogens. Examples include caffeine, nicotine, and morphine.

Flavonoids: A group of compounds known for their vivid colors and antioxidant properties. They are subgroups of polyphenols. Examples include quercetin, kaempferol, and catechins.

Phenolic compounds: A class of compounds that contain one or more phenol groups. They are acknowledged for their antioxidant, anti-inflammatory, and antimicrobial properties. Examples include catechins, tannins, and anthocyanins.

Terpenoids: A large class of compounds that are the building blocks of many essential oils and are known for their strong odors and flavors. Examples include limonene, menthol, and camphor.

Isoprenoids: A class of compounds that stem from the five-carbon isoprene unit and include steroids, carotenoids, and terpenoids.

Secondary Amines: A group of compounds that contain a nitrogen atom in their structure and are known for their role in plant defense against herbivores. Examples include tryptamine and indole alkaloids (Jamwal, Bhattacharya, & Puri, 2018).

These ingredients can be found in a variety of cosmetic products such as creams, serums, and masks. Many companies are now focusing on incorporating natural plant-based ingredients in their products, as they are considered to be safer and more gentle on the skin than synthetic ingredients. Additionally, these ingredients are readily available and can be sourced sustainably, which is an important consideration for many companies.

3. Mechanisms of action of plant-based antiaging ingredients

The mechanisms of action of plant-based anti-aging ingredients are complex and vary depending on the specific ingredient. However, some of the most common mechanisms include:

3.1. Antioxidant effect

The detrimental impact of oxidative stress is considered a principal mechanism behind the aging of skin. Oxidative stress is an imbalance between the production of reactive oxygen species (ROS) and their detoxification. ROS can be produced by both endogenous sources, such as the mitochondria in skin cells, and exogenous sources, such as UV radiation, pollution, and smoking. When there is an excess of ROS, they have the potential to cause damage to various cellular constituents, such as proteins, lipids, and DNA. This harm can lead to inflammation, reduced collagen synthesis, and increased breakdown of collagen and elastin fibers in the skin, which are important structural components that keep the skin firm and elastic. Over time, this damage accumulates and leads to observable signs of skin aging, such as fine lines, wrinkles, and other manifestations (Ahsanuddin, Lam, & Baron, 2016).

In addition, oxidative stress can also lead to a decline in the skin's natural antioxidant defense mechanisms. Antioxidants are molecules that neutralize ROS and prevent their damaging effects. However, with aging and exposure to environmental stressors, the skin's natural antioxidant defenses can become less effective, leading to an even greater buildup of ROS and exacerbating oxidative damage (Poljsak, Dahmane, & Godic, 2013).

To combat the effects of oxidative stress on skin aging, many anti-aging skincare products contain antioxidants namely vitamin C, vitamin E, and coenzyme Q10, which assist in neutralizing ROS and provide protection for the skin against further damage. In addition, lifestyle factors such as eating a healthy diet, avoiding smoking, and reducing exposure to UV radiation and pollution can also help to reduce oxidative stress and promote healthier, more youthful-looking skin (Shapiro & Saliou, 2001).

Phenolic compounds are a great diversity of plant secondary metabolites, such as flavonoids (anthocyanins, flavonols, flavones, etc.) and several classes of non-flavonoids (phenolic acids, lignins, lignans) that have been widely studied for their potential health benefits, including their antioxidant properties. In the context of cosmetics, phenolic compounds are often included in skincare products for their antioxidant activity, which in turn exert a protective effect against oxidative stress and other environmental stressors that contribute to skin aging. Phenolic compounds can act as antioxidants by donating electrons to free radicals and other reactive oxygen species (ROS), neutralizing them and preventing them from damaging cellular components such as proteins, lipids, and DNA. This can help reduce inflammation and oxidative damage in the skin, improving skin health and reducing the appearance of fine lines, wrinkles, and other signs of aging (Martinez, Estevez, & Silva-Pando, 2012) .

Some examples of plant extracts and the phenolic compounds within that are commonly used in cosmetics include:

Resveratrol of red grapes extract: A phenolic compound found in the skins of red grapes, resveratrol has been shown to have potent antioxidant and anti-inflammatory activity. It is often used in anti-aging skincare products and provide them anti-aging properties(Sueishi, Nii, & Kakizaki, 2017).

Catechins of Green tea extract: Green tea catechins, including epigallocatechin gallate (EGCG), are phenolic compounds that have been shown to have potent antioxidant and anti-inflammatory activity. They are often used in skincare products to help protect the skin from UV radiation and other environmental stressors (Musial, Kuban-Jankowska, & Gorska-Ponikowska, 2020).

Oleuropein of olive leaf extract: Oleuropein is the main phenolic compound the of the olive leaf extract. It has been found that oleuropein is an important source of natural antioxidants; it has effective antioxidant activity against different reactive species and recently it has been used in cosmeceuticals and antiaging ingredients (Tarbiat, Yener, Kashefifahmian, & Mohseni, 2022).

Coffeeberry extract: Coffeeberry extract, derived from the fruit of the coffee plant, contains a range of phenolic compounds, including chlorogenic acid and caffeic acid. It has been shown to have potent antioxidant activity and is often used in anti-aging skincare products to prevent and reduce the appearance of wrinkles. (Farris, 2007).

Rosa damascene Mill extract: R. damascene has a significant place in traditional system of medicine. It is an important plant with variety of applications in medicine. Studies have shown that R. damascene plant extract and its essential oil contain different kind of phenolic and flavonoids and function as natural antioxidant. Many studies suggest the therapeutic potential of R. damascene and its uses in pharmaceutical and cosmetic industries (Chaiyana, Charoensup, Sriyab, Punyoyai, & Neimkhum, 2021).

Pomegranate (Punica granatum L.) extract: Pomegranate extract contains a range of phenolic compounds, including ellagic acid and punicalagins, which have been shown to have potent antioxidant and anti-inflammatory activity. Pomegranate extract is often used in skincare products to help protect the skin from oxidative stress and improve skin health (Tozettoa et al., 2017).

While phenolic compounds have shown promise as antioxidants in cosmetics, it's worth noting that their effectiveness can vary depending on a range of factors, including their concentration in the product, the specific phenolic compounds used, and the formulation of the product.

3.2. Antimicrobial effect

Plant-based anti-aging ingredients are often included in cosmetic formulations for their potential antioxidant and anti-inflammatory properties, which can help to protect the skin from damage caused by environmental stressors and aging. Some of these ingredients also have antimicrobial properties that can help to prevent the growth of harmful bacteria on the skin and can be used as natural preservatives in cosmetic products (Glavac & Lunder, 2018).

Plant-based anti-aging ingredients with potential antimicrobial activity are listed below:

Tea tree (Melaleuca alternifolia) oil: One example of a plant-based anti-aging ingredient with antimicrobial properties is tea tree oil. Extracted from the leaves of the Melaleuca alternifolia plant, tea tree oil has been shown to exert antimicrobial property against a range of bacteria as well as fungi. It is often employed in skincare products to help prevent and treat acne and other skin infections (Kunicka-Styczynska, Sikora, & Kalemba, 2009).

Lemon Peel (Citrus limon) Oil: Studies revealed that the lemon peel essential oil shows considerable antimicrobial as well as antioxidant properties, which is attributed to the large content of flavonoids and polyphenols as well as terpenes, present in the essential oil. It is used in cosmetic products formulations for these purposes (Kunicka-Styczynska et al., 2009).

Grapefruit seed extract: Another plant-based ingredient with antimicrobial properties is grapefruit seed extract. This extract is derived from the seeds and pulp of grapefruits. The extract possesses a broad-spectrum antimicrobial properties against viruses, fungi, and bacteria, rendering them effective natural preservatives in cosmetic applications (Glavac & Lunder, 2018).

Manuka honey: Manuka honey, which comes from the nectar of the manuka tree in New Zealand, has been shown to have particularly potent antimicrobial activity. Methylglyoxal, the main constituent of manuka honey is responsible for the antimicrobial activity of this natural source (Juliano & Magrini, 2019).

Aloe vera: Aloe gel constituents (aloins) have also been isolated from Aloe vera (Aloe barbadensis) Aloe vera has been shown to have antibacterial activity against a range of common skin bacteria and is often used in skincare products for its soothing and hydrating properties (Alemdar & Agaoglu, 2009).

It's worth noting that the antimicrobial activity of these plant-based ingredients may vary depending on a range of factors, including the specific species of plant, the concentration of the active compounds, and the formulation of the cosmetic product.

3.3. Stimulation of collagen production

Collagen is a structural protein, which produces by fibroblasts and provide elasticity to skin, but its production declines with age. Recently finding ways to combat this problem is being promoted as an effective way to repair skin damage, which is helpful in healthy appearance of skin in the pursuit of beauty.

Labisia pumila extract: L. pumila extract is one of the plant-based ingredients, which stimulate collagen production. Studies have shown that this extract is highly capable of inducing human skin fibroblast cell growth after exposure to ultraviolet (UV) radiation. The beneficial effects of L. pumila extract on skin health can be attributed to its ability to enhance collagen synthesis in human dermal fibroblast cells, which is an essential component of skin integrity and strength (Chua, Lee, Abdullah, & Sarmidi, 2012).

Bambara groundnut (Vigna subterranea) extract: Bambara groundnut extracts exhibited the high antioxidant and stimulation of collagen activites and these biological activites might be related to their phytochemicals, especially phenolic and flavonoid contents (Chutoprapat, Malilas, Rakkaew, Udompong, & Boonpisuttinant, 2020).

3.4. Anti-collagenase effect

Collagen is a major component of the extracellular matrix in skin, and plays a key role in maintaining skin structure and elasticity. However, as the skin ages, collagen breakdown and synthesis become imbalanced, resulting in a decrease in collagen levels and leading to the formation of fine lines, wrinkles, and other signs of aging. Collagenase is an enzyme that breaks down collagen, and inhibiting its activity is one strategy for combating collagen loss and improving skin health (Khorramizadeh, Tredget, Telasky, Shen, & Ghahary, 1999).

Some plant-based anti-aging ingredients have been found to have anti-collagenase effects, which can help to preserve collagen levels and maintain skin structure. Here are a few examples:

Camellia sinensis (Green tea) extract: Catechin and epigallocatechin gallate, which are polyphenolic compounds present in green tea, have been reported to be robust bioflavonoids with strong antioxidant activity and possess the ability to inhibit collagenase enzyme activity. Studies have suggested that green tea catechins can help to inhibit collagen breakdown and promote collagen synthesis in the skin, improving skin elasticity and again, reducing the appearance of fine lines and locks the process of aging (Chu, Deng, Man, & Qu, 2017).

Licorice extract: A compound called glycyrrhizin, found in Licorice root, is another substance established to possess anti-collagenase effects. In the latest study, glycyrrhizin was found to inhibit collagen breakdown and improve skin elasticity in human skin samples (Assar et al., 2021).

Soybean extract: Aglycone isoflavones are actine ingredients of soybean extract, which have been shown to have anti-collagenase effects. Studies have found that soybean extract stimulates a collagen-I synthesis in the intracellular matrix of human fibroblasts (Bezerra et al., 2022).

Centella asiatica extract: Centella asiatica, also known as gotu kola, has been used in traditional medicine for centuries and is known for its wound-healing properties. The active compounds include Total triterpenes, Asiaticosides, Asiaticoside and Madecassoside. Studies have suggested that centella asiatica extract can help to inhibit collagen breakdown and promote collagen synthesis, improving skin elasticity and reducing the appearance of fine lines and wrinkles (Hashim et al., 2011).

3.5. Anti-Tyrosinase effect

Tyrosinase is an enzyme involved in the production of melanin, which gives color to the skin and hair. Overproduction of melanin can lead to hyperpigmentation, which is a common skin concern associated with aging. Therefore, inhibiting tyrosinase activity can be a useful strategy in anti-aging skincare (Skoczynska, Budzisz, Trznadel-Grodzka, & Rotsztejn, 2017).

Plant-based anti-aging ingredients have been found to have anti-tyrosinase effects, making them effective in reducing hyperpigmentation and improving skin tone (Mukherjee et al., 2018). Some examples of these ingredients include:

Licorice root extract: Contains phenolic compounds such as glabrene and isoliquiritigenin which inhibits tyrosinase activity and reduces melanin production (Nerya et al., 2003).

Green tea extract: Contains epigallocatechin gallate (EGCG), which inhibits tyrosinase activity and reduces melanin production (Korkmaz et al., 2019).

Mulberry extract: Contains morin, which inhibits tyrosinase activity and reduces melanin production (Cho, Che, Yin, & Jang, 2017).

Bearberry extract: Contains arbutin, which inhibits tyrosinase activity and reduces melanin production (Matsuda, Nakamura, Shiomoto, Tanaka, & Kubo, 1992).

Curcumin: Curcumin is a polyphenol yellow pigment found in rhizomes of curcuma species. Curcumin acts as a potent antioxidant and can also inhibit tyrosinase activity, reducing the production of melanin. Hence it is used in anti-wrinkle, anti-acne, and skin whitening products (Du et al., 2011).

These ingredients can be found in a variety of anti-aging skincare products such as serums, creams, and masks. When used regularly, they can help reduce the appearance of hyperpigmentation and improve skin tone, leading to a more youthful and radiant complexion.

3.6. Moisturizing effect

Maintaining adequate skin hydration is crucial in mitigating the effects of skin aging, as it promotes plumpness and elasticity. As such, cosmetic formulations should be designed to preserve the natural hydration levels of the skin and avert skin dryness. Plant-based anti-aging ingredients can also provide moisturization benefits in addition to their anti-aging effects. Dry skin is a common sign of aging and can make the skin appear dull, flaky, and wrinkled. Using moisturizing ingredients restore skin hydration and promote a more youthful appearance (Mlosek et al., 2013).

Plant oils have been integrated into foods, cosmetics, and pharmaceutical products throughout history. Some examples of plant extracts and oils that provide moisturization and anti-aging benefits include:

Aloe Vera extracts (Aloe barbadensis Miller): Aloe Vera extracts contains polysaccharides, Mannose and cellulosic glucose were the major polysaccharide components in Aloe Vera extract, often used in cosmetic formulations and impart moisturizing properties to the product. The topical application of aloe vera extracts is widely recognized for its beneficial effects on skin. Research has shown that, while also providing anti-inflammatory and antioxidant benefits, he topical application of aloe vera extract is effective in the treatment of sunburns, and wounds due to its hydrating properties (Razia et al., 2021).

Jojoba (Simmondsia californica) Oil: Jojoba oil which is derived from the extraction of Jojoba seed, compsed of long monounsaturated esters, fatty acids, alkyl esters and triglycerides which give the unique structure and properties in comparison with other typical oils. Jojoba oil is a lightweight oil that is similar in composition to the skin's natural oils, making it an effective moisturizer. It also contains antioxidants and anti-inflammatory compounds that help to protect the skin from damage (Rheins & Sondgeroth, 2009).

Rosehip Oil (Rosa canina L.): Rose hip oil extracted from its seeds consist high levels of unsaturated fatty acids such as linoleic acid, α-linolenic acid and oleic acid. These compounds provide an excellent moisturizing effect to the oil. Rose hip oil also contain significant quantity of phenolic acids, particularly vanillin, and vanillic acid. Numerous lipophilic antioxidants is also present in the oil, including tocopherols, carotenoids and vitamin C that provide relatively high protection against oxidative stress. They protect the skin from environmental stressors, promote collagen production and maintain skin hydration (Lin, Zhong, & Santiago, 2018).

Avocado oil (Persea Americana): Avocado oil is a rich source of acids such as oleic, linoleic, and palmitic acids, vitamin E and lecithin which are distinguished ingredients suitable for moisturization and enhanced skin nourishment. Moreover, avocado oil harbors phenolic compounds that are instrumental in revitalization of skin subjected to external stressors (Santos, Camargo, Boock, Bergamaschi, & Rocha, 2009).

Olive oil (Olea europaea): The incorporation of olive oil into cosmetic formulations, particularly skin and hair care products, is commonplace due to its many desirable attributes. Active components are mainly phenols, secoiridoids, and lignans. Numerous investigations have demonstrated the potent moisturizing and antioxidant effects of olive oil (Karagounis, Gittler, Rotemberg, & Morel, 2019).

These ingredients can be found in a variety of anti-aging skincare products such as moisturizers, serums, and masks. When used regularly, they can help to hydrate the skin, reduce the appearance of fine lines and wrinkles, and promote a more youthful and radiant complexion.

3.7. UV protection effect

The constant and repeated exposure to UV radiation is a leading factor in the acceleration of skin aging, with approximately 80% of premature facial skin aging being attributed to this cause. The detrimental effects of UV radiation on the skin, which include sunburns, wrinkles, premature aging, and skin cancer, highlight the importance of protection and prevention. It is well known that plant extracts have great potential to treat different skin diseases, and improve skin appearance. One primary way plant extracts play a role in tackling this factor is once more their inherent antioxidant activity. Antioxidants, including vitamins (such as vitamin C and E), flavonoids, and phenolic acids, have a critical function in counteracting free radical species, which are primarily responsible for premature skin aging caused by ultraviolet radiation (Skarupova, Vostalova, & Svobodova, 2020).

Exposure to UV radiation can lead to the breakdown of collagen and elastin fibers in the skin, resulting in wrinkles, sagging, and age spots. Due to the harmful effects of UV radiation, the use of sunscreen formulations has become essential to protect the skin from the damaging effects of UV radiation. These formulations act by either forming a protective barrier on the skin surface or absorbing the harmful rays to prevent the penetration of UV radiation into the skin. Sunscreen agents used in sunscreen formulations, are zinc oxide, titanium dioxide, oxybenzone, octacrylene, etc. Many of these ingredients have been found to have adverse effects, and none of them possess antioxidant properties that can protect the skin from damage caused by free radicals generated by UV radiation. Utilizing plant extracts and oils as potential agents for sunscreen formulations is beneficial due to their inherent photoprotective as well as antioxidant properties. Studies have shown that plant polyphenols are effective in neutralizing free radicals and preventing damage caused by UV radiation. As such, the incorporation of polyphenols into sunscreen formulations represents an attractive strategy for the development of products with both photoprotective and antioxidant activity. (Polonini, Caneschi, Brandao, & Raposo, 2011) (Rabinovich & Kazlouskaya, 2018).

Some examples of plant-based ingredients that provide UV protection and anti-aging benefits include:

Green Tea (Camellia sinensis) Extract: Contains polyphenols that have been shown to protect the skin from UV radiation and reduce the appearance of sun damage. Epigallocatechin-3-gallate (EGCG) and epicatechin-3-gallate (ECG) are the most active components present in green tea extract. Many studies revealed that topical application as well as oral consumption protect the skin against chemical and UVB-induced carcinogenesis and inflammation (Kim, 2006). Green tea phytochemicals are a potent source of exogenous antioxidants that could neutralize the excess endogenous reactive oxygen and reactive nitrogen species inside the body, and thereby reduce the impact of photoaging (Prasanth, Sivamaruthi, Chaiyasut, & Tencomnao, 2019).

Red Raspberry Seed Oil (Rubus idaeus L.): Raspberry seed oil is composed of different kinds of valuable bioactive compounds such as fatty acids, toco, flavonoids, phytosterols, monoterpenes and high levels of antioxidants; including vitamin E and carotenoids many other chemical constituents. These compounds are appreciated as a great source as sunscreen agents in cosmeceutical products (Sharif, Ahmad, Mohamad Yazid, & Yahya, 2021).

Almond (Prunus amygdalus, syn. Prunus dulcis) : is commercially known as almonds and is One of the most renowned oils used in cosmetic. Seeds are rich in saturated, monounsaturated and poly unsaturated fats and oil-soluble compounds such as phytonutrients such as phytosterols and tocopherols. Recent investigations suggest that the almond oil has significant antioxidant and anti-photo aging properties since it rich in phenolic and flavonoid compounds (Hajhashemi et al., 2018).

Shea butter (Vitellariaparadoxa): The shea tree is native to Africa. Shea Butter is derived from the fat of the shea tree seed. With a melting point that aligns with body temperature, shea butter is able to permeate the skin swiftly, leaving behind no greasy sensation. It consists of saturated (Palmitate and stearate), mono unsaturated (Linoleic) fatty acids and vitamin E. They synergically improve subcutaneous blood circulation, promote skin cell regeneration, and confer protection against harmful UV radiation (Sarruf et al., 2020).

Carrot (Daucuscarota) Seed Oil: With considerable quantities of vitamin A, carrot seed oil is an essential oil with pronounced antioxidant and antifungal attributes. It also contains carotenoids and vitamin E, which help guard the skin from UV radiation and also promote collagen production (Kurzawa, Wilczynska, Brudzynska, & Sionkowska, 2022) (Singh, Srivastava, & Yadav, 2021).

Cucumber (Cucumissativus): Cucumber extract is reach in water, fiber, minerals and vitamins such as ascorbic acid. Hence, it has strong moisturizing abilities as well as UV protection effects. Its topical use has also been shown to have skin tightening and exfoliating effects. These properties make cucumber extract to be excellent ingredients in a variety of anti-aging skincare products such as sunscreens, moisturizers, and serums. When used regularly, they can help to protect the skin from UV radiation, prevent premature aging, and promote a more youthful and radiant complexion (Siahaan, Pangestuti, Munandar, & Kim, 2017).

It's important to note that the mechanism of action of plant-based anti-aging ingredients may depend on the specific plant, the extract or compound used, and the concentration of the ingredient in the product. Therefore, a thorough research and understanding of the ingredient is crucial to evaluate the potential benefits of plant-based anti-aging ingredients.

4. Comparison of natural plant-based ingredients with synthetic ingredients

Natural plant-based ingredients are often considered to be safer and gentler on the skin than synthetic ingredients. They are derived from plants and are rich in phytochemicals, antioxidants and vitamins, that are beneficial for the skin. These ingredients are also less likely to cause irritation or allergic reactions, as they are not chemically altered. Additionally, many natural plant-based ingredients can be sourced sustainably, which is becoming an important consideration for many companies.

On the other hand, synthetic ingredients are often chemically altered in a laboratory, and are not found in nature. They are formulated to mimic the properties of natural ingredients, but they may not be as gentle or safe on the skin. Synthetic ingredients may also cause irritation or allergic reactions in some people, and may not be as effective as natural ingredients. Additionally, synthetic ingredients are often not biodegradable, which can have an environmental impact(Figueiredo et al., 2022).

It is important to note that there are some synthetic ingredients that are safe and effective to use in cosmetics, and there are also some natural ingredients that can be harmful if not used properly. Therefore, it is essential to research and understand the ingredients used in cosmetic products before using them.

5. Clinical studies on plant-based antiaging ingredients

Clinical studies on plant-based anti-aging ingredients are essential to confirm the effectiveness of these ingredients on human skin. These studies involve testing the ingredient on a group of human volunteers, and measuring the results through various methods such as visual assessment, skin hydration and collagen levels, and other objective measurements. These studies provide a more accurate understanding of how an ingredient will perform on real-world users and help to establish efficacy and safety.

There have been a number of clinical studies conducted on plant-based anti-aging ingredients in recent years. According to the a clinical study, topical application of a cream containing resveratrol penetrated by the chitosan-coated lipid microparticles, significantly improved the appearance of fine lines and wrinkles in participants (Scalia, Trotta, Iannuccelli, & Bianchi, 2015). Another study found that an emulsion containing Saussurea lappa plant extract, have shown high anti-wrinkle and skin hydration effect (Adnan, Akhtar, & Khan, 2017).

It is important to note that not all studies on plant-based anti-aging ingredients have been successful, and more research is needed to fully understand their effectiveness. However, the increasing number of these studies are providing a better understanding of which natural plant-based ingredients have the potential to be effective anti-aging ingredients and will likely to be useful for the cosmetic industry to develop new products that deliver real benefits to the consumers.

6. Safety and efficacy of natural plant-based antiaging ingredients

Natural plant-based anti-aging ingredients are generally considered to be safe for use in cosmetic products. However, as with any ingredient, there is always the potential for side effects or allergic reactions. It's important to conduct proper safety testing on any ingredient before it is used in a cosmetic product to ensure that it is safe for use. Additionally, the efficacy of these natural ingredients should be backed by scientific studies, as well as traditional knowledge and application (Juhasz, Levin, & Marmur, 2018).

The efficacy of natural plant-based anti-aging ingredients varies depending on the specific ingredient and the formulation in which it is used. Some ingredients have been extensively studied and have been shown to be effective in improving the appearance of fine lines and wrinkles, while others have not yet been studied enough to make definitive conclusions. It's essential to conduct thorough research on the efficacy of the ingredient, and to carefully evaluate the results of any studies that have been conducted (Majeed et al., 2020).

In general, natural plant-based anti-aging ingredients are considered to be a promising alternative to synthetic ingredients. They can provide similar benefits, such as antioxidant protection, collagen stimulation and UV protection, but without the potential risks associated with synthetic ingredients. However, more research is needed to fully understand the safety and efficacy of these ingredients and their long-term effects on human skin.

7. Formulation and stability of natural plant-based antiaging products

Formulating natural plant-based anti-aging products requires a thorough understanding of the ingredients and their properties. The choice of ingredients, the concentrations used, and the pH of the final product all play a role in determining the efficacy and stability of the product.

One of the main challenges in formulating natural plant-based anti-aging products is ensuring stability of the active ingredients. Many natural ingredients are sensitive to light, heat and oxidation, and can degrade over time. This can lead to a loss of efficacy and can even cause the product to become harmful. To overcome this challenge, manufacturers must carefully choose ingredients that are stable and can withstand the manufacturing process. They must also use proper packaging and storage to protect the products from light and heat (Tarbiat et al., 2022).

Another challenge in formulating natural plant-based anti-aging products is the pH balance. The pH of the skin is around 4.5 to 5.5, and it's essential to formulate products with similar pH levels to prevent skin irritation and to ensure that the active ingredients can penetrate the skin effectively (Paulo & Santos, 2019).

Furthermore, the shelf life of natural ingredients is usually shorter than synthetic ingredients, therefore it's crucial to use adequate preservatives and to store the products in optimal conditions to maintain their effectiveness. In addition, it's important to use ingredients that are ethically and sustainably sourced to ensure the preservation of natural resources and to guarantee the safety of the final product.

In conclusion, the complexity of formulating natural plant-based anti-aging products mandates a comprehensive knowledge of the ingredients and their properties. It's crucial to consider stability, pH balance, shelf life, preservation and sustainability when formulating these products to ensure that they are effective and safe for use.

8.1 Considerations in formulating natural plant-based antiaging products

When formulating natural plant-based anti-aging products, it is important to consider the safety and efficacy of the ingredients used. This includes selecting ingredients that have been scientifically proven to have anti-aging properties and are stable and safe for cosmetic applications. It is also important to use appropriate concentrations of active ingredients to ensure effectiveness without causing irritation or other side effects.

Another consideration in formulating natural plant-based anti-aging products is ensuring stability of the active ingredients. Many natural ingredients are sensitive to light, heat, and oxidation, and can degrade over time. To overcome this challenge, manufacturers must carefully choose ingredients that are stable and can withstand the manufacturing process. They must also use proper packaging and storage to protect the products from light and heat. Additionally, it's important to keep in mind that natural ingredients have shorter shelf life than synthetic ingredients and therefore it's crucial to use adequate preservatives and to store the products in optimal conditions to maintain their effectiveness (Bom, Jorge, Ribeiro, & Marto, 2019).

8.2. Challenges in stability of natural plant-based antiaging products

Stability is a major challenge in formulating natural plant-based anti-aging products. Many natural ingredients are sensitive to light, heat, and oxidation, which can cause them to degrade over time and lose their effectiveness. This can lead to a loss of efficacy and can even cause the product to become harmful.

One of the main challenges in stability is the use of plant extracts, which contain a complex mixture of different compounds. These compounds can interact with each other and with the other ingredients in the product, leading to changes in their properties over time. This can be particularly problematic for ingredients that are susceptible to light, heat and oxidation. For example, antioxidant compounds, which are commonly used in anti-aging products, can be highly susceptible to degradation due to exposure to light, heat, and oxidation, leading to a rapid loss of their beneficial effects. Another challenge in stability is the use of water-based natural ingredients, such as hydrosols, which are often used as a base for anti-aging products. These ingredients can be prone to bacterial growth, and can become contaminated if not properly preserved. In addition, the use of natural ingredients can also cause problems with formulation. Natural ingredients often have different pH levels, viscosities and solubility, which can make it difficult to create stable and consistent formulations. To overcome these challenges, manufacturers must carefully choose ingredients that are stable and can withstand the manufacturing process. They must also use proper packaging and storage to protect the products from light and heat. Additionally, it's important to use adequate preservatives and to store the products in optimal conditions to maintain their effectiveness (Aziz & Mohd Setapar, 2022).

8.3. Solutions to improve stability of natural plant-based antiaging products

There are several solutions that can be used to improve the stability of natural plant-based anti-aging products. One solution is to use ingredients that are more stable and can withstand the manufacturing process and storage conditions. For example, using plant extracts that have been standardized for a specific compound, such as an antioxidant, can help to improve stability as these compounds have been shown to be more stable than the whole plant extract. Another solution is to use ingredients that have been processed in a way that improves their stability, such as through incorporation of nanotechnology with phytocompounds (Aziz & Mohd Setapar, 2022).

Another solution is to use appropriate preservatives and packaging to protect the product from light, heat and oxidation. Many natural preservatives such as essential oils, have antimicrobial properties, and can be used to preserve the product from bacterial contamination. Additionally, using airtight and opaque packaging can help to protect the product from light and heat. This can also help to extend the shelf life of the product. It's important to note that preservatives should be used in appropriate levels to ensure the safety of the product and avoid causing irritation or other side effects(Dreger & Wielgus, 2014).

9. Conclusion

The anti-aging market is a rapidly growing industry, with consumers increasingly seeking products that can help to reduce the appearance of aging and improve the health of their skin. One of the key trends in this market is the increasing use of natural ingredients in cosmetics. Natural ingredients, such as plant extracts, have been revealed to have anti-aging properties and are generally considered to be safer and more sustainable than synthetic ingredients.

In this chapter, we have discussed the various natural plant-based ingredients that have been discovered and analyzed for their anti-aging properties. These include ingredients such as resveratrol, green tea, and hyaluronic acid, which have been found to have powerful anti-aging effects in both in vitro and in vivo studies. We have also discussed the challenges and solutions in formulating natural plant-based anti-aging products, including the importance of stability and standardization.

Natural plant-based ingredients and their utilization in anti-aging products is a promising trend in the cosmetics industry. As consumers continue to seek out more natural and sustainable options, companies that can successfully develop and market high-quality natural plant-based anti-aging products will have a strong competitive advantage. Additionally, ongoing research and development in this field will lead to the discovery of new natural ingredients with anti-aging properties and new methods for improving their stability, efficacy, and safety.

In this chapter, we have discussed the mechanisms of action of different plant-based anti-aging ingredients. These mechanisms include antioxidant properties, which help to protect the skin from damage caused by free radicals, as well as anti-inflammatory properties, which help to reduce inflammation and redness in the skin. Additionally, many plant-based ingredients have been found to have hydrating and moisturizing properties, which can help to improve the overall appearance and health of the skin.

Some key examples of plant-based anti-aging ingredients in cosmetic products include resveratrol, which is found in red grapes and has been shown to have powerful antioxidant and anti-inflammatory properties. Green tea, which is high in antioxidants and has been found to have anti-inflammatory and anti-carcinogenic properties. Another example is hyaluronic acid, which is found in the skin and is responsible for maintaining hydration, which is a key factor in preventing signs of aging. Furthermore, there are other natural ingredients like Aloe vera, vitamin C, vitamin E, and beta-carotene, and many other plant extracts with anti-aging properties.

Formulating natural plant-based anti-aging products presents a number of challenges, one of the most significant of which is stability. Natural ingredients are often highly perishable and can degrade quickly, making it difficult to maintain their effectiveness over time. Additionally, many natural ingredients are sensitive to light, heat, and oxygen, which can further decrease their stability. To address these challenges, several solutions have been proposed. One approach is to use standardized and processed ingredients, which can provide more consistent and stable products. Another approach is to use appropriate preservatives and packaging, which can help to protect the ingredients from degradation.

Another challenge is the lack of standardization and quality control for natural ingredients, which can lead to inconsistent and unreliable products. To overcome this challenge, companies should use standardized and purified ingredients, as well as conduct rigorous testing and quality control measures to ensure that their products are consistent and effective.

In addition to these challenges, there is a need for more research and development in this field. This includes identifying new natural plant-based ingredients with anti-aging properties, developing new methods for extracting and purifying these ingredients, and conducting more clinical studies to establish their safety and efficacy. Furthermore, there is also a need to develop new techniques and technologies to improve the stability of natural plant-based ingredients in cosmetic products.

The use of natural plant-based anti-aging ingredients in cosmetic products presents a number of challenges, but also offers significant opportunities for innovation and growth in the industry. By addressing the stability and standardization issues and through continued research and development, cosmetic companies can develop high-quality, effective, and sustainable products that meet the needs of consumers.

The safety and efficacy of natural plant-based anti-aging ingredients is of the utmost importance in order to ensure that cosmetic products are safe for consumers to use. While there is a growing body of research on the potential benefits of these ingredients, there is still a need for more clinical studies to establish their safety and efficacy. These studies should be well-designed, randomized, and controlled to ensure that the results are reliable and accurate. Additionally, the use of standardized extracts and purified compounds, as well as appropriate dosage and duration of use, is crucial in establishing the safety and efficacy of these ingredients.

It's important to note that just because an ingredient is natural, it does not necessarily mean that it is safe for all individuals, for example, individuals with allergies or sensitivities to certain plants should avoid products containing those ingredients. Furthermore, some natural ingredients may interact with certain medications or have other unintended effects. Therefore, companies and researchers should conduct thorough safety assessments before using these ingredients in products and make sure that the ingredients are safe for all consumers.

10. Future research directions

In order to continue to advance our understanding of natural plant-based anti-aging ingredients, there are several key areas of research that should be focused on in the future.

First, it is important to conduct more in-depth clinical studies to establish the safety and efficacy of these ingredients. While there has been a significant amount of research conducted on the individual mechanisms of action of different plant-based ingredients, there is still a need for more rigorous clinical trials to establish their safety and efficacy in humans.

Second, researchers should focus on identifying new natural plant-based ingredients with anti-aging properties. There are likely many other plants and botanicals that have yet to be discovered that may have powerful anti-aging properties. By identifying these new ingredients, researchers can help to expand the options available to cosmetic companies and consumers.

Third, research should be focused on developing new methods for stabilizing natural plant-based ingredients. As discussed in this chapter, one of the major challenges in formulating natural plant-based anti-aging products is stability. Improving the stability of these ingredients will help to ensure that they remain effective over time and can be used in a wider range of cosmetic products.

Fourth, there is a need for more studies that investigate the combination of different natural plant-based ingredients for anti-aging. It is possible that certain combinations of natural ingredients may have synergistic effects that are greater than the sum of their individual effects.

Finally, research should be directed at understanding the environmental impact of natural plant-based ingredients, as well as the sustainability of harvesting these ingredients. This would enable cosmetic companies to develop products that are not only effective but also environmentally friendly.

In conclusion, there is a significant opportunity for future research to continue to advance our understanding of natural plant-based anti-aging ingredients and to develop new and more effective cosmetic products. By focusing on these key areas of research, scientists and cosmetic companies can help to ensure that these ingredients remain a viable and important option for consumers in the future.

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Chapter 4

THE RELATIONSHIP BETWEEN INTESTINAL MICROBIOTA AND COMMON DISEASES IN OLD AGE

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1. Introduction

Vital conditions such as decreasing death and birth rates in the world and prolonging the average human lifespan have caused the transformation of the demographic structure. Among the rapidly aging world population, countries with a ratio of 65 years of age and older to the entire population between 7% and 10% are among the countries that are often refer to as the "older society" (Çapcıoğlu & Alpay, 2021). One of these countries is Turkey with a 9.7% elderly population (TUIK, 2022). Therefore, with the increase in the number of elderly individuals in the world and our country, health problems in societies have started to increase, showing diversity. Accordingly, research on the underlying mechanisms of the aging process and how it affects diseases has increased by coming to the fore.

Aging is a natural and complex process that begins as soon as all living organisms come into existence. Although aging has been defined from many different aspects such as biological, physiological, psychological, chronological, sociological, and cultural that need to be examined are still open (Tereci, Turan, Kasa, Öncel, & Arslansoyu, 2016; Tufan, 2016). In this review, we will focus on the parts covered by the biological and physiological aspects that are at the center of the aging processes. Biological aging is a multifactorial phenomenon with many dimensions. It is seen that aging that starts at the molecular level progresses in different ways at the cellular, organ and organism levels (Khan, Singer, & Vaughan, 2017; Park & Yeo, 2013). The biology of aging can essentially be defined as the disorganization or disruption of metabolic events in cells and tissues as a result of multifactorial effects in molecular pathways and degenerative processes. Therefore, aging is an important precursor in increasing susceptibility to many diseases (e.g., neurological diseases, diabetes, sarcopenia, etc.) (Figure 1).

Intestinal microbiota (IM), which is claimed to play a very active role in the formation of diseases, has emerged as a popular research area recently. Although the exact cause is unknown, IM changes with age. The losses seen in the body during the aging process are also valid for the species in the IM. Considering that many metabolic events in the organism occur through bacteria in the microbiota, the altered microbiota has a role in the development of common diseases in old age. Hippocrates said[1], "*Every disease begins in the gut*." This also confirms the current information and approaches.

1 *Hippokrátēs ho Kṓos: c. 460–c. 370 BCE*

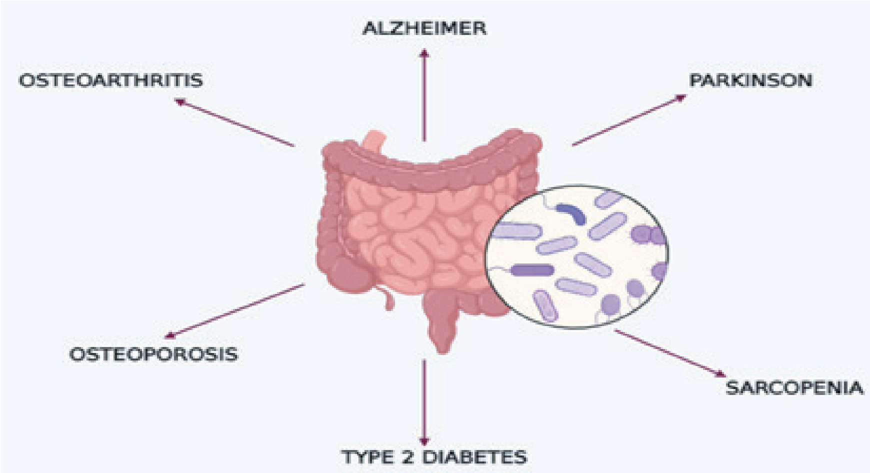

Figure 1. *Intestinal Microbiota and Diseases Affected*

2. Intestinal Microbiota

There are tens of thousands of microorganisms in the human organism, and most of them are those in the gut. Considering the number of various microorganisms living in human intestinal cells, it is seen that there are more (about 10 times) the number of all cells in the human body (Sender, Fuchs, & Milo, 2016). Various microbial communities, mostly bacteria, include archaea, viruses, fungi, and protozoa. However, under normal conditions, the predominance of IM is anaerobic bacteria. The number of bacterial species in the gut is thought to be between 500 and 1000 (Sommer & Bäckhed, 2013). *Firmicutes* and *Bacteroidetes*, known bacterial phyla, are among the most common in IM (Arumugam et al., 2011). Apart from these two phyla, there are also *Proteobacteria*, *Verrumicrobia*, *Actinobacteria*, *Fusobacteria* and *Cyanobacteria* phyla. According to the predominant interpersonal enterotypes, human IM is divided into 3 classes: *Bacteroides*, *Prevotella* and *Ruminococcus*. They differ in species and functional composition (Arumugam et al., 2011). IM varies among individuals due to factors such as the individual's diet, age, sex, and genetic background. Bacteria in the microbiota establish a symbiotic and mutualistic relationship with the host and provide benefits in the regulation of the homeostasis of the body, and they also mediate important metabolic events in humans such as helping digestion (especially in the digestion and absorption of carbohydrates), stimulating cell proliferation, and regulating the immune system (Guarner & Malagelada, 2003). The majority consists of bacterial species that play a role in healthy aging. They accomplish this important task by providing metabolites and functions. Microbial communities are also effective on systems and organs outside the gastrointestinal tract, such that they cross the intestinal barrier and trigger mechanisms that are beneficial or harmful to the organism in other tissues. For example, short-chain fatty acids and bile acids produced by microorganisms in the gut have beneficial effects on metabolism. However, it is also known that the produced trimethylamine-N-oxide and lipopolysaccharide induce proinflammatory events (C. Liu et al., 2021).

Most of the first microbiota formed during human birth comes from the mother (Quigley, 2017) and it develops in the first 2-3 years of life and becomes similar to the adult microbiota, and no major changes occur in the microbiota, which contains various microbial species in a stable manner until old age. However, it was determined that the microbial diversity in the gut began to decrease with the increase of biological age, regardless of chronological age (Maffei et al., 2017) (Figure 2). Physiological functions that begin to deteriorate with aging (especially intestinal functions and deterioration in development), age-related immune system insufficiency (immunosenescence), nutrition and lifestyle habits may cause negative changes in the structure of the IM of individuals in old age (Biagi et al., 2010; Kumar, Babaei, Ji, & Nielsen, 2016). At the same time, the fact that nutrition and lifestyle habits are country-specific allows the altered microbiota of individuals to differ according to societies (Biagi, Candela, Franceschi, & Brigidi, 2011). In addition to the increase in intestinal permeability with age, irregular and unhealthy diet, drug use, especially in the case of polypharmacy, lead to intestinal dysbiosis, which means the deterioration of the balance of microbiota such as reactive oxygen species (ROS), environmental toxins, proinflammatory factors. Dysbiosis in the aging gut causes a higher-than-normal natural immune response. This response contributes to the formation of dysplasia by causing chronic inflammation in the intestine. Intestinal dysplasia may also be one of the leading causes of unhealthy aging by triggering the deterioration of epithelial tissue (S. Kim & S, 2018). As a result of a study, it was found that intestinal dysbiosis plays a role in age-related deterioration (Saccon et al., 2021). Dysbiotic changes are involved in the formation of many diseases by affecting food signaling pathways.

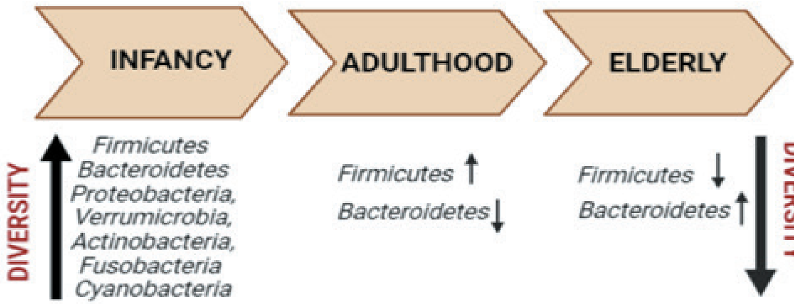

Figure 2. *Human Intestinal Microbiota (IM) Development*

Establishing a symbiotic relationship between the IM and the host cell aids in the immune response and digestion, and may contribute to longevity as a result (Biagi et al., 2010). Likewise, past studies have described changes in longevity and wellness through activation or inactivation of nutrient signaling pathways (a few references should be entered). Regulation of nutrition, which is also important for the health of IM, will affect food signaling pathways. However, as the beneficial effects of IM on lifespan were not observed in studies conducted by deactivating signaling pathways, we can conclude that these two conditions are not independent of each other (Han et al., 2017).

Transformations and changes in the microbiota of the gut, which are affected by physiological aging processes, have been a matter of curiosity. Especially in the last ten years, the number of studies on this subject has increased. When the data in the literature are examined, it is seen that microbial diversity generally decreases in old age (Kumar et al., 2016). This reduced diversity is associated with increased health risks (Shoaie et al., 2015). For this reason, the aged IM environment is considered suitable for the growth of pathogens. In studies conducted by creating an animal model, a decrease in species such as *Faecalibacterium prausnitzii* and *Bifidobacteria spp.* was observed in IM with aging. It has been concluded that *Bacteroidetes* and *Firmicutes* still dominate, as well as facultative anaerobes such as *Fusobacterium*, *Bacillus*, *Staphylococcus*, *Corynebacterium*, *Micrococcaceae bacteria* and many members of the *Proteobacteria* phylum in the gut microbiota of healthy centenarians compared to young and adults (Biagi et al., 2010). When comparing between *Bacteroidetes* and *Firmicutes*, the *Firmicutes* phylum was found to be less (Kostic, Howitt, & Garrett, 2013). The ratio of these two phyla is very important in the production of butyrate and propionate, which have recently been reported to have positive effects on healthy aging. In a study conducted with 178 elderly individuals, it was shown that microbial diversity may also change in geriatric individuals depending on diet (Claesson et al., 2012).

3. Intestinal Microbiota and Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disease that still remains unsolved. Amyloid β and Tau protein accumulation were two important factors that have been identified to date in the pathogenesis of AD. The presence of the APOE ε4 allele is one of the reasons for the genetic predisposition to AD. Microglia and astrocytes, which are known to be effective in the disease, have started to come to the fore in recent functional studies that also play a role in the pathogenesis. Apart from these biochemical responses, the vasculature, blood-brain barrier, and brain clearance systems such as the glymphatic 63, peripheral immune system, and gastrointestinal microbiome also have an impact on the clinical development of the disease (Scheltens et al., 2021). The duration of the symptoms of this disease, which is caused by various unidentified factors, varies from person to person. However, in general, the presence of symptoms is encountered within 10-20 years after amyloid pathology and the diagnosis of AD can be made (Sochocka et al., 2019). Alzheimer's is a common type of dementia in old age and is also the most common among dementia types. Many factors such as the individual's lifestyle habits, diet, exercise habits, presence of chronic diseases, polypharmacy, sleep patterns and health play a role in the pathogenesis of AD (De la Rosa et al., 2020; Lourida et al., 2013; Ooms et al., 2014). Apart from all the known factors in the onset of AD, another important issue that draws attention is the change in the microbiota. The amyloid cascade hypothesis, which advocates the formation of amyloid β deposits, is gradually losing its importance and the obvious reasons for the formation of AD are still being investigated. More attention has been focused on the possibility that it may be caused by neuroinflammatory changes. Considering that dysbiosis of the intestine with age can lead to a systemic inflammatory response, IM is thought to be an effective factor in AD. Therefore, studies proving the existence of a strong relationship between IM and AD are increasing.

A relationship occurs between the IM and the brain through the nervous system, the peripheral circulatory system, or chemicals that could cross the blood-brain barrier. The intestines have a nervous system of their own, called the enteric nervous system. There are nerves in the organism, such as the vagus nerve, that provide a connection between this system and the neurons in the brain. Thanks to such connections, called the "brain-gut-microbiota" axis, mutual interaction can be established between the IM and the brain (Pluta, Ułamek-Kozioł, Januszewski, & Czuczwar, 2020). Short-chain fatty acids such as acetate, butyrate, and propionate, which can affect brain functions, are produced in IM. Short-chain fatty acids affect a healthy life span. Butyrate has been shown to improve memory function in aged mice, providing evidence that this may have beneficial effects on healthy aging (Blank et al., 2015). Many neuromodulators and neurotransmitters such as serotonin, kynurenine, melatonin, catecholamines, acetylcholine, glutamate, biogenic amines, dopamine, and histamine are synthesized in the microbiota in addition to the short-chain fatty acids. It also takes part in the synthesis and release of amino acid metabolites such as homocysteine, GABA, and tryptophan (Figure 3). Tryptophan, the precursor of serotonin, is quite important in the anti-inflammatory response, as it is an effective amino acid in the kynurenine pathway. Disturbances in these processes regulated by B vitamins lead to the emergence of neurodegenerative diseases (Kalip & Atak, 2018). IM, which is an important part of the immune system, is responsible for the production and transmission of neurotoxic substances such as D-lactic acid, proinflammatory cytokines and ammonia to the brain. This shows that the brain-gut axis plays a role in immune, neuroendocrine and direct nervous mechanisms (Pluta et al., 2020).

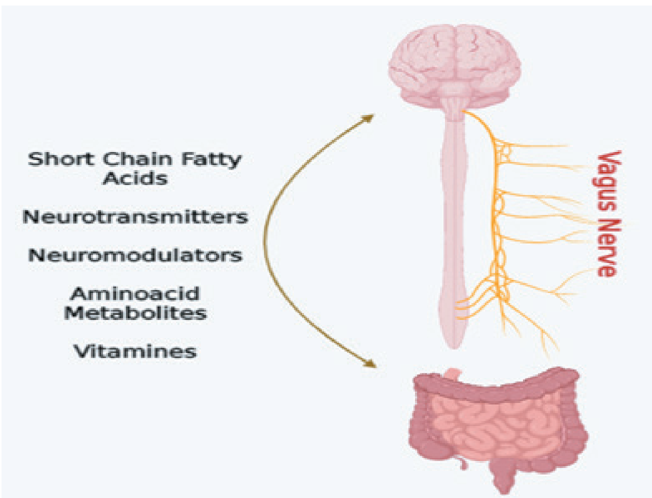

Figure 3. *Brain-Gut Axis*

In studies comparing the microbiota of AD and control groups, it was observed that microbial diversity and the number of *Firmicutes* decreased in people with AD. At the same time, an increase in *Bacteroidetes* was observed in individuals with Alzheimer's as well as in elderly individuals (Vogt et al., 2017). The results of a recent clinical study conducted in China also show parallelism with these data (P. Liu et al., 2019). An increase in *Proteobacteria* has been associated with AD. One of the significant reasons for the association of IM with AD was intestinal dysbiosis which occurs with aging creates an inflammatory reaction. Considering research have investigated that it has found that *Helicobacter pylori*, *Borrelia* *burgdorferi*, and *Chlamydia pneumonia* bacterial species increased the markers found in Alzheimer's patients. Thus, it has suggested that it has supported the role of inflammation in the pathogenesis of AD (Bu et al., 2015). It has a known fact that a high-fat diet can cause intestinal dysbiosis. Dysbiosis increases the formation of proinflammatory cytokines. In this way, it could trigger neuroinflammation (Marques, Meireles, Faria, & Calhau, 2016). The presence of bacterial species such as *Clostridium butyricum* in the intestine provides a neuroprotective effect by increasing the secretion of short-chain fatty acids and antioxidants that protect the brain from pathogens (J. Sun et al., 2020).

Actinobacteria, which are members of *Bifidobacterium,* are bacteria that live in the human intestine and have positive effects on health. IM analyses performed on Alzheimer's patients have shown that there has been a decrease in the number of *Actinobacteria* (Arboleya, Watkins, Stanton, & Ross, 2016). According to the results of a study conducted in elderly individuals with cognitive impairment, amyloid accumulation was observed in individuals with increased abundance of *Escherichia* and *Shigella* bacteria and decreased of *Eubacterium rectale* (anti-inflammatory bacteria type) bacteria (Cattaneo et al., 2017). In a placebo-controlled study of healthy older adults, those who consumed probiotics (*Eubacterium* and *Clostridiales*) had changed in IM. According to the mental flexibility test, those who consumed probiotics showed better improvement. The change in IM with the consumption of probiotics improves cognitive function and mood in the elderly (C.-S. Kim et al., 2021). These results prove that there is a relationship between IM and AD.

4. Gut Microbiota and Parkinson's Disease

Parkinson's disease (PD) is a slowly progressive and complex neurodegenerative disease that begins with the loss of dopaminergic neurons in the substantia nigra pars compacta. Dopamine deficiency in basal ganglia, α-synuclein aggregation, mitochondrial dysfunction, and Lewy bodies are involved in the pathogenesis of PD. PD, which develops under the influence of environmental and genetic factors, appears long after the onset of symptoms. Therefore, diagnosis might be delayed. There are motor and non-motor symptoms. Motor symptoms include bradykinesia, muscle stiffness, tremor, stance and gait disturbance, and slurred speech; non-motor symptoms include cognitive, olfactory, and sleep disturbance, pain, and fatigue. Advanced PD may lead to dementia (M.-F. Sun & Shen, 2018). The first symptoms of PD, begin much earlier than these symptoms, are related to the gastrointestinal system. Gastrointestinal system dysfunctions considered presymptomatic of PD are weight loss, constipation, gastroparesis, dysphagia, etc. (J.-S. Kim & Sung, 2015). The presence of gastrointestinal symptoms, which are common in PD, suggests a relationship with IM. Intestinal inflammation and constipation that begin years before motor symptoms are interesting (Sampson et al., 2016). Clinical and experimental research on this has begun to increase. Since PD is a neurodegenerative disease just like AD, it has similar microorganism species and pathways on the brain-gut-microbiota axis that play a role in AD.

When looking at the pathogenesis of PD, the most prominent is the formation and accumulation of α-synuclein. Aggregation of α-synuclein proteins is considered to lead to motor dysfunction in PD. It has not been clearly elucidated mechanisms of PD. However, it has been known that PD has two important pathological features; α-synuclein proteins affected the loss of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies in the pericardium. It has also been known to trigger PD by increasing the activation of microglia and creating neuroinflammation (Sanchez-Guajardo, Tentillier, & Romero-Ramos, 2015). In a study, it has concluded that α-synuclein accumulation was significantly reduced in germ-free (GF) Parkinson's disease mice (Sampson et al., 2016).

The relationship between the destruction of α-synuclein proteins, which is important in PD, and IM may be explained by the modulation of proteasome function of some bacteria in the microbiota (Cleynen et al., 2014). In other studies on this hypothesis, it has found that inflammation in the colon of Parkinson's patients causes dysbiosis and increases α-synuclein aggregation. Comparing with healthy and PD's individuals, it has been found that the mucosal and fecal microbial communities have significantly different (Keshavarzian et al., 2015). According to the findings of the study, *Blautia, Coprococcus,* and *Roseburia,* which are produced anti-inflammatory butyrate, decreased in Parkinson's patients. The decrease of these bacteria that produce short-chain fatty acids increases intestinal permeability and exacerbates microglia-mediated inflammation (Hirayama & Ohno, 2021). Likewise, a decrease is observed in the genus *Faecalibacterium*. However, it has found an increase of proinflammatory bacteria in PD's individuals. These results provided that altered IM may contribute to the development of PD pathology. Dysbiosis may occur in the intestine due to the reasons such as altered intestinal absorption and decreased gastric motility. As a result, mechanisms inducing PD may be activated.

In short, PD has associated with intestinal dysbiosis. A decrease in the microbial community in the families *Lachnospiraceae* and *Ruminococcaceae* has seen in stool samples from PD's individuals. The increase in *Proteobacteria*, one of the general findings in IM of elderly, it has also seen in PD's individuals. The decrease of *Prevotellaceae* and also the increase of *Enterobacteriaceae* could be the reason for the emergence of postural imbalance and dysbasia in PD's individuals. Conversely, some microorganisms in the gut may have beneficial effects because they could produce dopamine, which is critical for PD.

There is a link between intestinal permeability, dysbiosis, and neurological dysfunction. Some bacteria and endotoxins create an immunological response that promotes the production of proinflammatory cytokines with a change in permeability. In this way, activation of both enteric neurons and microglial cells could cause neurological impairment that spreads along the brain-gut axis (Mulak & Bonaz, 2015).

Two pathogens could be included as potential triggering factors in PD. The first of these may play a role in the pathogenesis of PD through gastric ulcers associated with infection by *Helicobacter pylori*. In another way, *Helicobacter pylori* infection increases the risk of PD because of predisposing to autoimmunity and causing neuronal damage. According to recent findings, a higher prevalence of *Helicobacter pylori* in Parkinson's patients compared to healthy individuals is important evidence (Blaecher et al., 2013). *Mycobacterium paratuberculosis*, another potential triggering factor for PD, initiates enteric infection and affects the central nervous system via the vagus nerve (Dow, 2014).

According to the literature, the IM influences the development and progression of PD. The molecular mechanisms by which dysbiosis, which occur in the intestines, triggers PD have not been fully elucidated. It is needed more extensive research.

5. Gut Microbiota and Sarcopenia

Sarcopenia is a disease characterized by progressive loss of physical function, muscle weight, and muscle strength associated with aging. It could progress to such an extent that it can affect the activities of daily living of elderly individuals. Sarcopenia, which is seen in 5-13% of individuals aged 60-70 years, could be seen in 11-50% of those aged 80 and over (Von Haehling, Morley, & Anker, 2010). Sarcopenia increases frailty and the risk of falls and fractures in the elderly (Wong et al., 2019). Regular exercise/physical activity and nutrition are the most important criteria for this disease. Protein intake, vitamin D and minerals, antioxidant supplements, etc. are important for muscle health (Beaudart et al., 2017).

At present, the mechanisms of sarcopenia have not been fully explained. However, in a study in mice, it has found that the signal of the ghrelin (hunger hormone) hormone produced by the stomach has a strong effect on the protection of aged muscle, with both intrinsic and extrinsic mechanisms. Since IM has found to induce proinflammatory mechanisms in the absence of ghrelin, it was concluded that ghrelin deficiency would cause muscle loss with aging (Wu et al., 2020). The effect of ghrelin on the muscles is mediated IM. Therefore, it has been thought that there may be a relationship between sarcopenia and IM.

Butyrate, one of the short-chain fatty acids, has anti-inflammatory effects and also reduces muscle atrophy in the aging process. Butyrate could be produced by strains of bacteria found in the gut, such as *Roseburia* and *ClostridiumXIVb*. The presence of bacterial species that produce some short-chain fatty acids which have positive effects on aging, reminds the importance of IM (Table 1).

Table 1. *Short-Chain Fatty Acids*

Short-Chain Fatty Acids
Acetate (Acetic Acid)
Butyrate (Butyric Acid)
Propionate (Propionic Acid)
Valerate (Valeric Acid)

The abundance of *Lactobacillus* and *Bifidobacterium* bacteria reduces the negative aspects of sarcopenia. The weight of the quadriceps, gastrocnemius and tibialis muscles in the study has found in younger mice more than in aged mice (Ni et al., 2019). It has found the application of *Lactobacillus* increased gastrocnemius muscle weight. In addition, the *Bifidobacterium* application increased the gastrocnemius and tibialis muscle weights. These practices also increased physical endurance and shortened the period of inactivity. In another study, it has determined that the duration of exercise endurance was reduced in mice without IM. In research comparing different microbiota states, IM has been proven to affect muscle mass, strength, and functional function by altering the activity of different antioxidant enzymes (Y. J. Hsu et al., 2015). Similar effects have observed when comparing the skeletal muscles of mice with pathogen-free IM with those of germ-free mice without IM. Muscle atrophy has detected in mice without IM, and decreased expression of insulin-like growth factor-1 (IGF-I), which has an important role in growth and development, as well as genes related to muscle growth (Lahiri et al., 2019).

Clinical studies, in addition to experimental studies with animals, provide similar results. The IM of individuals with and without regular exercise among daily lifestyle habits has compared by 16S rRNA gene analysis (Castellanos et al., 2020). The results showed that the IM of individuals who exercise regularly is in a better condition in terms of microbial stability and diversity than those who do not exercise regularly.

Also, among the groups compared, those who were active had more muscle mass. These data provide evidence for the connection between muscles and IM. A comparison study of elderly individuals with frailty and sarcopenia highlighted a correlation with changes in IM composition (Picca et al., 2019). This is in line with the findings of a much earlier experimental study on rats (Langille et al., 2014).

Based on the results of all these studies, it could be concluded that there is a link between IM and sarcopenia. Research on the subject has begun to be carried out in the past ten years. The importance of the link between IM-sarcopenia is increasing. Both experimental and clinical studies show that IM has effects on muscle function, strength, and especially mass. The existing studies that are still insufficient will be more comprehensive in the future and will help to explain the reason and mechanisms of the link between IM-sarcopenia.

6. Gut Microbiota and Type 2 Diabetes

Type 2 diabetes, which is one of the two types of diabetes mellitus, is a common disease in the elderly population. Diabetes is a metabolic disease characterized by conditions like chronic hyperglycemia and loss of β cells in the pancreas, which may occur due to genetic or environmental conditions associated with insulin secretion and function (Darenskaya, Kolesnikova, & Kolesnikov, 2021). According to the data of the International Diabetes Federation, type 2 of this disease, which has approximately 537 million people worldwide, is more common (Federation, 2021). In type 2 diabetes, the body begins to become insensitive to insulin. Insulin resistance occurs, and blood glucose level increases. Type 2 diabetes, which invites many important diseases, has symptoms such as delayed wound healing, frequent urination, xerostomia, blurred vision, skin infections, weakness, and numbness in the hands and feet (Greenhalgh, 2003; Vijan, 2010). The role of IM in the pathogenesis of type 2 diabetes, which is caused by increasing age, unhealthy and high-calorie diet, lack of physical activity, obesity, glucose intolerance, and oxidative stress has been one of the topics of interest in recent years.

In the past few years, a very comprehensive study was conducted that examined stool samples taken from individuals with type 2 diabetes and healthy individuals to determine the formation of dysbiosis in type 2 diabetes patients. There is also a decrease in the number of beneficial ones, such as bacteria that produce short-chain fatty acid (Qin et al., 2012). Diversity diminishes over time. In the intestine, bacterial genera such as *Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia,* and *Roseburia* are decreased in the presence of type 2 diabetes, and *Ruminococcus, Fusobacterium,* and *Blautia* tend to increase (Gurung et al., 2020). However, there is an inconsistency among the bacterial species belonging to the genus *Lactobacillus*. Some species in this genus increase in type 2 diabetes, while others decrease (Gurung et al., 2020). Some strains of the *Lactobacillus* genus combined with bacterial strains from different genera have had beneficial effects when supplementation is administered to patients with type 2 diabetes (Ejtahed et al., 2012; Tajabadi-Ebrahimi et al., 2017). Based on this, it is possible to conclude that *Lactobacillus* needs to be combined with other beneficial species for its anti-diabetic effect.

It is known that intestinal permeability increases in type 2 diabetes. If permeability is increased, microbial communities can migrate into the blood, resulting in endotoxemia (Cani et al., 2007). IM can affect the production of hormones that regulate glucose homeostasis and insulin resistance. Some bacterial species are involved in glucose metabolism, while others are involved in fatty acid oxidation, synthesis, and energy expenditure. In a study with rats, *Akkermansia muciniphila* is thought to be an effective strain in type 2 diabetes, as it was found to reduce lipotoxicity, alleviate oxidative stress, and improve liver function (Zhang et al., 2018). Similarly, the results of similar studies provide evidence for the relationship between IM and type 2 diabetes. Microorganisms can have effects on the organism through a multitude of mechanisms. They can use mechanisms that cause positive or negative consequences through lipopolysaccharide, short-chain fatty acids, and bile acids (Allin, Nielsen, & Pedersen, 2015). At the same time, IM affects the pathogenesis of type 2 diabetes due to the relationship of IM with the risk factors of type 2 diabetes. The best example is diet. Excessive consumption of high-fat foods leads to differences in IM bacterial species. In general, it causes harmful results such as endotoxemia or inflammation due to the increase in lipopolysaccharide. Deteriorations are observed in the absorption mechanisms of nutrients and type 2 diabetes can be triggered.

Discoveries of bacteria effective in the development of diabetes-related complications are increasing, but studies on the discovery of therapeutic microorganisms are insufficient (Iatcu, Steen, & Covasa, 2021). Dysbiosis in the IM has an impact on various complications such as diabetic nephropathy, diabetes-induced cognitive impairment, diabetic retinopathy, and neuropathy (Zhou, Sun, Yu, & Zhu, 2022). Studies with various animal models also show a link between IM and diabetes (Kieler et al., 2019; Okazaki et al., 2019; Yuxin Wang et al., 2020). Among them, the zebrafish model was used, and according to the results of the research, IM of people with type 2 diabetes and IM of diabetic zebrafish showed similarities, and it was found that various amino acid metabolism pathways were downregulated in both (Okazaki et al., 2019). Three potential biomarkers involved in the pathogenesis of obesity-related type 2 diabetes in rats were found as *Phocea*, *Pseudoflavonifractor*, and *Lactobacillus intestinalis* (Yuxin Wang et al., 2020).

In short, changing IM is associated with type 2 diabetes. As with most diseases, dysbiosis in the IM is especially involved in triggering this process. While IM dysbiosis stimulates the formation of type 2 diabetes, the presence of type 2 diabetes and its complications can also stimulate dysbiosis.

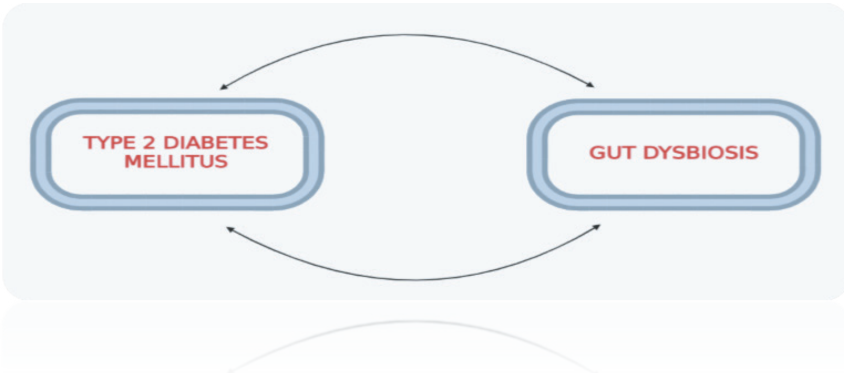

Figure 4. *Type 2 Diabetes and Gut Dysbiosis*

7. Gut Microbiota and Osteoporosis

Osteoporosis, a chronic metabolic bone disease with a high prevalence in the world, is defined by the World Health Organization as "a progressive systemic skeletal disease characterized by low bone mass and an increase in bone fragility and susceptibility to fracture as a result of deterioration in the microarchitecture of bone tissue" (Genant et al., 1999). In osteoporosis, the deterioration of the balance of osteoblast and osteoclast cells in bone tissue over time due to several factors leads to disruption in bone tissue (Noh, Yang, & Jung, 2020). Osteoporosis is a common health problem, especially in women and the elderly (Sözen, Özışık, & Başaran, 2017). Elderly individuals have a higher risk of experiencing accidents that may disrupt bone integrity, such as fractures. According to studies, approximately 33% of patients complain of osteoporotic hip fractures (Noh et al., 2020). In addition, this is an important factor affecting the quality of life of elderly individuals. Other risk factors for osteoporosis, which have an increased incidence in the postmenopausal period, include advanced age, polypharmacy, glucocorticoids, genetic predisposition, endocrine disorders, immobilization, hematopoietic disorders, and irregular nutrition (Compston, 2018; Noh et al., 2020; Seely, Kotelko, Douglas, Bealer, & Brooks, 2021).

In light of studies, it was determined that there is a relationship between changes in IM and bone health. In line with research, a new field called osteomicrobiology has emerged. Osteomicrobiology investigates the effect of microbiota on bone homeostasis, its role in processes related to bone formation and loss, and how bones regulate the aging mechanism (E. Hsu & Pacifici, 2018).

The first intriguing information about the relationship between bone development and IM emerged in 2012 from a study, based on the immune-modulating effect of IM, in mice (Sjögren et al., 2012). As a result of the comparison of bone mass of GF mouse and conventional mouse models, it has been observed that osteoclast cells decreased, and bone mass increased in GF mice. This result indicated that IM could be evaluated as a new therapeutic target for osteoporosis A similar study also demonstrated that bone remodeling was increased in aged mice with GF compared to non-GF mice (Novince et al., 2017). Results in GF mice showed that several factors could affect bone density.

The IM triggers the production of various hormones such as sex steroid hormones (androgens, estrogens, and progestogen) and serotonin or cytokines (leptin) (Bizzoca et al., 2020; E. Hsu & Pacifici, 2018; Markle et al., 2013; Yano et al., 2015). Estrogen, one of the sex steroid hormones, begins to decrease with the menopause period in women. Likewise, androgen is decreased in men during the andropause period. Therefore, their contribution to bone development also decreases. Leptin is a cytokine secreted from adipose tissue and is known to have a bone protective effect because it suppresses osteoclast activity According to the literature, bacterial species such as *Bifidobacterium* and *Lactobacillus*, which decrease with age in the microbiota, induce leptin production. 90% of serotonin has found in the gastrointestinal tract (Asano et al., 2012). Usually, a significant modulator of serotonin is bacteria in the gut (Yano et al., 2015). Serotonin mediates the regulation of vascular and heart functions, sleep, mood, thermoregulation, and gastrointestinal mobility. Serotonin can increase osteoclast differentiation and act on neighboring osteoblasts via the paracrine pathway. Accordingly, serotonin can have a role in bone remodeling (Chabbi-Achengli et al., 2012).

IM has regulatory effects on vitamins and minerals. These include vitamin D, calcium, and phosphate (Aksoy, Çelik, & Ustun, 2022). Intestinal absorption of vitamin D is enhanced by *Lactobacillus* bacterial genus present in the IM. Vitamin D is a type of vitamin used in the treatment of osteoporosis by providing the absorption of calcium and phosphate, which are important in bone metabolism and increasing some beneficial intestinal components (Bellerba et al., 2021). Calcium is the most important mineral known to be beneficial in bone health and development. When calcium is deficient or defective in absorption in the body, bone density begins to decrease. (Cashman, 2002). Calcium metabolism is affected by the relationship between calcium absorption and IM. *Bifidobacterium* and *Sutterella* in IM promote calcium absorption (Hua, Xiong, Yu, Liu, & Zhao, 2019).

Another mechanism that the microbiota affects in bone development is IGF-I (Yan et al., 2016). IGF-I is a growth factor that has endocrine, paracrine and autocrine effects on bone (Tahimic, Wang, & Bikle, 2013). In addition, IGF-I's direct effects on osteoblasts and osteoclasts promote bone formation and resorption (Fulzele et al., 2007; Yongmei Wang et al., 2006). In a study, it has determined that this growth factor has decreased in mice with IM dysbiosis, and it was observed that the reduction of IGF-I harmed the bones. As a result of the study, it has emphasized that short-chain fatty acids produced in IM increase the synthesis of IGF-I and this is important for the relationship between IM and bone development (Schwarzer et al., 2016).

Lifestyle changes, nutraceutical supplements, probiotic supplements, and drugs are also recommended in the treatment of osteoporosis (Seely et al., 2021). The purpose of probiotic supplementation in the treatment of osteoporosis is to stop or reverse the occurrence of osteoporosis. IM, which deteriorates with aging, causes suppression of the immune system. Also, it has induced increases inflammation, and osteolytic cytokines such as IL-6. In this case, it has aimed to regulate the affected bone health by stabilizing the IM with probiotic supplementation (Y. Q. Huang, Jiang, Su, Luo, & Hou, 2016).

Recently, scientists' interest in the gut-bone axis has increased. All this evidence shows that bone resorption and bone remodeling are closely related to IM. However, the role and mechanisms of IM in the development of osteoporosis need to be clarified.

8. Gut Microbiota and Osteoarthritis

Some diseases occur with changes in the musculoskeletal system in old age. One of the musculoskeletal diseases with the highest prevalence is osteoarthritis. Osteoarthritis occurs due to degeneration of the articular cartilage, deformities of the subchondral bone, and inflammation of the synovial membrane, and is a disease that triggers systemic inflammation (Hao et al., 2021). In addition, it is a multifactorial and non-communicable disease with a high risk of morbidity (Biver et al., 2019). Pain and swelling, limited joint range of motion, and poor physical functions associated with osteoarthritis affect the quality of life. In addition to factors that can be mechanical, biochemical, and cellular, IM can also be counted as a factor recently (Biver et al., 2019; Hao et al., 2021).

IM is responsible for maintaining many metabolic, immunological, structural and neurological functions (Adak & Khan, 2019). Musculoskeletal diseases are caused by metabolic syndromes such as abdominal obesity, dyslipidemia, hypertension, insulin resistance, proinflammatory and prothrombotic. The increased sensitivity of inflammation with aging is a risk factor for osteoarthritis as well as closely related to IM. This strengthens the possibility that IM may be associated with osteoarthritis. IM beneficial bacteria phyla decrease while opportunistic bacteria increase with increasing age. Opportunistic bacteria which increase in the intestinal flora initiate immune suppressive mechanisms by producing proinflammatory cytokines. The presence of increased metabolites and cytokines in the vascular system triggers systemic inflammation (Ramires et al., 2022; Santoro et al., 2018).

Recent studies have approached the relationship between osteoarthritis and IM. Some of the microorganisms in IM that production of short-chain fatty acids, enzymes and metabolites lead to both positive and negative effects on the intestinal-joint axis. Lipopolysaccharides, synthesized by microorganisms in IM, trigger osteoarthritis inflammation by inducing systemic inflammation (Z. Huang, Stabler, Pei, & Kraus, 2016) (Figure 5).

Intestinal dysbiosis is estimated to act by different mechanisms, depending on whether osteoarthritis occurs in the knee, hip, or hand (Hao et al., 2021; Wei et al., 2021; Yu, Yang, Cao, Bo, & Lei, 2021). A large population study in China found an increase in *Bilophila* and *Desulfovibrio* species and a decrease in *Roseburia* in IM of individuals with and without hand osteoarthritis (Yu et al., 2021). Another study, involving patients with knee or hip osteoarthritis, found increased growth of *Streptococcus* bacteria with a proinflammatory profile (Boer, Radjabzadeh, Uitterlinden, Kraaij, & van Meurs, 2017). Additionally, changes in IM with aging cause an increase in transforming growth factor-β (TGF-β). Increased levels of TGF-β cause synovial fibrosis in osteoarthritis (Blaney Davidson, Vitters, van den Berg, & van der Kraan, 2006).

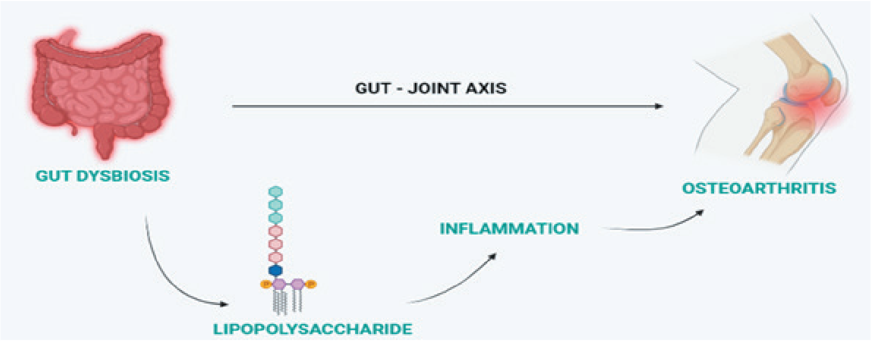

Figure 5. *Intestinal-Joint Inflammation Effect*

According to a cohort study on the relationship between osteoarthritis and IM in 2021, 3 causative microbial taxa (*Methanobacteriaceae* family, *Desulfovibrionales* order, *Ruminiclostridium5* genus) and 5 proposed microbial taxa were found to play a role in osteoarthritis (Yu et al., 2021).

In the same study, it was also found that the *Desulfovibrionales* team had positive effects on osteoarthritis and the protective effects of the *Methanobacteriaceae* family against osteoarthritis. Interestingly, another study found that *Methanobacteriaceae* was positively associated with proinflammatory factors in synovial fluid (Collins et al., 2015).

It has been suggested that physical exercise and probiotic supplements can be used in the treatment of osteoarthritis by directing the IM to positive changes (de Sire et al., 2020). IM analysis was also performed in the study applied to measure the therapeutic effect of quercetin on osteoarthritis (Lan et al., 2021). It has determined that the application of quercetin increased *Lactobacillus*, which has a beneficial effect on inflammation, and *Clostridia*. And also, it has been observed to reduce *Bacilli*. It has known that the administration of quercetin increases short-chain fatty acids. All these observations provide evidence for a relationship between IM's dysbiosis and osteoarthritis. There are few studies on the relationship between IM and osteoarthritis. Therefore, more studies are needed to explain their relationship.

9. Conclusion

The effectiveness of the intestine has been a matter of curiosity in recent years. In particular, research on this subject has increased to clarify how and by which mechanisms its relationship with diseases is achieved. It was widely thought that they remained stable at birth. However, with increasing evidence, when it has noticed that the components of IM began to change in old age, their effects on common diseases related to aging began to be investigated. Initially, scientists intensified experimental research to understand the relationship between the neuropathological diseases which are Alzheimer's and Parkinson's. Upon reaching striking results on these issues, its relationship with many different diseases began to be investigated.

This review aims to summarize the links between Alzheimer's, Parkinson's, Sarcopenia, Type II Diabetes, Osteoporosis, and Osteoarthritis diseases, which are known to be common in old age, and IM. As age progresses, there is a deterioration in the balance of beneficial and harmful microorganisms in IM. While the number of beneficial microorganisms is decreasing, the number of harmful microorganisms is increasing. Dysbiosis, which is more likely to develop with age in IM, paves the way for the pathogenesis of diseases. While its relationship with neuropathological diseases is a very popular research topic, there are very few studies on the link between IM and other diseases such as sarcopenia, type 2 diabetes, osteoporosis and osteoarthritis. Although studies are limited, they contain strong evidence. It is important to solve the mechanism of action of IM in ensuring healthy aging by reducing common diseases in old age. Therefore, in the future, there is a need for both experimental and clinical studies focusing on the gut-muscle, gut-bone, and gut-joint axis in addition to the gut-brain axis and studying the mechanisms in more detail and comprehensively.

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Chapter 5

ETHNOPHARMACOLOGICAL PROPERTIES OF ROSEHIP (*ROSA CANINA* L.) AND ITS IMPORTANCE OF PRODUCTION IN TURKEY

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Introduction

Flora richness is one of the most important natural resources for countries and living things. Turkey has an important place in the world in terms of plant species diversity due to its location at the intersection of European-Siberian, Iranian-Turanian and Mediterranean phytogeographic regions, differences in climate types, soil characteristics and elevation. With more than 12,000 plant taxa, it contains almost the same number of plant taxa as the entire European continent (Güner et al., 2012).

Medicinal and aromatic plants (MAPs) are an important part of this wealth and have significant use in the cosmetic, chemical, pharmaceutical and food sectors. The use of MAPs and products derived from them has increased significantly in recent years. Rosehip is one of these plants used by many sectors from medicinal to landscape, from plant production to industry. Rosehip, which is also classified as a non-woody herbal forest product, is a perennial medicinal plant in the form of trees and shrubs (BÜGEM, 2020a; OGM, 2008).

Ethnomedical uses of rosehip have been recorded in many countries since a long time. Approximately, 129 chemical compounds have been isolated and identified from rosehip. This fruit contains some major active components such as phenolic compounds, flavonoids, tannins, anthocyanin, fatty oil, organic acids and inorganic compounds. Scientific studies have suggested a wide range of pharmacological activities for rosehip including antioxidant, anti-cancer, anti-inflammatory, anti-obesity, hepatoprotective, nephroprotective, cardioprotective, antiaging, neuroprotective and antinociceptive activities. In particular, the rosehip powder and extract have been reported to exert therapeutic effects on arthritis (Ayati et al., 2018).

Rosehip, which is widely grown in Turkey, contains about 20 to 30 times more vitamin C than oranges. It also contains vitamins B1, B2, E, K and P, organic acids, polyphenols, mineral substances, especially potassium and phosphorus, and high antioxidant activity (Serteser et al., 2008; Ozturk-Yılmaz and Ercişli, 2011). Due to all these properties, rosehip fruit, which is popularly used in the treatment of diseases such as influenza, inflammatory diseases, chronic pain and ulcers (Guimarães et al., 2010), is also an important raw material for the pharmaceutical industry. In addition, it is used in various forms such as marmalade, pulp, fruit juice, jam and tea due to its rich nutritional content and nutritional properties (Ünalan, 2021).

In addition to being very suitable for organic agriculture due to its easy control of diseases and pests, rosehip has an extremely important potential for erosion control as well as supporting wildlife by spreading in natural areas. Due to its tolerance to different soil structures, its resistance to harsh climatic conditions, it offers ease of production to its growers. In this study, the ethnopharmacological properties of rosehip (*Rosa canina* L.) and its importance of production and potential to transform it into high value-added products will contribute to the country's economy are discussed.

Botanical Characteristics

Rosehip (*Rosa canina* L.) belongs to the genus *Rosa* of the Rosaceae family and is native to Northern and Central Europe, Western Asia and Anatolia. Of the approximately 100 species of rosehips found in the world, 27 species naturally grown in Turkey, of which *Rosa pisiformis* and *Rosa dumalis* subsp. *antalyensis* are endemic to Turkey (Ercisli and Guleryuz, 2005). The plant can grow in environmental conditions such as roadsides, valleys, garden groves and cemeteries (Türkben, 2003).

Rosehip is an erect or drooping, sometimes climbing, shrub-shaped plant that grows up to 1.5-3.5 m tall, sometimes climbing, with thorny stems and branches, the thorns are quite coarse, flattened and broad-based, shedding their single hairy compound leaves in winter (Mataracı, 2004). The compound leaf is 7-12 cm long and consists of 3 or 5 elliptic leaflets 1-3 cm long. Shoots and petioles are also spiny. The 2-4 cm diameter pink flowers have 5 petals. Fragrant pink and white flowers are followed by fruit formation. The two-lobed and heart-shaped petals have a pleasant odor. 1-2 cm long fruits are mostly egg-shaped. The fruits are dark orange or red in color with stinging sparse pubescence and bear many hard hairy seeds. The fruits ripen in September and remain on the branches until December (Mamıkoğlu, 2011).

Ethnobotanical Uses

People have been in interaction with the environment and plants from the existence of humanity to the present day. Rosehip is a fruit which is the topic of many folkloric narrations and which has many beliefs and rituals around it as well as being a mythological tree. Rosehip is also known by names such as gülburnu, gülelması, itburnu, göbek gülü, şillan, yaban gülü, deli gül (in Turkish) among the people. The use of rosehips as food is quite common in European and Asian countries. It was especially important in people's diets during the years of famine during World War I and II. Apart from food, the fruits and roots of rosehips are traditionally used as a remedy for colds, sore throats and stomach aches, hemorrhoids, itching and eczema. In this respect, it is stated that rosehip, which has been used since ancient times, was written in medical prescriptions for the treatment of diseases during the Ottoman period. Rosehip was used in the treatment of rabid dog bites in the 18th and 19th centuries. It is thought to be named dog or dog rose for this reason (Şar, 2011).

It is stated that rosehips were used in the Middle Ages for the treatment of bleeding gums, tapeworm, snake disease, kidney and gallstones, in Egypt for the treatment of scurvy, and in Rome for the treatment of abdominal pain. Also in ancient times the roots were used against rabies symptoms. Its seeds have a sedative effect. In addition to its strength-giving properties, it is also used against diabetes (Akçiçek, 1997). In fruit processing factories and enterprises in Gümüşhane, Erzincan and Tokat, rosehips are evaluated as fruit juice, marmalade, pulp, jam and tea bags. On the other hand, rosehip can also be used as a natural dye for dyeing woolen and cotton fabrics (BÜGEM, 2020a; Önal and Oruç, 2012). Together with the traditional use of rosehips in marmalade production, its consumption as herbal tea and fruit juice is rapidly becoming widespread. In the regions where it is found, the fruits collected by the local people are processed to meet the family's needs (Acar and Demir, 2001). Rosehip seeds, which are rich in unsaturated fatty acids (Omega 3, 6 and 9), are widely used in cosmetics and a significant part of the need is met by importing. It is very important to utilize this by-product and bring it into the economy (Özkan, 2021).

Rosehip also has an important potential for use in landscape purposes. It can be widely used due to its low maintenance and adaptability to many regions. Although its flowering period is generally short, its flowers of different colors can display extremely beautiful images. During this period, the rose scent it spreads around can be easily felt. On the other hand, the red-colored fruits that remain on the branch for a long time cause the formation of different landscapes. In addition, it is an important source of food for birds that take shelter in cities during the winter months and live in parks and gardens. This feature is also extremely important for wildlife in nature. Since it remains fruitful for a long time in the fall and winter months, it provides food support to many wild animals (Koçan, 2010).

Phytochemistry

The effective use of plants by agricultural, food and pharmaceutical industries is due to detailed knowledge of their secondary metabolites (Gruenwald et al., 2019). Rosehip is a fruit belonging to the genus *Rosa*, which is widely used in the food and pharmaceutical industries. In recent years, interest in rosehip species has increased due to their high content of bioactive components. Ascorbic acid, phenolic compounds, tocopherols, carotenoids, linoleic and linolenic acids are among the bioactive components abundant in rosehip flesh and peel (Medveckienė et al., 2020). Rosehips are found in various sizes and colors from yellow-orange to dark red depending on the carotenoid, flavonoid or anthocyanin content (Bhave et al., 2017). The weight of rosehips and seeds varies between 1.25 and 3.25 g, of which 29% is seed and 71% is pericarp (Chrubasik et al., 2008).

Rosehip fruits contain vitamins C, P, A, B1, B2, E and K. The mineral and vitamin content of the fruits is at a level to meet the entire daily vitamin C requirement of an adult human and a significant portion of other vitamin and mineral needs. In addition to the mineral substances (potassium and phosphorus elements), rosehip fruits are also used in the process of enriching fruit and vegetable juices and herbal teas with vitamin C in the food industry (BÜGEM, 2020a; Doğan et al., 2006). Due to its high vitamin C content (it is the fruit with the highest known vitamin C content), there is a growing interest in this product. It is also an important source of β-carotene and lycopene. It is popularly used as a treatment for ulcers and colds. The oil obtained from the seeds of rosehip fruit is very rich in unsaturated fat. This oil is also used in the cosmetics industry due to its skin-protective, anti-aging, anti-aging, anti-wrinkle properties, especially around the eyes and mouth, sun and harsh weather protection, healing and thickening of injured tissues, and cell regeneration (Ghazghazi et al., 2010).

In a study conducted with 4 different rosehip species (*Rosa pimpinellifolia*, *R. villosa*, *R. canina* and *R. dumalis*) collected from Eastern Anatolia (Ardahan), the total phenolic content of the fruits was determined as 1081-6298 mg gallic acid equivalent/100 g dry weight (Murathan et al., 2016). Another study conducted with *Rosa corymbifera*, *R. rugosa*, *R. alba* and *R. canina* species showed that *R. canina*, the most widely used rosehip species commercially, had the highest total phenolic matter and antioxidant activity (Kayahan et al., 2022).

Pharmacological Effects

Rosehip, which grows spontaneously in many parts of Anatolia, is a plant that is resistant to cold and seen as healing for many ailments. Some researchers have investigated the health effects of rosehip. Sharma et al. (2012) reported in a study that linolenic acid in rosehip regulates blood sugar and has a protective effect against neurological diseases and cardiovascular diseases. Rosehip prevents ulcer formation and contributes to the healing of respiratory diseases such as sore throat and colds. However, it has the effect of lowering bad cholesterol levels due to its pectin content. It also strengthens the body's defense system (Horvath et al. 2012). In addition, it is known that it prevents joint and bone diseases such as calcification and rheumatism by preventing the formation of inflammation and hesperidin has a protective effect against various eye diseases and cancer types (Jager et al. 2007; Fan et al. 2014).

Several *in vitro* studies have indicated antioxidant activities of rosehip. These antioxidant activities are not only due to the high amount of vitamin C but also due to a rich content of polyphenols, flavonoids, proanthocyanidins, vitamin E and carotenoids (Dubtsova et al. 2012; Ersoy et al., 2015). Fattahi et al. (2012) examined the antioxidant and anti-radical scavenging properties of *Rosa canina* and *Rosa pimpinellifolia* fruits and found that their radical scavenging ability was related to their phenolic content. Rosehip extract and a number of its bioactive compounds have been shown to reduce inflammation. Various molecular mechanisms have been suggested for the inflammatory action of rosehip, such as inhibition of the NF-kappaB signaling pathway which could attenuate pro-inflammatory enzymes (e.g. MMPs and COX-2) and decrease the production of pro-inflammatory cytokines (e.g. TNFα, IL-1β, IL-6 and CCL5) (Cheng et al., 2016).

Clinical and experimental studies have shown that administration of rosehip can reduce the risk of cardiovascular diseases (Andersson et al., 2012; Cavalera et al., 2017). Rosehip which is rich in antioxidants with high amounts of ascorbic acid and phenolic compounds that possess antiobesity, anti-inflammatory and antioxidative effects. Rosehip lowered plasma cholesterol and attenuated atherosclerotic plaque formation in a hypercholesterolemic mouse model. Administration of rosehip extract to high-fat diet (HFD)-fed mice could increase fecal cholesterol content and liver expression of LDLR gene as well as selected reverse cholesterol transport genes, and reduced blood pressure, oxidized LDL, total cholesterol and atherosclerotic plaque volume (Cavalera et al., 2017). In a randomized double blind placebo-controlled trial, administration of *R. canina* powder (40 gr, 6 weeks) reduced markers of cardiovascular risk in obese non-diabetic individuals (Andersson et al., 2012).

The impacts of various fractions of *R. canina* fruit on human colon cancer cells (Caco-2) were examined in an *in-vitro* environment. The data obtained from this study revealed that rosehip extract is an efficient antioxidant capable of having antiproliferative effect in this type of cancer cells (Jiménez et al., 2016). The efficacy of *R. canina* extract on colorectal cancers has been confirmed in another new study which depicted the selective cytotoxic effect of this extract on human colon adenocarcinoma (WiDr) cell lines compared with normal colon (CCD 841 CoN) cells. The cell cycle arrest was at the S phase. The extract induced apoptosis and repressed telomerase expressions (Turan et al., 2017). Both studies concluded that rose hip had the potential for the development of new natural anticancer agents.

One hundred patients with hip or knee osteoarthritis received 2.5 g standard rosehip powder or placebo twice a day for 4 months. The results revealed that, compared to placebo, rosehip powder could remarkably reduce the pain (Warholm et al., 2003). Furthermore, ninety-four patients with osteoarthritis of the hip or knee, who were over 35 years old, were randomly divided into two groups including the placebo group. The members of another group received 5 g rose hip powder daily for 3 months. The results indicated that, compared to the placebo group, treatment with rosehip could lead to a considerable pain reduction (Winther et al., 2005).

Importance of Medicinal and Aromatic Plant Agriculture

Medicinal and aromatic plants (MAPs) are plants that have many uses such as food, medicine, cosmetics, and spices, and that have been known to be used for similar purposes since the beginning of human history. While some of these plants are collected from nature, some of them are cultivated and produced. In parallel with the consumption of medicinal and aromatic plants in many different fields and industries, the world trade volume of these plants is increasing day by day. With the growth of the trade volume and the increase in demand, studies to enhance the production opportunities of these plants have also accelerated (Acıbuca and Bostan Budak, 2018).

It is known that people use many plants growing in the rich flora of our country for various purposes. Folk remedies prepared by people in Anatolia with plants, which are now traditional, are still used and continue to be discovered by believing in their healing power. It is important to protect this ecological and ethnobotanical richness of our country and transform it into economic wealth. In this framework, the Ministry of Agriculture and Forestry, General Directorate of Crop Production initiated the "Improvement of Cultivation of Medicinal and Medicinal Plants and Dye Plants Project" in 2015. This project was launched in 2015 by the Ministry of Agriculture and Forestry, General Directorate of Crop Production. The aim of this project is to produce medicinal and aromatic plants in the quality and quantity demanded by the sector and to supply the products obtained to international markets in finished and processed form (BÜGEM, 2020a).

Rosehip Production and Trade in Turkey

Although rose hips are found almost all over Turkey, they are more common in cooler and colder regions. It is extremely resistant to winter cold and can survive even in high mountains where temperatures sometimes drop below -40°C. It is also very resistant to drought as well as low temperatures and can easily grow in places with 300-350 mm rainfall, provided that soil conditions are adequate. Climate and soil conditions affect the size and ripening time of the fruit. The garden is planted in rows spaced 2-4 m apart, harvesting is carried out in September-November, and yields between 1-3 tons per decare can be obtained (Özçelik and Özçelik Doğan, 2018).

In rosehip production, once a plantation is established, the same plantation can be economically utilized for many years. Rosehip starts to generate income economically in the 3rd year, and in the 3rd year and afterward, the operating costs incurred are covered and profits are realized. Perennial plants such as rosehips are a field of activity that requires many years of effort. In this respect, it is of great importance to analyze the cost and profitability of perennial plants. It is a plant with low production costs because it bears fruit every year and can be cultivated without taking any precautions against many pests and diseases. This is an aspect that makes it easy to make organic production and gain a place in foreign markets (BÜGEM, 2020a).

According to the Farmer Registration System (FRS), rosehip cultivation, which was carried out on 999 hectares in 2010, increased 27 times by the end of 2019 and reached 27 thousand decares. According to the statistics of the Organic Agriculture Information System established within the General Directorate of Plant Production of the Ministry of Agriculture and Forestry, the amount of organic rose hips produced or collected from nature was 195 tons in 2014 and reached 3783 tons in 2018 (BÜGEM, 2020b). There is a rapid increase in production values, most of which are collected from nature. Looking at the distribution of rosehip areas by provinces according to FRS data; Kastamonu ranks first with 17340 decares of rosehip area. In 2019, Adana had 10.4% of the total area with 2803 decares, Bartın had 8% with 2154 decares, Bolu had 6.8% with 1839 decares, and Sinop had 3.8% with 1033 decares (Table 1). Since it is mainly consumed through collection from nature and there is no standardized production, the market demand is met from abroad from time to time. Production is mostly carried out by collecting from nature, and although there have been some attempts to cultivate it, it has not become widespread due to problems in seedling production and uncertainty of the market. When the foreign trade figures of the Turkish Statistical Institute between 2010 and 2019 are examined, it is seen that we have no exports, while imports amounted to 540 tons in total. Of these imports, 94% (505 tons) was from Georgia and the remaining 6% was from Iran (BÜGEM, 2020a). However, in 2020, it was recorded that 1224 tons of rosehips were exported to six countries, mainly the Netherlands, England and Austria, and about 107 tons of rosehips were imported from Georgia (Özkan, 2021).

Rosehip has a growing market both at home and abroad. With the right steps, it seems possible for it to become an important product in a short time. Because of its high adaptability, it is a plant that can be produced in marginal areas with little input. Since it yields regular products every year, it is possible to meet the demand of the market in a balanced way, thus preventing imports. Since it will reach economic yield in 3-4 years and full yield in 5-6 years, the desired targets can be achieved in a very short time. In addition to being very suitable for organic agriculture due to its easy control of diseases and pests, it has an extremely important potential for erosion control as well as supporting wildlife by spreading it in natural areas. Since it is harvested in autumn, it is also important in terms of utilizing the idle labor force during this period when agricultural activities decrease, especially in the interior (BÜGEM, 2020a; Koçan, 2010).

Table 1. *Distribution of rosehip areas by cities (data of 2019) (BÜGEM, 2020a).*

CITIES	Cultivation Area (daa)	Number of Manufacturer	CITIES	Cultivation Area (daa)	Number of Manufacturer
Kastamonu	17.340	39	Kırklareli	10	3
Adana	2.803	1	Isparta	8.43	2
Bartın	2.154	1	Eskişehir	8.11	1
Bolu	1.839	2	Çanakkale	7.2	5
Sinop	1.033	2	İzmir	6.34	4
Sivas	889	22	Kütahya	4.6	3
Tokat	298	48	Kırıkkale	4.1	1
Amasya	139	18	Zonguldak	1.89	1
Kayseri	105	6	Malatya	1.66	1
Samsun	96	16	Kırşehir	1.2	2
Çorum	93	19	Gümüşhane	1.03	1
Bursa	57	7	Bayburt	1	1
Erzincan	56	6	Balıkesir	0.5	1
Konya	34	7	Mersin	0.5	1
Sakarya	33	2	İstanbul	0,2	2
Nevşehir	27	2	Antalya	0.14	1
Çankırı	19	2	Elazığ	0.05	1
Ordu	14	1			
Total Area (daa)			**27.085**		
Total Number of Manufacturers			**232**		

Value-Added Analysis for Rosehip

The value chain actors are producers, collectors, processors, wholesalers and retailers and value added is generated in the following functions; - Exporters, - Local market buyers, - Retailers (pharmacies, herbalists, health food stores, cosmetics and perfumery industry, niche retail, pharmaceutical industry), - Wholesalers (local market sellers, other sellers, exporters and some local market sellers), - Integration of producers and wholesalers, - Processing (Small oil pressing workshops, processors such as creams, lotions, oil producers), - Collectors (Sub-collectors - local people, large collectors - outsiders), - Production (Collecting what grows in nature, cultivators, growers), - Input supply and supply (Seedling growers, input suppliers, packers, transportation, etc.) (BÜGEM, 2020a).

In the case of diversification and development of agro-industries (food, cosmetics, construction, fuel, forestry) that enable the transformation of rosehip production into high-value-added products, it has been determined that when the production process is started by using labor, knowledge and material resources; rosehip production with varieties suitable for their areas of use will increase the cultivation profit by 80%, marketing margin by 60%, fixed oil added value by 190%, 85% with its use in pharmacology and 120% with its processing as a traditional beverage (Fig. 1). These studies show that the manufacturing industry should have its own raw materials produced with the contracted production model and that this idle capacity should be strengthened with projects for added-value production (Özkan, 2021).

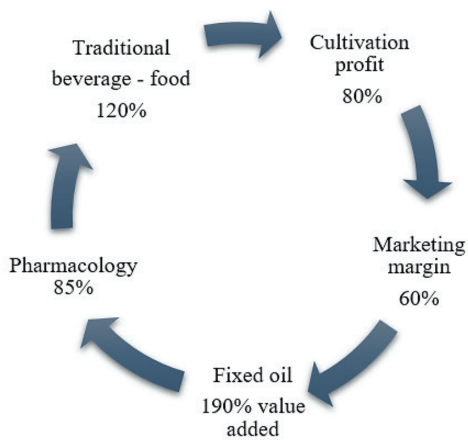

Fig. 1. *Rosehip value-added cycle (BÜGEM, 2020a).*

Conclusion and Suggestions

Turkey has an important place in the world in terms of plant diversity. Medicinal plants, which have a wide area in the flora of Turkey, have been used in traditional folk medicine for centuries as a preventive or therapeutic against various diseases. Medicinal plants and derivatives with ethnopharmacological uses have the potential to treat many health problems with no adverse events since they are made from natural products. Rosehip is one of the most widely used plants in folk medicine for the treatment of different diseases. In the context of protecting ecological and ethnobotanical richness and transforming it into economic wealth, the rosehip plant (*Rosa canina* L.) emerges a great potential. Rosehip is a very valuable product with high added value that is utilized in sectors related to functional food, herbal drug preparations, health and cosmetics. It is important to establish rosehip plantations in accordance with the technique in order to diversify agricultural production and to ensure that producers earn more income through the production of medicinal and aromatic plants with high added value.

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Chapter 6

DETERMINATION OF CHEMICAL RISK FACTORS IN CHEMICAL LABORATORIES

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INTRODUCTION

People work and take part in working life in order to live and continue their lives. Occupational accidents and occupational diseases are occupational risks that employees may encounter as long as they take part in working life. Risks also vary depending on the type of production and technology in the workplace. Perhaps the most risky group in this regard is the business lines in which chemicals are produced, processed, used or generated as waste (1,3). Today, with the developing technology, the number of chemicals used in different types and numbers is increasing. Due to the constantly changing chemicals in the industry, health and safety measures are often insufficient. Solvents (solvents), acids, bases, drugs, toxic gases, paints, volatile chemicals, explosives, etc., which are frequently encountered in working with chemicals. comes first. There are many chemicals that are not yet known what kind of dangerous properties many chemicals brought to our industry every day have. Considering such dangers, it is important to have information and warning signs on the chemicals used in terms of protection against possible dangers of this chemical. A systematic classification system has been established in order to protect employees and the environment from the harms of hazardous chemicals (1).

1. CHEMICAL RISK FACTORS

While it creates a danger and risk that will affect human health due to the use of chemical substances, it infects the human body in certain ways and causes occupational disease years later. While the chemicals used are transmitted to the human body through respiration, digestion and absorption, they penetrate mostly through the skin, that is, by absorption. The reason is that we have the largest surface area in our body (2,3). In parallel with the development of technology, the type and content of chemical substances that we use in our homes, workplaces, laboratories, briefly in every area of our daily life, are increasing rapidly. Depending on the type and amount of chemicals we use, they have the feature of being dangerous substances at certain rates, including at various steps between them in the processes from production to use. Hazardous substances have negative effects on the health of the individual and the society they form and the environment in which they live (10). The ILO explained that options and methods to be considered while classifying chemicals should be determined. When classifying chemicals, it divides chemicals into explosion, glare, oxidation, dangerous reactions such as toxic properties, corrosive and irritating effects on the skin, allergic and sensitization effects, carcinogenic effects, teratogenic and mutagenic effects, and effects on the reproductive system (1).

1.1. Classification of Chemical Substances

Hospital staff work in many laboratories such as biochemistry laboratory, microbiology laboratory, pathology laboratory, molecular laboratory, pharmaceutical laboratory, tissue examination, tuberculosis, etc. Staining bacteria such as blood group determination, x-ray solutions, use of latex, mercury, etc. They are exposed to multiple chemical risk factors such as heavy metals, pesticides, air fresheners, use of disinfectants. In order to be descriptive of the harm that may be caused by the chemicals penetrating the work done by laboratory workers, first of all, it is necessary to deal with the possible substance definitions (14).

a)Chemical Matter

All solid, liquid, gaseous and aerosolized substances with a definite chemical composition are called chemical substances. A chemical substance is a type of substance that has a fixed chemical composition and characteristic properties of a chemical substance. These chemical bonds are not broken down into their components by physical separation methods. It is defined as any element, compound or mixture found in the natural state, produced, emerging during any process or as a waste from any process (1,4).

b)Dangerous Chemical Substance

Substances and mixtures containing one or more of the classifications made according to ILO, or substances with chemical, physicochemical or toxicological properties other than this classification, and substances that pose a risk in terms of affecting the health and safety of workers by the way they are used or kept in the workplace, or substances with occupational exposure limit values are also included in the whole of dangerous goods (8).

c)Explosive Matter

Explosives are substances that react quickly without the contribution of any chemical from the environment as a result of heat, impact or friction. They are substances that explode spontaneously as a result of a reaction that can give off heat with instant gas distribution and/or with the effect of heating when closed. Pasty, liquid, solid, substances that can flash instantly are called explosives. For example; trinitrotoluen (4,5).

d)Oxidizer Matter

Maddelerle olan etkileşiminde ortama yüksek derecede ısı verebilen maddelere denir. Örneğin; oksijen (3).

e)Extremely Flammable Substance

It is a substance that is heated by contact with air at its own temperature, without any energy, and ignites. For example; ethyl alcohol.

f)Flammable Substance

They are liquid substances with a flash point between 21°C-51°C (12,13).

g)Very Toxic Substance

Substances that cause death or acute or chronic damage to human health when inhaled, inhaled or taken through the skin in very small amounts. For example; nicotine.

h)Toxic Substance

They are substances that cause acute or chronic problems or death on human health when inhaled, taken orally, absorbed through the skin in small amounts. For example; barium chloride.

i)Harmful Substances

Substances that cause acute or chronic damage or death to human health when inhaled, taken orally, or absorbed through the skin. For example; caffeine.

j)Corrosive Substances

They are substances that cause tissue destruction in contact with living tissue. For example; hydrochloric acid, sulfuric acid, caustic.

k)Irritant Substances

Substances that are classified separately from corrosive structures that cause local, erythema, eschar or edema in direct, long-term, sudden or ongoing contact with mucus tissue or skin are called (for example, fumaric acid).

l)Allergic Substances

They are substances that cause hypersensitivity when inhaled and interact with the skin.

m)Carcinogenic Substances

They are substances that cause cancer when taken orally, inhaled, and penetrate the skin and accelerate this situation. For example; such as cigarette smoke, pesticides, asbestos, vinylchloride, heavy metals, benzene, chromium powder, and nitrosamines (2).

n)Mutagen Substance

They are substances that can cause hereditary genetic damage or increase the effect of this damage when they enter the body through the mouth, respiratory tract and penetrate the skin. Radioactive material: The number of neutrons in the atomic nucleus of any substance is greater than the number of protons, creating an unstable structure in matter. Excess neutrons in the structure of matter break apart to emit rays such as alpha, beta and gamma. Substances that break down by scattering radiation are called radioactive substances (3).

o)Reproductive Toxic Substances

It is defined as substances that reduce the reproductive capacity of males and females and/or cause non-hereditary problems that affect the baby to be born or accelerate these negative effects as a result of inhalation, ingestion, or contact with freckles (7).

p)Environmentally Hazardous Substance

When such substances enter the environment, they can cause immediate or subsequent damage to the environment. For example; heavy metals (4).

1.2. Chemical Interactions

Interactions Using more than one chemical together will cause different types of effects.

• Independent action, chemicals can act independently of each other.

• Antagonism, the effect of one chemical can neutralize the effect of the other chemical.

• Synergistic effect, some chemical substances may have similar effects in the same direction in the same organ.

• Additive effect is equal to the sum of the effects of two chemicals moving in the same direction when they enter the organism, and their toxicological effects when they are independent of each other.

• Potentiation, one chemical substance increases the effect of another substance. In this increase, the first substance acts as a potentiator and the total effect is greater than the sum of the effects of both chemicals (1+1=4), sometimes a substance alone may not cause harm, but it may reduce the toxic effect of another chemical (0+1=3) (1.4)

1.3. Entry Ways of Chemicals into the Body

Chemicals are taken into the human body in three different ways. It consists of the respiratory tract, the digestive tract, and the absorption of the skin and eyes, which is called absorption (2,3).

a) Respiratory

Chemicals are taken into the human body by respiration by spreading as smoke, dust gas, mist and steam in the working environment. Workers working in these environments take chemicals into their bodies through the respiratory tract (9).

b) Absorption

The absorption of chemicals into the body through the skin is defined as the entry of chemicals into the body through absorption. While working with such chemicals, employees working without personal protective equipment, contacting undefined chemicals, or sweating by employees cause the skin to absorb these chemicals into the body (8).

c) Digestion

Chemicals such as swallowing dust in the atmosphere, eating and drinking something with unclean hands are transmitted to the body through the digestive tract.

1.4. Target Organs

When chemicals enter the human body, they cause local or systemic effects. The toxicities of chemicals are not the same in every organ. Organs showing toxic properties of chemicals (skin, lung, central nervous system, blood circulation system, liver, kidney) (2,3).

1.4.1. Effects of Chemical Substances on Our Body

The properties of chemical substances in the human body are listed below.

- Chemical interaction
- Frequency and duration of exposure
- Toxic property of chemical substance
- Physical properties of chemical substances
- Reception format
- The amount of chemical substance
- Physiological characteristics of the person
- Environmental features

1.5. Classification of Chemical Powders

Respirable Dust: It is called crystalline or amorphous powder with an aerodynamic equivalent diameter of 0.1-5.0 microns and fibrous dusts with a diameter of less than three microns and a length of at least three times its diameter (Anonymous 2013). Dust > 100 micron not inhaled. Dust < 10 micron reaches the bronchioles. The greatest danger is that dusts with a diameter of 0.1-5 microns reach the alveoli. (11,19)

1.5.1. Powders by Chemical Structure

A) Organic Powders

• Powders of Animal Origin (skin, hair, feather, etc.)

• Powders of Herbal Origin (flour, wood, cotton, straw, plant seeds, etc.)

• Powders of Synthetic Components (DDT, plastic, resin, trinitrotoluene, rubber, etc.)

B) Inorganic Powders

• Metallic powders (zinc, copper, iron powder, etc.)

• Powders of chemical compounds (zinc oxide, manganese oxide, etc.)

• Non-metallic powders (sulphur, coal dust)

• Powders of natural compounds (clays, minerals, ores, etc.)(19).

1.5.2. Powders in Terms of Biological Effects

• Allergic dusts: Animal feed, grass, grain, cotton, flax, hemp, flour, etc.

• Fibrogenic dusts: Asbestos, silica, etc.

• Carcinogenic dusts: Arsenic, asbestos and its compounds, beryllium, chromates (calcium, potassium, sodium), nickel and its compounds (nickel oxide, nickel sulfide) (2,3).

• Radioactive dusts: those that are harmful due to α and β rays. Uranium, cerium, tritium, and radium are its constituents.

• Toxic dusts: They cause chronic and acute poisoning. They play an active role in blood-forming organs. Heavy metal powders such as lead chrome.

• Inert dusts: Titanium dioxide, barium compounds, limestone, marble, gypsum dusts) (4).

1.6. Classification of Hazardous Chemicals

Hazardous chemicals are basically found in three different structures. Solids, liquids and gases. One of the most common features used in the classification of chemicals is based on lethal dose (LD50) and lethal concentration (LC50). Considering the health hazards of solid, liquid and gaseous chemicals, classifications are made according to the concentration of chemicals. These; Concentration of the irritation to be caused by corrosive and irritating chemicals in the body, which cause sudden death or not but cause permanent damage by the ingestion of toxic and harmful chemicals, harmful, irritating, harmful to the eye, respiratory tract or cancer, mutagenic and concentrations that cause teratogenic effects (15).

According to the quantity;

• The amount of chemical

• Emission in the environment

According to the doses;

• Lethal Dose (LD50)

• Lethal Concentration (LC50)

LD50: Digestion, absorption, etc., except for the respiratory tract. It is called the dose that kills 50% of the animals in that group when taken at once, under certain conditions, of a liquid or solid chemical substance that enters and acts on the living thing by other means. Its unit is mg/kg. LC50: It is the measure of the chemical compounds in the gas phase, which enters the living thing through respiration and acts in a short time. When certain conditions are met, it kills 50% of the animals in a group by respiratory tract. It is defined as the concentration of the chemical in the inspired air. Its unit is ppm or mg/m3 (16).

1.7. Classification of Chemical Gases

Gas is a substance that does not have a fixed shape and a definite volume at 25 °C and 760 mm Hg pressure, can spread indefinitely and can be turned into liquid or solid by pressure increase or temperature decrease (3,19).

1.7.1. Simple Asphyxiant Gases

Under normal conditions, they do not suffocate chemically. If they are too much in the area where they are, they replace the oxygen in the atmosphere and cause less breathing. Decreased oxygen levels can cause asphyxiation. Carbon dioxide, methane, ethane, propane, butane, hydrogen etc.

1.7.2. Asphyxiating Gases With Chemical Effects

Due to the chemical structure of gases, they show suffocating properties by preventing circulation and respiration. Carbon monoxide, hydrogen sulfide, hydrogen cyanide, etc.

1.7.3. Irritant Gases

Considering their acidic properties and solubility in water, they have an irritating effect on the respiratory systems. They can cause various degrees of irritation, mostly in the upper respiratory tract, eyes and skin. Such vapors, reaching the upper respiratory tract and lungs, irritate the tissues they come into contact with by causing an acidic solution with the moisture formed by the skin and tissues. In chlorine, sulfur dioxide and ammonia, the effect can be felt immediately. However, in nitrogen dioxide (NO2) and phosgene (COCl2), the effect can be felt after a few hours (4,5).

1.7.4. Toxic Gases and Vapors with Systemic Effects

They are gases and vapors that have toxic properties in certain systems of the body. It acts on the lung membranes or directly affects the circulation. It is effective on kidney, liver and sometimes on bone marrow. Substances harmful to internal organs include chloroform, alcohol; Lead and benzene are given as examples for those that affect blood-forming systems.

1. STORAGE OF CHEMICALS

Since the hazardous storage of chemicals directly affects the health and safety of employees, it is important to transport, store and dispose of chemicals correctly. For this reason, it is necessary to know the storage conditions for the correct storage of chemicals.

1.1.Storage Conditions

• Before storing chemical substances, a planning should be made considering the type and amount of the substance.

• Safety distances should be observed while storing chemicals.

• The warehouse area should be determined and necessary markings should be made.

• Attention should be paid to the chemical storage matrix, warnings and quantities of substances when storing substances with different properties in the same area.

• When stacking hazardous materials, attention should be paid to the stacking heights, and necessary precautions should be taken to prevent damage to the falling or overturned chemical.

• Flammable, caustic, etc., which may pose a danger when broken. Chemicals such as these should be at a maximum height of 40 cm from the ground.

• Other containers of dangerous substances, such as oxidizers, poisons, should be placed by taking precautions so that they do not fall more than 150 cm from the ground,

• There should be transitions between the stacks in the areas to be stacked, and the distance of these transitions should be adjusted considering the width and use of the work equipment to be used in that environment,

• If generalizations are made, storage should be done by maintaining a distance of 6 m for main roads, 2 m for secondary roads and 1 m for intermediate roads between crossings.

2.2. Storage Precautions of Carcinogens

• Containers containing carcinogenic substances should be labeled as "can cause cancer".

• Carcinogenic substances should be stored in accordance with the risk level.

2.3. Storage Precautions of Acids

• It should be stored securely in low shelf level or acid cabinets, in large acid bottles,

• Oxidizing substances should be stored in a separate area from organic acids and combustible materials by providing security measures,

• Remove acids, especially from bases and magnesium, potassium, sodium, etc. should be stored separately from active ingredients,

• Especially sodium cyanide, iron sulfide etc. substances and acids should be stored separately,

• Special transport vehicles should be used when transporting acid bottles.

2.4. Storage Precautions of Bases

•Bases should be kept separate from acids,

• Solutions of inorganic oxides should be kept in polyethylene containers and stored safely.

2.5. Storage Precautions of Toxins

• Material safety data sheets are used when storing toxic materials.

• Emergency action plans should be prepared in advance against emergencies that may occur in the environment, and emergency call center phone numbers should be posted (17,18).

2.6. Storage Properties of Combustible Materials

• Safe storage should be provided in an area where cleaning measures are taken against possible spills and intervention can be made by using personal protective equipment, by keeping a fire extinguisher in a place separate from flammable and combustible sources such as open flame, heat, sparks and oxidizing acids.

• In the storage of containers containing flammable liquids, the grounding system should be fixed and the highly flammable and volatile materials should be stored with specially designed cooling systems (19).

2.7. Storage Precautions of Photosensitive Chemicals

• Exposure of the chemical to light should be prevented.

• It should be stored in amber bottles in cool and dry places by taking safety precautions.

3. METHODS OF PROTECTION FROM CHEMICALS

There are more than one method to protect from chemicals. The most effective method of prevention is to eliminate the problem at its source. The correct order is to solve the problem first in the source, then in the environment and in the last person. If the problem cannot be eliminated at its source, that is, if it cannot be removed from the environment, the first thing to do is to replace the dangerous one with a non-hazardous or less dangerous one. If the room is not possible to reduce the risk in the environment by taking technical measures, if the room is not effective or sufficient, personal protection measures of the employee should be taken. More than one protection method can be applied at the same time (6).

3.1. Technical Safeguards

• Minimizing the harmful substance used, replacing it with a non-hazardous one if possible

• Closed working method

• Making the ventilation system according to the needs of the environment

• Safe storage and transportation

• Safety measures to be taken for wastes

• Workplace and production planning

• Regularity of production and field

• Periodic checks of machinery and equipment in the workplace

• Making protective enclosures for machinery and equipment

• Fire installation and controls

• Ambient measurements

3.2. Medical Protection Measures

• Employment health examinations

• Periodic health checks

3.3. Worker Protection Measures

To be educated about the use of personal protective equipment (mask, apron, overalls, work shoes, hard hat, etc.), cleaning and hygiene, workplace hazards and risks.

3.4. Education and Information

Employers are obliged to provide or have their employees receive training on basic occupational health and safety. Moreover; the information obtained as a result of the risk analysis, the new information about the changes in production, the properties of the chemicals used, the risk factors they create in terms of health and safety and the exposure limit values, the studies that need to be done to ensure health and safety in the environment, the contents of the material safety data sheets of chemicals. employees should be informed. Employers should ensure that necessary warning signs are used in areas where hazardous chemicals are present or are used, chemical labels are made, personal protective equipment is kept and their use is supervised, and necessary information is obtained from the suppliers of chemical substances when necessary (2,3,19).

CONCLUSION

In general, laboratories in almost every sector work with hazardous chemicals that are harmful to human health. All chemical risk factors that may be encountered in laboratories have been determined and it has been foreseen to take the following precautions.

• It is a legal obligation to have a Material Safety Data Sheet for every chemical used in the laboratory.

• All containers containing hazardous chemicals must be labeled with the full name of the chemical, its hazard class, expiration and production dates.

• Storage areas and cabinets should be determined according to the chemical type and hazard class.

• Appropriate and approved cabinets should be used for chemical storage, metal storage cabinets with locks should be used.

• Chemicals should be stored in cool, dry and well-ventilated areas away from sunlight.

• Flammable and explosive materials, acids and bases should not be stored together.

• Explosive chemicals should be stored in explosive warehouses.

• Toxic substances should be kept separate from other hazard classes and stored in a cool, well-ventilated place away from light and heat.

• Oxidizers should be kept away from combustibles and combustibles.

• Corrosive chemicals should be kept on lower shelves.

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