Current Researches in Health Sciences-IV

Editors: Assoc. Prof. Canan Demir
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Preface

Dear readers;

The Current Research in Health Sciences-IV book contains valuable scientific studies written according to certain criteria and included in 9 chapters in total. The book begins with the chapter "Mechanism of HIV-1 Reverse Transcriptase Inhibitors", which describes the basic life cycle of HIV. This is followed by the "Role of TRPV1 channel in Migraine: Current Overview" section, which discusses a therapeutic approach as a pharmacological target in the treatment of migraine, one of the most common chronic neurovascular diseases worldwide. Cancer is the second most common cause of death worldwide after cardiovascular diseases. The study titled "The Effect of Antioxidant Foods on Cancer Prevention", which discusses the effects of antioxidant foods on preventing cancer, takes its place in the third chapter of the book. In the next section, there is a study titled "Determination of Some Antioxidant Activities in Fruits of Noni (Morinda citrifolia), Food Supplement Mixture Containing Vitamin B3, Zinc, Vitamin B1, Coenzyme Q10 and Chromium", which includes the antioxidant values of noni fruit. Heavy metals, which are widely used in daily life and industry, pose significant risks to human health even in trace amounts. This risk increases depending on the dose and duration of exposure, and may even lead to the development of tumors and cancer. The book continues with studies titled "The Effect of Some Heavy Metals (Cobalt and Cadmium) on Biochemical Events" and "Physical Chemical Properties of Some Heavy Metals (Arsenic, Lead and Copper) and Their Effects on Health". Effects of heavy metals cobalt, cadmium, arsenic, lead and copper on human health. The seventh chapter of the book includes a study titled "Some Textile Dyes (Methylene Blue, Malahat Green and Crystal Violet) and Their Effects on Health", which explains the toxic effects of methylene blue, malahat green and crystal violet dyes used in textiles, cosmetics and many other fields. The eighth chapter of the book includes the study titled "Mobile and Portable Hospitals", which examines mobile and portable hospitals to provide health services in special situations such as war, disaster or in regions where there is no access to hospitals. In the last section, a study titled "Current Developments in Radiotherapy Quality Control Methods" is included. It is our greatest wish that this book will be an important resource for all science readers doing scientific research in the field of health. It was aimed to

prepare the book carefully within the time and resources available. We would like to express our gratitude to the publishing house and chapter authors who contributed to this edition.

Editors

Contents

Chapter 1

Mechanism of HIV-1 Reverse Transcriptase Inhibitors

Ofcan Oflaz[1]

Abstract

The HIV life cycle involves a series of intricate steps: viral entry, reverse transcription, integration into the host genome, transcription and translation, assembly, budding, maturation, and release. The reverse transcriptase (RT) enzyme, a pivotal player in this cycle, facilitates the conversion of viral RNA into double-stranded DNA during reverse transcription. Comprising polymerase and RNase H domains, RT's structure is crucial for its multifunctional role. The polymerase domain synthesizes a complementary DNA strand, while the RNase H domain degrades the RNA template. This enzymatic process results in the formation of a provirus integrated into the host cell's genome. Inhibitors targeting RT, classified into non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs), disrupt this critical step in the HIV life cycle. NNRTIs act allosterically to inhibit RT's activity, while NRTIs function as chain terminators during DNA synthesis, collectively impeding the virus's replication and offering crucial therapeutic interventions in managing HIV infections. Our book chapter covers the fundamental life cycle of HIV, the working mechanism of the RT enzyme, and the effects of inhibitors on this mechanism. The enzyme structure has been visualized using the UCSF Chimera program .

INTRODUCTION

The human immunodeficiency virus (HIV) is thought to have been transmitted from non-human primates to humans over the course of the 20th century. The emergence of HIV as the causative agent of Acquired Immunodeficiency Syndrome (AIDS) was identified shortly after the initial reports of the disease. Since then, HIV has become a global public health concern, with a significant proportion of the world's population being

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affected by the virus. Current estimates suggest that HIV positve globally exceeds 75 million.

The initial diagnosis of HIV infection occurred in 1981, signaling the start of the global HIV/AIDS pandemic. Since then, substantial advancements have been made in the fields of prevention, diagnosis, care and treatment of HIV/AIDS worldwide. Through the identification of newer, more effective and less toxic drug molecules, a decrease in the cost of therapy, and the implementation of innovative approaches to service delivery and treatment access, the disease has been transformed from a rapidly fatal condition to a manageable chronic illness. According to UNAIDS, global estimates indicate that 37.6 million individuals were living with HIV in 2021, with substantial variation in the numbers of affected individuals among different countries. Additionally, 1.5 million people acquired HIV worldwide in 2020, and an estimated 690,000 deaths occurred due to AIDS-related illnesses in the same year. Despite these successes, it remains a priority to ensure that all individuals living with HIV have access to antiretroviral therapy (ART) in order to reduce mortality and comorbidities and to curb further transmission of the virus (UNAIDS, 2022).

1. Life cycle of HIV

HIV is classified in the lentivirus subfamily of retroviruses, which are known to cause chronic, progressive infections. The term "lentivirus" is derived from the Latin word "lentus", meaning "slow", in reference to the prolonged incubation period of these viruses. $CD4^+$T lymphocytes, which are vital in the immune system, are the primary target of HIV. HIV gets into these cells and then kills these cells. Two types of HIV have been identified: HIV-1 and HIV-2 (National HIV Testing Guidelines, 2015). Lentiviruses are known as enveloped RNA viruses with a positive-sense, single-stranded genome. Once inside the cell, viral RNA is converted into double-stranded DNA by the reverse transcriptase enzyme packaged within the virion. HIV's genetic material has now become compatible with the nucleus of the cell. Viral DNA is transported to the nucleus of the cell and integrated into the host's DNA in cooperation with host cofactors via the integrase enzyme, also encoded by the viral genome. (Smith JA and Daniel R, 2006).

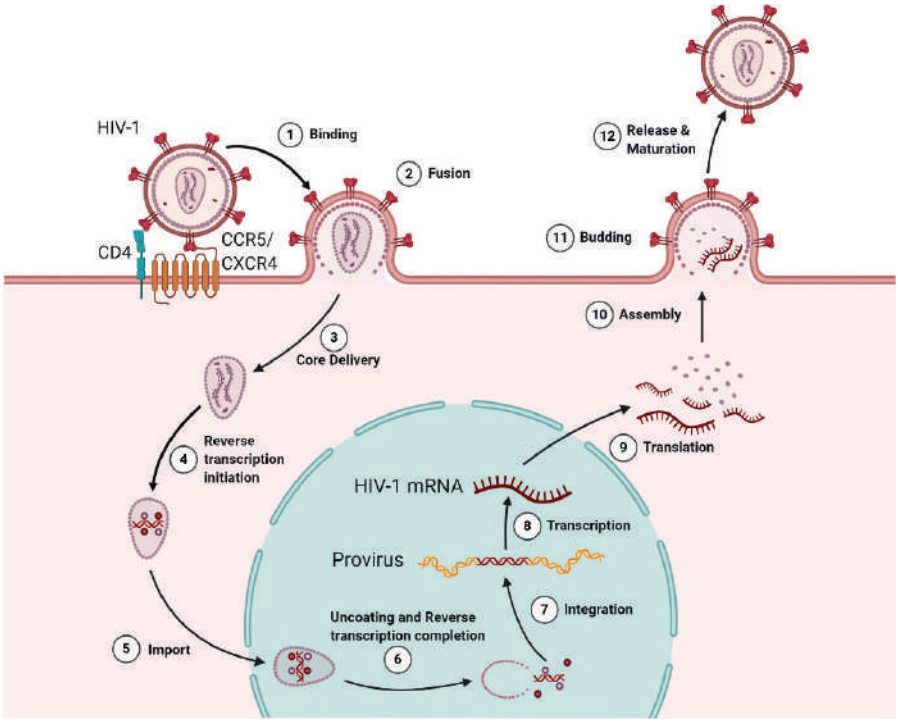


Figure 1. The HIV lifecycle (Ramdas P, et al. 2020)

The basic steps of the HIV life cycle (**Fig 1.**) can be summarized as follows:

1. **Binding:** As the initial stage of HIV infection, HIV must bind to host cell receptors. Host cell receptors (chemokine receptors) of the viral envelope glycoprotein bind with CXCR4 or CCR5 proteins. Specifically, the viral envelope protein binds to the CD4 receptor on the surface of the target cell, while a second viral protein, known as the co-receptor, must bind to one of two chemokine receptors (CXCR4 or CCR5) on the cell surface. These interactions pave the way for the virus to enter the host cell and allow it to initiate the replication process. (**Fig. 1.** Binding 1).
2. **Fusion:** Once binding is achieved, the virus content integrates with the host cell's membrane, causing the viral genetic material to enter the host cell and the "infection" process to begin (**Fig. 1.** Fusion).
3. **Core Delivery:** The virus content is completely transferred to the cell cytoplasm (**Fig. 1.** Core Delivery).

4. **RT Initiation:** The process of reverse transcription, catalyzed by the reverse transcriptase enzyme, initiates within the cytoplasm of the host cell (**Fig. 1.** Reverse transcriptase initiation).
5. **Import:** Thanks to the RT enzyme, the viral genome begins to become compatible with the host cell genome. In other words, DNA begins to be produced from RNA. The resulting DNA fragment passes into the nucleus (**Fig. 1.** Import).
6. **Uncoated and RT completion:** Once inside the host cell nucleus, the viral genome is not packaged like nuclear DNA and the reverse transcription process is completed (**Fig. 1.** Uncoated and Reverse Transcription completion).
7. **Integration:** Viral integrase enzyme is the enzyme that ensures the integration of viral DNA compatible with the host genome into the host genome and controls the process. In this step, the viral DNA is integrated into the host DNA (**Fig.1**. Integration).
8. **Transcription and translation:** The host cell sees the viral DNA as its own DNA and the process of producing viral proteins begins. Like the host's own genes, viral genes undergo transcription and translation (**Fig. 1.** Transcription and translation).
9. **Maturation:** In the final step of the HIV life cycle, all of HIV's proteins have now been produced. Viral RNA and viral proteins are brought together and packaged. As a result, a virion was formed. These virions move towards the cell membrane and are released into the extracellular environment by budding of the cell. The virus progeny begins a maturation process so that it can infect new hosts. (**Fig. 1.** Assembly, Budding and Release & Maturation) (Ramdas P, et al. 2020).

Anti retroviral therapy (ART) method has been adopted for the treatment of HIV infection. This method cannot completely clear the HIV infection from the host cell, but it stops the HIV replication process. Enzymes that play an active role in the HIV life cycle are inhibited, preventing the infection from progressing and causing AIDS. When ART is interrupted, viral replication quickly restarts. For this reason, continuity of ART application is very important. Disruptions in ART application are directly related to ART resistance (WHO, 2022).

2. Reverse Transcriptase

Temin and Baltimore discovered the reverse transcriptase (RT) enzyme with their work in 1970. After it was identified that RNA viruses have RNA-dependent DNA polymerase (RDDP) activity in their virions, studies on this enzyme accelerated. RT function is characterized by facilitating the synthesis of DNA complementary to RNA. While RNA is formed from DNA in cellular processes, the function of this enzyme runs counter to the central dogma of molecular biology. As a result of the discovery of RT, viruses that encode RT and use it as an important step in the virus life cycle were called retroviruses. Later studies revealed that RT also has DNA-dependent DNA polymerase (DDDP) function and can cleave RNA through ribonuclease H (RNase H) activity. With developing technologies, retroviruses and RT studies, especially the function of HIV RT in viral replication, have been shown to be very important and have attracted the attention of scientists.

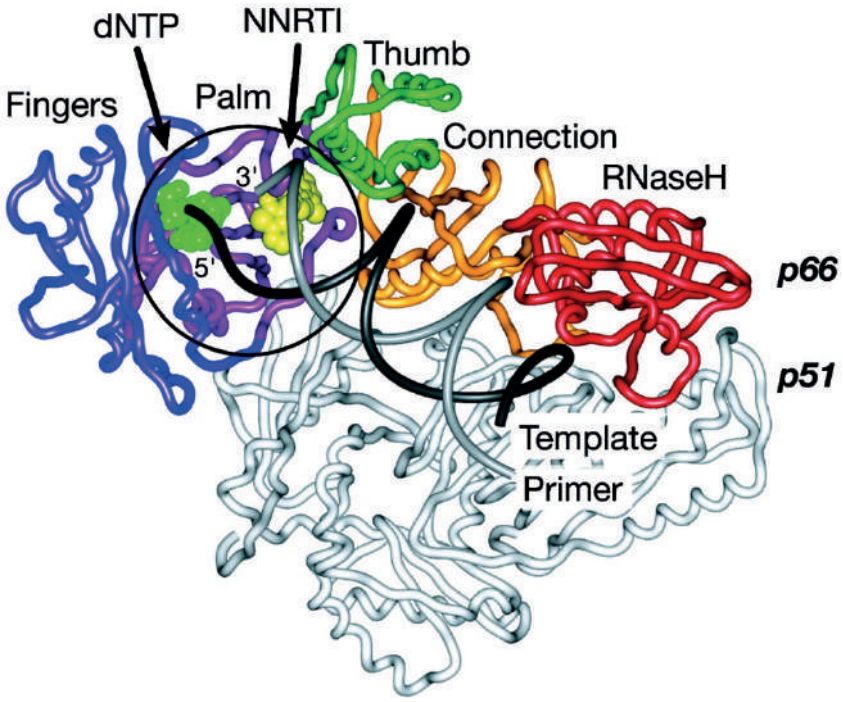


Figure 2. Structure of HIV RT (Pata JD, et al. 2004)

The RT enzyme produced by the Gag-pol gene consists of a 66-kD subunit of 560 amino acids (p66) and a 51-kD subunit of 440 amino acids (p51). When its structure is examined, it is an asymmetric heterodimer (Figure 2.). In these dimers, one p66 subunit is enzymatically active while the other copy

(p66') provides structural support. The RNase H domain, known to be localized at the C-terminus of p66, is disordered. The initial RT structure is cleaved by HIV protease, forming functional RT as a p66/p51 heterodimer; The p51 subunit contains approximately 440 amino acid residues. The first crystallization study of the RT enzyme was resolved in complex with the non-nucleoside reverse transcriptase inhibitor nevirapine (NVP). This structure is in complex with double-stranded DNA. As a result of this study, the RT structure provided insight into the basic properties of the multifunctional enzyme. As with the molecular structure of all other polymerases, the polymerase domain of RT consists of the fingers (1-85 and 118-155), palm (86-117 and 156-236), subdomains (319-426), thumb (237-237) 318) and is characterized by a hand-like conformation with connectivity. When the molecular structure of RT is examined in detail, the inactive p51 subunit and the p66 subunit have the same polymerase subdomains. In addition, it has become clear that the spatial localization of p51 results in an asymmetric organization of the heterodimer. The RT enzyme has been demonstrated to interact with the template/primer in a cleft extending from the polymerase active site containing catalytic aspartates (D110, D185, and D186) to the RNase H active site. The active sites are separated by a duplex length of 18 nucleotides (Ruiz F., etall, 2020).

2.1. Inhibitors of RT

Scientists are working intensively on the treatment of HIV infection. Many RT inhibitors have been developed for clinical use. The development of anti-HIV drugs falls into two main classes: nucleoside/nucleotide RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs). These inhibitors have been widely incorporated into HIV treatment regimens and continue to contribute significantly to the management of AIDS (**Fig.3.**).

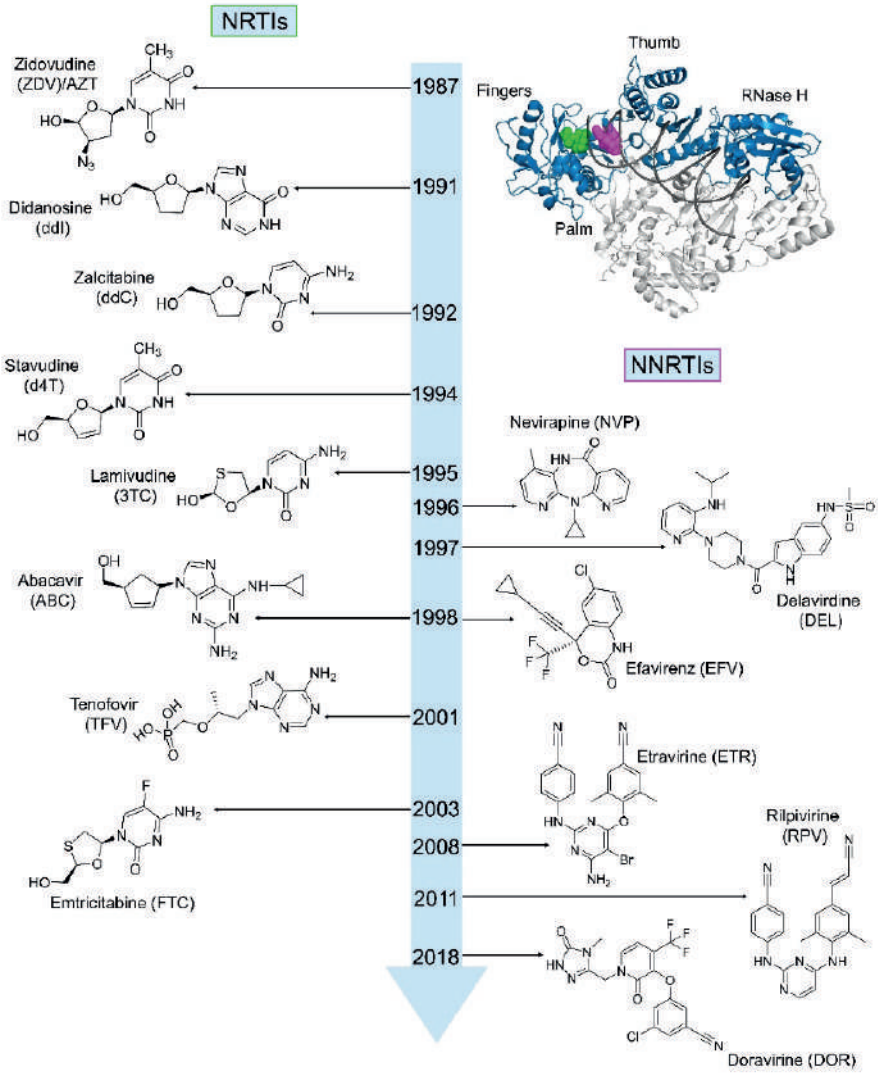


Figure 3. Timeline of HIV-1 RT-inhibiting drugs approved for clinical use (Singh A K. and Das K., 2022).

Despite these advances, structural changes of RT due to accumulation of mutations and the emergence of resistance to inhibitors due to the high rate of viral replication remain a major challenge in the treatment of HIV and the control of AIDS. This infection, which requires life-long treatment, also complicates the toxicity potential associated with long-term drug use. New drugs are periodically added to existing HIV inhibitors in order to control such problematic conditions and overcome resistance and toxicity. In addition to the existing RT drug classes, NRTIs and NNRTIs, alternative

druggable sites and other classes of RT inhibitors are beginning to be developed. This publication focuses on NNRTI and NRTI (Singh A K. and Das K., 2022).

2.1.1. NRTI

NRTIs are known as the first class of antiretroviral drugs to be approved by the FDA. NRTIs appear to be transported into cells by simple diffusion or facilitated diffusion mediated by nucleoside carrier structures. Lipophilic NRTIs such as tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), as well as azidothymidine (AZT), abacavir (ABC), and stavudine (d4T), have been observed to passively cross cellular membranes with nonfacilitated pathways. This transition is achieved due to its hydrophobic properties. However, NRTIs are also known to cross the cell membrane using various cell surface transporters that induce facilitated diffusion. A series of carrier proteins on cellular surfaces control and regulate the cellular uptake of NRTIs. Many of these transporters are in the class called solute carrier (SLC) family. SLC family members involved in NRTI transport include organic cation transporters (OCTs), organic anion transporters (OATs), concentrated nucleoside transporters (CNTs), and compensatory nucleoside transporters (ENTs). It has been discovered that the types of SLC families involved in NRTI transport vary depending on the type of organ involved. Absorptive cells in the small intestine actively use OCT1, OCT2, CNT1-3, OAT2, ENT1 and ENT2 transporters for NRTI uptake. In lymphocytes, ENT1 and ENT2 proteins are known to regulate the uptake of specific NRTIs such as AZT and didanosine (ddI). Hepatocytes use OAT2 and OCT1 carrier proteins for NRTI transport. In contrast, renal tubule epithelial cells directly uptake NRTIs via CNT1, CNT2, OAT1-4, and OCT2 transporter proteins.

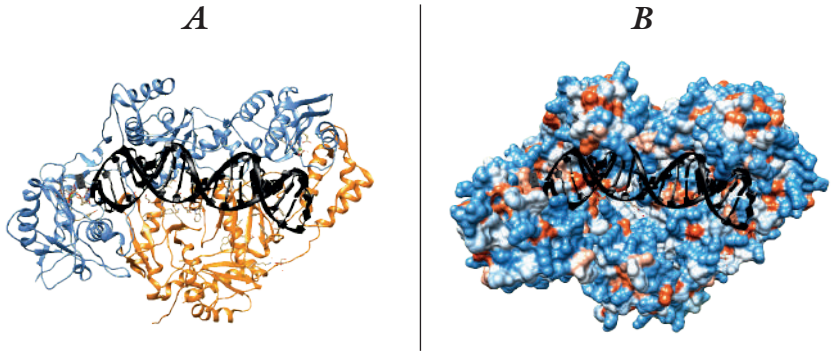


Figure 4. NRTI bind HIV-1 RT with DNA. Ribbon presentation (A), p66 (blue), p51 (orange), DNA (black). Hydropaty presentation (B), hydrophilic (blue), hydrophobic (red), notr (white), DNA (black) (Made with the UCSF Chimera)

NRTIs are known to act in two different ways, as prodrugs or active drugs. Upon cellular uptake, NRTI prodrugs act by being metabolized to the corresponding active drug form. This active form is then phosphorylated to the active diphosphate (DP) or triphosphate (TP) form. Once in its active form, the drug abruptly terminates viral DNA synthesis by first inhibiting the enzymatic activity of RT. In this way, it functions as a functional nucleoside analogue (**Fig. 4.**) (Han HK., 2011, Holec AD, et al., 2017).

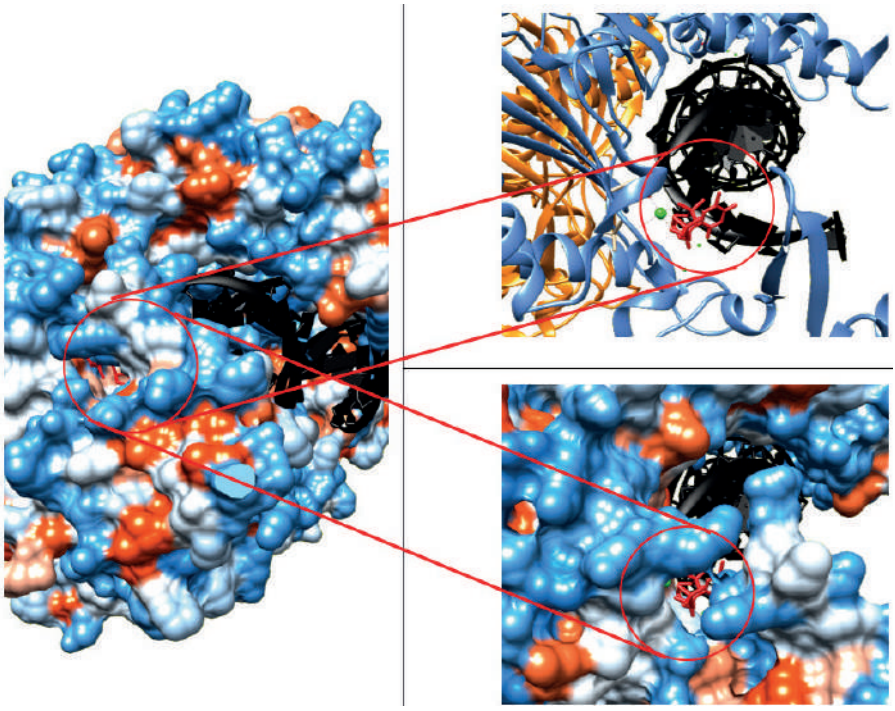


Figure 5. NRTI active site (Made with the UCSF Chimera)

These drugs must be administered in the form of prodrugs, which must be taken up by host cells and phosphorylated before becoming active. The host cell's kinases activate the inhibitor.

NRTIs lack a 3'-1 group on the 2'-deoxyribosyl moiety and have a nucleoside or hydroxyl base. The absence of the 3'-hydroxyl group in NRTI prevents the formation of 3'-5' phosphodiester bonds in growing DNA chains. As a result, viral replication is inhibited. An important feature of these drugs is that they are incorporated into the host cell during its own RNA-dependent DNA synthesis or DNA-dependent DNA synthesis. (Arts EJ and Hazuda DJ, 2012).

2.1.2. NNRTI

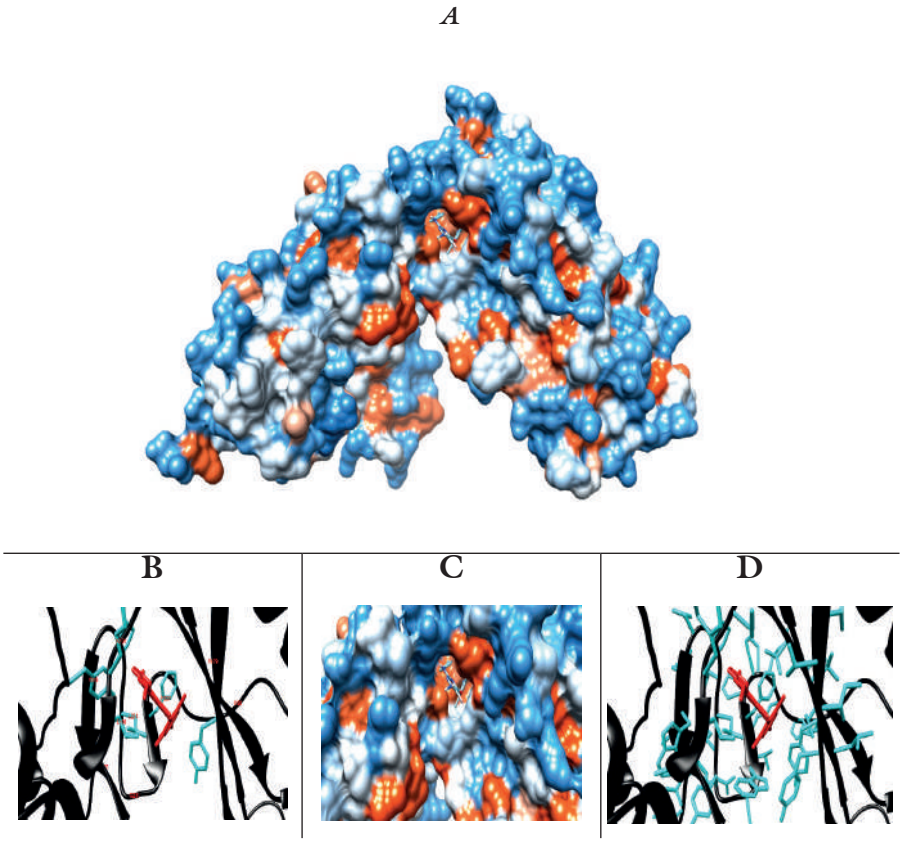
NNRTIs are other RT inhibitors used in the treatment of HIV-1 infection. They do not bind to the region where the NRTIs mentioned in the previous section bind; these inhibitors target the nucleoside non-binding pocket, which is a different region from the active site. By binding to the allosteric site of RT, NNRTIs inhibit the enzyme from efficiently converting viral RNA into DNA, a critical step in the viral life cycle (Sax PE, at all., 2014).

They are prescribed as an important inhibitor of antiretroviral combination therapy (cART) regimen to effectively manage HIV infection and AIDS treatment. It has been reported in the literature that their specific uses vary depending on factors such as drug resistance profiles and potential side effects. These inhibitors; Efavirenz (EFV), Nevirapine (NVP), Etravirine (ETR), Rilpivirine (RPV), Doravirine (DOR), Delavirdine (DLV).

EFV, NVP, and RPV are prominent NNRTIs, each exhibiting unique pharmacological properties. These drugs are highly selective for the HIV-1 reverse transcriptase, minimizing interference with host cellular processes. The efficacy and safety of NNRTIs have been well-documented in clinical trials, making them integral components of highly active antiretroviral therapy (HAART) regimens.

When the side effects of NNRTIs are examined, it is known that there are symptoms such as hepatotoxicity and rash. In such cases, patients need to be carefully monitored and guided. Especially when used as monotherapy or due to virological incompatibility, the development of resistance becomes a critical problem for the patient. After these situations occurred, trial of combination therapy promoted the control of RT resistance (De Clercq E., 2010, Soriano V, et al. 2007).

NNRTIs act through an allosteric mechanism, are noncompetitive, and differ from NRTIs and protease inhibitors. This effect is considered unlike any other, thought to be due to the ability of these inhibitors to bind to a specific hydrophobic pocket within the RT enzyme.



A. Hydrophobic surface visualization of RT (white: neutral, red: hydrophobic, blue: hydrophilic). B. Ribbon representation of the RT (black), etravirine (red), and associated amino acids (blue). C. Hydrophobic pocket of RT D. Ribbon representation of the RT(black), etravirine (red), and surrounding amino acids (blue) (Made with the UCSF Chimera).

Allosteric Inhibition: There is a hydrophobic pocket in a different location than the catalytic active site of the RT enzyme. NNRTIs inhibit HIV-1 reverse transcription by binding to this hydrophobic pocket. During this binding, conformational changes are triggered and inhibit the enzyme from performing its catalytic function.

Specificity: NNRTI inhibitors targeted to the hydrophobic pocket of the RT are specific only to this region. It is thought that it cannot bind to different regions of RT or to a different enzyme.

Non-Competitive Inhibition: NRTIs are known as competitive inhibitors. This is one of the situations that limits the activity of inhibitors.

NNRTs do not have such a situation. They cannot directly interfere with the binding of bases, which are the natural substrates of the RT enzyme.

Resistance Development: Despite the significant activity of NNRTIs, cases leading to the development of resistance mutations in the RT enzyme have been reported. Mutations in the hydrophobic pocket in the allosteric region of RT and that may affect this pocket reduce the binding affinity of NNRTIs by changing the shape of the pocket. This can lead to complete resistance or low-level resistance (Ren J., 2002, Rhee SY, et al., 2021).

3. MECHANISMS OF NNRTI RESISTANCE

NNRTIs) in the context of HIV treatment results from genetic mutations in the HIV-1 reverse transcriptase gene. These mutations (**Table 1.**) can affect the conformation of the NNRTI binding pocket, leading to reduced drug binding and inhibition. Common resistance mutations include K103N, Y181C, and G190A, which can confer varying degrees of resistance to different NNRTIs. The emergence of NNRTI resistance poses a challenge in managing HIV infections, necessitating tailored antiretroviral therapy regimens and adherence to resistance testing for optimized treatment strategies (Paredes and Clotet, 2010; Rhee et al., 2022).

	100 L	101 K	103 K	106 V	138 E	181 Y	188 Y	190 G	230 M
DOR	I	EP		AM		IV	L	SE	L
EFV	I	EP	NS	AM		CIV	L	ASE	L
ETR	I	EP			AGKQ	CIV	L	ASE	L
RPV	I	EP			AGKQ	CIV	L	ASE	L
NVP	I	EP	NS	AM		CIV	L	ASE	L

Table 1. Major Non-Nucleoside RT Inhibitor (NNRTI) Resistance Mutations -Stanford Drug Resistance DataBase

NNRTI resistance generally occurs by changing the amino acids located in this pocket and playing an active role in ligand interaction. Mutations trigger conformational changes. Ligand affinity decreases or disappears completely due to not only conformational changes but also changes in the physico-chemical properties in the region as a result of mutation.

While some mutations in this region may cause resistance to all NNRTIs, some mutations may not cause resistance to all. Additionally, different mutations in the region may have a synergistic effect and lead to resistance (**Table 1.**) (McClung RP, et al. 2022).

CONCLUSION

Today, all inhibitors are used in different combinations in the treatment of HIV infection. RT inhibitors are specifically reported in our book chapter. Additionally, the working mechanism of RT is explained in detail. It is expected that new RT inhibitors will be developed in the near future.

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Chapter 2

Role of TRPV1 channel in migraine: Current Overview

Adem Ahlatcı[1]

Abstract

Migraine is a neurological disease that is very common in society and is characterized by symptoms such as severe headaches, nausea, and sensitivity to light and sound. Absence from work, decreased productivity and healthcare costs due to migraine impose a high economic burden on patients and countries. For this reason, research on preventing or treating this disease continues intensively towards understanding migraine pathophysiology and drug discovery. In studies investigating migraine pathophysiology, new specific targets have emerged in drug development, such as the Calcitonin Gene and Peptide (CGRP) pathway. Current studies show that imbalance in neuronal calcium (Ca^{2+}) homeostasis is effective in the pathogenesis of neurodegenerative disorders. Transient receptor potential (TRP) cation channels are non-selective cation channels and integral proteins that are widely expressed in the membranes of cells and organelles, especially in mammalian cells, and are involved in various cellular functions. It is known that transient receptor potential (TRP) channels cause neuronal apoptosis in cases of oxidative stress and Ca^{2+} homeostasis in neurological diseases. Therefore, TRP channels in migraine may be useful in preventing cellular damage due to oxidative stress in neurological disorders. TRPV1 (Transient receptor potential family, transient receptor potential vanilloid receptor1) is a non-selective ion channel protein first expressed in the dorsal root, trigeminal and nodos ganglia. Therefore, it is clear that TRPV1 channels have an important role in migraine treatment. Additionally, it has been shown that by using TRPV1 channel antagonists, Ca^{2+} influx into the intracellular environment can be prevented and thus cell homeostasis can be preserved. In this review, we examined the role of the TRPV1 channel in migraine based on recent studies.

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1. Transient Receptor Potential (TRP) Channels

There are various receptors located at the endings of nociceptive sensory nerves that respond to thermal, mechanical or chemical stimuli with threatening/disturbing potential. Most of these are members of a family of nonselective cation channels called TRP channels (1).

TRP channels containing 28 members in mammals have been classified as a new cation channel family. TRP channels blood pressure and smooth muscle regulation of tone, renal Ca^{+2}/Mg^{+2} conduction, pungent taste and odorous compounds, such as perception of mechanical changes, pain, temperature, taste, smell, sound, light it plays a role in many very important processes (2-4).

The TRP family is divided into 7 subfamilies based on amino acid similarities (5). TRP conancial (TRPC) consists of seven subfamilies, TRP vanilloid (TRPV) consists of six subfamilies, TRP melastatin (TRPM) from eight subfamilies, TRP polysteine (TRPP) from three subfamilies, TRP mucolipin (TRPML) consists of three subfamilies and TRP ankyrin (TRPA) consists of a single member (6, 7) (Figure 1)

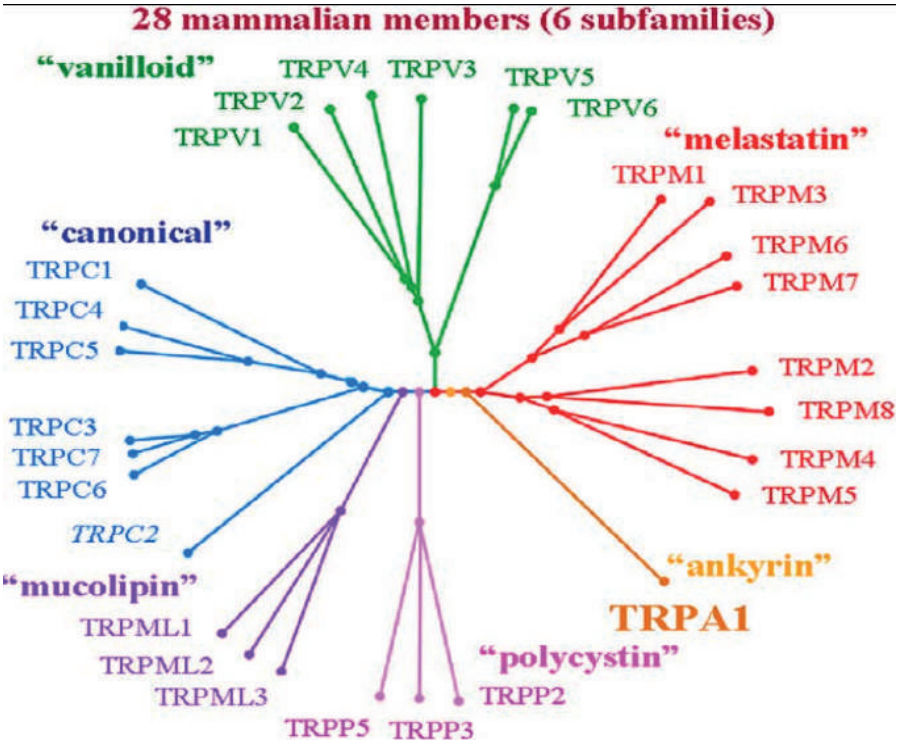

Figure 1. TRP channel superfamily (8).

It has been determined that TRP cation channels have important roles in the physiopathology of many diseases. Although these channels have many structural similarities, the activators of the subtypes of these channels differ. It is suggested that the basic structure of TRP channels consists of regions that cross the membrane 6 times, except for some TRPPs. It is known that the hydrophobic ring between segments 5 and 6 is the ion channel-forming pore and that the NH2 and COOH ends are located in the cytoplasm (Figure 2). TRP subtypes function by forming homo or heterotetrameric structures (10).

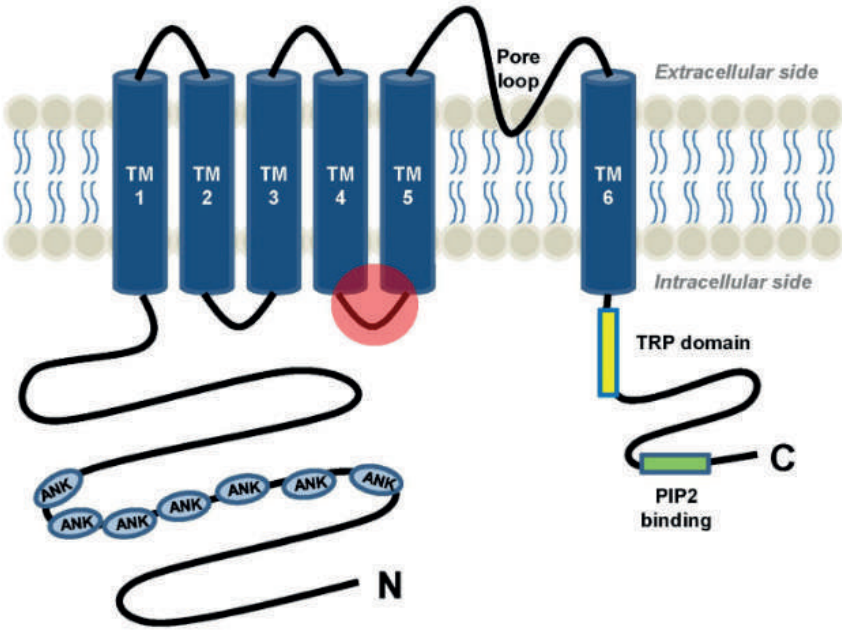

Figure 2. A topological structure of sensory TRP channels is illustrated (9).

In vivo, functional TRP assembly of channel complexes, homo/hetero multimerization and structural it is managed by complex formations with proteins (11). The differences between the physiological functions proposed in different tissues and the functions and properties of TRP channels observed in heterologous expression systems can be explained by these formations.

1.1. TRPV Cation Channels

The TRPV (vanilloid) family, which has six members in mammals, is divided into 4 subgroups are divided into: TRPV1/TRPV2, TRPV3, TRPV4 and TRPV5/6 (12, 13). TRPV Members of the family function

as tetrameric complexes. TRPV channels all have 3-5 NH_2-terminal ankyrin repeats (14).

TRPV2 is a voltage-activated channel and functions as a mechanosensor in vascular smooth muscle (15) and it probably plays a role in the pain pathway through degeneration of skeletal muscle and cardiac muscle (16). Physiological functions of the TRPV4 channel include central and peripheral thermosensitivity, mechanosensitivity, osmosensitivity and basal Ca^{2+} homeostasis (17). The highest Ca^{2+} selective channels of the TRP family are TRPV5 and TRPV6 channels, and these channels are regulated by Ca^{2+}. (18). While these two channels conduct calcium under physiological conditions, transports monovalent cations in the absence of extracellular calcium. TRPV5 in the kidney TRPV6 is important in the intestine while it is important for Ca^{2+} reabsorption (19). Among these channels, TRPV1 has attracted the most attention regarding pain modulation.

1.1.1. TRPV1 Cation Channel

TRPV1 is an ion channel activated by high temperature (43) and acid (pH5), which can produce effects similar to Capsaicin and CAP. TRPV1 is widely found in sensory neurons and ganglia. It is also found in other neurons and in various cells that do not contain neurons (20). When these receptors are activated by various stimuli, the flow of Ca+2 ions into the cell is stimulated (21, 22). Vanilloids are divided into two groups: exogenous and endogenous (23). Examples of endogenous vanilloids are pH changes and high temperature changes due to inflammation, and exogenous vanilloids include resinferatoxin, anandamide, found in cathus, and CAP, the active ingredient of hot pepper (24). CAP is the most commonly used exogenous vanilloid in the study of these channels (25).

TRPV1, pain transmission and inflammation-induced thermal hyperalgesia has been held responsible for the activation (26). By modulating TRPV1, which is located on the peripheral endings of nocireceptors that provide pain perception, perception of pain messages in the somatosensory system and the development of inflammatory thermal hyperalgesia can be achieved. By understanding the mechanisms underlying the modulation of TRPV1 by various agents, new treatment opportunities may be offered to reduce pain (27).

TRPV1 channels contain cysteine groups in their structure (28). Cysteines have an antioxidant role in many nerve cells. The amino acid cysteine is a source of many antioxidants such as glutathione (GSH) , lipoic acid and glutathione peroxidase. Studies have shown the regulatory role of GSH and N

acetyl cysteine (NAC) antioxidants in TRPV1 channel activation (29). When the cysteine groups in this TRPV1 structure are activated by oxidative stress and nitric oxide, TRPV1 channels open and NA^{+} and Ca^{+2} flows ocur (30).

2. Migraine

Migraine is a disease that is frequently encountered among neurological diseases, includes gastrointestinal and autonomic symptoms as well as neurological symptoms, has a high economic burden on society, and is characterized by recurrent headaches. While migraine negatively affects individuals' quality of life and business life, it also causes economic losses by increasing drug use (31).

The term 'migraine' means 'hemicrania' in Greek, 'half of the head', and it is known that in most migraine cases, the headache occurs on one side of the head. However, in some cases, it may be observed as bilateral pain in the back or front of the head (32). Patients also reported that they experienced neck pain before or during a migraine attack (33). It has been reported that some migraine patients may have stiffness in the neck area, head tilting forward, and trigger points in the neck muscles (34, 35).

The neurobiological mechanisms and changes in multisensory information processing related to the causes that lead to the onset of a migraine attack have not yet been fully explained. Although significant changes have occurred in recent years in the field of drug development for migraine treatment and various candidate molecules that are relatively selective to pain pathways have been discovered, the expected results have not yet been achieved (36). Thanks to triptans developed especially for migraine, better results have begun to be obtained in the treatment of primary headache disorders. However, despite the success of triptans, excessive drug use is associated with headaches and has significant side effects, although it is not seen in all migraine patients (37). To overcome these problems, monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) and its receptor have recently been developed, but safety problems have been reported as a drawback (38).

3. The role of TRPV1 Cation Channel in Migraine

The role of TRPV1 in stimulating sensory neurons involved in the transmission and determination of pain sensation has been addressed in many studies, and these channels have been shown to be important regulators of nociceptive and inflammatory pain.TRPV1 was the first TRP channel to be extensively studied in migraine and headache. Factors such as capsaicin

(CAP) or resinoferatoxin (RTX), heat, acid, oxidative stress products and endocannabinoids (Anandamide, etc.) that can produce CAP-like effects are called vanilloids. These activate TRPV1 channels. These channels are also activated by prostaglandins and bradykinin. TRPV1 is expressed trigeminal origin in humans which co-express and release CGRP. In recent studies, in the trigeminal ganglion, TRP channels co-localize with CGRP (39), and the number of CGRP and TRPV1 immune reaction cells increase in the trigeminal ganglion of migraine rats.

Migraine-related factors in the trigeminal nerve were evaluated as a result of the application of Xiongmatang extract to mice suffering from experimental migraine. At the end of the study, although the TRPV1 gene increased in the migraine model, it was found to be regulatory in mice given xiongmatang extract. Moreover, according to western blot results, although the CGRP gene was overexpressed in the migraine model, it was decreased in the treatment group (40). In the study conducted by Liao et al., an increase in TRPV1 levels was observed in the trigeminal ganglion cells of rats created as a migraine model with nitroglycerin compared to the control group (41).

Evans et al. suggested that the possible mechanism of action of sumatriptan, an antimigraine drug, is that it blocks TRPV1-mediated calcitonin gene related peptide (CGRP) release and that the TRPV1 channel should be targeted in treatment (42). Another study shows that Zhengtian (ZTP) can significantly improve headache migraine symptoms in drug-administered rats, and TRPV1 may be one of the important molecular mechanisms. It also highlighted the effect of ZTP on TRPV1 protein expression level in both cortex and hippocampus of mice (43).

Martins et al. showed in his study that transient receptor potential TRPV1 stimulation, which is a non-selective cation channel in sensory neurons, can trigger a severe headache attack and the trigeminovascular system can be activated. This results in a nociceptive response and calcium-dependent release of CGRP from the trigeminal nerve terminals in the dura. As a result, TRPV1 activation activates dural nociceptors, causing central sensitization and cutaneous allodynia (44).

To investigate the possible role of TRPV1 levels in migraine progression, a study evaluated the change in TRPV1 levels in plasma, hippocampus and somatosensory cortex in Epidosic Migraine (EM) and Chronic Migraine (CM) groups using a rat migraine model; Somatosensory cortex showed a significantly higher increase in TRPV1 in the CM group than in the EM group. This showed that headache severity and frequency may increase with increasing somatosensory cortex TRPV1 expression level (45).

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Chapter 3

The Effect of Antioxidant Foods on Cancer Prevention

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İsmail Deniz[2]

Abstract

Cancer is the second-most common cause of death worldwide, after cardiovascular diseases. With the development of cancer, significant changes occur within the cell. Due to the increase in diagnostic possibilities and the provision of more widespread health services to societies, it is possible to diagnose more and more patients with cancer every day. The development of technology increases people's exposure to cancer-causing substances, impacting the frequency of cancer. This study examined the effects of nutrition, one of the environmental factors, on cancer. The high mortality rate in cancer increases the importance of the subject even more. It is accepted that environmental factors play a role between 80 and 90% in the development of all cancers. It is recommended to consume vegetables and fruits. Processed red meat consumption should be limited. Avoid using frying oils for an extended period of time. Dietary recommendations are important for cancer prevention. Many factors, such as carotenoids, vitamins, phenolic compounds, terpenoids, and steroids in plants, have been shown to be effective in reducing the risk of disease. Antioxidants are still widely used to prevent or reduce the effects of cancer. However, an increasing number of studies suggest that antioxidant use may accelerate the spread of cancer, highlighting the need for further research on nutrition and cancer.

1.INTRODUCTION

Cancer is a general term used for various disease groups defined by uncontrolled and abnormal cell proliferation in which cells lose control of

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division (Todd and Wong, 1999). It has been the most common health problem in our country in recent years. Abnormal cell proliferation forms a tumor mass. A tumor is the uncontrolled proliferation of some cells in the body. The tumor disrupts normal functions in the area where it occurs. A tumor that grows in the area where it started and does not spread to other tissues is called a benign tumor, while a tumor that spreads to other tissues and grows is called a malignant tumor (Ünsal, 2018). The process of cancer development, called carcinogenesis, consists of three phases: initiation, promotion, and progression. The initiation phase is characterized by epigenome, chromosome, and DNA damage that regulates gene expression. The initial phase is followed by a long process. With inflammation, genomically unstable cells grow. In the progression phase, as the cells proliferate, they further damage their genome and transform into malignant tumors (Poirier, 1987). The main types of cancer are stomach cancer, cervical cancer, prostate cancer, pancreatic cancer, esophageal cancer, skin cancer, blood cancer, liver cancer, small intestine cancer, colon cancer, breast cancer, uterine cancer, kidney cancer, and lung cancer (Ministry of Health, 2021).

Although the reasons for the occurrence of cancer in a body are not fully known, the external and internal factors that may be factors in cancer formation are listed as follows:

- Genetic predisposition
- Poor eating habits
- Smoking and alcohol use
- Additives in food
- Radiation exposure
- Some chemical substances
- Some viruses and bacteria
- Prolonged exposure to sunlight
- Air pollution
- Exposure to an overdose of x-rays (Ministry of Health, 2021).

One of the most important requirements for a quality life is a healthy diet. Nutrients provide the necessary substances for the metabolic requirements of the organism, and in addition, they contain components that have positive effects on our health (Coşkun, 2005). Balanced and adequate nutrition during cancer treatment reduces the risk of infection, heals quickly, tolerates treatment-related side effects better, maintains energy and strength, preserves the body's nutritional stores and weight, and makes it feel better (Mandar, 2012).

Healthy nutrition is very important for preventing diseases. Antioxidant nutrition is especially important to get rid of the effects of free radicals. Food antioxidants are defined as substances that can neutralize some or all of the negative effects of free radicals in humans (Yılmaz, 2010). Cancer may develop for different reasons. Unhealthy diets, wrong lifestyles, sedentary lifestyles, and obesity increase the risk of cancer. Unhealthy diets and harmful foods have been observed to cause cancer. Improper nutrition, consuming cancer-causing foods, or not getting enough nutrition can cause cancer. Especially in obese individuals, the risk of kidney, breast, uterine, and colon cancer increases (Çevik & Pirinççi, 2017). Approximately 1/3 of all cancer cases are caused by the food consumed, and 1/3 of all cancer deaths are related to nutrition. Therefore, healthy nutrition, abstaining from alcohol and smoking, and physical activity are very important in cancer prevention (Özcan & Demir, 2004).

Epidemiologic studies show that obese people are more likely to develop certain types of cancer, such as breast, prostate, lung, ovarian, colon, rectum, and kidney cancer. It is estimated that a significant portion of these cancers are related to nutrition. Research has found that an increase in body mass index increases the risk of death from breast and prostate cancers at later ages (Okasha et al., 2002).

1.1.Cancer and the Antioxidant System

Antioxidant nutrients are nutrients that reduce free radicals and reactive compounds that occur during the normal physiological activities of humans or that are ingested through the environment and nutrition by giving electrons or hydrogen to them and thus significantly reduce the negative effects that may occur (Astley, 2003; Benzie, 2003; Erbaş, 2006). The antioxidant content of foods may vary according to the preparation, type, harvest time, harvest methods, climate, temperature, humidity, and light of the storage environment. Although the use of natural antioxidants reduces the risk of developing cancer and many other diseases, excessive use may cause toxic effects (Cornelli, 2009).

A good antioxidant eliminates free radicals, retains redox metals, and has a positive effect on gene expression. There are two types of antioxidants: enzymatic and non-enzymatic. Enzymatic antioxidants include Superoxide Dismutase, Catalase, Glutathione Peroxidase, Glutathione Reductase and Glucose 6-Phosphate Dehydrogenase. Nonenzymatic antioxidants are Mineral (Se, Zn), Vitamin (A, C, K and E), Carotenoids (B-carotene, Lycopene, Lutein, Zeaxanthin), Organosulfur Compounds (Allium, Allyl Sulfite, Indoles), Low Molecular Weight Antioxidants (GSH-Px, Uric

Acid), Antioxidant Cofactors (Coenzyme Q10) and Polyphenols (Moure et al., 2009).

The foods containing the most powerful antioxidants are Anthocyanins (Damson Plum, Blackberry, Blackberry, Black Mulberry, Cherry, Blueberry, Blueberry, Cherry), Catechins (Black tea and Green tea), Lycopene (Tomato, Pink Grapefruit, Watermelon, Apricot), Beta Carotene (Carrot, Melon, Mango, Apricot), Resveratrol (Grape, Blueberry, Cranberry), Elajic Acid (Pomegranate, Grape, Cherry, Strawberry), Capsaicin (Red Hot Pepper), Quercetin (Red Onion and Apple), Vitamin C (Grapefruit, Orange, Pepper, Broccoli, Kiwi, Rosehip), Vitamin E (Almonds, Sunflower Seeds, Wheat), Selenium (Potatoes, Sunflower Seeds, Eggs), Polyphenols (Green Tea, Raspberry, Soy, Strawberry, Plum, Apple, Blueberry), Glucosinolates (Broccoli, Brussels Sprouts, Watercress, Cauliflower), Lutein (Broccoli, Spinach, Kale, Red Grape, Kiwi) (Ratnam et al. , 2006). Some studies have found that patients who eat more fruits and vegetables (rich sources of antioxidants) are less likely to develop certain types of cancer (Willett, 1994).

Apple is superior at eliminating mutagens in the intestinal cavity due to its fibrous structure and pectin content, and it dilutes mutagens by being water-retentive. In this way, it reduces the activity of oxidative stress, indicating that it is an important herbal intestinal protector. In studies, it has been determined that apples and apple juice can prevent the formation of colon and lung cancer in humans due to the antioxidants, pectin, and vitamins they contain and may be protective against liver and breast cancer (Yılmaz, 2010; Gerhauser, 2008).

In a study, the relationship between dietary fat and distal colon cancer was examined. In countries with a high prevalence of distal colon cancer, 40–45% of daily calories were found to consist of saturated and unsaturated fats. In Japan, where the incidence of distal colon cancer is low, it was found that 10–15% of daily calories were provided from fats, and most of them were provided from unsaturated fats, especially from fish (Weisburger, 1992). Studies have shown that omega-3 fatty acids reduce the risk of cancer, and it has also been shown that the ratio of omega-6 and omega-3 in the diet is important. Studies have found that this ratio in the diet is important in reducing the risk of more than one type of cancer, especially breast cancer (Aksoy, 1984). Omega-3 fatty acids reduce the risk of cancer formation. They also slow down the growth of lung, colon, breast, prostate, and many other types of cancer. At the same time, omega-3 fatty acids increase the effectiveness of chemotherapy and radiotherapy and the response to

treatment. Omega-3 fatty acids also reduce and prevent weight loss, muscle loss, and cachexia seen in cancer (Muhsiroğlu, 2007).

Many studies have shown an association between salted foods and gastric cancer. In Hong Kong and South China, the incidence of nasopharyngeal cancer is also high due to high nitrosamine intake due to the high consumption of salted fish. Foods cooked using various cooking methods, such as smoking, high temperatures, and charcoal grilling, show high carcinogenic properties due to polycyclic hydrocarbons and heterocyclic aromatic amines (Yıldız and Demir, 2004).

A high animal protein intake will also increase saturated fat consumption. This has been associated with breast, uterine, gastrointestinal, colorectal, and pancreatic cancers and increases the risk of these cancers (Muhsiroğlu, 2007). Studies have shown that lean animal protein consumption is not associated with cancer. It has been reported that processed meats such as salami, sausage, and pepperoni have a high effect on the relationship between pancreatic cancer and meat consumption (Baysal and Criss, 2004). Nitrates and nitrites are frequently used in processed meat products such as sausage, salami, bacon, and fish as preservatives, colorants, flavor enhancers, and to maintain an antimicrobial environment. In addition, nitrites converted to nitrosamines have been reported to cause bladder cancer in animal models (Dönmez et al., 2010). It has been shown that women who were fed diets containing high amounts of vegetables, fruits, whole grains, fish, and poultry after breast cancer diagnosis had lower mortality rates than women fed diets containing processed foods, red meat, sweets, high-fat daily products, and French fries (Kroenke et al., 2005).

Vitamin A is a fat-soluble vitamin that plays a primary role in the normal growth and development of epithelial tissues. It is found as retinol and its esters in milk and offal and as provitamin A carotenoids in yellow and green leafy vegetables. Carotenoids are the pigments that give these fruits and vegetables their yellow, orange, and red colors. Carotenoids are divided into two groups: hydrocarbons and xanthophylls. Their antioxidant effects are due to their conjugated double bonds, which function both as free radical scavengers and single oxygen suppressors (Podselek, 2005). As the number of double bonds in carotenoids increases, antioxidant activity increases in parallel. The most effective antioxidant among carotenoids is lycopene; xanthophylls have the lowest antioxidant effect (Koca and Karadeniz, 2005).

Vitamin C, known as ascorbic acid, is a water-soluble vitamin with antioxidant properties and is involved in many enzymatic reactions (Moser and Benich, 1991). Its antioxidant properties are versatile. It acts both intracellularly and extracellularly as a water-soluble antioxidant. It prevents

lipid oxidation by different cellular mechanisms (Proteggente et al., 2002). Vitamin C is considered a free radical scavenger, and a high intake of vitamin C-rich foods (e.g., citrus fruits) may play a role in reducing the incidence of gastric cancer (Boyle and Levin, 2008). The most important sources of vitamin C are citrus fruits, tomatoes, potatoes, peppers, pumpkin, strawberries, fibrous green vegetables, and sprouts. High doses of ascorbic acid intake may cause diarrhea and crystal formation in the urine, leading to the risk of kidney stones in the renal tract and predisposing to gout by affecting uric acid excretion (Auer et al., 1998).

Vitamin E is one of the major fat-soluble vitamins and one of the eight substances called tocopherols. Vegetable oils, eggs, and cereals are rich food sources of vitamin E. Excessive intake of vitamin E may cause stomach upset, diarrhea, and dizziness, rather than the usual toxic effects (Sherwin, 1990). In addition, some randomized trials have shown that vitamin E intake may increase the risk of fragility and hemorrhagic stroke, so its use should be avoided, especially in cancer patients with uncontrolled hypertension and thrombocytopenia (Hartman et al., 1998).

Studies have shown that certain carotenoids, such as alpha-carotene, beta-carotene, lycopene, lutein, cryptoxanthin, and zeaxanthin, which are found in many foods, complete their formation and act as anticarcinogens in the organs where they are stored. Therefore, in addition to carotenoids with provitamin A activity such as beta-carotene, carotenoids without provitamin A activity such as canthaxanthin, lycopene, and lutein have antioxidant properties and prevent cancer formation in this way (Gerster, 1993; Le et al., 1993). Beta-carotene has been shown to inhibit cell growth in a cell cycle-dependent manner and trigger apoptosis in cancer cells (Kotake-Nara et al., 2001).

Due to thermal and oxidative reactions occurring in frying oils, the use of the same oil for a long period of time adversely affects the acceptability and nutritional value of products fried in that oil. Volatile spoilage compounds such as aldehydes, ketones, hydrocarbons, alcohols, acids, esters, and aromatic compounds are formed in oils by oxidation (Fujisaki et al., 2002). Using frying oils more than three times causes the oil to burn. Burnt oil contains carcinogens (Koçak, 2012). Studies have reported that cooking methods such as barbecue, grilling, and pan-frying are more effective in heterocyclicamine formation compared to cooking methods such as microwave cooking and boiling or steaming (Ferguson, 2010). In addition, it has been determined in many studies that the use of spices and plant extracts rich in components with antioxidant effects prevents the formation of heterocyclicamine. Spices used in the preparation of mixtures such as meatballs are added not only

in Turkey but also all over the world to give color, flavor, and aroma to the product. In their study, in which they examined the inhibitory effect of black pepper on heterocyclicamine formation in meatballs made from minced meat, they reported that black pepper inhibited heterocyclicamine formation between 48.8 and 65.8% (Öz and Kaya, 2011).

1.2.Foods that Increase Cancer Growth

- Salted foods,
- Smoked foods,
- Hamburger,
- Meat cooked over direct fire,
- Foods with added nitrites and nitrates, such as sausage, salami,
- A diet poor in vegetables and fruits,
- Butter, suet, and fried foods (Coulston et al., 2001).

1.3.Foods that Reduce Cancer Formation

- Dried legumes: lentils, chickpeas, beans, kidney beans, peas, and soybeans
- Fruits: Orange, grapefruit, lemon, rosehip, blackberry, cranberry, apple, pear, quince, plum, cherry, sour cherry, strawberry, melon, watermelon, grape, fig, pomegranate, mulberry, banana, date
- Nuts: Chickpeas, chestnuts, almonds, hazelnuts, pistachios, walnuts
- Cereals: Whole wheat bread, wholemeal bread, rye bread, oat bread, bulgur
- Animal Products: Eggs, skimmed or low-fat milk, yogurt, cheese, cottage cheese, cottage cheese, yogurt, and kefir (Coulston et al., 2001).

1.4.Ways to Prevent Cancer and Nutrition Recommendations

- Achieving and maintaining a healthy body weight (maintaining a body mass index between 21-23)
- Ensuring that 15-30% of daily energy is obtained from fats
- Limiting red meat protein energy to 10% per day (avoiding over-salted foods such as pickles and pickled meats, paying attention to low-heat cooking)
- Storing food in conditions that prevent mold and fungus (refrigerating and freezing perishable foods)
- Paying attention to identifying and monitoring whether various chemical contaminants, pesticides, wastes, and additives in food are within safe limits

- Regular physical activity (brisk walking for 1 hour a day, more vigorous exercise for 1 hour a week) (Yıldız and Demir, 2004; Baysal and Criss, 2004).

It should be noted that cancer is a very general term. Since the development of tumors is a multi-stage process, it distinguishes patients with cancer from each other. Although cancer varies according to its origin, the organ in which it is located, and the cell type, success in treatment can be achieved if it is treated in the light of specific, accurate information, not general information from hearsay. Furthermore, it is important to avoid the uncontrolled and unsupervised use of antioxidants since they have been found to trigger cancer instead of preventing its development (Çiftçi, 2017). There are many factors that increase the risk of cancer. Studies have shown that nutrition is important in creating cancer risk. Medical nutrition therapy is always an effective method for treating cancer. The idea of eliminating cancer with medical nutrition therapy is a fictitious idea, while the idea of affecting the speed of cancer is a real approach. Dietary advice is important for cancer prevention. Healthcare providers should offer individuals preventive nutrition recommendations before cancer develops. However, researchers need to conduct more studies on nutrition and cancer.

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Chapter 4

Determination of Some Antioxidant Activities in Food Supplement Mixture Fruit Containing Noni (Morinda Citrifolia), Vitamin B3, Zinc, Vitamin B1, Coenzyme Q10 and Chromium

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Abstract

Nitric oxide has important functions in cardiovascular, neurological, immunological and many biological systems). Noni (*Morinda citrifolia*) has been found to have antitumor, antiproliferative, proapoptotic, anti-angiogenesis, anti-migratory, anti-inflammatory and immunomodulatory activities. The aim of this study is to determine some antioxidant activities in food supplement mixture fruit containing Noni (*Morinda citrifolia*), Vitamin B3, Zinc, Vitamin B1, CoenzymeQ10 and Chromium. In this study, antioxidant activities were determined by spectrophotometric method. While the MDA level was found to be 0.0012 (mmol/L); the SOD activity was 1377.483 (U/L); reduced glutathione (GSH) level 725.251(mg/dl); catalase (CAT) activity 1275.035 (U/L); glutathione reductase activity (GR) 1439.041 (U/L), and glutathione peroxidase (GPx) activity were found to be 1215.055 (U/L). Some antioxidant activities such as SOD, GR, GST, GPx, GSH and CAT were found to be high in the noni fruit. Malondialdehyde (MDA) level was found to be low. Antioxidant activities were found to be very high in the noni extract. Noni fruit or its extract can be consumed against oxidative stress. We think that this study will contribute to the literature.

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1. Introduction

Free radicals are unpaired electron pairs. The main free radicals are compounds such as hydroxy (OH-), peroxy (ROO.), and superoxide (O_2-) radical. When free radicals are formed, they become stable. Also, these radicals enter the structure of cells and damage them. As a result of this damage, various may diseases occur. Free oxygen radicals have been implicated in the etiopathogenesis of a number of diseases, according to reports. It has been determined that free oxygen radical damage occurs in diseases such as bladder disease, prostate cancer, sepsis, myocardial infarction, stroke, perinatal hypoxic brain injury, glomerulonephritis, uveitis, various cancers and arthritis in laboratory, clinical and experiments. However, antioxidants protect the cell against these radicals (Sosa et al., 2013; Sayır et al., 2019; Günes et al., 2020; Gündüz et al., 2021).

Nitric Oxide is a gas with the chemical formula N-O. It carries datas at the cellular level and can effectively penetrate the cell membrane thanks to its gaseous structure.

Since the past, the importance and benefits of medicinal plants for human health have been investigated. Plants have very important roles in the treatment and prevention of diseases. Herbal medicines have been developed with the extracts of plants used by the public. Also, people have managed to protect themselves from diseases for years (Mill, 1982).

Morinda citrifolia is rich in nutritional value. It has strong antioxidant activity. It strengthens the immune system and balances acid and base in the body. It contains rich minerals and vitamins. It is also present in various alkaloids, polysaccharides, various enzymes and many components (Akihisa et al., 2007; Zhou and Huang, 2022).

This study's objective is to ascertain some antioxidant activities in food supplement mixture fruit containing Noni (*Morinda citrifolia*), Vitamin B3, Zinc, Vitamin B1, CoenzymeQ10 and Chromium.

2. Analysis Method

Noni (Morinda citrifolia), food supplement mixture containing Vitamin B3, Zinc, VitaminB1, CoenzymeQ10 and Chromium, contains malondialdehyde (MDA), which is an oxidative stress parameter, and superoxide dismutase (SOD), reduced glutathione (GSH), catalase (CAT), glutathione peroxidase (Some antioxidant activities such as GSHPx), glutathione reductase (GR) and glutathione S-transferase (GST) were determined spectrophotometrically.

2.1 Measuring the activity of superoxide dismutase (SOD)

Determination of superoxide dismutase (SOD) activity SOD activity was determined according to the method by Popov et al (Popov et al., 2004).

% Inhibition = [(Blank OD – Sample OD) / Blank OD] × 100

2.2 Measuring the level of reduced glutathione (GSH)

GSH was determined according to the method made by Tietz. 800 μl of phosphate buffer was added to 200 μl of serum. Initial absorbance (OD1) at 412 nm was measured. 100 μl of Ellman reagent was added to the same tube and then the second absorbance (OD2) was measured (Tietz, 1969).

Calculation:

The concentration of glutathione was expressed in units of mmol/g of protein.

C / 1000 = (OD2-OD1) / 13600 x E1 x 5/2 x ½

13600: Molar extinction coefficient of yellow color formed during the

interaction of GSH and DTNB.

E1: If a band with a width greater than 6 nm is used, a derivative extrusion

coefficient is used that corrects for both light path and bandwidth differences.

The width of the tape we use is 2 nm.

It was taken as E1=1 in the calculations.

1000: conversion coefficient to mmol.

C: mmol / glutathione (mg/dl)

2.3 Catalase (CAT) activity measurement

The Aeibi method was utilized in this investigation to ascertain CAT activity. First, 1.4 ml of 30 mM hydrogen peroxide (H_2O_2) was placed in the blank tube and 0.1 ml of phosphate buffer was added to it. 1.4 ml of 30 mM hydrogen peroxide (H_2O_2) was placed in the sample tube and 0.1 ml of sample was added on it and the tubes were vortexed. The absorbance values were then measured twice at 240 nm at thirty-second intervals by the spectrophotometric method (Aeibi, 1948).

Activity account:

Activity= (2.3/ΔX) × [(log A1 / log A2)]

ΔX: 30 seconds

2.3: 1mmol optical density of H H_2O_2 in 1cm light path.

2.4 Glutathione reductase (GR) activity measurement

The activity of glutathione reductase was quantified according to the method of Goldberg and Spooner (Jiang and Zhang, 2002).

2.5 Glutathione S-transferase activity measurement

Glutathione-s-transferase activity was performed using the determination method suggested by Mannervik et al. (Mannervik and Guthenberg, 1981).

2.6 Glutathione peroxidase (GPx) activity measurement

Beutler's method of determination was applied to determine glutathione peroxidase activity (Beutler et al., 1983).

2.7 Measuring the level of malondialdehyde (MDA)

Malondialdehyde, Lipid Peroxidation's final product as a result of the reaction of fatty acids with free radicals, was measured with thiabarbituric acid (Jentzsch et al., 1996). 200 ml of serum was placed in the sample tube. 800 ml of phosphate buffer, 25 ml of BHT solution and 500 ml of 30% TCA were added to it. The tubes were mixed by vortexing and kept on ice for 2 hours. It was then centrifuged at 2000 rpm for 15 minutes. 1 ml of the obtained supernatant was taken and transferred to another tube. Then, 75 ml of EDTA and 250 ml of TBA were added to this mixture. The tubes were mixed by vortex again and kept in a hot water bath for 15 minutes. The tubes were then brought to room temperature. Absorbance values were read in the spectrophotometer at 532 nm.

Calculation of malondialdehyde level:

C=F× 6.41× A

C: Concentration

F: Dilution factor

A: Absorbance

3. Results

While the MDA level was found to be 0.0012 (mmol/L), the SOD activity was 1377.483 (U/L); reduced glutathione (GSH) level 725.251(mg/dl); catalase (CAT) activity 1275.035 (U/L); glutathione reductase (GR)

1439.041 activity and glutathione peroxidase (GPx) activity were found to be 1215.055 (U/L).

Table 1. MDA level and SOD, GSH, CAT, GR and GPx activities

Parameters	
GPx(U/L)	1215.055
MDA (mmol/L)	0.0012
GSH (mg/dl)	725.251
CAT (U/L)	1275.035
SOD (U/L)	1377.483
GST (U/L)	1288.015
GR (U/L)	1439.041

4. Discussion

MDA is a marker reflecting oxidative stress. Also , MDA shows lipid peroxidation (Sudha et al., 2001). Antioxidants fight free radicals and also reduce the effects of free radicals. SOD, CAT, GST, GR (glutathione reductase), GPx (glutathione peroxidase) and GSH are the main antioxidants. Antioxidant enzymes are protective type enzymes that increase their activity under oxidative stress conditions. Antioxidants are required as compensatory mechanisms of oxidative stress. SOD is a very powerful antioxidant enzyme (Güneş et al., 2020). CAT is one of the most important antioxidant agents (Gündüz et al., 2021). GSH level protects the cell against reactive oxygen molecules (Gündüz et al., 2021).

Polyphenols have very strong antimicrobial and antioxidant activity. So, these are natural compounds versus synthetic foods.

Nitric Oxide (NO gas) is a substance that provides the circulatory system throughout the body and also supports energy increase. It is also a molecule of life that helps in many other functions of the body. L-Arginine amino acid is a source of NO. The use of NO reduces intimal thickening in atherosclerosis. Thus, in hypertension, L-Arginine also reduces blood pressure as it increases nitric oxide production. As a result, it reduces the proliferation rate in vascular smooth muscle cells (Moncada and Higgs, 1993).

In literature studies, *Morinda citrifolia* (Noni) has found to alleviate DNCB-induced atopic dermatitis in NC/Nga mice by modulating immune

balance and skin barrier function (Kim et al., 2020). In another study, *M. citrifolia* has reported to have antitumor, antiproliferative, proapoptotic, antiangiogenesis, antimigratory, anticancer, anti obesity, anti-inflammatory and immunomodulatory activities. Additionally, thanks to its many properties, it may be a possibly useful medicinal plant for cancer treatment (Chanthira Kumar et al., 2020; Yilmaz et al., 2020).

Some antioxidant activities such as SOD, GST, GR, GPx, GSH and CAT were found to be high in the noni fruit. On the other hand, level of MDA was found to be low. Antioxidant activities were found to be very high in the noni extract. We think that this study will contribute to the literature. More future clinical studies are needed. Thus, the role of *M. citrifolia* in the treatment of cancer and other diseases may be more important. Noni fruit or its extract can be consumed against oxidative stress.

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Chapter 5

Effect of Some Heavy Metals (Cobalt and Cadmium) on Biochemical Events

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Abstract

Heavy metals have been spreading into the atmosphere and soil through human activities and natural means since ancient times. Earthquakes, volcanic eruptions, floods, etc. Heavy metals entering surface and subsurface waters for various reasons spread throughout the ecosystem. But natural spread also has its limits. Water and air pollutants from industrial activities are more likely to be chemically released into the environment. Industrialization has led to heavy metal pollution, which has increased over time. We are exposed to more than 35 metals in our external environment, 23 of which are heavy metals. The definition of heavy metal is used for metals with a density above 5 g/cm^3. Lead (Pb), cadmium (Cd), chromium (Cr), iron (Fe), cobalt (Co), copper (Cu), nickel (Ni), mercury (Hg) and zinc (Zn) are frequently encountered. Heavy metals are released into the atmosphere from a variety of sources and through various process steps. Heavy metals entering the atmosphere from various sources can affect the ecological balance by mixing with the soil, surface waters, and even groundwater through dry and wet accumulation.

1. INTRODUCTION

Toxic metals can be defined as heavy metals regardless of their atomic weight or density (Singh et al., 2011). Density is often considered the determining factor, and metals with a density above 5 g/cm^3 are defined as heavy metals (Järup, 2003). Heavy metals are a group of environmental chemicals that are ubiquitous and non-biodegradable (Wu et al., 2016).

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Pollution of the biosphere with heavy metals is a serious problem for the world. The release of these metals into the environment has increased significantly, mainly due to human activities related to fossil fuel use, ore mining and processing, municipal waste, fertilizers, pesticides and urban wastewater (Basile et al., 2012).

Assessment of the risks of chemicals to humans is based on the assumption that these chemicals are genotoxic or non-genotoxic. Genotoxic carcinogens and their metabolites are thought to act through a mechanism of action that involves direct and possibly irreversible covalent binding to DNA, whereas non-genotoxic carcinogens or their metabolites are thought to act through a mechanism of action that involves covalent binding to DNA. As noted in the risk and hazard definitions above, for risk assessment purposes, lifetime exposure to genotoxic carcinogens at threshold or no-potential-effect doses is a linear "low-dose response." The threshold below which no significant evoked effects are observed. It is considered a non-genotoxic carcinogen. This suggests that homeostatic mechanisms can compensate for biological perturbations caused by low intake levels, and that structural or functional changes that could lead to adverse effects, including cancer, are observed only at higher intake levels (Dorne et al., 2011).

Heavy metals affect the human body by causing the production of reactive oxygen species (ROS) and contributing to oxidative stress toxicity. This may affect some enzymes, organelles and components involved in metabolism, detoxification and damage repair, leading to DNA damage, carcinogenesis or apoptosis (Tchounwou et al., 2012). This damage, which occurs during intracellular metabolic processes, affects organs and systems, causing kidney, cardiovascular, developmental and neurological diseases, reproductive disorders and various types of cancer (Goyer and Clarkson, 1996).

1.1 Heavy Metals

"Heavy metals" are metals with a density of 5 g/cm^3 or more, which have been used since ancient times when humans began to process metals. This allows 53 out of 90 naturally occurring elements to be identified as heavy metals (Abernathy et al., 1999; Holleman, 2019). Metals are elements that readily donate electrons to form bright cations with characteristic colors. 84 of the 118 elements in the periodic table have metallic properties. Most metals are used in industry due to their good electrical and thermal conductivity and good machinability. Heavy metals are generally defined as metals with a density above 5 g/cm^3, but in medicine, this definition is expressed as metals that have toxic effects on biological systems, regardless

of the atomic weight of the element. There are more than 60 metals in this group, including lead, cadmium, chromium, iron, cobalt, selenium, copper, nickel, mercury and zinc (Öztoprak, 2018).

All soils contain almost every metal on the periodic table, but the proportions of metals in soil vary greatly. Heavy metals in soil;

1) It binds to the crystal structure of primary and secondary minerals,

2) It binds to the surface of secondary minerals such as clay, oxide, carbonate,

3) It binds to organic matter in the soil and

4) They occur free and as ions and are water-soluble organic and inorganic compounds (Peters, 1987; Alloway, 2013; Davidson, 2013; Young, 2013).

However, heavy metals are generally found stable on Earth as compounds containing carbonates, phosphates, silicates and sulphides (Rose et al., 1979; Kahvecioğlu et al., 2003; Young, 2013). However, thanks to human interventions such as pH, temperature, soil biology, agricultural methods used, products grown, new chemicals added to the soil and irrigation, heavy metals that are tightly bound to soil minerals can be converted into soil minerals. It can transform into forms that can be absorbed by minerals (Brümmer and Helms, 1983; Jorgensen, 1993; McLaughlin et al., 1994; Cieśliński et al., 1996; Weggler et al., 2004. Jiang et al., 2008).

Naturally occurring heavy metals on Earth are released from local areas to various environmental regions through natural events such as volcanic eruptions, atmospheric precipitation, rock collapse, sea salt dispersion, forest fires, erosion and wind (Ali et al., 2021). Anthropogenic releases of heavy metals date back to ancient times, when they were used for various purposes such as jewelry, hookahs, and weapons, and have been used for centuries without any known biological effects on humans. Their increasing use with the age of industrialization has led to a rapid increase in their distribution and increased contact with living organisms. Compared to natural processes, anthropogenic activities release three times more chromium and arsenic, six times more lead and mercury, eight times more cadmium and 19 times more selenium into the soil (Kahvecioğlu et al., 2003). The industrial sectors that most effectively emit heavy metals into the environment include the steel industry, waste incineration and power plants, fertilizer industry, chlor-alkali industry and glass manufacturing (Kahvecioğlu et al., 2003).

A significant portion of heavy metals in industrial wastewater is found in sewage sludge, and the dissolved portion ultimately flows into surface

waters and oceans. From there, heavy metals mix with drinking water, air and soil and enter the food chain. Since heavy metals, which accumulate from the first step of the food chain to the top, have very long half-lives and cannot be easily metabolized, they tend to accumulate in the tissues after entering the human body through breath, skin and mouth (Kahvecioğlu et al., 2003; Bakar and Baba, 2009). Heavy metals show their effects by binding to the sulfhydryl groups of enzymes and proteins and forming reactive oxygen species (ROS). Active oxygen species that reduce the functionality of important macromolecules also cause oxidative stress. Oxidative stress can be followed by disruption of cell membrane structures, inhibition of enzymes and proteins, structural changes, DNA damage, apoptosis and carcinogenesis (Babali-mood et al., 2021).

While heavy metals accumulate and affect target organs in the body, they also affect many metal-sensitive organs and systems. These effects include organ dysfunctions, metabolic disorders, changes in hormonal effects, congenital diseases, immune system dysfunctions, cancer, etc. (Öztoprak, 2018; Babali-mood et al., 2021). Heavy metals are found in very low concentrations in the body and are therefore considered trace elements. Trace elements are divided into physiological and toxic elements according to their presence in the body. Various physiological trace elements such as copper (Cu), selenium (Se), zinc (Zn), molybdenum (Mo), manganese (Mn) and cobalt (Co) play important roles as cofactors in some enzymes, vitamins and hormones. These physiological trace elements must be present in the body at a certain concentration (1 to 10 ppm (mg/L)), and their deficiency not only causes various diseases but, if necessary, can also cause toxic substances such as heavy metals to remain in the body. Toxic heavy metals such as cadmium (Cd), lead (Pb), mercury (Hg), arsenic (As) and chromium (Cr) have no important function in the body and can harm humans even at very low concentrations. Toxic (1-10 ppb (μg/L)). These are metals that have toxic effects on the body (Tchounwou et al., 2012; Öztoprak, 2018).

1.2 Heavy Metal Sources and Ways of Distribution in Nature

Sources of heavy metals occur naturally and are not due to human influence. These metals have always entered our world through meteorites from the formation of the Earth to the present day, and they continue to enter our world in the same way, albeit to a lesser extent. While the Earth was still a mass of lava, due to its density, these metals turned into liquid magma and a significant portion of it accumulated in the center of the Earth. Some of it remained in the magma and mantle layers. The accumulation of heavy metals in the Earth's crust continued as meteor showers continued to

impact the Earth even after cooling began (Photos, 1989; Kabata-Pendias and Pendias, 2000). In addition, heavy metals from magma and mantle layers still reach the earth's surface, especially through volcanic eruptions, earthquakes and rock fractures, and are dispersed by precipitation (Lahd Geagea et al., 2008; Pirrone and Mason, 2009).

Another important source is industrial facilities that use heavy metals or products containing heavy metals in their operating processes. Various heavy metals found in such products used in industrial facilities spread to the environment, especially through water, precipitation, air and leakage from the storage areas used by the company (Nriagu and Pacyna, 1988; Lehndorff and Schwark, 2008). For this reason, heavy metal pollution can be seen mainly in developed countries. Many studies have shown that heavy metals accumulate more in the air, soil and water of developed countries in the Northern Hemisphere than in countries in the Southern Hemisphere (Birke and Rauch, 1999; Ikem et al., 2008). Moreover, in the Southern Hemisphere, a significant portion of atmospheric heavy metals are natural, whereas in some places in the Northern Hemisphere, up to 80% are man-made (Buat-Ménard, 1984).

Highways are another important source of heavy metal emissions into the environment. An accumulation occurred for approximately 100 years, until the use of unleaded gasoline was phased out in countries around the world in recent years by Blay-Miguel and colleagues (Puxbaum and Limbeck, 2004). In addition, cadmium released from vehicle tires is an important pollutant that causes problems on highways and roads and in crowded urban areas due to vehicle use (Jankiewicz and Adamczyk, 2007; Rao et al., 2016).

Another source that releases heavy metals into the environment, especially agricultural lands, is the agricultural sector. Chemical fertilizers, pesticides and agricultural machinery commonly used in agricultural production processes around the world are also important sources of heavy metals (Goodroad and Caldwell, 1979). Many heavy metals, especially cadmium, found in phosphate fertilizers, are polluted in agricultural lands by the farmers themselves. Phosphate fertilizers produced worldwide contain high amounts of cadmium, depending on the source, and ongoing agricultural activities lead to continued cadmium accumulation in agricultural soils (Dahl et al., 2008).

In addition, many pesticides used against diseases, pests and weeds in agriculture contain heavy metal active substances and/or additives (Hoch, 2001). Even if the excessive use of such substances is ignored, the heavy metals contained in these substances can be mixed directly into the soil with

rain and the soil of some parts of the plant, even when used in large quantities or applied to the plant surface. It then accumulates in the soil. Moreover, in many countries, especially in developed countries where agriculture is intensive, a significant number of farmers use unnecessary and excessive amounts of pesticides (Matschullat, 2000). For this reason, many researchers continue to work on some methods to reduce the use of agricultural pesticides, such as critical thresholds, the use of alternative methods, natural control agents and the use of natural medicines (Alengebawy et al., 2021).

1.2.1 Some Heavy Metal and Its Effects

1.2.1.1 Cobalt

Cobalt is hard, shiny silver and has a brittle structure. It is a ferromagnetic metal and its behavior is similar to nickel and iron. Magnetic permeability is about two-thirds that of iron. Pure cobalt is obtained by reducing the resulting compound with aluminium, carbon or hydrogen, and in its pure form, it has the highest known Curie temperature (1121 °C). For this reason, it is used in the production of materials that require magnetic properties at high temperatures (Fang et al., 2017). Cobalt (Co) is one of the transition elements in group IX B of the periodic table, with an atomic number of 27 and a density of 8.90 g/cm^3. Cobalt is found at 0.001% in the Earth's crust and occurs as a byproduct of other metals, especially copper. The main cobalt ores are cobaltite (CoAsS) and erythrite ($Co_3(AsO_4)_2$) (Anonima, 2023). Although it is found everywhere in nature, it constitutes only 0.001% of the earth's crust. It is found in small amounts in rocks, soil, plants, animals and nodules on the seabed. Metamorphic rock formations are based on cobalt concentrates. Therefore, the cobalt content in metamorphic rocks depends mainly on the amount of the element in the volcanic or sedimentary rock source. Cobalt is obtained as a by-product of mining, particularly from ores of copper, nickel, silver, gold, lead and zinc. Cobalt is one of the most basic elements in the world. Although pure cobalt has little use, its use as an alloying element and chemical resource makes it strategically important. It has important application areas in industrial and military applications. Cobalt is most commonly used in superalloys and special steels used in the rocket industry, as well as in rechargeable batteries for portable electronic devices such as cell phones and laptops. Its compounds are used as catalysts in the petroleum and ceramic industries, as pigments in paints, and as drying agents in inks and varnishes.

Cobalt, in the form of cobalamin, is an important component of vitamin B12, which is essential for red blood cell production and preventing

pernicious anemia. This means that it belongs to the group of trace elements necessary for humans. Cobalt is abundant in organ meats such as liver and molluscs such as oysters and mussels, which contain vitamin B12 (Goyer and Clarkson, 1996). Human cobalt intake varies greatly from person to person and is generally between 5 and 50 μg/day. Most of the cobalt consumed by humans is inorganic and represents only a small fraction of vitamin B12. Cobalt compounds other than cobalamin can cause toxic effects on living organisms (Aitio, 2015).

Exposure of the general population to cobalt occurs primarily through the consumption of food and drinking water. However, because cobalt is used in a variety of applications, you may come into contact with cobalt in consumer products. Sources of exposure include leather products (shoes, jewelry, clothing), jewelry, mobile phones, chemicals, cutting oils, cement, laptops, etc. takes place. Cobalt is the most common source of exposure that causes dermatitis when used outside of work. You may also be exposed to cobalt in cosmetics. Studies have shown that eye shadows, especially those produced in China, contain cobalt concentrations above 10 μg/g. Cobalt concentrations of up to 1.30 μg/g in lipstick and 2.2 μg/g in skin creams have been measured (Anonimb, 2023).

Cobalt salts are used in paint dryers, as catalysts and in the production of many pigments. It has been used for centuries to color porcelain, glass, ceramics, tiles and enamel (Goyer and Clarkson, 1996).

Cobalt is beneficial for humans because it is part of vitamin B12, which is essential for human health. Cobalt stimulates the production of red blood cells and is therefore used to treat anemia in pregnant women. However, excessive cobalt intake causes erythropoietic effects. Chronic oral administration of large amounts of cobalt to treat anemia can lead to the development of goiter. Epidemiological studies have shown that the incidence of goiter is higher in regions with high cobalt concentrations in water and soil. This goitrogenic effect has been demonstrated when administered orally to children at a dose of 3-4 mg/kg during the treatment of sickle cell anemia (Goyer and Clarkson, 1996).

Cobalt (+2) ions are genotoxic, and some types of cobalt have been shown to have carcinogenic effects in laboratory animals. The main target organ of cobalt in humans is the respiratory system. In the workplace, workers are exposed to inorganic cobalt compounds primarily through inhalation of dust. Observed health effects include decreased lung function, asthma, interstitial lung disease, wheezing, and shortness of breath (Aitio, 2015). Other target organs include the hematopoietic system, cardiac muscle,

thyroid, and nervous system. Patients with cobalt alloy implants, especially metal hip prostheses, may experience endogenous cobalt exposure, which may be associated with local or systemic toxicity (Aitio, 2015). Cobalt added to beer to increase foam has also been reported to cause symptoms similar to cardiomyopathy and heart failure (Goyer and Clarkson, 1996).

Cobalt does not accumulate in the body and is mostly rapidly excreted in the urine. Cobalt concentrations in urine or blood can be used as biomarkers of recent exposure to soluble cobalt species (Aitio, 2015). At relatively high exposures, there is a rapid and sustained decrease in excretion for approximately 24 hours, followed by a more gradual phase of elimination. At low exposure levels, urinary cobalt excretion is relatively constant but may be 4 to 10 times higher than in unexposed individuals. Slow elimination may continue for at least 4 weeks after exposure. Changes in blood cobalt concentrations are smaller but do occur post-exposure (Alexandersson, 1998). In healthy people, the average blood cobalt concentration is 0.6 μg/L and the urine cobalt concentration is 0.42 μg/g creatinine (Anonimb, 2023).

1.1.1.2 Cadmium

Cadmium is a silvery-white, soft, electropositive and malleable metal with many properties similar to zinc. Cadmium and its compounds are highly toxic substances. Cadmium does not occur naturally as a single mineral. It is found in very small amounts in zinc minerals as $CdCO_3$ or CdS. Cadmium is found in less than 1 mg/kg in the earth's crust (EFSA, 2009). Cadmium (Cd) is a toxic heavy metal with atomic number 48 and density 8.65 g/cm3, located in the transition metals section of group II B of the periodic table. It is found in the earth's crust at concentrations of 0.1-0.5 ppm and is generally obtained as a byproduct of zinc, lead and copper production (Faroon et al., 2013). Cadmium forms compounds in the +2 oxidation state and is not found in pure form in nature. Compared to other heavy metals, cadmium has the highest water solubility. In terms of its chemical properties, it is between zinc and mercury and is close to zinc. When it reacts with acids, it forms salts such as cadmium nitrate, cadmium chloride and cadmium sulfate, which are easily soluble in water. Cadmium does not dissolve in alkaline environments such as alcohol (Öztoprak, 2018; Anonim, 2023). The amount of cadmium released into nature is 25,000 to 30,000 tons per year, of which 4,000 to 13,000 tons come from human activities. The main source of cadmium that affects human life. Tobacco smoke, refined foods, hookah, coffee, tea, coal combustion, shellfish, fertilizers used during the seeding stage, and smoke generated during industrial production. Cadmium is especially used in rechargeable batteries and alloys (EFSA, 2009).

Cadmium has very soft physical properties, so it can be easily processed into wire rod, plate, etc. can be processed into . Cadmium is often used as an electrode component in the production of Ni-Cd batteries. Cadmium compounds are used as pigments in engineering plastics, ceramics, glasses, enamels and toners. Cadmium has excellent corrosion resistance, so it is widely used as a coating material for metals such as steel and iron. Cadmium is also used as a plastic stabilizer, heat and light stabilizer in polyvinyl chloride (PVC) production, and lawn fungicide (Faroon et al., 2013; Aitio, 2015). Cadmium ions exert their effects on oxidative stress by binding to antioxidants containing sulfhydryl groups such as: B. Glutathione. It also binds to metalloenzymes that bind to cadmium, zinc, magnesium, selenium, calcium and iron metals and destroys their functionality. This inhibition of the enzymes glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) increases free radicals. Oxidative stress is necessary for cadmium toxicity. It promotes tumor development through effects on mutagenesis and cell cycle. The main carcinogenic mechanisms caused by cadmium include induction of inflammatory processes, oxidative stress, delayed apoptosis, DNA damage, decreased DNA repair capacity, altered gene expression, cell proliferation, and abnormal DNA methylation (Genchi, 2020).

Because cadmium is chemically similar to zinc, it binds to the zinc site in the active site of histone demethylases and to the zinc finger motifs of steroid hormone receptors and other DNA-binding molecules, causing changes in academic functions. There are epidemiological studies showing an association between occupational (inhalation) exposure to cadmium and lung cancer. For this reason, IARC classifies cadmium and its compounds as "Group I substances" that are carcinogenic to humans. There is insufficient evidence that it is carcinogenic when ingested (Sheikh et al., 2023). The more soluble cadmium chloride, cadmium oxide fumes and cadmium carbonate are the most toxic cadmium compounds. Exposure to cadmium oxide fume causes metal fume fever, characterized by fatigue, headache, chills, dry throat and nose, irritability, and fever. Inhalation of cadmium vapor or other heated cadmium-containing substances may cause acute chemical pneumonia and pulmonary edema. Inhalation of high doses can be fatal (Goyer and Clarkson, 1996; Anonymous, 2020).

Cadmium, carried in the blood by binding to albumin, is mostly taken up by the liver, where it induces metallotia (MT) synthesis. Cadmium metallothiene complexes do not readily cross the placental barrier or the blood-brain barrier and therefore have very low toxicity to the fetus and central nervous system. Cadmium accumulates in the body, especially in the

liver and kidneys, but also in the bones, pancreas and muscles. The kidney is considered a critical organ after long-term exposure (Aitio, 2015).

Long-term exposure to cadmium causes lower respiratory tract fibrosis, alveolar damage leading to emphysema, chronic bronchitis, and chronic obstructive pulmonary disease (COPD). Destruction of alveolar macrophages is responsible for the lesions occurring in the lungs. The released enzymes cause irreversible damage to the alveolar basement membrane, including septal rupture and interstitial fibrosis. Cadmium has been found to increase pulmonary toxicity by reducing alpha-1-antitrypsin activity (Goyer and Clarkson, 1996; Anonymous, 2020).

People with severe cadmium nephropathy may experience excessive calcium excretion associated with kidney stones and increased urine output. Skeletal changes are likely related to calcium loss and include bone pain, osteomalacia, and osteoporosis. Itai-Itai disease is the first disease described to be caused by cadmium poisoning, including severe bone deformities and symptoms of chronic kidney disease (Goyer and Clarkson, 1996; Anonymous, 2020).

Epidemiological studies have shown an association between occupational (inhalation) exposure to cadmium and lung cancer. Results from an epidemiological study of 20,459 participants in Belgium and the United States showed consistent evidence that lifelong environmental cadmium exposure causes lung cancer through creatinine and urine cadmium measurements (Nawrot et al., 2020). Another cohort study reported that the mean blood cadmium concentration of breast cancer patients was more than 3 μg/L, i.e., 2.35 times higher than that of controls. The same group of researchers investigated the relationship between the presence of cadmium in the blood and nasopharyngeal cancer and reported that the average cadmium concentration in the blood was significantly higher in cases than in controls (Peng et al., 2015). Other studies have also been reported showing that environmental exposure to this toxic metal may be associated with prostate, bladder, pancreatic, and kidney cancers (Genchi, 2020).

Conclusion

Heavy metals have significant effects on human health, even in trace amounts. Heavy metals are widely used in our daily life and industry. Contact with heavy metals has increased, especially with the increase in industrial activities. The release of heavy metals into the atmosphere, soil and water, whether natural or human-made, poses a great danger to humanity. This risk increases depending on the dose and duration of exposure, and may

even lead to the development of tumors and cancer. Serious health problems occur especially after exposure during childhood and accumulation in the body for many years. Studies on arsenic, cadmium, nickel and chromium have shown that these metals are highly carcinogenic to humans. Depending on the degree of exposure, they can affect biochemical processes in the body and cause disorders.

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Chapter 6

Physical Chemical Properties of Some Heavy Metals (Arsenic, Lead And Copper) and Their Effects on Health

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Abstract

Heavy metals are associated with industrial processes, environmental pollution and natural resources and can have serious adverse effects on human health. Due to their toxic properties and their tendency to accumulate in biological systems, these metals can damage vital organs such as the nervous system, kidneys and liver. Through their chemical reactivity and by affecting biological systems, they can disrupt enzyme function, cause DNA damage and have carcinogenic properties. Due to their bioaccumulation, long-term exposure, even at low levels, can lead to serious health problems.

Arsenic causes serious health problems with long-term exposure. Chronic arsenic exposure can lead to skin lesions, cancer, circulatory system problems, nervous system damage and damage to internal organs. Arsenic from water sources can be a major health problem, especially in some areas.

Lead exposure occurs mainly through paint, water pipes, paint in old buildings, industrial waste and some foods. When it enters the body through

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inhalation or from sources such as water and soil, it is harmful to humans, especially children and fetuses. It negatively affects brain development and causes mental retardation, behavioral problems and learning difficulties. In adults, lead exposure can cause nervous system damage, high blood pressure, kidney problems and reproductive problems.

Copper is essential for the body but can be toxic in excessive amounts, causing gastrointestinal problems, liver damage, kidney problems and neurological disorders.Copper is commonly found in water pipes, some pesticides, copper containers and some foods. Uncontrolled exposure to these metals can lead to health problems, so it is important to limit or eliminate their sources and intake.

Long-term exposure to these heavy metals can cause serious health problems. Therefore, controlling heavy metals, reducing environmental contamination and minimizing exposure is critical for human health. To protect human health, drinking water sources should be controlled, food should be consumed from safe sources and appropriate measures should be taken to reduce exposure.

INTRODUCTION

Health; It is a phenomenon that has become a problem since the existence of human beings and is in constant search. Throughout our lives, it is expected to be a step towards a solution rather than a problem, which is why many developments in the field of health continue today. The negative external factors that our body is exposed to are increasing day by day. The understanding of healthy life will come to good places with the effect of scientific studies.

Heavy metals can become toxic even at low concentrations. They also have negative effects on human health. Some heavy metals (Arsenic, As; lead, Pb; copper, Cu; etc.) are sometimes necessary for us, but they can be toxic even if they are in excess in our bodies (Dağhan, 2011). Environmental pollution caused by heavy metals is a study that is in the focus of everyone. These current studies have drawn attention to the contents and reflections of heavy metals, their harm to the external environment and living health, the identification of polluted environments and the methods and possibilities of purification of these environments in order to prevent their negative effects on nature and living health. Therefore, the nature polluted by heavy metals can be purified by certain methods (chemical, physical, etc.) in order to prevent adverse effects on human health (Kocaer and Başkaya, 2003). Heavy metals can enter our body in various ways. Unfortunately, when they are in excessive amounts compared to our body density, removal from our body is not so fast, this excess has a toxic effect on our body (Pak J Bot,

2008, Biotechnol Adv, 2006). In this study, the physicochemical properties of some heavy metals such as arsenic (As), lead (Pb) and copper (Cu) and their effects on human health were investigated in detail.

1.Physical and Chemical Properties of Arsenic

Arsenic, a heavy metal with atomic number 33, melting temperature 887.15 °K, boiling temperature 1093.15 °K and mass number 74.92 g/mol, is in the VA group in the periodic table. It is a heavy metal between metal-metal in terms of structure. Since arsenic has both of these properties (metal-ametal), it is called a semi-metal in chemistry (Anal Chim Acta, 2003). Arsenic, which is not very important for humans, is a natural component of nature. It is toxic in non-organic form. Within the framework of the impact of industrialization, it is possible to find arsenic in chemical reactions of fossil fuels, in synthetic fertilizers, in the elimination of problems of unnatural wastes, almost everywhere (Proteomics, 2006). The general distribution of arsenic in nature (the earth's crust) is about 6 milligrams per kilogram, making it one of the most common elements in nature (Bissen, M., and Fritz H.F., 2003). In addition to natural arsenic in the form of yellow and gray crystals, it is common to find arsenic in nature in compounds with the elements sulfur (S), chlorine (Cl) or oxygen (O). Arsenic, which forms compounds with the elements mentioned above, appears in non-organic form. As I mentioned above, arsenic in its non-organic (inorganic) form is toxic. It is possible to find hydrogen (H) and carbon (C) elements in the bond structures of arsenic classified as organic. It is also possible to find non-organic arsenic in some rocks and soil, especially in ores containing copper (Cu) or lead (Pb) (Erdoğan, 2005). Normally, organic arsenic is encountered in drinking water; however, the organic form of arsenic is less important in terms of urgency because it is metabolized and is no longer toxic by methylation (Singh, T. S., and Pant, K.K., 2003).

1.1 Arsenic Sources

Arsenic in nature can be formed as a result of active volcanic movements, as well as natural processes, as a result of human events such as industrialization every day, as a result of pollution in the air we breathe, the soil we step on, and drinking water (Erdoğan, 2005).

1.1.1 Natural Resources

Arsenic, which is abundant in the earth's crust, is found in air, water, soil and living structures in highly variable parameters (DIP, A., 2001).

Some of the minerals are rich in arsenic and as a result of the weathering of minerals, arsenic in the soil passes into the water in the soil (Fujimoto, M., 2001). In some areas of heated water, arsenic, which is a heavy metal, is observed in high amounts (DIP, A., 2001). While arsenic concentration in salty waters is at low levels, it is at much higher levels in waters such as hot springs compared to salty waters. A certain part of the natural arsenic is mixed with atmospheric gases, and the remaining part can be formed due to the evaporation of high temperatures as a result of the movements of volcanic mountains. It is also possible to come across the synthesis of arsenic as a result of evaporation in the oceans and seas. Some fires, especially forest fires, can mix with nature. If we need to talk about more important sources, the most important of these is coal from fossil fuels. Depending on the types of coal, it is also possible to find different amounts of arsenic in its content (Erdoğan, 2005).

1.1.2 Non-natural Resources

The contamination of water, air and soil with arsenic as a result of human activities is a well-known phenomenon. These human behaviors can be classified as the discharge of unnatural wastes, the smelting of arsenic-rich minerals, the burning of some fossil fuels such as coal, and the use of arsenic in some industries (Leist, M., Casey, R.J., and Caridi, D., 2000). The unconscious release of arsenic-containing industrial wastes into nature is effective in the pollution of water and air as a result of natural events. As a result of these behaviors, people actually expose themselves to toxic effects with their own hands. Therefore, these unnatural sources will pollute the nature with more arsenic (Chakravarty, S., Dureja, V., Bhattacharya, G., Maity, S., and Bhattacharjee, S., 2002). Arsenic is released from the smelting of some minerals (copper, lead, nickel, zinc, etc.). Therefore, it is assumed that a large amount of arsenic is formed annually. Arsenic has also been found in abundant amounts in the soil in the light of mining studies in some geographical regions of the world (Smedley, P.L., Kinniburgh, D.G., 2002).

As a result of the burning of some fossil fuels in factories and households, arsenic oxide (As O46) enters the air and arsenic emission occurs. The mixing of ash waste resulting from the combustion of fossil fuels into the soil is also an activity that contributes to soil pollution. The burning of waste oil is an activity that causes less emissions compared to the burning of coal. Oil, which is a fossil fuel, contains a small amount of arsenic (0.134 mg/kg). Currently, arsenic compounds are used to produce glass in organized industries. This contributes to a certain degree of sensitivity of the resistive strength of the material and better wear conditions. In addition, it is known

that arsenic is used in the production of instruments that absorb toxic gases and give clean air to nature and in industries such as light technology (Fujimoto, M., 2001, Leist, M., Casey, R.J., and Caridi, D., 2000).

Some arsenic-containing chemicals (insecticides, herbicides) used in the agricultural sector have caused arsenic contamination of the soil. Since these chemicals contain high levels of non-organic arsenic compounds such as calcium arsenate, sodium arsenate and zinc arsenite, they have led to excessive arsenic residues. When we look at the agricultural sector, these practices are used by many countries to protect plants in forestry activities, although these practices remain in history. In a country like the United States, a high proportion of arsenic consumption is used for conservation purposes, as in the forestry sector (Leist, M., Casey, R.J., and Caridi, D., 2000).

2.Toxicity

Many formations containing arsenic in their structure are toxic. The most toxic of these formations is known as AsH3 (Arsin gas). If we consider the exposure time to this gas, it can be fatal (250 mg/m3) in a short time like 30 minutes. If we look at some other formations; NaAsO2 (sodium arsenate) between 14 and 18 mg/kg, NaNO3 (sodium arsenite) 4.5 mg/kg, MMA (mono methyl arsenic acid) 1800 mg/kg, DMA (dimethyl arsenic acid) 1200 mg/kg, As O23 (arsenic trioxide) average lethal dose is 34.5 mg/kg (Bissen, M., and Fritz H.F., 2003). As a result, it has been observed that non-organic forms of arsenic are more toxic than organic ones (Ng J.C., Wang J., and Shraim, A., 2003).

3. Harmful Effects of Arsenic on Human Health

Arsenic, which has toxic properties, is absorbed in our body as a result of activities such as feeding and breathing. Although the absorption rate of non-organic arsenic in the stomach and intestine is very high, the most absorption occurs in the Intestinum tenue (small intestine). Most of the arsenic taken into our body through breathing (80%) results in absorption. Inorganic arsenic is converted into compounds that are less reactive in our body than organic arsenic. The volume of methylation in adults is approximately 400 μg/day to 500 μg/day (Bissen, M., and Fritz H.F., 2003). Mono methyl arsenic acid (MMA) and dimethyl arsenic acid (DMA) are simply excreted from the body through the excretory system. However, when the methylation rate is low, toxic effects are possible (Ng J.C., Wang J., and Shraim, A., 2003). The estimated half-life of arsenic in the human body is four days (Erdoğan, 2005).

While the kidneys and liver are the organs that are most severely affected by rapid arsenic ingestion, our brain, which we thought would not be affected, is badly affected. Arsenic taken orally unexpectedly causes many side effects in our body. The resistance of our body exposed to toxic effects decreases. Some of these symptoms include burning in the mouth, vomiting, severe abdominal pain, nausea, leg cramps and burning in the throat. As a result of these events, death occurs within a few hours as a result of heart failure and circulation. Such high doses of toxic exposure can be easily recognized by the physical appearance of the poisoned person. In daily intake, arsenic accumulates in our skin, nails and hair, which are rich in keratin. In addition, high amounts accumulate in our lungs. Studies conducted with appropriate methods for diseases have revealed that the presence of excess arsenic in the water we drink increases the risk of kidney, spleen, lung, etc. cancer. In addition, scientific experiments have shown that arsenic entering our body destroys our hormonal system (Lenoble, V., Bouras, O., Deluchat, V., Serpaud, B., and Bollinger, J.C., 2002). The presence of arsenic in drinking water above a certain dose (50μg/l) can increase our body's cancer risk up to 1 percent (Morales, K.H., Ryan, L., Kuo, T.L., Wu, M.M., and Chen, C.J., 2000).

Some of the symptoms of high doses of arsenic poisoning can be listed as hyperpigmentation (skin discoloration), diarrhea, paralysis, hyperkeratosis (flaking of the skin), weakness, cancer, some nervous system diseases, anemia, high blood pressure, some circulatory system diseases, diabetes, wear and tear of blood tissue. Among these symptoms, skin diseases are the most prominent. The cancer effect occurs in certain doses in our body after a long period of time such as ten years. Kidney, bladder, lung and liver organs are the places where cancer is found (Fujimoto, M., 2001). Our body, which is exposed to arsenic for many years, is unable to eliminate even the deformation of DNA (Morales, K.H., Ryan, L., Kuo, T.L., Wu, M.M., and Chen, C.J., 2000).

4. Physical and Chemical Properties of Lead

The element lead, with atomic number 82, atomic weight 207.19 g/mol, specific gravity 11.34 g/cm3 and symbol Pb, is a bright, dense element that conducts heat and electricity like other metals. Lead is a non-reactive transition element compared to other elements. Unlike most metals, lead is widely used industrially due to its low melting point, ease of forming, ideal alloying properties and softness. Today, lead is used in construction and sanitary materials production, architectural paints, cable production, insulation and solder production, primer paints against moisture, pesticides,

hair dyes and cosmetics, rubber industry, glass industry, automotive industry, etc. (Dündar and Aslan R, 2005).

Due to the widespread use of lead in industry, human exposure to lead has become a widespread health problem and a major problem in both developed and developing countries (Özbolat, 2016).

Lead metal is resistant to sulfuric and phosphoric acids, but not to hydrochloric or nitric acids. Organic acids such as acetic acid dissolve lead in the presence of oxygen (Boldyrev, 2018). Lead is not a very reactive element, but it dissolves slowly in water under certain conditions. Therefore, lead is more susceptible to oxidation in humid environments. Lead reacts with carbon dioxide in the atmosphere to form bird carbonate. The most common lead compounds in nature are sulfur-containing galena (PbS), carbonate-containing cerussite (PbCO3) and sulfate-containing anglesite (PbSO). Lead carbonate forms a protective layer for lead. The widespread use of lead in industry and its partial solubility also increase exposure to this heavy metal. It is becoming a major problem in both developed and developing countries. The organic form of lead to which we are most exposed is tetraethyl lead (PbC2 H5).

4.1 Possible Sources of Lead Exposure

4.1.1 Smoking and Food

For non-smokers, the biggest source of daily lead intake is food and dust. As for food, cereals and legumes can contain high levels of lead, and spices may also be contaminated with lead. The use of lead-containing foods, especially acidic foods and beverages, stored or sold in metal cans can significantly increase the lead content in food and beverages. Eating fish raised in lead-contaminated water makes it easier for people to become infected. Since alcoholic beverages are acidic and lead dissolves faster in acidic environments, the storage and handling of alcohol and alcoholic beverages in metal cans can easily leach lead to consumers. Leaded pottery and ceramics transferred from tableware to food is also a source of exposure, and smoking greatly increases lead absorption. During breastfeeding, even small amounts of lead can pass into breast milk, exposing the baby to lead (Dursun et al. 2016).

4.1.2 Lead-based paints

Direct or indirect human exposure to lead in paints is common. Toys, furniture and park playgrounds painted with lead-based paint are common sources of lead pollution.

4.1.3 Lead in soil

Lead does not normally occur in soil. However, houses painted with lead-based paint or dust from home renovations, lead-contaminated soil and soil contaminated with batteries or battery waste are all sources of lead.

4.1.4 Lead in air and dust

Lead added to gasoline to prevent engine explosions is the main source of airborne lead, and lead pollution increases with traffic density. Most airborne lead is in the form of fine particles with an average mass equivalent diameter of less than 1 μm. This indicates that some of the lead in the air is transported over long distances. Lead is removed from the atmosphere by dry or wet precipitation. The residence time of lead-containing particles in the atmosphere depends on many factors, including particle size, wind flow, precipitation and emission levels. Chipping, peeling or crumbling of lead-based paint in older homes contributes to children's exposure, especially if some young children put pieces in their mouths or lick their dusty fingers. For various reasons, lead in residential paint can also produce lead dust, which can accumulate on floors, carpets, toys and other objects, leading to human exposure. Lead-containing dust can also settle on the clothing of industrial workers, leading to exposure.

4.1.5 Lead in Water

Years ago, lead was present in tap water that was piped into the city through lead pipes. According to WHO, the lead content in tap water should not exceed 0.01 mg/l (WHO, 2000). Lead is also found in metal alloys used in the joints of copper alloy pipes, which replaced the abandoned lead pipes in the 1960s. Lead in tap water rarely comes from dissolution from natural sources, but mainly from lead pipes or household plumbing systems with lead-lined pipes and fittings. So lead pollution persists. Concentrations are higher in water that is in contact with lead for long periods of time (e.g. overnight) (Dündar and Aslan, 2005). Lead concentrations can therefore vary throughout the day, making flushing faucets before use a control mechanism. If you suspect that the pipes in your home are damaged, you should flush them every time you use hot or cold water, or by running the tap for a few minutes in the morning. Lead is most soluble in soft acidic water.

4.1.6 Occupational Exposure

Occupational lead exposure is the leading cause of lead poisoning in adults. Lead workers who manufacture and use radiation protection equipment are

constantly exposed to lead. Such workers are at high risk of lead poisoning. People working in lead-containing areas, auto mechanics, painters, potters and construction workers are generally more likely to be exposed to lead (Wani, et al., 2015).

4.1.7 Lead in household items

Some kitchen utensils, such as old pottery and ceramic pots, may contain lead. Acidic substances in these items can move with the glaze and increase the release of lead. Therefore, it is more dangerous to store acidic foods such as tomato sauce, orange, tomato and other fruit juices and vinegar in glass containers (Tchounwou et al., 2012). 1.8. Clothing and Metal Jewelry: Metal-based jewelry and various clothing accessories also contribute to lead exposure. Various metals used in clothing accessories are often used without being tested for lead. Candle wicks, costume jewelry and children's backpacks have been found to contain toxic levels of lead (Sanborn et al., 2002).

4.1.8 Clothing and Jewelry

Metal-based jewelry and various clothing accessories also contribute to lead exposure. Various metals used in clothing accessories are often used without being tested for lead. Candle wicks, costume jewelry and children's backpacks have been found to contain toxic levels of lead (Sanborn et al., 2002). 1.9. Toys and School Supplies: Some children's toys and school supplies are made from lead-containing materials (e.g. some plastics and paints) or paint materials may contain lead (Şimşek and Önal, 2019). 1.10. Folk remedies and cosmetics: Some cosmetics, especially those from the Middle East, India and Asia, may contain high levels of lead. For example, certain types of cabbage (kajal, surma, sindoor) have been reported to contain high levels of lead. Some traditional medicines and cosmetics (such as cabbage) contain lead. Moisturizers, hair dyes and some cosmetics (such as eye shadow, eyeliner and lipstick) may contain lead. Consumers therefore need to be careful to buy and use only regulated products. Various cosmetic products such as kohl, kohl (alcohol), kajal, tiro and tozali also contain large amounts of lead. Using cabbage results in repeated ingestion of particles from your hands into your eyes and mouth. Toxic levels of lead have also been reported in spices produced in some Far Eastern countries (Debnath et al., 2019).

5. Effects of Lead on Human Health

Exposure to lead causes a variety of harmful effects in humans. These effects can range from mild clinical symptoms to acute or chronic very

severe poisoning. Human exposure to lead occurs primarily through the gastrointestinal and respiratory tracts. The circumstances of the effect depend on factors such as the degree of exposure, the physiological and psychological characteristics of the person or the general condition of the tissues, organs or systems exposed to lead (Boskabady et al., 2018). The clinical manifestations and progression of lead exposure differ between adults and children. This is because organs and systems are affected differently. In addition, some people are sensitive to lead toxicity.

In addition, the diet and psychological structure of the person also affect the clinic (Çaylak and Halifeoğlu, 2010). Lead exposure is associated with many health effects in adults. Most adults with elevated blood lead levels have been exposed to lead at work. Mining, blacksmithing or welding, construction including building renovation and remodeling, metals, food and canning containers, glazed porcelain and ceramic materials, glassware, automotive, lead-acid batteries, smelting, shooting ranges, automotive battery manufacturing and disposal, car radiator repair, pottery and stained glass work are important areas of lead exposure (Özbolat and Tuli, 2016). The main routes of lead exposure are the respiratory and gastrointestinal tracts. Tetraethyl lead (Pb(C2H5)4) used in Benzin 124 is also easily absorbed through the skin. About 35-40% of inhaled lead accumulates in the lungs. 37% of lead particles smaller than 1 μm are found in the alveolar region and 50% of the lead accumulated in the respiratory tract is absorbed and enters the systemic circulation (Levin and Goldberg, 2000). Of the lead ingested through food, 5-15% is absorbed from the gastrointestinal mucosa and the rest is excreted in the feces. The intake depends on the age of the individual, pregnancy status, the availability of elements such as iron, zinc, phosphate, magnesium, etc., and thus dietary characteristics.

It is estimated that healthy people ingest up to 200 mg of lead every day through their diet. In our country, adults are reported to ingest about 70 μg of lead per day through food (Fişek and Piyal, 1991).

Lead is widely distributed in the body after exposure and disrupts various biochemical processes by binding to sulfhydryl groups and other nucleophilic functional groups and contributing to oxidative stress (Kasten-Jolly et al., 2010). If you want to assess your lead exposure, you can rank it as follows: Blood lead levels above 15 mcg/dL are associated with reproductive problems, including cardiovascular disease, neurological disorders, reduced kidney function and adverse effects on sperm and semen. Delayed pregnancy, low sperm count and motility. Blood lead levels below 10 μg/dL are associated

with decreased kidney function, increased blood pressure, hypertension and the development of essential tremor, a degenerative disease of the central nervous system. The most prominent symptom of poisoning is involuntary tremor of the arms and hands while eating or writing. There is also evidence that adults with blood lead levels below 5 μg/dl may have reduced kidney function (WHO, 2010). More research is needed to fully understand the varying health effects of lead from person to person.

5.1 Lead Metabolism

Lead is absorbed into the body primarily through inhalation, then through the mouth with food and to a lesser extent through the skin. The particle size of lead is important for inhalation absorption. Those larger than 1 μm in diameter enter the digestive tract via the mucociliary pathway of the respiratory tract. Those between 0.5 and 1 μm in diameter enter the blood via the alveoli. Of the daily intake of lead, 40% comes from cooking utensils, 16% from food and the rest from airborne dust particles (Bellinger, 2004). The World Health Organization (WHO) reports that the permissible amount of lead in drinking water is 10 μg/L. A lack of the minerals phosphorus and calcium in the foods you consume will accelerate the absorption of lead from your intestines. When sufficient calcium is present in foods, lead absorption is reduced 10-fold (Campbell and Osterhoudt, 2000). Therefore, calcium supplementation and consumption of milk and dairy products are important for people who have been or may be exposed to lead. Adults absorb an average of 10-15% of their food intake, but this can be as high as 50% in infants, young children and pregnant women. In children, intestinal absorption is the most common route and absorption is increased when dietary levels of iron, calcium, phosphorus or zinc are low.

Lead accumulates in calcified tissues due to its low phosphate solubility (Vijayamar et al., 2012). No matter how lead enters the body, it first binds to hemoglobin in red blood cells. Once bound to red blood cells, lead circulates in the body through the blood and is stored in organs and tissues. Approximately 93% of the RBCs in the bloodstream are bound to red blood cells, the remaining 6% are bound to serum albumin, and the remaining small amount is in free ionized form in plasma. The concentration of lead in plasma is more important than in whole blood for its distribution to target organs such as the brain, lungs, spleen, renal cortex, aorta, teeth and bones. Bones are the main target organ of lead toxicity. 94% of the lead consumed by adults and 73% of the lead consumed by children is deposited and stored in the bones. The movement of lead from the blood into soft tissues is slow

and takes about 4 to 6 weeks. This is not the case in the brain, where lead crosses the blood-brain barrier slowly and has a half-life of more than 12 months. The placenta does not prevent the passage of lead and the fetus is exposed to lead through the mother (Şanlı et al. 2005). The estimated half-life of lead in blood is 35 days, 40 days in soft tissues and 20-30 years in bones (Papanikolaou et al., 2005).

The bone metabolic cycle is higher in children than in adults. Older people tend to accumulate lead. It inhibits the production of osteoblasts, the bone-forming cells. It also reduces active vitamin D 1,25(OH)2D3 by inhibiting renal hydroxylase enzyme activity, which is essential for vitamin D production (Needleman et al. 2004; Piomelli et al. 2002). In other words, exposure to pathological levels of lead can cause serious health problems such as orthoporosis, bone tumors and rickets in both adults and children (Figure 3). Lead is excreted in the urine and the rest in the intestines. Breast milk has also been shown to contain very low levels of lead (Rebelo, 2016).

5.2 Acute lead poisoning

Acute lead poisoning is a rare disease. Many records show that acute poisoning can exacerbate chronic lead poisoning if large amounts of lead are suddenly released from the bones into the bloodstream. Acute poisoning occurs in the form of gastrointestinal toxicity, but Encephalopathy can also occur in children. Acute encephalopathy occurs at blood lead concentrations between 80 and 100 μg/dl (Şanlı et al. 2005). Symptoms of acute lead poisoning usually include loss of appetite, dysphagia, abdominal pain, metallic taste, constipation or diarrhea (lead sulfide can turn stools black), vomiting, hyperactivity or lethargy, ataxia, behavioral changes, convulsions, coma (Papanicolaou, 2005).

5.3 Chronic lead poisoning

In adults, there is mild gastrointestinal and central nervous system disturbance, sometimes with flaccidity of the wrists, rarely with colic. In children, poisoning is manifested by weight loss, weakness and anemia. Early symptoms in children may be mild neuropsychological impairments that adversely affect behavior and social interactions in the classroom. Chronic lead poisoning is divided into three stages: mild, moderate and severe.

5.3.1 Mild poisoning

Blood lead concentration: 40-60μg/100ml: Muscle pain, tingling numbness, fatigue, irritability, abdominal pain.

5.3.2 Moderate poisoning

Blood lead concentration: 60-100μg/100ml: Joint pain (especially at night), muscle fatigue, chills, headache, diffuse abdominal pain, loss of appetite, metallic taste, vomiting, constipation, weight loss, high blood pressure.

5.3.3 Severe poisoning

Blood lead concentration higher than 100 μg/100 ml: lead paralysis, dropping of the wrists or feet, blue-black lead streaks (Burton's streaks) with spasms of the gums and tenderness around the navel. Colic - Severe, intermittent abdominal pain. There may be tenderness around the umbilicus (Vijayakumar et al., 2012).

5.4 Effects of lead on some important organs

5.4.1 Lead and the nervous system

Lead is a neurotoxic substance. In the early years of development of the nervous system, it can cause permanent damage, particularly in areas associated with learning pathways and memory consolidation processes. Chronic exposure to lead in childhood can therefore continue to have harmful consequences into adulthood. Chronic lead exposure in the first few years of life can cause various cognitive impairments in children and may also affect neurological development and intelligence (Souza et al., 2018).

5.4.2 Lead and the Cardiovascular System

Several epidemiological and clinical studies have revealed an association between chronic lead exposure and hypertension. The study examined 543 men aged 40 to 59 years and found a significant association between lead in the blood and systolic and diastolic blood pressure. Vaziri et al. reported that chronic lead exposure in young adult rats promotes autonomic dysfunction with increased chemoreceptor sensitization, leading to marked impairment of autonomic function in the cardiovascular and respiratory systems (Vaziri et al., 2008).

5.4.3 Lead and the Urinary System

The kidneys are usually responsible for excreting toxic substances through the urine. This is one of the most important areas affected by lead accumulation. Exposure to low levels of lead at a young age has been shown to cause glomerular hypertrophy, which is characterized by

an increase in glomerular capillary volume. Lead exposure can impair glomerular development and ultimately lead to kidney failure later in life (Orr and Bridges, 2017). Lead is one of several toxic substances associated with chronic kidney disease. Lead exposure is associated with nephropathy, renal adenocarcinoma and metabolic bone defects. Chronic lead exposure causes leukocyte infiltration. 130 It causes progressive tubulointerstitial nephritis characterized by interstitial fibrosis and tubular atrophy. Lead causes oxidative stress and calcium deposition in kidney cells. We know that there are changes in distribution. Lead also binds to the renal tubules, which also has an effect. Acute exposure impairs the transport of soluble acids and amino acids within the renal tubules. A common defect of Fanconi syndrome (Hashi, 2017).

6. Physical and Chemical Properties of Copper

The element copper is found in many parts of the world and its name is derived from the Latin word for Cyprus (aes cyprium, Cyprium ore, Cyprium, later Cuprum), where it was first discovered. The heavy metal has an atomic number of 29 and a toxic weight of 63.57 g/mol. Copper has a specific gravity of 11.34 g/cm3, a melting point of 1083 °C and a boiling point of 2300 °C. (Raven, J.A., et al, 1999.) Copper is one of the essential micronutrients abundant in various rocks and minerals. It is required for various metabolic processes in both prokaryotes and eukaryotes. At least 30 copper-containing enzymes are known that function as oxygen transporters (hemocyanins) or redox catalysts (cytochrome oxidase, nitrate reductase). Copper, Cu, is a transition metal with three oxidation states: Cu+1 and Cu+2. It is classified as a heavy metal because its density exceeds 5 g/cm3.

Its colors are yellow, dark red and brown. Copper is a soft metal. Because it is a soft metal, it is easy to shape. Copper was one of the first metals used in human history. It was used to make jewelry, weapons and other necessities in everyday life. Currently, more than 13 million tons of copper are consumed. This usage makes it the second most used metal in the world. Copper is used in its pure form as well as in its compounds.

6.1 Uses of Copper Compounds and Sources of Copper Exposure

Today, more than 400 copper alloys are used. Brass and bronze alloys are widely used, especially in jewelry. Brass, bronze, nickel and aluminum alloys are also used in coin making. Among these are very high electrical conductivity, wear and corrosion resistance, and the ability to be drawn and forged from structures and materials. Copper is therefore a component of many alloys. It reacts with acidic substances such as hydrochloric acid,

nitric acid and sulfuric acid. When copper is oxidized, it forms various compounds; sulfates, nitrates and chlorides. When these compounds enter food, poisoning known as "copper theft" occurs. For this reason, copper pots are coated with tin. Copper also has antiseptic properties. Because of this property, medicines used to treat some skin conditions contain copper.

Copper compounds, especially copper sulphate (eye stone), are used in agriculture to kill microorganisms. Recently, oxidized copper chloride has been used for this purpose instead of copper sulfate. Copper compounds are also widely used in the production of rayon threads, in the ceramic, glaze and glass industries, in pharmaceuticals and coatings. Copper's chemical resistance and appearance make it a popular material for many building and decorative materials, as well as for painting ship hulls and building exteriors. Copper's properties also allow it to be used in many plaques, vases, flower pots and other materials. Due to its high melting point, copper is widely used in cookware such as teapots and pots, as well as in industrial distillation, heating and cooling systems and plumbing equipment. Another important use of copper is in transportation vehicles, where large quantities of copper and copper materials are used (Dameron, C. et al, 1999). It is used in distilled spirits, beer vinegar, petroleum and sugar industries.

6.1.1 Some Applications of Compounds

Copper acetate is used as a fungicide, textile dye and as a catalyst in some organic reactions.

Copper arsenate; insecticides, wood preservatives.

Copper carbonate; Used as paint, varnish, ceramic products, pigments.

Copper chloride is used as a catalyst for photography, deodorants, organic chemicals and petroleum products.

Copper oxide is used as a catalyst in viscose, ceramics, colored glass and chemicals.

Copper sulphate is used in insecticides, viscose, anthelmintics, dyes, leather and wood products.

6.1.2 Uses of Copper

Electrical industry; Motors, generators, dynamos, control panels, conductive materials, lighting, communications and all household appliances.

Construction industry; Construction, decorative materials and alloys.

Means of transportation; All land and sea transportation vehicles.

Industrial machinery; ventilation, heating, agricultural machinery.

7. Effects of Copper on Human Health

In addition to its use in various environmental areas, copper is also found in trace amounts in living organisms, thus playing important roles in various biological processes (Chemosphere et al, 2021). Copper (Cu) is found in almost all tissues and is involved in various metabolic reactions. It is absorbed by living organisms through inhalation of air, drinking water, digestion of food or skin contact with copper-containing compounds (Alkış, M., 2011). Copper is important for the functioning of the body, but it is also the main component of hair, soft parts of the skin, bones and some internal proportions. Copper, which averages between 50-120 mg in adults, is an essential element for the metabolic reactions of amino acids, fatty acids and vitamins under normal conditions. Copper is involved in the structure of metalloenzymes and has many functions as a biocatalyst in human metabolism.

Cytochrome c oxidase, dopamine β-hydroxylase, urate oxidase, superoxide dismutase, tyrosinase, amine oxidase and ascorbate oxidase are the main known copper metalloenzymes. It is also essential for the regular utilization of iron in the body. Without copper, iron cannot bind to hemoglobin Copper is present in all organs and tissues of the human body. Concentrations range from a few ppm to 100 ppm. It is found in high concentrations in the liver. It is also found in large quantities in various parts of the brain, heart, stomach and intestines. Copper, an essential nutrient and toxic substance, is absorbed from the small intestine. Absorbed copper is loosely bound to serum albumin and amino acids and distributed throughout the body. Copper enters the liver as copper-albumin-copper-histidine complexes and is used in the synthesis of ceruloplasmin in parenchymal cells. Approximately 90% of the copper in mammalian plasma is in the form of copper metalloproteins and ceruloplasmin. (Shorrocks, 1984) Copper is a metal that accumulates in mammalian tissues and can cause toxic effects when tissue concentrations reach critical levels. Exposure to this metal has been reported to cause pathological changes in many tissues, especially in the liver and kidneys (Alkış M, 2011). (Alkış M, 2011) The most serious copper-related poisoning occurs by mouth (Yang, J. et al, 2016).

Acute poisoning is rare. The LD50 (lethal dose) for acute poisoning by oral ingestion in humans is 100 mg/kg, but treatment up to 600 mg/kg is possible. “Menkes syndrome” occurs when the absorption of copper from

the intestines is blocked. In this disease, plasma copper and copper oxidase levels are low. Growth slows down, body temperature drops, hair turns gray and brain degeneration occurs. Copper deficiency reduces the risk of heart disease. "Wilson's disease" occurs when copper absorption from the intestines increases. Copper accumulates in the brain and liver. It is normally excreted in the feces and to a lesser extent in the urine (Zucchini IC and others). The use of copper-containing utensils when preparing or serving food can cause copper poisoning. Nausea, vomiting, heartburn and diarrhea are symptoms of copper poisoning. Copper; A normal adult contains up to 100-150 mg of copper. About 90% of this is stored in muscles, bones and liver. Copper deficiency may occur in people with severe malnutrition and impaired intestinal absorption. In this case, anemia, skin and bone defects, mental development disorders are observed. Excess copper is poisonous. Ingestion of more than 15 mg of elemental copper causes symptoms such as nausea, vomiting, diarrhea, abdominal pain and widespread muscle pain. High intake during pregnancy can cause miscarriage. Depression, coma and death can also occur (Stern, B., 2007).

CONCLUSION

Although some activities that benefit some people, such as industrialization, bring great benefits to humanity, they also bring serious public health problems such as exposure to heavy metals such as lead (Pb), arsenic (As) and copper (Cu). In Turkey, research on the health effects of heavy metals such as lead (Pb), arsenic (As) and copper (Cu) and how to avoid exposure is scarce and insufficient. It is necessary to increase tests for lead (Pb), arsenic (As) and copper (Cu) heavy metal levels in adults who are at higher risk of exposure and to take precautions against possible negative effects. Especially people who frequently come into contact with heavy metals at workplaces should be more conscious and scientific research on this subject should be increased. In this study, we have compiled and presented the physicochemical properties of some heavy metal elements such as lead (Pb), arsenic (As), copper (Cu) and their effects on human health in detail. The positive and negative effects of these heavy metals on human health as a result of their interactions were discussed in detail.

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Chapter 7

Some Textile Dyeing Materials (Methylene Blue, Malachite Green and Crystal Violet) and Their Effects on Health

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Abstract

Dyes are substances that produce color in the most appropriate way and cause changes in the structure of substances. In leather, pharmaceutical, food, cosmetics, textile factories , etc. It is widely used. Although it is estimated that around 7x105 tons of dyestuffs are produced annually worldwide, the majority of dyestuffs produced (54%) are used in the textile industry. As a result, approximately 10-15% of the paint used in the dyeing process ends up in wastewater. Dyes, It is resistant to light, temperature and oxidative deterioration. Therefore, dyes are not biodegradable, which causes negative toxic effects in wastewater, the environment and human health. The decrease in the amount of dissolved oxygen in water negatively affects the habitat of aquatic life. This materials are not biodegradable , live potentially for organisms toxic to be And some of dyes carcinogenic to be It poses a serious threat to human health due to threatening. In this study, the usage areas, physicochemical structures and health effects of malachite green, crystal violet and methylene blue dyes were examined in detail.

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1.INTRODUCTION

1.1 Dye

Fabric, fiber or similar materials to color the organic substances used for dyeing are called dyes. However, not every substance gives color. And This Therefore it cannot be described as paint. Paints are created by mixing the binders without dissolving them and layer by layer without changing the structure of the material . These are mixtures applied in layers . This process is superficial and can be repaired by physical means . Dyes are substances that produce color in the most appropriate way and cause changes in the structure of substances . In leather, pharmaceutical, food, cosmetics, textile factories , etc. It is widely used . Paint is rubbed off the surface cannot be removed. This is because, of the paint physically or chemically with the surface of the material interaction is to enter (Önal and Tantekın , 2018, Aybar, 2023).

1.2 Dye Matter

Dyes are chemical substances that give color to materials or cause color changes. These substances are often used to color fabric, paper , plastic, leather, food, metal and other materials. These organic compounds are produced naturally from plant waste and animal skin, but most are produced synthetically. The use of dyestuffs has a wide range of industrial applications and is used for aesthetics, identification, security, marking and many other purposes. It is widely used in the food industry, textile industry, automotive industry and many other industries. Although it is estimated that around 7x105 tons of dyestuffs are produced annually worldwide, the majority of dyestuffs produced (54%) are used in the textile industry. As a result, approximately 10-15% of the paint used in the dyeing process ends up in wastewater (Oyar, 2020).

Textile dyes are chemical substances used to give color or color changes to textile materials. These substances are generally in liquid or powder form and provide coloration by interacting with textile fibers. Textile dyestuffs are widely used in coloring cotton, wool, silk, synthetic fibers and other textile materials. Color options and application methods are diverse, offering a wide range of colors and design possibilities in the textile industry.

The textile dyeing process generally begins with dissolving or dispersing the dyestuff in water. The textile material is then contacted with this dye solution. This interaction allows the dyestuff to adhere to the textile fibers.

The color is then fixed, usually by a fixing process, making the material washable and color-fast.

Cosmetic, It is widely used in many areas such as paper and textile. Environmental impact of paints used increasingly It is important. The most important of these environmental effects is industrial of wastewater important to the extent to contamination path trench (Aybar,2023).

Dyes; It is resistant to light , temperature and oxidative deterioration. Therefore, dyes are not biodegradable, which causes negative toxic effects in wastewater, the environment and human health potential quality carries (Karadağ, 2007; All Cebeci,2020).

Colored water disrupts its naturalness and reduces dissolved oxygen permeability. The decrease in the amount of dissolved oxygen in water negatively affects the habitat of aquatic life. This materials are not biodegradable , live potentially for organisms toxic to be and some of dyes carcinogenic to be It poses a serious threat to human health due to threatening (Karadağ, 2007; Tüm Cebeci, 2020).

These dyes, which are used in every aspect of life in daily routine, mix with water. Some of these dyestuffs.

2. MALACHITE GREEN

2.1 Structure

Malachite, consisting of basic copper carbonate it is a light green mineral. Malachite is a common copper ore. Each sometimes together with copper sulphides, especially chalcopyrite, and also this it is found at the end of oxidation in the upper parts of the deposits .

Malachite green (MG) is a synthetic color used in dyeing textiles such as silk, fabric , wool and leather. Cationic one it is paint and same in time fishery in the field It is also preferred as a fungicide. Molecular formula; C52H54N4O12 and its molecular weight is 927 mol /g (Benek.2022).

20. From the first quarter of the century popular halo incoming malachite green in water living and on land toxic to living animals , toxic to humans It has carcinogenic effects . Solubility in water increasingly high MG, which is broken down by microorganisms difficult therefore, it stays in water for a long time (Benek. 2022).

One of the reasons for the popularity of MG is its use in the treatment of parasites. Use and especially trout plays an effective role in the treatment of kidney diseases. This feature MG's use of lead to rapid increase has opened

however years as we go in the water paint concentration in has increased. This situation, some studies MG to the paint exposed remainder fish of your eggs in offspring A lot to abnormality From where is to show upon, America in 1978 Unified States to take some measures and MG use led to the limitation (Atamanalp , 2003; Tanyol, 2017; Uysal and Belibağlı , 2020).

2.2 Usage Areas

Used in silk, leather and paper dye. It prevents the fungal disease called saproleglia in fish eggs . It is used as a dye for microscopic analysis of cells and culture samples. Jimenez staining involves staining bacteria red with a dye. Malachite green, on the other hand, colors bacteria blue-green, making them more visible. Leuco-Malachite Green (LMG) is used to reveal seemingly missing blood in criminal activities. Hemoglobin in the blood reacts with hydrogen peroxide to form colorless LMG. Since the LMG is chromatic, the color turns green. This is how blood is dye. Direct staining of bacterial endospores . It is used as a pH indicator.

Laboratory Applications: Malachite green is used in biology and chemistry laboratories to color cells and tissues under the microscope.

Use as an Antiseptic: Malachite green can also be used in medical applications such as wound cleansing and treatment of skin infections due to its antiseptic properties.

Skin and Feather Coloring: It can be used in animal husbandry to color the skin and feathers. However, this application should generally be done in a controlled manner.

Textile Dyeing: Malachite green can be used in the textile industry to dye cotton, wool and other fibers.

Water Purification: In some cases , malachite green can be used in water purification processes to control bacteria and other microorganisms.

Biostaining: Used to identify cell nuclei and other cellular structures in biological samples. This is especially common in histology studies.

2.3 Physical Chemical Effects

Malachite green is Cu2(OH)2CO3. It is a copper-containing compound and is widely used as a colored pigment.

Malachite green malachite It does not contain minerals . their names origin simply of colors similar from being It is due to.

2.4 Effects On Health

Its structure is in the form of a green color called chromatic malachite green. After being absorbed into the body, it is converted into two different forms through metabolism. The first form is the carbinol form. The carbinol form has the ability to quickly cross cell membranes. Once inside the cells, it is converted to a form called leukomalachyte green (LMG). Although LMG is toxic , it remains in the body longer than other forms.

Malachite of green Carcinogenicity As a result of the test , two 100 ppb (parts per billion) throughout the year in concentration Tumor formation was observed in rats administered malachite green . Therefore It was concluded that this chemical is carcinogenic .

Health problems were reported in Canada in 1992 in people who consumed seafood containing malachite green.

This chemical in canada Class 2 (to health damaging being possibility of low) aspect classified. Because the chemical was found to cause liver tumors.

However, due to its low cost and ease of use malachite green In some countries it is now only about water in products is used . In research conducted in China, Taiwan and Hong Kong in 2005, it was revealed that this toxic substance was detected in fish. 2006 In the US Food and Drug Administration (Food oath Drug Administration (FDA).

The use of the chemical malachite green in water-related products forbidden is from china person consumption for imported made in fish detection was made specified. In June 2007, the FDA approved malachite they contain green for from china sea products banned its import .

Jimenez painting, staining bacteria red with a dye Contains. Malachite green colors bacteria blue-green. more visible to be provides. Leuco -Malachite green (LMG), crime in its activities seemingly loss bring out blood using for . Hemoglobin in blood, hydrogen peroxide with It reacts with colorless LMG . Since the LMG is chromatic , the color turns green. Blood This way makes. bacterial endospores directly dyeing. PH used as an indicator .

Malachite green is a dyestuff that carries potential health risks due to the copper salts it contains. Copper can be toxic when taken in excessive amounts . Exposure through inhalation or skin contact is one way in which such substances can harm health.

Overexposure to copper-containing substances such as malachite green can lead to gastrointestinal upset , difficulty breathing, skin irritation, and

other health problems. When working with such substances, appropriate safety precautions should be taken and exposure limits should be observed. Therefore, people working with such chemicals must follow safety procedures.

3 CRYSTAL VIOLET

3.1 Structure

Crystal Violet, with the molecular formula k, C25H30ClN3 and a molecular mass of 407.99 g/ mol , located in the triphenylmethane group , is a cationic dyestuff widely used in laboratory applications and microscopy studies.

3.2 Usage Areas.

Crystal violet offers a wide range of uses in textile applications such as silk and cotton dyeing, in dye and ink manufacturing, as a bacteriostatic agent in veterinary medicine, as a nutritional supplement as an anti-parasitic and anti-fungal agent in poultry, and as a disinfectant on human skin. In addition, since it is the active ingredient of gram stain and a protein dye, it is a dye that is frequently used in microbiology and to enhance bloody fingerprints.

Gram staining technique is a microbiological staining method used to distinguish bacterial species. With this technique, bacteria are easily identified and classified. The reactions of bacteria stained with the Gram staining technique share common features with bacterial groups that are closely related in terms of development. Recognition of bacteria is an important issue, especially in drug use. While some antibiotics affect especially gram-positive bacteria, some of them affect more gram-negative bacteria.

Gram-negative bacteria are bacteria that do not retain crystal violet dye during gram staining procedures. While gram-negative bacteria lose their blue color, gram-positive bacteria continue to retain the blue color even after washing with alcohol. Therefore, gram-positive bacteria are bacteria that turn very blackish blue and purple under the microscope after going through the gram staining process.

In fish farms, fish are given some chemicals and feed. These include the chemical compound crystal violet , which is given to fish eggs to make them strong against bacteria, fungi, various viruses and parasites . After the previously widely used malachite green compound was banned with new

legal regulations, crystal violet compound is used as an effective disinfectant today.

3.3 Physicochemical Properties

Located in the triphenylmethane group , it has the molecular formula C25H30ClN3 and a molecular mass of 407.99 g/ mol .

3.4 Effects On Health

Offering a wide range of uses, KV is a carcinogenic dye, and since it is cationic , it can cause eye irritation and permanent damage to the cornea. In extreme cases, it can cause respiratory problems and kidney failure (Saeed et al., 2010 ; Chakraborty et al., 2011).

Like malachite green, crystal violet compound is converted into two different forms by metabolism . When it quickly passes through cell membranes and enters the cell, it turns into another form called leuco crystal violet . In laboratories, in seafood products within the scope of chemical tests, leuko crystal Violet dyestuff analyzes are performed and LC-MS/MS method is used in these analyses.

Defined as liquid chromatography - mass spectrometry, this method is a chemical analytical method that combines the mass analysis capabilities of mass spectrometry with the physical separation properties of liquid chromatography . These studies are based on standards published by domestic and foreign organizations.

4.METHYLENE BLUE

4.1 Structure

Methylene blue is a dye that is chemically a type of organic compound. It is a dyestuff frequently used in the scientific world and also a medicine. It's chemical formula is C16H18ClN3S. Its molecular weight is 319.85 g/ mol . The structure of the compound contains an aromatic ring, methylene (CH3) groups and an azomethine (N=N) bond. It is used as a dyeing agent with coloring properties , especially known as a histology staining agent used to stain cells in biological studies.

Since it is used in the treatment of various diseases in the aquarium hobby, it is generally available in the form of solutions on the market. However, it is found in dark green crystal or powder form. Its solutions are dark blue in color. It has a light scent.

4.2 Usage Areas

Methylene blue is known as a dye and histology staining agent commonly used in laboratory and industrial applications. Here are some uses of methylene blue

Histology and Biology:

Methylene blue is frequently used as a histology staining agent used to examine cells and tissues under a microscope. This is important for examining biological samples and determining cell structures.

Microbiology:

Methylene blue is used as a staining agent in microbiological studies to identify bacteria and other microorganisms. It is especially widely used in the Gram staining method.

Veterinary Medicine:

Cell and tissue sample Water Analysis in animals: Methylene blue can be used to determine the presence of bacteria and microorganisms in water samples.

Textile Dyeing:

Methylene blue can be used in the textile industry to color fibers such as cotton, silk and wool.

Use as an Antiseptic:

Because it has antiseptic properties, it can be used in some cases to clean wounds and treat skin infections.

Factors to consider when using methylene blue are its potential for toxicity and the application of correct safety procedures. Its application and usage areas span a wide range of interdisciplinary fields. It can be used in veterinary medicine practices to examine the

4.3 Physicochemical Properties

Chemical Formula:

Methylene blue has the chemical formula C16H18N3SCl. Methylene blue, a cationic dye; C16H18N3SCl.3H2O and its molecular weight is 373.9 gmol-1 a strong adsorption ability (Gür,Demir ,Kul 2021).

Color and Appearance:

Methylene blue usually has a dark blue color and can often be found in solid crystal or powder form. Solubility: Methylene blue is generally soluble in solvents such as water and alcohol. This feature makes it easy to use, especially in laboratory applications.

pKa Value:

Because methylene blue contains an ammonium group, it can accept several different protons and therefore have various pKa values. These values vary depending on the acidic and basic environments in the solution.

Spectral Properties:

the UV- Vis spectrum, indicating the ability of methylene blue to absorb light at certain wavelengths .

Chemical Stability :

Methylene blue can remain stable under some conditions, but can degrade when exposed to light and other conditions.

Toxicity : Methylene blue can be toxic when taken in excessive amounts . Therefore, caution should be exercised during its use.

These properties are important for understanding how to use methylene blue in a laboratory and industry applications and under what conditions it may be stable or reactive. When working with any chemical, it is important to follow proper safety procedures and local regulations.

4.4 Effects On Health

Methylene blue may cause different health effects depending on the area where it is used and the level of exposure . It is a dyestuff generally used in histology and microbiology studies in laboratories. However, the following effects can be observed:

Respiratory System Effects: Exposure to methylene blue may cause respiratory irritation. This is especially true in cases of exposure in dust or vapor form .

Skin and Eye Irritation: May cause irritation to skin or eyes in case of direct contact. In case of improper use, contact with skin or eyes may cause effects such as redness, burning or itching.

Genotoxic Effects: Some studies have shown that methylene blue may cause genotoxic effects. This means it can damage DNA.

Toxicity : In cases of high exposure , methylene blue can be toxic and cause serious effects on the organism.

4.Conclusion and Recommendation

Appropriate safety precautions should be taken when using dyestuffs . In laboratory work, correct protective equipment must be used and safety instructions must be followed. People working with chemical dyestuffs must comply with occupational health and safety standards. Should be developed to minimize the environmental impacts of dyestuffs .

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Chapter 8

Mobile and Portable Hospitals

Bilge Büyükşirin[1]

Abstract

Access to medical care is one of the fundamental needs of every individual. Hospitals mostly provide services in buildings located in city centers. However, mobile hospitals are needed to provide health services in special situations such as wars and disasters or in regions that do not have access to hospitals. Today, mobile hospitals provide services on land, at sea and even in the air. In this study, mobile and portable hospitals used today and in the recent past are examined.

1. Introduction

The word "hospital" comes from the Latin word "hospes" which means "a welcomed stranger" or "a guest" (Skeat, 1893). The related Latin word "hospitium" comes from the same root and means "hospitality" which describes the relation between guest and shelter suplier. Early usage of the word "hospital" was used to signify a place to house and maintain the needy people. By time this word diverged into two branches, first one is hostel and the other one is hospital as we understand today.

The modern meaning of the word "hospital" describes a healthcare institution which provides patient treatment with healthcare staff by using specialized health science and medical equipment (WHO, 2023). The general hospitals usually have an emergency room, services that specialize in various fields and intensive care units. The majority of hospitals are fixed-site hospitals. But in special cases such as wars, disasters and epidemics or in hard-to-reach regions mobile or portable hospitals are needed (Khanna & Narula, 2016).

Mobile and portable hospitals are equipped enough to perform a surgical operation and are practical enough to be quickly installed in a desired area.

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First portable hospitals were military tents looking after injured soldiers at wars. We see many examples of these kind of military hospitals since ancient civilizations. By the development in medical sciences and transportation technologies the mobile and portable hospitals also developed. Today we have various kinds of mobile and portable hospitals at ground, sea and air.

This study focuses on the mobile and portable hospitals. In the study initially, a brief history of portable and mobile hospitals has been narrated. Then types and structure of portable and mobile hospitals have been discussed. And finally, some recent disasters and function of the portable and mobile hospitals in that urgent situations have been examined.

2. On The Land

2.1. Field Hospitals

Treatment of injured soldiers during the war emerged by a natural need. Besides being a wounded human needing help, the injured soldiers affect the mood of the whole army. In the front lines injured ones slows down the health soldiers and by inevitable pain sounds they put the healthy ones in fear also. Thus, medical evacuation is a crucial need not only for the injured soldier but also for the whole army. But transporting the injured soldiers to rear general hospitals usually increase the mortality risk or it is not possible or too costly in many cases. For this reason, we see the military field hospitals are placed near the front lines and continuously serving.

The field hospitals are in use from ancient times to modern times. The field hospitals usually consist of portable tents housing the medical crew and equipment. By the World War I and World War II we see the development of the MASH (mobile army surgical hospital) units in US army (King & Jatoi, 2005). The first MASH units were including only a single division formed for emergent surgical operations. By time the divisions of the MASH units are increased and they transformed into all-purpose hospital with 200-300 bed capacity (Woodard, 2003).

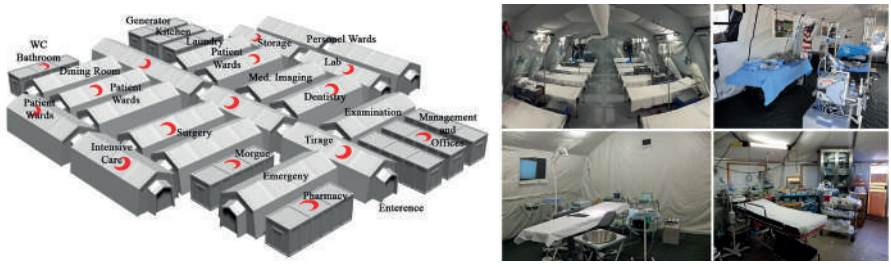

Figure 1. All-purpose Field Hospital. (LiveScience, 2020)

Plan of the field hospital changes depending on the size and purpose. A modern all-purpose field hospital includes tirage room, emergency unit, medical imaging unit, surgical operation rooms, pharmacy and laboratory, intensive care unit, dental and eye units, kitchen, supply and storage units as shown in Fig-1.

In general, wide portable tents are used for living areas at the field hospitals. These tents may have their pre-installed air ventilations and electric cables. Besides tents metal containers are also used at the field hospitals. The generators, water treatment and other supply equipment are usually placed in to the containers. These containers may have their own wheels or they can be carried trucks and placed with mobile cranes.

The field hospitals are also in service during disasters, epidemics and humanitarian crisis. We see many examples of field hospitals, operated by international aid organizations and armies of several nations, at major earthquakes such as İzmit (1999), Kashmir (2005), Haiti (2010) and more (Talbot et al., 2012). In Syrian refugee crisis at 2015 Turkey set up many filed hospitals and shelters at the Syrian border to help refugees (Köseoğlu & Çevikel, 2014). Most of these field shelters are still in use. During Covid-19 China and some other countries deployed their mobile field hospitals to slow down the spread of the virus and quarantined patients (Chen et al., 2020).

2.2. Mobile Medical Units

The multi division field hospitals require flat wide regions for set-up. And they usually need trucks for transportation and mobile cranes for setup. For small or single division needs motorized mobile medical units can be used. These units usually consist of a trailer pulled by a truck as shown in Fig-2. The trailer can be expandable to increase the interior area. When compared to field hospitals these units are more agile thanks for having their motorization.

Figure 2. Mobile Medical Unit (Matthews, 2023).

Depending on the medical application various equipment can be installed to the trailer. The services provided by mobile medical units may include public health, dentistry, ophthalmic surgery, general surgery, first aid and emergency, blood donation, disease testing and even medical imaging (Marques et al., 2011; Morano et al., 2014; Toppenberg et al., 2020). These mobile medical units can be in a routine for visiting people having low access (Khanna & Narula, 2016) or they can be put in charge in emergency and disaster situations (Taylor et al., 2007). In emergency and disaster situations with their agility and mobility these units usually give first response until bigger facilities being constructed.

3. At The Sea

It is predicted that dedicated ships to treat wounded soldiers are in use since ancient civilizations. When their names are examined, it is thought that the Roman ship Aesculapius and Athenian ship "Therapia" was one of ancient hospital ships. The earliest recorded British hospital ship was a vessel named as Goodwill, which is accompanied to Royal Navy (Sutherland Shaw, 1936). We see the invention and usage of the hospital ships were for mainly military purposes. But today we also have hospital ships owned by civilian organizations.

3.1. Military Hospital Ships

After 1700s it is known that almost every navy have used hospital ships at their fleets. These ships were carrying a special crew of health carers and medicines of their time and they were in use to house wounded and sick soldiers during naval wars or even in land wars. The ships of British Royal Navy HMS Grampus, HMS Dreadnought, HMS Caledonia and HMS Hamadryad can be given as examples for 1800s (Carradice, 2013). During World War I HMHS Aquitania, HMHS Mauretania, HMHS Britannic and HMHS Llandovery Castle served for British Royal Navy (McCutcheon, 2015). Here the HMHS abbreviation means "Her Majesty`s Hospital Ship". In Fig-3 pictures of HMHS Aquitania, HMHS Mauretania and HMHS Britannic is given.

The international laws on the hospital ships were first covered by the Hague Convention X of 1907 (Best, 1999). Depending on the convention the hospital ships were painting with red cross over white background to indicate that they are not armed. However even though the international laws, the HMHS Llandovery Castle and some other ships were sunk by German submarines (Hunt, 1920; William Jr, 2012). Similar to British navy, every navy held its own hospital ships during the war. From these SS

Maheno and SS Marama serviced for New Zelland, SS Mexique and SS Flandre for France, HS Vpered and SS Portugal for Russia, HS Marechiaro for Italy and SS Ophelia and HS Tabora for Germany. These ships were equipped with medical devices and healthcare crew, they housed and treated thousands of injured during their use (Kludas, 1985).

Figure 3. Hospital Ships of WWI (DeviantArt, 2019, 2022).

We see that before World War II British hospital ships were in majority. However, after World War II, hospital ships belonging to the US Navy came to the fore (Goodman, 2016). Today many of the navies includes modern hospital ships in their fleet equipped with emergency, surgery and intensive care units and their health personal.

3.2. Civilian Hospital Ships

3.2.1. Mercy Ships

It is estimated that 5 billion people around the world have no access to an affordable and trustable surgery (Meara et al., 2015). The Mercy Ships is a non-governmental organization aiming to supply healthcare supply and surgical treatment to poor countries and they are in service since 1978.

The first Mercy Ship was 1953 built Italian passenger liner "Anastasis". Anastasis acquired by the organization in 1978 and used until 2007. The Anastasis was equipped with three fully-equipped operating rooms, a hospital ward, a dental clinic, a laboratory and an X-ray unit. In its 30-year service time Anastasis performed over 1 million healthcare operations. The second Mercy Ship was "Island Mercy". It was a Newfoundland coastal ferry donated to the organization in 1983 and serviced until 2001. The Island Mercy supplied eye and dental services over 130 thousand people from Africa, South America and South Pacific. The third Mercy Ship was "Caribbean Mercy". It is acquired from a Norwegian ferry company in 1994 and serviced until 2007. The Caribbean Mercy and his crew contributed more than 20% of Mercy Ships' total missions in its 13-year service time. The crew was able to perform dental and eye surgeries on the ship. Besides

the surgeries the ship was also a medical school for local health-care workers (Mercy, 2023).

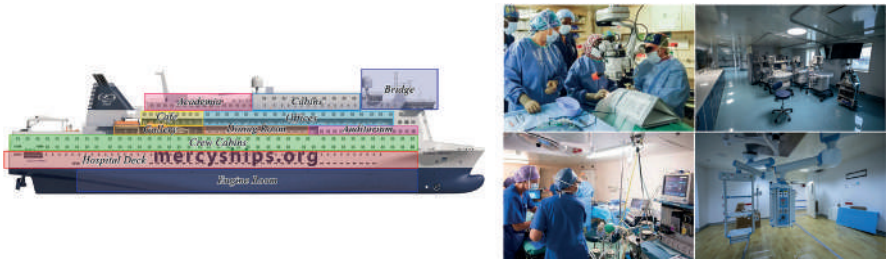

Figure 4. Global Mercy Hospital Ship (Mercy, 2023).

Today, Mercy Ships operates with two ships named Global Mercy and Africa Mercy. The Global Mercy is known to be the largest purpose-built civilian hospital ship. It is constructed at the Tianjin Xingang Shipyard of China and it is delivered to the organization in 2021. The Global Mercy shown in Fig-4 holds 7 intensive care units, 6 surgical operating rooms, 199 bed capacity and dental and eye services. The second active ship of the organization is the152 m long Africa Mercy. After the Global Mercy, the Africa Mercy is the second largest hospital ship holding 5 surgical operating rooms, intensive care units and 82 bed capacity (Mercy, 2023).

The Global Mercy and Africa Mercy have performed out a wide range of surgeries like maxillofacial and plastic reconstructive surgery, tumour removal, cleft lip repair, palate repair, orthopedic operations, cataract removal, obstetric fistula repair, thyroid surgery and debilitating burn contractures (Cheng et al., 2022; Cheng et al., 2012; M'Pele, 2021). In addition to these services, they also provide basic medicine, dentistry, ophthalmology and other trainings as on-shore programs.

3.2.2. Esperanza del Mar and Juan de la Cosa

Esperanza del Mar and Juan de la Cosa are hospital ships under control of Spanish Ministry of Employment and Social Security. They hold intensive care units, surgical operating rooms and bed capacity of 10 and 15. These two ships serves for Spanish fishermen.

4. In The Air

We see first trials of the aeromedical operations occurred just after a few years of the invention of stable planes. The first of these trials was French Aerochir. By the time and developments in the aviation technology the use

of planes for healthcare purposes gained speed. Today there are dozens of military flying hospitals and even civilian hospital jets.

4.1. The Aerochir

The Aerochir is known for to be the first aircraft which carries a medical team and equipment to the war field. Aerochir was built on French Voisin-X airplane which was introduced at 1917 (Wikipedia, 2023). At Fig-5 a close-up photo and medical set-up near the plane is given. Two compartments under the wing were used for storage and transfer of the medical equipment of the time including an X-ray machine. The Voisin-X airplanes normally used to have two seats but in the available pictures of the Aerocir a crew of three is seen.

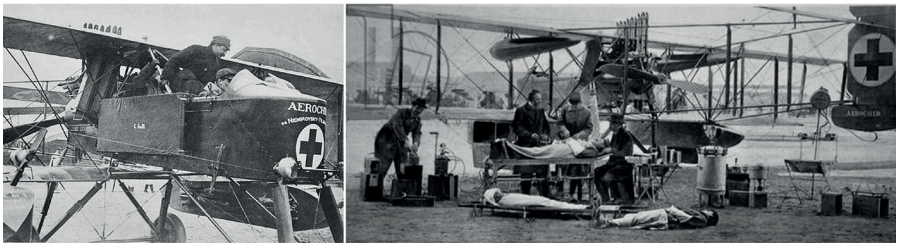

Figure 5. Aerochir (Airwar, 2022).

This crew was responsible for flying the plane, reaching to the war field and giving medical service at the field. For this a flat landing region and clean place for medical treatment was enough. The medical equipment of the Aerochir was portable. They used to set up at the field and, after the medical treatment, they removed to the storage compartments of the plane. It is known that Aerocir was in service between 1918 and 1920 in the French colonial wars (Lam, 2005).

4.2. C-9A Nightingale (1968-2005)

C-9A Nightingale is a modification of McDonnell Douglas DC-9 airplane to serve as aeromedical evacuation (Birtles, 2002). C-9A Nightingale is able to carry 40 patients unable to walk or 40 bedridden patients. The plane has an up opening wide door placed at the cabin and a hydraulic ramp to carry patients and medical equipment to the plane as shown in Fig-6 (AMCM, 2023). The interior of the plane is redesigned to contain patient beds, medical equipment, medical refrigerators, oxygen and vacuum supplies. Additionally, there were compartments for management, intensive care and quarantine. Depending on the needs the medical crew of the C-9A Nightingale was able

to give medical treatment during flight for urgent patients. More than ten C-9A Nightingale airplane were produced and they serviced from 1968 to 2005 for US air force and its allies (Drummer & Wilcoxson, 2001).

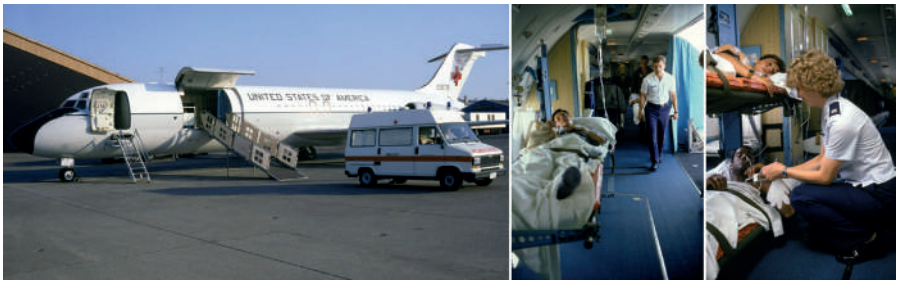

Figure 6. C-9A Nightingale (NaraArchive, 2023).

4.3. Boeing C-17 Globemaster

Previously Lockheed C-130 Hercules was in use as main cargo plane of US Airforce. In 1995 Boing C-17 Globemaster started to take the mission of C-130s. The C-17 Globemaster has an enormous takeoff capacity of 74 tons and a large cargo deck with 27 m length by 5.5 m width by 3.76 m height (Taylor, 1996). C-17 Globemaster is in use in the air forces of United States, United Kingdom, Canada, Australia, England, India, United Arab Emirates, Qatar and Kuwait (Hoyle, 2017).

Besides cargo carrying these big airplanes are in use for medical evacuation of injured soldiers from the field. The wide cargo deck of the C-17 Globemaster makes it suitable for various uses and missions. During medical evacuation missions, thanks to its flexibility the cargo deck of C-17 can be rearranged depending on the status of the injured soldiers.

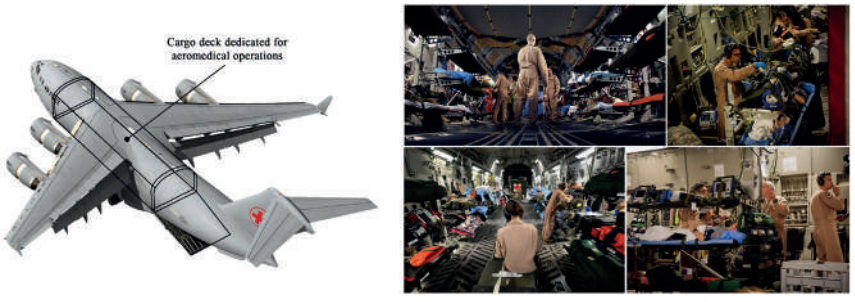

Figure 7. Aeromedical C-17 Globemaster (AFMS, 2019).

At Fig-7 illustration of C-17 Globemaster and photos of its medical deck is given. At its missions this plane can hold a fully equipped emergency unit or stacks bunk beds can be placed to carry bedridden patients (Upadhyay & Guru, 2016). It is known that C-17 Globemaster is used in many aeromedical evacuation missions around the world. But most of these missions were under control of US Airforce and they were for military purposes.

4.4. Orbis: The Flying Eye Hospital

Orbis project first envisioned by Dr. David Paton at 1960s. Dr. Paton was aware of the l lack of eye care and ophthalmic teaching in developing nations. For people at developing countries, it was unreachable to have even an easy eye treatment. And these types of countries were too insufficient to graduate their doctors in enough numbers. The vision of Dr. Paton was to construct a charity organization to supply ophthalmic teaching and treatment for developing countries (Munsell & Frank, 2006).

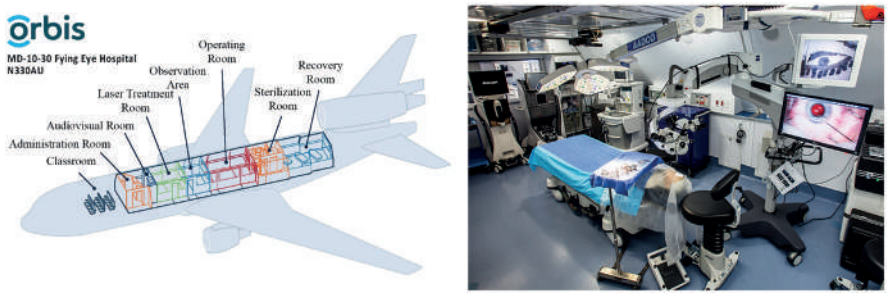

Figure 8. Orbis Flying Eye Hospital. (Orbis, 2023)

In 1980 United Airlines donated one McDonnell Douglas DC-8 airplane to the Orbis project. The plane was modified and equipped for ophthalmic teaching and treatment (Watts et al., 1998). In 1982 the Orbis plane flew to Panama for its first mission. Latterly FedEx donated a McDonnell Douglas DC-10 donated to the project. The old DC-8 airplane replaced with the DC-10. The interior design of the Orbis DC-10 is illustrated at Fig-8. Orbis holds latest medical equipment needed for eye-treatment and also audio-visual simulation systems for virtual training. Orbis have flew over 95 countries to give education and eye-treatment (Orbis, 2023).

5. Conclusion

In the study, mobile and portable hospitals serving on land, at sea and in the air were examined. When we look at the history of mobile and portable

hospitals, we see that they first emerged for the treatment of the wounded in wars. Today, mobile hospitals are used for both military and civilian purposes. The most common type of mobile hospital used on land is the field hospitals. On the other hand, motorized mobile health clinics are used for routine public health programs or to provide rapid support in emergency situations. Mobile hospitals used in maritime first appear as separate ships that support the war fleet. Besides navy medical ships, civilian hospital ships supported by charities provides health care support for poor countries. Mobile hospitals used in aviation became widespread later than the others and they are generally used for military evacuation operations. However, there are civilian initiatives to use airplanes to provide healthcare.

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Chapter 9

Current Quality Control Methods in Radiotherapy

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Abstract

Quality control is of critical importance to ensure the accurate and reliable implementation of treatment in radiotherapy. Radiotherapy is a primary method of treating diseases such as cancer, aiming to destroy cancer cells or control their growth using high-energy X-rays or gamma rays. The quality control process encompasses a comprehensive series of procedures involving regular examination and evaluation of elements like radiotherapy devices, dosimetric components, and treatment planning systems. The primary objectives of quality control are to enhance patient safety, ensure accurate dose delivery, and optimize treatment outcomes. Due to its inclusion of critical parameters and safety measures, this process holds significant importance in the field of radiotherapy.

The quality control process begins with the examination of treatment devices and components. Linear accelerators are the most commonly used devices in radiotherapy. Quality control procedures for linear accelerators involve various steps, including reference dose measurement, dose output calibration, isocenter dose measurements, accuracy of irradiation, beam profile control, and dynamic field control. The control of simulation and imaging devices such as CT simulation, MRI, PET/CT, and ultrasound plays a crucial role in radiotherapy preparation. The quality control of these devices ensures the accuracy of elements such as calibration, visualization of anatomical structures, and assessment of image quality.

Ion chambers, diode detectors, two-dimensional dosimeters, diamond detectors, thermoluminescent dosimeters (TLD), Metal-Oxide-Semiconductor Field-Effect Transistor (MOSFET) detectors, and gel dosimeters are used for the control of devices and components in radiotherapy and are examined for calibration, accuracy, and sensitivity. Dosimetric devices

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like ion chambers and diode detectors are vital for accurately measuring radiation doses. Two-dimensional dosimeters and film dosimeters, with their advantages and disadvantages, contribute to treatment plan verification and patient safety. While diamond detectors offer high precision, they come with higher production costs. Thermoluminescent dosimeters, using materials like LiF, provide accurate measurements and a wide dose range. MOSFET detectors, as semiconductor-based devices, respond quickly to radiation and are valuable for real-time dosimetry during treatment. Gel dosimetry, utilizing gel materials, offers high precision in measuring radiation doses but requires complex laboratory analysis.

In conclusion, the comprehensive quality control methods in radiotherapy are of vital importance for ensuring patient safety, treatment success, and the accurate operation of equipment. These controls, conducted in accordance with national and international protocols, adapt to evolving standards and technologies, contributing to the overall effectiveness and safety of the radiotherapy process.

Introduction

Radiation therapy (RT) is a treatment method used to treat diseases such as cancer or alleviate pain. RT aims to destroy cancer cells or control their growth using high-energy X-rays or gamma rays. It can be administered alone or in conjunction with other cancer treatment methods such as surgery or chemotherapy. High-energy radiation can disrupt the DNA structure of cancer cells, halting or reducing their growth. Radiotherapy can be applied as neoadjuvant or adjuvant treatment. Neoadjuvant treatment is used to shrink or control tumors before surgery, enhancing the effectiveness of surgery. Adjuvant treatment is administered after surgery to reduce the risk of cancer cells returning. RT is also employed to control the spread of cancer cells or alleviate symptoms caused by metastatic tumors (Sonke, Aznar, and Rasch 2019)

Quality control in radiotherapy is a comprehensive process and one of its most crucial parameters. This process involves regular inspection and evaluation of elements such as radiotherapy devices, dosimetric components, and treatment planning systems. The purpose of quality controls is to ensure the safe, effective, and accurate implementation of the treatment process. Quality control is employed to enhance patient safety, ensure the delivery of accurate doses, and optimize treatment outcomes. The quality control process holds significant importance in radiotherapy (Moran et al. 2011)

Quality control in radiotherapy can be categorized into the following main topics:

Quality Control of Treatment Devices

Linear accelerators (LINAC) are among the primary devices used in radiotherapy. LINACs are devices used to accelerate high-energy particles such as electrons or protons for various applications, including cancer treatment in RT. Medical LINACs consist of essential components such as an electron gun, radiofrequency (RF) system, electromagnet fields, flattening filter, collimator, jaws, multileaf collimator, monitoring and control system, dose measurement systems, and cooling systems. LINACs must be regularly checked for dose output, energy levels, beam profiles, and other features (Létourneau et al. 2018).

Quality control for LINACs, the most commonly used devices in radiotherapy, involves fundamental steps such as reference dose measurement, dose output calibration, isocenter dose measurements, accuracy of the irradiation field, beam profile control, and dynamic field control (Létourneau et al. 2018)

Reference Dose Measurement

Reference dose measurement assesses whether the radiation dose produced by the device is appropriately delivered to a specific target area. The LINAC's reference dose is measured along a specific depth across a defined field, confirming the accuracy of the dose output at the reference point.

Dose Output Calibration

Dose output calibration ensures that the radiation doses produced by LINAC align with the doses determined during treatment planning. This process aims to determine the LINAC's capability to generate doses accurately, ensuring the safe and precise application of radiotherapy treatments.

Isocenter Dose Measurements

Isocenter dose measurements are taken at the LINAC's isocenter point, corresponding to the focal point in the treatment field. These measurements are crucial for evaluating the dose distribution at the isocenter point and verifying the accuracy of treatment plans. They play a critical role in patient safety and treatment effectiveness.

Accuracy of the Irradiation Field

The accuracy of the irradiation field is assessed through jaw and multileaf collimator (MLC) control. Jaw and MLC positions are evaluated to ensure they conform to predefined values.

Beam Profile Control

Beam profile control involves checking the homogeneity and uniformity of the beam. Profile measurements are used to identify abnormalities in the beam's diameter and intensity.

Dynamic Field Control

Dynamic field control assesses the accuracy of dose output when using dynamic or moving fields during treatments. This is essential for determining whether the LINAC delivers accurate doses to moving targets during treatment.

Additional Controls

High voltage and current components should be checked regularly to ensure proper functioning at specified energy levels. Field dosimetry is performed to verify the dose in the beam field, commonly using ion chambers. Ion chambers are employed to confirm that the dose is delivered uniformly to the targeted areas. Quality controls for imaging systems that serve as references for RT should be conducted regularly to ensure accurate target positioning. The image quality, accuracy of treatment plans, and precision of patient positioning must be assessed. Controls for accessories used in the LINAC, as well as other equipment connected to it, should also be performed regularly. These controls are crucial for maintaining the correct position of the patient during treatment (Létourneau et al. 2018).

Regular controls ensure that the devices are functioning correctly and that treatment plans are implemented safely and effectively. The quality control process is carried out according to protocols established in accordance with national and international standards. The regularity of these controls is critical for the safety and effectiveness of the radiotherapy process.

Quality Control of Simulation and Imaging Devices

Simulation and imaging devices are essential components in radiotherapy preparation, providing detailed information for treatment planning. The main simulation and imaging devices include Computed Tomography (CT) Simulation, Magnetic Resonance Imaging (MRI), Positron Emission Tomography/Computed Tomography (PET/CT), and ultrasound devices.

Computed Tomography Simulation

CT simulation devices are crucial for detailed imaging of a patient's anatomical structures, aiding in the creation of radiotherapy plans. Quality

control for CT simulation devices involves checking the accuracy of the device's calibration and ensuring the proper visualization of the patient's anatomical structures. Field numbers for Hounsfield units in CT numbers of water-equivalent materials must be verified against specified reference values. Additionally, the functionality of the device, including bed movement, scanning speed, and dose acquisition features, should be regularly checked (Stoel et al. 2008).

Magnetic Resonance Imaging

MRI is used in radiotherapy to visualize detailed anatomical structures and lesions. Quality control for MRI devices involves evaluating image quality regularly. MRI images should provide clear, sharp, and accurate anatomical information. Tests should be conducted for the strength and homogeneity of the magnetic field. The calibration of radiofrequency coils and other accessories is essential for accurate signal reception and functioning within a homogeneous magnetic field. The quality of MR signals is calibrated to ensure accurate magnetization and signal acquisition. Software updates for MRI devices are performed regularly, and the environmental conditions of the device, such as temperature and humidity, are monitored to ensure proper functionality (Bezin et al. 2015).

Positron Emission Tomography/Computed Tomography (PET/CT)

PET/CT devices combine positron emission tomography and computed tomography features to provide detailed anatomical and metabolic information. Quality control processes for PET/CT devices include assessing hardware, software, and imaging performance. CT quality is checked for factors such as resolution, contrast, dose, and homogeneity. PET sections measure metabolic activity using radiopharmaceuticals, and the quality of PET images is evaluated for resolution, sensitivity, and radiopharmaceutical distribution. The quality of obtained PET and CT images is assessed for contrast, resolution, homogeneity, and artifact control. The operating parameters and imaging protocols of the device should be regularly checked and updated (Somer, Pike, and Marsden 2012).

Ultrasound Imaging

In radiation therapy, ultrasound devices are commonly used to visualize the patient's anatomical structures and tumors during the treatment planning. Ultrasound, an imaging technique, utilizes high-frequency sound waves to visualize reflections of tissues within the body. These images provide crucial information for treatment planning and target definition before the actual

treatment. The frequency settings of ultrasound devices should be regularly checked, as operating at the correct frequency influences image resolution and penetration depth. Calibration of the device is conducted to ensure accurate measurement of ultrasound signals, a critical aspect for providing precise anatomical information. Contrast and resolution of images should be monitored to accurately visualize anatomical structures and identify tumors. Image artifacts, such as false reflections or distortions, may occur, making interpretation difficult; hence, regular control processes are necessary. The quality of the gel and probe used during ultrasound should also be verified for proper acoustic transmission and imaging. Regular checks and updates of device operating parameters and imaging protocols ensure accurate operation and compliance with contemporary techniques (Tome et al. 2002).

Additionally, additional imaging components used during radiation therapy are available, known as Image-Guided Radiation Therapy (IGRT) systems. IGRT systems are employed to verify patient positioning, and their accuracy should be regularly assessed. The simulation table, ensuring accurate movement towards the beam target, and laser equipment, crucial for precise treatment delivery, also require consistent evaluation. Laser beams used for defining the treatment area must be accurately targeted and regularly inspected.

Quality control processes are determined based on each device's specific features and the manufacturer's recommendations. Implementing appropriate quality control protocols ensures the acquisition of accurate and reliable images and the accurate formulation of treatment plans, contributing to the safe and effective management of the treatment process.

Treatment Planning Systems

Treatment planning systems are platforms where pre-treatment radiation therapy plans are developed. Beam data obtained from linear accelerator devices or other radiation therapy devices are loaded into these systems. Data from imaging devices are transferred to these systems in DICOM format. Treatment planning systems perform calculations based on this data to create a radiation therapy plan. Regular checks of treatment plans are essential to ensure the delivery of the appropriate dose to targeted tumor areas without harming normal tissues. Quality control of treatment planning involves evaluating the accuracy and suitability of dosimetric plans to be used during radiation therapy treatment (Anjum et al. 2017)

Basic steps for treatment planning quality control include the verification of patient and imaging information. Patient information must be accurate

and complete, including identity details, dates, and other critical patient data. Imaging information (CT, MRI, PET, etc.) must be verified for accurate referencing and target definition. Tumor targets and normal tissues must be accurately defined, relying on clinical and imaging data. Advanced imaging methods may be employed when necessary to identify tumors, normal tissues, and organs at risk. The accuracy of dose calculation algorithms must be checked for dose calculation and dosimetric parameter control. This assessment evaluates the reliability of dose maps and dosimetric parameters. The treatment field must accurately encompass the tumor target, delivering minimal dose to normal tissues. Dose distribution must align with the planned target doses, and patient-specific quality controls are performed to verify the congruence of planned and targeted doses. After passing quality control, the implemented plan is checked for accurate positioning using patient positioning devices. IGRT systems, used to verify patient positioning, must undergo regular accuracy evaluations. These steps contribute to ensuring the reliability and accuracy of treatment planning. Quality control is regularly performed to detect errors in the radiation therapy process, enhance patient safety, and optimize treatment effectiveness. All measurements and controls must comply with international protocols published by organizations such as the American Society for Radiation Oncology (ASTRO), European Society for Radiotherapy and Oncology (ESTRO), and American Association of Physicists in Medicine (AAPM) (Palmans et al. 2018).

Data Backup and Management in Radiation Therapy

Information flow and data backup are crucial for monitoring patient treatment. Regular backup of patient treatment information, dosimetry plans, and other critical information, along with verifying the accuracy of information flow, is part of quality control. This control process aims to ensure the security and integrity of patient information used in the radiation therapy process. Essential steps for data backup and information flow quality control include daily backups of patient information, treatment plans, dosimetric data, and other critical information. Backup processes include the control of backup devices and media types. The integrity of backed-up data is regularly checked. In case of any damage or deficiencies in data files, swift intervention is necessary. Database integrity and relationships are reviewed. Security walls and access controls are regularly implemented to ensure information flow security. Security walls are installed to prevent unauthorized access to the system. Information flow and integration processes between different systems are regularly maintained. Ensuring smooth information flow among different devices, software, and information systems used in radiation therapy

is crucial. Software and technological updates for data management and backup systems are regularly monitored. The integration and compatibility of updates with the system must be ensured. Backup strategies are reviewed based on current needs and standards, and data recovery processes are regularly tested. Emergency recovery plans and processes are established for any unforeseen circumstances, including equipment failures, natural disasters, or cyber-attacks. Emergency plans are regularly reviewed and updated to minimize information loss (Moran et al. 2011).

Quality Controls are applied to ensure the security, integrity, and accuracy of information used in radiation therapy. This control process holds critical importance in ensuring that patient data is safe and accessible. Additionally, personnel training and information updates in radiation therapy are integral parts of quality control. Training and quality assurance programs in radiation therapy are critically important to ensure that radiation therapy applications are conducted safely, effectively, and in compliance with standards. Personnel training programs should include basic training programs, professional development, and training on new technologies. Basic training programs for novice radiation therapy personnel should cover principles of radiation therapy, device usage, dosimetry, patient positioning, and safety topics. Radiation therapists should be encouraged to participate in regular continuous education and development programs to keep their knowledge and skills up to date. Special training programs should be organized when new devices and technologies are introduced. Radiation therapy staff should be regularly trained, and they should have up-to-date information (Moran et al. 2011).

Quality Control Procedure

Radiation therapy treatment devices should be regularly calibrated and maintained to ensure the accurate application of doses, a critical aspect for patient safety. Dosimetric measurements and device controls are performed to verify that treatment doses are accurately calculated and applied. Auxiliary imaging methods like IGRT devices are regularly checked to ensure accurate patient targeting. Treatment planning processes are assessed with quality control protocols to confirm the accurate identification of tumor targets and normal tissues. Patient positioning devices and systems are checked to ensure accurate positioning during treatment (Xing et al. 2006).

Various quality control methods are employed for RT devices and components. These tests, including daily, weekly, or monthly routine checks, are conducted to ensure that devices function properly, and treatment

processes adhere to standards. Performance tests for treatment devices and dosimetric systems are conducted using various phantoms. These measurements follow specific quality control protocols. These protocols are determined and applied in accordance with national and international standards. All conducted quality control activities are regularly recorded and reported.

Although these programs and quality control methods are performed according to national and international protocols, each application can be customized according to the needs and practices of a specific institution. Quality control processes assist the radiation therapy team in continuously adapting to evolving standards and technologies.

Dosimetric Equipments

Dosimeters measure the radiation dose administered to a patient. It is crucial to ensure the accurate operation and regular calibration of these devices. Field Dosimeters and Ion Chambers are employed to verify the delivery of precise doses during treatment. Dosimetric controls offer a preventive approach to detect and rectify potential errors in the radiotherapy process, thereby enhancing patient safety and maximizing treatment effectiveness. Radiotherapy centers develop quality control programs in accordance with national and international standards, regularly reviewing these programs. Quality control of dosimetric devices ensures the accurate and reliable delivery of doses in radiotherapy applications.

Various detectors are used for dosimetry in Radiotherapy (RT). These detectors evaluate energy response during the quality control process, checking whether the dose is accurately measured at specific energy levels. Ion Chambers, Diode detectors, Two-Dimensional Dosimeters, Diamond Detectors, Thermoluminescent Dosimeters (TLD), MOSFET detectors, and gel dosimeters are commonly used in RT dosimetry.

Ion Chambers

Ion chambers are crucial dosimetric devices for measuring radiation doses. Quality control assesses the calibration and accuracy of these chambers. Monitoring is conducted through calibration measurements at specific energy levels and target areas to ensure accurate dose measurement. An ion chamber is a dosimetric device consisting of a chamber filled with gas that measures ionization, determining the radiation dose. Ion chambers find applications in medical radiotherapy, nuclear medicine, industrial radiography, and nuclear energy (Saminathan et al. 2010).

There are three main types of ion chambers, with Cavity Ionization Chambers commonly used for high dose rates and values. Vented Ionization Chambers allow the release of gas from the ion chamber to the atmosphere or an enhanced chamber. Geiger-Muller Counters, based on the principle of ion chambers, are often used to measure low dose rates and are commonly referred to as counting devices. Cylindrical ion chambers are widely used in RT. These chambers consist of basic components such as a cavity, gas, and electrodes. The cavity is a chamber, usually cylindrical or box-shaped, filled with gas, typically inert gases like argon or helium. These gases initiate ionization processes by interacting with radiation. Electrodes within the ion chamber measure the electric current carried by ions formed in the gas. Calibration is necessary due to changes in air mass within the ion chamber volume, requiring pressure and temperature corrections.

Ion chamber measurements require accurate calibration and regular maintenance. Calibration is typically performed at specific time intervals and dose ranges. Ion chambers provide accurate measurements at high dose rates, have a broad dose range, and exhibit linear responses. However, disadvantages include their large, complex, and costly nature, limitations in measuring doses in air, water, or other media, and longer response times compared to other dosimetric devices (Gómez et al. 2022).

Diode Detectors

Diode detectors are devices used in radiotherapy to measure and monitor radiation doses. They are especially useful for measuring surface doses and verifying if radiation doses are delivered according to the treatment plan. Diodes generate electron-hole pairs when traversed by ionizing particles, creating an electric current during irradiation. The resulting current difference serves as the detector's signal and is connected to an electrometer for measurement. Diode detectors are compact, exhibit high sensitivity to radiation, and are independent of pressure and temperature changes. They find applications in small field dosimetry, such as IMRT and stereotactic treatments.

However, diodes have energy dependence and recombination characteristics, making them responsive to radiation damage. They also exhibit directional dependencies, with sensitivity varying up to 3% when irradiated perpendicular to the beam. Proper orientation and shielding are necessary to optimize their performance, especially in low-energy scattered photon conditions (Laub and Crilly 2014).

Two-dimensional Dosimeters

Two-dimensional dosimeters are devices that measure and track radiation doses in a specific plane. In radiotherapy, 2D arrays and film dosimeters are common among two-dimensional detectors. These detectors are used to verify treatment plan accuracy, optimize radiation doses, and ensure patient safety. 2D arrays consist of devices arranged in a matrix, with each detector measuring radiation doses and transmitting results to a computer. Flat panel detectors, such as electronic portal imaging detectors, measure radiation doses in a plane by using materials like amorphous silicon or brittle polycrystalline silicon, undergoing changes in properties when exposed to radiation. These changes are then used to determine the absorbed dose.

Film dosimeters determine the distribution of radiation dose. The quality control process assesses film calibration and accuracy. Film dosimetry measurements, made using a radiation-sensitive film, evaluate the accuracy of doses used in treatment planning periodically. Film dosimeters come in radiographic and radiochromic types.

Radiographic film dosimeters include conventional radiographic films used in medical imaging and examinations. They exhibit a wide dynamic dose range, low energy dependence, and directional sensitivity. However, they cause low-energy photon scatter due to their high atomic number materials. Film dosimeters have directional dependence.

Radiochromic film dosimetry incorporates a special gelatin layer that undergoes chemical changes when exposed to radiation. The layers consist of carbon, hydrogen, oxygen, and nitrogen. Color or optical density changes in the film are measured and analyzed to determine the radiation dose. Radiochromic films are independent of energy, exhibit dose-linear responses, and have high spatial resolution. They do not require post-irradiation processing, are insensitive to light, and offer high surface sensitivity. Radiochromic films are used in IMRT and stereotactic treatment plans for verification, MLC quality control, penumbra assessments, and surface dose measurements.

Advantages of film dosimetry include high resolution and sensitivity, the ability to determine dose distribution in 2D or 3D, quick measurement and evaluation due to advanced film technologies. However, disadvantages include long processing procedures, the need for special equipment and conditions for certain films, and the inability to reuse film dosimeters after initial use. Key factors in film dosimeter use include regular calibration,

ensuring proper development conditions, and using accurate techniques to minimize measurement errors (Butson et al. n.d.).

Diamond Detectors

Diamond detectors are high-performance detectors used to measure radiation doses. Typically made from single-crystal diamond material, these detectors measure changes in the electrical properties of diamond crystals when exposed to radiation, determining the radiation dose. Diamond detectors, especially those made from high-purity single-crystal diamond material, are semiconductor devices. When exposed to radiation, they undergo changes in electrical conductivity due to the creation of electron-hole pairs in the diamond crystal. The resulting alterations are measured between electrodes located at the tip of the diamond detector, determining the radiation dose.

Diamond detectors are highly sensitive to radiation and offer high-precision measurements, providing reliable results even at low doses. The linear response of single-crystal diamond to radiation ensures high linearity. Diamond detectors provide accuracy and reliability, rapid response in dose measurement, longevity, and resistance to radiation damage. They exhibit a proportional response to absorbed dose rate, homogeneous directional dependence, and excellent spatial resolution, making them ideal for small field dosimetry with high dose gradients. Despite these advantages, diamond detectors have higher production and processing costs compared to other detectors, and the production and processing of single-crystal diamonds are challenging (Schirru et al. 2010).

Termoluminescent Dosimeters

Termoluminescent dosimeters (TLDs) are dosimeters that use thermoluminescent materials to measure radiation doses. Thermoluminescence is the phenomenon where the energy given to a crystal is re-emitted as light photons when the crystal is heated.

TLD dosimeters are made from chemical substances such as LiF (Mg, Ti), Li2B4O7, CaSO4, and CaF2. The most commonly used TLD material is LiF (Lithium Fluoride). LiF crystals, when exposed to radiation, exhibit thermoluminescent light emission when heated to a specific temperature. Another commonly used TLD material is Calcium Sulfate ($CaSO_4$), which is sensitive to alpha, beta, and gamma radiations. Magnesium Fluoride (MgF_2), another material, is sensitive to ultraviolet (UV) radiation. TLDs

are typically used in the form of rods (cylinders) or chips (squares) and can also be found in powder form.

When exposed to radiation, the electrons of atoms inside the crystal are captured by traps. Upon heating the crystals, the electrons freed from the traps emit visible light of equal energy between two energy levels. The intensity of the emitted light is proportional to the absorbed radiation dose by the crystal. The graphs of changes in emitted light intensity over temperature or time create glow curves. The total area under a glow curve corresponds to both the radiation absorbed by the crystal and the total light emitted due to the crystal's heating. TLD measurements require a reader device, consisting of a TLD oven that reveals the absorbed dose through heat, a photomultiplier tube, and a printer screen. TLDs are compact, exhibit a long measurement range, and provide dose-proportional responses. The detector's dose effect will be erased after the reading process. Each dose on the TLD will be read once, making TLDs preferred for skin dose and measurements at radiation field edges. Advantages of TLDs include high sensitivity, long-term stability, dose repeatability, and the ability to work over a wide dose range. However, disadvantages include long readout times and limited dose measurement capabilities in specific energy ranges (Lonski et al. 2014).

MOSFET Detectors

Metal-Oxide-Semiconductor Field-Effect Transistor (MOSFET) detectors are semiconductor-based detectors used for dosimetry, measuring radiation doses in radiotherapy applications. While MOSFET is a fundamental semiconductor component in transistor technology, it can measure radiation doses when utilized as a detector. MOSFET detectors are typically silicon-based and consist of a capacitor and a transistor. The transistor, a key part of the structure, includes a metal coating with an added insulating layer (oxide layer) electrically charged by the examined radiation effect. When the detector is exposed to radiation, ionization of atoms in the oxide layer occurs, affecting the transistor structure. Changes in the electrical properties of the transistor due to radiation-induced alterations in the oxide layer enable the reading of the transistor's characteristics and the determination of radiation dose. MOSFET detectors respond rapidly to radiation, offering high resolution even at low doses and the ability to measure radiation doses inside a patient during treatment. However, drawbacks include being single-use, not reusable after calibration, sensitivity to operating temperatures, and direct impact from temperature changes (Kohno et al. 2008).

Gel Dosimetry

Gel dosimetry is a dosimetric technique used to achieve high dose sensitivity. In this method, a gel material is employed, and the chemical changes within the gel, measured when exposed to radiation, provide dose information. To ensure alignment between planned and measured doses, measurements taken during gel dosimetry use are regularly monitored. Gel dosimetry has various types, including Normoxic Polymer Gel Dosimetry, Ferrous Sulfate Gel Dosimetry, and Fricke Gel Dosimetry (Farhood et al. 2018).

Normoxic Polymer Gel Dosimetry involves a gel that measures changes in dose when exposed to radiation. It typically operates in an oxygen-rich environment. Ferrous Sulfate Gel Dosimetry uses a gel containing ferrous sulfate. Changes occur in the gel due to interactions between iron ions when exposed to radiation. Fricke Gel Dosimetry uses a gel containing radioactive iron in water. Reaction occurs among iron ions when exposed to radiation, and changes are measured to determine the dose. The gel is prepared by mixing predetermined materials, usually including water, gelatin, food coloring, and radiation-sensitive materials. The prepared gel is exposed to radiation, which may occur during radiotherapy treatment or in a laboratory setting with a specific dosage applied (Farhood et al. 2018). Chemical changes in the gel due to radiation exposure are analyzed. These changes, often measured using specialized analysis techniques like magnetic resonance imaging or optical methods, are converted into radiation dose. Advantages of gel dosimetry include the ability to measure 3D dose distributions, high resolution and sensitivity, and the acquisition of dosimetric data in real-time or shortly afterward. Disadvantages include the time-consuming nature of the process, requiring more complex analyses in a laboratory setting. Factors such as the chemical stability and reproducibility of the gel need attention in gel dosimetry, making it a significant dosimetric technique, especially in radiotherapy applications for treatment planning and dose control (Atiq et al. 2017).

Conclusion

Quality control methods in Radiotherapy (RT) are employed to ensure accurate and reliable application throughout every stage of the treatment process. These controls encompass processes from treatment planning to dose application and patient monitoring. The necessity of quality control methods is primarily related to ensuring patient safety and maximizing treatment effectiveness.

The aim of Radiotherapy quality control is to ensure that the correct doses are accurately directed to the appropriate target. Improper application of the target can lead to serious health problems. Therefore, quality control methods, including treatment planning, dosimetry, the performance of radiotherapy devices, patient position control, and imaging, should be utilized. It is essential to regularly maintain radiotherapy equipment during the quality control process, detect equipment malfunctions early, and make corrections. This ensures that the devices consistently operate accurately and reliably. Radiotherapy devices are complex and delicate machines, emphasizing the significant importance of regular maintenance and quality control.

In conclusion, Radiotherapy quality control methods are of critical importance to ensure patient safety, enhance treatment success, and sustain the accurate operation of equipment. These controls, by providing consistency and accuracy at every stage of the treatment process, contribute to helping patients achieve the best clinical outcomes.

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