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Option: Immuno-Oncology

The Effect of hot water on inflammation induced by hypercholesterolemia in rats

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Dedication

Thanks to ALLAH who have lightened my path and who granted me the ability to accomplish this work.

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To my univercity MENTOURI my home for five years, thank you all.

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Abbreviations

CHD: Coronary Heart Disease

CRP: C-Reactive Protein

CVD: Cardiovascular Disease

CD: Crohn's Disease

FA: Fatty Acid

FH: Familial Hypercholesterolemia

GI: Gastrointestinal Tract

HDL: High Density Lipoprotein

HMG-CoA: Hydroxyl-Methyl Glutaryl -Coenzyme A

IDL: Intermediate Density Lipoprotein

IBD: Inflammatory Bowel Disease

LDL: Low Density Lipoprotein

MUFA: Monounsaturated Fatty Acid

Ox-LDL: Oxidized LDL

PUFA: Polyunsatureted Fatty Acid

ROS: Reactive Oxygen Speices

SFA: Saturated Fatty Acid

SMCs: Smooth Muscle Cells

TFA: Trans Fatty Acid

T- CH: Total Cholesterol

TG: Triglycerid

UC: Ulcerative Colitis

VLDL: Very Low Density Lipoprotein

Figure

Figure

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INTRODUCTION

Lipids are considered one of the most elemental nutrients for humans. It may lead to disruption of signaling network and could be associated with some pathological stats, such as cancer, cardiovascular and similarly with inflammatory complication **(Jana et al., 2015).** The most commun dietary fatty acids have been subdivised into three broad classes: Saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs) **(food and agriculture organization of the United Nations, 2010).** Diets that are high in fats, particularly aliment fat: cholesterol, hydrogenated fat and omega-6 fatty acids (found in animal products and vegetable oil) have been associated with significant increases in the risk for inflammatory bowel disease (IBD) **(Persson et al., 1992).** Saturated and Trans fatty acids are less healthy kinds of fats. They can increase the risk of heart disease by increasing the total and LDL cholesterol **(Ward, 2008).**

Hypercholesterolemia is clinically characterized by an increase of the total- and low-density lipoprotein (LDL) cholesterol in plasma. It represents a high risk for the development of atherosclerosis **(Ondrejovičová, 2010**). In addition, it has been demonstrated that increased intracellular generation of reactive oxygen species (ROS) plays an important role in chronic inflammatory responses to atherosclerosis **(Rui et al., 2008)**, and it could be a major contributing factor to the tissue injury and fibrosis that characterize Crohne's disease **(Alzoghaibi, 2013).**

Atherosclerosis is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol. It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells and promoted by low density lipoproteins LDL is commonly referred to as a hardening or furring of the arteries. It is caused by the formation of multiple plaques within the arteries **(Jagdish, 2009).**

The use of water for various treatments (hydrotherapy) is probably as old as mankind. Hydrotherapy is one of the basic methods of treatment widely used in the system of natural medicine, which is also called as water therapy.

Hot Water purifies the toxin, helps melting the fat deposits and destroys harmful bacteria in our body. It is the most important catalyst in losing weight, it can also help the gastrointestinal tract to function even better. It's get rid of fat, reduce obesity, and cured high blood cholesterol, Stroke, Gastroenterisis, Heart Disease **(Alhajri, 2010).**

Objectives

- Evaluate the effect of saturated, Trans fatty acids and hot water on the weight and diet of rats.
- Evaluate the effect of hot water on hypercholesterolemia induced by Trans fats by measuring the levels of T-Ch, HDL-c, LDL-c and TG.
- Evaluate the effect of hot water on the inflammation by measuring C-reactive protein induced by hypercholesterolemia.

Chapter 01

Cholesterol and Hypercholestrolemie

I. CHOLESTEROL

I.1.Definition of cholesterol

Cholesterol is a waxy, fat- like substance that has many critical functions in the body **(Michael and Murayn., 2013).** It from the Greek word (chole means – bile, sterol) it's an animal sterol which occurs either free or as fatty esters **(Geetha et al., 2005)** and **(Jeremy, 2002)**. It is a component of membranes in body cells, required for normal development of the brain and nervous tissue. Cholesterol is the precursor to bile acids, steroid hormones, and the precursor to vitamin D **(Alberti et al., 2001)**. It is an oil-based substance and does not mix with the blood, which is water-based, it is an essential substance for the body. However, if concentrations in the blood get too high, it becomes a silent danger that puts us at risk of a heart attack **(Markus, 2015).**

I.2.Structure of cholesterol

The molecular formula of cholesterol could be written as $C_{27}H_{45}OH$, it's composed of three regions (Hydrocarbon tail, ring structure region with 4 hydrocarbon rings and hydroxyl group) (figure 01) **(Maxfield and Van, 2010).** Cholesterol molecular weight is: 386.65354 g/mol **(Kathleen, 2017).**

I.3.Transport of cholesterol

Cholesterol transport through the vascular system **(Tyler et al., 2009)**. Multi-cellular organisms solve the problem of cholesterol transport by esterifying the sterol with long-chain fatty acids and packaging these esters within the hydrophobic cores of plasma lipoproteins. The major classes of plasma lipoproteins are:

a- Very low density lipoprotein (VLDL).

b- Intermediate density lipoprotein (IDL).

c- Low density lipoprotein (LDL).

d- High density lipoprotein (HDL) **(Michael et al., 1995).**

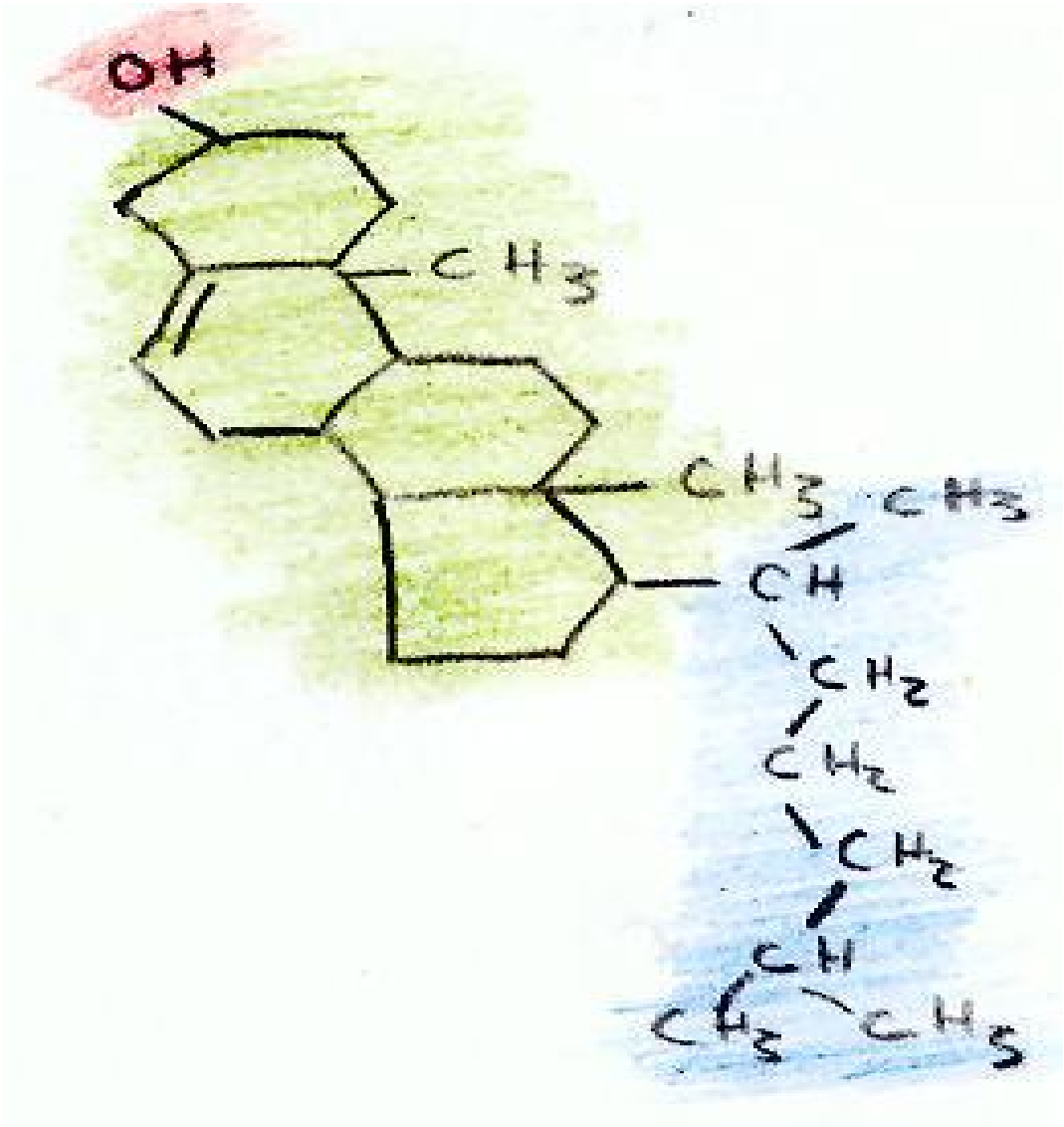

Figure01: Structure of cholesterol **(Maxfield and Van, 2010).**

-Hydrocarbon tail (shown in blue)

-Ring structure region with 4 hydrocarbon rings (shown in green)

-Hydroxyl group (shown in red) **(Maxfield and Van, 2010).**

I.4. High and low density lipoprotein

I.4.1.Low density lipoprotein LDL

Low density lipoproteins (LDL) transports cholesterol to all parts of the body where it is needed **(Alice et al., 2005)**. LDL is the classic antagonists of the circulatory system due to their propensity to bind to connective tissue in the intimal sub-layer of arteries. These processes are the motivation for the bad cholesterol **(Tyler et al., 2009).**

I.4.2. High density lipoprotein HDL

High density lipoprotein (HDL) particles promote vascular health by extracting cholesterol from tissues and delivering it back to the liver **(Tyler et al., 2009).** HDL is labeled "good" because it carries cholesterol away from the body for eventual disposal **(Alice et al., 2005).**

I.5. Biosynthesis of Cholesterol

Cholesterol can be obtained from the diet or it can be synthesized de novo **(Jeremy, 2002).** Synthesis of cholesterol occurs in virtually all cells of the Body and the major portion is synthesized by liver cells **(Alice et al., 2005)**. Cholesterol synthesis has been described as involving two pathways **(Rafael et al., 1990)** which controlled by mechanisms that turn the process on and off, depending on the body's needs **(Alice et al., 2005).**

I.5.1.Exogenous Pathway

The exogenous pathway starts with the intestinal absorption of cholesterol from dietary sources (Figure 02). Unesterified cholesterol coupled with various lipoprotein particles called chylomicrons. The chylomicrons in turn are secreted into intestinal lymph enter the bloodstream through the thoracic duct, and bind to the wall of capillaries in adipose and skeletal muscle tissue. Then cholesterol after a series of reaction either converted into bile acids, excreted in bile, or incorporated into lipoproteins originated in the liver **(Rafael et al., 1990).**

I.5.2.Endogenous Pathway

The endogenous system through which cholesterol reaches the plasma from the liver and other non intestinal tissues pathways (figure02) **(Rafael et al., 1990).** Cholesterol is synthesized via a cascade of enzymatic reactions known as the mevalonate pathway synthesis (Figure 03) **(Pedro et al., 2013).**

a. Formation of acetyl CoA

A molecule of acetic acid combines with coenzyme A (CoA) to produce Acetyl CoA in the presence of an enzyme Acetyl CoA synthetase.

b. Formation of acetoacetyl CoA

Two molecules of acetyl-CoA condense to form an acetoacetyl-CoA molecule, catalyzed by the enzyme “thiolase”.

c. Formation of HMG CoA

The acetoacetyl-CoA further undergoes condensation with one more molecule of acetyl-CoA to form HMG-CoA (3-Hydroxy 3-Methyl Glutaryl-CoA). The enzyme which mediates this reaction is called HMGCoA synthetase.

d. Formation of mevalonate

The HMG-CoA is reduced to form mevalonate by NADPH + H+ dependent reductase (HMG-CoA reductase). This is the rate limiting enzyme in the pathway of cholesterol biosynthesis.

e. Mevalonate thus formed is then converted to squalene through various steps.

f. Squalene, with the formation of various intermediates finally gives rise to the end product cholesterol **(Geetha et al., 2005).**

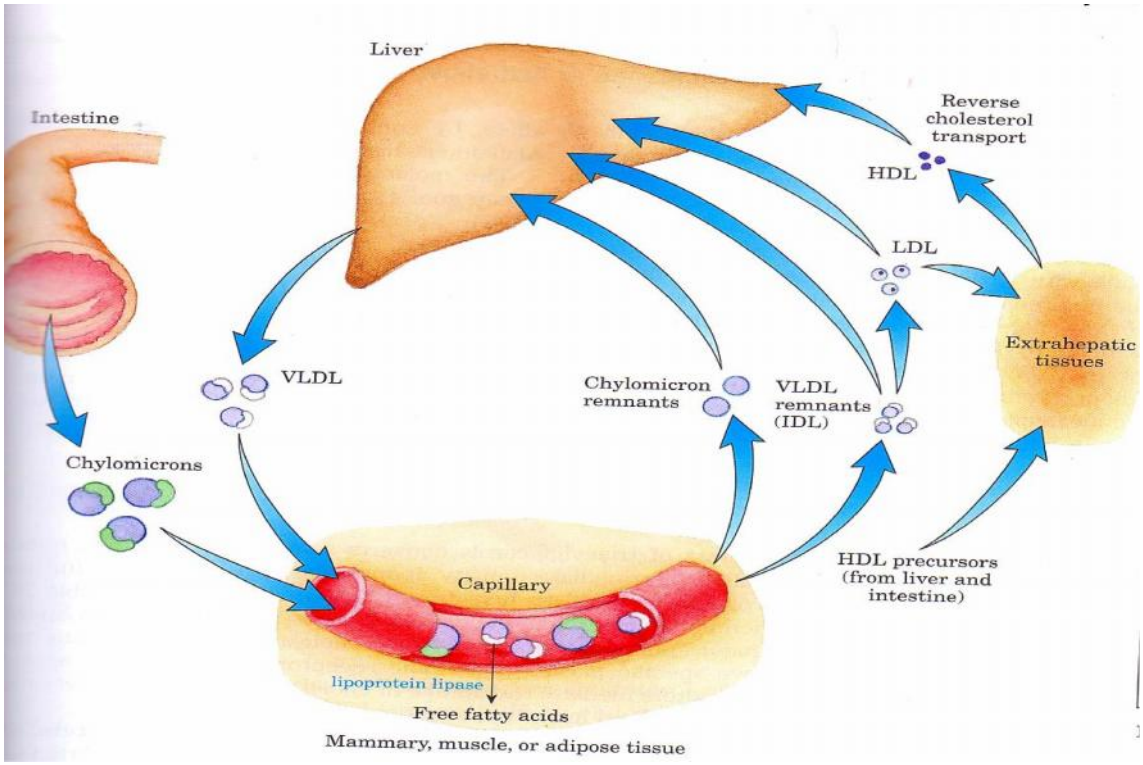

Figure02: The exogenous and the endogenous pathway synthesis of cholesterol **(Gillman et al., 1985)**

Acetic acid + CoA
⇩ Acetyl CoA Synthesize
2 Acetyl CoA
⇩ Thiolase
Aceto acetyl CoA
⇩ HMG CoA Synthetase
HMG CoA
(3-hydroxy 3-methyl glutaryl CoA)
⇩ HMG CoA Reductase
Mevalonate
⇩
Squalene
⇩
Cholesterol

Figure 03: The mevalonate pathway synthesis of cholesterol **(Geetha et al., 2005).**

I.6.Biological functions of cholesterol

Cholesterol, contrary to its popular image as a potent enemy of health and longevity, is actually a crucial substance that performs innumerable vital functions in the body:

1. It is an essential element of cell membranes, where it provides structural support and may even serve as a protective antioxidant **(Anthony, 2005).**
2. Maintain cellular integrity **(Hanrui et al., 2014).**
3. Together with sun exposure, cholesterol is required to produce vitamin D **(Geetha et al., 2005).**
4. Cholesterol is the starting point for the synthesis of several groups of very important biochemicals, including the male and female sex hormones **(Alice, 2005).**
5. Cholesterol is needed for the synthesis of bile acids, which are essential for the absorption of fats **(Anthony, 2005).**
6. Cholesterol is essential for conducting nervous impulses, especially at the level of the synapse **(Anthony, 2005).**

II.HYPERCHOLESTEROLEMIA

II.1. Definition of hypercholesterolemia

Hypercholesterolemia, defined as excessively high plasma cholesterol levels, it is an excess amount of low-density lipoprotein (LDL). LDL, or bad cholesterol, is the type of cholesterol that sticks to artery walls, builds up and thickens, which can reduce the flow of blood **(Phoebe et al, 2010).** Hypercholesterolemia is a problem faced by many Societies and is a cause of concern for health professionals, since it constitutes one of the major risk factors for the development of cardiovascular diseases **(Sheyla et al., 2005).** Numerous studies have clearly established that hypercholesterolemia leads to an inflammatory response **(Phoebe et al., 2010).**

II.2.Causes of hypercholesterolemia

Three primary disorders causing hypercholesterolemia have been identified **(Rafael at al., 1990).**

II.2.1.Genetic

High levels of cholesterol may be inherited because genes may influence the metabolism of LDL (bad cholesterol) **(Kathleen, 2017).**

II.2.1.1. Polygenic hypercholesterolemia

Polygenic hypercholesterolemia includes a group of related disorders in which multiple genes apparently interact to cause an elevation in LDL. Increased rate of formation of LDL, defective clearance of LDL, or both could be responsible for this elevation **(Rafael et al, 1990).**

II.2.1.2. Familial hypercholesterolemia

Familial hypercholesterolemia is a common disorder caused by mutations **(Isabel, 2013)** and **(Talmud, 2013)** passed down from either the mother or father causes a missing or malfunctioning LDL receptor. The LDL accumulates to dangerous amounts in the blood **(Daniel et al., 2003).**

II.2.1.3.Familial combined hypercholesterolemia

Defined as a common metabolic disorder characterized by: increase in cholesterol and/or triglyceride in at least two members of the same family, intra-individual and interfamilial variability of the lipid phenotype and increased risk of premature coronary heart disease (CHD) **(Sniderman et al., 2002).**

II.2.2.Foods high in saturated fats and Cholesterol

Cholesterol levels can become elevated by a diet high in saturated fat and Trans fatty acids, also known as trans fat**,** Trans fatty acids (TFA) are unsaturated fatty acids with at least one double bond in the trans (hydrogen on opposite sides) position (Figure04) **(Corey, 2017)**. TFAs are found in processed foods made with partially hydrogenated vegetables oils such as, cookies, snack foods **(Guy, 2008).** Diets with a lot of these two types of fat contribute to high levels of low-density lipoprotein (LDL) cholesterol **(Anna, 2016)** and **(Corey, 2017).**

II.2.3.Other diseases

Some people suffering from diabetes may have high levels of cholesterol **(Kathleen, 2017).**

II.3. Types of hypercholesterolemia

There are six types of hypercholesterolemia (Table01) **(Phoebe et al., 2010).**

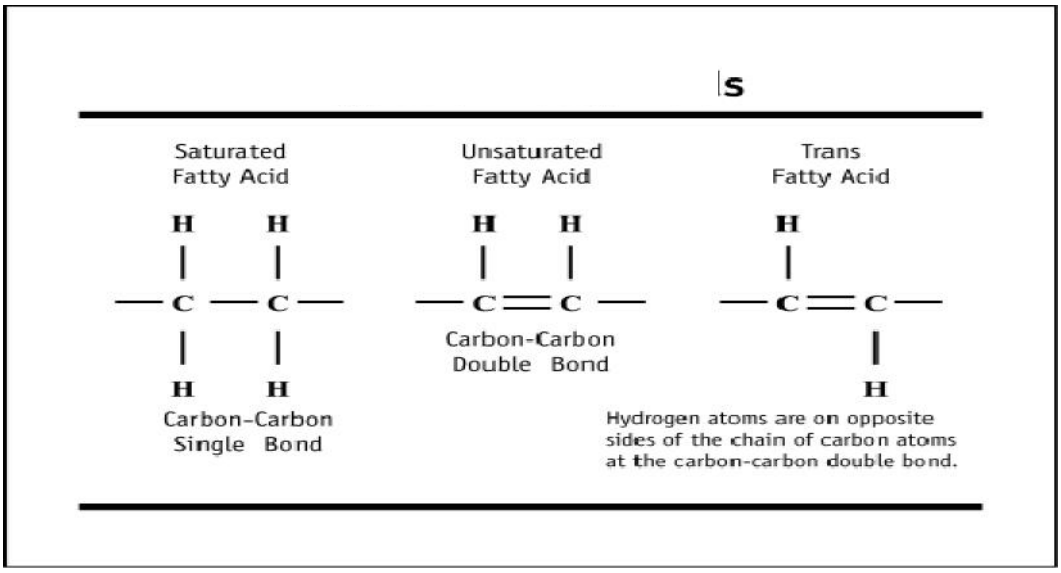

Figure04: Types of fatty acids showing Trans configuration **(Guy, 2008).**

Table01: Types of hypercholesterolemia **(Maxfield, 2010)**

Type of hypercholesterolemia	Elevated lipoprotein(s) present	Serum lipid pattern
Type 1	elevated chylomicrons	associated with lipoprotein lipase deficiency, apolipoprotein C-II deficiency
Type 2a	elevated LDL	associated with familial hypercholesterolemia, polygenic hypercholesterolemia, familial combined hypercholesterolemia
Type 2b	elevated LDL and VLDL	associated with familial combined hypercholesterolemia
Type 3	elevated intermediate-density lipoprotein	associated with dysbetalipoproteinemia
Type 4	elevated VLDL	associated with familial hypertriglyceridaemia, familial combined hyperlipidaemia, sporadic hypertriglyceridaemia, diabetes
Type 5	elevated chylomicrons and VLDL	associated with diabetes.

II.4. Consequences of hypercholesterolemia

Hypercholesterolemia plays an important role in the development and pathogenesis of various human diseases **(Manuela, 2004).**

a- Numerous studies have clearly established that hypercholesterolemia leads to an inflammatory response within the microvasculature **(Phoebe et al., 2010).**

b- Studies in different human populations also have shown that those with high concentrations of plasma cholesterol have more atherosclerotic disease than those with low cholesterol **(Scott et al., 1978).**

c- Hypercholesterolemia is associated with an increased risk for coronary heart disease (CHD) **(Cathreen and George., 2017).**

d- Atherosclerosis due to FH (Familial hypercholesterolemia) manifests primarily in adulthood; it has a precocious inception as early as the 1st decade of life **(Mithun, 2014).**

III. Relationship between oxidative stress, hypercholesterolemia and atherosclorosis.

Oxidative stress is a situation that introduces a high production of oxidants or a low level of antioxidants, which results in an imbalance between oxidant and antioxidant systems causing free radical damage **(Raynoo et all., 2015).** Oxygen free radical and lipid peroxides (oxidative stress) are highly reactive and represent very damaging compounds. Oxidative stress could be a major contributing factor to the tissue injury and fibrosis that characterize Crohn's disease **(Alzoghaibi, 2013).** Hypercholesterolemia , diabetes mellitus (DM), arterial hypertension, smoking, age, and nitrate intolerance increase the production of free ROS **(Georgia et al., 2009)**. Several lines of evidence demonstrate that oxidative stress plays an important role in the pathogenesis and development of cardiovascular diseases, including hypertension, dyslipidemia, atherosclerosis, myocardial infarction, angina pectoris, and heart failure **(Taibur et al., 2012).**

Chapter02

Inflammatory disease

IV. INFLAMMATION

IV.1. DEFINITION

The word inflammation comes from the Latin *"inflammo"*, meaning *"I set alight, I ignite »*, or inflammare (to set on fire) **(Christian, 2015)** and **(Scott, 2004)**. Inflammation underlies a wide variety of physiological and pathological processes **(Ruslan, 2008)**. It is a biological reaction to a disrupted tissue homeostasis **(Noah et al., 2012)**. It is the body's attempt at self protection, the aim being to remove harmful stimuli, including damaged cells, irritants, or pathogen and begin the healing process **(Christian, 2015)**.

Inflammation is critical for the development of many complex diseases and disorders including autoimmune diseases, metabolic syndrome, neurodegenerative diseases, cancers, and cardiovascular diseases **(Masaaki and Toshio, 2012).**

IV.2. TYPES OF INFLAMMATION

IV.2.1. Acute inflammation

The acute inflammation is characterized by increased blood flow and vascular permeability along with the accumulation of fluid, leukocytes, and inflammatory mediators such as cytokine **(Carol et al., 1997).** It is starts rapidly and quickly and becomes severe. The Signs and symptoms are only present for a few days, but in some cases may persist for a few weeks **(Christian, 2015).**

IV.2.2. Chronic inflammation

Chronic inflammation is characterized by the development of specific humoral and cellular immune responses to the pathogen(s) present at the site of tissue injury **(Carol et al., 1997).** This means long-term inflammation, which can last for several months and even years **(Christian, 2015).**

IV.3. C- REACTIVE PROTEIN

IV.3.1. C-reactive protein and inflammation

Since inflammation is believed to have a role in the pathogenesis of cardiovascular events, measurement of markers of inflammation has been proposed as a method to improve the prediction of the risk of these events **(Paul et al., 2000).**

In the presence of an acute-phase stimulus, several proteins are up-regulated. C-reactive protein (CRP) is one of the most important acute-phase proteins. Stimuli that induce an acute-phase reaction can be of various origins: infectious (bacterial, fungal, mycobacterial, or severe viral), inflammatory, stress, tissue necrosis, trauma, childbirth, and neoplasia **(Séverine, 2004).**

IV.3.2. definition

C- reactive protein (CRP) is a major acute-phase plasma protein displaying rapid and pronounced rise of its serum concentration in response to infection or tissue injury **(Volanakis, 2001)**. CRP was so named because it was first discovered as a substance in the serum of patients with acute inflammation that reacted with the C- (capsular) polysaccharide of pneumococcus **(Moneer et al, 2012)**. C-reactive protein (CRP) is known to most clinicians as a marker of inflammation but has many other functions besides this **(Séverine et al., 2004).**

IV.3.3. structure of the C-reactive protein

C-reactive protein (CRP) belongs to the pentraxin family of calcium dependent ligand-binding plasma proteins. The human CRP molecule is composed of five identical non-glycosylated polypeptide subunits each containing 206 amino acid residues. The protomers are non-covalently associated in an annular configuration with cyclic pentameric symmetry. The pentraxin family, named for its electron micrographic appearance from the Greek penta (five) ragos (berries), is highly conserved in evolution **(Amit et al., 2014)** (Figure05).

IV.3.4.Function of the C-reactive protein

The main biologic function of CRP is determined by its ability to recognize pathogens and damaged cells of the host and to mediate their elimination by recruiting the complement system and phagocytic cells **(Volanakis, 2001)** and **(Séverine et al., 2004).** CRP therefore is

an important molecule in the host's innate immune system and in the protection against autoimmunity **(Séverine et al., 2004).**

IV.3.5.C-reactive protein level and clinical implication and indication

CRP usually isn't present in the blood. In adults, results may be reported as less than 0.8 mg/dl (less than 8 mg/l). An elvated CRP level may be present in rheumatoid artirits, rheumatic fever, complications of diabetes, obesity, cancer, acute bactérials and viral infections, inflammatory bowel disease, hodshkin's disease, and systemic lupus erytheromatosus **(Lippincott and Wilkins, 2009).**

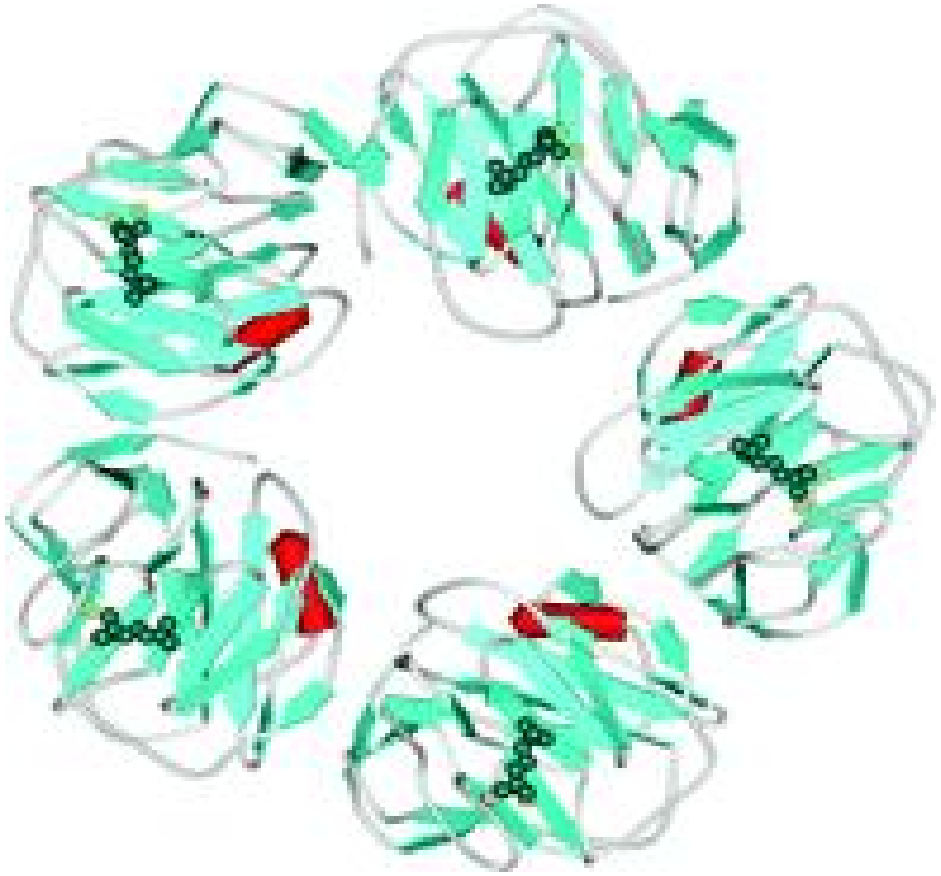

Figure 05: The Crystal structure of C-reactive protein complexed with phosphocholine. The calcium ions are yellow, and phosphocholine is green **(Steven et al., 2004).**

V.ATEROSCLOROSIS

The Elevated levels of blood lipids are well documented risk factors for cardiovascular disease (CVD) **(Robert, 2013).** Hypercholesterolemia is clinically characterized by an increase of the total and low-density lipoprotein (LDL) cholesterol in plasma. It represents a high risk for the development of atherosclerosis **(Pirinccioglu et al., 2010)**. The concept that dietary cholesterol contributes to hypercholesterolemia and cornory heart disease CHD risk has been a fundamental part of public health **(Donald, 2000)**. The cardiovascular disease, which causes coronary artery and peripheral artery disease, is the largest single cause of death and disability in the industrialised world **(George and Johnson, 2010).**

V.1.Definition

Atherosclerosis is the pathology that underlies cornory heart disease CHD. It is defined as a focal, inflammatory fibroproliferative response to multiple forms of endothelial injury. The response - to - injury hypothesis was proposed by Russell Ross and colleagues over 30 years ago **(George and Johnson, 2010).** Atherosclerosis is a chronic disease of the vascular wall and a primary cause of myocardial infarction, stroke **(Aldons, 2000)** and peripheral vascular disease **(Oliver, 2013)**. Atherosclerosis is characterized by the progressive accumulation of lipids **(Aldons, 2000)**, and leukocytes in the arterial wall **(Oliver, 2013).**

V.2.The anatomy of a normal artery

A large artery consists of three morphologically distinct layers. (Figure 06)

1-The intima, the innermost layer, is bounded by a monolayer of endothelial cells on the luminal side and a sheet of elastic fibres, the internal elastic lamina, on the peripheral side. The normal intima is a very thin region (figure07) and consists of extracellular connective tissue matrix, primarily proteoglycans and collagen.

2- The media, the middle layer, consists of smooth muscle cells SMCs.

3-The adventitia, the outer layer, consists of connective tissues with interspersed fibroblasts and smooth muscle cells (SMCs) **(Aldons, 2000).**

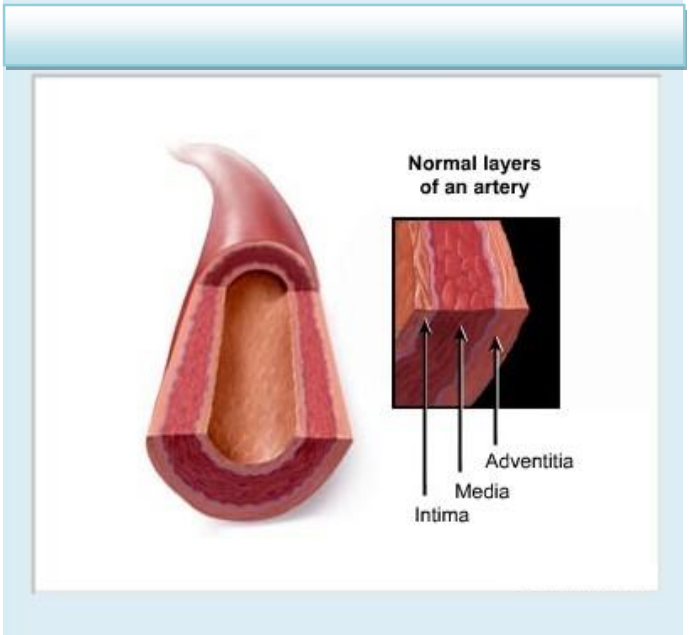

Figure 06: Anatomy of normal arterial **(web site1)**

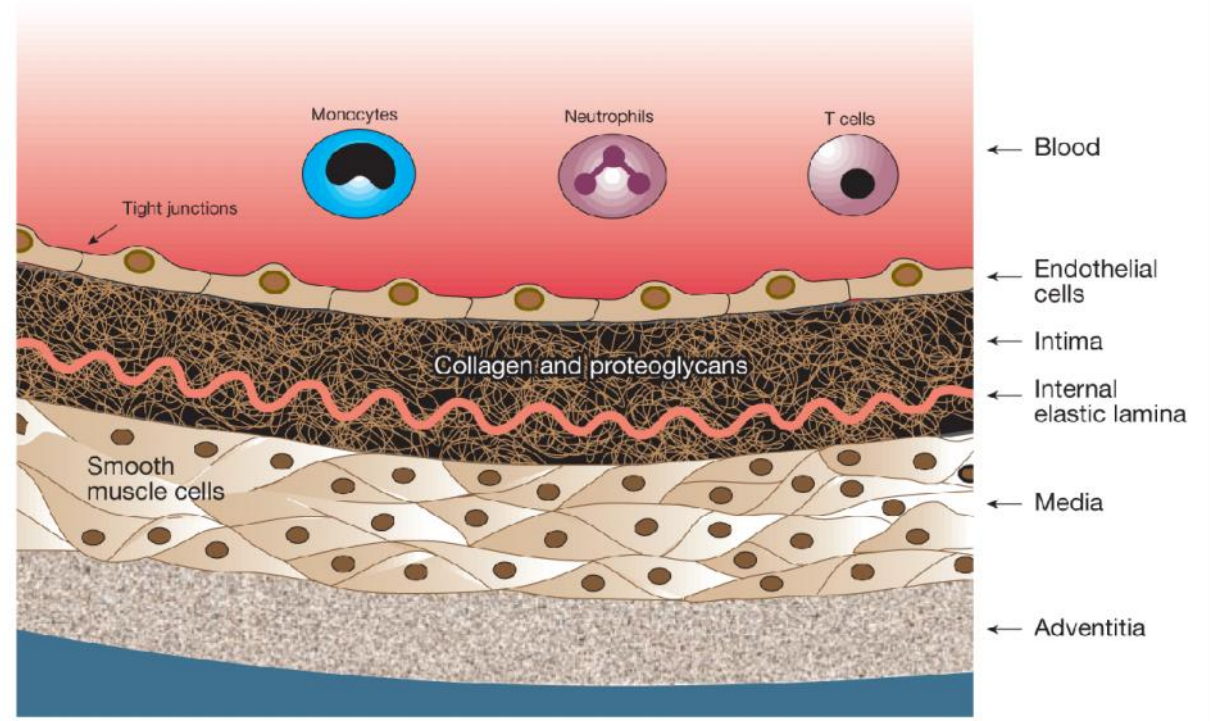

Figure 07: Anatomy of normal arterial and composition **(Aldons, 2000)**

V.3. Atherosclorosis development

There are six types lesion of atherosclerosis as shown in the (figure08):

1. The initial or type 1 lesion: consisting of lipids deposits in the intima.

2. Fatty streak or type II lesion: are visible as yellow colored streak, patches, or spots on the intimal surface of arteries. Mecrosccopically these lesions are characterized by intracellular accumulation of lipids (foam cell).

3. The fatty streak progress to **type III or intermediate lesion** this growth characterised by extracellular pools of lipids.

4. Type IV lesion or atheroma the pools coalesce to create a core of extracellular lipids

5. Type V lesion or fibroatheroma, the blood vessel architecture is destroyed, smooth cells proliferation and collagen deposition.

6. Type VI lesion; hemorrage or thrombus thus resulting in vessel occultation **(Leon, 2004).**

V.4. Atherosclerosic plaque

The atherosclerotic plaque is cholesterol and fatty acid **(Gerald, 2012).** In addition to lipids, atheromata also contain leukocytes **(Oliver, 2013)** the formation of plaques constituted by a cholesterol-rich core (atheroma) **(Caroline et al., 2017).** The atheroma ("lump of wax", from *Athera*, wax in Greek), which is the nodular accumulation of a soft, flaky, yellowish material at the center of large plaques, composed of macrophages nearest the lumen of the artery **(Jagdish, 2009)** surrounded by a fibrous cap (sclerosis). The histological classification describes the progression of lesions: types I and II are early lesions (intimal thickening and fatty streaks), whereas types II to VI lesions correspond to advanced lesions (fibro-lipidic , calcified and complicated plaques) **(Caroline et al., 2017).**

V.5.Cause of Atherosclorosis

A Numerous experimental and epidemiological studies have linked hypercholesterolemia and high serum levels of low-density lipoprotein (LDL) to the development of atherosclerosis and its complications **(Oliver, 2013)**. The low density lipoprotein particle has been shown to be a strong independent risk factor for atherosclerotic events **(Gerald, 2012)**.

The evidence is overwhelming that elevated and/or modified LDL is a major risk factor for atherosclerosis **(Gerald, 2012).** The LDL lipids are oxidized (LDL-ox) **(Taibur *et al*., 2012)** by free radicals, particularly oxygen free radicals (ROS) **(Jagdish, 2009).**

The oxidized form of LDL (ox-LDL) is capable of initiating processes that contribute to the formation of atherosclerotic lesions **(Taibur et al., 2012).**

1-When oxidized LDL comes in contact with an artery wall, a series of reactions occur to repair the damage to the artery wall caused by oxidized LDL **(Jagdish, 2009).**

2-oxLDL is taken up by macrophages and induces the release of factors that recruit other cells and stimulate smooth muscle cell proliferation.

3-oxLDL may also up- regulate expression of cellular adhesion molecules that facilitate leukocyte binding. All of these events speed up the formation of plaque , which may results heart attack and stroke in many patients **(Taibur et al, 2012)** and **(Georgia, 2009)** (Figure09)**.**

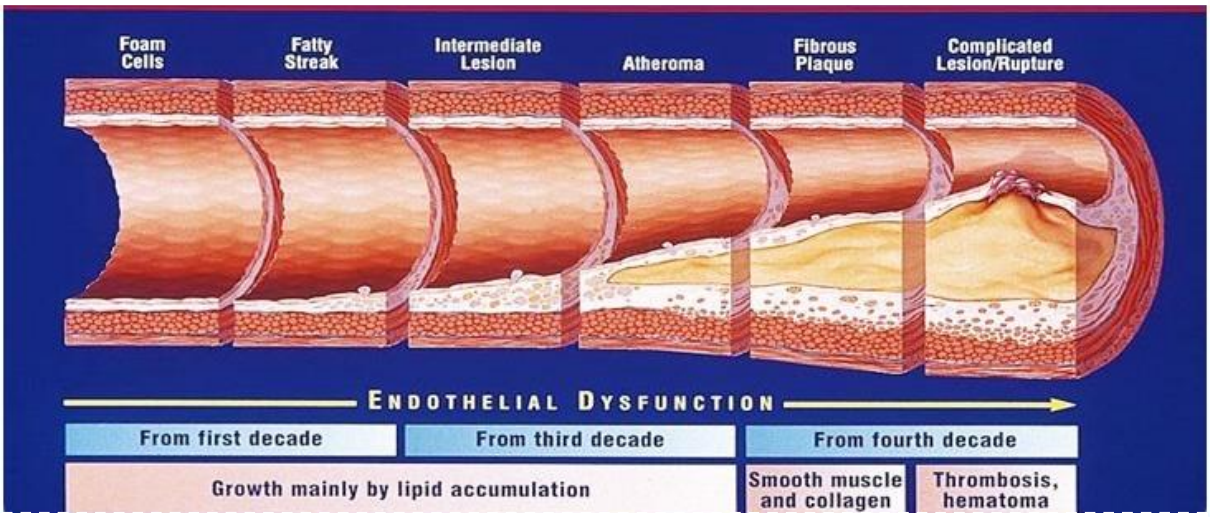

Figure 08: Devlopement of atherosclerosis **(Stary et al., 1995)**

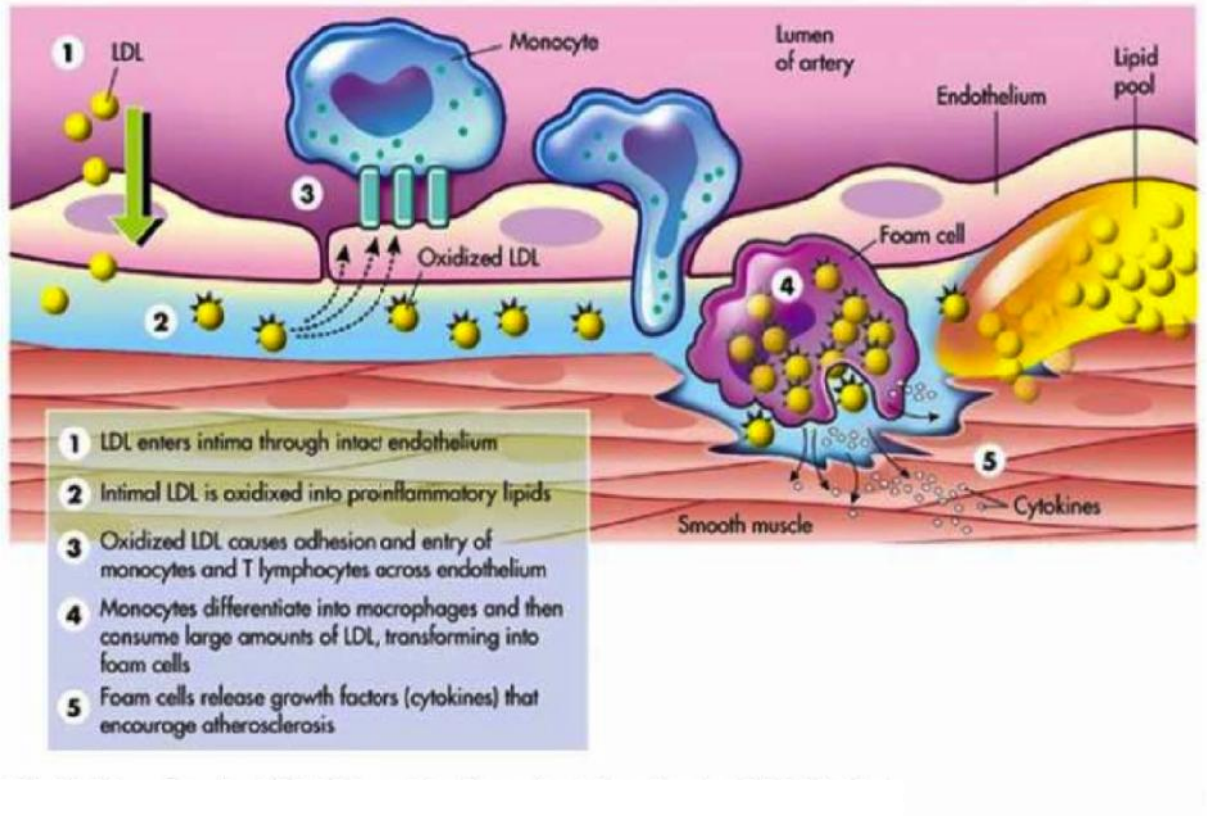

Figure 09: Endothelial injury dysfunction (cause of atherosclorosis) **(web site2)**

VI.INFLAMMATORY BOWEL DISEASE (IBD)

VI.1. Definition

Inflammatory bowel disease (IBD) represents a chronic inflammatory disorder of the intestine, generally classified by histopathological and clinical features into two major entities: Crohn's disease (CD) and ulcerative colitis (UC) **(Aris, 2011).** The pathophysiology is not fully understood but is thought to be caused by a complex interplay between gut microbiota, dysregulation of the host's immune system, genetic susceptibility and environmental factors **(Aaron, 2015).**

The inflammation may affect male and female adults and children equally, and it has a peak age at onset between 15 and 25 years of age, a lesser peakage at onset exists between 55 and 65 years of age **(Barletta et al., 2004).**

VI.2.Colon's anatomy

The large intestine, or colon, serves as a reservoir for the liquids emptied into it from the small intestine **(Kara, 2010)**. It extends from the end of the ileum to the anus. It is about 5 feet long, being one-fifth of the whole extent of the intestinal canal **(Wikibooks contributors, 2006)**

The large intestine can be divided into the cecum, ascending colon, transvers colon, descending colon and sigmoide colon **(Kara, 2010)** rectum, and anal canal ***(*Wikibooks contributors, 2006)** (Figure10)

VI.3. Mucusa anatomy

The mucosa, or inner lining of the gastrointestinal tract (GI), is a mucous membrane.it is the absorptive and secretory layer. It is composed of:

(1) A layer of epithelium in direct contact with the contents of the GI tract

(2) A layer of connective tissue called the lamina propria.

(3) A thin layer of smooth muscle (muscularis mucosae) **(Gerard, 2008).**

There are specialized goblet cells that secrete mucus throughout the GI tract located within the mucosa. On the mucosa layer there are Villi and micro villi **(Wikibooks contributors, 2006).**

VI.4. Types of inflammatory bowel disease

VI.4.1. Ulcerative colitis (UC)

Ulcerative colitis (UC) is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon, it almost invariably involves the rectum and may extend in a proximal and continuous fashion to involve other portions of the colon **(Aris, 2011).** Ulcerative colitis is majorly associated with oxidative stress and inflammation in colon tissue leading to damage **(Suluvoy et al., 2017).** Ulcerative colitis symptoms are classically, bloody diarrhea, abdominal pain and urgency. Rarely, patients may present with weight loss or other systemic symptoms, such as a lowgrade fever. The disease typically starts gradually and progresses for several weeks **(Joseph et al., 2014).**

VI.4.2.Crohn's disease (CD)

The disease is named after Dr. Burrill B. Crohn, who published a landmark paper with colleagues Oppenheimer and Ginzburg in 1932 that described what is known today as Crohn's disease **(Crohn's and Colitis Foundation, 2016).** This disease is characterized pathologically as a recurrent granulomatous inflammation of all layers of the bowel wall **(Alzoghaibi, 2013).**

Crohn's disease (CD) remains one of the major challenges in luminal gastroenterology **(Georgia et al., 2002)**. Crohn's disease (CD) is defined as a transmural inflammation process which can affect any part of the gastrointestinal tract involving the terminal ileum and right colon preferentially, but also the small bowel, colon ,rectum and the perineal area **(Cortot, 2003)** and **(Georgia et al., 2002)**. The main symptoms are diarrhea, abdominal pain, weight loss often accompanied by extra digestive manifestations such as fever, aphtosis **(Cortot, 2003).** Unlike UC, CD is commonly associated with complications such as abscesses, fistulas and strictures **(Zhang et al., 2014)** (Figure 11) and (Figure 12)

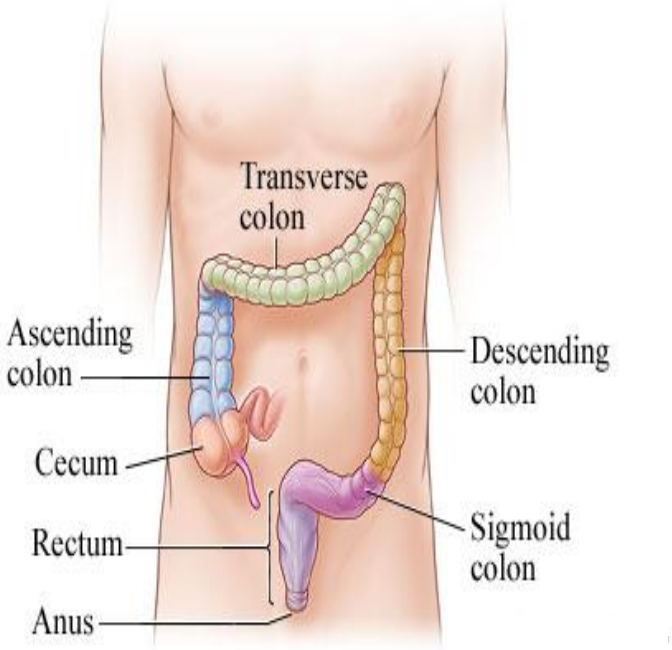

Figure 10: colon's anatomy **(Web site3).**

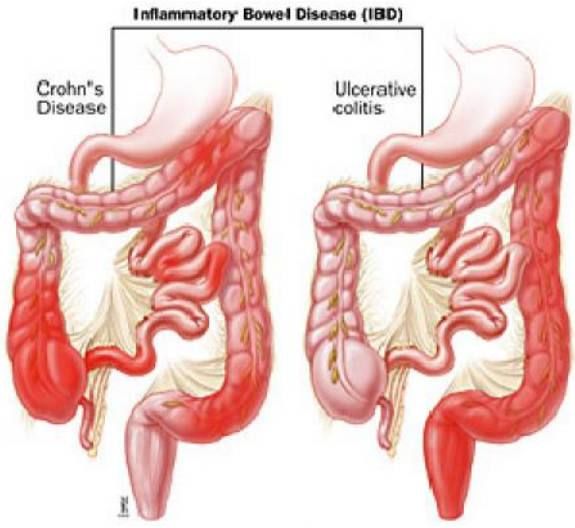

Figure 11: Crohn's disease and ulcerative colitis **(web site4)**

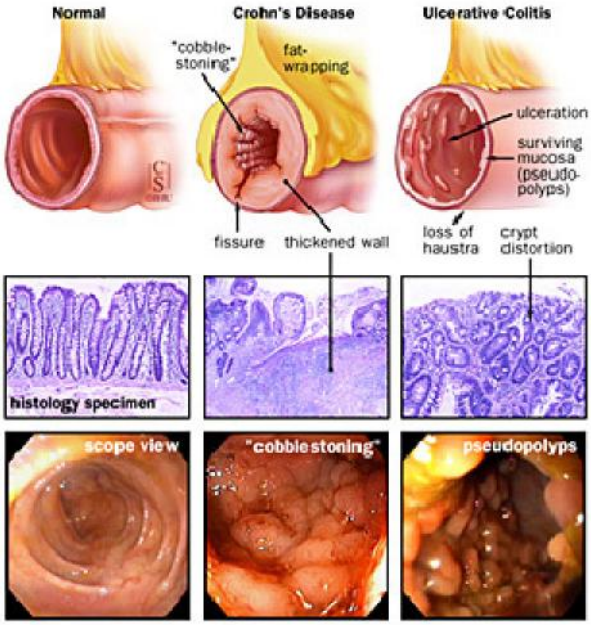

Figure12: Anatomic distribution of Crohn's disease and ulcerative colitis **(web site4)**

Chapter03

Hot water

VII. HOT WATER

VII.1. Definition of water

Water is the most important chemical component on the earth's surface **(Garrette and Grisham, 2000).** It is a unique, ubiquitous substance that is a major component of all living things **(Kim and Johnson, 2001).** It about 70% of Earth's surface, makes up about 70% of your mass, and is essential for life. Water is the only substance that exists naturally on Earth in all three physical states of matter: gas, liquid, and solid and it is always on the move among them **(Shakhashiri, 2011).**

VII.2. Structure

Water molecules have a simple structure: two hydrogen atoms bonded to one oxygen atom **(Shakhashiri, 2011)**. The chemical formula for water is H2O. Water contains strong covalent bonds that hold the two hydrogen atoms and one oxygen atom together **(Vaclavik and Christian, 2014)**. Molecular weight: 18 g/mol **(Kim and Johnson, 2001).**

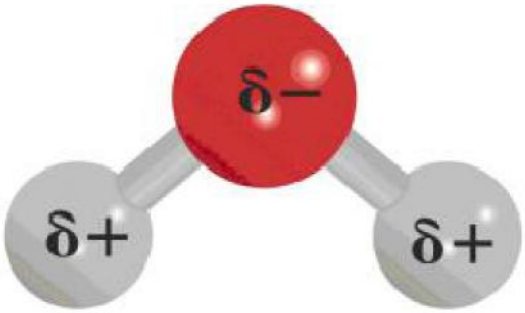

Figure 13: Water molecules **(Shakhashiri, 2011)**

VII.4. Hydrotherapy

The use of water for various treatments (hydrotherapy) is probably as old as mankind. Hydrotherapy is one of the basic methods of treatment widely used in the system of natural medicine, which is also called as water therapy. Hydrotherapy is the external or internal use of water in any of its forms (water, ice, steam) for health promotion or treatment of various diseases with various temperatures, pressure, duration, and site. It is one of the naturopathic treatment modality used widely in ancient cultures including India, Egypt, and China **(Mooventhan et al., 2014).**

VII.5.The miracle and wonder of treatment with hot water

Heat is the only element that destroy harmful bacteria, melts the fats and neutrelizes the toxines that spread in our bodies from the food preservative today's world.

The only means to split H with O by heating water which will there after burn the O from water in a form of odoerless and colorless, however, drinking at least (8) glasses of hot water daily , with enough heat affordable for our bodies. We end up inhaling a large quantité of H, wich considered as the main body's nutrient element **(Alhajari, 2010).**

VII.6. Benefits of drinking hot water

Prevent various diseases, symptoms and allergies. Heal people in pain, with sickness, allergies and diseases even if how critical it is. Get rid of fat. Reduce obesity, heals bronchial asthma, diabetes, hypertension, high cholesterol… etc, Improve brain memory. Possess a good looking body. To be healthy, we must drink the required quantity of Hot Water in a day. Health is wealth, so we have to keep a healthy body to have a wealthy lifestyle **(Alhadjri, 2010)** (Figure14).

Figure 14: Benefits of warm water intake **(Dhrubo Sen et al., 2015)**

Materials and methods

Materials and methods

1. Materials

1.1. Animals

The experiment was performed on 20 males young rats Wistar Albinos, (1-2 Months) weighing between (57.1g-126.7g). All animals were born in animal house (university des frères Mentouri constantine), and they were housed in cages with free access to water and diet every day at room temperature. Composition of diet is shown at (Table 02).

1.2. Blood samples

After 21 days of experiment, animals were fasted overnight and the blood was obtained from the retro orbital sinus and collected into EDTA tubes.

2. Methods

2.1. Biochemical analysis

2.1. a. Treatment of rats

After acclimatization to the laboratory conditions for 10 days, the twenty rats were divided into four groups and fed for 21 days with control and experimental diets (table 03).

All animals in the groups I (C) and IV (HW) were fed with animal diets however the groups II (CH/W) and III (CH/HW) were fed with diet rich in trans fats, the groups I and II have drink normal water but III and IV have drink hot water (around 50°C) (table 10), the animals were kept in cages, the weight and diet and water consumed by rats were taken throughout the experiment at the same time. After 21days, the animals were fasted overnight, and the blood was collected for biochemical analysis.

Table 02: Composition of diet taken by rats during 21days

Animal diet	**Trans fats material**
Corn	Chips(6g per day)
Soy	Vegetable oil (10g)
Barley	Cheese(6g per day)
Cellulose	Cake (12g per day)
Minerals	
Vitamins	

Table 03: Treatment of rats for 21 days

Experimental group	Treatment	Number of animals	Duration of experiment	Daily dose
GI(C)	Normal water +Animal Diet	5	21	175ml/5rats
GII(CH/W)	Normal water +Animal diet+Trans fats	5	21	175ml + 34g/5rats
GIII(CH/HW)	Hot water + Animal diet+Trans fats	5	21	175ml + 34g/5rats
GIV(HW)	Hot water+ Animal Diet	5	21	175ml/5rats

2.1. b. Lipids determination

The objective of lipids determination is to detect the hypercholesterolemia.Total cholesterol, HDL-c, LDL-c, and triglyceride were measured using colorimetric automatic procedures (Auto-Analyser type integra roche 400) at laboratory of AL AMINE Constantine.

2.1. c. High Sensitivity C-reactive protein (hs-CRP) determination

The Objective of hs-CRP measurement is to evaluate the possibility of infection or inflammatory disease. The plasma hs-CRP values were measured by immunoturbimetric method on auto-analyzer (laboratory AL Alamine).

2.2. Histological analysis

After blood samples collection, the animals were kept in the laboratory for another extra 5 days of treatment, the G I (C) and G IV (HW) were fed with animal diet and supplemented with bread and they have drink normal water and hot water respectively, however the groups II and III they were fed with diet rich in trans fats and supplemented with animal fats which is source of saturated fatty acids and bread and they have drink normal and hot water respectively (Table04). Then after this period of twenty six days of the experimental work the animals were sarificed and organs (liver, heart, aorta, spleen and intestine) dissected and weighed immediately in the wet state. After that some of these samples (liver, heart, aorta and sigmoid colon) were rinsed from all adherent adipose tissue in Nacl (0.9%) then the samples were fixed in formol (10%) for histological investigation.

Table 04: Composition of diet taken by rats during 5extra days of treatment.

Animal diet	**Trans fats material**
Corn	Chips(6g per day)
Soy	Vegetable oil (10g)
Barley	Cheese(6g per day)
Cellulose	Fats (6g per day)
Minerals	Cake (12g per day)
Vitamins	
Bread	

Results and Discussion

1. Results

1.1. Animals investigations

1.1.1. Diet variation

- **Control group I (group C)**

The diet taken from the group I (C) during the first, second and third week was (46,71g±1.82), (59,03g±6.56) and (42,63g±9.51) respectively. There is a difference very highly significantly in diet consumption between weeks p= 0.002.

The tukey's test indicated that the diet consumed by rats in the second week is increased significantly when it is compared to the first week p=0.023. However the diet consumed by rats in the third week is decrease highly significantly when it is compared to the second week p=0.002 (Figure15) and (Table05 annex).

- **Cholesterol/water group II (CH/W)**

In the group II (CH/W), the consumption of diet during the first until the third week was (47.16g±5.39), (41.91g±2.19) and (43.32g±22.14) respectively. There is a difference in diet consumption between weeks p=0.806.

The tukey's test indicated that the diet consumed by rats in the third week is decreased not significantly when compared to the first week p>0.05 (Figure 15) and (Table06 annex).

- **Cholesterol/hot water group III (group CH/HW)**

The diet taken from the rats in group III (CH/HW) during three weeks was (49.71g±12.94), (22.30g±3.34) and (29.22g±20.16) respectively. There is a difference in diet consumption between weeks p=0.014.

The tukey's test indicated that the diet consumed by rats in the second week is decreased significantly when it is compared to the first week p=0.013 (Figure15) and (Table07 annex).

- **Hot water group IV (group HW)**

The diet taken from rats in group IV (HW) during the three weeks was (43.64g±5.12), (45.26g±13.06) and (33.99g±12.32) respectively. There is a difference in diet consumption between weeks p= 0.229.

The tukey's test indicated that the diet consumed by rats in the third week is decrease not significantly when it is compared to the first week p>0.05 (Figure15) and (Table08 annex).

1.1.2. The weight variation

- **Control group I (group C)**

  The weight of rats group I (C) during the first, second and third weeks was (103,02g±1, 22), (101.15g±1.80) and (105.09g±2) respectively. There is a difference very highly significantly in weight values between groups of weeks p=0.003.

  The tukey's test indicated that the weight of rats in the third week is increased significantly when it is compared to the second week p=0.002 (Figure16) and (table 05 annex).

- **Cholesterol/water group II (group CH/W)**

  The weight of rats group (CH/W) during the first, second and the third weeks was (104,36g±3,59), (114,9g±5,59) and (127,88g±1,43) respectively. There is a difference very highly significantly in weight values betweens weeks p=0.000.

  The tukey's test indicated that the weight of rats in the second week is increased highly significantly when it is compared to the first week p=0.001,and also in the third week is increased highly significantly when it is compared to the first and the second weeks p=0.000 (Figure16) and (Table 06 annex).

- **Cholesterol/hot water group III (group CH/HW)**

  The weight of rats group (CH/HW) during the first, second and the third weeks was (69,29g±2.48), (79,11g±3.22) and (88,4g±2,15) respectively. There is a difference very highly significantly in weight values between weeks p=0.000.

  The tukey's test indicated that the weight of rats in the second and the third weeks is increased very highly significantly when it is compared to the first week p=0.000, and in the third week is increased very highly significantly when it is compared to the second week p=0.000 (Figure16) and (Table 07annex).

- **Hot water group IV (group HW)**

  The weight of rats group (HW) during the first, second and the third weeks was (74,86g±1,56) (66,15g±2.20) and (73,38g±3,18) respectively. There is a difference very highly significantly in weight values between weeks p=0.000.

  The tukey's test indicated that the weight of rats in the second week is decreased very highly significantly when it is compared to the first week p= 0.000 and in the third week is increased when it is compared to the second week p=0.000 (Figure16) (Table 08annex).

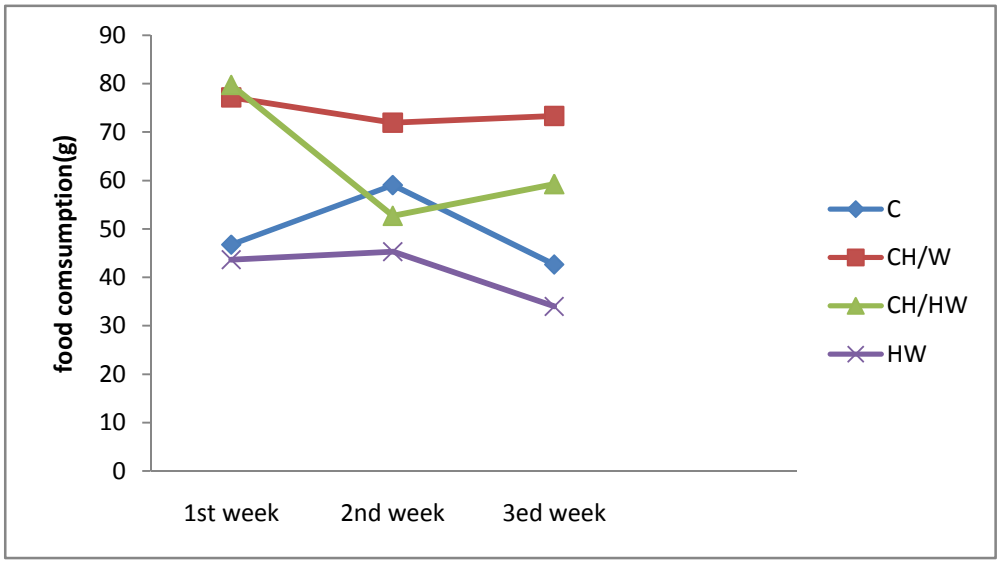

Figure 15: The effect of Trans fats and hot water intake on the diet in rats during 21 days

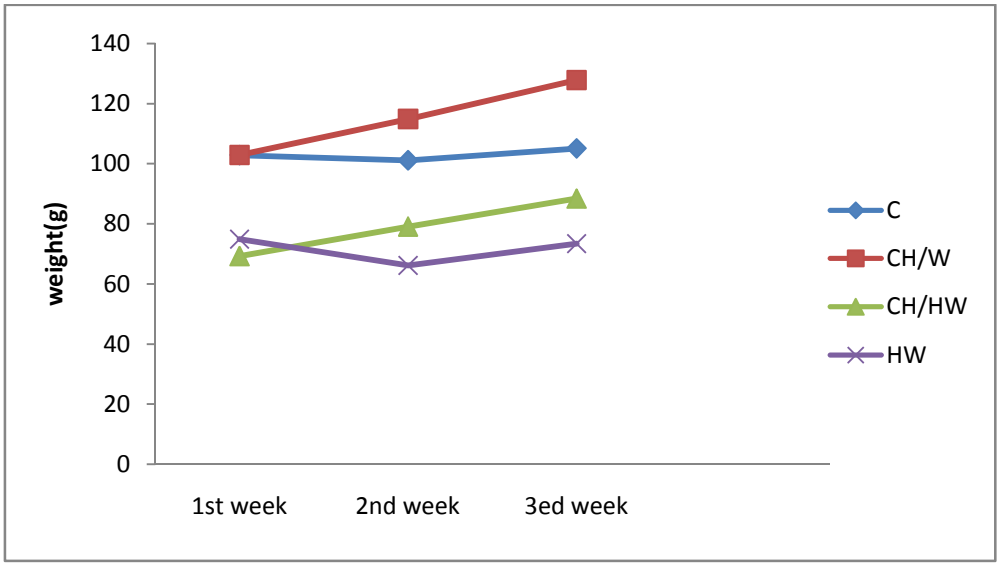

Figure16: The effect of Trans fats and hot water intake on the weight of rats during 21 days.

1.1.3. Water consumption

- **Control group I (C)**

  The quantity of water consumed by the rats in group I (C) during the first, second and the third week was (93.83ml±9.67), (116.71ml±14.16) and (117.79ml±50.75) respectively. There is a difference not significantly in water consumption p=0.395.

  The tukey's test indicated that the water consumed by rats in the third week is increased not significantly when it is compared to the first week p>0.05 (Figure 17) and (Table09 annex).

- **Cholesterol/water group II (CH/W)**

  The consumption of water in group II (CH/W) during the first, second and the third weeks was (104.17ml±8.86), (115.86ml±9.37) and (110.71ml±8.53) respectively. There is a difference not significantly in water consumption p=0.125.

  The water consumed by rats in the third week is increased not significantly when it is compared to the first weeks p>0.05 (Figure17) and (Table 09 annex).

- **Cholesterol/hot water group III (CH/HW)**

  The consumption of hot water in group III (CH/HW) during the first, second and the third week was (112.50ml±19.53), (80.14ml±6.42) and (70.56ml±10.99) respectively. There is a difference very highly significantly in the water consumption between weeks p=0.000.

  The tukey's test indicated that the water consumed by rats in the second week is decreased highly significantly when it is compared to the first week p= 0.002 and also in the third week is decrease very highly significantly when it is compared to the first week p=0.000 (Figure17) and (Table09annex).

- **Hot water group IV (HW)**

  The consumption of hot water in group IV (HW) during the first, second and the third week was (126.33ml±25.53), (85ml±21.68) and (90.21ml±9.38) respectively. There is a difference highly significantly in water consumption between weeks p=0.006.

  The tukey's test indicated that the water consumed by rats in the second week is decreased highly significantly when it is compared to the first week p= 0.008 and also in the third week is decreased significantly when it is compared to the first week p=0.020 (Figure17) and (Table09annex).

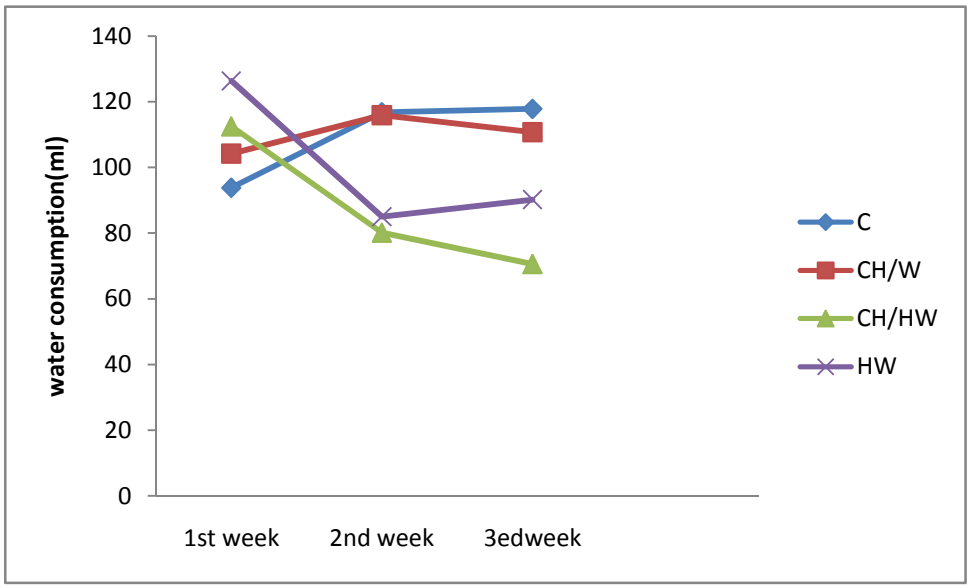

Figure 17: Water consumption during 21days of treatment

1.2. Biochemical results

1.2.1. Lipids status

1.2.1. a. Total cholesterol

The concentration of total cholesterol was (0.73g±0.10) in group I,(0.81g±0.14) in group II, (0.80g±0.03) in group III and (0.89g±0.10) in group IV, our data indicated that the cholesterol is decreased in group III when it is compared to the group II and IV but not significantly $p>0.05$ (figure 18).

1.2.1. b. Triglyceride

The concentration of Triglyceride was (0.54g±0.11) in group I, (0.57g±0.17) in group II , (0.44g±0.09) in group III and (0.77g±0.25) in group IV. The Triglyceride concentration was decreased in group III but not significantly when it is compared to the other groups $p>0.05$ (Figure 19).

1.2.1. c. HDL-c

The concentration of HDL-c was in group I (0.73g±0.11), in group II (0.79g±0.15), in the group III (0.81g±0.07), and in group IV (0.84g±0.17). We have observed an increase in the concentration of HDL-c in group III when it is compared to the group I and II, however the concentration of HDL-c in the group IV was higher than the other group but not significantly $p>0.05$ (Figure 20).

1.2.1. d. LDL-c

The results of the determination of LDL-c in group I (0.08g±0.01), group II (0.13g±0.06), group III (0.10g±0.03) and group IV (0.10g±0.02) showed that there was a difference between groups but not significantly $p>0.05$ Our data indicated that the LDL-c concentration was decreased in group III and IV treated with hot water when it is compared to the other groups treated with normal water $p>0.05$ (Figure21).

1.2.2. hs-CRP

The values of hs-CRP were in the group I (0.27g±0.12), group II (0.66g±0.28), group III (0.37g±0.12) and group IV (0.7g±0.18). Our result indicated that the hs-CRP concentration was decreased in group III when it is compared to the groups II and IV but it was slightly higher than group I (Figure22).

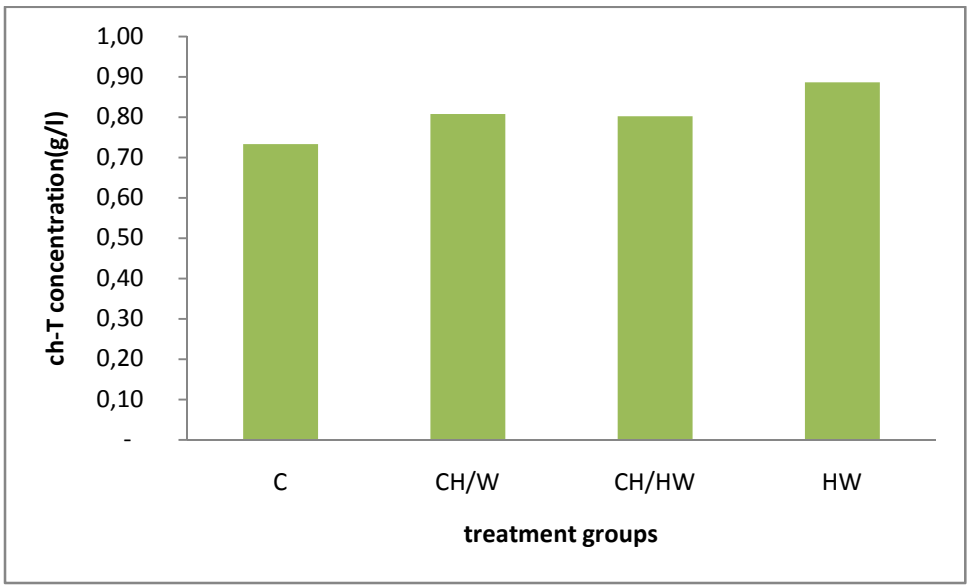

Figure 18: The interaction of Trans Fats and hot water on Total cholesterol in rats 21 days of experimental study

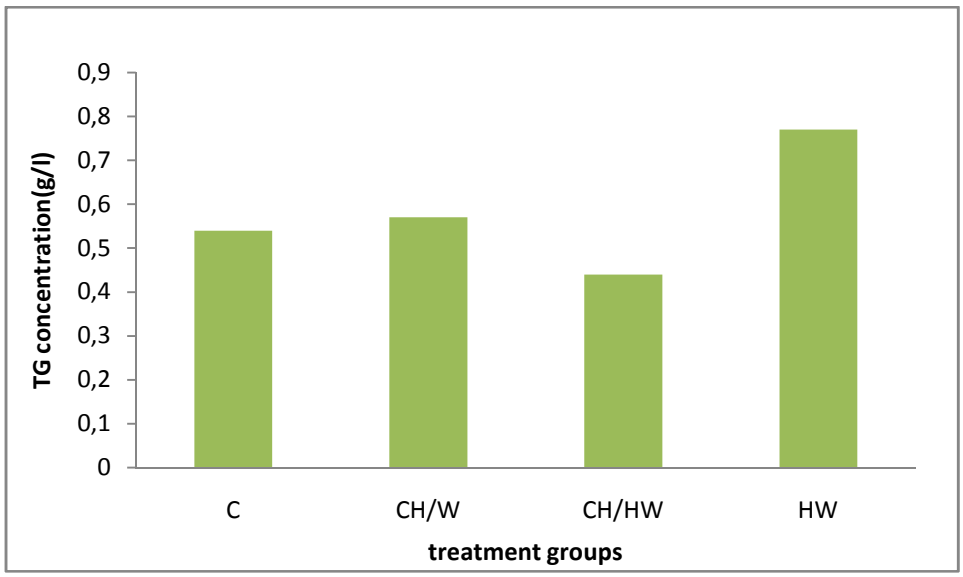

Figure19: The interaction of Trans Fats and hot water on Triglyceride in rats 21 days of experimental study

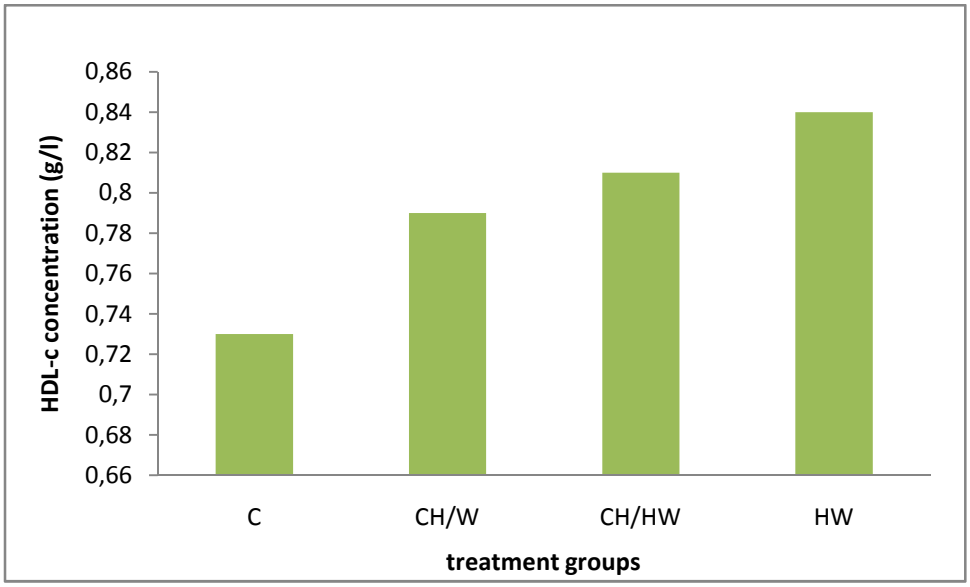

Figure 20: The interaction of Trans Fats and hot water on HDL-c in rats 21 days of experimental study

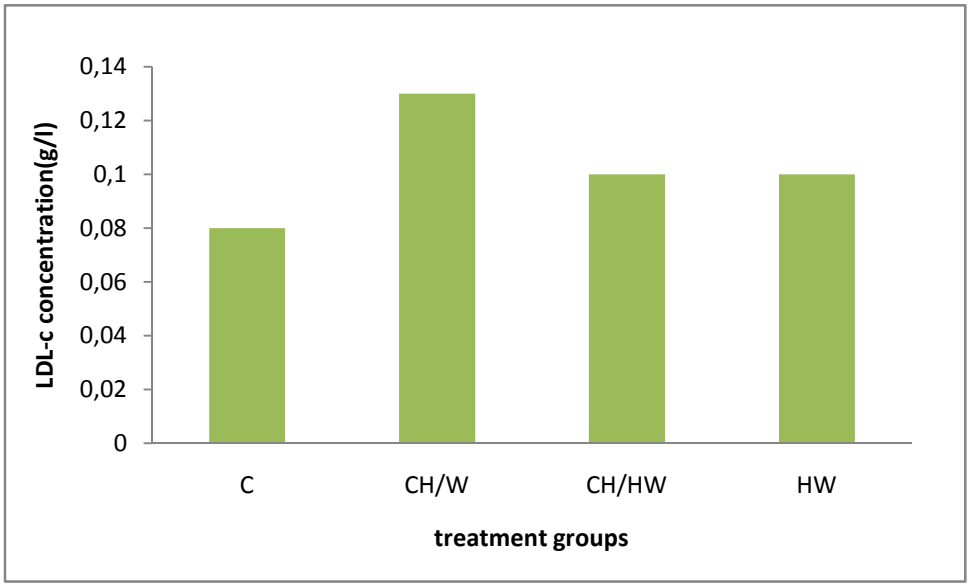

Figure 21: The interaction of Trans Fats and hot water on LDL-c in rats 21 days of experimental study

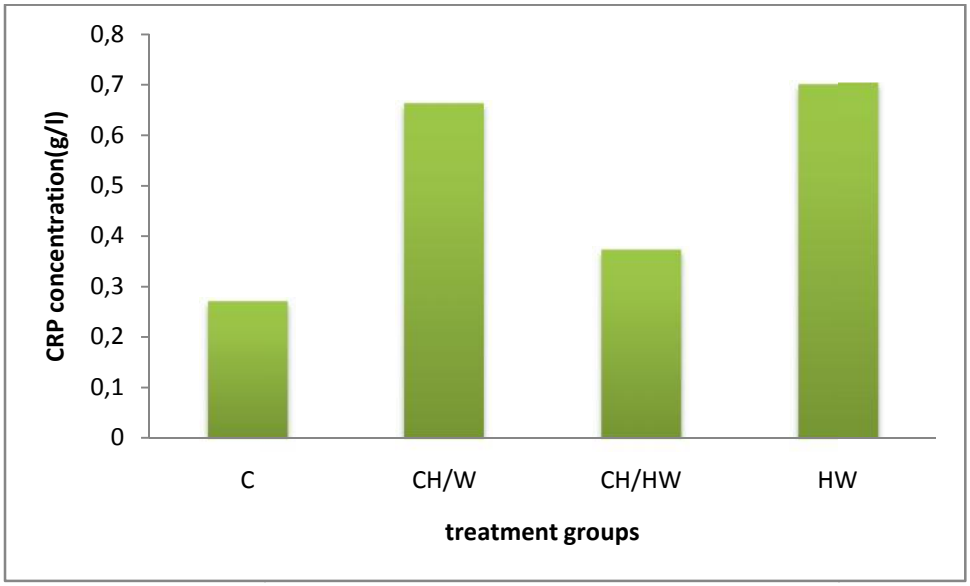

Figure 22: The interaction of Trans Fats and hot water on hs-CRP in rats 21 day of experimental study

1.3. Behavior and morphological investigations

During our study we have noticed that the animals in the group III (CH/HW) are very active when it is compared to other groups. Also we have observed nodules(0.47g, 1.50g and 3.77g) in the neck of three rats in group II (CH/W) and more adipose tissue , otherwise the other groups don't present any nodules and less adipose tissue (photo 01) also we have observed modification on renal color in rat at group II (photo 02).

1.4. Histological investigation

The weight of organs (liver, heart, aorta, spleen and intestine) in group I was (5.69g, 0.46g, 0.15g,0.51g and 11.65g) respectively. The weight of organs (liver, heart, aorta, spleen and intestine) in group II was (6.14g, 0.55g, 0.17g, 0.64g and 9.79g) respectively. The weight of organs (liver, heart, aorta, spleen and intestine) in group III was (4.70g, 0.40g, 0.15g and 9.33g) respectively. The weight of organs (liver, heart, aorta, spleen and intestine) in group IV was (5.50g, 0.42g, 0.15g and 0.40g) respectively (Figure 27). The organs fixed into the formal solution are kept for future work.

Photo 01: Shows the appearance of nodules in the neck of rats (GII) during 26 days of experimental study

Photo 02: Shows the morphological change in the kidney of rats in (G II) during 26 days of experimental study

Discussion

Hypercholesterolemia is important in approximately 50 percent of patients with cardiovascular disease, and also it's an indirect factor for the inflammatory bowel disease, other factors need to be taken into consideration. High plasma concentrations of cholesterol, in particular those of low density lipoprotein (LDL) cholesterol, is one of the principal risk factor for atherosclerosis **(Frinklin et al., 2017).**

In this study we have observed that the weight of rats fed with diet rich in Trans fat and have drink normal water is increased during 21 days of the experimental study. Our result agrees with those of **(Zerizer, 2006)** who reported that an increase in body weight of rats administered with 200 mg/kg of L-methionine during 21 days. However, we have detected that rats diet consumption is decreased during 21 days of the experimental study. Our result is not agrees with those of **(Zerizer, 2006)** who reported that the diet is increased in rats fed with L-methionine during 21 days of experimental study.

Also we have obtained that the weight of rats is increased in group fed with diet rich with Trans fat and have drink hot water. Our result is agrees with those of **(Zerizer, 2006)** who reported that an increased in body weight of rats administrated with 200 mg/kg of L-methionine and treated with B9 and B12 (0.7mg/kg) and (0.75mg/kg) respectively.

Also we have detected that the quantity of diet consumed by rats is decreased during the experimental study. Our results are not agrees with those of **(Zerizer, 2006)** wh-o reported that the diet consumed by rats fed with L-methionine and treated with vitamin B9 and B12 is increased during 21 days of experimental study.

We could explain that by the influence of hot water on the enzymes which helps the metabolism reaction **(Alhajri, 2010)**.

The increase of levels T-Ch, TG and LDL-c and decrease in HDL-c in rats fed with diet rich with Trans fats. Our result agree with those of **(Deborad et al., 2013)** who reported that, the intake of high levels of saturated fatty acids, Trans fatty acids increase the blood concentration LDL, TG and T-Ch while decreasing the level of HDL. Otherwise, the level of lipids status (T-Ch, TG and LDL-c) are decreased and HDL-c are increased in rats fed with Trans fats and treated with hot water. This results are in agreement with the work of **(Sakhri, 2014)** who reported that, the lipids status concentration (T-Ch, TG, LDL-c) are decreased and HDL-c concentration increase in mice treated with olive oil.

Also in our study we have confirmed the inflammation process by the increase of hs-CRP in rats fed with trans fats and decreased in rats fed with trans fats and treated with hot water.

This result is agree with those of **(Dorghal and Houadek, 2014)** who reported that the concentration of hs-CRP is decreased in the mice administrated L-methionine and treated with *Vitis vinifera* (500mg/kg) for 12 days.

Our results are in agreement with those of **(Alhadjri, 2010)** who reported that hot water dissolve the lipids in our organism and healing the inflammation.

Inflammation in the etiology of vascular events is becoming more obvious as a result of both clinical and laboratory studies. C-reactive protein a non specific indicator of inflammation, has emerged as a useful parameter for assessing individual risk of cardiovascular disease and acute events. When added to conventional measurements such as cholesterol fractions (LDL and HDL), CRP enhances their discriminatory power **(Scott, 2007).**

We confirmed in this study that the decrease of lipids status and hs-CRP could suppress their cytotoxic effect on the organ tissue by the inhibiting of the tumor formation and adipocyte cells proliferation which due to the inhibitor of pro-inflammatory cytokines.

Otherwise, during our experimental study we detected that the lipids status (T-Ch, TG, LDLc) are increased and the hs-CRP in group of rats fed with animal diet and treated with hot water, this is may due to the animal diet alone is poor from vitamins.

Conclusion

Conclusion

In this study we evaluated the relationship between hypercholesterolemia induced by Trans fats acid with atherosclerosis and inflammatory bowel disease (IBD).

The recommended consumption of hot water play a role on the body weight, and it has an anti-inflammatory effect for long or short term. So the use of hot water seems to have an interest in prevention of atherosclerosis and inflammatory bowel disease (IBD).

The present experimental finding showed that hot water therapy process has a positive effect on the inflammation and a decrease in lipids status.

Based on the present results, our futur work and prespectives can evaluate many topies:

-We need to keep the water at the same temperature (50°C) for the hole day and night.

-Preparation of histological section on different organs (Liver, heart, aorta, sigmoid colon).

-Measurement of anti-oxidants, GSH, catalase.

-Treatment of animals (rats and mice) with margarine during 21 days or more.

- Determination of pro-inflammatory cytokines.

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Summary

Summary

Cholesterol is a “fat-like” substance present in all body cells , it is a basic component of all cellular membranes and precursor of several hormones, vitamins, and bile acids, and therefore is an essential molecule for life. However, the consumption of saturated and Trans fatty acid is the major causes for the elevation of LDL-c in plasma which is a risk factor for the development of atherosclerosis and inflammatory bowel.

In the present study, we evaluated the benefit of hot water therapy on the inflammation induced by saturated and Trans fats during 21 days in rats, which was evaluated using the detection of hs-CRP and lipids status.

The results showed that the amount of hot water 60-175ml per day for rats could decrease the levels of hs-CRP and lipids status (T-Ch, TG and LDL-c) and increase the concentration of HDL-c.
For this reason, we considered that the hot water is a natural hydrotherapy during short or long term dependent on type of disease.

Key word: Fatty acid, Cholesterol, Hypercholesterolemia, Atherosclerosis, Inflammatory bowel disease, CRP, Hot water.

Résumé

Le cholestérol est une substance présente dans toutes les cellules du corps, c'est un composant basique de toutes les membranes cellulaires et précurseur de plusieurs hormones, vitamines et acides biliaires, donc c'est une molécule essentielle à la vie. Cependant, la consommation d'acide gras saturé et de Trans est la principale cause de l'élévation du LDL-c dans le plasma, ce qui est un facteur de risque pour le développement de l'inflammation intestinal et d'athérosclérose.

Dans la présente étude, nous avons évalué le bénéfice du traitement de l'eau chaude 60-175 ml par jour sur l'inflammation induite par les graisses saturées et Trans pendant 21 jours chez les rats, qui a été évaluée en utilisant la détection de hs-CRP et le statut lipidique.

Les résultats ont montré que la quantité d'eau chaude pourrait diminuer les niveaux de hs-CRP et les concentration des lipides (T-Ch, TG et LDL-c) et augmenter la concentration de HDL-c. Pour cette raison, nous avons considéré que l'eau chaude est une hydrothérapie naturelle à court ou à long terme qui dépend du type de la maladie.

Mot clés: Acide gras, Cholestérol, Hypercholestérolémie, Athérosclérose, Maladie inflammatoire de l'intestin, CRP, L'eau chaude.

ملخص

الكولسترول هو مادة "تشبه الدهون" موجودة في جميع خلايا الجسم، بل هو عنصر أساسي لجميع الأغشية الخلوية و المنتج للعديد من الهرمونات، الفيتامينات والأحماض الصفراوية، وبالتالي هو جزيء أساسي للحياة. مع ذلك، فإن استهلاك الأحماض الذهنية المشبعة والمتحولة و هو السبب الرئيسي لارتفاع البروتين الذهني منخفض الكثافة في البلازما وهو عامل خطر لتطوير تصلب الشرايين والتهاب الأمعاء.

في هذه الدراسة، قمنا بتقييم فوائد العلاج بالماء الساخن على الالتهاب الناجم عن استهلاك الدهون المشبعة والدهون المتحولة خلال 21 يوما عند الجرذان، والتي تم تقييمها باستخدام الكشف عن البروتينسي التفاعلي والكشف عن نسبة الدهون.

أظهرت النتائج أن كمية 60-175مل من الماء الساخن في اليوم بالنسبة للجرذان يمكن أن تقلل من نسبة البروتينسي التفاعلي و نسبة الدهون في الدم (الكولسترول، الجليسيريدات، البروتين الذهني منخفض الكثافة). و زيادة نسبة البروتين الذهني عالي الكثافة.

و لهذا السبب، اعتبرنا أن الماء الساخن هوعبارة عن علاج طبيعي خلال فترة قصيرة أو طويلة الأمد اعتمادا على نوع المرض.

الكلمات الرئيسية: الأحماض الذهنية، الكولسترول، ارتفاع الكولسترول في الدم، تصلب الشرايين، التهاب الأمعاء، البروتينسي التفاعلي ، الماء الساخن.

Annex

1.Chemicals

- Chloroform
- Formol 10%
- Distilled water
- NaCl 0, 9%
- Ethanol

2.Equipments

- Capillary
- Balance (0,001)
- Dissection kit
- Centrifuge (EZ Swing 3K)
- EDTA tubes
- Hotplate Stirrer (JLabTech)

-Tube eppenderf

-petri box

-Spss logecial

3.Preparation of solutions

1-NaCl

0.9 g → 100 ml

X g → 1000 ml

$0.9\ g \times 1000\ ml / 100\ ml = 9\ g$

2-formol 10%

(10 ml formol(37%) + 27 ml of distilled water.)

Table 05: The average weight and diet in group I (Control) during 26 days.

Days	Weight average (g)	Average per week (g)	Food consumed (g)	Average per week (g)
Day : 01	102.4	103.02	/	
Day : 02	103.46		46.99	
Day : 03	104.53		46.99	
Day : 04	103.76		46.53	46.71
Day : 05	103.11		48.21	
Day : 06	103.46		42.97	
Day : 07	100.42		48.58	
Day : 08	100.74	101.15	56.73	
Day : 09	99.61		66.69	
Day : 10	98.48		66.69	
Day : 11	100.23		60.4	59.02
Day : 12	103.32		55.44	
Day : 13	101.95		60.87	
Day : 14	103.74		46.37	
Day : 15	103.45	105.09	49.2	
Day : 16	102.94		50.76	
Day : 17	102.43		50.76	
Day : 18	106.76		27	42.63
Day : 19	105.45		49.25	
Day : 20	106.69		29.61	
Day : 21	107.93		41.83	
Day : 22	Blood samples	117.65	fasted	
Day : 23	112.72		38.38	
Day : 24	117.52		38.38	40.63
Day : 25	119.31		40.21	
Day : 26	121.06		45.56	

Table 06: The average weight and diet in group II (CH/W) during 26 days.

Days	Weight average (g)	Average per week (g)	Food consumed (g)+30(g)Fatty food	Average per week (g)
Day : 01	98.92	104.36	/	
Day : 02	101.48		51.36	
Day : 03	104.05		51.37	
Day : 04	111.50		51.95	47.16
Day : 05	104.20		38.23	
Day : 06	105.25		41.34	
Day : 07	105.13		48.73	
Day : 08	105.96	114.9	43.46	
Day : 09	109.79		43.96	
Day : 10	113.63		43.17	
Day : 11	113.24		43.17	41.92
Day : 12	119.22		37.76	
Day : 13	119.11		42.4	
Day : 14	123.36		39.55	
Day : 15	126.18	127.88	62.34	
Day : 16	126.74		13.76	
Day : 17	127.3		13.76	
Day : 18	127.36		77.65	43.32
Day : 19	127.69		52.19	
Day : 20	129.40		47.28	
Day : 21	130.55		36.26	
Day : 22	Blood samples	118.1	fasted	
Day : 23	124.86		15.24	
Day : 24	119.23		15.24	
Day : 25	115.99		26.09	17.01
Day : 26	112.35		11.48	

Table 07: The average weight and diet in group III (CH/HW) during 26 days.

Days	Weight average (g)	Average per week (g)	Food consumed (g) +30(g)fat food	Average per week (g)
Day : 01	64.9	69.29	/	
Day : 02	67.57		64.35	
Day : 03	70.24		64.35	
Day : 04	68.25		26.36	49.71
Day : 05	69.39		50.76	
Day : 06	72.27		47.9	
Day : 07	72.42		44.56	
Day : 08	73.58	79.11	26.77	
Day : 09	75.75		17.72	
Day : 10	77.93		17.73	
Day : 11	80.05		26.02	22.30
Day : 12	82.74		21.91	
Day : 13	81.53		22.12	
Day : 14	82.19		23.84	
Day : 15	84.60	88.4	19.31	
Day : 16	86.24		7.85	
Day : 17	87.88		7.85	
Day : 18	88.76		20.73	29.22
Day : 19	90.25		64.55	
Day : 20	90.34		51.61	
Day : 21	90.79		32.66	
Day : 22	Blood samples	88.50	Fasted	
Day : 23	89.35		5.68	
Day : 24	87.92		5.69	
Day : 25	88.81		19.39	12.68
Day : 26	87.95		19.97	

Table 08: The average weight and diet in group IV (HW) during 26 days.

Days	Weight average (g)	Average per week (g)	Food consumed (g)	Average per week (g)
Day : 01	76.5	74,86	/	
Day : 02	76.36		43.53	
Day : 03	76.23		43.54	
Day : 04	73.57		41.54	43.63
Day : 05	75.13		52.85	
Day : 06	74.24		44.9	
Day : 07	72.01		35.47	
Day : 08	69.65	66,15	69.21	
Day : 09	67.94		51.05	
Day : 10	66.24		51.06	
Day : 11	63.38		39.39	45.26
Day : 12	65.75		40.58	
Day : 13	63.09		42.37	
Day : 14	67.08		23.17	
Day : 15	67.91	73,38	38.35	
Day : 16	70.17		20.75	
Day : 17	72.44		20.75	
Day : 18	74.01		19.56	33.98
Day : 19	76.04		46.52	
Day : 20	75.43		50.42	
Day : 21	77.64		41.55	
Day : 22	Blood samples	84,37	fasted	
Day : 23	80.86		17.75	
Day : 24	84.09		17.75	22.04
Day : 25	85.93		28.61	
Day : 26	86.61		24.07	

Table 09: The water consumed by rats during 26 days.

Days	Group 01 (control/normal water) (ml)	Group 02 (cholestérol+normal water) (ml)	Group 03 (cholestérol+hot water) (ml)	Group 04 (hot water) (ml)
01	****	****	****	****
02	85	115	135	127.5
03	85	115	135	127.5
04	95	100	125	175
05	105	90	95	130
06	85	100	95	103
07	108	105	90	95
08	125	122	85	110
09	110	110	87.5	55.5
10	110	110	87.5	55.5
11	145	129	75	90
12	122	100	81	109
13	105	125	70	100
14	100	115	75	75
15	110	120	72	90
16	112.5	107.5	62.5	77.5
17	112.5	107.5	62.5	77.5
18	238	100	74	90
19	85.75	120	88.94	102
20	83.61	120	80	92
21	82.2	100	54	102.5
22	Fasted	Fasted	Fasted	fasted
23	71.35	100	75.58	45
24	71.35	100	75.59	45
25	90	100	93	88
26	93	110	54	37

Benefits of Drinking Hot Water

Therapeutic Methods of Drinking Hot Water (TMDHW) - For Adults

* The recommended consumption of Hot Water shall be at 3 liters daily minimum up to 4 liters maximum.

*Glass, mug or tumbler size - 500 ml, taken in different gulps, not one gulp.

* The maximum consumption of Hot Water shall be 1 liter within One Hour.

Option 1 – Drinking Method for glass size 500 ml

* One to two glasses early in the morning, once you wake up and before brushing your teeth – at standing position (Very important)

* One glass, after brushing your teeth, before having your breakfast.

*One to two glasses throughout the morning.

*One glass 15-30 minutes before lunch. (Very important).

*One to two glasses in the evening.

* One glass, one hour before going to bed (optional.)

Option 2 – Drinking Method for glass size 240-300 ml

* Two glasses of hot water, early in the morning, once you wake up and before brushing your teeth – at standing position – Very important

*One glass of hot water, after brushing your teeth, before having your breakfast (optional).

*Two to three glasses of hot water throughout the morning.

* One glass of hot water at least 15-30 minutes before lunch – Very important.

*Two to three glasses of hot water throughout the evening.

*One glass of hot water, one hour before going to bed.

- The temperature of water shall be around 50oC (122oF), a little bit less than the temperature of hot tea (Alhadjri, 2010).

Table 10: Composition of water used in the experiemental work(www.guedila.com)

Composition	**Mg/litre**
Calcium (ca)	78
Magnésium (Mg)	37
Soduim (Na)	29
Potasuim p	2
Sulfates	95
Chlorures	40
Nitrates	4.5
Nitrites	-0.01
Ph	7.35
R.S à 180c	564

Diseases cured in People from drinking hot water therapy

1-Asthma

2- Hypertension (High Blood Pressure)

3- Diabetes Mellitus

4- Migraine & Headache

5- Anemia

6- Series of back pain

7- Urinary Calculus (Stones in the Kidneys)

8-Urinary Tract Infection

9- High Blood Cholesterol

10- Rheumatism & Arthritis

11-Stroke (Cerebral Vascular Accident)

12-Sexual and body weakness

13-Tiredness & Fatigue

14-Tonsilittis

15-Gastroenterisis

16-Insomnia (lack of sleep)

17-Colds, Flu & Fever

18-Heartburn, Ulcer, Constipation (difficulty in passing motion)

19-Parkinsonism (Involuntary Movement of the Body due to old age)

20-Skin Diseases

21-All Kinds of Infections

22-Alzheimer (defects of the Brain)

23-Heart Disease & Heart Abnormality since birth

24-Cancer (there is one case diagnosed and further follow up in other cases is being monitored)

25- Purifying and Regularizing Women's monthly Period (Alhajri, 2010) and (Dhrubo Sen et al., 2015).

College Year: 2016-2017 **Presented by:** Guennoub Sabrina
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Title:The effect of hot water on inflammation induced by hypercholesterolemia in rats

Thesis submitted for the degree of Master of Immuno-oncology

Summary

Cholesterol is a “fat-like” substance present in all body cells , it is a basic component of all cellular membranes and precursor of several hormones, vitamins, and bile acids, and therefore is an essential molecule for life. However, the consumption of saturated and Trans fatty acid is the major causes for the elevation of LDL-c in plasma which is a risk factor for the development of atherosclerosis and inflammatory bowel.

In the present study, we evaluated the benefit of hot water therapy on the inflammation induced by saturated and Trans fats during 21 days in rats, which was evaluated using the detection of hs-CRP and lipids status.

The results showed that the amount of hot water 60-175ml per day for rats could decrease the levels of hs-CRP and lipids status (T-Ch, TG and LDL-c) and increase the concentration of HDL-c.
For this reason, we considered that the hot water is a natural hydrotherapy during short or long term dependent on type of disease.

Key word: Fatty acid, Cholesterol, Hypercholesterolemia, Atherosclerosis, Inflammatory bowel disease, CRP, Hot water.

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