CARDIOPROTECTIVE EFFECT OF AEGLE MARMELOS BAEL AGAINST DOXORUBICIN INDUCED MYOCARDIAL TOXICITY IN ALBINO RATS

Dissertation

Submitted in partial fulfillment of the requirements for

the award of the degree of

MASTER OF PHARMACY

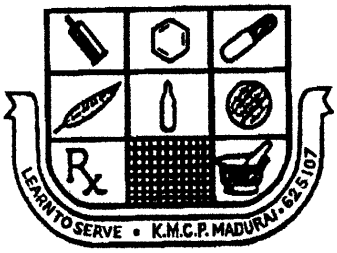
IN

PHARMACOLOGY

OF

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI



DEPARTMENT OF PHARMACOLOGY

K.M.COLLEGE OF PHARMACY

UTHANGUDI, MADURAI - 625 107

TAMIL NADU

APRIL – 2012

CERTIFICATE

This is to certify that the dissertation entitled **"CARDIOPROTECTIVE EFFECT OF AEGLE MARMELOS BAEL AGAINST DOXORUBICIN INDUCED MYOCARDIAL TOXICITY IN ALBINO RATS",** submitted by **Mr. BIPIN CHANDRA BHATT** in partial fulfillment for the degree of **"Master of Pharmacy** in **Pharmacology"** under The Tamilnadu Dr. M.G.R Medical University Chennai, at K.M. College of pharmacy, Madurai-107, is a bonafied work carried out by him under my guidance and supervision during the academic year of 2011 – 2012. This dissertation partially or fully has not been submitted for any other degree or diploma of this university.

GUIDE

Mr.V.PANDIARAJAN , M.Pharm.,

Asst. Professor,

Department of Pharmacology,

K.M.College of pharmacy,

Uthangudi, Madurai-625107

PRINCIPAL

Dr. S. JAYAPRAKASH, M.Pharm, Ph.D.,

Professor and HOD,

Department of Pharmacology,

K.M.College of pharmacy,

Uthangudi, Madurai-625107

HOD

Mr.N.CHIDAMBARANATHAN, M.Pharm, Ph.D.,

Asst. Professor,

Department of Pharmacology,

K.M.College of pharmacy,

Uthangudi, Madurai-625107

ACKNOWLEDGEMENT

The success of secret undaunted ardor, motivation, dedication, confidence on self and above all the blessing of god .I bow in reverence to the Almighty for bestowing upon the all his kindness that has helped me throughout the journey of my life . Success is an outcome of the collaborated efforts aimed that achieving different goals. I hereby take this opportunity to acknowledge all those who have helped me in the completion of this dissertation work.

With deep sense of gratitude and veneration I express my profound sense of the appreciation and love to my beloved father ***Mr. JAWAHAR LAL BHATT,*** for providing me love like heaven's caring arms and a very secure childhood both materially and emotionally. His fundamental truths which exist as divine power can lift one up from confusion, misery, melancholy, failure and guide one's a true place. I love you Always My "Dad".

Driving force behind all this is my mother. ***Mrs.LUXMI BHATT,*** I am especially grateful to her constant love, affection, moral support, guidance and sacrifices, which has been always showered upon me in all walk of my life.

With sincere note gratitude especially thanks to old Principal of our esteemed institute ***Dr.(Prof.) A.J.M. Christina, M.Pharm., Ph.D.,*** Principal and Head, of Department of Pharmacology, K.M. College of Pharmacy, Uthangudi, Madurai for her most valued suggestions and encouragement during the course of study.

It is an honor to pay my respect and heartfelt thanks to our most Respected Principal ***Dr. S. Jayaprakash, M. Pharm., Ph.D.,*** K.M. College of Pharmacy , Uthangudi, Madurai, for providing necessary facilities to carry out this dissertation work successfully.

It give me immense pleasure to express my deepest thanks, heartfelt, indebtedness and respectful Guide ***Asst.Prof.Mr.V.Pandiarajan,M.Pharm.,*** Department of Pharmacology, K.M. College of Pharmacy, Madurai, for providing much of suggestions, encouragements during the project.

It give me immense pleasure to express my deepest thanks, heartfelt, indebtedness and respectful Co-Guide ***Prof .N. Chidambaranathan, M.Pharm.,Ph.D,*** Head, Department of Pharmacology, K.M. College of Pharmacy, Madurai, for providing much of suggestions, encouragements during the project. Without his critical evaluation and deep-rooted knowledge this thesis would now have become reality. His constants quest for knowledge and strive for excellence will always remain a source of inspiration to me. His parental care and patience will always be remembered.

"Thank you sir" for all you has done for me.

With deep sense of veneration and gratitude I am really indebted to ***Asst.Prof.G.Nalini,M.Pharm.,*** Department of Pharmacology, K.M. College of Pharmacy, Madurai. For providing much of stimuli in the form of suggestions, guidance and encouragements at all stages of my work.

With sincere note of gratitude I specially thanks to ***Mr.Vinoth Prabhu, M.Pharm.,*** Lecturer**,** Department of Pharmacology, K.M. College of Pharmacy, Uthangudi, Madurai for his most valued suggestions and encouragement during the course of study.

My sincere thanks to ***Dr.D.Stephen*** (Head, Department of Botany, American College, Madurai) for his help in identification & authentification of the plant.

I also extend my gratitude to management and staffs of **Bose Clinical Laboratory and Vijay Clinical Laboratory, Madurai** for evaluating hematological examination of the samples.

I will always be thankful to ***Mrs. A. Shanthi, B.A., M.L.I.Sc., M.Phil,*** Librarian**,** ***Mrs.Angelo Marina Priya*****,** Library assistant**,** ***Mrs.Shanmuga Priya, D.Pharm,*** Store In-Charge**,** ***Mrs.Tamilselvi, D.Pharm*****,** Lab. Asst, ***Mrs. Nallamal*** and ***Mr.K.C.Karthikeyan*****,** Compuer Lab of my college and all others for their prayers and support and wonderful help and encouragement.

I heartily thanks to all my classmates ***Mr. T.KIRAN KUMAR, Mr. SIVA VENKATA SUBASH.KARRE, Mr. C.SAKTHIVEL, Mr. VIVEK CHATARPATHI,***

Miss. K. BRINDA, Miss. REENU JACOB, Miss. LAKHSMI SURYA NARAYANAN, For their support and kindly help during the project.

I am very much indebted to my beloved brother ***Mr. SATISH CHANDRA BHATT,*** *and* ***Mr. GYRISH CHANDRA BHATT*** and my ***bhabiji*** and my lovely ***sister*** who are living in the depth of my heart and for being my guiding spirit whose blessing and love have given the strength and inspiration to complete this work successfully .

I would like to mention once again, Word is not enough to express my heartfelt thanks to my elder brother ***Mr. SATISH CHANDRA BHATT***. For their timely extend help and encouragement during my work.

My humble thanks to all the mentors, well wishers, near and dear ones who helped me in their own way.

Thanks you All……

CONTENTS

1. INTRODUCTION

DEFINITION

The cardiovascular system includes the heart and the blood vessels and is responsible for the transport of blood throughout the body[1].

DESCRIPTION

The main components of the cardiovascular system are the heart, arteries, arterioles, capillaries, venules, and veins. Adults have approximately 60,000 miles (96,000 km) of blood vessels. By moving blood throughout this network of vessels, the cardiovascular system supplies all cells of the body with oxygen and nutrients and removes carbon dioxide and other waste products.

THE HEART

The heart is the focal point of the cardiovascular system. It supplies the driving force for the movement of blood. The heart functions as a pump, actively forcing blood out of its chambers and passively relaxing to allow the next quantity of blood to enter. On refilling, the blood does not get actively sucked into the heart, but moves into the chambers due to the underlying pressure of the cardiovascular system as a whole.

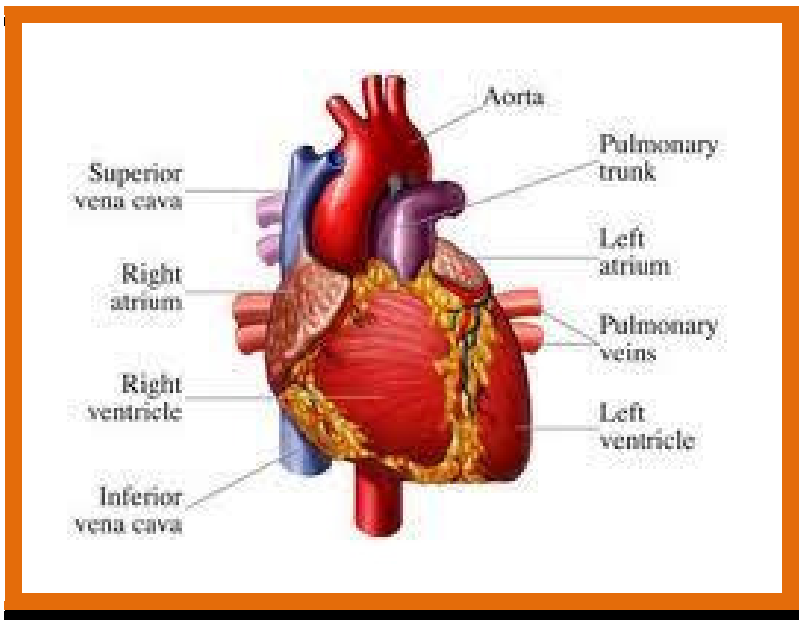


Fig.No.1

The heart is cone-shaped, pointing down and to the left, and is located left of centre of the chest between the lungs. The organ is made of three types of tissue: the myocardium (middle layer), the epicardium (outer layer), and the endocardium (thin inner layer). A fluid-filled sac called the pericardium surrounds the heart, helping to reduce friction during contraction. When the myocardium applies force on the blood by contracting, the cells of the tissue become short and thick. The contraction phase of the myocardium is called systole. This is followed by relaxation of the cells, where they become thinner and longer. The relaxation phase is called diastole.

The heart functions as a double pump, with both the right and left heart having a structure to receive blood and a structure to pump the blood. The blood-receiving structures are called the atria and the blood-pumping structures are called the ventricles. During a heartbeat, the two atria contract together, moving the blood from the atria to the ventricles. Then, while the two atria relax and refill, the two ventricles contract, moving the blood out of the heart. This system means that blood leaves the heart in pulsed waves.

The right atrium and ventricle pump blood from the heart to the lungs using a subset of the blood vessels called the pulmonary circulation system. The blood travels to the lungs where it gives off waste carbon dioxide and receives oxygen, then returns to the left side of the heart to be pumped to the rest of the tissues and organs of the body. The blood vessels that carry blood to the body are called the systemic circulation system. In a healthy heart, blood does not pass directly between the left and right sides of the heart. The two atria are separated by a wall known as the atrial septum and the wall separating the two ventricles is known as the ventricular septum.

Valves within the heart ensure that the blood travels in the right direction. On the right side of the heart, the tricupsid valve allows blood to travel only from the right atrium to the right ventricle. The mitral valve performs the same function on the left side of the heart. As the blood levels the right ventricle to go to the lungs, the pulmonary valve controls the direction of the blood flow, while the aortic valve functions between the right ventricle and the aorta, the largest artery.

During diastole, when the ventricles relax, the mitral and tricupsid valves open, allowing blood to flow into the ventricles. At the same time, the aortic and

pulmonary valves are closed to prevent reentry of the blood that had been pumped from the heart. During systole, when the ventricles contract, the mitral and tricupsid valves close to prevent backflow and the aortic and pulmonary valves open to allow the blood to leave the heart. There are no valves at the atrial inputs, part of what ensures consistent blood inflow into the ventricles.

The heart works on an electrical conduction system, as the cells contract in response to electrical signals. All cells of the heart can contract spontaneously, with the beginning of the heartbeat dependent on the cells with the most rapid innate rate. These cells are located in the sinoatrial (SA) node of the heart, sometimes called the heart's natural pacemaker. The electrical signal moves from the SA node to the atrium, in a cluster of conducting cells called the atrio-ventricular (AV) node. The slowing of the signal at this point allows the atria to contract slightly before the ventricles, giving the ventricles more time to fill before they contract. The signal passes on to the electrical network of the ventricles, called the His-Purkinje system, which causes the ventricles to contract. The electrical workings of the heart can be visualized using an electrocardiography unit.

Overall, heart rate is controlled by signals from the autonomous nervous system to the SA node. The autonomic nervous system automatically controls the heart rate as well as many other functions of the body including breathing, blood pressure, and excretion. The system is extremely flexible and can double the heart rate in as fast as three to five seconds[2-3].

THE ARTERIES AND ARTERIOLES

Blood leaving the heart from either the left or right ventricle enter a network of vessels called the arteries. Arteries are highly elastic vessels, having flexible fibers in their structure and a relatively thick layer of smooth muscle. Larger arteries have three layers—the inner (intima), the middle (media) and the outer (adventitia). Blood flows through the central opening, known as the lumen, which is lined with endothelial cells. The layers of the blood vessels interact to exert major control over blood pressure and where the blood flows. The adventitia contains the nervous control

and blood vessels for the arteries, the media contains smooth muscles and the endothelial layer of the intima is important for sensing environmental changes.

The aorta, the largest artery, branches directly off the left ventricle and is especially elastic because of the addition of cardiac muscle cells in the area where it branches off the heart. The elastic qualities of arteries are important so that they can expand to receive the blood volume under high pressure and contract to continue forcing the blood into the rest of the circulatory system. The elasticity of the arteries is a significant component of the blood pressure during diastole, when the ventricles of the heart relax.

From the left ventricle the coronary arteries, which supply blood to the heart itself, emerge from the aorta. Then the aorta makes a large U-turn in the chest, eventually becoming the abdominal artery. Major branches to the head (carotid arteries), arms (axillary arteries) and legs (femoral arteries) come off this one vessel. The flow of blood in the arteries is pulsile, increasing and decreasing with each heartbeat, about 70 times per minute. The flow of blood in the branch arteries accounts for the pulse that can be felt in the wrists and neck.

The other major artery, the pulmonary artery, carries blood from the right ventricle to the lungs. Although the systemic arteries carry oxygenated blood, the arteries of the pulmonary system carry deoxygenated blood to the lungs. A vessel is called an artery because it carries blood away from the heart, not because the blood it carries contains oxygen.

As arteries move away from the heart, they branch into smaller vessels called arterioles. Arterioles are structurally similar to arteries and play an important role in directing blood to the parts of the body needing it most, such as muscles under stress.

THE VEINS AND THE VENULES

The major veins of the body are collectively called the venae cavae. The superior vena cava takes in blood from the arms through the axillary veins, from the head through the jugular veins and from the heart through the coronary veins. The inferior vena cava collects the blood from the legs from the femoral veins and from

the abdomen from the hepatic, portal, and renal veins, among others. Both the superior and inferior venae cavae empty into the right atrium.

The pulmonary vein brings blood oxygenated in the lungs back to the left atrium, so it can be pumped to cells throughout the body. As with arteries, veins are not so named because the vessel carries deoxygenated blood but by their role in bringing blood back to the heart.

Veins have the same three structural layers as arteries but the layers contain less elastic tissue and muscle components, making the walls thinner and six to ten times more expandable. The blood pressure in veins is lower than in the arteries, so to keep the blood flowing to the heart there are one-way valves that prevent backflow. Additionally, the action of the muscles in the legs help to return the blood to the heart, a mechanism called the venous pump.

As veins move further from the heart they branch into smaller structures known as venules. The venules end in very thin blood vessels known as the capillaries.

THE CAPILLARIES

The arteries and the veins are connected by the vessel web of the capillaries. The lumen of these vessels is very small, to the extent that blood cells must line up single file to pass through the thinnest of them. Capillary walls are also very thin, allowing the passage of gases and nutrients between the blood cells and the cells of the body.

The exact role of the capillaries varies depending on the part of the body in which they are located. The capillaries of the pulmonary circulation are found in the air sacs of the lungs, called alveoli, and it is there that the exchange of oxygen into the blood and carbon dioxide out of the blood occurs. In the kidneys, the capillaries in the organ's tubules are the point where waste products are taken out of the blood to be excreted in the urine. The capillaries of the intestine are the location where nutrients from digested food are absorbed into the bloodstream. Capillaries serving the muscles bring in oxygen and nutrients and take away carbon dioxide and waste products.

FUNCTION

For reference, at any particular point in time, about 9% of the body's blood is located in the pulmonary circulation and about 7% is in the heart's circulation. The remaining 84% is located in the systemic circulation, with 64% in the veins, 13% in the arteries, and 7% in the arterioles and capillaries. The greater percentage in the veins is due to the less elastic nature of the vessels and the tendency of the blood to pool there.

As the pulmonary circulation has a relatively smaller network of vessels when compared to the systemic circulation, the right side of the heart doesn't have to work as hard as the left side to move the blood. Accordingly, the left side of the heart is larger and more muscular. The passive-filling nature of the heart keeps the unequal balance in blood volume between the pulmonary and systemic circulation. Without active filling, the physical differences between the systemic and pulmonary capillaries such as relative size of the vessel bed and relative elasticity determine the blood distribution. If the heart was a different kind of pump, cardiac characteristics, such as rate or stroke volume (amount of blood pumped by one contraction of the left ventricle) would govern the relative volumes.

One way to visualize the function of the cardiovascular system is to follow the movement of one blood cell throughout the body. The path can begin at the left ventricle, where an oxygenated blood cell is pumped out by contraction of the myocardium, through the aortic valve into the aorta. The cell follows the curve into the abdominal artery and into the axillary artery into the arm. The artery subdivides into smaller and smaller branches, small enough to be called arterioles. Blood is needed at a muscle in the arm, so the arterioles are open to keep a large quantity of blood flowing in that direction. The blood cell continues through smaller vessels until it is in a capillary bed next to a muscle cell.

There the cell gives up its oxygen cargo, takes up carbon dioxide waste produced by the muscle and begins the journey back to the heart. Travelling through the capillaries to the venules and then into the axillary vein, the cell goes into the superior vena cava and into the right atrium. The right atrium contracts, and the cell moves through the tricuspid valve into the right ventricle. On the next systole, the cell

rushes out of the right ventricle, through the pulmonary valve into the pulmonary artery to the lungs. The branches of vessels grow smaller and smaller, until the cell is in the capillaries of the alveoli where it releases the carbon dioxide to the lung space to be exhaled and picks up another load of oxygen.

Travelling back to the heart through the veins of the pulmonary circulation system, the cell enters the left atrium through the pulmonary vein. When the atrium contracts, the cell goes through the mitral valve into the left ventricle, having made one cycle through the cardiovascular system. In this way, the cardiovascular system supplies all the cells of the body with oxygen and nutrients and carries away carbon dioxide and other wastes.

ROLE IN HUMAN HEALTH

It is difficult to overestimate the role the cardiovascular system plays in human health, with literally every cell of every tissue dependent on its function for survival. The cardiovascular system is the way the body transports things to and from the body's cells. Oxygen, nutrients, and hormones are carried from the point these substances are made or brought into the body to the cells for their use. Cellular wastes are transported from the cells to the lungs, kidneys, or liver to be broken down or removed from the body. The circulatory system is also one of the transport systems (along with the lymph) for the immune cells responsible for protecting the body from disease.

Changes in the functioning of the circulatory system have far reaching effects. A defect of the circulatory system, heart disease, is the number one cause of death in humans. Some of the common names and medical terms for the symptoms of a malfunctioning cardiovascular system include

- chest pain (angina pectoris)
- shortness of breath (dyspnea)
- general tiredness (fatigue)
- swelling (edema)
- loss of consciousness (syncope)
- light-headedness (presyncope)

- palpitations (arrhythmia or extrasystoles)
- limb pain or tiredness (claudication)
- abnormal skin color (pallor, cyanosis, erythemia, necrosis)
- sores on skin (ulceration)
- collapse (shock)
- sudden changes in vision, strength, coordination, speech, or sensation

COMMON DISEASES AND DISORDERS

Diagnosing cardiovascular disease can be complicated because often more than one cardiovascular problem exists at the same time in the same person. Symptoms of one problem can mask symptoms of another. Sometimes the multiple problems have a common cause or one cardiovascular problem can be causing another. This can make diagnosis and treatment a difficult task.

HIGH BLOOD PRESSURE

The most common cardiovascular disease is high blood pressure (hypertension), affecting one in four Americans (one in three black Americans). Blood pressure is measured in millimetres of mercury, based on how high the pressure in the arteries can raise a column of mercury above baseline using a blood pressure cuff. With a generally accepted normal of systolic to diastolic of 120/80, the disease is categorized into three stages. The systolic measurement, the diastolic measurement, or both can be elevated with hypertension.

Stage 1 disease is present with systolic measurements of 5.12–5.47 in (130–139 mm) Hg, stage 2 with 6.29–7.04 in (160–179 mm) Hg, and stage 3 with 7.08 in (180 mm) Hg or higher. For diastolic measurements, stage 1 occurs from 3.54–3.89 in (90 to 99 mm) Hg, stage 2 with 3.93–4.29 in (100 to 109 mm) Hg, and stage 3 with measurements above 4.33 in (110 mm) Hg. Treatment decisions for hypertension take into account not only the measured blood pressure, but also the presence of other cardiovascular disease, hereditary risk factors, evidence of damage to internal organs, and lifestyle (stress, diet, exercise).

Primary hypertension is associated with a persistent increase in resistance of blood flow in the arterioles, the smaller branches off the arteries. The precise cause is unknown.

HEART DISEASE

Some specific diseases of the heart include cardiomyopathy, congenital heart disease, heart valve defects, myocardial infarction (heart attack), problems of the pericardium and arrhythmias. If any of these diseases cause the heart to lose its ability to pump blood effectively, the patient is said to have heart failure. Because poor pumping ability often results in an accumulation of fluid in the tissues and lungs, it is often called congestive heart failure.

Cardiomyopathy is a disease of the heart muscle with multiple causes and is the number one reason people undergo heart transplants. Categorized by the type of muscle damage, there are three general types of cardiomyopathy: dilated, hypertrophic, and restrictive. Dilated cardiomyopathy refers to the enlargement of the heart that is a response to the overall myocardial weakness. Many problems can cause dilated cardiomyopathy, including viral infections, excessive alcohol intake, and myocarditis (inflammation of the heart).

Hypertrophic cardiomyopathy is an abnormal over-growth of the heart muscle. An inherited disease, the overgrown muscle blocks the movement of blood both into and out of the heart. The most common cause triggering hypertrophic cardiomyopathy is hypertension. Restrictive cardiomyopathy is due to a stiffening of the heart muscle that prevents it from fully relaxing during diastole. This problem is a symptom of other diseases such as hemochromatosis (a defect in iron use by the body) or amyloidosis (overproduction of antibodies by the bone marrow that cannot be broken down).

Congenital heart disease is caused by defects of the heart present at birth. Defects can be relatively mild and asymptomatic to severe and life-threatening. Some more common problems are abnormally formed blood vessels that block blood flow, malformed heart valves, incorrect connections between arteries, veins, and the heart, or defects in the atrial or ventricular septa. The most common congenital heart defect

is a combination of four problems called the teralogy of Fallot. With this problem the ventricular septum is incomplete, there is an obstruction to blood flow beneath the pulmonary artery, the aorta is shifted rightward and the right ventricular wall is thickened.

Any of the hearts valves can obstruct blood flow if they are too stiff (stenosis) or don't close properly and allow blood to leak (regurgitation). Valve problems can cause congestive heart failure or heart enlargement, which can lead to angina or heart arrhythmias. Causes of valve disease include congenital defects, calcium deposits, and infections, such as endocarditis (a bacterial infection of the endocardium, the lining of the heart). Severe valve problems can be treated by removal of the diseased valve and replacement with an artificial valve.

A myocardial infarction (heart attack) is death of heart tissue due to the sudden lack of blood flow from the coronary arteries. Doctors believe the most common cause of the blockage is a blood clot that formed at a rupture of an atherosclerotic plaque that has broken loose. The results of the heart attack are dependent on the amount of heart tissue that is damaged. With less than 10% of the heart affected, there is a reduction in the ability of the heart to pump blood, but a normal lifestyle can often be maintained. At 25% enlargement of the heart and heart failure is a common result. If 40% or more of the heart is damaged, shock or death usually occurs.

Pericarditis is inflammation of the pericardium, usually caused by a viral infection. Although this disease can cause sharp, piercing chest pain, it is usually self-limiting and ordinarily does not lead to further problems. Pericardial effusion is a collection of fluid around the heart in the pericardial sac. If the fluid amount is great enough, it can reduce the heart's ability to expand and receive blood, reducing its efficiency. This condition is known as cardiac tamponade. A final condition of the pericardium is pericardial constriction, an abnormal inflexibility of the pericardial membrane. Some types of pericarditis often result in this problem. If the inflexible membrane causes heart failure, it can be removed surgically.

Arrhythmias are abnormal heartbeats. Very broadly, arrhythmias can be classified into four different types: conduction system abnormalities, abnormally slow, abnormally fast, and irregular. Conduction system abnormalities are seen using electrocardiography units and do not directly cause an outwardly altered heartbeat. An example is some heart blocks, where the electrical signal adopts alternative paths in the heart to avoid nonconductive tissue.

Slow heartbeat (brachycardia) is the most common cause for the implantation of a pacemaker and can be caused by problems with the autonomic nervous system, the SA node, or the conduction system. Abnormally fast heartbeats (tachychardia) can be atrial flutter, the presence of an extra, abnormal pathway for electrical conduction in the heart, or ventricular tachychardia (V-tach). Some common irregular heartbeats include extra beats (extrasystoles) and atrial fibrillation, where the atria stop having effective contractions and beat chaotically at several hundred times per minute.

ARTERIAL DISEASE

Some diseases of the arteries include atherosclerosis, arterial thrombosis, aneurysm, and arteritis. The most common cause of heart attacks, coronary artery **disease** is the blockage of one or more of the vessels that supply blood to the heart. The arteries can be obstructed by a blood clot (thrombosis), atherosclerosis, or a coronary spasm. These problems can be treated with drugs that dissolve the clot or surgical procedures that remove or circumvent the blockages, such as coronary angioplasty or bypass surgery.

Atherosclerosis is caused by the degradation of the lining of the arteries (endothelium) and the resultant plaque, a build-up of platelets, cholesterol and other substances such as calcium that forms at the site. Atherosclerosis occurs to some extent in everyone and can occur in any of the body's arteries. Depending on the location, the disease can lead to other cardiovascular problems such as heart attack, leg pain, stroke and aneurysm. Arterial thrombosis is another way that arteries can be blocked, but in this case an abnormal blood clot, called an embolus, is responsible. This condition presents with very similar symptoms to atheroscloerosis. If it occurs in a coronary artery, it can cause heart attacks.

An aneurysm is an abnormally widened area of an artery. A common site for this problem is in the abdominal aorta and it is usually caused by atherosclerosis. Aneurysms can be surgically treated if detected before rupture. A final disease of the arteries is arteritis, an inflammation of the arteries. This problem is usually a part of another general disease, such as Takayasu's disease, temporal arteritis, Buerger's disease and polyarteritis nodosa.

VENOUS DISEASE

Some diseases of the veins include venous thrombosis, thrombophlebitis, pulmonary embolism and varicose veins. Blockages in the veins are not usually caused by atherosclerosis but by blood clots or venous thrombi. Venous thrombosis and the resulting inflammation, thrombophlebitis, can occur in superficial veins, usually a relatively minor problem, or in deep veins, a more serious condition where the threat of the clot breaking off and traveling to the heart or lungs is present.

These conditions are generally treated with blood-thinning drugs. If the clot does travel and get lodged in the lungs the condition is called a pulmonary embolism. This is a serious problem that often requires hospitalization. If blood-thinning drugs do not resolve the problem, surgical removal of the clot can be necessary.

Varicose veins refer to a condition where the veins become abnormally dilated and most commonly appear as soft bluish bulges in the legs. Caused by elevated pressure in the veins and the resulting damage to the valves within the vessels, varicose veins, unless severe, are a cosmetic problem. They can be treated with surgery, injections (sclerotherapy), or lasers[4-6].

MYOCARDIAL INFARCTION

DEFINITION

Myocardial infarction commonly known as a heart attack, is the irreversible necrosis of heart muscle secondary to prolonged ischemia. This usually results from an imbalance in oxygen supply and demand, which is most often caused by plaque rupture with thrombus formation in a coronary vessel, resulting in an acute reduction of blood supply to a portion of the myocardium.

Myocardium is the name of the heart muscle that pumps blood into the body through a well organized system of blood vessels.

Infarction is the medical term describing the death of tissue due to interference with its oxygen-rich blood supply.

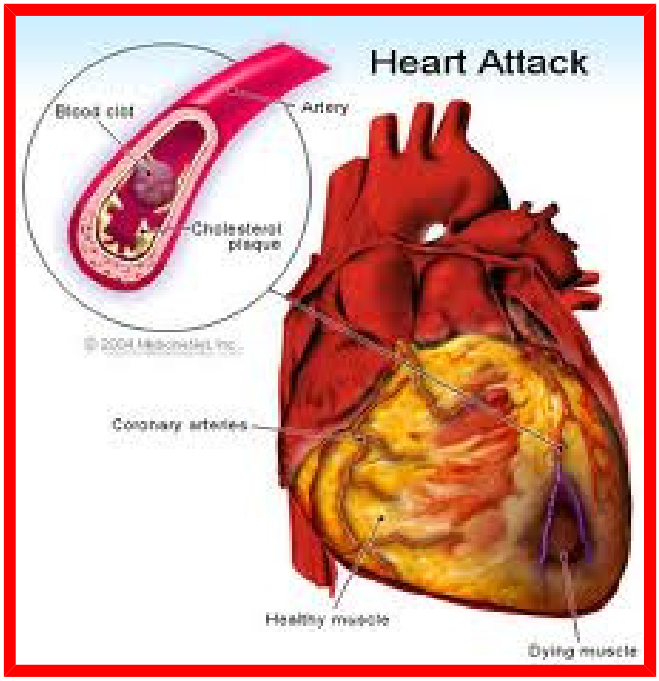


Fig.No.2

A heart attack occurs as the result of a blockage that developed within one or more coronary arteries which supply the heart muscle with blood. The heart muscle is similar with any other muscle in the body and requires oxygen-rich blood to function normal. When the oxygen level decreases or drops completely, its tissue suffers serious damage. Coronary arteries are the blood vessel system that encircles the heart like a crown and supplies blood to and from the heart muscle (myocardium) itself. The blockage is a direct cause of coronary artery disease, a medical condition that affects the arterial blood vessels due to accumulation of fatty deposits and fibrous tissue (called plaque) in the walls of the arteries. When the arterial plaque loses their surface layers, blood can start coagulating on the rough surfaces of the blood vessel wall. In time, this process can lead to a sudden obstruction of the entire blood vessel. The acute or total reduction of blood supply to a certain portion of the myocardium causes serious tissue damages. The heart tissue starts to die when it is deprived of

oxygen-rich blood for more than 30 minutes. When the loss of heart muscle is so great that the heart's normal functioning cannot be maintained or the heart electrical functioning (pumping blood) is impaired, the heart attack can be lethal. In rare cases, a heart attack can be caused by a spasm of a coronary artery. The coronary artery spasm can restrict or spasm off and on the artery walls disrupting thereby the flow of blood (known in medical terms as ischemia) to a portion of the myocardium. A coronary artery spasm affects normal coronary arteries or those affected by atherosclerosis. It usually occurs when the person is resting. Myocardial infarction is considered part of a spectrum referred to as acute coronary syndrome (ACS). The ACS continuum representing ongoing myocardial ischemia or injury consists of unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). Patients with ischemic discomfort may or may not have ST-segment or T-wave changes denoted on the electrocardiogram (ECG). ST elevations seen on the ECG reflect active and ongoing transmural myocardial injury. Without immediate reperfusion therapy, most persons with STEMI develop Q waves, reflecting a dead zone of myocardium that has undergone irreversible damage and death. Those without ST elevations are diagnosed either with unstable angina or NSTEMI—differentiated by the presence of cardiac enzymes.

Both these conditions may or may not have changes on the surface ECG, including ST-segment depression or T-wave morphological changes. Myocardial infarction may lead to impairment of systolic or diastolic function and to increased predisposition to arrhythmias and other long-term complications. [7- 11]

CLASSIFICATION OF MYOCARDIAL INFARCTION

There are three different criteria to classify the types of heart attacks.

I. The part of the heart that was damaged.

II. The changes seen on an electrocardiogram.

III. The anatomic (or morphologic) extent of necrosis.

I. According to the first criterion, there are two types of heart attacks:

1. **Anterior infarct**. Anterior infarct is the most dangerous type of heart attack and is caused by a blockage in the branch of the left coronary artery. It affects the lower chamber on the left side of the heart (left ventricle which pumps blood to all parts of the body) and damages the front part of the heart.

2. **Posterior or inferior infarct**. Posterior infarct is a less serious form of heart attack and is caused by a blockage in the right coronary artery or one of its branches. It affects the back or the base of the heart.

II. According to the second criterion, there are two types of heart attacks:

1. **ST segment elevation myocardial infarction (STEMI)**. This type of heart attack is caused by a prolonged period of blocked blood supply and affects a large portion of the myocardium. It causes significant changes on the electrocardiogram and in the level of blood chemical markers.

2. **Non-ST segment elevation myocardial infarction (NSTEMI or Non-STEMI).** This type of heart attack is caused by a partial or temporary blockage in the blood supply and the extent of the damages is minimal. NSTEMI does not cause changes on the electrocardiogram; however the blood markers will indicate the occurrence of a heart attack by illustrating the tissue damage which has occurred.[12]

III. According to the third criterion, there are two types of heart attacks:

1. **Transmural myocardial infarction**. This type of heart attack results in the death of the three layers of tissue (epicardium, myocardium, and endocardium) of the myocardial wall.

2. Nontransmural myocardial infarction (Subendocardial). This type of heart attack results in the death of a limited area of myocardial wall tissue. Usually involving a small area in the subendocardial wall of the left ventricle, ventricular septum or papillary muscles. Subendocardial infarcts are thought to be a result of locally decreased blood supply, possibly from a narrowing of the coronary arteries. The subendocardial area is farthest from the heart's blood supply and is more susceptible to this type of pathology. [13]

The phrase "heart attack" is sometimes used incorrectly to describe sudden cardiac death, which may or may not be the result of acute myocardial infarction. A heart attack is different from, but can be the cause of cardiac arrest, which is the stopping of the heartbeat and cardiac arrhythmia, an abnormal heartbeat. It is also distinct from heart failure, in which the pumping action of the heart is impaired; severe myocardial infarction may lead to heart failure, but not necessarily.

A 2007 consensus document classifies myocardial infarction into five main types: [14]

- **Type 1** – Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.

- **Type 2** – Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.

- **Type 3** – Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

- **Type 4** – Associated with coronary angioplasty or stents:

    - Type 4a – Myocardial infarction associated with PCI.

    - Type 4b – Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy.

- **Type 5** – Myocardial infarction associated with CABG

EPIDEMIOLOGY

Myocardial infarction is a common presentation of ischemic heart disease. The WHO estimated in 2002, that 12.6 percent of worldwide deaths were from ischemic heart disease[15] with it the leading cause of death in developed countries, and third to AIDS and lower respiratory infections in developing countries.[16] Worldwide more than 3 million people have STEMIs and 4 million have NSTEMIs a year.[17] Coronary heart disease is responsible for 1 in 5 deaths in the United States. It is becoming more common in the developing world such that in India, cardiovascular disease (CVD) is the leading cause of death.[18] The deaths due to CVD in India were 32% of all deaths in 2007 and are expected to rise from 1.17 million in 1990 and 1.59 million in 2000 to 2.03 million in 2010.[19] Although a relatively new epidemic in India, it has quickly become a major health issue with deaths due to CVD expected to double during 1985–2015.[20-21] Mortality estimates due to CVD vary widely by state, ranging from 10% in Meghalaya to 49% in Punjab (percentage of all deaths). Punjab (49%), Goa (42%), Tamil Nadu (36%) and Andhra Pradesh (31%) have the highest CVD related mortality estimates.[21] State-wise differences are correlated with prevalence of specific dietary risk factors in the states. Moderate physical exercise is associated with reduced incidence of CVD in India (those who exercise have less than half the risk of those who don't).[20]

CAUSES OF MYOCARDIAL INFARCTION

Atherosclerosis

Atherosclerosis is a gradual process by which plaques (collections of dead tissue, cholesterol, fats, inflammatory blood cells, calcium, and scar tissue that is held in place by a fibrous cap) are deposited in the walls of arteries. Cholesterol plaques cause hardening of the arterial walls and narrowing of the inner channel (lumen) of the artery. Arteries that are narrowed by atherosclerosis cannot deliver enough blood to maintain normal function of the parts of the body they supply. For example, atherosclerosis of the arteries in the legs causes reduced blood flow to the legs. Reduced blood flow to the legs can lead to pain in the legs while walking or exercising, leg ulcers, or a delay in the healing of wounds to the legs. Atherosclerosis

of the arteries that furnish blood to the brain can lead to vascular dementia (mental deterioration due to gradual death of brain tissue over many years) or stroke (sudden death of brain tissue). In many people, atherosclerosis can remain silent (causing no symptoms or health problems) for years or decades. Atherosclerosis can begin as early as the teenage years, but symptoms or health problems usually do not arise until later in adulthood when the arterial narrowing becomes severe. Smoking cigarettes, high blood pressure, elevated cholesterol and diabetes mellitus can accelerate atherosclerosis and lead to the earlier onset of symptoms and complications, particularly in those people who have a family history of early atherosclerosis. Coronary atherosclerosis (or coronary artery disease) refers to the atherosclerosis that causes hardening and narrowing of the coronary arteries. Diseases caused by the reduced blood supply to the heart muscle from coronary atherosclerosis are called coronary heart diseases (CHD). Coronary heart diseases include heart attacks, sudden unexpected death, chest pain (angina), abnormal heart rhythms and heart failure due to weakening of the heart muscle.

Atherosclerosis and Angina Pectoris

Angina pectoris (also referred to as angina) is chest pain or pressure that occurs when the blood and oxygen supply to the heart muscle cannot keep up with the needs of the muscle. When coronary arteries are narrowed by more than 50 to 70 percent, the arteries may not be able to increase the supply of blood to the heart muscle during exercise or other periods of high demand for oxygen. An insufficient supply of oxygen to the heart muscle causes angina. Angina that occurs with exercise or exertion is called exertional angina. In some patients, especially diabetics, the progressive decrease in blood flow to the heart may occur without any pain or with just shortness of breath or unusually early fatigue.. Exertional angina typically lasts from one to 15 minutes and is relieved by rest or by taking nitroglycerin by placing a tablet under the tongue. Both resting and nitroglycerin decrease the heart muscle's demand for oxygen, thus relieving angina. Exertional angina may be the first warning sign of advanced coronary artery disease. Chest pains that just last a few seconds rarely are due to coronary artery disease. Angina also can occur at rest. Angina at rest more commonly indicates that a coronary artery has narrowed to such a critical degree

that the heart is not receiving enough oxygen even at rest. Unlike a heart attack, there is no permanent muscle damage with either exertional or rest angina.

Atherosclerosis and Myocardial infarction

Occasionally the surface of a cholesterol plaque in a coronary artery may rupture, and a blood clot forms on the surface of the plaque. The clot blocks the flow of blood through the artery and results in a heart attack (Fig.1). The cause of rupture that leads to the formation of a clot is largely unknown, but contributing factors may include cigarette smoking or other nicotine exposure, elevated LDL cholesterol, elevated levels of blood catecholamines (adrenaline), high blood pressure, and other mechanical and biochemical forces.. while heart attacks can occur at any time, more heart attacks occur between 4:00 A.M. and 10:00 A.M. because of the higher blood levels of adrenaline released from the adrenal glands during the morning hours. Increased adrenaline, as previously discussed, may contribute to rupture of cholesterol plaques. Approximately 50% of patients who develop heart attacks have warning symptoms such as exertional angina or rest angina prior to their heart attacks, but these symptoms may be mild and discounted. Another rare cause of heart attack is Micro vascular disease. It is a condition in which very small branches of arteries become damaged. This damage results in blockage of the vessels, therefore impairing the blood flow. [17-20]

MYOCARDIAL INFARCTION SIGNS AND SYMPTOMS

A heart attack is a medical emergency that requires immediate treatment in order to increase the chances of survival. It is vital to early recognize the heart attack symptoms. However, each patient reacts differently when experiencing a heart attack. Symptoms can range from none to a significant number of manifestations. Up to 25% of heart attacks do not display symptoms and are known as silent heart attacks. However, most heart attacks do produce symptoms which are usually severe and frightening. (Approximately one quarter of all heart attacks are silent, without chest pain or new symptoms. Silent heart attacks are especially common among patients with diabetes mellitus.)

Although chest pain or pressure is the most common symptom of a heart attack, heart attack victims may experience a variety of symptoms including:

- **Chest discomfort:** Most heart attacks debut with a mild pain or discomfort. This discomfort is felt like a pressure, squeezing, or fullness. The chest discomfort can lasts for more than few minutes or comes and goes away.

- **Discomfort in other parts of the body:** The chest pain can radiate in other parts of the body such as jaw, one or both arms, shoulder, back, neck and stomach.

- Arm pain (more commonly the left arm, but may be either arm).

- Severe upper back pain.

- Toothache, headache.

- Palpitations (feeling like your heart is beating too fast or irregularly).

- Dyspnoea or shortness of breath with or without chest discomfort.

- Cold sweats or paleness (Sweating, which may be extreme).

- Fatigue.

- Impending sense of doom.

- Fainting.

- Light-headedness, dizziness.

- Nausea, vomiting, and/or general epigastric (upper middle abdomen) discomfort.

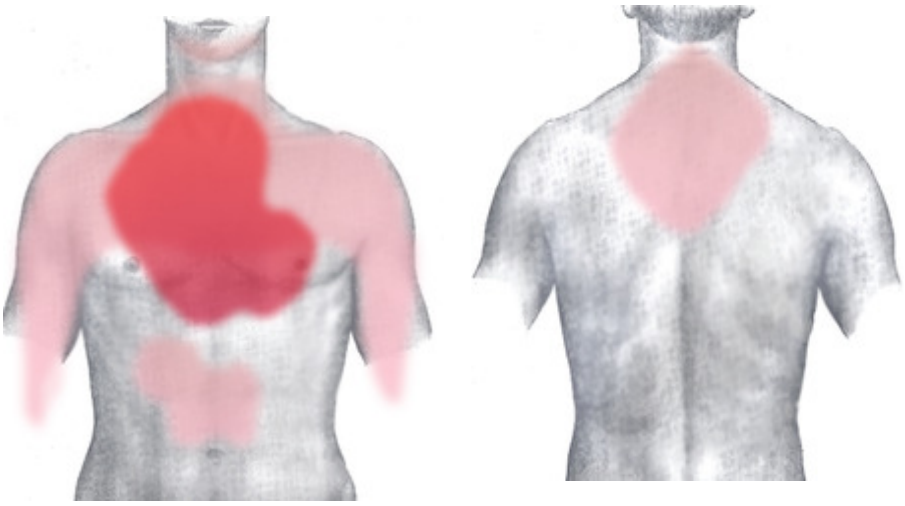
- Heartburn and/or indigestion.

- General malaise (vague feeling of illness).

- Anxiety.

- Wheezing.

Women may display slightly different or less noticeable symptoms. The most common heart attack symptom in women is chest pain or discomfort, or "heartburn". Women more than men experience shortness of breath, nausea/vomiting, back or jaw pain, clammy skin, or unexplained fatigue. A person can suffer a heart attack at any given moment (while working, resting, or engaged in physical activity). However, it was noticed that most cases of heart attack occur around the early hours of morning or during physical activity. In 50 percent of cases, a heart attack is warned by signs that occur hours, days, or weeks in advance. [21-24]



(Dark red = most typical area, light red = other possible areas)

Fig.No.3. **Rough diagram of pain zones in myocardial infarction**

COMPLICATIONS OF MYOCARDIAL INFARCTION

Myocardial infarction complications may occur immediately following a heart attack (in the acute phase), or may need time to develop (a chronic problem). After an infarction, an obvious complication is a second infarction, which may occur in the domain of another atherosclerotic coronary artery or in the same zone if there are any live cells left in the infarct.

1) Congestive heart failure.
2) Myocardial rupture.
3) Arrhythmia.
4) Pericarditis (Inflammation around the lining of the heart).
5) Cardiogenic shock.
6) Ventricular fibrillation.
7) Irregular heartbeats, including ventricular tachycardia.
8) Pulmonary embolism (Blood clot in the lungs).
9) Stroke (Blood clot to the brain).
10) Side effects of drug treatment.

Congestive heart failure

A myocardial infarction may compromise the function of the heart as a pump for the circulation, a state called heart failure. There are different types of heart failure; left- or right-sided (or bilateral) heart failure may occur depending on the affected part of the heart, and it is a low-output type of failure. If one of the heart valves is affected, this may cause dysfunction, such as mitral regurgitation in the case of left-sided coronary occlusion that disrupts the blood supply of the papillary muscles. The incidence of heart failure is particularly high in patients with diabetes and requires special management strategies.[25]

Myocardial rupture

Myocardial rupture is most common three to five days after myocardial infarction, commonly of small degree, but may occur one day to three weeks later. In the modern area of early revascularization and intensive pharmacotherapy as treatment for MI, the incidence of myocardial rupture is about 1% of all MI.[26] This may occur in the free walls of the ventricles, the septum between them, the papillary muscles, or less commonly the atria. Rupture occurs because of increased pressure

against the weakened walls of the heart chambers due to heart muscle that cannot pump blood out effectively. The weakness may also lead to ventricular aneurysm, a localized dilation or ballooning of the heart chamber. Risk factors for myocardial rupture include completion of infarction (no revascularization performed), female sex, advanced age and a lack of a previous history of myocardial infarction. In addition, the risk of rupture is higher in individuals who are revascularized with a thrombolytic agent than with PCI. The shear stress between the infarcted segment and the surrounding normal myocardium (which may be hypercontractile in the post-infarction period) makes it a nidus for rupture.[27-29] Rupture is usually a catastrophic event that may result a life-threatening process known as cardiac tamponade, in which blood accumulates within the pericardium or heart sac and compresses the heart to the point where it cannot pump effectively. Rupture of the intraventricular septum (the muscle separating the left and right ventricles) causes a ventricular septal defect with shunting of blood through the defect from the left side of the heart to the right side of the heart, which can lead to right ventricular failure as well as pulmonary over circulation. Rupture of the papillary muscle may also lead to acute mitral regurgitation and subsequent pulmonary edema and possibly even cardiogenic shock.

Arrhythmia

Since the electrical characteristics of the infracted tissue change arrhythmias are a frequent complication. The re-entry phenomenon may cause rapid heart rates (ventricular tachycardia and even ventricular fibrillation) and ischemia in the electrical conduction system of the heart may cause a complete heart block (when the impulse from the sinoatrial node, the normal cardiac pacemaker, does not reach the heart chambers).[30-32]

Pericarditis

As a reaction to the damage of the heart muscle, inflammatory cells are attracted. The inflammation may reach out and affect the heart sac. This is called pericarditis. In Dressler's syndrome, this occurs several weeks after the initial event.

Cardiogenic shock

A complication that may occur in the acute setting soon after a myocardial infarction or in the weeks following it is cardiogenic shock. Cardiogenic shock is defined as a haemodynamic state in which the heart cannot produce enough of a cardiac output to supply an adequate amount of oxygenated blood to the tissues of the body. While the data on performing interventions on individuals with cardiogenic shock is sparse, trial data suggests a long-term mortality benefit in undergoing revascularization if the individual is less than 75 years old and if the onset of the acute myocardial infarction is less than 36 hours and the onset of cardiogenic shock is less than 18 hours. If the patient with cardiogenic shock is not going to be revascularized, aggressive haemodynamic support is warranted, with insertion of an intra-aortic balloon pump if not contraindicated. If diagnostic coronary angiography does not reveal a culprit blockage that is the cause of the cardiogenic shock, the prognosis is poor.[33]

Ventricular fibrillation

Injury to heart muscle also can lead to ventricular fibrillation. Ventricular fibrillation occurs when the normal, regular, electrical activation of heart muscle contraction is replaced by chaotic electrical activity that causes the heart to stop beating and pumping blood to the brain and other parts of the body. Permanent brain damage and death can occur unless the flow of blood to the brain is restored within five minutes. Most of the deaths from heart attacks are caused by ventricular fibrillation of the heart that occurs before the victim of the heart attack can reach an emergency room. Those who reach the emergency room have an excellent prognosis; survival from a heart attack with modern treatment should exceed 90%. The 1% to 10% of heart attack victims who later die frequently had suffered major damage to the heart muscle initially or additional damage at a later time. Deaths from ventricular fibrillation can be avoided by cardiopulmonary resuscitation (CPR) started within five minutes of the onset of ventricular fibrillation. CPR requires breathing for the victim and applying external compression to the chest to squeeze the heart and force it to pump blood. In 2008, the American Heart Association modified the mouth-to-mouth instruction of CPR and recommends that chest compressions alone are effective if a bystander is reluctant to do mouth-to-mouth. When paramedics arrive, medications

and/or an electrical shock (cardio version) can be administered to convert ventricular fibrillation back to a normal heart rhythm and allow the heart to pump blood normally. Therefore, prompt CPR and a rapid response by paramedics can improve the chances of survival from a heart attack. In addition, many public venues now have automatic external defibrillators (AEDs) that provide the electrical shock needed to restore a normal heart rhythm even before the paramedics arrive. This greatly improves the chances of survival.

Pathophysiology of Myocardial Infarction

The pathophysiology of myocardial infarction entails the entire process of what causes a myocardial infarction and how it eventually happens. As mentioned earlier, the most common etiological factor that is responsible for a myocardial infarction is the presence of an atherosclerotic plaque in the region of the coronary arteries. Plaque in arteries is a condition wherein there is the presence of a blockade in the form of a plug made of cholesterol, lipids and platelets among other cells. The actual development of a plaque that is large enough to cause atherosclerosis symptoms takes years to form. Although there may be some amount of plaque erosion due to the action of metalloproteases, leading to thinning of the plaque, the thickness may still be large enough to lead to an obstruction. This leads to disruption in the flow of blood from the coronary arteries to the heart muscle cells. One of the most important factors in myocardial infarction pathophysiology is the fact that the size of the thrombus is what dictates the percentage of block. And it is the percentage of block which will decide the extent of damage rendered to the heart muscles.

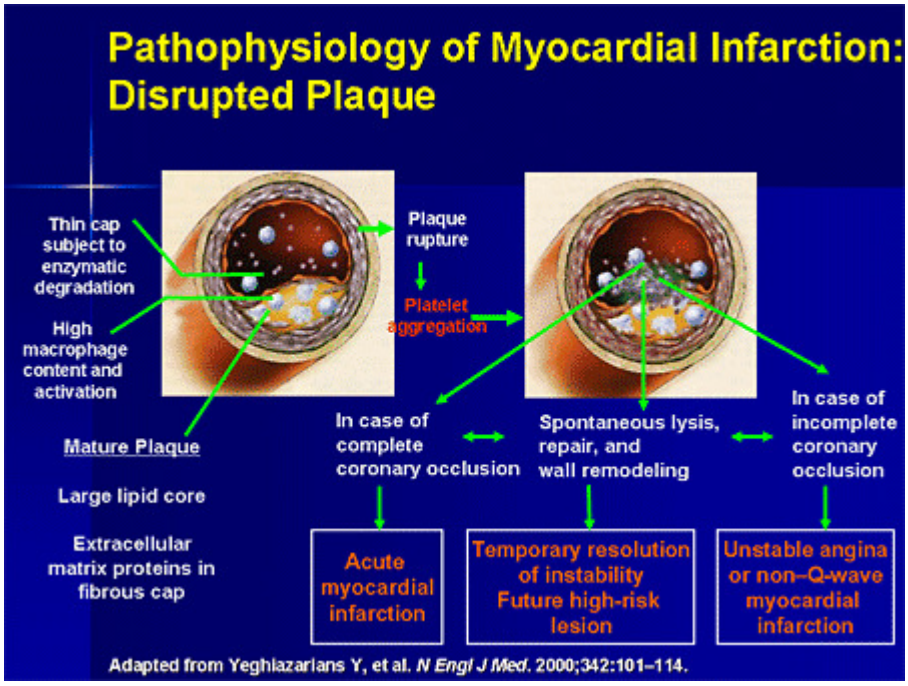


Fig.No.4 **Pathophysiology of Myocardial Infarction**

If decreased amount of blood flow to the heart lasts long enough, it eventually triggers a process known as the ischemic cascade. This causes the heart muscle cells that are supplied by that vessel to die due to hypoxic necrosis. In the region of the dead muscle cells, a collagen scar forms. Due to this, that portion of the heart will permanently get damaged. This scarring of the myocardium also puts the patient at risk for potentially life threatening cardiac arrhythmia as that part of the heart will not be able to pump out enough blood, as required by the rest of the body. The main basis of myocardial infarction pathophysiology lies in the fact that injured heart tissue conducts electrical impulses at a rate that is much slower than normal heart tissue. This difference in conduction rate of impulses between injured and non-injured tissue of the heart can trigger possible arrhythmias, which could even be the eventual cause of death. The most serious of these arrhythmias is ventricular fibrillation, a very fast and chaotic heart rhythm that is the leading cause of sudden cardiac arrest. Another life threatening arrhythmia is ventricular tachycardia which also usually results in rapid heart rates that prevent the heart from pumping blood effectively and efficiently to different parts of the body. This may result in lowered cardiac output and a dangerous fall in blood pressure, which can lead to further coronary ischemia and extension of the infarct, which may eventually culminate in the death of the person.

This was all about the myocardial infarction pathophysiology. There are various risk factors that are associated with myocardial infarction. These include a previous history or a family history of cardiovascular diseases, old age, smoking, obesity and high levels of cholesterol in the blood, kidney diseases, etc. Thus, it is best to try and stay fit so as to keep the possibility of heart diseases at an all time low. [34]

Fig.No.5 **Heart showing anterior left ventricle wall infarction.**

Diagnosis of Myocardial Infarction and Related Procedures & Tests

A heart attack is a process that spans over several hours and a fast diagnosis can increase the chance of survival and minimize the damages. A heart attack diagnosis involves a physical examination, a medical review of health problems and diagnostic tests.

I. Physical examination. During a physical examination the medical team will check the pulse and blood pressure. The heart and lungs will be listening with a stethoscope and the patient is usually hooked up to a heart monitor.

II. Medical review of health problems. During the medical health review, the doctor collects information regarding past medical problems such as a history of heart diseases in the family, past heart or blood vessel problems, a review of heart attack risk factors, and present symptoms.

III. Diagnostic tests. Diagnostic tests are divided in two categories: non-invasive tests and invasive tests.

The category of non-invasive tests includes: [21-21]

1. Echocardiogram
2. Electrocardiogram (ECG or EKG)
3. Chest X-ray
4. Coronary Artery Disease Screening Tests
5. Hormone Therapy
6. Exercise Stress Test

The category of invasive tests includes: [21-24]

1. Coronary Artery Bypass Graft
2. **Blood tests**

- Homocysteine
- C-Reactive Protein (CRP Test)
- Triglycerides Test

- Erythropoietin (EPO Test)
- Troponin I and troponin T Test
- CPK and CPK-MB Test
- Serum myoglobin Test

3. **Cardiac catheterization**
4. Pacemaker

5. Biventricular Pacemaker

6. Angioplasty and Stents

The category of non-invasive tests:

1. Echocardiography

An echocardiogram (often called "echo") is a graphic outline of the heart's movement. During this test, high-frequency sound waves, called ultrasound, provide pictures of the heart's valves and chambers. This allows the technician, called a sonographer, to evaluate the pumping action of the heart. Echo is often combined with Doppler ultrasound and color Doppler to evaluate blood flow across the heart's valves. Echocardiogram is a non-invasive diagnostic test that can determine whether the heart muscle has suffered changes and detect blood clots. It is similar with an ultrasound producing visual images of the heart. This test can provide information regarding the heart's strength which is essential in determining the severity of the heart attack, which portion of the heart may have been affected and what coronary artery is blocked. In normal conditions, approximately 60% of the blood in the left ventricle is pumped out each time the heart contracts. If Echocardiogram reveals 40 to 45 % of the blood is pumped out, the patient has suffered a minor heart attack. When 30 to 40 % of the blood is pumped out, the patient has suffered a moderate to severe heart

attack. When only 10 to 25% of the blood is pumped out, the patient has suffered a massive heart attack.

Key points

- Echocardiography (echo) is a painless test that uses sound waves to create pictures of your heart.
- This test gives your doctor information about the size and shape of your heart and how well your heart's chambers and valves are working. In addition, a type of echo called Doppler ultrasound shows how well blood flows through the chambers and valves of your heart.
- Your doctor may recommend Echo if you have signs and symptoms of heart problems. The test can be used to confirm a diagnosis, determine the status of an existing problem, or help guide treatment.
- There are several types of Echo. Trans thoracic and stress echo are standard types of the test. Tran's oesophageal echo (TEE) is used if the standard tests don't produce clear results. A fetal echo is used to look at an unborn baby's heart. A three-dimensional (3D) echo may be used to help diagnose heart problems in children or plan and monitor heart valve surgery.
- Echo is done in a doctor's office or hospital. The test usually takes up to an hour to do. A standard echo doesn't require any special preparations or follow up. If you're having a TEE, you usually shouldn't eat or drink for 8 hours prior to the test.
- During a standard echo, your doctor or sonographer will move a wand-like device called a transducer around on your chest to get pictures of your heart. During a TEE, the transducer will be put down your throat to get a better view of your heart.
- A cardiologist (heart specialist) will review the results from your echo.

- You usually can go back to your normal activities right after having echo. If you have TEE, you may be watched for a few hours at the doctor's office or hospital after the test.

- Transthoracic and fetal echo have no risks. If you have TEE, some risks are associated with the medicine given to help you relax. Rarely, the tube used in TEE can cause minor throat injuries. The risks for stress echo are related to the exercise or medicine used to raise your heart rate. Serious complications from stress echo are rare.

2. Electrocardiogram (ECG or EKG)

Electrocardiogram is the first test done by the medical team to diagnose a heart attack. This test establishes whether a heart attack is in progress or has already occurred by recording the electrical activity of the heart. When the heart muscle has suffered injuries, it doesn't conducts electrical impulses normally, and a special device registers these changes through a set of electrical sensors (leads) attached to certain location on the arms, legs, and chest. EKG leads are attached to the body while the patient lies flat on a bed or table. Leads are attached to each extremity (four totals) and to six pre-defined positions on the front of the chest. A small amount of gel is applied to the skin, which allows the electrical impulses of the heart to be more easily transmitted to the EKG leads. The leads are attached by small suction cups, Velcro straps, or by small adhesive patches attached loosely to the skin. The test takes about five minutes and is painless. In some instances, men may require the shaving of a small amount of chest hair to obtain optimal contact between the leads and the skin.

The following can be measured or detected by ECG

- The underlying rate and rhythm mechanism of the heart.
- The orientation of the heart (how it is placed) in the chest cavity.
- Evidence of increased thickness (hypertrophy) of the heart muscle.
- Evidence of damage to the various parts of the heart muscle.
- Evidence of acutely impaired blood flow to the heart muscle.
- Patterns of abnormal electric activity that may predispose the patient to abnormal cardiac rhythm disturbances.

3. Chest X-ray

This is an additional test used to visualize the shape and size of the heart, the width of aorta and the condition of the lungs. A chest X-ray is a radiology test that

involves exposing the chest briefly to radiation to produce an image of the chest and the internal organs of the chest. An X-ray film is positioned against the body opposite the camera, which sends out a very small dose of a radiation beam. As the radiation penetrates the body, it is absorbed in varying amounts by different body tissues depending on the tissue's composition of air, water, blood, bone, or muscle. for example, absorb much of the X-ray radiation while lung tissue (which is filled with mostly air) absorbs very little, allowing most of the X-ray beam to pass through the lung. Due to the differences in their composition (and, therefore, varying degrees of penetration of the X-ray beam), the lungs, heart, aorta, and bones of the chest each can be distinctly visualized on the chest X-ray. The X-ray film records these differences to produce an image of body tissue structures and these are shadows seen on the X-ray. The white shadows on chest X-ray represent more dense or solid tissues, such as bone or heart and the darker shadows on the chest X-ray represent air filled tissues, such as lungs.

4. Coronary Artery Disease Screening Tests

Coronary artery disease (CAD) is atherosclerosis (plaque in artery walls) of the inner lining of the blood vessels that supply blood to the heart. A similar term, arteriosclerosis which means hardening or stiffening of the arteries is sometimes interchanged with atherosclerosis by some authors. CAD is a common form of heart disease and is a major cause of illness and death. CAD begins when hard cholesterol substances (plaques) are deposited within a coronary artery. The coronary arteries arise from the aorta, which is adjacent to the heart. The plaques narrow the internal diameter of the arteries (Figure.7) which may cause a tiny clot to form which can obstruct the flow of blood to the heart muscle. Symptoms of CAD include:

- Chest Pain (angina pectoris) from inadequate blood flow to the heart;
- Heart Attack (acute myocardial infarction), from the sudden total blockage of a coronary artery; or
- Sudden death, due to a fatal rhythm disturbance.

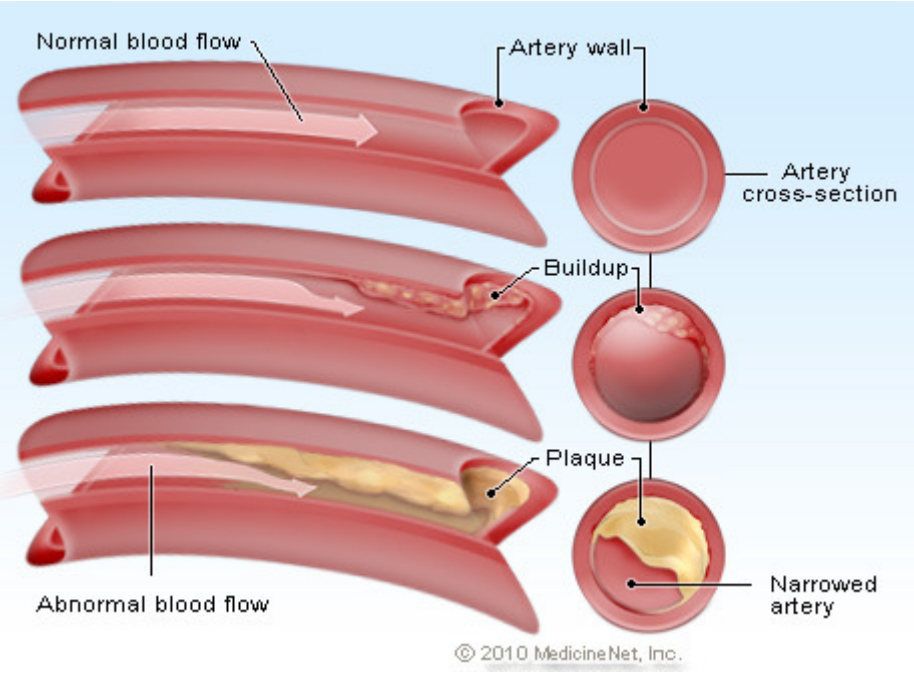


Fig.No.6 **The plaques narrow the internal diameter of the arteries**

In many patients, the first symptom of CAD is myocardial infarction or sudden death, with no preceding chest pain as a warning. For this reason, doctors perform screening tests to detect signs of CAD before serious medical events occur so the tests are designed to detect plaque (Figure.5) before a coronary artery becomes completely blocked. Screening tests are of particular importance for patients with risk factors for CAD. These risk factors include a family history of CAD at relatively young ages, an abnormal serum cholesterol profile, cigarette smoking, elevated blood pressure (hypertension) and diabetes mellitus.

5. Hormone Therapy

Menopause

Menopause is the stage in a woman's life when menstruation stops and she can no longer bear children. During menopause, the body produces less of the female hormones, estrogen and progesterone. After menopause, the lower hormone levels cause the monthly menstrual periods to stop and gradually eliminate the possibility of becoming pregnant. These fluctuations in hormone levels can also cause troublesome

symptoms, such as hot flashes (a sudden sensation of warmth, sometimes associated with flushing and often followed by sweating) and sleep disturbance. Sometimes women experience other symptoms, such as vaginal dryness. While many women encounter little or no trouble during menopause, others endure moderate to severe discomfort. The lower estrogen levels of menopause can lead to progressive bone loss that is especially rapid in the first five years after menopause. Some bone loss in both men and women is normal as people age. Lack of estrogen after menopause adds another strain on the bones in addition to the usual age-related bone loss. When bone loss is severe, a condition called osteoporosis weakens bones and renders them susceptible to breaking. For more, please read the osteoporosis article.

Estrogen therapy and Hormone therapy (HT)

Estrogen, in pill, patch, or gel form, is the single most effective therapy for suppressing hot flashes. The term estrogen therapy, or ET, refers to estrogen administered alone. Because ET alone can cause uterine cancer (endometrial cancer) (see below), a progestin is administered together with estrogen in women who have a uterus to eliminate the increased risk. Thus, the term estrogen/progestin therapy, or EPT, refers to a combination of estrogen and progestin therapy, as is given to a woman who still has a uterus. This method of prescribing hormones is also known as combination hormone therapy. The term hormone therapy (HT) is a more general term that is used to refer to either administration of estrogen alone (women who have had a hysterectomy), or combined estrogen/progestin therapy (women with a uterus). All forms of hormone therapy (HT) that are FDA-approved for therapy of hot flashes are similarly effective in suppressing hot flashes. The term "hormone therapy" or "HT" is replacing the outdated terminology "hormone replacement therapy" or "HRT."

6. Exercise Stress Test

A stress test can be used to test for heart disease. Stress tests are tests performed by a doctor and/or trained technician to determine the amount of stress that your heart can manage before developing either an abnormal rhythm or evidence of ischemia (not enough blood flow to the heart muscle). The most commonly performed

stress test is the exercise stress test. The exercise stress test also called a stress test, exercise electrocardiogram, treadmill test, graded exercise test, or stress ECG is a test used to provide information about how the heart responds to exertion. It usually involves walking on a treadmill or pedaling a stationary bike at increasing levels of difficulty, while your electrocardiogram, heart rate and blood pressure are monitored.

There are many different types of stress tests, including:

- **Dobutamine or Adenosine Stress Test:** This test is used in people who are unable to exercise. A drug is given to make the heart respond as if the person were exercising. This way the doctor can still determine how the heart responds to stress, but no exercise is required.
- **Stress echocardiogram:** An echocardiogram (often called "echo") is a graphic outline of the heart's movement. A stress echo can accurately visualize the motion of the heart's walls and pumping action when the heart is stressed; it may reveal a lack of blood flow that isn't always apparent on other heart tests.
- **Nuclear stress test:** This test helps to determine which parts of the heart are healthy and function normally and which are not. A very small and harmless amount of radioactive substance is injected into the patient. Then the doctor uses a special camera to identify the rays emitted from the substance within the body; this produces clear pictures of the heart tissue on a monitor. These pictures are done both at rest and after exercise. Using this technique, a less than normal amount of thallium will be seen in those areas of the heart that have a decreased blood supply.

Preparation for these types of stress tests will vary from preparation for the exercise stress test.

The category of invasive tests:

1. Coronary artery bypass graft (CABG) surgery

According to the American Heart Association 427,000 coronary artery bypass graft (CABG) surgeries were performed in the United States in 2004, making it one of the most commonly performed major operations. CABG surgery is advised for selected groups of patients with significant narrowing's and blockages of the heart arteries (coronary artery disease). CABG surgery creates new routes around narrowed and blocked arteries, allowing sufficient blood flow to deliver oxygen and nutrients to the heart muscle.

2. Blood tests:

a) Homocysteine

Homocysteine is an amino acid that is produced by the body, usually as a byproduct of consuming meat. Amino acids are naturally made products, which are the building blocks of all the proteins in the body. Elevated levels of homocysteine (>10 micromoles/liter) in the blood may be associated with atherosclerosis (hardening and narrowing of the arteries) as well as an increased risk of heart attacks, strokes, blood clot formation and possibly Alzheimer's disease. In 1969, Dr. Kilmer S. McCully reported that children born with a genetic disorder called homocystinuria, which causes the homocysteine levels to be very high, sometimes died at a very young age with advanced atherosclerosis in their arteries. However, it was not until the 1990's that the importance of homocysteine in heart disease and stroke was appreciated.

b) C-Reactive Protein (CRP Test)

C-reactive protein (CRP) is a blood test marker for inflammation in the body. CRP is produced in the liver and its level is measured by testing the blood. CRP is classified as an acute phase reactant, which means that its levels will rise in response to inflammation. Other common acute phase reactants include the erythrocyte sedimentation rate (ESR) and blood platelet count. In general, the main causes of

increased CRP and other markers of inflammation are burns, trauma, infections, inflammation, active inflammatory arthritis and certain cancers. The elevation of CRP has also been recently linked to atherosclerosis and heart disease. Atherosclerosis or cholesterol plaguing of the arteries is known to have an inflammatory component that is thought to cause the rise in CRP levels in the blood. Atherosclerosis is also felt to be affected by age and other cardiovascular risk factors including diabetes mellitus, high cholesterol, high blood pressure and cigarette smoking. In atherosclerosis, the blood vessel wall becomes injured. This injury acts as focus of inflammation and leads to the formation of plaques in the blood vessel walls. The plaques typically contain blood cells of inflammation, cholesterol deposits and debris from the injured cells in the blood vessel lining. The accumulation of these elements leads to narrowing of the wall of the blood vessel. The blood vessel narrowing can hinder the blood flow and the plaque can rupture and flake off of the blood vessel wall causing blockage and leading to strokes and heart attacks. The burden of plaques in the body can be proportional to the degree of CRP elevation in persons with atherosclerosis. Atherosclerotic plaques can exist in different stages throughout the body.

c) Triglycerides Test

Triglycerides are chemical compounds digested by the body to provide it with the energy for metabolism. Triglycerides are the most common form of fat that we digest and are the main ingredient in vegetable oils and animal fats. The triglyceride molecule is a form of the chemical glycerol (tri=three molecules of fatty acid + glyceride=glycerol) that contains three fatty acids. To be absorbed, these parts are broken apart in the small intestine and afterwards are reassembled with cholesterol to form chylomicrons. This is the source of energy for cells in the body. Fat cells and liver cells are used as storage sites and release chylomicrons when the body needs the energy. Elevated triglyceride levels are a risk factor for atherosclerosis, the narrowing of arteries with the buildup of fatty plaques that may lead to heart attack, stroke, and peripheral artery disease. Markedly elevated triglyceride levels may also cause fatty liver disease and pancreatitis.

Elevated triglyceride levels in the blood may be associated with other diseases including:

- Poorly-controlled diabetes.
- kidney disease.
- Some medications (for example, beta blockers, diuretics, birth control pills).

Alcohol consumption can raise triglyceride blood levels by causing the liver to produce more fatty acids. However, there are some beneficial aspects of moderate alcohol consumption, defined as one alcoholic beverage per day (a glass of wine, a bottle of beer, or an ounce of hard liquor), that may balance this triglyceride rise. Moderate consumption may mildly increase HDL (the good cholesterol) levels in the bloodstream and red wine, which contains antioxidants, may decrease the risk of heart disease. However, it is not recommended that people start to drink alcohol to obtain these effects. Triglyceride levels in the blood are measured by a simple blood test. Often, triglycerides are measured as part of a lipoprotein panel (lipid panel) in which triglycerides, cholesterol, HDL (high density lipoprotein), and LDL (low density lipoprotein) are measured at the same time. Fasting for 9-12 hours before the test is required. Fat levels in the blood are affected by recent eating and digestion. Falsely elevated results may occur if the blood test is done just after eating. Elevated triglycerides place an individual at risk for atherosclerosis. Triglyceride and cholesterol levels are measured in the blood to provide a method of screening for this risk.

- **Normal triglyceride levels** in the blood are less than 150mg per deciliter (mg/dL).
- **Borderline levels** are between 150-200 mg/dL.
- **High levels of triglycerides** (greater than 200 mg/dl) are associated with a increased risk of atherosclerosis and therefore coronary artery disease and stroke.
- **Extremely high triglyceride level**s (greater than 500mg/dl) may cause pancreatitis (inflammation of the pancreas).

d) Erythropoietin (EPO Test)

Erythropoietin is a protein with an attached sugar (a glycoprotein). It is one of a number of similar glycoproteins that serve as stimulants for the growth of specific types of blood cells in the bone marrow. Erythropoietin (EPO) is a hormone produced by the kidney that promotes the formation of red blood cells by the bone marrow. The kidney cells that make erythropoietin are specialized so that they are sensitive to low oxygen levels in the blood that travels through the kidney. These cells make and release erythropoietin when the oxygen level is too low. The low oxygen level may indicate anemia, a diminished number of red blood cells, or hemoglobin molecules that carry oxygen through the body. Erythropoietin stimulates the bone marrow to produce more red blood cells. The resultant rise in red cells increases the oxygen-carrying capacity of the blood.

As the prime regulator of red cell production, erythropoietin's major functions are to:

1. Promote the development of red blood cells.
2. Initiate the synthesis of hemoglobin, the molecule within red blood cells that transports oxygen.

No. Erythropoietin is produced to a lesser extent by the liver. Only about 10% of the erythropoietin is produced in the liver. The erythropoietin gene has been found on human chromosome 7 (in band 7q21). Different DNA sequences flanking the erythropoietin gene act to control liver versus kidney production of erythropoietin. The erythropoietin hormone can be detected and measured in the blood. The level of erythropoietin in the blood can indicate bone marrow disorders, (such as polycythemia, or increased red blood cell production) kidney disease, or erythropoietin abuse. Testing erythropoietin blood levels is thus of value if:

- Too little erythropoietin might be responsible for too few red blood cells (such as in evaluating anemia, especially anemia related to kidney disease).
- Too much erythropoietin might be causing too many red blood cells (polycythemia).

- Too much erythropoietin might be evidence for a kidney tumor.
- Too much erythropoietin in an athlete may suggest erythropoietin abuse.

e) Troponin I and Troponin T Test

Troponin is a complex of three regulatory proteins that is integral to muscle contraction[35] in skeletal and cardiac muscle, but not smooth muscle. Discussions of troponin often pertain to its functional characteristics and/or to its usefulness as a diagnostic marker for various heart disorders. Troponin is attached to the protein tropomyosin and lies within the groove between actin filaments in muscle tissue. In a relaxed muscle, tropomyosin blocks the attachment site for the myosin cross bridge, thus preventing contraction. When the muscle cell is stimulated to contract by an action potential, calcium channels open in the sarcoplasmic membrane and release calcium into the sarcoplasm. Some of this calcium attaches to troponin which causes it to change shape, exposing binding sites for myosin (active sites) on the actin filaments. Myosin binding to actin forms cross bridges and contraction (cross bridge cycling) of the muscle begins. Troponin is found in both skeletal muscle and cardiac muscle, but the specific versions of troponin differ between types of muscle. The main difference is that the TnC subunit of troponin in skeletal muscle has four calcium ion binding sites, whereas in cardiac muscle there are only three. The actual amount of calcium that binds to troponin varies from expert to expert and source to source. Both cardiac and skeletal muscles are controlled by changes in the intracellular calcium concentration. When calcium rises, the muscles contract, and when calcium falls, the muscles relax. Troponin is a component of thin filaments (along with actin and tropomyosin), and is the protein to which calcium binds to accomplish this regulation. Troponin has three subunits, TnC, TnI, and TnT. When calcium is bound to specific sites on TnC, tropomyosin rolls out of the way of the actin filament active sites, so that myosin (a molecular motor organized in muscle thick filaments) can attach to the thin filament and produce force and/or movement. In the absence of calcium, tropomyosin interferes with this action of myosin, and therefore muscles remain relaxed. Troponin I have also been shown to inhibit angiogenesis in vivo and in vitro. [36]

Individual subunits serve different functions:

- Troponin C binds to calcium ions to produce a conformational change in TnI.
- Troponin T binds to tropomyosin, interlocking them to form a troponin-tropomyosin complex.
- Troponin I binds to actin in thin myofilaments to hold the troponin-tropomyosin complex in place.

Smooth muscle does not have troponin.Troponin levels can be used as a test of several different heart disorders, including myocardial infarction. [37]

f) CPK-MB test

The CPK-MB test is a cardiac marker [38] used to assist diagnoses of an acute myocardial infarction. It measures the CKM and CKB isoenzymes of phosphocreatine kinase. In some locations, the test has been superseded by the troponin test. However, recently, there have been improvements to the test that involve measuring the ratio of the CK-MB1 and CK-MB2 isoforms.[39] The newer test detects different isoforms of the B subunit specific to the myocardium whereas the older test detected the presence of cardiac-related isoenzyme dimers.

g) Serum myoglobin test [40-42]

Serum myoglobin is a test that measures the amount of myoglobin in the blood. Myoglobin is a protein in heart and skeletal muscles. When you exercise, your muscles use up any available oxygen. Myoglobin has oxygen attached to it, which provides extra oxygen for the muscles to keep at a high level of activity for a longer period of time. When muscle is damaged, myoglobin is released into the bloodstream. The kidneys help remove myoglobin from the body into the urine. In large amounts, myoglobin can damage the kidneys. Myoglobin levels may be obtained to confirm suspected muscle damage, including heart and skeletal muscle damage. The normal ("negative") range is 0 to 85 nanograms per milliliter (ng/mL).

Note: Normal value ranges may vary slightly among different laboratories. Talk to your doctor about the meaning of your specific test results. Greater-than-normal levels (a "positive" result) may indicate:

- Heart attack
- Malignant hyperthermia (very rare)
- Muscular dystrophy
- Rhabdomyolysis
- Skeletal muscle inflammation (myositis)
- Skeletal muscle ischemia (blood deficiency)
- Skeletal muscle trauma

3. Cardiac catheterization.

Cardiac catheterization (also called cardiac cath or coronary angiogram) is an invasive imaging procedure that tests for heart disease by allowing your doctor to "see" how well your heart is functioning. During the test, a long, narrow tube, called a catheter, is inserted into a blood vessel in your arm or leg and guided to your heart with the aid of a special X-ray machine. Contrast dye is injected through the catheter so that X-ray movies of your valves, coronary arteries and heart chambers can be created. This procedure is also known as arteriogram. Cardiac catheterization is usually used during the first hour of a heart attack to visualize the inside of the blood vessels within the heart. It helps to determine which artery suffered an occlusion or blockage, which arteries are narrow, and to assess the damages resulted during the heart attack. This imaging test can be performed in the presents of a dye agent injected into the heart arteries through a catheter (placed in one of the leg or arm arteries). The infusion of the dye agent produces a "hot flash" sensation in the body that lasts between 10 and 15 seconds.

4. Pacemaker

A pacemaker is a small device that's placed in the chest or abdomen to help control abnormal heart rhythms. This device uses electrical pulses to prompt the heart to beat at a normal rate. Pacemakers are used to treat arrhythmias (ah-RITH-me-ahs). Arrhythmias are problems with the rate or rhythm of the heartbeat. During an arrhythmia, the heart can beat too fast, too slow, or with an irregular rhythm.

A heartbeat that's too fast is called tachycardia (TAK-ih-KAR-de-ah). A heartbeat that's too slow is called bradycardia (bray-de-KAR-de-ah). During an arrhythmia, the heart may not be able to pump enough blood to the body. This may cause symptoms such as fatigue (tiredness), shortness of breath, or fainting. Severe arrhythmias can damage the body's vital organs and may even cause loss of consciousness or death. A pacemaker can relieve some arrhythmia symptoms, such as fatigue and fainting. A pacemaker also can help a person who has abnormal heart rhythms resume a more active lifestyle. Faulty electrical signaling in the heart causes arrhythmias. A pacemaker uses low-energy electrical pulses to overcome this faulty electrical signaling. Pacemakers can:

- Speed up a slow heart rhythm.
- Help control an abnormal or fast heart rhythm.
- Make sure the ventricles contract normally if the atria are quivering instead of beating with a normal rhythm (a condition called atrial fibrillation).
- Coordinate the electrical signaling between the upper and lower chambers of the heart.
- Coordinate the electrical signaling between the ventricles. Pacemakers that do this are called cardiac resynchronization therapy (CRT) devices. CRT devices are used to treat heart failure.
- Prevent dangerous arrhythmias caused by a disorder called long QT syndrome.

Pacemakers also can monitor and record your heart's electrical activity and heart rhythm. Newer pacemakers can monitor your blood temperature, breathing rate, and other factors and adjust your heart rate to changes in your activity. Pacemakers can be temporary or permanent. Temporary pacemakers are used to treat temporary heartbeat problems, such as a slow heartbeat that's caused by a heart attack, heart

surgery, or an overdose of medicine. Temporary pacemakers also are used during emergencies. They're used until a permanent pacemaker can be implanted or until the temporary condition goes away. If you have a temporary pacemaker, you'll stay in a hospital as long as the device is in place. Permanent pacemakers are used to control long-term heart rhythm problems. This article mainly discusses permanent pacemakers, unless stated otherwise. Doctors also treat arrhythmias with another device called an implantable cardioverter defibrillator (ICD). An ICD is similar to a pacemaker. However, besides using low-energy electrical pulses, an ICD also can use high-energy electrical pulses to treat certain dangerous arrhythmias.

5. Biventricular Pacemaker

A biventricular pacemaker is a special pacemaker used for cardiac resynchronization therapy in heart failure patients. In the normal heart, the heart's lower chambers (ventricles) pump at the same time and in sync with the heart's upper chambers (atria). When a person has heart failure, often the right and left ventricles do not pump together. When the heart's contractions become out of sync, the left ventricle is not able to pump enough blood to the body. This eventually leads to an increase in heart failure symptoms, such as shortness of breath, dry cough, swelling in the ankles or legs, weight gain, increased urination, fatigue, or rapid or irregular heartbeat.

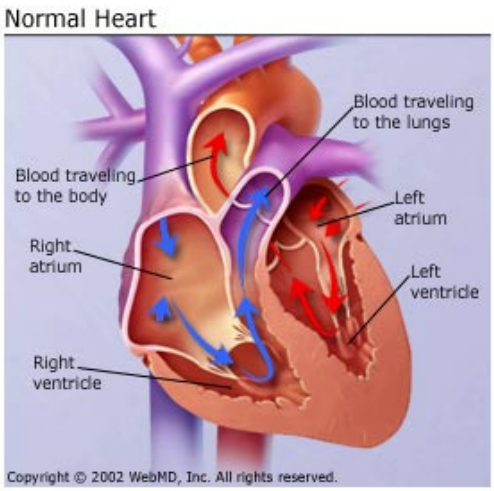


Fig.No.7 **Blood travelling pathways**

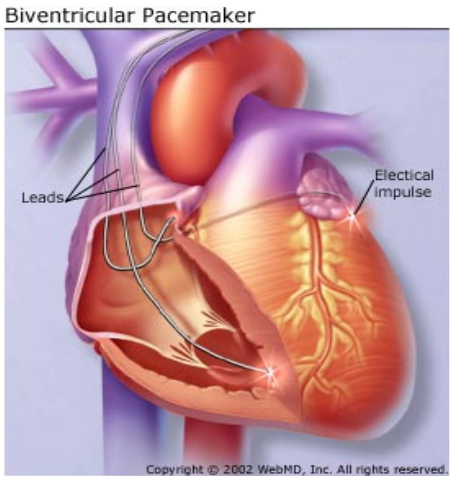


Fig.No.8**. Biventricular pacemaker**

in heart	**in heart**

Cardiac resynchronization therapy (CRT), also called biventricular pacing, uses a special kind of pacemaker, called a biventricular pacemaker, designed to treat the delay in heart ventricle contractions. It keeps the right and left ventricles pumping together by sending small electrical impulses through the leads. This therapy has been shown to improve the symptoms of heart failure and the person's overall quality of life. Leads are implanted through a vein into the right ventricle and into the coronary sinus vein to pace or regulate the left ventricle. Usually (but not always), a lead is also implanted into the right atrium. This helps the heart beat in a more balanced way. Traditional pacemakers are used to treat slow heart rhythms. Pacemakers regulate the right atrium and right ventricle to maintain a good heart rate and keep the atrium and ventricle working together. This is called AV synchrony. Biventricular pacemakers add a third lead to help the left ventricle contract at the same time as the right ventricle.

6. Angioplasty and Stents

Balloon angioplasty of the coronary artery, or percutaneous transluminal coronary angioplasty (PTCA), was introduced in the late 1970's. PTCA is a non-surgical procedure that relieves narrowing and obstruction of the arteries to the muscle of the heart (coronary arteries). This allows more blood and oxygen to be delivered to the heart muscle. PTCA is now referred to as percutaneous coronary intervention or PCI, as this term includes the use of balloons, stents and atherectomy devices. Percutaneous coronary intervention is accomplished with a small balloon catheter inserted into an artery in the groin or arm, and advanced to the narrowing in the coronary artery. The balloon is then inflated to enlarge the narrowing in the artery.

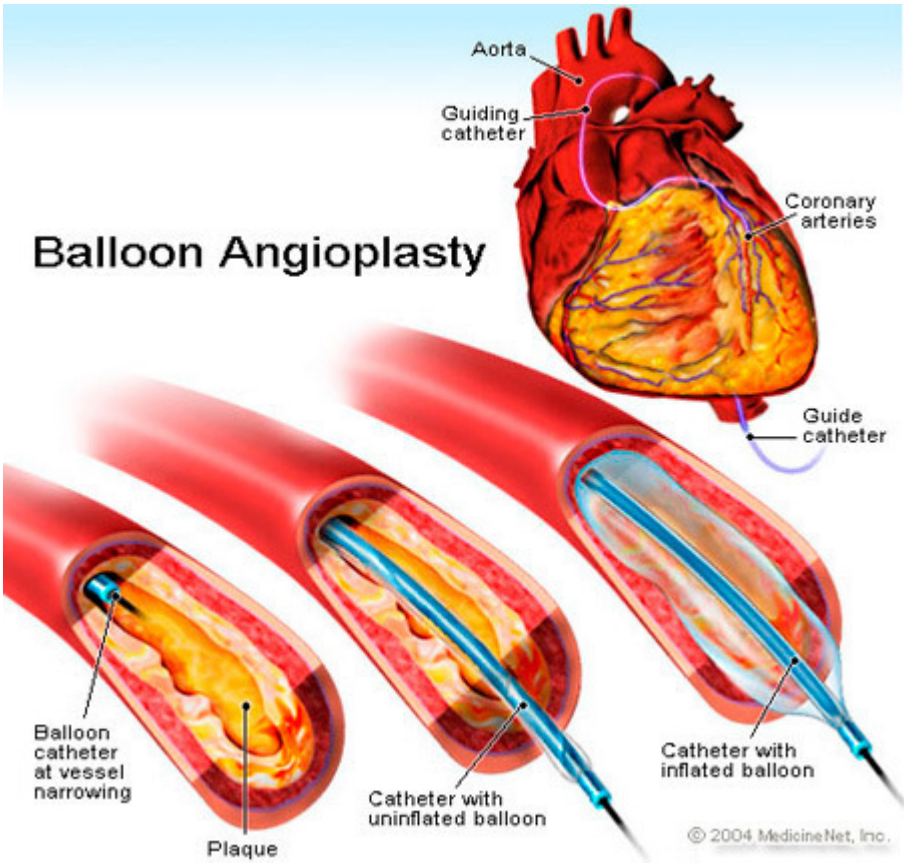


Fig.No.9 **Balloon angioplasty for obstructed coronary artery of heart muscle**

When successful, percutaneous coronary intervention can relieve chest pain of angina, improve the prognosis of individuals with unstable angina and minimize or stop a heart attack without having the patient undergo open heart coronary artery bypass graft (CABG) surgery.

In addition to the use of simple balloon angioplasty, the availability of stainless steel stents, in a wire-mesh design, have expanded the spectrum of people suitable for percutaneous coronary intervention, as well as enhanced the safety and long-term results of the procedure. Since the early 1990's, more and more patients are treated with stents, which are delivered with a percutaneous coronary intervention balloon, but remain in the artery as a "scaffold". This procedure has markedly reduced the numbers of patients needing emergency CABG to below 1%, and particularly with the use of the new "medicated" stents (stents coated with medications that help prevent plaque formation), has reduced the rate of recurrence of the blockage in the

coronary artery ("restenosis") to well below 10%. At present, the only patients treated with just balloon angioplasty are those with vessels less than 2mm (the smallest diameter stent), certain types of lesions involving branches of coronary arteries, those with scar tissue in old stents, or those who cannot take the blood thinner medication known as clopidogrel bisulfate (Plavix), which is taken over the long-term following the procedure. Various "atherectomy" (plaque removal) devices were initially developed as adjuncts to percutaneous coronary intervention. These include the use of the excimer laser for photoablation of plaque, rotational atherectomy (use of a high-speed diamond-encrusted drill) for mechanical ablation of plaque and directional atherectomy for cutting and removal of plaque. Such devices were initially thought to decrease the incidence of restenosis, but in clinical trials were shown to be of little additional benefit, and now are only used in selective cases as an adjunct to standard percutaneous coronary intervention (percutaneous artery intervention).

RATIONALE FOR PHARMACOLOGIC TREATMENT OF MYOCARDIAL INFARCTION [43]

1. Improve Myocardial Oxygen Supply/Demand Ratio

- Restore coronary blood flow
  - Dilate coronaries (inhibit vasospasm)
  - Coronary thrombolysis
  - Inhibit coagulation and platelet function

- Decreased myocardial oxygen consumption
  ↓ Heart rate
  ↓ Catractility
  ↓ Afterload
  ↓ Preload

2. Pain Management

- Analgesic drugs

3. Control Heart Rhythm

- Suppress arrhythmias

4. Inhibit Cardiac Remodeling

- Inhibit sympathetic activity
- Inhibit cardiac effects of angiotensin II

CLASSES OF DRUGS USED TO TREAT MYOCARDIAL INFARCTION AND ITS PHARMACOLOGY [44]

Classes of drugs used in the treatment of myocardial infarction are given below.

A. Vasodilators (dilate arteries and veins)

1. Nitrodilators

- Isosorbide dinitrate
- Isosorbide mononitrate
- Nitroglycerin
- Erythrityl tetranitrate
- Pentaerythritol tetranitrate
- Sodium nitroprusside

2. Angiotensin Converting Enzyme Inhibitors (ACE Inhibitors)

- Benazepril
- Captopril
- Enalapril

- Fosinopril
- Lisinopril
- Quinapril
- Ramipril

3. Angiotensin receptor blockers (ARBs)

- Candesartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan

B. Cardiac depressant drugs (reduce heart rate and contractility)

1**.** Beta-blockers

2**.** Calcium-channel blockers

- Amlodipine
- Felodipine
- Isradipine
- Nicardipine
- Nifedipine
- Nimodipine
- Nitrendipine

3. Centrally-acting sympatholytics

- Clonidine
- Guanabenz
- Guanfacine
- A-methyldopa

C. **Antiarrhythmics** (if necessary)

D. **Anti-thrombotics** (prevent thrombus formation)

- Anticoagulant
- Anti-Platelet Drugs

E. **Thrombolytics (**dissolve clots - i.e., "clot busters")

- Plasminogen activators

F. **Analgesics** (reduce pain)

- Morphine

ANIMAL MODEL FOR PRE CLINICAL RESEARCH IN MYOCARDIAL INFARCTION

MI is one of the leading causes of death in the world, induced by a blockage in coronary arteries as a result of atherosclerosis or thrombosis [45]. It is characterized by necrosis of myocardiocytes due to a reduction in blood supply. The conventional clinical treatments, such as percutaneous coronary intervention, coronary-artery bypass graft surgery and anti- or dissolution- thrombotic therapy can reduce death rate to a certain extent [46]. Heart transplantation is greatly restricted due to the limited source of donor hearts. Therefore, more effective approaches are urgently needed to treat this disease. On the basis of animal models established in experimental research, the mechanisms underlying the development of cardiovascular diseases at the cellular and molecular level have been clarified and the potential treatment options using protein, gene and stem cell therapy have been proposed, which have achieved satisfactory results.

Animal Models of MI

MI in animal models can be mainly achieved by two methods. The first is to fully block or partially narrow the coronary artery, which often leads to acute ischemia. This can be achieved by a surgical procedure or by drug intervention. The

other method is to induce atherosclerosis in coronary arteries, which would more closely mimic the disease progression in humans; however, this approach is rarely adopted in research studies, since it is time-consuming [47]. In this section we focus on the commonly used methods to create MI in small animals.

1. Surgical Ligation Model
2. Cauterization and Cryo-Injury ModeL
3. Balloon Occlusion Model
4. Pharmacologically-Induced Model
5. The use of Stem Cells to Study MI

1. Surgical Ligation Model

Occluding different regions of the coronary arteries via a thoracotomy to induce MI has been used for decades. Ligation of the left anterior descending coronary artery (LAD) to create anterior wall infarction of the left ventricle (LV) has been described by many workers. The surgical procedure can be divided into three steps. In brief, the heart of an animal under anaesthesia is exposed following a left thoracotomy at the fourth intercostal space. The pericardium is carefully broken and the LAD ligated with a suture placed just distally (1mm) from tip of the left auricle. The procedure is considered successful if the electrocardiogram (ECG) shows ST-segment elevation and the anterior wall of the left ventricle becomes whitish. Finally, the lungs are inflated and the chest closed. This permanent ligation of the LAD can cause irreversible damage to the myocardium, which is stable and easily reproduced. It has been extensively employed in studies on MI therapy using techniques such as; cell implantation, genetic modification and the administration of cytokines. Further ligation of the LAD can also produce a HF model or an ischemia–reperfusion model by subsequently removing the occlusion. However, the difficulty in operating on small rodents, particularly mice and the relatively high surgical mortality, due to the size of the wound created has to be addressed. In addition, the coronary ligation procedure often gives rise to apical aneurysmatic infarcts of variable size.

2. Cauterization and Cryo-Injury Model

The surgical procedures for cauterization or cryo-injury induced MI have been previously studied using various animal models. In brief, the heart is exposed following intercostals thoracotomy. Cauterization or cryo-injury is induced with an electrocoagulation knife for 1 to 2 seconds or a cryoprobe for 10s, respectively, on the anterior LV free wall.

The position of the probe can be set accurately using the pulmonary artery as an anatomical landmark. The MI caused by cauterization or cryo-injury is stable and easily produced in a short period of time, without the interference of the coronary arteries collateral circulation. It is particularly suitable for use in small animal such as the mouse. The necrosis of myocardiocytes is ascribed to tissue damage caused by burning or the ultra-low temperature. Unfortunately, cauterization or cryo-injury is not guaranteed to induce myocardium ischemia or tissue damage that closely mimics the natural ischemia-initiated infarction. In fact, myocardial injury from cauterization or cryo-injury shows pathophysiological changes that are not associated with myocardial infarction.

3. Balloon Occlusion Model

The balloon occlusion model was developed from percutanous translaminal coronary angioplasty and was applied in large animal models. Cohen et al. developed this occlusion model in small animals by encircling a superficial branch of the rabbit left coronary artery with a balloon occludes. Briefly, after left thoracotomy, the open end of a balloon occluder is placed around the branch of the exposed left coronary artery (LCA). The occluder is connected to a vacuum pump or compressed air to control balloon inflation and coronary occlusion. The use of this model reduces mortality and the size of the surgical wound when compared with LAD ligation-induced MI. The procedure is reliable and reproducible, allowing the accurate positioning of the balloon, making it the first choice model to induce post-infarct reperfusion. However, balloon angioplasty requires a high level of surgical expertise and is not easily applicable in small animals without extensive training.

4. Pharmacologically-Induced Model

Drug-induced myocardial ischemia is a convenient procedure, since it does not require complicated surgery. Isoproterenol, Adriamycin and ergonovine have been

often used to induce MI. Signal et al. induced myocardial ischemia in rats with isoproterenol. Similarly, Chagoya et al. developed a rat MI model by utilising isoproterenol; and Arteaga de Murphy and his group successfully duplicated the MI model in rats with a subcutaneous injection of isoproterenol. While, Arnolde et al. created an ischemia model in rabbits by the intraperitoneal injection of adriamycin. Drug-induced ischemia can be easily achieved, since it increases myocardial oxygen consumption or induces coronary artery spasm to reduce blood flow; however, drug safety and the difficulty in accurately positioning the infarct region make this model rarely used in clinical research.

5. The use of Stem Cells to Study MI

Studies using myocardial infarct animal models have indicated that transplantation of mesenchymal stem cells (MSC), umbilical cord blood cells, bone marrow-derived haematopoietic stem cells, skeletal myoblasts, endothelial progenitor cell (EPC), cardiac stem cells, embryonic stem cells (ESC), or induced-pluripotent stem cell have the potential to improve the function of ventricular muscle after MI. Clinical trials have also produced some encouraging results. However, the current experimental evidence suggests that the benefits of cell therapy are modest. Several recent reviews have summarized systematically the application of stem cell following MI. The past decade has shown that translating the potential benefit of stem cell therapy into actual clinical practice still needs a lot of work and many barriers would need to be overcome before this therapy can attain its full potential.

2. REVIEW OF LITERATURE

T.Vijay, et al., (2011) Phytochemical Studies By GC-MS And Cardio protective Effect Of *Grewia Hirsuta* (Gh) On Doxorubicin Induced Cardiotoxicity In Albino Rats

The present study was designed to scientifically evaluate the cardio protective potential of the ethanol extract of Grewia hirsuta (GH) on Doxorubicin (DOX) induced cardio toxicity, in albino rats. DOX is one of the most effective chemotherapeutic drugs in cancer; however, its incidence of cardio toxicity compromises its therapeutic index. DOX-induced heart failure is thought to be caused by reduction/oxidation cycling of DOX to generate oxidative stress and cardio myocyte cell death. Histology of Dox-induced heart of rats pretreated with GH showed a significant recovery from cell damage. The present findings have demonstrated that the cardio protective effects of GH in DOX-induced oxidative damage may be due to an augmentation of the endogenous antioxidants and inhibition of lipid peroxidation of cell membrane.[48]

Velliyur Kanniappan Gopalakrishnan, et al., (2011) Cardioprotective effect of Aqueous and Ethanol extract of Aerva lanata (Linn.) against doxorubicin induced cardiomyopathy in rats

To analysis the cardio protective effect of aqueous and ethanol extract of A.lanata on doxorubicin induced cardiomyopathy in wistar rats. It was showed that all the three extracts of A.lanata has cardioprotective activity similar to that of aspirin. By all these finding A.lanata has showed significant cardio protective activity, which provides scientific proof of these traditional values.[49]

Shreesh Kumar Ojha, et al., (2009) *Withania somnifera* Dunal (Ashwagandha):

A Promising Remedy for Cardiovascular Diseases*Withania somnifera* Dunal (Ashwangdha). It is a common ingredient of polyherbal or herb mineral formulations and used for preventive or therapeutic polypharmaceutical use. It has been demonstrated to possess adaptogenic, anti-inflammatory, antioxidant, anti-platelet,

antihypertensive, hypoglycemic and Hypolipidemic effects which may contribute to its cardio protective properties.[50]

K. Sakthivel, et al., phytoconstituents analysis by GCMS, cardioprotective and antioxidant activity of buchanania axillaris against doxorubicin-induced cardio toxicity in albino rats

The present study was designed to scientifically evaluate the cardioprotective potential of the ethanol extract of Buchanania axillaries (BA), on Doxorubicin (DOX) induced cardiotoxicity, in albino rats. The present findings have demonstrated that the cardioprotective effects of BA in DOX-induced oxidative damage may be due to an augmentation of the endogenous antioxidants and inhibition of lipid peroxidation of cell membrane.[51]

T.Vijay, et al., (2011) Cardioprotective, antioxidant activities and Phytochemical analysis by GC-MS of *Gmelina*m *arborea* (GA) in Doxorubicin-induced myocardial necrosis in *Albino* rats

Supplementations with *Gmelina arborea* (*Verbenaceae*) were proven effective in reducing oxidative stress associated with several ailments. Pretreatment of GA significantly guarded against DOX-induced rise of serum lactate dehydrogenase (LDH). GA alleviated histopathological changes in rats' hearts treated with DOX. In conclusion, GA protects against DOX-induced cardio toxicity in rats. The study can be attributed, at least in part, to GA's antioxidant activity.[52]

T.Vijay, et al., Analysis of phytoconstituents by GC-MS and therapeutic efficacy of *Grewia umbelliferea*(Gu) on Doxorubicin induced cardio toxicity in *albino* rats.

Supplementations with *Grewia umbelliferea* (GU) were proven effective in reducing oxidative stress associated with several ailments. Pretreatment of GU significantly guarded against DOX-induced rise of serum lactate dehydrogenase (LDH). GU alleviated histopathological changes in rats' hearts treated with DOX. In conclusion, GU protects against DOX-induced cardiotoxicity in rats. This can be attributed, at least in part, to GU's antioxidant activity.[53]

M.H. Abdel-Wahab, et al., (2007) Influence of *p*-coumaric acid on doxorubicin-induced oxidative stress in rat's heart

The ability of *p*-coumaric (PC) acid, a member of phenolic acids, to protect rat's heart against DOX-induced oxidative stress was investigated. The data presented here indicate that PC protects rat's hearts against DOX-induced oxidative stress in the heart. It may be worthy to consider the usefulness of PC as adjuvant therapy in cancer management.[54]

D. Rajaprabhu, et al., (2007) Protective effect of Picrorhiza kurroa on antioxidant defense status in adriamycin-induced cardiomyopathy in rats.

The present study examined the protective effects of Picrorhiza kurroa, an ayurvedic medicinal plant, on myocardial antioxidant defense system in adriamycin-induced cardiomyopathy in rats. The protective effect of P. kurroa might be ascribable to its membrane-stabilizing property and/or antioxidant nature. [55]

Patel Soncharan et al., (2010) Protective effect of *Syzygium cumini* seeds against doxorubicin induced cardiotoxicity in rats.

Syzygium cumini Linn. Seeds possessing potent antioxidant and cardio protective properties were evaluated against Doxorubicin induced cardio toxicity in rats. *Syzygium cumini* seeds were found to be more effective in restoring lipid profile changes in rats and antioxidant enzyme activities in heart tissue. So the study shows that *Syzygium cumini* seeds possess antioxidant and cardio protective effects.[56]

Raja Kumar Parabathina, et al., (2011) effects of vitamin E, morin, rutin and quercetin against dox induced oxidative stress

The development of oxidative stress was prevented by using natural antioxidant vitamin E (50 IU/kg body weight) and flavonoids morin, rutin and quercetin a poly phenolic compounds available in plants. This model can suggest that fields of Biochemistry and Pharmacology had good scope to evaluate the metabolic diseases and disorders.[57]

Raja Kumar Parabathina, et al.,(2010) Cardioprotective effects of vitamin E, morin, rutin and quercetin against Doxorubicin induced oxidative stress of rabbits

A biochemical study the rabbit model, the development of cardio myopathy was prevented by reducing oxidative stress using natural antioxidant vitamin E (50 IU/kg body weight) and flavonoids morin, rutin and quercetin, which are generally available in the natural diet. By this study, the author suggests that rabbits are good experimental models to conduct various types of experiment in Biochemistry and Pharmacology.[58]

Khatib N.A, et al (2010) Evaluation of Methanolic Extract of Cassia Fistula Bark for Cardio protective Activity

Cassia fistula is the family of leguminaceae is traditional used cardiopathy and heart disease. The cardio protective effect of Methanolic extract of C.fistula(MECB) bark against doxorubicin significant decreased the elevated level of serum enzymes histological disturbance and electrocardiogram change to normal myocardial functioning. The result suggested that MECB has cardio protective effect in DXR induced myocardial damage rats.[59]

Muresan Ariana, et al (2006) studied the effect of the grape seed extract in ehrlich ascitic carcinoma.

The grape seed extract (GSE) of Burgand mare de recas grape variety was evaluated for anti tumor activity against Ehrlich ascites carcinoma (EAC) bearing swiss albino mice.The result indicated that GSE does not dot possess antitumor activity against Ehrlich ascetic carcinoma cell, does not interfere antitumor effect of the doxorubicin in EAC bearing mice and decrease the lipid peroxidation induced by doxorubicin treatment.[60]

BC Koti, et al (2008) cardioprotective activity of lipistat against doxorubicin induced myocardial toxicity in albino rats.

Lipistan increase decrease level of GSH, SOD and CAT and decrease the increase level of the malondialdehyde in cardiac tissue. The resulted support the lipid lowering and antioxidant properties of lipistat, which indicate that cardio protective property against doxorubicin induced cardio toxicity.[61]

A.H.S. Thippeswamy, et al (2011) Protective role of phyllanthus naruri extract in doxorubicine induced myocardial toxicity in rats.

Pretreatment with the Aq.E.PN significantly protect myocardium from the toxic effect of doxorubicin reducing elevated level of the biomarker and diagnostic enzymes like lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), alanine aminotransferase (ALT), to the normal level. The result suggests a cardioprotective effect of P. niruri due to its antioxidant properties.[62]

Thiruvenkadam Devaki, et al (2007) protective efficacy of nordostachys jatamansi (rhizomes) on mitochondrial respiration on and lysosome hydrolases during doxorubicin induced myocardial injury in rats.

These finding suggest that cardio protective efficacy of Nordastachys jatamansi could be mediated possible through its antioxidant effects as well as by attenuation of oxidative stress.[63]

M.Hassanpour Fard, et al (2008) cardioprotective activity of fruit of lagenaria siceraria (malina) standley on doxorubicin induced cardio toxicity in rats.

Histopathological study of LS treated group showed protection against myocardial toxicity induced by doxorubicin .It is concluded that Lagenaria siceraria possess cardio protective effect against doxorubicin induced cardiac toxicity in rats. [64]

S.Shah, et al (2009) protective effect of ephedra nebrodensis on doxorubicin induced cardiotoxicity in rats.

Treatment with Ephedra nerbrodensis (100mg/kg and 200mg/kg) significantly decrease the day level of Lipid peroxidase value (LPO) and cardiac marker enzymes. The result suggested that Ephedra nerbrodensis has potential in the preventing the cardio toxicity effect induced by doxorubicin.[65]

Eman M. Ei-Sayed, et al (2011) cardioprotective effect of curcuma longa l. Extracts against doxorubicin – induced cardiotoxicity in rats.

Oral administration of curcuma longa L. ethanolic extract or water extracts (200mg/kg) before doxorubicin produced a significant protection which was evidenced significant reduction in mortality, CK-MK and lactate dehydrogenate (LDH) activity. In conclusion, curcuma longa extract renders resiliency against doxorubicin cardio toxicity due to their contents of polyphenolic compound that might serve as novel adjuvant therapy with doxorubicin.[66]

Mahmoud A.Mansour (2008) protective effect of the 6-Gingerol against cardio toxicity induced by doxorubicin.

Administration of 6- Gingerol (10mg/kg/day p.o.)In drinking water starting 5 days before and continuing during the experimental period and significantly ameliorated myocardial toxicity induced by DOX. The current data support 6-Gingerol as a potentially selective cardio protective agent against cardio toxicity induced by DOX and it may therefore improve the therapeutic index of DOX.[67]

Gaurav kaithwas, et al (2010) effect of aloe vera (aloe barbadensis miller) gel on doxorubicin induced myocardial oxidative stress and calcium overload in albino rats.

Administration of A.vera gel (100and 200 mg/kg) orally for 10 days produced a significant protection against cardiotoxicity induced by DOX. The result reveals that A. vera gel produced a dose dependent protection against DOX induced cardiotoxicity.[68]

Suvara Kimnite Wattanapitayakul, et al (2005) antioxidative and cardioprotective effect of phyllanthus urinaria l. on doxorubicin - induced cardiotoxicity.

In this study investigated the antioxidative and cytoprotective effect of phyllanthus urinaria (PU) against DOX toxicity using H9c2 cardiac myoblasts. Our result suggest that PU protection against DOX cardiotoxicity was mediated through multiple pathway and this plant may serve as an alternative source of antioxidant for prevention of DOX cardio toxicity.[69]

Monira A. Abd Ei Kader, et al (2011) effect of grape seed extract in the modulation of matrix metalloproteinase-9 activity and oxidative stress induced by doxorubicin in mice.

The present study was designed to test whether grape seed could attenuate the increase in the matrix metalloproteinase-9 activity and prevent the doxorubicin-induced cardio toxicity in mice. Pretreatment with GS extract (100mg/kg b.wt daily for 12 days) effectively inherited the adverse effect of doxorubicin and protect against cardiac damage via suppression of oxidative stress.[70]

Davey M.S, et al., (2011) Inotropic and cardioprotective effect of terminalia paniculata roth bark extract in doxorubicin induced cardiotoxicity in rats

Supplementations with Terminalia Paniculata bark extract were proven effective in reducing oxidative stress associated with several ailments. The aim of the current study was to investigate the potential protective effect of ethanolic extract of Terminalia Paniculata(EETP) bark against doxorubicin induced cardiotoxicity in rats and to compare with vitamin E, A known cardioprotective antioxidant. Finally we concluded that Terminalia paniculata bark extract exerts equipotent cardioprotective and inotropic activity in the experiment model of doxorubicin induced myocardial infarction in rats as compared to vitamin E, a known cardio protective antioxidant. [71]

3. RESEARCH ENVISAGED

3.1 FOCUS OF THE PRESENT STUDY

Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years and have served humans as well as valuable components of medicines, seasonings, beverages, cosmetics and dyes. Herbal medicine is based on the premise that plants contain natural substances that can promote health and alleviate illness. In recent times, focus on plant research has increased all over the world and a large body of evidence has collected to show immense potential of medicinal plants used in various traditional systems. Today, we are witnessing a great deal of public interest in the use of herbal remedies[72].

In traditional medicine, natural or crude phytoextracts are considered as alternative medicines, because some natural constituents present in them counter balance the side effects of synthetic medicines[73]. It is therefore obvious that the therapeutic potential and risk efficiency of traditional medicinal plants is based on the direct assessment of phytoextracts as well as effects of their purified compounds.

Furthermore many western drugs had their origin in plant extract. There are many herbs, which are predominantly used to treat cardiovascular problems, cancer, central nervous system, digestive and metabolic disorders. Given their potential to produce significant therapeutic effect, they can be useful as drug or supplement in the treatment / management of various diseases. Herbal drugs or medicinal plants, their extracts and their isolated compounds have demonstrated spectrum of biological activities. Ethno pharmacological studies on such herbs/medicinally important plants continue to interest investigators throughout the world.

This study aims to give an overview on the recent development of herbal medicine in the prevention and treatment of myocardial infarction and covers the possible mechanism of action of hydro alcoholic extract of (Aegle Marmelos) (L.) Corr in treatment of myocardial infarction. The different parts of Bael are used for various therapeutic purposes, such as for treatment of Asthma, Anaemia, Fractures,

Healing of Wounds, Swollen Joints, High Blood Pressure, Jaundice, Diarrhoea Healthy Mind and Brain Typhoid Troubles during Pregnancy. [74]

Aegle marmelos has been used as a herbal medicine for the management of diabetes mellitus in Ayurvedic, Unani and Siddha systems of medicine in India [75], Bangladesh [76] and SriLanka.[77] The main usage of the parts of this tree is for medicinal purposes. The unripe dried fruit is astringent, digestive, stomachic and used to cure diarrhea and dysentery.[78] Sweet drink prepared from the pulp of fruits produce a soothing effect on the patients who have just recovered from bacillary dysentery.

Hence, in this study hydro alcoholic extract of (Aegle Marmelos) (L.) Corr has evaluated for cardio protective activity against Doxorubicin induced myocardial infarction.

3.2 PLAN OF WORK

Cardio protective activity of (Aegle Marmelos) (L.) Corr in animal model has been planned to be carried out in the following steps.

It is planned to carry out this work as outlined below.

1. Extraction of fruit plant of (Aegle Marmelos) (L.) Corr using increasing polarity solvent with Soxhlet apparatus.
2. Phytochemical evaluation of hydro alcoholic extracts of (Aegle Marmelos) (L.) Corr
3. In-vivo evaluation of myocardial infarction activity of hydro alcoholic extract of (Aegle Marmelos) (L.) Corr
    a) Induction of myocardial infarction using Doxorubicin
    b) Treatment protocol
    c) Study of various biochemical parameters in the blood,
        - ✪ Aspartate Aminotransferase (AST)
        - ✪ Alanine Aminotransferase (ALT)
        - ✪ Lactate Dehydrogenase (LDH)
        - ✪ Creatine Phosphokinase (CPK)
        - ✪ Alkaline Phosphatase (ALP)
    d) Study of various oxidative parameters in Homogenate Heart Tissues,
        - ✪ MDA
        - ✪ GSH
        - ✪ SOD
        - ✪ CATALASE
    e) Statistical Analysis

Dr. D. Stephen,
Lecturer,

The American College,
Department of Botany.
Madurai-2

CERTIFICATE

This is to certify that the plant specimen brought to me by **Mr. BIPIN CHANDRA BHATT,** II year **M. Pharm (Pharmacology), Student of K. M. College of Pharmacy,** Madurai has been identified as fruit of *Aegle marmelos bael* belonging to family Rutaceae.

Dr.D.Stephen.

Date : 27/08/2011
Madurai
Tamil nadu

4. PLANT PROFILE

BOTANICAL NAME : *Aegle marmelos bael*

SYNONYMS : *Aegle correa, Allocryptopine.*

SCIENTIFIC CLASSIFICATION

Kingdom	:	Plantae
Sub Kingdom	:	Tracheobionta
Division	:	Magnoliophyta
Super Division	:	Spermatophyta
Class	:	Magnoliopsida
Sub Class	:	Rosidae
Order	:	Sapindales
Family	:	Rutaceae
Genus	:	Aegle corr.serr
Section	:	Fruit
Species	:	Aegle marmelos(L.) corr.serr

COMMON NAMES

Tamil	:	Vilva
Common	:	Bael
Sanskrit	:	Bilva
Hindi	:	Bel,sirphal
Malayalam	:	Kuvalam
Telugu	:	Bilva
English	:	Bael tree, stone apple, Holy fruit apple

NATIVE RANGE

Western Himalayas, Andaman island, Bangladesh

BIOPHYSICAL LIMITS

Height	:	6.0-7.5 m
Girth	:	90-120 cm
Mean annual temperature	:	48.89°C

Soil Type: Well drained soil, it has grown well and fruited on oolitic lime stone of southern Florida.

BIOLOGY

The fruits can be harvested in January (2 to 3 month before full maturity) and ripened artificially in 18 to 24 days by treatment with 1000 to 1500 ppm and storage at 30°C. A tree may produce as many as 800 fruit in a season but an average crop is 150 to 200 or in the better cultivars up to 400.

BOTANIC DESCRIPTION

Bael (Aegle Marmelos Linn), family Rutacae, is also known as Bale fruit tree, is a moderate sized , slender, aromatic tree, 6.0 -7.5 m in height, and 90 to 120 cm in girth, with a somewhat fluted bole of 3.0-4.5 meter growing wild throughout the deciduous forests of India, ascending to an altitude of 1200 meter in the western Himalayas and also occurring in Andaman island.[79] This is generally considered as sacred tree by the Hindus, as its leaves are offered to Lord Shiva during worship. According to Hindu mythology, the tree is another form of Lord Kailashnath.[80] Leaves, fruit, stem and roots of this tree at all stages of maturity are used as ethno medicine against various human ailments.

PHYTOCHEMICAL CONSTITUENTS

Various phytoconstituents have been isolated from the various parts of Aegle marmelos, which may be categorized as;[81]

Leaf : Skimmianine, Aegeline, Lupeol, Cineol, Citral, Citronella, Cuminaldehyde, Eugenol, Marmesinine

Bark : Skimmianine, Fagarine , Marmin

Fruit: Marmelosin, Luvangetin, Aurapten, Psoralen, Marmelide, Tanni

MEDICINAL USES:

The different parts of Bael are used for various therapeutic purposes, such as for treatment of Asthma, Anaemia, Fractures, Healing of Wounds, Swollen Joints, High Blood Pressure, Jaundice, Diarrhoea Healthy Mind and Brain Typhoid Troubles during Pregnancy.

Aegle Marmelos has been used as a herbal medicine for the management of diabetes mellitus in Ayurvedic, Unani and Siddha systems of medicine in India, Bangladesh and SriLanka. The main usage of the parts of this tree is for medicinal purposes. The unripe dried fruit is astringent, digestive, stomachic and used to cure diarrhea and dysentery. Sweet drink prepared from the pulp of fruits produce a soothing effect on the patients who have just recovered from bacillary dysentery.

The ripe fruit is a good and simple cure for dyspepsia. The pulp of unripe fruit is soaked in gingerly oil for a week and this oil is smeared over the body before bathing. This oil is said to be useful in removing the peculiar burning sensation in the soles. The roots and the bark of the tree are used in the treatment of fever by making a decoction of them. The leaves are made into a poultice and used in the treatment of opthalmia. The leaf part of the plants have been claimed to be used for the treatment of inflammation, asthma, hypoglycemia, febrifuge, hepatitis and analgesic. The mucilage of the seed is a cementing material. The wood takes a fine polish and is used in building houses, constructing carts, agricultural implements. A yellow dye is obtained from the rind of the unripe fruits. The dried fruits, after their pulp separated from the rind are used as pill boxes for keeping valuable medicines, sacred ashes and tobacco. In Homeopathic treatments it is largely used for conjunctivitis and styes, rhinitis, coccygodynia, nocturnal seminal emission with amorous dreams, chronic dysentery. Ayurveda prescribes the fruit of the herb for heart, stomach, intestinal tonic, chronic constipation and dysentery; some forms of indigestion, typhoid, debility, cholera, hemorrhoids, intermittent fever, hypocondria, melancholia and for heart palpitation. The unripe fruit is medicinally better than the ripe fruit. Leaf poultice is applied to inflammation; with black pepper for edema, constipation and jaundice.

Fig. No.10

Fig. No.11

5. PHYTOCHEMICAL AND QUALITATIVE ANALYSIS

EXTRACTION METHODS

The plant fruit of *Aegle marmelos bael* were collected and authenticated. The plant fruit of *Aegle marmelos bael* was dried in the shade. Then the shade – dried fruit were pulverized to get coarse powder, sieved under mesh no.60. The powdered whole plant where extracted using petroleum ether at 40 – 60°C using soxhlet apparatus for 72 hrs.

Dry coarse Fruit material extracted by soxhlet method

By petroleum ether (72 hrs)

Marc-I

Marc-I Extracted with chloroform

(40 hrs)

Extracted with Benzene

(40 hrs)

Extracted with water (30%) + Ethanol (70%)

(40 hrs) **Marc-II**

Brownish colour Residue

Myocardial Infarction activity

Chart 1: Extraction procedure.

The extraction was continued for 40 hrs with chloroform and benzene. The extraction was continued for 40 hrs with alcohol and distilled water using soxhlet apparatus at 70 – 80°C. The solvent was removed in vacuum to provide a dry extract (9.8% w/w, as compared to the powdered material).

Preparation of extracts using various non polar solvent (petroleum ether, chloroform, benzene) and polar solvent (ethanol, distilled water) as a solvent[82]. Brownish colour residue was obtained. The chemical constituents of the hydro alcoholic extract were identified by qualitative analysis and pharmacological screening.

PHYTOCHEMICAL SCREENING

The alcoholic extracts of *Aegle marmelos bael was* analysed for the presence of flavonoids, alkaloids, glycosides, steroids, phenols, saponins, terpenoid, cardiac glycosides and tannins according to standard method[83].

Steroids (Salkowski's test)

About 100mg of *Aegle marmelos bael* dried extract was dissolved in 2ml of chloroform. Sulphuric acid was carefully added to form a lower layer. A reddish brown colour at the interface was an indicative of the presence of steroidal ring.

Cardiac glycosides (Keller Killiani's test)

About 100mg of extract was dissolved in 1ml of glacial acetic acid containing one drop of ferric chloride solution. This was then under layer with 1ml of concentrated sulphuric acid. A brown ring obtained at the interface indicated the presence of a de oxy sugar characteristic of cardenolides.

Saponins

A drop of sodium bicarbonate was added in a test tube containing about 50ml of an aqueous extract of samples. The mixture was shaken vigorously and kept for 3minuts. A honey comb like froth was formed and it showed the presence of saponins.

Tannins (Lead acetate test)

In a test tube containing about 5ml of an aqueous extract, a few drops of 1% solution of lead acetate was added. Formation of a yellow or red precipitate indicated the presence of tannins.

Terpenoids

2ml of chloroform and 1ml of conc. H_2SO_4 was added to 1mg of extract and observed for reddish brown colour that indicated the presence of terpenoid.

Glycosides

A small amount of hydro alcoholic extract of samples was dissolved in 1ml water and then aqueous sodium hydroxide was added. Formation of a yellow colour indicated the presence of glycosides.

Flavonoids

In a test tube containing 0.5ml of alcoholic extract of the samples, 5 to 10 drops of diluted HCl and small amount of Zn or Mg were added and the solution was boiled for few minutes. Appearance of reddish pink or dirty brown colour indicated the presence of Flavonoids.

Alkaloids (Mayer's test)

1.36gm of Mercuric chloride and 5gm of KI were dissolved in 60ml and 10 ml of distilled water respectively. These two solvents were mixed and diluted to 100ml using distilled water. To 1ml of acidic aqueous solution of samples few drops of reagent was added. Formation of white or pale precipitate showed the presence of alkaloids.

Phytochemical test revealed the presence of alkaloid, anthroquinone glycoside, saponins, flavonoids, polysaccharides, steroid, tannin and results are given in table1.The presence of heavy metals namely arsenic, mercury, cadmium and lead were analysed in the sample, the concentration of all the heavy metals were below the WHO/FDA permissible limits. The presence of pesticide residue organochlorine pesticide, organo phosphorous pesticides and pyrethroids were not detected in the sample.

Table 1: Preliminary Phytochemical Tests for hydro alcoholic extract of fruit of *Aegle marmelos bael*

S. NO.	DIFFERENT CONSTITUENTS	TEST PERFORMED	RESULTS
1	Alkaloid	Dragendorff's test	+ve
2	Coumarin	Alkaline test	+ve
3	Flavone	Shinoda test	+ve
4	Steroid	Liebermann-Burchard reagent	+ve
5	Tannin	Neutral fecl3	+ve
6	Glycoside/sugar	Molisch's test	+ve
7	Terpenoid	Noller's test	+ve
8	Saponin	NaOH solution	+ve

6. PHARMACOLOGICAL EVALUATION

EXPERIMENTAL MODEL

For the study of cardio protective activity, an experimental model is selected in such way that it would satisfy the following condition;

- ❖ The animal should develop myocardial infarction rapidly and reproducibly.
- ❖ Pathological changes in the site of induction should result from myocardial infarction formation.
- ❖ Cardiac necrosis can be produced by injection of natural and synthetic sympathomimetics in high doses, infarct-like myocardial lesions.
- ❖ The symptoms should be ameliorated or prevented by a drug treatment effective in human beings.
- ❖ The drug tested should be administered orally.
- ❖ Drug dosage should approximate the optimum therapeutic range for human, scaled the test animal weight[84].

ANIMAL MODEL FOR MYOCARDIAL INFARCTION

MI is one of the leading causes of death in the world, induced by a blockage in coronary arteries as a result of atherosclerosis or thrombosis. It is characterized by necrosis of myocardiocytes due to a reduction in blood supply. The conventional clinical treatments, such as percutaneous coronary intervention, coronary-artery bypass graft surgery and anti- or dissolution / thrombotic therapy can reduce death rate to a certain extent. Heart transplantation is greatly restricted due to the limited source of donor hearts. Therefore, more effective approaches are urgently needed to treat this disease. On the basis of animal models established in experimental research, the mechanisms underlying the development of cardiovascular diseases at the cellular and molecular level have been clarified and the potential treatment options using protein, gene and stem cell therapy have been proposed, which have achieved satisfactory results.[85]

TECHNIQUE FOR INDUCING MYOCARDIAL INFARCTION

MI in animal models can be mainly achieved by two methods. The first is to fully block or partially narrow the coronary artery, which often leads to acute ischemia. This can be achieved by a surgical procedure or by drug intervention. The other method is to induce atherosclerosis in coronary arteries, which would more closely mimic the disease progression in humans; however, this approach is rarely adopted in research studies, since it is time-consuming. In this section we focus on the commonly used methods to create MI in small animals.

1. Surgical Ligation Model
2. Cauterization and Cryo-Injury Model
3. Balloon Occlusion Model
4. Pharmacologically-Induced Model
5. The use of Stem Cells to Study MI

Induction of myocardial injury:

Doxorubicin (Dox) is an anthracycline antibiotic that is widely used as a chemotherapeutic agent .However the administration of Dox know to induce numerous cardiotoxic effects including transient arrhythmias, nonspecific electrocardiographic abnormalities, pericarditis and acute heart failure (Billing et al 1978 and Bristow et al 1978) Also cause congestive heart failure months or year after treatment. The mechanism of Dox induced cardiac injury has been actively investigated and several hypotheses have been suggested to explain the acute and chronic cardiotoxicity of Dox. Myocardial infarction((MI) an acute condition of necrosis of the myocardium that occurs a result of imbalance between coronary blood supply and myocardial demand (de bono and boon,1992) Dox induced cardiotoxicity in rat was associated with increased lipid peroxide levels in the myocardium (Myers et al 1977)

Rats are treated with different doses of extract of *Aegle Marmelos Bael* orally using an intra-gastric tube daily for 14 days. Myocardial injury is induced in

experimental rats by injection of DOX (3 mg kg-1, i.p) daily up to 14days while normal control and DOX treated rats are given an equivalent volume of the vehicle.

Treatment protocol:

The experimental rats are divided into five groups of 6 animals each and treated as follows:

Group 1: Normal Control Rats
Group 2: Rats treated with DOX (3 mg/ kg)
Group 3: Rats treated with Vitamin E (25mg/Kg) and DOX (3mg/kg)
Group 4: Rats treated with hydro alcoholic extract of Aegle Marmelos at a dose of 100mg/kg and then DOX (3mg/kg)
Group 5: Rats treated with hydro alcoholic extract of Aegle Marmelos at a dose of 200mg/kg and then DOX (3 mg/ kg)

EVALUATION OF MYOCARDIAL INFARCTION

Biochemical analysis:

Dissection and Homogenization

After the experimental period the rats were sacrificed by euthanasia method. Blood was collected and serum supernatant was for the assay of marker enzymes Alkaline Phosphatase (ALP), lactate dehydrogenase (LDH), Aspartate Transaminase (AST), Alanine Transaminase (ALT) and Creatine Phosphokinase (CPK). The heart was dissected out, immediately washed in ice-cold saline and a homogenate was prepared in 0.1 M Tris-KCl buffer (pH 7.4) for the estimation of Glutathione (GSH), Malondialdehyde (MDA), Superoxide dismutase and catalase.

Determination of Creatine phosphokinase

Creatine phosphokinase kinase activity was assayed using a commercial kit obtained from Agappe Diagnostics, Kerala, India. The reaction mixture contained 0.05 ml of serum, 0.1 ml of substrate, 0.1 ml of ATP solution and 0.1 ml of cysteine–hydrochloride solution. The final volume was made up to 2.0 ml and incubated at 37°C for 30 minutes[86]. The reaction was arrested by the addition of 1.0 ml of TCA and the contents subjected to centrifugation. 0.1 ml of the supernatant was made up to 4.3 ml with water. 1.0 ml of ammonium molybdate reagent was added incubated at room

temperature for 10 minutes. 0.4 ml of ANSA was added and the colour developed was read at 640 nm after 20 minutes[87].

Determination of Lactate dehydrogenase (LDH)

Activity of Lactate dehydrogenase (LDH) was assayed by Niel and method. To a set of tubes, 1 ml of the buffered substrate and 0.1 ml of sample was added and the tubes were incubated at 37°C for 15 min. After adding 0.2 ml of NAD solution, the incubation was continued for another 15 min. The reaction was then arrested by adding 1ml of DNPH reagent and the tubes were incubated for further period of 15 min at 37°C. 0.1 ml of serum was added to blank tubes after arresting the reaction with DNPH. 7 ml of sodium hydroxide solution was added and the colour developed was measured at 420 nm[88].

Determination of AST and ALT

Activities of AST and ALT were assayed. In different tubes, 1 ml of the buffered substrate was added to 0.1 ml of sample and incubated at 37°C for 30 min. Then 1 ml of DNPH reagent was added to arrest the reaction. To the blank tubes, 0.1 ml of sample was added only after the addition of DNPH reagent. The tubes were kept aside for 15 min and then 10 ml of sodium hydroxide was added and read at 520 nm[89].

Statistical Analysis

The results of cardio protective activity are expressed as mean ± SEM from six animals in each group. Results were statistically analyzed using one-way ANOVA followed by Newman Keul's multiple range test for individual comparisons; $p<0.01$ was considered significant. GraphPad InStat version 3.00 of GraphPad Software, Inc. (San Diego, CA), was used for statistical analysis.

7. RESULTS

Effect of *Aegle Marmelos Bael* on Dox-induced cardiac toxicity was established by measuring cardiac biomarker enzymes and endogenous antioxidants enzymes.

General observation and mortality

The general appearance of all groups of animals was recorded throughout the study. In Dox-treated group, the animal fur became scruffy and developed a pink tinge. These rats also had red exudates around the eyes and nose, soft watery feces and enlargement of abdomen. These observations were significantly less in *Aegle Marmelos Bael* -treated group.

Serum enzyme biomarkers

Animals treated with Dox showed significant increase in the levels of CPK and LDH compared to normal Table No.2. *Aegle Marmelos Bael* +Dox treated group shown significantly lower levels of CPK and LDH as compared to Dox treated group.

The myocardial damage in the various treated groups was determined by estimating the activities of AST, ALT and ALP Table. No.2. These biochemical markers were significantly increased in the Dox group compared to control ($P<0.01$). Aegle Marmelos Bael pretreatment group showed significant reduction in AST, ALT and ALP levels as compared to Dox-treated group.

Oxidant and antioxidant status

Effect of Dox on tissue lipid peroxidation, antioxidant and antioxidant enzymes is shown in Table No.3. The MDA levels were increased. GSH, SOD and CAT levels were significantly decreased in Dox-treated group as compared to normal group. Aegle Marmelos Bael+Dox treated group showed significant decrease ($P<0.01$) in the level of MDA and increase in the status of antioxidant enzymes.

Table No.2

Effect of *Aegle Marmelos Bael* on AST, ALT, ALP, CPK and LDH enzyme activities in doxorubicin-treated rats

Treatment	AST	ALT	ALP	CPK	LDH
Normal Control	66.62±1.36	30.62±1.11	120.80±3.06	152.40±3.66	222.20±8.52
Toxic Control	192.56±7.92*a	60.86±2.55*a	240.18±6.38*a	318.18±6.57*a	406.52±12.30*a
Standard Control	88.26±2.35*b	38.15±1.75*b	160.22±4.32*b	222.26±4.22*b	280.36±9.20*b
Treatment Control (Low dose)	126.90±5.30*b	49.30±2.12*b	190.62±4.55*b	272.30±4.68*b	326.15±10.62*b
Treatment Control(High dose)	106.32±4.92*b	42.60±1.96*b	176.25±3.65*b	242.20±3.65*b	298.42±9.45*b

- Values are expressed as mean ± SEM
- a* - values were significantly different from Normal control (GI) at P<0.01
- b* - values were significantly different from Toxic control (GI) at P<0.01

Table No. 3

Effect of *Aegle Marmelos Bael* on oxidative status in doxorubicin-treated rats				
Treatment	**MDA (n mol MDA/g of wet tissue**	**GSH (n mol/g of wet tissue)**	**SOD (units/mg of protein**	**Catalase (units/mg of protein)**
Normal Control	8.12±0.56	2.82±0.16	38.56±0.72	60.62±1.45
Toxic Control	51.72±1.82*a	1.62±0.13*a	23.55±0.56*a	39.46±1.30*a
Standard Control	25.45±0.76*b	1.86±0.22*b	28.52±0.68*b	45.22±1.96*b
Treatment Control(Low dose)	39.26±1.10*b	2.22±0.35*b	34.10±0.78*b	50.66±2.12*b
Treatment Control(High Dose)	32.25±0.98*b	1.93±0.30*b	30.16±0.82*b	48.12±2.06*b

- Values are expressed as mean ± SEM
- a* - values were significantly different from Normal control (GI) at P<0.01
- b* - values were significantly different from Toxic control (GI) at P<0.01

8. DISCUSSION

The study reveals the cardioprotective effect of *Aegle Marmelos Bael* against Dox-induced cardiotoxicity in rats. Following lines of evidence can be emphasized from the present study. *Aegle Marmelos Bael*, has been traditionally used in medicine and culinary practices in India, possesses hepatoprotective, chemopreventive effects against various cancers and lipid lowering properties. The present study is aimed to investigate the cardioprotective effects of oral administration of *Aegle Marmelos Bael* against Dox -induced cardiotoxicity.

In the Dox-treated group, the animal fur became scruffy and developed a pink tinge which in the later days of observation period was followed by red exudates around the eyes and nose. Necrosis was also observed at the site of Dox injection. These changes were less pronounced in case of *Aegle Marmelos Bael* treated group animals, which accounts for the effective cell protecting property of *Aegle Marmelos Bael* with anti-inflammatory, antioxidant and antifibrotic effect.

The study revealed severe biochemical changes as well as oxidative damage in the cardiac tissue after the chronic treatment with Dox. Transaminases such as ALT and AST are liberated into the serum after extensive tissue injury. Because the heart muscle is rich in both (especially AST), it suggests that their increased level is an indicator of myocardial damage.

The Dox-treated group showed marked elevation in serum levels of AST and ALT as compared to vehicle-treated group. The mild elevations of AST have been associated with liver injury or myocardial infractions. Greater the injury size, higher the activity of AST. This result implies that the Dox when taken for long period of time could cause both liver and heart injury. A typical myocardial injury gives an AST/ALT ratio greater than 1. However, AST/ALT ratio less than 1 are found due to release of ALT from the affected liver.[90] Since the result showed AST / ALT ratio to be greater than 1 with higher doses over a long period of time, Dox is likely to lead myocardial damage.

In *Aegle Marmelos Bael*+Dox treated group, AST and ALT levels significantly decreased as compared to Dox treated group; therefore, present results suggest that treatment of *Aegle Marmelos Bael* may inhibit myocardial damage. These findings confirm that *Aegle Marmelos Bael* is responsible for maintenance of normal structural and architectural integrity of cardiac myocytes, which can be accounted for membrane stabilizing property of *Aegle Marmelos Bael*, as evident from the near normal serum enzymatic activities of AST and ALT.

The serum ALP, LDH and CPK enzyme activities are important measures of both early and late phases of cardiac injury. It is reported that serum LDH and CPK were increased after Dox administration in mouse. The present results are in good agreement with our earlier findings.[91] ALP activity on endothelial cell surface is responsible, in part, for the conversion of adenosine nucleotides to adenosine, a potent vasodilator and anti-inflammatory mediator that can protect tissues from the ischemic damage that results from injury. This may account for the elevation of ALP in the Dox group, where tissue injury and inflammation are prominent. On the other hand, CPK and LDH are not specific for myocardial injury individually; however, evaluation of these enzymes together may be an indication of myocardial injury. In the preventive group, i.e. *Aegle Marmelos Bael* +Dox, the ALP, LDH and CPK enzyme levels were decreased to a level near to that of control group, suggesting that *Aegle Marmelos Bael* may protect the myocardial tissue against Dox toxicity.

The mechanism of cardiotoxicity induced by Dox is not clearly known from the present study, although large body of evidence indicates toward the formation of oxygen free radicals, which can damage cells by lipid peroxidation. In rat treated with Dox, we found significant increase in heart tissue MDA levels suggesting increased lipid peroxidation. Cardiac tissue damage may be due to increased oxidative stress and depletion of antioxidants similarly in rats reported earlier.[92]

In our study, Dox treated rats showed increase in heart tissue MDA levels with decrease in levels of GSH, SOD and CAT, which confirms the oxidative stress and cardiac damage. *Aegle Marmelos Bael* prevented the Dox-induced changes in MDA

and enzyme levels. Significant increase in the GSH, SOD and CAT activity and decrease in lipid peroxidation in heart tissue of *Aegle Marmelos Bael* +Dox treated groups was found. The study suggests the protective effect of *Aegle Marmelos Bael*.

It is commonly accepted that SOD protects against the free radical injury by converting O^{2-} radical to H_2O_2 and prevent the formation of OH radicals through O^{2-} driven Fenton reaction[93] and the H_2O_2 can be removed by catalase. Administration of *Aegle Marmelos Bael* improved the antioxidant status and thereby preventing the damage to the heart, mainly because of the antioxidant sparing action of Aegle Marmelos Bael.

The antioxidant mechanism of *Aegle Marmelos Bael* may include one or more of the following interactions. Scavenging or neutralizing of free radicals,[94] inhibition of oxidative enzymes like cytochrome P_{450},[95] oxygen quenching and making it less available for oxidative reaction, interacting with oxidative cascade and preventing its outcome[96] and disarming oxidative properties of metal ions such as iron.[97] Thus, in this work, *Aegle Marmelos Bael* effectively prevented tissue damage by decreasing the oxidative stress and restoring the antioxidant status.

9. CONCLUSION

In this study I conclude that the cardiotoxicity induced by Dox is related with oxidative stress. Anti-proliferative, anti-initiation and free radical scavenging properties of *Aegle Marmelos Bael* may boost myocardial integrity and attenuate the cardiac toxicity.

Aegle Marmelos Bael has shown to be cardioprotective, which may be attributed to its potent antioxidant properties.

10. BIBLIOGRAPHY

1. Braunwald., Eugene. *Heart Disease: A Textbook of Cardiovascular Medicine.* Philadelphia, PA: W.B. Saunders Company, **2001,** *9:* 250-256.
2. Gersh., Bernard, J. New York: William Morrow and Company. *Mayo Clinic Heart Book*., **2000,** *2:* 410-416.
3. Crumlish, Christine. When Time is Muscle. *American Journal of Nursing.,* **Jan-2000,** *4:* 26.
4. Thomas, Donna., Jean, G., and Harrah., Barbara., F. A New Look at Heart Failure. *Home Healthcare Nurse*, **Mar-2000,** *367:* 262-272.
5. Anderson., Robert, M., *The Gross Physiology of the Cardiovascular System, **2000,** 3:*23-28.
6. Michelle, L., Johnson, M.S., J.D. *Heart Information Network.* **Apr-2001,** 490-495.
7. Rathore, S.S., Gersh, B.J., Weinfurt, K.P., Oetgen, W.J., Schulman, K.A., Solomon, A.J. The role of reperfusion therapy in paced patients with acute myocardial infarction. Am Heart J**., Sep-2001,** *142(3):* 516-519.
8. Ryan, T.J. Percutaneous coronary intervention in ST-elevation myocardial infarction**.** Curr Cardiol Rep., **Jul-2001,** *3(4):* 273-279.
9. Siddiqui, M.A., Tandon, N., Mosley, L., Sheridan, F.M., Hanley, H.G. Interventional therapy for acute myocardial infarction. J La State Med Soc., **2001,** *153(6):* 292-299.
10. Costa, E., Silva, R., Pellanda, L., Portal, V., Maciel, P., Furquim, A., Schaan,B. Transdisciplinary approach to the follow-up of patients after myocardial infarction. Clinics (Sao Paulo)., 2**008,** *63(4):* 489-496.
11. Sleight, P. Medical interventions in acute myocardial infarction**.** J Cardiovasc Pharmacol**., 1990,** *5:* 113-119.
12. Moe, K.T., Wong, P. Current trends in diagnostic biomarkers of acute coronary syndrome. *Ann. Acad. Med. Singap.,* **2010,** *39 (3):* 210–215.
13. Reznik, A.G. Morphology of acute myocardial infarction at prenecrotic stage (in Russian). *Kardiologiia.,* **2010,** *50 (1):* 4–8.
14. Thygesen, K., Alpert, J.S., White, H.D. "Universal definition of myocardial infarction". *Eur. Heart J.,* **2007,** *28 (20):* 2525–2538.
15. Robert., Beaglehole. The World Health Report 2004 – *Changing History. World Health Organization*., **2004,** 120–124.

16. "Cause of Death — UC Atlas of Global Inequality". Center for Global, International and Regional Studies (CGIRS) at the University of California Santa Cruz. Retrieved **Dec-2006,** *78:* 1200-1206.
17. White, H.D, Chew, D.P. Acute myocardial infarction. *Lancet,* **2008,** *372 (9638):* 570–584.
18. Mukherjee, A.K. Prediction of coronary heart disease using risk factor categories. *J Indian Med Assoc.,* **1995,** *93 (8):* 312–315.
19. Ghaffar, A., Reddy, K.S., and Singhi, M. Burden of non-communicable diseases in South Asia. *BMJ,* **2004,** *328 (7443):* 807–810.
20. Rastogi, T., Vaz, M., Spiegelman, D., Reddy, K.S., Bharathi, A.V., Stampfer, M.J., Willett, W.C., and Ascherio1, A. Physical activity and risk of coronary heart disease in India. *Int. J. Epidemiol.,* **2004,** *33 (4):* 1–9.
21. Gupta, R., Misra, A., Pais, P., Rastogi, P., and Gupta, V.P. Correlation of regional cardiovascular disease mortality in India with lifestyle and nutritional factors. *International Journal of Cardiology.,* **2006,** *108 (3):* 291–300.
22. Anderson, J.L., Adams, C.D., Antman, E.M., Bridges, C.R., Califf, R.M., Casey, D.E. Guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction**.** J Am coll Cardiol., **2007,** *50:* 157.
23. Kushner, F.G., Hand, M., Smith, S.C., King, S.B, Anderson, J.L., Antman, E.M. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation., **2009,** *120(22):* 2271-2306.
24. Antman, E.M., Libby, P., Bonow, R.O., Mann, D.L., Zipes, D.P, Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine**., 2007,** *8:* 51.
25. Goodman, S.G., Menon, V., Cannon, C.P., Steg, G., Ohman, E.M., Harrington, R.A. Acute ST-segment elevation myocardial infarction: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest**.**, **2008,** *133:* 708-775.
26. Canto, J.G., Shlipak, M.G., Rogers, W.J., Malmgren, J.A., Frederick, P.D., Lambrew, C.T., Ornato, J.P., Barron, H.V., Kiefe, C.I. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA.,* **2000,** *283 (24):* 3223–3229.

27. Yip, H.K., Wu, C.J., Chang, H.W., Wang, C.P., Cheng, C.I., Chua, S., Chen, M.C. Cardiac ruptures complicating acute myocardial infarction in the direct percutaneous coronary intervention reperfusion. *Chest.,* **2003,** *124 (2):* 565–571.
28. Becker, R.C., Gore, J.M., Lambrew, C., Weaver, W.D., Rubison, R.M., French, W.J., Tiefenbrunn, A.J., Bowlby, L.J., Rogers, W.J. A composite view of cardiac rupture in the United States National Registry of Myocardial Infarction. *J Am Coll Cardiol.,* **1996,** *27 (6):* 1321–1326.
29. Moreno, R., Lopez., Sendon, J., Garcia, E., Perez, D.E., Isla, L., Lopez, S.A., Ortega, A., Moreno, M., Rubio, R., Soriano, J., Abeytua, M., Garcia-Fernandez, M.A. Primary angioplasty reduces the risk of left ventricular free wall rupture compared with thrombolysis in patients with acute myocardial infarction. *J Am Coll Cardiol.,* **2002,** *39 (4):* 598–603.
30. Shin, P., Sakurai, M., Minamino, T., Onishi, S., Kitamura, H. Post infarction cardiac rupture. A pathogenetic consideration in eight cases. *Acta Pathol Jpn.,* **1983,** *33 (5):* 881–893.
31. Podrid., Philip., Peter, J., Kowey, R. Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management. *Lippincott Williams & Wilkins*, **2001,** *2:* 280-286.
32. Sung., Ruey., Michael, J., Lauer, R. Fundamental Approaches to the Management of Cardiac Arrhythmias. *Springer,* **2002,** *4:* 198-204.
33. Josephson., Mark, E. Clinical Cardiac Electrophysiology: Techniques and Interpretations. *Lippincott Williams & Wilkins*, **2002,** *4:* 405-411.
34. Hochman, J.S., Sleeper, L.A., Webb, J.G., Sanborn, T.A., White, H.D., Talley, J.D., Buller, C.E., Jacobs, A.K., Slater, J.N., Col, J., McKinlay, S.M., LeJemtel, T.H. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic shock. *Engl J Med.,* **1999,** *341 (9):* 625–634.
35. http://www.buzzle.com/articles/myocardial-infarction-pathophysiology.html Published on 6/3/2010 by Dr. Sumaiya Khan downloaded on 5-7-2011.
36. Troponin at *Dorland's Medical Dictionary.*
37. Moses., Marsha, A.,Wiederschain, D., Wu, I., Fernandez, C., Ghazizadeh, V., Lane, W. Flynn, E. Sytkowski A., Tao T., Langer, R. (1999). Troponin I is

present in human cartilage and inhibits angiogenesis. *Proceedings of the National Academy of Sciences of the United States of America.,* **1999,** *96 (6):* 2645–2650.

38. Kooij., Viola. (2011). Contractile Function of the Human Myocardium. Impact of Troponin Phosphorylation. *Vrije Universiteit Amsterdam.*, **2011,** *32:* 108-114.
39. Guzy, P.M. Creatine phosphokinase-MB (CPK-MB) and the diagnosis of myocardial infarction. *West. J. Med.,* **1977,** *127 (6):* 455–460.
40. Use of Cardiac Markers in the Emergency Department. *E-Medicine*, **2009,** 01-10.
41. Amato, A.A., Brooke, M.H., Bradley, W.G, Daroff, R.B, Fenichel, G.M, Jankovic, J. Disorders of skeletal muscle. Neurology in Clinical Practice., **2008,** *5:* 83.
42. Barohn, R.J., Goldman, L., Ausiello, D. Muscle diseases. *Cecil Medicine.*, **2007**, 23:447.
43. http://www.cvpharmacology.com/clinical topics/myocardial infarction-.html downloaded on 12.07.2011.
44. http://www.cvpharmacology.com/.../myocardial%20infarction-3.htm.
45. Thygesen, K., Alpert, J.S., White, H.D. Universal definition of myocardial infarction. *Eur Heart J.,* **2007,** *28:* 2525-2538.
46. Choi, D., Hwang, K.C., Lee, K.Y., Kim, Y.H. Ischemic heart diseases: current treatments and future. *J Control Release.,* **2009,** *140:* 194- 202.
47. Russell, J.C., Proctor, S.D. Small animal models of cardiovascular disease: tools for the study of the roles of metabolic syndrome, dyslipidemia, and atherosclerosis. *Cardiovasc Pathol,* **2006,** *15:* 318-30.
48. 1.Vijay, T., Dhana Rajan,M.S., Sarumathy, K., Palani, S., Sakthivel, K., Phytochemical studies by GC-MS and cardioprotective effect of grewia Hirsuta on doxorubicin induced cardiotoxicity in albino rats. International Journal of universal pharmacy and life sciences, **2011**;(1):1-18.
49. P.Gopalakrishnan, V.K., Paramasivam, R., Dominic, S., Chinthamorthy, A., Cardioprotective effect of aerva lanata (Linn) against doxorubicin induced cardiomyopathy in rats. Asian pacific journal of Tropical Biomedicine, **2011**;1-7.

50. Shreesh kumar ojha, Dharamvir singh Arya, Withania somnifera Dunal (Ashwagandha) a promising remedy for cardioprotective diseases **2009**;4(2):156-158.
51. Sakthivel, K., Palani, S., Santhosh kalash, R., Devi, K., Senthil kumar,B.Phytoconsituents analysis by GC-MS,cardioprotective and antioxidants activity of buchanania axillaris against doxorubicin- induced cardiotoxicity in albino rats, International Journal of Pharmaceutical Studies and Research,**2010**;(1):34-48
52. Vijay, T., Dhana Rajan, M.S., Sarumathy, K., Palani, S., and Sakthivel, K., Cardioprotective, antioxidant activities and Phytochemical analysis by GC-MS of *Gmelinarborea* (GA) in Doxorubicin-induced myocardial necrosis in *Albino* rats, Journal of Applied Pharmaceutical Science,**2011**; 01 (05); 198-204.
53. Vijaya, T., DhanaRajan, M.S., Sarumathy, K, Palanie, S., Sakthivel, K., Analysis of phytoconstituents by GC-MS and therapeutic efficacy of *Grewiaumbelliferea*(gu) on Doxorubicin induced cardiotoxicity in *albino* rats, IJPI's Journal of Pharmacology and Toxicology,**2009**;(1:3)61-74.
54. Abdel-Wahab, M.H., El-Mahdy, M.A., Abd-Ellah, M.F., Helal, G.K., Khalifa, F., Hamadaa, F.M.A., Influence of *p*-coumaric acid on doxorubicin-induced oxidative stress in rat's heart, Pharmacological Research, **2003**;48 461–465.
55. Rajaprabhu, D., R. Rajesh, Jeyakumar1,R., Buddhan,S., Ganesan B., and Anandan,R. Protective effect of Picrorhiza kurroa on antioxidant defense status in adriamycin-induced cardiomyopathy in rats, Journal of Medicinal Plant Research,**2007**; 1 (4), 080-085.
56. Patel Soncharan, Shanmugarajan T.S., Somasundaram I. and Maity Niladri, Protective effect of *Syzygium cumini* seeds against doxorubicin induced cardiotoxicity in rats, IJPLS Journal**, 2010**;1(6):343-349.
57. Raja Kumar Parabathina, E.Murlinath, G.Kishore and Kaza. Somasekhara Rao, Effect of vitamin E, morin, rutin andquercetin against doxorubicin induced oxidative stress, International Journal of Applied Biology and Pharmaceutical Technology**, 2011**;(2):399-408**.**
58. Raja Kumar Parabathina, G. Vijaya Raja, M. Nageswara Rao, G. Srinivasa Rao and Kaza Somasekhara Rao, Cardioprotective effects of vitamin E and quercetin against doxorubicin induced oxidative stress of rabbits:

A biochemical study, Journal of Chemical and Pharmaceutical Research,**2010**;2(3):754-765.

59. Khatib,N.A.,Wadulkar,R.D.,Joshi,R.K.,Majagi,S.I.,Evaluation of Methanolic extract of cassia fistula bark for cardio protective activity, international journal of research in ayurveda & Pharmacy,**2010**;1(2):565-571.
60. Muresan Adriana ,soimita suciu,simona clichci,Doina Daicoviciu,, study of the effect of the Grape seed extract in Ehrlich Ascitic Carcinoma, Buletin USAMV-CN, **2006**;(63):page no.114-119.
61. Koti, B.C. ,Viswanathswamy , A.H.M.,Jyoti wagawade & Tippeswamy, A.H.M.,Cardioprptective Activity of lipistat against doxorubicin induced myocardial yoxicity inalbina rats. Indian journal of experimental biolology,**2009**;(47):page no. 41-46.
62. Tippeswamy, A.H.M., Akshay shirodkar, Koti,B.C., Jaffa r sadiq, Praveen, D.M., Viwanathaswamy, A.H.M., Mahesh patil, Indian journal of Pharmacology,**2011**;(43): page no.31-36.
63. Rajakannu Subashini, Arunachalam Gnanapragasam, Subraman ian Senthilkumar,Surindar kumar Yogeeta & Thiruvenkadam Devaki, Journal of heath science,**2007**;(53):page .no. 67-76.
64. Hassanpour Fard, Bodhankar,S.L., Mdhumira Dikshit, Cardioprotective activity of fruit of Lagenaria Siceraria(Molina) Standely on doxorubicin induced cardiotoxicity in rats, International journal of Pharmacology,**2008**;4(6): page .no.466-471.
65. Shah,S., Mohan M.H., Kasture,S., sanna, C., Maxia, A., Protective effect of Ephedra nebrodensis on doxorubicin induced cardioprotoxicity in rats, Iranian journal of Pharmacology & Therapeutics ,**2009**;(8): page 61-66.
66. Eman M., EI- Sayed, Amal,S. Abd EI- azeem, Abeer A. Afify, Manal H.Shabana & hanaa H. Ahmed, Cardioprotective effect of Curcuma longa L. Extacts against doxorubicin- induced cardiotoxicity in rats, journal of medicinal plants research ,**2011**;5(17): page no. 4049- 4058.
67. Mahmoud A. Mansour, .,Saleh A Bakeet ,Abdulaziz M. Aleisa ,Salim S. AI-Rejaie, Abdulaziz A. AL-yahya, Mubarak EI-Ameen & Othman A. AL-Shabhana, Protective effect of the 6- Gingerol Against Cardiotoxicity induced by Doxorubicin, The open Pharmacologycal journal **2008**;(2): page no. 20- 23.

68. Gaurav kaithws, Kiran Dubey& K.K Pilani, Effect of aloe vera(aloe barbedensis Miller) Gel on Doxorubicin- Induced Myoacardial oxidative stress and calcium overload in albino rats, Indian journal of experimental biology **2011**; (49): page no. 260-268.
69. Linda C., Suvara Kimnite W., Angkana H.,Suphan C.,Somchit N.,Supatra S., Antioxidative and cardioprotective Effect of the Phyllanthus urinaria L. On Doxorubicin Induced Cardiotoxicity, Biol. Pharm. Bull,**2005**;28(7): 1165-1171.
70. Monira A.Abd EI Kader , Nermin M., EI-Sammad, Amal A.fyiad, Effect of the Grape seed extract in the Modulation of Matrix Metalloproteinase-9 Activity and Oxidative stress Induced by Doxorubicin in Mice, Life science Journal **2011**;8(3): Page no. 510-515
71. Davey, M.S., Atlee,C.W., Inotropic and Cardioprptective effect of Terminalia Panichulata Roth Bark Extract in the in Doxorubicin Induced Cardiotoxicity in rats, International journal of Research in Ayurveda & and Pharmacy **2011**;2(3): page no. 869-875.
72. Arulmozhi, S., Sathiya, Narayanan, L. Pharmacological activities of *Alstonia scholaris Linn. (*Apocynaceae) - A Review. *Pharmacognosy Reviews.,* **2007,** *1(1):* 163-170.
73. Young, I.S., J.A. Purvis., J.H. Lightbody., A.A. Adgey., and E.R. Trimble. Lipid peroxidation and antioxidant status following thrombolytic therapy for acute myocardial infarction. *Eur. Heart J.,* **1993,** *14:* 1027-1033.
74. Saswati Parichha, **2004**, "Bael (Aegle Marmelos): Nature's Most Natural Medicinal Fruit", Orissa Review.
75. Kar A. Choudhry B. K. and Bandhopadhyay N. G., "Comparative evaluation of hypoglycemic activity of some Indian medicinal plants in alloxan diabetic rats" J Ethnopharmacol. **2003**, 84, Page No.105-108.
76. Lampronti I, Martello D., Bianchi N., Borgatti M., Lambrtini E.,. Piva R, Jabbars S., Choudhuri M. S., Khan M. T. and Gambari R., "*In Vitro* antiproliferative effect on human tumor cell lines of extracts from the bangladesi medicinal plant Aegle marmelos Correa." Phytomedicine, **2003**, 10, Page No. 300-308.

77. Karunanayake E. H., Welihinda J., Sirimanne S. R. and Sinnadorai G., "Oral hypoglycemic activity of some medicinal plants of Sri Lanka" J Ethnopharmacol, **1984**, 11, Page No. 223-231.
78. http://www.hort.purdue.edu/newcrop/parmar/01.html/
79. C.S.I.R., **1985**, "The wealth of India" National Institute of Science communication and Information Resources", Volume- I (A), 86.
80. Purohit S. S and Vyas S. P, "In: Aegle marmelos Correa ex Roxb, (Bael), Medicinal plant cultivation- A scientific approach", Agrobios, Jodhpur, **2004**. P.P.498-504.
81. Maity P., Hansda D., Bandyopadhyay U. & Mishra D.K., "Biological activities of crude extracts of chemical constituents of Bael, Aegle marmelos (L.) Corr." Indian Journal of Experimental Biology, 2009, Vol 47, p.p. 849-861.
82. Vinod, D.R. Pharmacognosy and phytochemistry*, Carrier Publication.,* **2007,** *1:* 129-303.
83. Kokate, C.K., Purohit, A.P., Gokhale, S.B. Pharmacognosy, *Nrali Prakashan.,* **1999,** *13:* 92-93.
84. H. Gerhard, Vogel. Drug discovery and evaluation: pharmacological assays. **2002,** *2:* 191-192
85. Lopez, A.D. and C.C. Murrau. The global burden disease, 1990-2020. *Nat. Med,* **1998,** *4:* 124-123.
86. Okinaka, S., H. Kumogai., S. Ebashi., Serum creatine phosphokinase activity in progressive muscular dystrophy and muscular disease. *Arch. Neurol.,* **1961,** *4:* 520-525.
87. Varley, H., Gowenlock, A.H., and Bell, M. Enzymes in practical clinical biochemistry, 5th edition. *William Heinemann medical books,* **1984,** *1:* 685-770.
88. King, J. The Dehydrogenase of Oxido Reductase Lactate Dehydrogenase. In: *Practical Clinical Enzymology*, **1965,** 83-93.
89. Mohun, A., and I.J. Cook. Simple methods for measuring serum levels of glutamic-oxalo acetic and glutamic-pyruvic transaminase in routine laboratories. *J. Clin. Pathol.,* **1957,** *10:* 394-399.

90. Visser MP, Krill MT, Muijtjens AM, Willems GM, Hermens WT. Distribution of enzymes in dog heart and liver:Significance for assessment of tissue damage from data on plasma enzyme activities. Clin Chem. **1981**;11:1845–50.
91. Koti BC, Vishwanathaswamy AH, Wagwade J, Thippeswamy AH. Cardioprotective effect of lipistatagainst doxorubicin induced myocardial toxicity in albino rats. Indian J Exp Biol. **2009**;47:41–6.
92. Doroshow JH. Effect of anthracycline antibiotics on oxygen radical formation in rat heart. Cancer Res. **1983**;43:460–72.
93. McCord JM, Fridovich I. The utility of superoxide dismutase in studying free radical reactions. J Biol Chem. **1969**;244:6049–55.
94. Grisham M, McCord J. Chemistry and cytotoxicity of reactive oxygen metabolites. In: Taylor A, Matalon S, Ward P, editors. Physiology of oxygen radicals. Bethesda: Am Physiol Soc; **1986**. pp. 1–18.
95. Appiah R, Commandeur JN, Vermeulen NP. Inhibition of human recombinant cytochrome P450s by curcumin and curcumin decomposition products. Toxicology. **2007**;235:83–91.
96. Sandur SK, Ichikawa H, Pandey MK, Kunnumakkara AB, Sung B, Sethi G, et al. Role of pro-oxidants and antioxidants in the anti-inflammatory and apoptotic effects of curcumin (diferuloylmethane) Free Radic Biol Med. **2007**;43:568–80.
97. Miriyala S, Panchatcharam M, Rengarajulu P. Cardioprotective effects of curcumin. Adv Exp Med Biol. **2007**;595:359–77.