ISSN No:-2456-2165

A Review on Recent Advancements in the Treatment of Coronary Artery Disease

Anupama Kumari*
Faculty of Pharmaceutical Sciences
Baddi University of Emerging Sciences
& Technology, Himachal Pradesh

Robin Sharma
Sun Pharmaceuticals PVT.
Ltd. Baddi,
Himachal Pradesh

Abstract:- The term "CAD" stands for "coronary artery disease." The majority of deaths are caused by it globally. It is a disorder when the heart can no longer adequately pump blood to the body's tissues because to a build-up of plaque in the blood arteries (a condition known as atherosclerosis). Heart failure can result from this condition. The main risk factors for CAD are hypertension, dyslipidemia, obesity, inactivity, and elevated levels of C-reactive protein and blood sugar. Medical, surgical, and herbal treatments are currently available. While this treatment can increase a patient's quality of life and chances of survival, it has no effect on the speed of the disease. Clinical researchers have been working with biotechnology and tissue engineering to identify new therapeutic approaches that may result in stem cell therapy, nanotechnology, gene therapy treatments, and robots. The primary goals of these innovative methods are to lessen and heal myocardial damage and enhance blood flow to the ischemic heart's myocardium. Clinical studies on stem cell-based therapy have produced effective and hopeful outcomes, including decreased myocardial cell death, decreased scarring, increased angiogenesis, and improved heart function. The development of a nanotechnology method that aids in targeted drug distribution, boosts therapeutic effectiveness, and lengthens the duration of action. A novel approach is gene therapy, which promotes angiogenesis. These emerging treatments have the potential to be potent substitutes for current treatment modalities thanks to the significant and ongoing work of researchers and doctors around the world.

Keywords:- *Atherosclerosis, Coronary artery disease, stem cell, Nanotechnology, Gene therapy.*

I. INTRODUCTION

Ischemic heart disease is another name for coronary artery disease. The Greek words ischein, which means "to hold," and haima, which means "blood," are combined to form the English word "ischemia." It is a condition where the buildup of plaque (artheroscelerosis) in the walls of the arteries that provide blood to the heart and other regions of the body causes damage to the heart muscle. Due to the creation of plaque, arteries can become narrowed or blocked, which can hinder blood flow. Since the blood veins that deliver oxygen-rich blood to the heart's muscles and aid in its pumping are called the coronary arteries. Blood flow restriction causes a shortage in nutrients and oxygen as well as a failure to remove metabolic waste from the tissue, which results in cell damage and death[1].

Despite significant improvements in its management, coronary artery disease continues to be the leading cause of mortality globally. It is the serious illness that affects millions of individuals every day. More people die from it each year than from chronic lower respiratory disease and all other types of cancer combined. About 17.7 million deaths worldwide in 2015 were attributable to cardiovascular disease (CVD), or 31% of all fatalities. Approximately 7.4 million of them were caused by coronary artery disease, while 6.7 million were caused by stroke [2]. According to the American Heart Association, around 42.1% of deaths in 2018 were attributed to coronary heart disease, with stroke (17%) and other CVD (17.4%) following closely behind. According to estimates, coronary artery disease raised death and morbidity rates from 6.8 million in 2000 to 8.9 million in 2019 [3]. Around 18.6 million people died in 2019.

ISSN No:-2456-2165

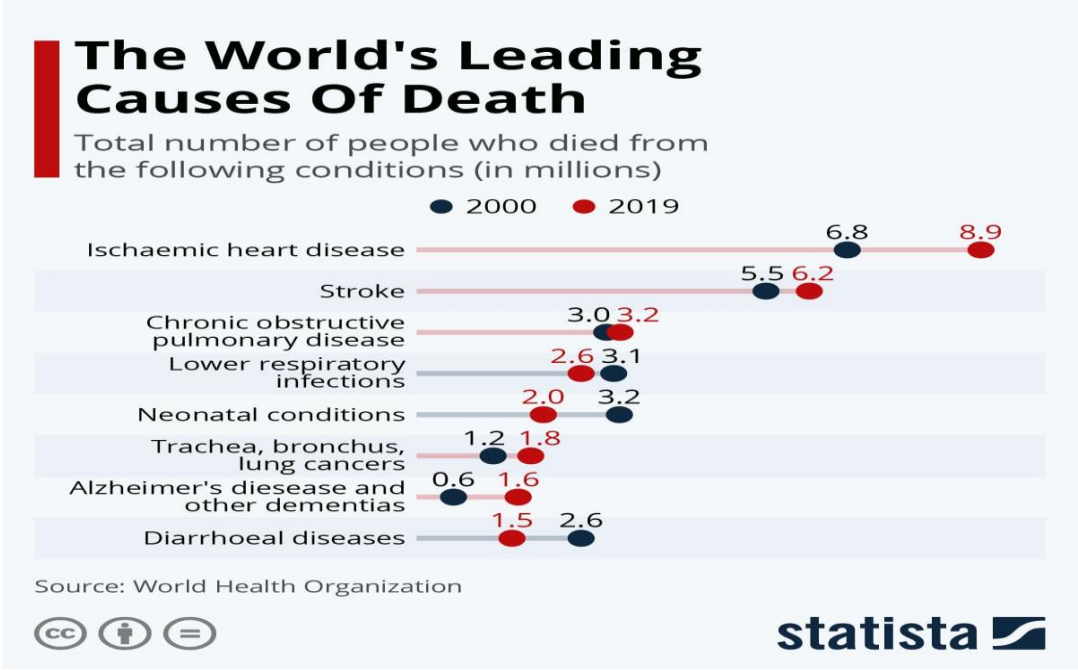

Fig. 1: People death due to various diseases[4]

Reducing the number of risk factors that lead to poor cardiovascular health and raise the likelihood of disease can avoid a significant amount of death from coronary artery disease. There are now two types of treatments: medicinal and surgical therapy, or a combination of the two, as well as some herbal medications. There has been substantial progress achieved in creating novel treatments for patients suffering with CAD & its consequences as a result of the tireless efforts of researchers & physicians worldwide. Drugs, robotic surgery, and nanotechnology have all been used as tactics. These articles will provide a summary of the research on various methods for treating coronary artery disease in terms of medicines and biomarkers[5].

II. SYMPTOMS OF CAD

- Pain -Due to Angina pectoris(chest pain) & myocardial infarction(heart attack).
- Dyspnea–Shortness of breath, is a feeling of not being able to breathe properly.
- Abdominal symptoms - symptoms like nausea, indigestion and constipation.
- Altered pulse-changes in pulse rate like tachycardia(fastheartrate),bradycardia(slow heartrate), heart block(completely blocked heartbeat).
- Clamminess &Sweating -on palms & faces because of the sympathetic nervous system.
- Decreased B.P–Lowering of B.P causes the decreased in cardiac output.
- Haemoptysis - coughing of blood because of rupture of pulmonary artery.
- Pyrexia - Increase in temperature for one or two days after occlusion leading to infarction. This is due to the necrosis of Cardiac muscle cell.
- Pigmentation alteration - Alteration of skin colour. [1,6,7]

III. ETIOLOGY

A. Reduction in myocardial oxygen supply due to :

- **Atherosclerotic heart disease /vast majority** - The great majority of cases of atherosclerotic heart disease - plaque formation obstructs blood flow, which in turn reduces the amount of oxygen reaching the heart.
- **Coronary artery spasm / varient angima –**It is also known as varient angima, is a key factor in the development of ischemic heart disease. It describes an abrupt vasoconstriction of blood arteries, which could result in a decrease in blood and oxygen delivery.
- **Arterial Embolism –** This condition happens when a blood clot obstructs an artery's blood flow.
- **Aortic stenosis -** Itcauses the obstruction of blood flow acrossthe aortic valve.
- **Anaemia -** This condition is caused by a deficiency in red blood cells, which ultimately reduces the amount of blood and oxygen reaching the affected organs.
- **Beri beri disease–** A condition that results in paralysis and cardiac failure.
- **Cardiomyopathy -** It is a condition that affects the heart muscle, causing it to become abnormally enlarged, thickened, or rigid. Less effective blood pumping by the heart muscle frequently results in heart failure and a blood backup into the lungs or the rest of the body.

B. Increase in myocardial oxygen demand due to :

- Myocardial hypertrophy – It is an abnormal thickening or expansion of the heart muscle caused by an increase in the size of the cardiomiyocytes and a change in other heart muscle components such the extracellular matrix.
- Severe tachycardia –It increases oxygen demand and strain by having an abnormally fast or erratic heartbeat (heart rate over 100 beats/min).

ISSN No:-2456-2165

- Severe hyperthroidism -(overactive thyroid gland) a condition in which excess thyroid hormone is produced – due to which heart and pheripheral vascular system is affected which ultimately cause hypertension ,CAD and heart failure.
- Severe anemia - The body receives less oxygen due to a lack of RBCs, which increases the workload on cardiac muscle and causes the heart to contract more forcefully (+positive intropic effect)[1, 6, 7].

C. Clinical manifestations :

- **Angina pectoris –** It is a condition characterised by episodes of chest pain brought on by inadequate cardiac oxygenation. Ischemia causes pain, but not enough to kill myocytes. It can either be stable (occurring predictably at a specific level of effort), be unstable (prinzmetal/variant angina), or be triggered by a vascular spasm (occuring with prgresively less exertion or even at rest).
- **Acute myocardial infarction** -Myocardial infarction(heartattack)blood flow is reduce to such degree that heart of cell die, duration of ischemia is sufficient to cause cardiomyocyte death.
- **Chronic IHD with CHF -** Mechanical pump failure is finally caused by progressive cardiac decompensation following an acute myocardial infarction or as a result of an accumulation of minor injuries.
- **Sudden cardiac death (SCD)/ Cardiac arrest** – Occur as a consequence of tissue damage from myocardial infarction. It is the abrupt loss of heart function,breathing and consciousness.
- **Acute coronary syndrome -** Acute coronary syndrome is a term used to describe persistent chest pain that does not go away after 15 to 20 minutes and is not relieved by glyceryl trinitrate. This type of pain can be caused by either unstable angina or MI of either type.[1, 6,7]

IV. PATHOPHYSIOLOGY OF CAD

Obstructive atherosclerotic plaque that reduces blood flow to the myocardium is the hallmark of CAD. The endothelium lining of blood arteries is harmed as a result of a number of lifestyle variables, including hypertension (high blood pressure), cellular injury, hyperlipidemia, hereditary factors, and others, which lead to the development of atherosclerotic plaque. Vasomotor neuron releases noradrenaline, which works on the alpha receptor of smooth muscles and narrows the blood vessels. This is accomplished by decreasing NO in the blood (Nitric oxide). Nitric oxide is a vasodilator that activates guanylate cyclase, which in turn causes cGMP to close voltage-gated calcium channels. Because Endothelin-1, a vasoconstrictor released by endothelial cells, and inflammatory mediators like thromboxane A2, which encourage vasoconstriction and platelet aggregation, cause calcium levels to drop, cells become less constricted. Our blood contains lipoprotein, which is used to transfer fats from the blood to various body regions. Low density lipoproteins, which are less likely to be absorbed by cells and more likely to be detected circulating freely in the blood, enter the intima and undergo oxidation under various stressful situations, such as hypertension. The oxidised LDL draws circulating monocytes, which then multiply to form tissue macrophages, T-lymphocytes, and local macrophages at the site of inflammation (Tissue). In order to draw in more macrophages, the macrophages then accelerate the oxidation of low density lipoproteins. Additionally, the clotting component fibrin adheres to this location. This causes the plaque at the site of the injury to expand (Thrombus). The development of thrombi leads to arterial occlusion, which in turn reduces blood flow and oxygen delivery to the body. Consequently, this creates a primary IHD/CAD cause.[1,6,7].

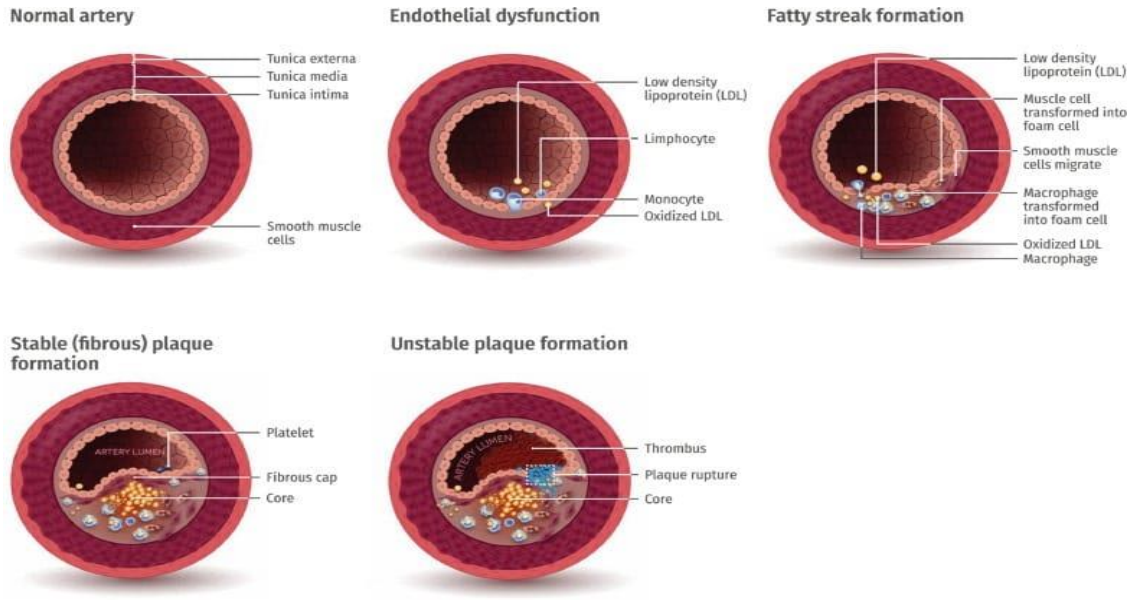

Fig. 2: Pathogenesis of atherosclerosis plaque formationn [8]

ISSN No:-2456-2165

V. RISK FACTORS

A. Major risk factor

- **Modifiable factor –** Dyslipidaemia (abnormally high levels of cholesterol or fats in the blood), hypertension (which likely causes mechanical damage to the artery wall due to increased blood pressure), smoking (which increases risk and severity due to a lower level of HDL and a buildup of carbon monoxide in the blood that leads to carboxy-haemoglobin and eventually favours atherosclerosis), and diabetes mellitus (most commonly type 2 diabetes, which increases platelet aggregation, LDL,& decrease in HDL.)
- **Constitutional factor –** These factors include age (atherosclerosis lesions are found to worsen with age), sex (more prevalent in men than women), genetics (related to inherited disease), families (people with a history of diseases like diabetes, hypertension, and hyperlipoproteinemia), and racial facial characteristics (blacks have generally less severe atherosclerosis than whites).

A. New risk factors

These factors include obesity, hormones (oestrogen insufficiency), physical inactivity, stressful life circumstances, alcohol usage, elevated C-reactive protein, prothrombotic factor, and environmental factors [1, 2, 6].

VI. DIAGNOSIS OF CAD

- **Electrocardiogram (EKG or ECG) –**It is an instrument which helps to record the electrical signal that travels through the heart& detection of CAD.
- **Echocardiogram-**It is an instrument which uses sound waves for producing the image of heart & determine whether all parts of heart wall are contributing normally to heart's pumping activity.
- **Nuclear stress test-** It is a test which measure the blood flow to the heart muscles at rest & during stress.
- **Cardiac CT scan-** It helps to see the calcium deposits in the artery that can narrow the arteries.
- **Cardiac catheterization-**It is a test in which long thin flexible tube (catheter) is inserted into the artery, so as to check the blockage of an artery.
- **High sensitive C- reactive protein blood test -** It measure the levels of inflammation (whether the C-reactive protein high or not) in the body.
- **Computed tomography angiogram**: It uses CT and contrast dye to view the 3D pictures of the heart and detect blockages in the coronary arteries.
- **Nuclear imaging:** This test produces images of the heart after administering a radioactive tracer.[9]

VII. TREATMENTS OF CORONARY ARTERY DISEASE

A. HERBAL TREATMENTS

- **GARLIC *(Allium sativum):*** It Lowers blood pressure, reduces platelet aggregation, increases fibrinolytic activity, and lowers serum cholesterol and triglyceride levels. Allicin, a compound found in garlic, is produced when Allinin, an ingredient, interacts with Allinase. Allicin has powerful antibacterial activities, antioxidant qualities by reducing reactive oxygen species, and glutathione production increasing. This allicin passes through self condensation to form ajoenes, which inhibits collagen-induced platelet aggregation and has antithrombotic action [10, 11, 12, 13, 14].

- **OLEOGUM RESIN *(Commiphoramukul)***–It is used to treat lipid disorders by enhancing hepatic LDL cholesterol uptake & metabolism. Guggulosterone, one of its active ingredients, has anti-inflammatory properties and inhibits the oxidation of LDL. Z isomer of guggulsterone is more powerful than E isomer. It exhibits antithrombotic effect and decreases LDL levels [10, 15].

- **ARJUNA BARK (*Terminalia arjuna)*-** Arjuna bark includes polyphenol and flavonoids that boost cardiac tissue's antioxidant defense and promote blood flow. It shields the heart from the oxidative stress brought on by ischemia reperfusion injury. Additionally, it includes tannins and glycosides, which function as antioxidants to prevent free radical damage to the blood vessels and heart muscle. In the treatment of chest discomfort, it is helpful [16].

- **OLIVE OIL *(Oleaeuropaea)*-** It is made from the fruit of the olive tree. It is used to lower blood pressure, lower cholesterol, and enhance blood vessel lining. By stopping the LDL from oxidising, the phenolic molecule oleuropein has antioxidant action. It causes anti-inflammatory effects by preventing lipoxygenase activity and LTB4 synthesis. It stops monocytes from sticking to the endothelium, which stops the pathogenesis of atherosclerosis. Olive leaf tyrosol and hydroxycytosol have cardiac-protective properties [13, 17, 18].

- **VITAMIN K2 (Menaquinones K4–K10**)- These are mostly generated from bacteria and are most frequently present in fermented foods. Vitamin K serves as a cofactor for the enzyme gamma glutamyl carboxylase, which turns protein-bound glutamate residues into gamma carboxy glutamate (GLA protein), which is involved in protein coagulation and prevents calcium from building up in the walls of arteries, thereby preventing atherosclerosis [19, 20].

- **HAWTHORN LEAF *(Crataegusoxyacantha***)- It works well to reduce blood lipid levels. It contains oligomeric proanthocyanidins and flavonoids, both of which have negative ionotropic and antioxidant

ISSN No:-2456-2165

effects. It suppresses TXA2 production, which stops platelet aggregation. On coronary arteries, it has a vasodilating action [10, 11, 12, 13].

- **SCUTELLARIN *(Erigeron breviscapine)***- This is a flavonoid glycoside that enhances blood flow, microcirculation, and hemodynamics. It contains antiapoptotic, antioxidant, and anti-inflammatory properties in addition to vasodilating actions. It encourages angiogenesis, or the development of new blood vessels from endothelium that already exists [21].

- **TETRANDIN*E* *(Stephaniatetrandria)*–** Bisbenzylisoquinoline alkaloid, an active component, inhibits the release of endothelium-derived NO as well as NO generation by inducible NO synthase. It also shows an anti hypertensive impact through their vasodilating effect. When membranes are depolarized with KCl or when the alpha adreno receptor is activated with phenylephrine, it prevents vasocular contraction. Calcium channels of the L and T types are inhibited [10, 11, 22].

- **FLAXSEED OI*L* *(Linumusitatissimum*)**- It is abundant in alpha linolenic acid, an important n-3 poly- unsaturated fatty acid that reduces the risk of cardiovascular disease and hyperlipidemia. Additionally, it includes phytoestrogens, which slow the development of atherosclerosis and lignans, which have antioxidant action [12].

- **ASIAN GINSENG *(Panax ginseng)***- It contains ginsenosides, which enhance the release of NO produced from endothelial cells, alter calcium channels in myocardial cells, block the generation of ROS, and lessen platelet adhesion [10,12,13].

B. MEDICATION TREATMENTS

a) ANTICOAGULANT AGENTS

- Parenteral anticoagulants:
  - **Indirect thrombin inhibitors –** These are those inhibitors which bind to antithrombin III (a naturally occurring blood anticoagulant) and speed up the action of antithrombin III. Factor Xa and thrombin are inactivated by antithrombin. Antithrombin interactions with thrombin and factor Xa are accelerated by medications like heparin, while interactions with factor Xa alone are accelerated by low molecular weight heparin. Because they are less prone to have negative effects and have a longer half life, LMWH are more efficient and safe than heparin
  - **Direct thrombin inhibitor-** It binds directly to thrombin & inactive it without the need to combine with and activate antithrombin III. The recognition site of thrombin is not where it binds reversibly, only the catalytic site. medication such as Argatroban, Lipirudin, and Bevlirudin.

Uses - Treatments for patients with thrombocytopenia caused by venous thromboembolism.

- Oral anticoagulant:
  - **Vitamin k antagonist –** Vitamin k reductase transforms vitamin k into the active form (reduced vitamin k), which is necessary for the activation of clotting factors II, VI, IX, and X. Following this activation, it is changed into an inactive form (vitamin k epoxide), which the enzyme vitamin k epoxide reductase then reactivates. Warfarin and other medications like it both block the enzymes that stop the production of clotting factor.
  - **Direct factor Xa inhibitor**- It directly binds to & inactivate factor Xa instead of inhibiting its synthesis. Ex- Rivaroxaban
  - **Oral direct thrombin inhibitor** –Drugs like dabigatranetexilate, a prodrug that hydrolyzes into dabigatram thrombin inhibitors after oral treatment, reversibly block the catalytic site of thrombin, and cause the fast anticoagulant action [23]

b) ANTIPLATELET AGENTS (Antithrombotic drugs)
Drugs that interfere with the platelet functions.

- **Aspirin-** The enzymes Cox1 and TX synthase, which are both produced from arachidonic acid, are acetylated and inhibited by aspirin. Because TXA2 inhibits adenylyl cyclase and lowers cAMP levels, which speeds up platelet aggregation, pGI2 is crucial for maintaining natural resistance to arterial thrombosis. Inhibiting the cyclooxygenase pathway, aspirin thereby prevents platelet aggregation.
- **Clopidogrel -** The binding of adenosine diphosphate to its platelet receptor (P2Y12 - purinergic receptor), which is necessary for platelet activation and prevents platelet aggregation, is selectively and permanently inhibited. The purpose of using it is to prevent thrombosis, transient ischemia episodes, and unstable angina pectoris.
- **Glycoprotein II_b/II_a receptor antagonist**- It is an inhibitor of platelet aggregation that works by blocking the GP IIb/IIIa receptor, which is found on the surface of fibrinogen-containing platelets and to which collagen, thrombin, TXA2, and ADP bind to cause platelet aggregation. Example: Eptifibatide and tirofiban. [23]

c) HYPOLIPIDAEMICC AGENTS
The cholesterol-lowering medication statins is also referred to as an HMG-CoA reductase inhibitor. It prevents the enzyme HMG CoA reductase from converting HMG CoA into mevalonate, the precursor for the production of cholesterol. The level of cholesterol is lowered as a result. For example, prvastatin, lovastatin, pitavastatin, rosuvastatin, and atorvastatin. [23]

ISSN No:-2456-2165

d) Beta- BLOCKER AGENTS (Beta - Adrenergic blocker)
These medications block the effects of the catecholamines norepinephrine and epinephrine on the receptors for the adrenal glands. Due to the beta-1 receptors located on the heart, there is an increase in heart rate, myocardial contractility, and vasodilation. Therefore, these agents function by lowering the demand for oxygen, which results in negative inotropic and chronotropic activity. consequently, a general drop in blood pressure. Propranolol is a non-selective beta blocker, whereas medications like Metaprolol and Atenolol are cardio selective beta blockers. [23]

e) C^{a2+}CHANNEL BLOCKER
These are the substances that prevent L-type Ca2+ channels from opening. As Ca2+ is taken in by the heart's L-type channel, it activates myosin light chain kinase, which phosphorylates light chain myosin, creating actin-myosin cross bridges that ultimately cause vasoconstriction. Thus, these drugs prevent the entry of Ca2+ ions, which reduces myocardial contractility, lowers blood pressure, slows the conduction of electrical activity inside the heart, and causes vasodilation. For example
- **Dihydropyridine derivative**- Derivatives of the drug dihydropyridine were once used to lower arterial pressure and systemic vascular resistance. for example :Nifedipine, Amlodipine, and Felodipine.
- **Phenylalkylamine derivatives-** Drugs like verapamil, have both positive inotropic and positive chronotropic effects.
- **Benzothiazepine derivatives** : These drugs, like dilitazem, have both cardiac depressant and vasodilator effects. [23].

f) ACE INHIBITOR
It is a substance that prevents the conversion of Angiotensin I to Angiotensin II by the Angiotensin converting enzyme. Because AGII causes vasoconstriction and the synthesis of aldosterone, which ultimately result in elevated B.P. Therefore, these substances produce vasodilation and prevent the blood's ability to retain Na+ and H2O. For example, fosinopril, captopril, enalpril, lisinopril, and benzopril. [23]

g) VASODILATORS
An agents used to dilate an artery.
- **(NITRATES) -** It eases the smooth muscles of the arteries and veins. It does this by releasing free nitrite ions from nitrates, which are then transformed into NO and produce vasodilation. These NO trigger guanylyl cyclase activity, which elevates intracellular cGMP levels. CGMP in turn encourages myosin light chain dephosphorylation, which lowers Ca2+ ions and, ultimately, causes smooth muscles to relax. For example-Isosorbidedinitrate, isosorbidemononitrate, and glyceryl trinitrate.

h) Dipyridamole
It is an arterial dilator. By potentiating PGI2, raising cAMP in platelets, and enhancing the anti aggregatory effect, it prevents platelet aggregation. By inhibiting adenosine's uptake and degradation, a local mediator involved in the autoregulation of coronary flow in response to ischemia, it increases overall coronary flow. [23]

i) DIURETICS
An agents which cause net loss of Na^+ & H_2O. These drugs are used in the treatment of hypertension, cardiac edema.
- **HIGH EFFICACY DIURETICS (Inhibitors of $Na^+/k^+/2Cl^-$ cotransport)-** Also referred to as high ceiling loop diuretics. It works by inhibiting Na+/K+/Cl- symporters in the thick ascending limb loop of Henle, which boosts the excretion of Na+ (approximately 25% of filtered sodium ions are expelled), K+, and 2Cl-. Ex: Furosemide, bumetanide, torasemide.
- **MEDIUM EFFICACY DIURETICS (Inhibitors of Na^+ / cl^- symport)-** Also referred to as saluretics or thiazide diuretics. These medicines compete for the chloride binding site of the Na+/cl- symporter and prevent the reabsorption of Na+ and cl- ions after being actively secreted in the proximal convoluted tubule, loop of Henle, and distal convoluted tubule. Hydrochlorothiazide, cyclopenthiazide, ethylchlorothiazide, and polythiazide are other examples.
- **WEAK EFFICACY DIURETICS (Carbonic anhydrase inhibitors)-** It works by acting on the early proximal convoluted tubule, which contains the carbonic anhydrase enzyme. As there is no exchange of Na+ and H+ ions, it prevents the creation of H2Co3, which results in the excretion of Na+ and HCo3- ions. At any other website, these are not very successful. Ex: Dichlorophenamide, Methazolamide, Acetazolamide.
- **MINERALCORTICOID RECEPTOR ANTAGONIST -** It antagonize the effect of aldosterone. It acts on late distal convoluted tubule. Ex - spironolactone.[23]

j) ANGIOTENSIN RECEPTOR ANTAGONIST (Angiotensin II inhibitor):
It inhibits the binding of angiotensin II to the AT1 receptor, which is found on the heart and kidney, blocking the effect of angiotensin II. These receptors trigger the contraction of vascular smooth muscle through the Gq protein and IP3 signal transduction pathway. It lowers blood pressure and prevents aldosterone from being produced. For example, Candesarton, Losarton, Eprosarton, Valsarton, Azilsarton, and Irbesarton [23].

ISSN No:-2456-2165

C. Revascularization therapy / surgical TREATMENt

- **Coronary Artery bypass graft** - This kind of open heart surgery is the most frequent. Improved blood flow to the heart is achieved with CABG surgery. The only patients for whom it is prescribed have significant coronary artery disease (CAD) that puts them at risk for a heart attack. In a CABG procedure, the blocked coronary artery is joined to a healthy artery or vein from the patient's body. Bypassing the obstructed section of the coronary artery, the grafted artery or vein circumvents it. As a result, the obstruction is circumvented and oxygen-rich blood is directed to the heart muscle. According to the quantity of arteries being bypassed, this kind of surgery often takes 4 to 6 hours. Patients with two or three vessel disease and high SYNTAX scores are advised to undergo CABG. Patients with low SYNTAX scores with left main disease or one or two vessel disease are also more likely to benefit from CABG. When compared to PCI, CABG has produced better results for patients with multi-vessel disease. Compared to PCI, it works better. The SYNTAX score, a metric for estimating the complexity of coronary lesions, aids in choosing between PCI and CABG. [24]
- **Percutaneous coronary interventions /Coronary angioplasty** - PCI is a minimally invasive, non-surgical therapy that aims to increase blood flow to ischemic tissue and relieve coronary artery constriction or blockage. A little balloon is injected during the treatment to force the fatty tissue within the constricted artery outward. The blood may now flow more freely as a result. To keep the artery open, a wire mesh tube called a bare metal stent is typically inserted into it. Stents that release drugs are also an option. These disperse drugs to prevent the artery from constricting once more. Over the past few years, percutaneous coronary intervention has seen widespread use. 80% of PCI procedures use stents. Short-term mortality, MI, and target vessel revascularization have all significantly decreased in PCI patients over the past 20 years. If the patient has significant symptoms, failed medical therapy, high risk coronary architecture, or declining LV function, PCI is preferred over medical therapy. [24]

D. NEW STRATEGIES FOR CAD TREATMENT

- **STEM CELL THERAPY -**Its objectives include promoting cardiac cell regeneration and enhancing the blood flow to ischemic parts of the heart [5, 25]. Undifferentiated, self-renewing, clonogenic (from identical clones), and multipotent cells are referred to as stem cells (able to differentiate into wide array of specialised cell type). The ultimate goal of stem cell therapy is to treat mi by increasing cardiac function and rebuilding blood vessels and cardiomyocytes. In regenerative surgery, immature progenitor cells are injected into an infarcted area in the hope that they would develop into new blood vessels and heart muscle cells [26]. Recently, it has received a lot of attention[27]. Different types of stem cells have been applied via various methods to treat CAD. It can also be used to treat non-ischemic cardiomyopathy, peripheral vascular disease, and ageing in addition to treating CAD. [28]

- **Different types of stem cells are used for regenerative therapy:**
  - **Embryonic stem cells (ESC)-** These are derived from the blastocyst's inner cell mass and have the ability to self-renew and differentiate into the three cell types of ectoderm, endoderm, and mesoderm[26,28,29]. These totipotent cells can develop into a range of cell types, including CM, endothelium (the lining of blood vessels), and cardiac pacemaker cells, and they exhibit the greatest potential for organ regeneration[30]. However, they also raise the possibility of teratoma and arrhythmia development. The production of pure and mature cardiomyocytes is also difficult[29]. Due to the origin and isolation techniques of ESC, there are social and ethical issues[30**].** ESC-derived CM are able to have a beneficial effect on the heart, improving cardiac function with little to no teratoma formation and lessened scarring. Due to this, human ESC was embedded in a fibrin matrix and subsequently applied to a patient in the First phase clinical trial-1 (ESCORT, NCT02057900) by epicardial delivery. The patient had severe heart failure. The first clinical case report using cardiac progenitor cells derived from embryonic stem cells demonstrated symptomatic improvement, echocardiographically evident new contractility, and an LVEF improving from 26% to 36% after 3 months—all without complications like arrhythmia or tumour formation[29].
  - **Induced pluripotent stem cells:** These cells have characteristics of ESCs and were created by nuclear reprogramming and ectopic expression of the stemness factor from adult somatic cells. iPSCare was programmed to address the ESC's moral problems[30]. They are favoured because of their shape, expression of SC markers, and capacity to develop into many cardiomyocytes. Transplanted cardiomyocyte-like cells made from iPSCs can enhance heart function and lessen harmful remodelling processes[29]. They can also integrate into the host tissue.
  - **Skeletal myoblast -** They come from a population of progenitor cells called satellite cells, which are found beneath the basal lamina of skeletal muscle fibres. Due to their simple accessibility from autologous muscle biopsies, fast in vitro expansion, tolerance to ischemic circumstances, myogenic capacity, and minimal risk of tumorigenicity, skeletal myoblasts are employed for heart regeneration. Both in preclinical and clinical trials, they were the first cell type to be evaluated for heart regeneration[29].
  - **Cardiac stem cell -** These are the multipotent cells that can self-renew and produce cardiomyocytes, endothelial cells, smooth muscle, and assist the regeneration of damaged heart tissue in adult

ISSN No:-2456-2165

mammals[26,29]. When compared to other cell types, it expresses cardiac-specific markers and can develop into cardiomyocytes more successfully. Cells must be ex vivo expanded before transplantation, which can be expensive and difficult to isolate/extract[31]. Cardiovascular stem cells (CSCs) come in a variety of forms, including ckit+ cells, Isl 1+ cells (insulin gene enhancer protein), stem cell antigen (Sca)-1+ cells, cardiac mesoangioblasts, cardio sphere derived cells, and epicardial progenitors, all of which express marginally different but overlapping surface markers[29,31]. 2011 findings from the first phase I clinical trial (SCIPIO, NCT00474461) showed that intracoronary infusion of autologous c-Kit+ CSCs in patients with ischemic cardiomyopathy did not result in any deaths or CSC-related side events. The CADUCEUS experiment (NCT00893360), in which CDCs generated from endomyocardial biopsy tissue were administered to patients with LV dysfunction after MI, further supported the advantages of CSCs. Along with improving regional contractility and systolic wall thickening, the transplantation of CDCs also decreased the size of infarcts, increased the amount of viable myocardium, and was safe and feasible for intracoronary SC injection [29].

- **Mesenchymal stem cell -** In addition to placenta and umbilical cord blood, they are also present in bone marrow and adipose tissue [31]. They have the capacity to separate into lineages such osteocytes, chondrocytes, adipocytes, myocytes, and marrow stroma[29, 31]. The ability of these cells to release soluble growth factors and cytokines, which have endocrine and paracrine effects, adds to their therapeutic efficacy. The ability to use allogeneic cells is made possible by immunological modulatory properties they possess. The homing, mitogenic, apoptotic, and angiogenic factors released by MSCs have cardiac protective effects[31]. A longer-term effectiveness of these cells needs to be supported by additional research. In patients who underwent percutaneous coronary intervention for acute STEMI, the BOOST study involved intracoronary delivery of autologous bone marrow-derived MSCs. When cultivated with immune cells in vitro, MSCs produced from adipose tissue had stronger immunosuppressive effects than MSCs derived from bone marrow or umbilical cord matrix. Using adipose-derived cells activated with VEGF-A165, the mesenchymal stromal cell therapy in patients with chronic myocardial ischemia (My Stromal Cell Trial) is a phase II trial looking at the impact on patients with chronic ischemic heart disease and refractory angina. Due to their simplicity in liposuction isolation and their immunosuppressive properties, these cells are preferred [31].
- **Bone marrow derived mononuclear cell -** These are the cells that can be transplanted into the body with the greatest ease. They can be separated from the bone marrow and are widely recognized based on their cell surface markers. However, because the extracted cells contain a large variety of cells with a small percentage of stem cells, their therapeutic potential is limited[5].
- **Mechanism of SC in cardiovascular regeneration-** The capacity of SCs to repair damaged tissue is mainly based on indirect/paracrine mechanism which involves the release of soluble factors by positively influences the remodeling of the extracellular matrix (ECM) in the injured tissue & direct mechanism involves differentiation of SC intocardio myocytes, endothelial and smooth muscle cells [29].

- **NANOTECHNOLOGY:** Using materials in the nanoscale range as diagnostic tools or to deliver therapeutic substances to specific targeted locations in a controlled manner, nanomedicine and nano delivery systems are relatively young but quickly emerging fields of science. Between 1 and 100 nm in size, nanomaterials have a significant impact on the frontiers of nanomedicine, influencing everything from tissue engineering to drug delivery, microfluidics, and drug delivery systems to biosensors[32]. It is used in treatments for atherosclerosis by lengthening the time that an agent circulates throughout the body, decreasing the cytotoxicity of drugs that are used off-target, increasing drug solubility, lowering dosage requirements, combining therapeutic and diagnostic agents to create theranostic agents, and lengthening the time that an agent accumulates at particular sites. These drug delivery methods can either be active (conjugating tissue- or cell-specific ligands to either the Nano carriers or the pharmaceuticals) or passive (coupling the medications to macromolecules)[33]. The FDA has only recently approved liposomes for use in nanomedicine[34]. Under the brand name Liprostin, phase III clinical trials for the liposomal medication delivery of prostaglandin E-1 (PGE-1) are now being conducted. PGE-1 has pharmacological qualities like anti-inflammatory, vasodilation, and inhibition of platelet aggregation and leukocyte adhesion. PGE-1 was encapsulated into lipid nanoparticles, which decreased PGE-1 degradation and enhanced the anti-inflammatory action and therapeutic result prolongation[35]. [Liposomes are more equipped to deliver pro-angiogenic medicines to the infarct microvasculature and can minimise restenosis and neointimal formations when they include the bisphosphonate alendronate. FDA-approved polymers include polylactic acid (PLA), polyglycolic acid (PGA), and polylactic-co-glycolic acid (PLGA) nanoparticles[34]. Better results have been obtained using quercetin (Qu) encapsulated within polymeric nanoparticles made of poly(lactic-co-glycolic acid) (PLGA) for the prevention of atherosclerosis[35]. Poly(lactic-co-glycolic acid)-based polymeric stent coatings (also known as nanocoatings-64) are used to manage the release of the medicine paclitaxel and polyethylene glycol is utilised to lessen platelet adhesion[5,25]. Micelles are employed for the distribution of medications that control infarct healing

ISSN No:-2456-2165

during the chronic stage of MI as well as the delivery of cardio protective medications required for the acute stage of MI[34]. It is possible to encapsulate and transport either bioactive medicinal compounds, diagnostic agents, or both using the hydrophobic core of micelles [33]. Using poly(ethylene glycol) and poly(propylene sulphide), block copolymer micelles were created (PEG-PPS). In order to treat atherosclerosis, the micelles are employed to solubilize andrographolide, a plant-derived molecule that has cardiac protective properties and reduces inflammatory response and reactive oxygen species (ROS) levels. Nucleic acids are delivered via lipid nanoparticles (LNPs)[35]. For the delivery of nattokinase, a dendrimer made of poly (glutamic acid) and poly(ethylene glycol) (PEG) (Gn-PEG-Gn) has been reported (NK). NK is a thrombolytic medication with excellent levels of safety and few adverse effects, but it is highly susceptible to deterioration from the outside environment. In order to make NK-loaded G3-PEG-G3 dendrimer for clinical application, good thrombolytic activity in vitro was demonstrated. NO encapsulated dendrimers are employed as an individualised treatment for tissue damage to stop atherosclerosis[35]. To re-endothelialize damaged arteries and lessen hyperplasia, gel-based nanoparticles and rapamycin (antiproliferative and antiapoptotic impact) are used[5,25]. utilisation of core/shell nanoparticles that have been loaded with vascular endothelial growth factor (VEGF) for the regeneration of ischemic hearts[35]. Iron oxide nanoparticles are used as MRI contrast agents, while non-metallic nanoparticles like Quantum dots (QDs), or semiconductor nanocrystals, are focused on fluorescence imaging in particular due to their distinctive luminous properties and monitor monocyte-macrophages in atherosclerosis plaque[32]. Biomimetic HDL can be created by the use of nanotechnology. A liposomal formulation containing dimyristoyl phosphatidylcholine (DPMC), a crucial HDL surface component that facilitates the extraction of cholesterol from peripheral tissues, has demonstrated lower aortic cholesterol content and plaque volume as one such example. D-phenylalanyl-L-prolyl-L-arginyl-chloromethyl ketone (PPACK), which covalently attaches to the surface of long-circulating perfluorocarbon-core nanoparticles and exhibits significant thrombin-inhibiting function, has demonstrated improved improvements in anti-thrombotic activity[36]. The antimitotic medication paclitaxel has been demonstrated to have considerable antiproliferative and restenosis effects without severe toxicity[5] when it is administered as albumin-based nanoparticles. Through the targeted and site-specific delivery of precise medications, nanotechnology provides numerous advantages in the treatment of chronic human diseases[32]. In order to modulate lipid abnormalities, reduce inflammation and angiogenesis within atherosclerotic plaques, and prevent plaque thrombosis, a variety of medications may be delivered using a safe and effective platform made possible by nanotechnology [36].

- **GENE THERAPY:** Gene therapy is a group of procedures that enables the insertion and expression of a therapeutic gene in target cells with a genetic disorder of some kind (not necessarily hereditary), allowing the correction of improper gene products that cause diseases and serving as an alternative to the treatment of genetically transmitted diseases[37]. Cardiac gene therapy modifies gene expression for myocardial regeneration using growth factors, genes, or small molecules [38]. Plasmids, adenoviruses with a brief expression profile and adeno-associated viruses (aav), lentiviruses, and retroviruses that are ideal for long-term expression of the therapeutic genes are the most often employed vectors to transduce cells. The goal of gene therapy is to successfully express the therapeutic gene that has been delivered so that the target organ can begin to create RNA or protein[39]. Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), Hepatocyte Growth Factor (HGF), Plasmid and Aenoviral vector, which govern endothelial migration, proliferation, survival, and proteolytic activity, are some of the agents used to increase angiogenesis to treat CAD. In order to halt the disease-causing genes that are ideal for the long-term expression of the therapeutic genes, Adeno-associated viruses (AAV), lentiviruses, and retroviruses transfer their genetic material into the host and replace the original disease-causing genes[40].

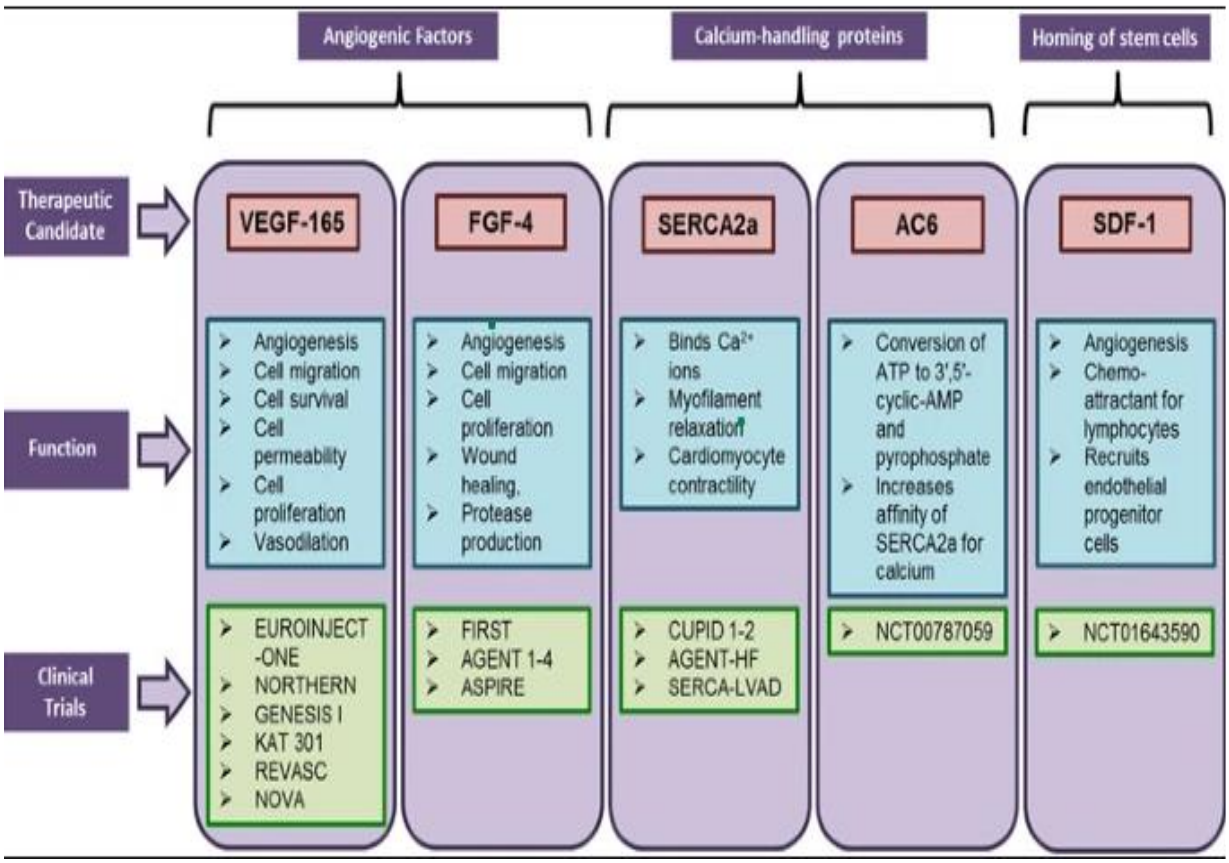

Fig. 2: Gene therapy clinical trials for CAD[41]
(Vascular endothelial growth factor (VEGF-165), Fibroblast growth factor(FGF-4),Sarco-Endoplasmic Reticulum Calcium-ATPase(SERCA2a), Adenylyl cyclase-6 (AC6), Stromal cell Derived factor-1(SDF-1)

VIII. CONCLUSION

In these reviews, a variety of techniques have been employed to treat CAD, such as herbal therapy, which makes use of numerous herbs that have anti-thrombotic, antihypertensive, anticoagulant, and vasodilator effects. Pharmaceutical medications that combat atherosclerotic disease and aid in enhancing blood flow are also employed. However, these traditional treatments only have short-term advantages. Therefore, when standard treatments are ineffective, clinical researchers have created a new strategy to treat CAD that uses myocardial regeneration for the long-term benefits. When all other treatments for ischemic heart disease have failed, gene therapy has become a potentially useful alternative. SC transplantation has also become a novel strategy for repairing cardiac tissue injury. The goal of nanotechnology is to deliver nano scale drugs to the target site for longer-lasting and more effective therapeutic effects. These cutting-edge methods are producing positive effects in the treatment of CAD, lowering mortality & morbidity rates.

REFERENCES

[1.] Kumar V, Abbas AK, Fausto N, Aster JC. Robbins and Cotran pathologic basis of disease, professional edition e-book. Elsevier health sciences; 2014 Aug 27.
[2.] World Health Organization. Health topics: Cardiovascular diseases. Fact Sheet. Available online: http://www. who. int/cardiovascular_diseases/en/(accessed on 11 December 2020). 2013.
[3.] Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, Elkind MS. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation. 2021 Feb 23;143(8):e254-743.
[4.] Chart: The World's Leading Causes Of Death | Statista https://www.statista.com/chart/amp/23755/total-number-of-people-who-died-from-the-following-conditions
[5.] Kandaswamy E, Zuo L. Recent advances in treatment of coronary artery disease: role of science and technology. International journal of molecular sciences. 2018 Jan 31;19(2):424.
[6.] Kumar Vinay, Cotran R.S, Robbins S.L; "basic pathology, Philadelphia; WB Saunders company"; edition 7th, 2003

[7.] Bullock Shane, Hales Majella; "principle of pathophysiology"; Pearson Australia group ltd.; edition 1st, 2013
[8.] Acharya UR, Fujita H, Lih OS, Adam M, Tan JH, Chua CK. Automated detection of coronary artery disease using different durations of ECG segments with convolutional neural network. Knowledge-Based Systems. 2017 Sep 15;132:62-71.
[9.] Phad LG, Bardale RV, Haridas SV, Jiwane AS. The study of heart diseases in western Maharashtra Population. Journal of Forensic Medicine and Toxicology. 2022;39(1):94-8.
[10.] Mashour NH, Lin GI, Frishman WH. Herbal medicine for the treatment of cardiovascular disease: clinical considerations. Archives of internal Medicine. 1998 Nov 9;158(20):2225-34.
[11.] Tachjian A, Maria V & Jahangir A; "Use of Herbal Products& potential interaction in patient with cardiovascular diseases"; Journal of the American college of cardiology, 55(6); Published 2010; page no. 515-525
[12.] Liperoti R, Vetrano DL, Bernabei R, Onder G. Herbal medications in cardiovascular medicine. Journal of the American College of Cardiology. 2017 Mar 7;69(9):1188-99.
[13.] Liu C, Huang Y. Chinese herbal medicine on cardiovascular diseases and the mechanisms of action. Frontiers in pharmacology. 2016 Dec 1;7:469.
[14.] Qidwai W, Ashfaq T. Role of garlic usage in cardiovascular disease prevention: an evidence-based approach. Evidence-Based Complementary and Alternative Medicine. 2013 Oct;2013.
[15.] Deng R. Therapeutic effects of guggul and its constituent guggulsterone: cardiovascular benefits. Cardiovascular drug reviews. 2007 Dec;25(4):375-90.
[16.] Priya N, Mathur KC, Sharma A, Agrawal RP, Agarwal V, Acharya J. Effect of Terminalia Arjuna on total platelet count and lipid profile in patients of coronary artery disease. Advances in Human Biology. 2019 Jan 1;9(1):98.
[17.] de Souza PA, Marcadenti A, Portal VL. Effects of olive oil phenolic compounds on inflammation in the prevention and treatment of coronary artery disease. Nutrients. 2017 Sep 30;9(10):1087.
[18.] Omar SH. Oleuropein in olive and its pharmacological effects. Scientia pharmaceutica. 2010 Jun;78(2):133-54.
[19.] Haugsgjerd TR, Egeland GM, Nygård OK, Vinknes KJ, Sulo G, Lysne V, Igland J, Tell GS. Association of dietary vitamin K and risk of coronary heart disease in middle-age adults: the Hordaland Health Study Cohort. BMJ open. 2020 May 1;10(5):e035953.
[20.] Kurnatowsko I, Grezelak P, Masajtis- zagajewsk A, Kaczmarska M, et al; "Effect of vitamin K2 on progression of atherosclerosis & vascular calcification in Nondialyzed patients with chronic kidney disease stages 3-5"; PolskieArchiwumMedycynywewnetrznei; Volume 125(9); published July,2015; page no. 267-276
[21.] Huang H, Geng Q, Yao H, Shen Z, Wu Z, Miao X, Shi P. Protective effect of scutellarin on myocardial infarction induced by isoprenaline in rats. Iranian journal of basic medical sciences. 2018 Mar;21(3):267.
[22.] Kwan CY, Achike FI. Tetrandrine and related bis-benzylisoquinoline alkaloids from medicinal herbs: cardiovascular effects and mechanisms of action. Acta Pharmacologica Sinica. 2002 Dec 1;23(12):1057-68.
[23.] Tripathi K.D; "Essential of Medical pharmacology"; JAYPEE brothers medical publisher Ltd.; Edition 7th, 2013
[24.] Ahmad Mansoor, et Al; "Percutaneous Coronary Interventions"; StatPearls Publishing,31 December 2021.
[25.] Singh Ram B, Isaza Adrian, et Al; "New Technologies for Treatment of Coronary Artery Disease"; BiomedicalJournalScience&Technology; volume 13; published 25 January 2019
[26.] Michler RE. The current status of stem cell therapy in ischemic heart disease. Journal of Cardiac Surgery. 2018 Sep;33(9):520-31.
[27.] Yu H, Lu K, Zhu J, Wang JA. Stem cell therapy for ischemic heart diseases. British medical bulletin. 2017 Jan 1;121(1):135-54.
[28.] Sunkomat JN, Gaballa MA; "Stem cell therapy in ischemic heart disease" Cardiovascular Drug Revise volume 21; published April 2003; page no.327-342
[29.] Müller P, Lemcke H, David R. Stem cell therapy in heart diseases–cell types, mechanisms and improvement strategies. Cellular Physiology and Biochemistry. 2018;48(6):2607-55.
[30.] Grimaldi V, Mancini FP, Casamassimi A, Al-Omran M, Zullo A, Infante T, Napoli C. Potential benefits of cell therapy in coronary heart disease. Journal of cardiology. 2013 Nov 1;62(5):267-76.
[31.] Faiella W, Atoui R. Therapeutic use of stem cells for cardiovascular disease. Clinical and Translational Medicine. 2016 Dec;5(1):1-8.
[32.] PatraJayanta Kumar, et al; "Nano based drug delivery system: recent developments & future prospects"; Journal of Nano biotechnology; Volume 16 (1) 71; published 19 September 2018
[33.] KarimiMahidi, et al; " Nanotechnology in diagnosis and treatment of coronary artery disease"; Nano medicine (London, England); Volume 11(5); published 2016; page no. 513-530
[34.] Fan Chengming, Joshi Jyotsana, et Al; "Nanoparticle-Mediated Drug Deliveryfor Treatment of Ischemic HeartDisease"; Frontiers in Bioengineering&. Biotechnology; volume 8; published 02 June 2020
[35.] Chandarana M, Curtis A, Hoskins C. The use of nanotechnology in cardiovascular disease. Applied Nanoscience. 2018 Oct;8(7):1607-19.
[36.] Rhee JW, Wu JC. Advances in nanotechnology for the management of coronary artery disease. Trends in cardiovascular medicine. 2013 Feb 1;23(2):39-45.
[37.] Eibel Bruna, et Al; "Gene therapy for ischemic heart disease: review of clinical trials"; Revista Brasileira de cirurgia cardiovascular: orgao oficial dasociedade Brasileira de cirurgia cardiovascular; volume 26; published April 2011; page no. 635-646
[38.] Patel V.B., Ryan C.T., Crystal R.G., Rosengart T.K.; "Gene Therapy for Coronary Artery Disease"; Cardiac Surgery, Springer, Cham; published Jan 2011
[39.] Korpela H, et Al; " Gene Therapy for ischemic heart disease & Heart failure"; Journal for internal

medicine"; volume 290; published March 2021; page no. 567-582
[40.] Rincon MY, Vanden Driessche T, Chuah MK. Gene therapy for cardiovascular disease: advances in vector development, targeting, and delivery for clinical translation. Cardiovascular research. 2015 Oct 1;108(1):4-20.
[41.] Matkar, P., Leong-Poi, H. & Singh, K; "Cardiac gene therapy: are we there yet?"; GeneTherapy; volume 23(8-9); published August 2016; page no. 635-648.