Review Article

The Effect of Antioxidants and Cardiovascular Drugs in the Treatment of Cardiac Diseases

Swadesh Kumar Pattanik, Kishanta Kumar Pradhan*

Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi, Jharkhand, INDIA.

ABSTRACT

Background: Reactive oxygen species mediate oxidative stress, is one of the major causes of the athero-thrombotic process involved in the etiology of peripheral arterial disease, ischemic strokes, and heart attack. Angiotensin-1 receptor blockers, beta-blockers, angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers are traditional cardio-protective drugs. But the problem associated with these medications is, a person diagnosed with high blood pressure in younger age, has to take these drugs for lifelong, which may lead to develop harmful drug-induced diseases on long-term use like Alzheimer's disease, Raynaud's phenomenon, decreased levels of plasma catecholamines, etc. **Materials and Methods:** Among all anti-hypertensive agents, angiotensin-1 receptor blockers are safer as they have minimal long-term health hazards. Many pieces of the literature suggest that, intake of foods rich in anti-oxidant reduces the chance of cardiovascular disease, as they consume free radicals formed by various endogenous systems, pathological states or exposure to different physiochemical conditions, and improper oxidation of lipids. We can focus on synergistic benefit of both anti-hypertensive drug and antioxidants. **Conclusion:** Hence, we can assume that, intake of antioxidant as an active pharmaceutical ingredient may positively benefit in the treatment of cardiovascular diseases. Co-administration of existing cardiovascular drug and a suitable antioxidant(s) may produce a better result.

Keywords: Cardiovascular diseases, Oxidative stress, Reactive oxygen species, Antioxidants, AT1 receptor blocker.

INTRODUCTION

Oxidative process plays an essential part in the development and progression of some chronic diseases, e.g., "arthritis, cancer, atherosclerosis, ocular diseases, and reperfusion injury in association with myocardial infarction. "From *in vivo* and *in vitro* studies, the finding data suggests that when low density lipoproteins get oxidised by reactive oxygen species, that promotes several steps in atherogenesis,[1] endothelial cell damage,[2,3] foam cell accumulation,[4-6] blocking of blood vessels,[7,8] and synthesis of auto-antibodies.[9] Additionally, animal studies suggest that free radicals may directly damage arterial endothelium,[10] interfere with normal vasomotor regulation, and promote thrombosis.[11,12] Oxidative damage to our cardiac health may enhance athero-genesis by a series of reactions. In aerobic organisms, numerous biological systems and mechanisms have evolved to reduce uncontrolled oxidation and its damaging effects. Cardiovascular disease (CVD) is a broad term used to define a sequence of disorders linked to heart and blood vessels, including coronary artery diseases, peripheral vascular disease, hypertensive heart disease, atherosclerosis, and congestive cardiac failure. If it remains untreated, it may lead to end-organ damage, strokes, and cerebral artery diseases. This is one of the potential causes for a casualty in developed countries. In the United States, cardiovascular death rates are almost twice the rate of death caused by cancer within two decades.[13] Antioxidants can mitigate the activities of free radicals and other reactive oxidative species, which are involved in developing atherogenesis.[14,15] Hence it is considered as a natural defence system

Submission Date: 10-07-2022;
Revision Date: 11-09-2022;
Accepted Date: 22-10-2022.

DOI: 10.5530/001954642291

Correspondence:
Dr. Kishanta Kumar Pradhan,
Assistant Professor, Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi-835215, Jharkhand, INDIA.
Email id: kkpradhan@bitmesra.ac.in

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for human health. Several epidemiological studies along with data obtained from observational literature suggest a beneficial effect of antioxidant-rich foods. Specific antioxidants have curing effects on the risk of cardiovascular disease and stroke,[16-21] these beneficial effects of antioxidant also contribute to cellular health by participating in detoxification, biosynthesis, energy metabolism, and cellular signalling. Optimal balance is essential between the pro-oxidants produced in the body and the antioxidant as a defence system to maintain health.[22] A review of data obtained from the significant epidemiological studies confirms a favourable association between more intake of foods rich in antioxidants with less risk of ischemic heart diseases and stroke.[23] Several studies prove a positive association between the effects of antioxidants (Vitamin status - plasma Vitamin E and C levels) and the structural integrity of various body organs.[24] "A prospective cohort study designed to investigate the genesis of atherosclerosis, demonstrated a significant inverse relationship between Vitamin C intake and wall thickness in both sexes, even after adjusting for age and significant risk factors".[25] Compared to the data from latest studies,[24] only wall thickness of female patients was correlated with Vitamin E intake than in male subjects. By this review we have tried to find out the contribution of antioxidants in reducing the chances of cardiovascular diseases. How it can be use along with the existing cardiovascular drugs basing on different pharmacokinetic parameters. A future scope to evaluate the combination therapy on the cardiovascular disease model with lesser doses of a cardiovascular drug and antioxidant with the help of an *in-vivo* study.

CARDIOVASCULAR DISEASE

Cardiovascular diseases are cardiac conditions that include structural problems, diseased vessels, and blood clots. Irrespective of age, some most common types of cardiovascular diseases are coronary heart disease, heart failure, cardiac arrest, high blood pressure, arrhythmias, coronary artery disease, congenital heart disease, stroke, etc. Among all non-communicable disease events, cardiovascular disease having a large portion. It accounts for an estimated 31 percent of disease burden and worldwide mortality rate.[26] Further, rates of cardiovascular diseases are increasing in developed countries. As per studies from the Heart Outcomes Prevention Evaluation (HOPE), the statistical data for mortality due to increase in ischemic heart disease is approximately 29 percent and mortality due to cerebrovascular disease increased up to 28 percent in developed countries within three decades i.e., 1990 to 2020.[27-28] Many factors are responsible for the occurrence and persistence of cardiovascular diseases; some of the crucial elements are ROS production, heavy consumption of unhealthy food, lifestyle modification, stress and tension, smoking tobacco, etc.

Significant causes of cardiovascular diseases

Reactive oxygen species

It includes free radicals like- lipid radicals (ROO^{-}), hydroxyl radical (HO^{-}), superoxide anion (O_2^{-}), nitric oxide (NO), and some non-free radicals such as hypochlorous acid (HClO), hydrogen peroxide (H_2O_2), and peroxy-nitrite ($ONOO^{-}$). They have oxidizing effects, hence contribute to oxidative stress. Reactive oxygen species are highly reactive free radicals; therefore, they are chemically unstable. They usually contain oxygen, customarily produced by xanthine oxidase, lipoxygenases, nicotinamide adenine dinucleotide phosphate oxidase, or uncoupling of nitric oxide synthase in mitochondria or vascular cells. When any alteration occurs in the antioxidative capacity of human physiology, due to several pathophysiological conditions, then equilibrium between the production of free radicals and antioxidative neutralization gets disturbed. That leads to tissue injury and other physiological issues. Besides several health issues, cardiovascular disease is the most critical health hazard caused by these free radicals.

Improper diet, lifestyle, environmental factor

It is a significant risk factor for coronary heart diseases. Excessive salt intake from processed foods, unhealthy dietary habits also contribute to mass gain. High amounts of salt, processed meats, white rice, sugar, bacon, red meat, soda, baked foods, saturated fat and refined carbohydrates, bread, pizza, and pasta raise the risk for a heart attack or stroke. Obesity is always the first step towards cardiovascular problems. Due to an unhealthy diet and overeating, a critical imbalance between calorie input and calorie burning occurs, leading to excess production and deposition of fat in the body, known as obesity. Later on, fats get deposited on the inner walls of blood vessels and coronary arteries, producing several cardiovascular diseases and other related problems. A person's or population's lifestyle plays a vital role in risk for development or dying from cardiovascular disease. This strong relationship has always been a research tool for scientists over the past half-century. In some people, heredity becomes a significant factor. In others, personal health habits, environmental and cultural exposure. Hence, we can conclude that cardiovascular disease is a multifactored process contributed by various

behavioural and biological characteristics and numerous well-established and emerging risk factors.

Smoking

It increases the formation of plaque in blood vessels. Arteries that carrying blood to the muscle fibre of heart get narrowed by plaque or blocked by clots, which leads to coronary heart diseases. Cigarette smoke contain chemicals that makes blood thicker and form clots inside arteries and veins. It hardens the blood vessels; the problem occurs in managing blood pressure due to loss of flexibility.

Pathophysiology of Cardiovascular Diseases

Several complications associated with persistently elevated blood pressure are; chest pain, damage to the kidney, risk of heart attack and stroke, heart failure, vision problems, sexual dysfunction, increased risk for peripheral artery disease, and hypertensive crisis. Some other general symptoms are; dizziness, light-headedness, blurry vision or other vision problems, bleeding from the nose, severe headaches, shortness of breath, chest discomfort or pain, a feeling of anxiety, or that something is not correct. Early detection of elevated blood pressure levels is crucial for the prevention, management, and heart disease interventions. It provides scope for assessment before microvascular or macrovascular damage occurs. If early symptoms are not treated on time, consistent blood pressure of 180/120 mmHg or more may result in a high chance of death within a period of twelve months, with an average survival rate of nine to ten months. Prolonged, untreated high blood pressure can also result in blindness, kidney disease, heart attack and stroke. In countries like India, 80% of the population resides in rural areas. Some of the significant causes of death related to high blood pressure are, lack of social awareness, ignorance of initial symptoms of cardiological problems, improper food habits, lack of facilities for medication, late diagnosis, superstitious beliefs, etc. It occurs in developed countries and urban areas due to adaptation of modern lifestyle, lack of physical labour and exercise, over-consumption of unhealthy processed foods, drug-induced hypertension, stress and tension, environmental factors like pollution, etc.

Commonly Prescribed Anti-hypertensive Drugs

Researchers have invented many medicines by considering various pathways involved to increase blood pressure. Patients are using those anti-hypertensive drugs for decades. Some of the drug acts by reducing blood viscosity are blood thinners like warfarin, aspirin, apixaban, dabigatran, edoxaban, heparin, rivaroxaban. Some medications that can lower blood cholesterol levels are known as cholesterol-lowering or lipid-lowering agents; for example, statins: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, nicotinic acids: niacin, cholesterol absorption inhibitor: ezetimibe.

Combined Drug Therapies to Treat Heart Diseases

Besides monotherapy, combinations of drugs are also available in the market for the treatment of CVDs. It mainly includes two agents of the different classes of cardiovascular medicines and has proven to have better therapeutic values. Some of the examples are the combination of statin (i.e., lipid-lowering medicines) and cholesterol absorption inhibitors: Simvastatin with ezetimibe, sacubitril is a prodrug along with valsartan, an angiotensin receptor blocker used for chronic heart disease, a calcium channel blocker "amlodipine" given along with "perindopril" is an angiotensin-converting enzyme (ACE) inhibitor, used to manage hypertension. "aspirin" and "omeprazole" this combination used to reduce the risk of stroke or heart attack. Patients who have, had or are at risk of these cardiac conditions and are also at risk of developing a stomach ulcer when taking aspirin. "Aspirin" is in a class of medications called antiplatelet agents. Nebivolol is a Beta-1 adrenergic receptor antagonist, and valsartan is an angiotensin receptor blocker used to manage high blood pressure well. Some other drugs used to treat cardiovascular diseases are beta-blockers, angiotensin-converting enzyme blockers, diuretics, calcium channel blockers, AT1(Angiotensin-1) Receptor blockers. As per exhaust literature study data, drugs for the treatment of CVDs have been developed from half of the century ago. They are used to reduce elevated blood pressure but fail to protect from end-organ damage. As we know, once a patient is diagnosed with high blood pressure. Mostly, they have to take medication for life long. We cannot avoid side effects, adverse effects, and long-term complications in such a scenario. More or less, every class of anti-hypertensive drug produces some long-term side-effects or some severe adverse effects, which may prove fatal before heart failure. Based on risk-benefit assessment, the health complicacy and risk factors of death increase significantly.

Short-term and long-term complications with existing cardiovascular therapy (Table 1)[66-84]

REACTIVE OXYGEN SPECIES

ROS is a chemically unstable molecule containing oxygen and readily reacts with other molecules present

Table 1: List of existing cardiovascular drugs with their long-term and short-term side effects.

Class of drugs	Examples	Short term effects	Long term effects
Beta-blockers	Propranolol[62-63] Metoprolol[64] Atenolol[65]	Hypoglycemia, Fatigue, and Insomnia. Insulin resistance, Hallucinations. Headache G.I disturbances	Decrease levels of plasma catecholamine Raynaud's phenomenon Sexual disturbances Bronchospasm, Exertional dyspnoea Nightmares/sleep disturbances
ACE inhibitor	Captopril[66] Enalapril[67] Lisinopril[68]	Rash Loss of taste perception Postural hypotension Lethargy Tachycardia Vomiting	Neutropenia, Agranulocytosis, Proteinuria, Aplastic anaemia Skull hypoplasia, anuria Hypotension, renal failure, and death(pregnancy) Angioedema
Cal. channel Blocker	Verapamil[69] Nifedipine[70] Diltiazem[71] Amlodipine[72]	Hypersensitivity Fever, Eosinophil Oedema, Flushing, Dizziness and headache Reflex tachycardia	Dilation of coronary arteries Decreased platelet aggregation Bradycardia, Hypotension and Palpitations Liver injury with jaundice Sleep disturbances, pruritus, urticaria
Diuretics	Indapamide[73] Furosemide[74] Spironolactone[75]	Hypovolemia hypersensitivity ototoxicity Systemic alkalosis Electrolyte imbalance	Sexual dysfunction In males (gynecomastia, loss of libido, and general feminization) In females (menstrual irregularities) Ototoxicity or permanent deafness
AT-1 Receptor blocker	Telmisartan[76] Irbesartan[77] Candesartan[78] Olmesartan[79] Valsartan[80]	Headache, dizziness Nausea Upper respiratory tract Infections Back pain	No significant data

N.B: As data supporting from literature, AT1 receptor blockers are comparatively safer among all classes of antihypertensive drugs, as they have minimal short-term side effects and rare long-term adverse effects.

in the cell. They generate during mitochondrial oxidative metabolism, cellular response to cytokines, xenobiotics, and bacterial invasion. Oxidative stress is the imbalance due to excess production of ROS or oxidants which exceeds the cellular capability to establish an effective antioxidant response.[29] A build-up of ROS in cells may cause damage to intracellular organelles like; DNA, RNA, and proteins. These damaging effects may cause cell lysis. ROS are free radicals, also referred to as oxygen radicals. It acts as cell signalling molecules that involve in normal biological processes. Whenever excess generation of ROS occurs, it provokes damage to multiple cellular organelles and their functions. By definition, free radicals possess an unpaired electron, making them highly reactive and damaging all macromolecules, including lipids, proteins, and nucleic acids. Which ultimately disrupts normal physiology. Hence reactive oxygen species are toxic to cells.

ROS Related Health Hazards

Free radicals are capable to produce oxidative stress, a process that is capable of triggering cell damage. The formation of free radicals in our body is a natural process that forms during heavy exercise and as and when the body converts food into energy by mitochondrial respiration. Some environmental sources facilitate free radical exposure, such as cigarette smoke, air pollution, harmful radioactive substances, and ultra-violet radiation from the sun. Oxidative stress plays an active role in numerous diseases, including cardiovascular diseases, cancer, Parkinson's disease, Alzheimer's disease, diabetes, and eye diseases such as age-related macular degeneration and cataracts. Antioxidants are molecules that are capable of counteracting oxidative stress. A considerable number of experimental data from laboratory experiments (e.g., in cells or animal studies) are available for justification. However, there is a debate whether consuming large amounts of antioxidants as supplements may benefit health. Also, some concerns regarding the consumption of antioxidant supplements in excessive doses may be harmful. In case of carcinogenesis, oxidative stress mechanisms have a potential role in the initiation,

promotion, and malignant conversion (progression) stages of carcinogenesis, and oxidative damage to DNA. In the case of neurodegenerative conditions, like; Huntington's disease, Alzheimer's disease, and Parkinson's disease, result from oxidative stress pathogenesis in the brain. In case of inflammation/ infection, an extensive set of documents proves the association between inflammation and oxidative stress. Inflammatory mediated substances like; macrophages, eosinophils damaged surrounding tissues initiate further radical reactions. Oxidative stress is associated with the pathogenesis of autoimmune diseases like; rheumatoid arthritis, systemic lupus erythematosus and radical production. That produces connective tissue damage along with biomolecule modification. Hence those modified biomolecules cause antigen-driven auto-antibody production by getting exposure to the systemic circulation.

Characteristics of Oxidative Stress

Oxidative damage and lipid peroxidation are essential factors of the progression of cardiovascular disease.[30] Harmful oxidations are generally mediated by reactive oxygen species. It includes mitochondrial respiration, both enzymatic and non-enzymatic chemical reactions (radical theory of aging).[31] Oxidative stress amplifies blood pressure elevation. Other factors include salt, renin angiotensin system proteins, sympathetic hyperactivity.[32] Major source of ROS, that cause CVDs is a family of non-phagocytic NADPH oxidases.[33] Other sources include mitochondrial electron transport enzymes, i.e., Xanthine oxidases, uncoupled nitric oxide synthase,[34] etc. When there is an imbalance between the pro-oxidants and the antioxidants, it leads to oxidative stress.[35] Endogenous antioxidant production decreases due to excessive pro-oxidant production.[36] The use of antioxidant is a proven protective major to avoid oxidative stress-mediated by reactive oxygen species as it neutralizes the free radicals.

ROS mediated cardiovascular problems (Figure 1).[37]

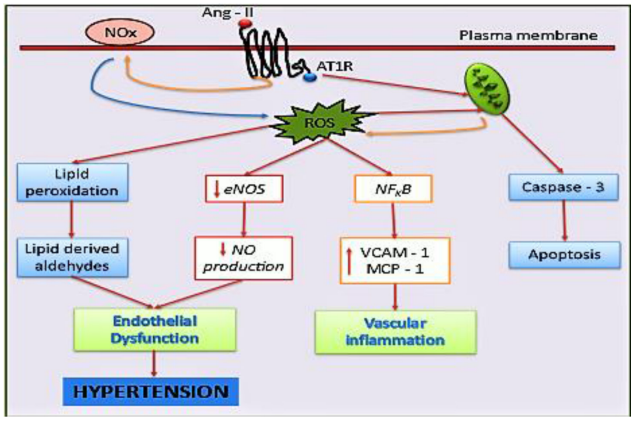


Figure 1: Angiotensin induced ROS production through the activation of mitochondrial enzymes and NADPH oxidase NOx.

(NADPH- Nicotinamide adenine dinucleotide phosphate hydrogen, NO- nitrous oxide, NOx- nitrous oxidase NF- necrosis factor, VCAM-Vascular cell adhesion molecule, MCP- membrane cofactor protein)

ANTIOXIDANT

Free radicals are molecules produced when our body breaks down food or gets exposed to tobacco smoke or radiation. Antioxidants are substances that protect cells from free radicals, which may play a role in heart disease, cancer, and other diseases. Examples of antioxidants include selenium, lutein, Vitamin C, Vitamin E, beta-carotene, lycopene, and zeaxanthin. This fact provides basic information regarding antioxidants and summarizes what the science says about antioxidants and their effects on health, and suggests sources for additional information. Vegetables and fruits are healthy foods and rich sources of antioxidants.

Benefits of Antioxidant Treatment

Antioxidants like; ellagic acid, quercetin, epigallocatechin-3-O-gallate, genistein, lycopene, indole-3-carbinol, SOD (Superoxide dismutase), coenzyme Q10, Vitamin E, and Vitamin C are pharmacologically active compounds. They function as prophylactic and therapeutic agents for diseases related to oxidative stress. The effect of antioxidant can improve by the application of novel drug delivery systems.[38] Lycopene, an essential chemical component in tomatoes, has significant antioxidant potential in *in-vitro* studies. It plays a role in preventing prostate cancer and cardiovascular disease in humans. It is probably due to the antioxidative property of lycopene.[39] Rat mitochondria get affected through β-adrenergic agonists and produce myocardial damage, on which ellagic acid shows protective action. Ellagic acid acts by scavenging free radical and metal chelating activities were confirmed by *in vitro* studies.[40] Cardio-metabolic syndrome risk factors (CMSRF) may reduce by foods rich in poly-phenolic compounds by improving vascular health, reducing insulin resistance, cholesterol-lowering effects, modulation of inflammation, and endothelial function. Oxidative stress plays a significant role in the pathological mechanism underlying Alzheimer's disease, which is considered the most common disorder across the globe. It can cause by a disbalance between ROS and antioxidant molecules. The antioxidative properties of catechin are well-established by various "*in vitro*, *in vivo*, and physical methods". Catechin produced beneficial effects on the molecular mechanisms involved in

extracellular matrix degradation, angiogenesis, multidrug resistance, and regulation of cell death in cancers and related disorders.[41]

Literature supporting data regarding Antioxidant benefits in CVDs

Oxidative damage to low-density lipoprotein, which makes some change in the vessel both structurally and functionally, is responsible for the development of atherosclerosis.[42] This LDL generates free radicals upon improper beta-oxidation and produces reactive oxygen species, creating cardiovascular disease, cancer, immunological problems, etc. It was found that cardiovascular risk factors with oxidative stress and antioxidant therapy for treating cardiovascular diseases in clinical trials.[43] Potent antioxidant and neuro-protective free-radical scavenger, Stilbazulenyl nitrone (STAZN), are marked cardio-protection when given immediately before reperfusion.[44] Some vitamins like Vitamin E and Vitamin C supplementation have antioxidant properties and provide cardiovascular benefits in a specific diabetic sub-population. As the literature suggests, many herbal medicines have antioxidative properties. They are used to treat cardiovascular diseases mediated by ROS. They are capable of scavenging free radicals, inhibit lipid peroxidation, and enhance the activity of SOD.[45] Polyphenol obtained from natural sources carries antioxidative property with it and contribute to health promotion.[46] Naturally occurring drugs have antioxidative properties and are beneficial for cardiovascular disease, e.g., Resveratrol-a natural poly-phenolic compound, protective against oxidative damage in cardiovascular disease.[47] Antioxidant agents may have a role in the prevention and treatment of hypertension.[48] Combination of drugs is not new in the pharmaceutical field. Combining antioxidant with cardiovascular drugs may increase drug effect through acting enzymatically, scavenging internally formed free radicals, or any other mode of action that will produce synergistic action and a better therapy against CVD.[49] Advanced analytical instruments like UPLC-ESI-MS/MS and modern scientific methods can simultaneously be utilized for drug's bio-analytical and pharmacokinetic parameter studies.[50] Research animals are valuable tools in developing therapeutic interventions and understanding a disease's pathophysiology. The advantages of developing an animal model to study hypertension and atherosclerosis are that an animal model is easily manageable, comparable with human models, and we can easily control environmental factors.[51] The induction of hypertension by various animal models is a challenging task. Some of the established methods are there. Still, selecting an animal model depends upon the type of research and the suitability of the study.[51] From the literature review, we found that many natural compounds possess antioxidative properties. Due to their medicinal value reduces free radicals in our bodies and protects us from some severe oxidative stress-mediated complications. Oxidative stress is one of the major causes of cardiovascular diseases. Current cardiovascular medications may produce complications like Alzheimer's disease in long-term use. Combining safer cardiovascular drug with a suitable antioxidant may synergize if we formulate a combination therapy. Hence, we can expect a better cure for cardiovascular complications.

Role of Antioxidant in Cardiovascular Disease Management

As part of a natural defence system, antioxidants can mitigate the activity of free radicals and other oxidative species that have a role in developing atherogenesis.[52] A good number of works from the literature have suggested some advantageous effects of foods rich in antioxidant and specific antioxidants on the risk of cardiovascular diseases and stroke.[53] Oxidative functions also contribute positively to the health of the cell by their participation in biosynthesis, detoxification, and cellular signal, energy metabolism.[54-56] A balance between pro-oxidants and antioxidant defence systems is essential to maintain good health.[35,39,55] Synthetic antioxidants are reported to be dangerous for human health recently. Hence an antioxidant obtained from natural sources should be used for medicinal purposes.

Natural sources of antioxidants (Table 2)

Some of the drinks containing maximum antioxidants are: (Herbal tea, Coffee, Beet juice, Pomegranate juice, Acai juice, Coconut water, green juice). From some of the scientific studies, it has been found that artificial antioxidants like; "Butylated Hydroxy-anisole (BHA), Butylated Hydroxy-toluene (BHT), Tertiary Butyl hydroquinone (TBHQ), Propyl Gallate)" possesses several adverse effects, hence toxic for human use.[57-58] Natural oxidants are good for medicinal use as they are suitable for biological systems and doesn't produce unwanted adverse effects.

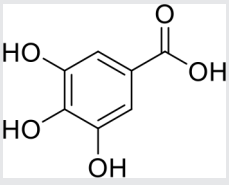
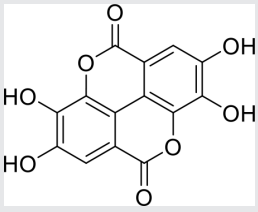
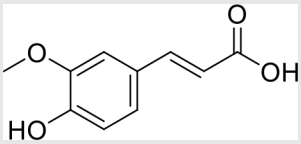
List of natural antioxidants and their properties (Table 3).[81-117]

Gallic acid can become a suitable candidate as, it is having antioxidative property, anti-hypertensive action along with other health benefits. Gallic acid shows cardioprotective activity through its antihyperglycemic, anti-lipid peroxidative, and antioxidant effects. In an

Table 2: Antioxidants obtained from natural sources.

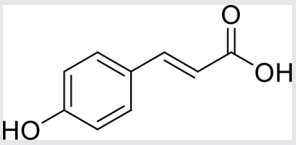
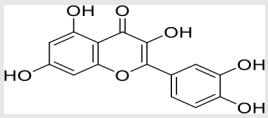
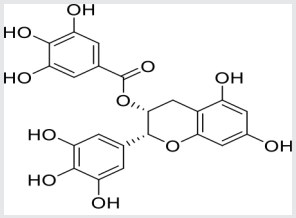
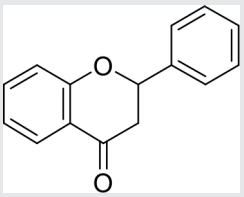
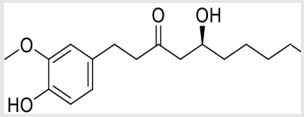
Common name	Part used	Chemicals used as Anti-oxidant
Turmeric	Leaf	curcumin, beta-pinene, camphene, eugenol, beta-sitosterol
Ashwagandha	Root, leaf, seed	steroidal lactone, withanolides, glycine, withane
Chirayita	Whole plant	xanthones, mangiferin, swertinin, chirantin, arginine
Makoi	Leaf	poly-phenolic compounds, flavonoids, steroids
Safed-Chandan	Heartwood bark	volatile oil, santalol, sitosterol
Babchi	Seed	monoterpene oil
Tulsi	Leaf	volatile oil, thymol
Karela	Root, leaf, fruit, seed	stearic acid, triterpene, glycosides
Mango	Root, leaf, fruit	cyanogenetic glycosides, Mangiferin, gallic and ellagic acid, quercetin
Mulethi	Root	glycyrrhizin, flavonoids, liquiritin, rhamnol
Fennel	Fruit oil	volatile oil, fenchone, estragole, limonene, anethole
Amla	Fruit	vitamin C, polyphenols
Carrot	Root	carotenes, glycosides, flavonoids, quaternary bases
Akasha Bela	Stem	flavonoids, dulcitol, bergenin, coumarins, glycosides

Table 3: List of natural antioxidants and their properties.

Classification	Name and structure	Chemical details	Pharmacological actions	Adverse effect
Class – Polyphenols **Subclass –** Phenolic acid (hydro-benzoic acid)	**Name –** Gallic acid (GA)[81-86]  **IUPAC name:** 3,4,5-trihydroxy benzoic acid	M.F- $C_7H_6O_5$ M.W: 170.12 g/mol B.P- 501.1±50.0 °C at 760 mmHg M.P - 260°C Solubility- Methanol, ethanol, water, DMSO, and dimethylformamide (DMF)	Gallic acid can scavenge free radical hence antioxidant in nature. GA is being used as anti-microbial, anti-carcinogenic, anti-mutagenic, anti-angiogenic. It also treats cancer, lipid-related diseases, microbial infections, etc.	No such adverse effects
Class – Polyphenols **Subclass –** Phenolic acid (hydro-benzoic acid)	**Name –** Ellagic acid (EA)[87-90]  **IUPAC name:** 2,3,7,8-Tetrahydroxy-chromeno[5,4,3-cde] chromene-5,10-dione	M.F- $C_{14}H_6O_8$ M.W: 302.197 g/mol B.P- 796.5±60.0 °C at 760 mmHg M.P - 360°C Solubility- soluble in DMSO, Less soluble in water and methanol.	Natural sources include green tea, pomegranate, strawberries, blackberries, raspberries, walnuts, and the bark of eucalyptus. anti-oxidant, anticarcinogenic, antifibrosis, anti-plasmodial activity, and chemo-preventive activity.	No such adverse effects were observed.
Class – Polyphenols **Subclass –** Phenolic acid (hydroxycinnamic acid)	**Name –** Ferulic acid[91-93]  **IUPAC name:** (2*E*)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoic acid	M.F- $C_{10}H_{10}O_4$ M.W: 194.18 g/mol B.P-372.3°C M.P- 168-171°C Solubility- soluble in organic solvents such as ethanol, DMSO, and dimethylformamide (DMF).	Ferulic acid is a free radical scavenger. It inhibits enzymes that catalyze free radical generation and enhances scavenger enzyme activities, melanogenesis, enhances angiogenesis, and accelerates wound healing.	Few side effects like: redness, rashes

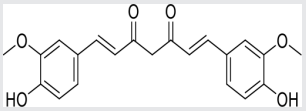
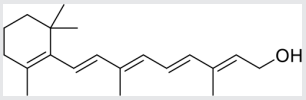
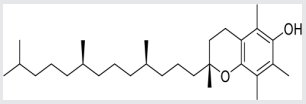
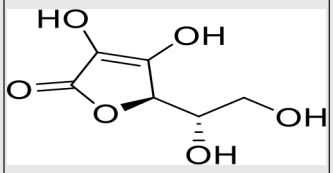
continued...

Table 3: Cont'd.

Classification	Name and structure	Chemical details	Pharmacological actions	Adverse effect
Class – Polyphenols **Subclass** – Phenolic acid (hydroxycinnamic acid)	**Name –** p- coumaric acid [94-95]  **IUPAC name**: 2*E*)-3-(4-Hydroxyphenyl) prop-2-enoic acid	M.F- $C_9H_8O_3$ M.W: 164.0473 g/mol M.P- 210 to 213 °C (410 to 415 °F; 483 to 486 K) Solubility- soluble in organic solvents such as ethanol, DMSO, dimethylformamide (DMF)	p-Coumaric acid (p-CA) phenolic compound found in mushrooms, cereals, fruits, and vegetables. It has antiviral, anti-oxidant, anti-microbial, anti-inflammatory, anti-cancer, immunomodulatory, anti-mutagenic, antidiabetic, and anti-hyper-lipidemic properties.	No-toxic Effects in animal experiments and human studies.
Class – Polyphenols **Subclass** – Flavonoids	**Name –** Quercetin[96-99]  **IUPAC name**: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chrome-4-one	M.F- $C_{15}H_{10}O_7$ M.W: 302.236 g/mol B.P- 642.00 to 643.00°C. M.P- 316°C. Solubility- (2 mg/ml in ethanol), (30 mg/ml in DMSO and DMF) sparingly soluble in aqueous buffers.	Beneficial against many diseases, including cancer. It prevents lipid peroxidation, acts as anti-aging due to free radical scavenging activity.	Headache, Numbness and tingling, Shortness of breath, Nausea and vomiting, Kidney damage.
Class – Polyphenols **Sub class** – Flavonoids	**Name –** Epigallocatechin 3 gallate (EGCG)[100-104]  **IUPAC name**: [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl) chroman-3-yl] 3,4,5 trihydroxybenzoate	M.F- $C_{22}H_{18}O_{11}$ M.W: 458.372 g/mol M.P- 140-142°C B.P- 909.1±65.0 °C at 760 mmHg Solubility - in water	Epigallocatechin-3-gallate gives beneficial health effects to ameliorate metabolic diseases. It reduces free radical-induced lipid peroxidation.	Nausea, heartburn
Class – Polyphenols **Subclass** – Flavonoids	**Name –** Flavanones[105-106]  **IUPAC name:** 2,3-dihydroflavone	M.F- $C_{15}H_{12}O_2$ M.W: 224.25 g/mol M.P- 77.0°C B.P- 386.2±42.0°C at 760 mmHg Solubility - in water	Citrus fruits contain a high number of flavanones. Functional hydroxyl groups in flavonoids mediate Anti-oxidative effects. They act by scavenging free radicals or by chelating metal ions.	Nausea, headache, tingling of extremities in some people
Class – Polyphenols **Subclass** – Flavonoids	**Name –** Gingerol[107-109]  **IUPAC name**: (S)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone	M.F- $C_{17}H_{26}O_4$ M.W: 294.38 g/mol B.P- 453.0±35.0 °C at 760 mmHg Solubility-ethanol, DMSO, and dimethylformamide (DMF)	The isolated anti-oxidants are of two groups; gingerol-related compounds and di-aryl-heptanoids. They scavenge free radicals, hence are anti-oxidants.	Cardiac arrhythmias (if overdosed) Abdominal discomfort, dermatitis the central nervous system, depression,

continued...

Table 3: Cont'd.

Classification	Name and structure	Chemical details	Pharmacological actions	Adverse effect
Class – Polyphenols **Subclass** – Flavonoids	**Name –** curcumin[110-111]  **IUPAC name**: (1*E*,6*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione	M.F-$C_{21}H_{20}O_6$ M.W: 368.38 g/mol B.P-591.4 °C Solubility-water, high temp in acids	Curcumin is a highly potent lipid-soluble anti-oxidant. It acts through its pro-oxidant/anti-oxidant effects. Due to its free radical scavenging property, it aborts ROS-mediated tumours.	constipation, dyspepsia, diarrhoea, distension, gastroesophageal reflux, vomiting, yellow stool, and stomach pain.
Class – Vitamin **Subclass** – Fat-soluble	**Name –** Vitamin-A[112-113]  **IUPAC name**: (2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl) nona-2,4,6,8-tetraen-1-ol	M.F- $C_{20}H_{30}O$ M.W: 286.5 g/mol B.P- 137-138°C M.P - 63.5°C Solubility- Readily soluble in ether, acetone, fats, oils, *and* chloroform. Soluble in alcohol. Insoluble in water.	Vitamin A acts as antioxidant due to the hydrophobic chain of polyene units. That is capable of neutralizing radicals, quenching singlet oxygen, and combine with stabilizing peroxyl radicals.	Sleepiness, vomiting, vision problems, diarrhoea, loss of consciousness, headache, increased risk of pneumonia.
Class – Vitamin **Subclass** – Fat-soluble	**Name –** Vitamin-E[114-115]  **IUPAC name**: (2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol	M.F- $C_{50}H_{29}O_2$ M.W: 430.7 g/mol M.P- 3 °C Solubility-In pure water, these vitamins have very low solubility 20.9 mg/L.	The mechanism of vitamin E's anti-oxidant effect is in the termination of lipid peroxidation	Blood-thinning and stroke
Class – Vitamin **Subclass** – water-soluble	**Name –** Vitamin-C[116-117]  **IUPAC name**: (*R*)-3,4-Dihydroxy-5-((*S*)-1,2-dihydroxyethyl) furan-2(5*H*)-one	M.F- $C_6H_8O_6$ M.W: 176.124 g·mol^{-1} B.P-553 °C M.P – 190°C Solubility- water, ethanol	Vitamin C scavenges ROS and protect proteins from alkylation by electrophilic lipid peroxidation products. Used as an anti-oxidant.	NA

acute oral toxicity study, at a dose of 5000 mg/kg any signs of lethal toxicity were not observed. And in a subacute toxicity study, 1000 mg/kg was found to be non-toxic, indicating the safety of gallic acid.[59] It is predominantly found in all individual plants Amla (*Emblica officinalis),* Baheda (*Terminalia belerica),* Haraida (*Terminalia chebula)* which used in a very famous Ayurvedic formulation TRIPHALA.

HYPOTHESIS FOR SYNERGISTIC EFFECTS OF COMBINED DOSAGE FORM

Safer Anti-hypertensive Drug

Numerous side effects occur through different anti-hypertensive drug treatments (Table 1). AT1 receptor blockers are comparatively safer among all classes, showing fewer short-term and almost no long-term adverse effects. The modulation in the heart after myocardial infarction (MI) is facilitated by the renin-angiotensin system blocking at the AT1 receptor site, without any prior change of angiotensin converting enzyme, leading to reduction of oxidative stress.[60] Specifically, blocking the AT1 receptor provides a positive health benefit, as AT2 mediated actions are antagonistic to AT1. Over three years of observational study, hypertensive participants demonstrated executive function, worse baseline memory, and faster memory decline. Unless they were ARB users, follow-up with normotensive subjects showed normal memory compared to those taking other anti-hypertensive drugs.

As compared to other anti-hypertensive drug users Blood brain barrier (BBB)-crossing ARBs (valsartan, telmisartan, candesartan) users were observed with superior memory performance over the time. BBB-crossing medications (ARBs or ACEIs) give a better list-learning memory performance than all other groups, including normotensive subjects. These findings demonstrate that ARBs, especially BBB-crossing variety, are associated with more remarkable memory preservation than other anti-hypertensive medications.[61] Hence, ARBs are comparatively safer.

Significance of antioxidant along with anti-hypertensive drugs in management of CVDs

ARBs act on AT1 receptor, and antioxidants act on those check points where ROS generates.

Hence, both the drugs may act synergistically as shown in Figure 2 and 3.

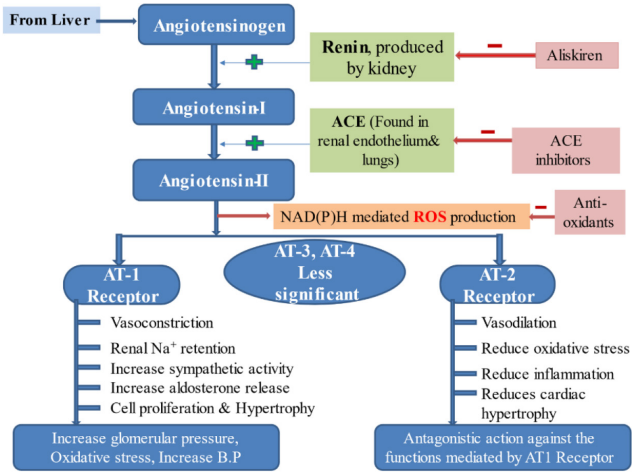


Figure 2: RAAS system and mechanism of action for anti-hypertensive drugs at different checkpoints. (-) is blocking action, (+) is promoting action).

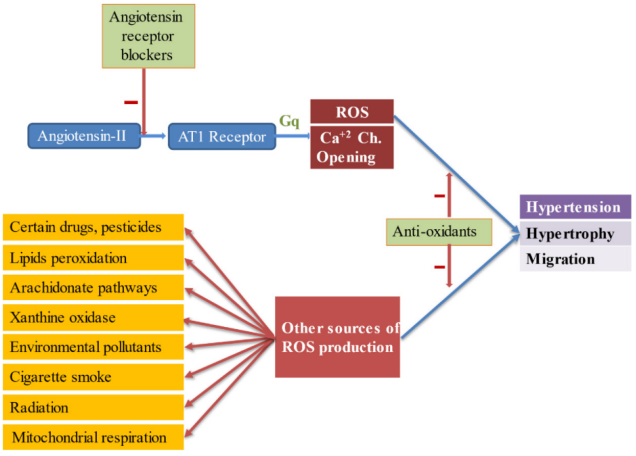


Figure 3: Combined effect of AT1 Receptor blocker along with anti-oxidants. (-) is blocking action, (+) is promoting action.

DISCUSSION

Based on the literature, we found that some antioxidants give excellent results in treating cardiovascular disease. They reduce the chance of cardiovascular risk up to a significant extent. Besides cardiovascular disease, they are having beneficial effects against other ROS-mediated diseases. A robust body of comprehensive data supports AT1 Receptor blockers as effective drugs, well-tolerated among other anti-hypertensive medicines. They have minimal long-term side effects. Hence, studies on combined therapy of AT1 Receptor blockers with antioxidant should be done, which will decrease the occurrences of cardiovascular risk in comparison with monotherapy of cardiovascular drug medications.

CONCLUSION

Several studies suggest the anti-hypertensive properties of antioxidative drugs, but no successful formulation has been reported yet. Several anti-hypertensive drugs have been invented and prescribed by physicians. On long-term use, several side effects and adverse effects like; Raynaud's phenomenon, sexual disturbances, bronchospasm, Alzheimer's disease are common. If hypertension develops in the early stage (age 25-30 years), the patient will have to take medication for a lifetime. In such cases, dose-dependent adverse effects are unavoidable. This study focuses on combining a safe and suitable antioxidant(s) with existing anti-hypertensive drug(s) (from the literature survey, we found AT1 receptor blockers have comparatively fewer long-term side effects) to get a synergistic effect of both antioxidant and anti-hypertensive drugs. Reports from the literature explain a complete study on major causes of cardiovascular disease development, the role of ROS for cardiovascular disease initiation and further development, currently available treatments and associated short-term and long-term complications and how antioxidants can successfully treat the health hazard. Based on the above facts, we can have a bright scope to develop a new drug regimen and innovative formulations that can prove to be safer and more effective fixed-dose formulation as compared to existing marketed formulations.

ACKNOWLEDGEMENT

Authors are thankful to Head, Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi for providing necessary facilities.

CONFLICT OF INTEREST

The authors declare that, there is no conflict of interest.

ABBREVIATIONS

CVD: Cardiovascular Disease; **CVDs:** Cardiovascular Drugs; **HOPE:** Heart Outcomes Prevention Evaluation; **ROS:** Reactive Oxygen Species; **ROO·:** Lipid radicals; **HO^{-}:** Hydroxyl radical; **O_2^{-}:** Superoxide anion; **NO:** Nitric oxide; **HClO:** Hypochlorous acid; **H_2O_2:** Hydrogen peroxide; **$ONOO^{-}$:** Peroxynitrite; **ACE:** angiotensin-converting enzyme; **AT1:** Angiotensin-1 Receptor; **AT2:** Angiotensin-2 Receptor; **NADPH:** Nicotinamide Adenine Dinucleotide Phosphate; **CMSRF:** Cardio-Metabolic Syndrome Risk Factors; **SOD:** Superoxide Dismutase; **LDL:** Low Density Lipoprotein; **STAZN:** Stilbazulenyl Nitrone; **UPLC-ESI-MS/MS:** Ultrahigh Performance Liquid Chromatography-Electrospray Ionization-Mass Spectroscopy/Mass Spectroscopy; **BHA:** Butylated Hydroxy-anisole; **BHT:** Butylated Hydroxy-toluene; **TBHQ:** Tertiary Butyl hydroquinone; **MI:** Myocardial Infarction; **ARBs:** Angiotensin Receptor Blockers; **ACEIs:** Angiotensin Converting Receptor Blockers; **BBB:** Blood Brain Barrier.

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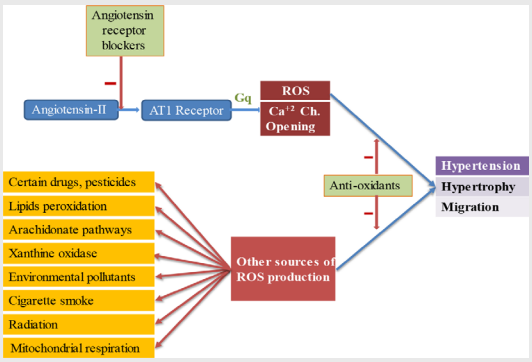
PICTORIAL ABSTRACT



Combined effect of AT1 Receptor blocker along with anti-oxidants. (-) is blocking action.

SUMMARY

In this review article the focus has been shifted from conventional cardiovascular treatment towards a new dimension of health care. Brief elaboration of problems associated with regularly used marketed anti-hypertensive formulations is mentioned. Based on comprehensive literature review, we have tried to find out safest anti-hypertensive drug having very less long-term side effects. Besides that, some health benefits of antioxidants of natural source have also been excavated from literatures of time-to-time findings. A proposal for combining both the drugs in a single formulation to get synergistic effect have been established with adequate justifications. Undoubtedly the findings are going to be a revolutionary change in field of medicine and will be proved beneficial for human kind in near future.

About Authors

Swadesh Kumar Pattanik: He has completed Master of Pharmacy (Pharmaceutical Quality Assurance) from Birla Institute of Technology, Mesra in the Academic year (2017-19). He is currently pursuing Ph.D. degree in Pharmacy from Birla Institute of Technology, Mesra. He has more than 5 numbers of conferences in his research credential.

Kishanta Kumar Pradhan: He is working as an Assistant Professor at the Department of Pharmaceutical Sciences and Technology, BIT Mesra. He is actively involved in the following research fields: Method development & validation, Impurity profiling and metabolite studies of drug and drug products as per ICH guidelines. Analytical profiling of natural products by advanced instrumental techniques and studies on different activities (Anticancer, Antidiabetic etc.) He has more than 30 numbers of research publications and 22 numbers of Conferences in his research credential.

Cite this article: Pattanik SK, Pradhan KK. The Effect of Antioxidants and Cardiovascular Drugs in the Treatment of Cardiac Diseases. Indian J of Pharmaceutical Education and Research. 2023;57(1):1-14.