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Cardiovascular Diseases and Role of Medicinal Plants as a Re-Emerging Health Aid

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ABSTRACT

Cardiovascular disorders like heart failure, hypertension, myocardial infraction, ventricular fibrillation and atrial fibrillation are affecting millions of people every year. Reactive oxygen metabolites (ROMs) and reactive nitrogen metabolites (RNMs) play major role in damaging basic bio-molecules (protein, DNA) ultimately causing cardiovascular disorders, ageing etc. Although human endogenous anti-oxidants antagonize the damaging effect of reactive species but many a times they are not sufficient in neutralizing them. Demand of natural products and that too from plants as a health supplement is increasing day by day in all parts of the world. Cardiac glycosides especially cardenolides and its congeners have shown to be effective in variety of heart ailments. Many others plants like *Berberis aristata, Polygonatum sibricum, Nigella sativa* and groups of compounds like flavonoids have been explored as wonderful medicines for heart disorders. The current review centers on brief detail of plants and their active compounds in association with cardiovascular diseases. Further studies are needed for improving the clinical indications and the efficiency of these plants and compounds.

INTRODUCTION1

Cardiovascular Disorders: An Insight

Ever since William Harvey defined an animal's heart as "the supreme ruler of everything within them, the sum of their microcosm," in *De Motu Cordis* in 1628, the heart has been one of the most widely studied organs of the body and fortunately so, given that heart disease is the world's leading cause of death (1). Despite of incredible advances in the diagnosis and treatment of cardiovascular diseases, the incidence, prevalence, morbidity and mortality resulting from these diseases continue to escalate Cardiovascular disease (CVD) encompasses the entire spectrum of heart disease, ranging from coronary artery disease (CAD), stroke, hypertension, elevated cholesterol, angina and acute myocardial infarction, an ultimate insult to the body. Each year, around 8 million people die from heart attacks and many millions more suffer from, and eventually succumb to heart diseases such as congestive heart failure (CHF) and arrhythmia. Global figures are rising, yet calculations suggest that this number could be slashed by around 50 per cent. In United States, heart failure afflicts more than 4.5 million patients and approximately 4, 00, 000 new cases are diagnosed annually (2). Both the incidence and prevalence of heart failure increase dramatically with age. The prevalence of heart failure nearly doubles with each decade of life after the age of 50. Heart failure represents a significant cause of mortality in the senior population. Consequently, heart failure has become one of the most expensive health problems around the world (3).

However, diseases would be offset to some degree as the world's population ages, diets become more fat-laden and lifestyles more sedentary, as all these factors are detrimental to a healthy heart (4). Although scientific study of the heart began four centuries ago, the past few decades have seen a paradigm shift in research. We are now able to monitor the process of contraction and relaxation that underlies the gross function of the heart at close quarters by tracking the movement of calcium and other ions within myocytes. Ultra structural examination of ion channels is revealing how the regular rhythmic beating of the heart can become disordered. Thus, as with all diseases, understanding the processes involved at the molecular and genetic level is enabling us to make in roads in preventing and treating heart disease (5).

Knowledge about the physiology, structure and molecular biology of cardiac ion channels/ion transporters has grown substantially in recent times. The fruitful combination of herbal drugs with state-of-the art has advanced the treatment and understanding of many cardiovascular disorders (6).

The rapid progress in this field holds the promise of providing a detailed understanding of the basic determinants of different cardiac disorders in the very near future and it may then be possible to target the development of the drug. Progress in phytopharmacology might facilitate prerequisites for more individualized therapy. A thorough screening is always an essential part in drug discovery, which may possibly identify natural products at use which will benefit in most of cardiac therapy. Plant research is at the forefront of using these new approaches to find an effective and, perhaps even more important, safe pharmacological treatment for cardiovascular disorders. The impressive advances in natural drug discovery and the basic science of cardiac disease will most likely over the next decade translate into significant impact on the clinical therapeutic opportunities available for treatment of

cardiovascular diseases.

TYPES OF CARDIOVASCULAR DISORDERS

Heart Failure

Heart failure is a pathophysiologic state in which the heart, via an abnormality of cardiac function, fails to pump blood at a rate commensurate with the requirements of the metabolizing tissues and pumps only from an abnormally elevated diastolic filling pressure. Heart failure may be caused by myocardial failure but may also occur in the presence of near-normal cardiac function under conditions of high demand (7).

Heart failure is being increasingly recognized all over India (8), Hypertension and ischemic heart disease are the two cardinal causes of heart failure in developing countries like India. Over the years, a voluminous amount of literature has accumulated regarding various facets of hypertensive heart failure. Despite this, the risk and mechanisms of heart failure in patients with hypertension is not completely understood. Further, due to the common coexistence of coronary artery disease (CAD) and hypertension in the population, the relative contributions of CAD and hypertension to heart failure have been difficult to disentangle (9).

In terms of incidence, prevalence, morbidity, and mortality, the epidemiologic magnitude of congestive heart failure (CHF) is staggering. In the United States, the estimated annual cost of heart failure is $60 billion; the estimated annual cost of inpatient care of patients with CHF is $23 billion. Approximately 1 million US hospital admissions per year are attributable to a primary diagnosis of acutely decompensated heart failure. CHF is a worldwide problem, but few accurate financial data are available. As discussed elsewhere, the most common cause of CHF in industrialized countries is ischemic cardiomyopathy.

Despite recent advances in the management of patients with heart failure, morbidity and mortality rates remain high, with an estimated 5-year mortality rate of 50%. Assigning figures for inpatient mortality rates is difficult because the causes and the severity of heart failure vary considerably. The most recent estimates of inpatient mortality rates indicate that death occurs in up to 5-20% of patients (7, 10).

Hypertension

Hypertension is one of the most common diseases afflicting humans throughout the world. Because of the associated morbidity and mortality and the cost to society, hypertension is an important public health challenge. Over the past several decades, extensive research, widespread patient education, and a concerted effort on the part of health care professionals have led to decreased mortality and morbidity rates from the multiple organ damage arising from years of untreated hypertension. Hypertension is the most important modifiable risk factor for coronary heart disease (the leading cause of death in North America), Stroke (the third leading cause in United States), congestive heart failure, end-stage renal disease, and peripheral vascular disease.

Since 1942, there have been several small and large population-based studies on hypertension. A recent publication found no less than 34 references. A meta-analysis showed an increase in the prevalence of hypertension over the years, especially of systolic levels, more in urban than in rural areas. Recent studies using the criterion of 140/90 mmHg as the cut-off point for hypertension have shown a prevalence of 10%– 30.9% in urban areas, while earlier reports since 1950 showed a prevalence of 1%–3%. The reason for the increasing trend has been attributed to the same factors as those for CAD. Hypertension appears to be the most important risk factor for the development of CAD throughout India. In a study in Delhi involving 8000 subjects, the most important risk factor for CAD was hypertension in over 50% of subjects, young and old, followed by smoking and diabetes. This has also been seen at AIIMS, New Delhi and CMC, Vellore (8).

The National High Blood Pressure Education Program (NHBPEP) has reported estimates of hypertension prevalence in United States. The hypertension survey was conducted from 1989-1994, and actual blood pressure and self-reported information was used. The data estimated 43.3 million adults with hypertension in November 1991. Overall, approximately 20% of the world's adults are estimated to have hypertension. The 20% prevalence is for hypertension is defined as blood pressure in excess of 140/90 mm Hg. The prevalence dramatically increases in patients older than 60 years (11).

In the Framingham Heart Study, the age-adjusted risk of congestive heart failure was 2.3 times higher in men and 3 times higher in women when highest blood pressure was compared to the lowest. Multiple Risk Factor Intervention Trial (MRFIT) data showed that the relative risk for coronary heart disease mortality varied from 2.3-6.9 times higher for persons with mild-to-severe hypertension compared with normal blood pressure.

A progressive rise in blood pressure with increasing age is observed. The MRFIT survey reported that the prevalence of hypertension grows significantly with increasing age in all sex and race groups. The age-specific prevalence was 3.3% in white men (aged 18-29 years); this increased to 13.2% in the group aged 30-39 years. The prevalence further increased to 22% in the group aged 40-49 years, to 37.5% in the group aged 50-59 years, and to 51% in the group aged 60-74 years (12).

Myocardial Infarction

Myocardial Infarction (MI) is irreversible necrosis of heart muscle secondary to prolonged ischemia. This usually results from an imbalance of oxygen supply and demand. The appearance of cardiac enzymes in the circulation generally indicates myocardial necrosis. MI now is considered, more appropriately, part of a spectrum referred to as Acute Coronary Syndromes (ACSs), which also includes unstable angina and non–Q-wave MI (NQWMI). Patients with ischemic discomfort may or may not have ST-segment elevation. The majority of those with ST-segment elevation will develop Q waves. Those without ST elevation ultimately will be diagnosed for unstable angina or NQWMI on the basis of the presence of cardiac enzymes. MI may lead to impairment of systolic or diastolic function and to increased predisposition to arrhythmias and other long-term complications (13).

Cardiovascular diseases cause 12 million deaths throughout the world each year, according to the third monitoring report of the World Health Organization, 1991-93. They cause half of all deaths in several developed countries and are one of the main causes of death in many developing countries; they are the major cause of death in adults everywhere (14).

Specific mortality data ideal for making comparisons with other countries are not available in India. This is due to inadequate and inappropriate death certification, and multiple concurrent causes of death. The annual surveys conducted by the Registrar General of India cover about 0.5% of rural deaths in India. The subjects covered under "circulatory diseases" include MI. The figures published by the World Health Organization (WHO), drawn mainly from this source and for what they are worth, show a much higher prevalence in India than in many other developing countries (8).

Beginning in the 1960s through the 1990s, investigators in India have estimated the prevalence of CAD in several urban and rural populations. Overall, prevalence estimates obtained from the studies performed in the last decade range between 7.6% and 12.6% for urban populations, and 3.1% to 7.4% for rural populations. The difference in prevalence between the urban and rural populations has been accounted for by the differing prevalence of risk factors in these two groups. The largest study, by far, was the one by Chadha *et al.*, who collected data from over 13500 urban dwellers in Delhi. Using clinical and ECG criteria, the prevalence rate of CAD was 9.7%, but major Q waves were seen in only 80 (1.4%) of the 5621 ECGs obtained (15).

In a rural population in Rajasthan, it was found a 3.5% prevalence of CAD. The prevalence of major Q waves was, however, very low, being present in only 2% of the highest risk subgroup (16). In an analysis of the available data, it was found that the prevalence of CAD had increased significantly over the last four decades. However, this inference has to be weighed against the potential confounding influences of the different methodologies used and the various ethnic groups studied (17). More recently, in an urban population in south India, it was found a prevalence of 11%. Again, the prevalence of documented MI or major Q waves was only 2.5% (18). It is unclear whether these differences are due to the small sample sizes or the different demographic characteristics of the populations studied. Another more plausible explanation is that the epidemiologic transition has not yet had its full impact among urban Indians.

Myocardial disease is the also a leading cause of death in the United States; approximately 500,000-700,000 coronary-artery–related deaths occur each year. Ischemic heart disease is the leading cause of death worldwide. Approximately 6.3 million deaths due to heart disease occurred in 1990 worldwide, which represents 29% of all deaths. The prevalence of coronary artery disease (CAD) is increasing rapidly in non industrialized countries (19).

Ventricular Fibrillation

Ventricular fibrillation (VF) is rare in the pediatric population, and, when it does occur, VF is usually a degeneration of other malignant arrhythmias (e.g, ventricular tachycardia [VT]). In adults, VF is preceded by VT in approximately 80% of cases. Primary VF is uncommon in children. In a study of pediatric out-of-hospital arrests, VF was the initial rhythm in 19% of cardiac arrests (20). Causes of VF varied and included medical illness, overdose, drowning, and trauma; only 2 of 29 patients had congenital heart disease. Thus, VF is not an unusual terminal rhythm in cardiac arrest resulting from a variety of causes.

The incidence of VF from all causes is very low in the pediatric population. In studies of pediatric cardiac arrests, VF was the first identified rhythm in 6-19% of patients, with asystole as the most frequent rhythm identified first (21).

Atrial Fibrillation

Atrial fibrillation (AF) is a common arrhythmia and a significant public health problem in the United States, affecting 2.2 million Americans and almost 5% of the population older than 69 years. Prevalence of AF increases with advancing age. Data from the Framingham heart study show that AF is associated with a 1.5- to 1.9-fold higher risk of death, which may be due to thromboembolic stroke. While patients can be asymptomatic, many experience a wide variety of symptoms including palpitations, dyspnea, fatigue, dizziness, angina, and congestive heart failure (CHF). In addition, the arrhythmia can be associated with hemodynamic dysfunction, a tachycardia-induced cardiomyopathy, and systemic embolism (22).

Overall, approximately 15-25% of all strokes in the United States (75,000/year) can be attributed to AF. Known risk factors include male sex, valvular heart disease (rheumatic valvular disease), CHF, hypertension, and diabetes. Additional risk factors, such as advanced age and prior history of stroke, diabetes, and hypertension, place patients with pre existing AF at even higher risk for further such as stroke.

AF affects 2.2 million Americans, it can occur without any other medical conditions, as it does in 10-15% of individuals (lone AF); however, AF is associated more frequently with hypertension; organic heart disease; CHF; ischemic heart disease; and valvular, dilated, hypertrophic, restrictive, and congenital cardiomyopathies (22).

OXIDANTS, ANTI-OXIDANTS: ROLE AND SIGNIFICANCE IN CARDIOVASCULAR SYSTEM

There is an explosion of global awareness concerning increasing imbalances in natural ecosystem; therefore various measures are being taken up to correct the root cause of the imbalance. Human beings constantly struggle against changing environmental conditions to maintain optimum health and vigour throughout their life. The human body depends on the enormous holistic interaction between internal and external factors. When this interaction is in a state of equilibrium, man enjoys health and when it fails, either due to internal deficiency or hostile environmental factors, the balance is disturbed leading to disharmony and disease.

It is increasingly being realized about body's natural ecosystem that majority of disease/disorders are mainly due to the imbalance between pro-oxidant and anti-oxidant homeostatic–phenomenon in the body. Pro oxidant conditions dominate

either due to the increased generation of free radicals and their poor quenching into the body.

Chemical compounds and reactions capable of generating potential toxic oxygen species/free radicals are referred to as pro–oxidants. Free radicals are highly reactive molecules generated predominantly during cellular respiration and normal metabolism. Imbalance between cellular production of free radicals and ability of cells to defend against them is referred to as Oxidative Stress (OS). On the other hand, compound and reactions disposing these species, scavenging them, suppressing their formation are called anti-oxidants (23).

Free radicals can be defined as chemical species possessing an unpaired electron which is formed by hemolytic cleavage of covalent bond of a molecule, by the loss of a single electron to a normal molecule. Most of the molecular oxygen consumed by aerobic cells during metabolism is reduced to water by using cytochrome oxidase in mitochondria (24).

However, when oxygen is partially reduced it becomes 'activated' and reacts readily with variety of biomolecules. This partial reduction occurs in one electron steps, by addition of one, two and four electrons to O_2 which leads to successive formation of reactive oxygen species (ROS). The oxidants /free radicals are species with a very short half life, high reactivity and damaging activity to macromolecules like proteins, DNA, and lipids (25).

These species may be either oxygen derived Reactive oxygen metabolites (ROMs) or Reactive nitrogen metabolites (RNMs). The oxygen derived includes O_2^- (Superoxide), OH (Hydroxyl), HO_2 (hydro peroxyl), ROO (peroxyl), RO (Alkoxyl) as free radicals and H_2O_2 (Hydrogen peroxide), HOCl (hypochlorus acid), O_3 (ozone) and $^1O_2$ (singlet oxygen) as non-radicals. Similarly nitrogen derived oxidant species are mainly NO (Nitric Oxide), ONOO (Peroxynitrite), NO_2 (nitrogen dioxide) and dinitrogen trioxide.

Reactive Oxygen Metabolites (ROMs)

The exogenous source of ROMs include electromagnetic radiation , cosmic radiation, cigarette smoke, car exhaust, UV light, ozone and low wavelength electromagnetic radiations. Similarly the endogenous sources of ROMs are mitochondrial electron transport chain, respiratory burst by phagocytes, beta oxidation of fat in peroxisome, auto oxidation of amino acids, catecholamines, heamoglobin, and ischemia reperfusion injury, overproduction of O_2 takes place in various chronic anti inflammatory cases, induced by drug toxin, stress, tissue injury and heavy exercises (26).

$$O_2 + H_2O \longrightarrow H_2O_2$$

The production of O_2 and H_2O_2 in presence of metal catalyst may lead to the formation of most reactive ·OH. O_2 is reduced to H_2O_2 by catalytic activity of SOD (super oxide dismutase). Accumulation of O_2 and H_2O_2 results in the formation of ·OH which oxidizes lipids giving rise to lipid peroxidation (LPO). H_2O_2 is known to cause DNA breaks in intact cells and purified DNA. Malionaldehyde (MDA) which is a major end product and an index of LPO, cross links DNA and proteins and nucleotides on the same and opposite strands. MDA is a major reactive aldehyde resulting from the peroxidation of biological membrane polyunsaturated fatty acids. It is secondary product of LPO, used as an indicator of tissue damage by a series of chain reactions (27).

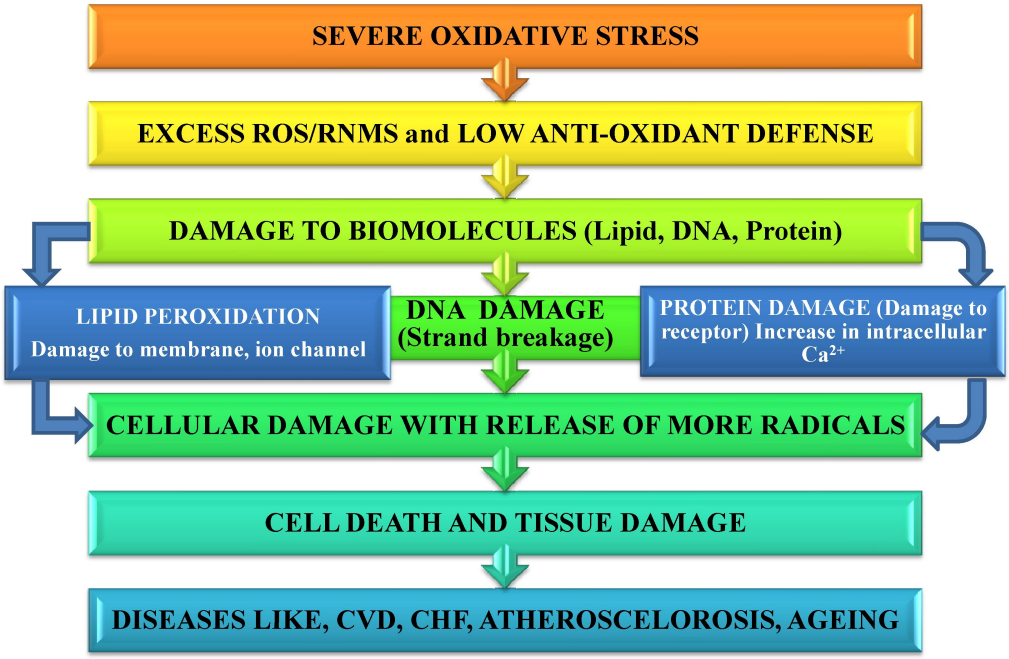


Figure 1 : Flow chart showing responses and signals during oxidative stress

Reactive Nitrogen Metabolites (RNMs)

Of the RNMs, Nitric oxide is the most important nitrogen derived physiological free radical and one of the smallest molecules in nature. It was considered as mere toxic pollutant; however studies reported that it relaxes smooth muscle and is involved either in causation or recovery of several studies. NO is synthesized from L–arginine by a family of enzymes nitric oxide synthetase (NOS) in two steps.

NO rapidly undergoes addition, substitution, redox and chain terminating reactions. These reactions serve as the molecular basis for its biological effects in human body. NO acts as "Double Edged Sword" in health and disease. The main physiological role of NO is controlled by type 1 and type III NOS expressions via intracellular Ca–calmodulin complex dependent mechanism. Both the deficiency and excess of NO are believed to be involved in different pathophysiological states like stroke of brain, Ischemia, GI dysfunction and achalasia (28).

Increased type II NOS expression and NO production occur in bacterial sepsis and hyperdynamic states like cirrhosis, it also plays an important role in inflammatory diseases like bronchial asthma, arthritis and ulcerative colitis. In diabetes mellitus inducible NOs over expression plays an important role in beta cell destruction by the inhibition of mitochondrial enzymes.

Peroxynitrite ($ONOO^-$) is another powerful oxidant that interacts with a wide range of targets to cause tyrosine metabolism, thiol oxidation, lipid peroxidation, DNA strand break, guanosine nitration /oxidation and ultimately leads to cell death. When overall generation of ROMs and RNMs exceeds the total anti-oxidant activity in the body, the resulting condition is called as oxidative stress. This oxidative damage is considered to play a causative role in ageing and several degenerative diseases associated with it, such as heart disease, cataracts, cognitive dysfunction and cancer (29).

NATURAL ANTI-OXIDANTS IN THE CARDIAC PROTECTION

Humans have anti-oxidant systems to protect against free radicals. These systems include some anti-oxidants produced in the body (endogenous) and others obtained from the diet (exogenous). The first include (a) enzymatic defenses, such as Se- glutathione peroxidase, catalase, and superoxide dismutase, which metabolize superoxide, hydrogen peroxide and lipid peroxides, thus preventing the formation of most of the toxic $HO^{\cdot}$ and (b) nonenzymatic defenses, such as glutathione histidine-peptides , the iron binding proteins transferrin and ferritin and dihydro lipoic acid, reduced CoQ_{10} melatonin, urate and plasma protein thiols, with the last two accounting for the major contribution to the radical trapping capacity of plasma. The various defenses are complementary to each other, since they act against different species at different cellular compartments. However, despite these defense anti-oxidants (able either to suppress free radical formation and chain initiation or to scavenge free radical and chain propagation), some ROS still escape to cause damage. Thus the body anti-oxidant system is provided also by repair anti-oxidants (able to repair damage, and based on proteases, lipases, transferases, and DNA repair enzymes). SOD, Catalase, Glutathione peroxidase are enzymatic anti-oxidants of first lines of defense against O_2, H_2O_2 mediated injury. The term "anti-oxidants" has been defined as "any substance that delays and inhibits oxidative damage to target molecule" (30).

MEDICINAL PLANTS: RE-EMERGING HEALTH AID

Humankind first utilized materials found in environment on an empirical basis to cure various ailments. Natural products from plants and animals traditionally have provided the pharmaceutical industry with one of its important sources of lead compounds in search of new drugs and medicines. The search for new pharmacologically active agents from natural resources such as plants, animals and microbes led to discovery of many clinically useful drugs. Over the past two decades, researchers have also turned to many of the traditional folk medicines – invariably a "cocktail" of natural products to uncover the scientific basis of their remedial effects which improves the efficacy as to enhance modern medical practices (31).

The growing awareness of the harmful effects of chemotherapy made people to explore the time tested remedies from traditional alternative medicine. India being a tropical country is blessed with vast natural resources and ancient knowledge for its judicious utilization. However, in order to make these remedies acceptable to modern medicine, there is a need to evaluate them to identify the active principles and understand the mechanism of action.

The exploitation of plants folk medicine has a long and honorable history and the use of medicinal plants still vastly exceeds the use of modern synthetic medicine. The WHO estimates that 65- 80 percent of the world's population use traditional medicine as their primary form of health care and 80 percent of traditional medicines involves plant extracts. These medicines from indigenous plants would be an immense benefit especially to inhabitants of developing countries, since the cost of these drugs would be within their means. Plants are also appreciated in pharmaceutical research as the major resource for molecules and medicines and a growing body of medical literature supports the clinical efficacy of herbal treatments.

The use of herbal medicines has been increasing in developing countries in recent years. In USA, currently the value of herbs, supplements and products related to Complementary and Alternative Medicine (CAM) is estimated to six to eight billions dollars and is expected to grow at the rate of ten to twelve percent every year (32). Even in developing countries, plant drugs are proving to be of great importance. In USA for example 25% of all prescriptions contained plant extracts or active extracts derived from higher plants. In contrast, public interest in medicinal plants is growing exponentially during the past decade. The use of plants for medicines still vastly exceeds the use of modern synthetic drugs. The WHO estimates that 60-80% of world's population are focused towards traditional medicine as their primary form of health care and about 85% involves use of plant extracts.

Since at one time, all drugs were obtained from natural sources. It was also linked with the initial development of the science of pharmacology, which used natural products to educate physiologic process and even define them, as nicotinic and muscuranic receptors (33). The pharmacological evaluation of natural products therefore forms an intrinsic part of pharmacognosy. Herbal medicines is currently enjoying a revival in popularity the west (31). Traditional Chinese, Ayurvedic and Unani systems of medicine are spreading throughout the world with increasing population movement. Herbal medicines, as effective and potent medicines and its compounds served as templates for the development of many drugs.

The world wide 'green' revolution is in the belief that herbal remedies are safer and less damaging to the human body than synthetic drugs. Furthermore, underlying this upsurge of interest in plants is the fact that many important drugs in use today are derived from plants or from starting molecules of plant origin. Plants have also yielded molecules that are extremely valuable tools in the characterization of enzymes and classification of receptor (34).

One major criterion for the selection of a plant for such study is traditional healer's claims for its therapeutic usefulness. It is thus worth reflecting on the cultural environment in which traditional healers use plant remedies as well as the methods of plant use, in order to strengthen the research design. Virtually every human society evolved an indigenous health care system to cope with illness. Today, phytomedicines are flooding the markets of advanced countries and consumers world over have shown preferences for natural herbal based formulation with the advent of automated high throughput screening methods. The pharmaceutical industry in the west has demonstrated a renowned commitment to searching for new medicinal agents from higher plants. Ethnobotanical input has also influenced this movement and is fast becoming a chief strategy for development of drug and the list of medicinal plants in India is endless and the country is bestowed with a plethora of plant wealth.

Diseases of cardiovascular system constitute major causes of conditions like hypertension lead to other types of disease such as stroke, kidney and heart diseases, blood pressure is itself affected by other existing states like atherosclerosis and arrhythmias and need to be treated. Resurgance in the use of herbal medicines world wide has offered an excellent opportunities to Indian scientist to look for the therapeutic leads from our ancient system of Ayurveda that could be utilized for drug development.

The recent approach towards plant drug development aims primarily at the utilization of leads available with the ancient scriptures like Ayurveda and application of modern phytochemical techniques to understand the active principles. Various estimates indicate that 70-80% of the population in developing countries account for over 50% of world population of herbal traditional remedies. The plant kingdom already furnishes many important cardiovascular drugs. The cardiac glycosides, digoxin and lanatosides, oaubin and others, which have positive inotropic effect on the heart, are still the drugs of choice for congestive heart failure. The growing awareness of harmful effects of chemotherapy pursued people to explore the time-tested remedies from traditional alternative medicine (35).

Cardenolides: An Overview

Cardiac glycosides were used as poisons in medieval times in Africa and south America natives for the preparation of arrow and spear poisons for hunting. The cardenolides are one of the fascinating series of natural products, which have been isolated from plants and many compound are still the first choice of drug in heart failure.

Plant families containing cardiac glycosides viz, Asclepediacea, Liliacea, Ranunculaecea, Scrophularacea, and Fabacea. Cardiac glycosides are complex in nature and several sugars are found to be attached to 3-OH group of the aglycone either alone or a series of two, three or four combined monosacchrides like glucose, rhamnose, digitoxose, anti-arose, digitalose, cymarose and oleandrose etc. The monosacchrides commonly occur as triose or tetrose; the most common linkage in monosacchride is 1-4 β linkage with the sugar via axial 3 –OH group, which is β to angular methyl groups.

The cardenolides are most prevalent in nature, which are C-23 steroids having 17 β side chain and α, β unsaturated five membered lactone ring. An usual aspect of chemistry of cardenolides is that the C, D in ring structure has the cis configuration. It has been observed that aglycones in which α, β unsaturated lactone ring attached at 17 position of steroid nucleus and having trans configuration of A, B ring structure in case of 5 β cardenolides and cis configuration in case of 5 α cardenolides have moderate cardiac activity.

The cardiotonic activity is associated with special structure of aglycone is modified in regard to solubility and the nature of conjugated residue. Their administration in cases of impaired heart function leads to decrease rate and increased intensity of heart beat; while over dosage leads to cardiotoxicity. The successful discoveries made in the field of cardioactive glycosides have been due to aid of modern sophisticated instrumental technology like UV, IR, Mass spectrometry, ^{13}C NMR and ^{1}H NMR spectroscopy.

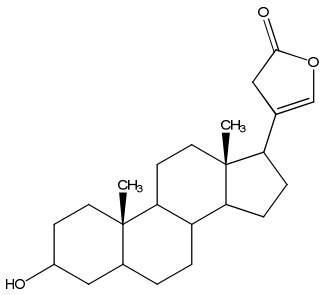
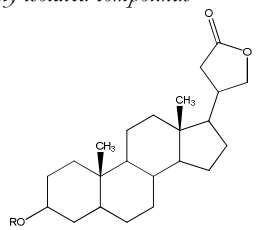
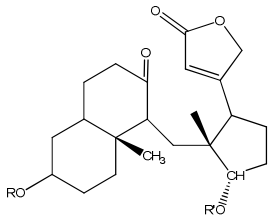


Figure 2 : Cardenolide nucleus

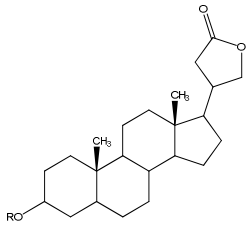
Figure 3 : Structures of previously isolated compounds



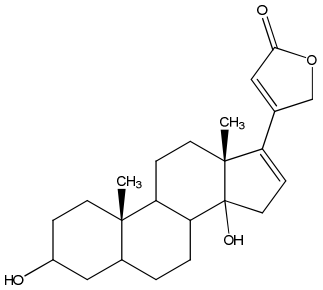
Structure 1: R – Rhamnose



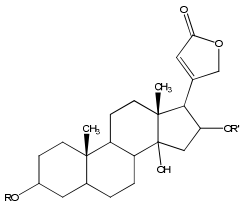
Structure 2: R – Digitose, R' – Neriose



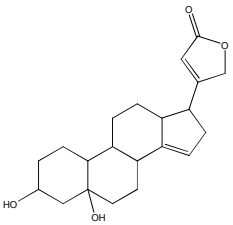
Structure 3: R' = H, R = Acovenose



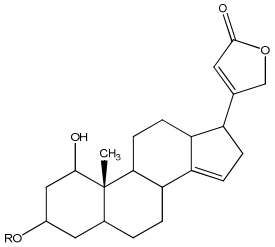
Structure 4



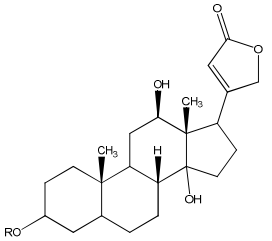
Structure 5: R = R' = OH
Structure 6: R = Rhamnose , R' = C– CH_3
Structure 7: R = H , R' = C–CH_2CH_3O



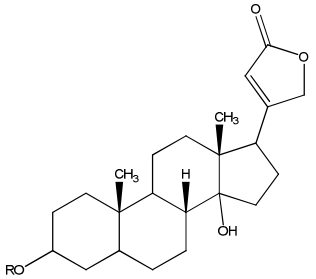
Structure 8



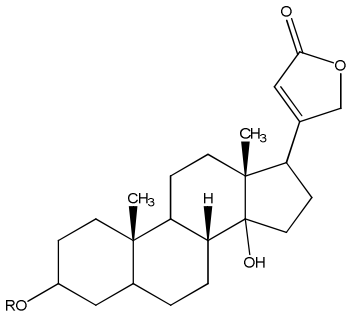
Structure 9



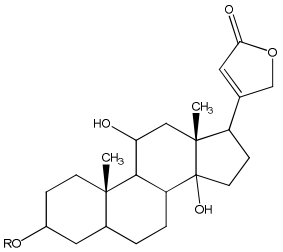
Structure 10: R = Digitoxose + Glucomethylose
Strcuture 11: R = Digitoxose + Digitoxose + Glucomethylose
Structure 34: R = Dgitoxose
Structure 27: R = 6 – deoxyallose + Xylose



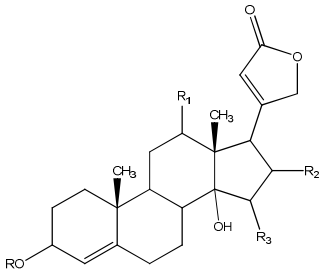
Structure 12: R = Digitalose, R' = H
Structure 13: R = Glucose + Digitalose R' = H
Structure 14: R = Glucose + Fucose , R' = H
Structure 15: R = Digitalose , R' = OCHO



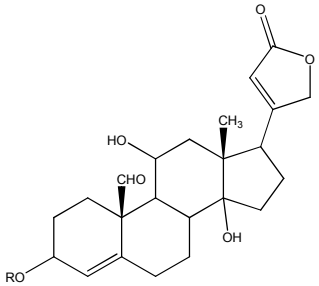
Structure 17: R = Glucose + 3- O – Acetyl digitoxose
Structure 18: R = Glucose + Gluco methylose
Structure 19: R = Glucose + gluco methylose + Digitoxose
Structure 20: R = Glucose + Glucomethylose + Digitoxose



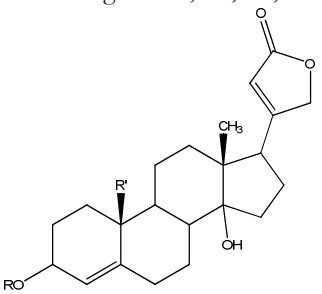
Structure 21: R = 6' deoxyl allose xylose rhamnose
Structure 22: R = 6' deoxyl allose +Xylose + Apiose
Structure 24: R = Digitoxose + Xylose +Apiose
Structure 26: R = Rhamnose + Apiose



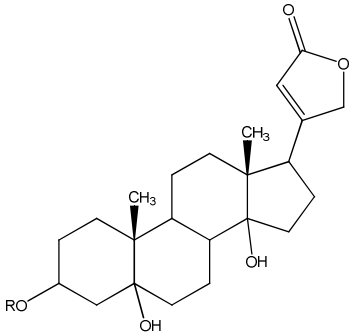
Structure 23: R = Digitoxose + Xylose +Rhamnose
Structure 25: R = Digitoxose + Xylose + Rhamnose
Structure 27: R = Digitose + Xylose + Rhamnose
Structure 33: R = Canarose , R1, R2, R3 = H
Structure35: R = Digitoxose, R1, R2, R3 = H

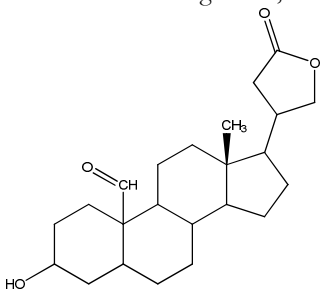


Structure 29: R=Xylose + Glucose



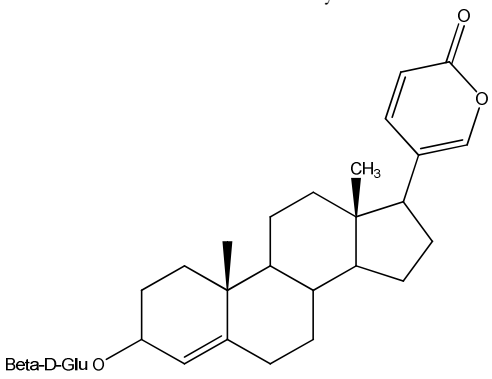
Structure 30: R = Digitalose, R' = CHO
Structure 31: R = Digitalose, R' = CH_2OH



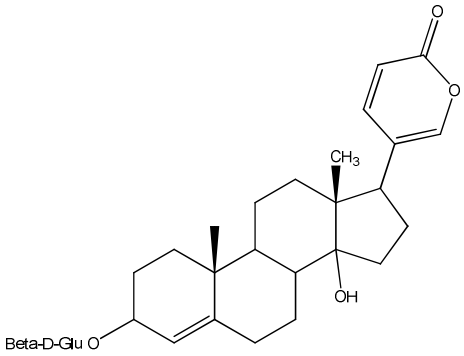


Structure 36

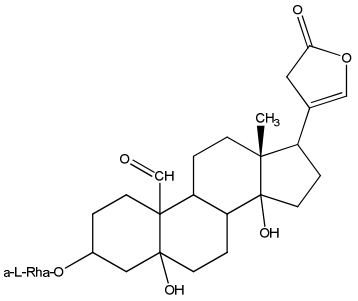
Structure 32: R = Glucose + Xylose



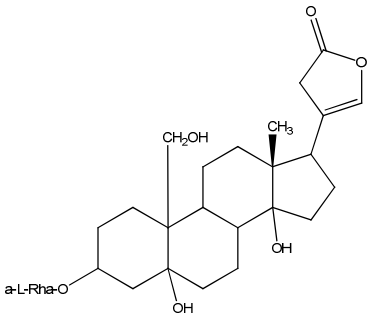
Structure 37: Scillaren A



Structure 38 Scillirobioside



Structure 39: Convallotoxin



Structure 40: Convallotaxol

Table 1 : Different cardiac glycoside of plant origin.

Structure	Cardenolides	Plant	Family	Reference
1	Acospectoside	*Acokanthera oblongifoia*	Apocyanceae	36
4	16 – anhydro gitoxigenin	*Acokanthera oblongifoia*	Apocyanceae	36
5	Gitoxigenin	*Acokanthera oblongifoia*	Apocyanceae	36
6	Rhodexin B	*Acokanthera oblongifoia*	Apocyanceae	36
7	Propionyl gitoxigenin	*Acokanthera oblongifoia*	Apocyanceae	36
9	Digitoxigenin- 3- O- β- Digitoxoside- β- D - glucomethyloside.	*Digitalis lanata*	Scrophulariaceae	37
10	Digoxigenin- 3- O - β - D- digitoxoside - β- D- glucomethyloside	*Digitalis lanata*	Scrophulariaceae	37
11	Diginatigenin- 3 – O - β- D- digitaloside	*Digitalis lanata*	Scrophulariaceae	37
12	Odoroside – H	*Digitalis lanata*	Scrophulariaceae	38
13	Odorobiosde – G	*Digitalis lanata*	Scrophulariaceae	38
14	Gluco digifucoside	*Digitalis lanata*	Scrophulariaceae	38
15	Verodoxin	*Digitalis lanata*	Scrophulariaceae	38
16	Strospeside	*Digitalis lanata*	Scrophulariaceae	38
17	Digitoxigenin – 3- O - β- D- glucosyl- 3- O – acetyl- β- D- digitoxoside.	*Digitalis cardiensis*	Scrophulariaceae	39
18	Gitoxigenin – 3- O - β- D- glucosyl- β- D- glucomethyloside.	*Digitalis cardiensis*	Scrophulariaceae	39
19	Gitoxigenin – 3- O - β- β - D- glucosyl- β- D – glucomethylosy- β- D- bisdigitoxoside	*Digitalis cardiensis*	Scrophulariaceae	39
20	Gitoxigenin – 3- O - β- D- glucosyl- β- D – glucomethylosy- β- D- digitoxoside	*Digitalis cardiensis*	Scrophulariaceae	39

21	Sarmentogenin – 3- O – 6'- deoxy- β- D- allosido - β- D- xylosido -α- L – rhamnoside	*Ornithogatum boucheanum*	Liliaceae	40
22	Sarmentogenin – 3- O – 6'- deoxy- β- D- allosido - β- D- apioside	*Ornithogatum boucheanum*	Liliaceae	40
23	15 β- 16- dihydroxyurarigenin – 3- O - β- D-digitoxosido - β- D- xylosido - α- L – rhamnoside	*Ornithogatum boucheanum*	Liliaceae	40
24	Sarmentogenin – 3-O- β- D- digitoxosido - β- D-xylosido - β- D- apioside	*Ornithogatum boucheanum*	Liliaceae	41
25	Syrigenin – 3 – O - β- D- digitoxosidio- β- D- xylosido - α- L – rhamnoside	*Ornithogatum boucheanum*	Liliaceae	40
26	Sarmentogenin – 3- O - α - L – rhamnoside - β - D- apiosde	*Ornithogatum boucheanum*	Liliaceae	40
27	Uzarigenin – 3- O - β- D- digitoxosido - β- D- xylosido - α - L- rhamnoside	*Ornithogatum boucheanum*	Liliaceae	40
28	Digitoxigenin – 3 – O- 6' – deoxy - β- D- allosido - β- D- xyloside	*Ornithogatum boucheanum*	Liliaceae	40
29	Hyrcanoside	*Coronilla varina*	Fabaceae	41
30	Peruviside	*Thevetia species*	Apocynaceae	42
31	Ruvoside	*Thevetia species*	Apocynaceae	42
32	Periplogenin – 3- O - β - D- glucopyranosyl – (1-5)- O - β - D- xylofuranoside	*Strebulus asper*	Moraceae	43
33	Uzarigenin – 3- β - O – canoroside	*Isoplexis chalcantha*	Scrophulariaceae	44
34	Digitoxigenin – 3 - β - O – digitoxoside	*Isoplexis chalcantha*	Scrophulariaceae	44
35	Uzarigenin – 3 - β - O – digitoxoside	*Isoplexis chalcantha*	Scrophulariaceae	44
36	Strophantidin	*Strophanthus kombe*	Apocynaceae	45
37	Scillaridin A	*Urginea maritima*	Liliaceae	45
38	Scillaridin B	*Urginea maritima*	Liliaceae	45
39	Convallotoxin	*Convalaria majalis*	Liliaceae	45
40	Convallotaxol	*Convalria majalis*	Liliaceae	45

Plants used in cardiovascular disorders

Cardiovascular medicines have evolved steadily over the past two decades with emphasis placed on prevention, early diagnosis and aggressive intervention. Herbs have been used as medical treatments since the beginning of civilization and for cardiovascular diseases, like congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis and arrhythmia. Constant research is necessary to elucidate the biological activities of the medicines now being used to treat CVS diseases (46).

Berberis aristata fruit extract exhibited a positive inotropic action in isolated cardiac tissues. Organic solvent fractionation revealed that the cardiotonic activity was concentrated in butanolic fraction. Data collected indicated the presence of an active principle present in *Berberis aristata*, which causes a selective inotropic effect involving actin, myosin co-operatively mechanism leading to isolation of cardioactive compound (47).

Hirai *et al*. investigated cardiotonic effect of the rhizomes of *Polygonatum sibricum* (48). Effects of "Kyushin' drug containing toad venom on congestive heart failure in rabbits were examined by Morshita *et al.* (49). The beneficial effect of kyushin on heart failure model resulted in potent cardiotonic activity.

Cardiovascular actions of the volatile oil obtained from black seeds (*Nigella sativa*) were studied, involving the effects on the arterial blood pressure and heart of urethane anaesthesised rats in comparison with those of its constituent thymoquinone. Mechanism of action elucidated that cardiovascular depressant effects were mediated mainly centrally involving 5- hydroxytryptamine and muscuranic mechanism and Nigella sativa oil was found to have centrally acting anti-hypertensive effect (50).

Abdalla *et al.* studied the positive inotropic effects of oblongine alkaloids, an alkaloid from *Leontice leontopetalum* on guinea pig isolated muscle and heart (51). The ethanolic extracts of the roots of *cryptolepsis sanguenilonia* with its main constituent cryptolepine were isolated by coloumn chromatography and a negative chronotropic effects were displayed (52).

Cardiovascular responses in the normotensive rats produced marked and persistant hypotensive effects on intravenous administration of gamibirine isolated from *Uncaria calophylla* (53). Tanghinin and its acetylated derivative acetyl tanghinin, two cardiotonic glycosides isolated from *Tanghinia venenifera* were evaluated and found that higher concentrations possessed inotropic effect, which was dropped rapidly with a rise in a diastolic tension (54). Dehydroevidamine, an alkaloid isolated from *Evodia rutacarpea* caused reduction in blood pressure and decreased heart rate contributing to potent hypotensive effect (55). Cardiovascular pharmacology of aqueous extracts of *Desmodium stycracifolium* was studied. Both in-vivo and in-vitro studies proved that extracts produced successive hypotensive effects (56).

Tripathi *et al.* investigated the effect of *Inula racemosa* root powder in patients with ischemic heart diseases and it was found that the powder prevented ST-segment depression and T-wave inversive, which was observed in the post exercise ECG. Adrenaline induced hyperglycemia was counteracted in rats and showed negative inotropic and chronotropic effect on frog's heart indicating that one of the constituents of *Inula racemosa* may have adrenergic beta-blocking activity (57).

Taesotikul *et al.* investigated the effect of crude alkaloid fraction from the stem of *Taber naemontana pandacaqu* on the blood pressure and heart rate in conscious and aneasthetized rats. Their findings suggested that the hypotensive and bradycardiac response of the first phase involved cholinergic and central mechanism whereas the second phase involved mechanism mediated by central biogenic amines acetyl choline and histamine (58).

Desai *et al.* isolated 13 new derivatives of diterpenoid alkaloids and established their structures alkaloids data analysis. Preliminary in-vivo cardiovascular actions such as hypotension, bradycardia and ventricular arrhythmias were tested using male sprague-dawley rats. A highly selective β_1-adrenergic blockade with partial β_2- agonist activity was observed from ferulic acid (59).

An active component of *Ligusticum wallichii* was evaluated using wistar rats for cardiovascular activities. It was observed that ferulinolol markedly inhibited tachycardial effects induced by isoproterenol but no blocking effect on the arterial pressor responses induced by phenylephrine. The above findings suggested the ferulinolol possess β-adrenergic blocking activity (60).

Liao *et al.* evaluated the effect of tetramethyl pyrazine, and active constituent of chinese herb on hypotension, vascular hyporeactivity to norephinephrine, release of tumor necrosis factor-A and nitric oxide in a rat model of circulatory shock induced by bacterial endotoxin. Their investigation suggested that tetramethyl pyrazine attenuated the early hypotension and delayed circulatory failure caused by endotoxin in the rat (61).

Cardiovascular effects of aspidofractinine type alkaloids from Kopia were studied by Mok *et al.* (62). Intravenous injection of kopsingine produced dose-related decrease in the mean arterial blood pressure and heart rate in aneasthesized hypertensive rats. Modifications in molecular structure of this constituent resulted in increase in blood pressure. The anti-hypertensive effect of kopsingine and pressor effect of some of its congers was ascribed to central as well as peripheral actions.

Heubach and Schule, reported that the analgesic compound lappaconitine, a C_{19} diterpenoid alkaloid from *Aconitum sinomonatanum* is an inhibitor of voltage dependent sodium channels. They investigated the cardiac effects of lappaconitine and it's metabolite in electrically stimulated guinea-pig heart. It was observed that the compounds exerted negative inotropic action and concluded that lappaconitine is a naturally occurring compound with class-I anti-arrythmic action (63).

The cardiotonic effect of the rhizome of *Polygonatum sibiricum* was investigated in the left atria of rats. Methanolic extract in a concentration 1-7 mg/ml was found to strongly inhibit cAMP phosphodiesterase. The findings suggested that the cardiotonic effect was due to stimulation of β-adrenoreceptors through stimulation of sympathetic nerves (64).

Effect of trilinolein, a triacyglycerol isolated from *Panax pseudoginseng* was studied on superoxide dismutase (SOD) activity and left ventricular pressure in isolated rat heart subjected to hypoxia and normoxic perfusion. Better preservation was observed with trilinolein and myocardial protection was related to an anti-oxidant effect through potentiation of SOD (65).

Cardiovascular effects of green beans (*Phaseolus aureus*) common rue (*Ruta graveolens*) and kelp (*Lamanaria japonica*) were studied in normotensive rats. Examination of the actions at tissue level revealed the rue had positive chronotropic and positive inotropic effects and green beans and kelp alone showed negative chronotropic effects. A number of mechanisms identified suggested that these plants contained cardioactive substances having direct effect on cardiovascular system (66).

Elucidation of cardiovascular activities of andrographolide and aqueous fraction of *Andrographis paniculata* for the first time was carried out by Zhang and Tan in anaesthetized sprague dawley rats. Their studies indicated that hypotensive action of the n-butanol fraction was not mediated through effects on the β-adrenoreceptors, muscarinic and cholinergic receptor (67).

Effect of the aqueous extracts of the bark of *Terminalia arjuna* on coronary flow in isolated perfused rabbit heart preparation was reported by Bhatia *et al.* (68). It was found to increase the coronary flow supporting its clinically reported anti-anginal activity and its use as a cardioprotective.

Fahim *et al.* reported Ajmaloon to be a potent anti-hypertensive drug producing dose-dependent fall in blood pressure of rabbit and monkey. It was also determined that

non interfere with the normal baroreceptor mediated reflex regulatory mechanism freeing from the problem of postural hypotension (69).

In normal and hyperlipidemic rats, Bopanna *et al.* studied the cell culture extract of *Hemidesmus indicus*. It was reported that the administration of atherogenic diet concurrently with *Hemidesmus indicus* lowered the levels of cholesterol and lipids in liver, heart and serum while feacal excretion of cholesterol and phospholipids were significantly increased (70).

Sympathomimetic activity of an ethanolic extract of *Scoparia dulcis* was investigated in rodent *in-vivo* and *in-vitro* preparation. High performance liquid chromatographic analysis of the aqueous fraction revealed that the presence of both noradrenaline and adrenaline in the plant extract and the results indicated that both catecholamines accounted for the hypertensive and inotropic effects obtained after parenteral administration of extracts (71).

Identification of coumarins from natural source and study of therapeutic application depending on the pattern of substitution was done by Hoult and Paya (72). Of these, Osthole from *Angelica pubescens* caused hypotension *in vivo*, inhibited platelet aggregation and smooth muscle contraction *in vitro*. Simple coumarins were found to be scavengers of superoxide anion radicals and aqueous alkyl peroxyl radicals and both 5, 7 and 6, 7 dihydroxy 4-methylcoumarin were found to reduce the derivation of ventricular fibirillation in post ischemic reperfused isolated rat hearts.

Influence of the many flavonoids from crataegus species on coronary flow, heart rate and left ventricular pressure, velocity of contraction and relaxation was investigated using lagendroff's perfused isolated guinea pig hearts. Results suggested that, an inhibition of 3, 5 cyclic adenosine monophosphate phospho diesterase was the underlying mechanism of cardiac action (73).

Plants as anti-oxidants

Owing to the incomplete efficiency of our endogenous defence systems and the existence of physio-pathological situations (cigarette smoking, air pollutants, UV radiation, high polyunsaturated fatty acid diet, inflammation, ischemia/ reperfusion, etc) in which ROS are produced in excess and at the wrong time and place, dietary anti-oxidants are needed for diminishing the cumulative effects of oxidative damage over the life span (74). Well established anti-oxidants derived from the diet are vitamins C, E, A and carotenoids, which have been studied intensely. Besides these anti-oxidant vitamins, other substances in plants might account for at least a part of the health benefits associated with the vegetable and fruit consumption. Over the past decade evidence has been accumulated that polyphenols are an important class of defence anti-oxidants. These compounds are widespread actually in all plants with often at high levels including phenolics, phenolic acids, flavonoids, tannins and lignans (75).

Flavonoids as natural anti-oxidants

Flavonoids are formed in plants from the aromatic amino acids and phenylalanine and tyrosine and malonate. The basic flavonoids structure is the flavan (2- phenyl- benzo-pyran) nucleus, which consists of 15 carbon atom arranged in three rings, which are labeled as A, B and C in figure 4.

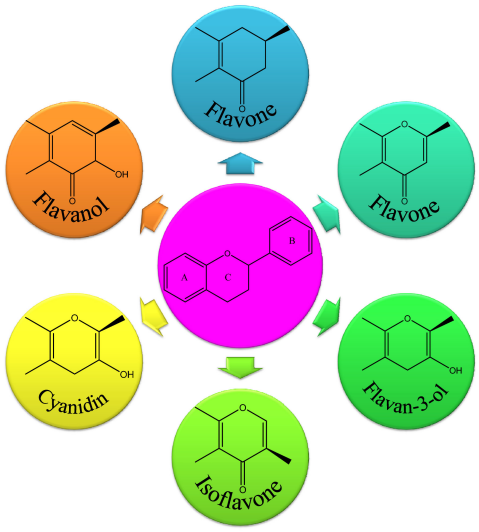


Figure 4 : Skeletal structure of flavonoids and related structures

With increasing knowledge about various free radicals and free radical scavengers, several structural determinants have been proposed. The following structural determinants for effective scavenging activity by flavonoids. The O- dihydroxy catechol structure in ring B, which is the obvious radical target site for all flavonoids, with a saturated 2, 3 double bond. The 2, 3 double bond in conjugation with an oxo function which is responsible for electron delocalization from the B ring. The additional presence of both 3 and 5 hydroxyl groups for maximum radical scavenging potential and strong radical absorption.

Reactive oxygen species (ROS) are implicated in many pathogenic process including cardiovascular system. Detoxification of ROS by anti-oxidants affords protection against such diseases. This is a growing body of evidence suggesting that anti-oxidants contribute to cardioprotection. Miura *et al.* suggested that flavonoids which possess pyrogallol and catechol moieties in their structure show strong H_2O_2 generating activity via an O_2 anion radical and also possess inhibitory activities in rat liver microsomal lipid peroxidation. Flavonoids which generate H_2O_2 can scavenge free radicals (76).

Anti-oxidant activity of 24 ferulic acid related compounds together with 6 gallic acid was evaluated by using several physical systems as well as their radical scavenging activity by Kikuzaki *et al.* (77). Ferulic acid was found to be most effective anti- oxidant among the tested phenolic acids. Kim *et al.* investigated the free radical scavenging activity of panax ginseng using electron spin resonance spectrometer and spin trapping techniques. Hydroxyl radical and superoxide radicals generated by UV radiation were significantly scavenged by ginseng (78).

Free radical scavenging properties of wheat grain extracts was evaluated by DPPH and ESR method by Acuna *et al.* (79). Results showed that the akron type of wheat extracts having

the greater activity to quench DPPH. Radical scavenging effect on DPPH revealed that the methanolic extract of the aerial parts *Lactuca scariola* showed stronger activity (78). Brazilian plant extracts were tested against stale DPPH free radical by measuring the discoloration of the solution. It was observed that ethyl acetate and n-butanol partitions possess higher anti-oxidant activity (80). Gao *et al.* isolated three new phenyl-ethanoid glycoside from whole plant of *Caryopteris incana* and exhibited higher DPPH radical scavenging activity (81).

Four types of galloyl flavanol glycosides isolated and the chemical structures were elucidated from *Pemphis acidula.* Examinations of DPPH radical anti-radical activity suggested the efficient activity of flavanol glycosides (82). Garcinol, a poly-isoprenylated benzophenone derivative purified from *Garcinia indica* fruits. It was further studied for anti-oxidative, chelating, free radical scavenging activity and results indicated that garcinol to be beneficial as a potent anti-oxidant (83). A large number of anti-oxidants have been demonstrated to induce beneficial effects on human health and disease prevention.

PRESENT STATUS AND FUTURE PROSPECTS

The molecular components of free radical biology and biological inter relationship of these components in mediating various diseases process are beautifully being unraveled for better understanding and exploitation in biomedical and clinical sciences (84).

Parallel identification and isolation of anti-oxidant principles from natural resources are simultaneously presenting enormous scope for their better therapeutic application. A possible protective role by flavonoid therapy against coronary heart disease (CHD) has been reported in four out of six epidemiological studies (85). Sustained interest in the use of anti-oxidants for the treatment of human disease and the role of anti-oxidant in prevention of disease development offer better understanding for the development of newer and better therapeutic entities. The impressive advances in anti-oxidant drug discovery and the basic science of cardiac diseases will most likely translate over the next decade into a significant impact on the clinical therapeutic opportunities available for treatment of cardiovascular diseases.

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