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EXPLORING THE THERAPEUTIC POTENTIAL OF NATURAL PRODUCTS IN HEART FAILURE

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ABSTRACT

Ventricular filling or blood ejection can be structurally or functionally impaired, leading to heart failure, a complex clinical condition. Fatigue, dyspnea, and fluid retention are the results of this. Heart failure may result from conditions affecting the myocardium, endocardium, pericardium, or heart valves. Severe hyperthyroidism and vitamin deficiencies are two more metabolic and nutritional disorders that can lead to heart failure. Daucus carota, Nerium oleander, Amaranthus Virdis, Ginkgo biloba, Terminalia arjuna, Picrorhiza kurroa, Salvia miltiorrhiza, Tinospora cordifolia, Mucuna pruriens, Hydrocotyle asiatica, Bombax ceiba, and Andrographis paniculate are a few well-known medicinal plants that are used to treat CVD. Flavonoids, polyphenols, plant sterol, plant sulphur compounds, and terpenoids are the active phytochemicals present in these plants. Preventing low-density lipoprotein oxidation, which encourages vasodilatation, is one way that flavonoids generally work. By reducing the blood's absorption of cholesterol, plant sterols can prevent CVD. By inhibiting the synthesis of cholesterol and activating nuclear factor-erythroid factor 2-related factor 2 (Nrf2), plant sulphur compounds also reduce CVD. Terpenoids reduce atherosclerotic lesions in the aortic valve, while quinone reduces the risk of CVD via boosting ATP generation in the mitochondria. Given the rising incidence of CVD, a number of physiologically active substances with established biological effects have been discovered in a variety of plants; nonetheless, suitable CVD prevention and treatment strategies are still needed. To fully

comprehend the mechanism and phytochemicals found in particular plants that treat CVD, more research is required.

KEYWORDS: Heart failure, Cardio vascular disease, ischemic heart disease.

Heart failure

Heart failure is a lifelong condition in which the heart muscle can't pump enough blood to meet the body's needs for blood and oxygen.

At first the heart tries to make up for this by

- **Enlarging:** The heart stretches to contract more strongly and keep up with the body's demand to pump more blood. Over time, this causes the heart to enlarge.
- **Developing more muscle mass:** The increase in muscle mass occurs because the contracting cells of the heart get bigger. This lets the heart pump more strongly, at least initially.
- **Pumping faster:** This helps increase the heart's output.

The body also tries to compensate in other ways

- The blood vessels narrow to keep blood pressure up, trying to make up for the heart's loss of power.
- The kidneys retain more salt and water rather than excrete it through urine. This creates increased volume of blood, which helps to maintain blood pressure and allows the heart to pump stronger. But over time this extra volume can overtask the heart, making heart failure worse.

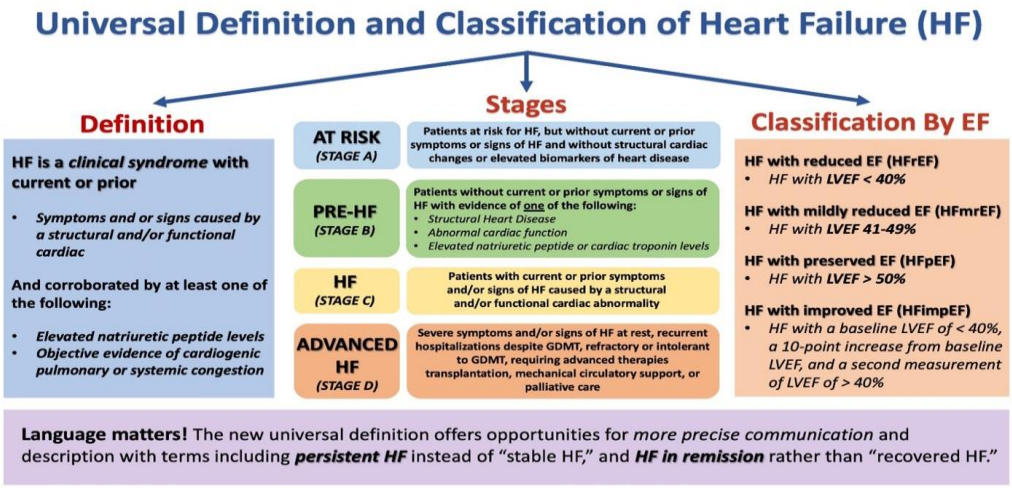

Figure 1: ***Courtesy of Gibson GT, Blumer V, Mentz RJ, Lala A.***[1]

Etiology

There are many etiologies of CHF, and coronary artery disease (CAD).Ischemic heart disease is the most common cause. Every attempt should be made to identify causative factors to help guide treatment strategies. The etiologies can be broadly classified as intrinsic heart disease and pathologies that are infiltrative, congenital, valvular, myocarditis-related, high-output failure, and secondary to systemic disease.[3] These classifications have significant overlap. The 4 most common etiologies responsible for about two-thirds of CHF cases are ischemic heart disease, chronic obstructive pulmonary disease (COPD), hypertensive heart disease, and rheumatic heart disease. Higher-income countries have higher rates of ischemic heart disease and COPD; lower-income countries have higher rates of hypertensive heart disease, cardiomyopathy, rheumatic heart disease, and myocarditis.

Ischemic heart disease is by far the most common cause of CHF worldwide. Ischemia leads to a lack of blood flow to heart muscles, reducing the EF. Incidence is increasing in developing countries as they adopt a more Western diet and lifestyle, and improved medical care decreases the infectious burden in these countries (myocarditis is often infection-related.)

Heart failure affects about 40 million people worldwide. Heart failure can be caused by many things, but the most common risk factors are high blood pressure, coronary artery disease (blockages in the arteries of the heart), diabetes, obesity, smoking, and genetics.

Signs and symptoms of heart failure include weakness or decreased energy; trouble breathing with walking, daily activities, or exercising or when lying flat; weight gain; leg swelling; and abdominal swelling or feeling full.[2]

Epidemology

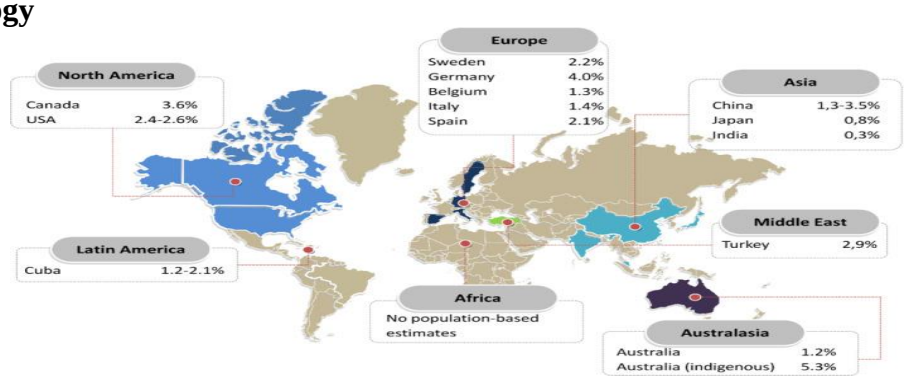

Figure 2: Heart failure prevalence in population-based research worldwide, broken down by region and percentage.[7]

1. Heart failure (HF) affects over 6.7 million Americans over the age of 20, and its prevalence is predicted to increase to 8.7 million by 2030, 10.3 million by 2040, and 11.4 million by 2050.[4]
2. The lifetime risk of HF has increased to 24%; approximately 1 in 4 persons will develop HF in their lifetime.
3. The proportion of younger patients with HF is increasing compared to the proportion of older patients.
4. Twenty-four to thirty-four percent of Americans have pre-HF (Stage B), and about one-third of all adults in the country are at risk for HF (Stage A). Obesity, hypertension, and clusters of comorbidities have all been linked to an increased risk of heart failure.
5. Compared to other racial and ethnic groupings, Black people have a higher incidence and prevalence of heart failure. Over time, HF has become more common in Black and Hispanic people.[5]
6. HF mortality rates have been increasing since 2012 with a more pronounced acceleration in 2020-2021. The age-adjusted HF mortality rates were higher in 2021 than in 1999. HF was a contributing cause in approximately 425,147 deaths and accounted for 45% of cardiovascular deaths in the U.S. in 2021.
7. Black, American Indian, and Alaskan Native individuals have the highest all-cause age-adjusted HF mortality rates compared with other racial and ethnic groups. From 2010 to 2020, HF mortality rates have increased for Black individuals at a rate higher than any other racial or ethnic group, particularly for individuals below the age of 65.[6]
8. A greater relative annual increase in HF-related mortality rates has been noted for younger (35-64 years) compared with older (65-84 years) adults.
9. Highest HF death rates have been reported in the Midwest, Southeast, and Southern states. Rural areas demonstrate higher HF mortality rates for both younger and older age groups compared with urban areas.
10. Rates of HF hospitalizations have increased since 2014. This increase was consistent between age groups and sexes, with the highest rates being among Black patients. Between 2020-2022, HF hospitalization rates were temporarily reduced during COVID-19 pandemic.

Natural medicines as a cardiovascular disease treatment approach by controlling oxidative stress

In the realm of CVD, finding safe and effective medications made from natural ingredients is a popular topic. Because of their safety characteristics, medicinal plants offer significant benefits in the treatment of cardiovascular disease. In addition to lowering cardiovascular risk generally, medicinal plants have been shown to have positive benefits on conditions like hypertension, hyperlipidaemia, atherosclerosis, and chronic heart failure.[8]

More and more medicinal plants are being used as natural antioxidants in the clinic to lessen oxidative damage in cardiovascular tissue. Numerous medicinal plants can yield active ingredients with antioxidant properties. Polysaccharides, flavonoids, and phenols from traditional Chinese herbal medicine are a few examples.[9]

S. No	Active ingredients	Natural drug	Mechanism of action	Treatment disease
1	Ginsenoside Rb_1	*Panax ginseng*	• Inhibits the expression of proapoptotic genes *Bax*, *Bad*, and *Fas* • Increases the activity of antioxidant enzyme • Reduces the oxygen free radicals	(1) Coronary heart disease (2) Ischemia-reperfusion injury
2	Ginsenoside Rg_1	*Panax ginseng*	• Inhibition of *caspase-3*, *Bax*, and *ap-JNK* expression • Increases the expression of *p-ERK* • Reduces ROS	(1) Coronary heart disease (2) Ischemia-reperfusion injury
3	Ginsenoside Rg_2	*Panax ginseng*	• Inhibition of *CK* and *LDH* • Reduced LPO • Increases the activity of *SOD*, *CAT*, and *GSH-Px*	(1) Coronary heart disease (2) Ischemia-reperfusion injury
4	Orientin	*Passiflora* leaves	• Reduces ROS • Increases the activity of antioxidant enzyme • Regulating *AMPK*, *Akt*, *mTOR*, and *Bcl-2*	(1) Coronary heart disease (2)Atherosclerosis
5	Allicin	*Allium* in *Liliaceae*	• Scavenging free radicals • Inhibits the formation	Hypertension

			of ROS • Increases the activity of antioxidant enzyme	
6	Curcumin	Rhizome of a turmeric plant	• Reducing the formation of peroxides • Inhibiting the expression of *Bax*, *beclin-1*, *BNIP3*, and *SIRT1* • Inhibiting *PI3K-AKT-mTOR* signal transduction	Hypertension
7	Delphinidin-3-glucoside	Anthocyanidin	• Inhibits the expression of *NOX2/NOX4* and *cas pase3* • Reduces ROS • Induces autophagy through *AMPK/SIRT1*	(1) Coronary heart disease (2) Ischemia-reperfusion injury
8	Hawthorn leaf flavonoids	Genus	• Inhibit the formation of LPO • Increase the activity of antioxidant enzyme • Inhibit free radical reaction	(1) Coronary heart disease (2) Atherosclerosis (3) Hyperlipidemia

Ginsenosides

Plants of the genus Panax generate ginsenosides, a class of bioactive substances that are nontoxic and have antioxidant properties.[10] The myocardium is protected, myocardial ischemia and hypoxia are improved, intracellular calcium excess is decreased, and free radicals are scavenged by ginsenosides Rb1, Rg1, and Rg2. According to a substantial amount of data, ginsenosides Rb1, Rg1, and Rg2 may be protective against CHD.[11] Cardiomyocyte apoptosis can be decreased by ginsenoside Rb1, which can also upregulate mTOR signalling, prevent oxidative stress, and limit the expression of genes that promote apoptosis, such as Bax and Fas. According to a recent study, Rb1 could activate the PI3K/Akt/Nrf2 signaling pathway, increase the activity of antioxidant enzymes, and lessen myocardial damage caused by free radicals.[12]

Ginsenoside Rg2 could reduce oxidative stress injury and improve myocardial ischemia and hypoxia by regulating the activities of serum creatine kinase (CK), lactate dehydrogenase (LDH), lipid peroxides (LPOs), superoxide dismutase (SOD), and glutathione peroxidase (GPX) in rats. Ginsenoside Rg2 was also shown to reduce oxidative stress in human epidermal keratinocytes.[13]

Because ginsenoside Rg1 upregulates the AMPK/Nrf2/HO-1 signaling pathway, it may contribute to antioxidant defence. Furthermore, it demonstrated protective properties against cardiac dysfunction brought on by STZ. Subsequent research revealed that Rg1 lowered ROS and apoptosis via the Nrf2/ARE signaling pathway, enhanced cell viability, and stimulated the expression of antioxidant proteins. Therefore, it is hypothesized that Rg1 may help cardiomyocytes survive by preventing oxidative stress.[14]

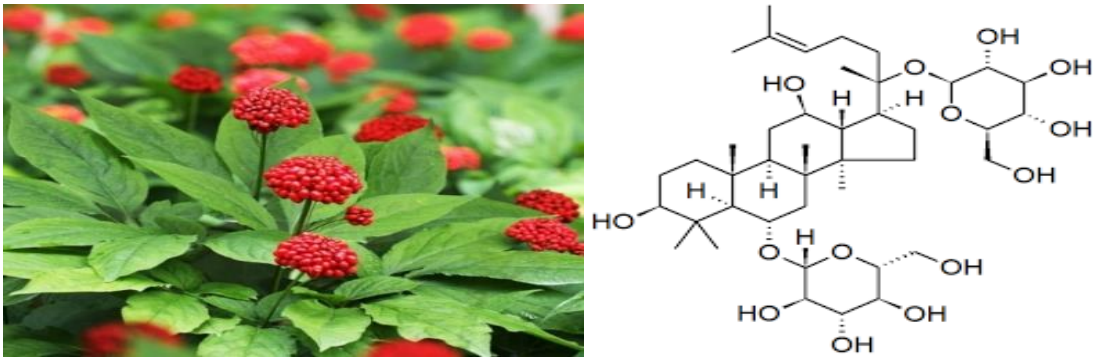

Figure 3: Shows Panax Ginseng and Structure of ginsenoside.

Orientin

One flavonoid found in natural plant extracts is called orientin. Orientin is a flavonoid monomer found in medicinal plants such as Ocimum sanctum, bamboo leaf, and Calendula officinalis, and is commonly used clinically to prevent and treat cardiovascular diseases with a wide range of anti-oxidative, antiapoptotic, antithrombotic, and antiarrhythmic effects. In addition to its anti-cancer and antioxidant qualities, orientin has been shown to improve antioxidant defence, aid in heart remodelling, and prevent myocardial ischemia-reperfusion injury.[15] According to studies, orientin can lower ROS levels and prevent the rise in TNF-α, IL-6, and IL-1β brought on by oxLDL. By lowering oxidative stress, boosting the activity of antioxidant enzymes, and preserving the structural integrity of red blood cells, orientin also shields them from oxidative damage. Additionally, research has shown that orientin can control apoptosis through the maintenance of autophagic balance and AMPK, Akt, mTOR, and Bcl-2 signaling. Furthermore, orientin shields cardiac cells from damage caused by hypoxia-reoxygenation.[16]

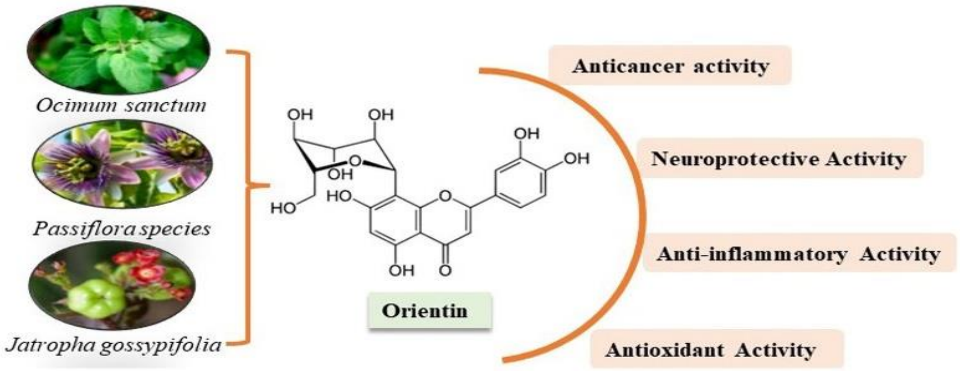

Figure 4: Orientin and Its sources.

Allicin

The sulphur-containing substance known as allicin is taken from the bulb of the Allium plant (Liliaceae). Alliinase changes allicin, which has a high hydrophobicity. Through the cell membrane, it can swiftly enter the intracellular area. By scavenging free radicals, lowering reactive oxygen species, promoting glutathione synthesis, and controlling NOS, allicin can have an antioxidant effect. Additionally, it has been mentioned as a possible medication for the management and prevention of high blood pressure.[17,18]

According to studies, allicin can significantly reduce H2O2-induced apoptosis, boost SOD and NO levels, and suppress the production of ROS and Enos.[19] Allicin may reduce oxidative stress-induced vascular endothelial damage by protecting vascular endothelial function through its antioxidant action. Research has shown that allicin can decrease the vascular response to angiotensin-II, boost Nrf2 expression, decrease oxidative stress, relieve high blood vessel tension, and downregulate AT1R/KEAP1 expression. Allicin may therefore be an additional promising medication for the treatment of hypertension.[20]

Figure 5: Allicin and Its properties.

Curcumin

The turmeric plant's rhizome contains a polyphenol component called curcumin. The pharmacological properties of curcumin include anti-inflammatory, antioxidant, antifibrotic, and anticancer properties. The potent antioxidant properties of curcumin have been shown in experimental investigations. By lowering the production of peroxides in blood vessels, curcumin prevents oxidative stress. It also lowers vascular resistance, restores vascular responsiveness, and prevents the onset and progression of hypertension.[21] In H9c2 cardiomyocytes, curcumin can also prevent H/R-induced apoptosis and autophagy by upregulating Bcl-2 and suppressing the expression of SIRT1, BECN1, BNIP3, Bax, and BECN1. By blocking PI3K-AKT-mTOR signal transduction, encouraging BECN1 and Bcl-2 dissociation, blocking FOXO1 acetylation, and lowering oxidative stress, curcumin controls autophagy, preserving vascular endothelial cell function and regulating blood pressure.[22]

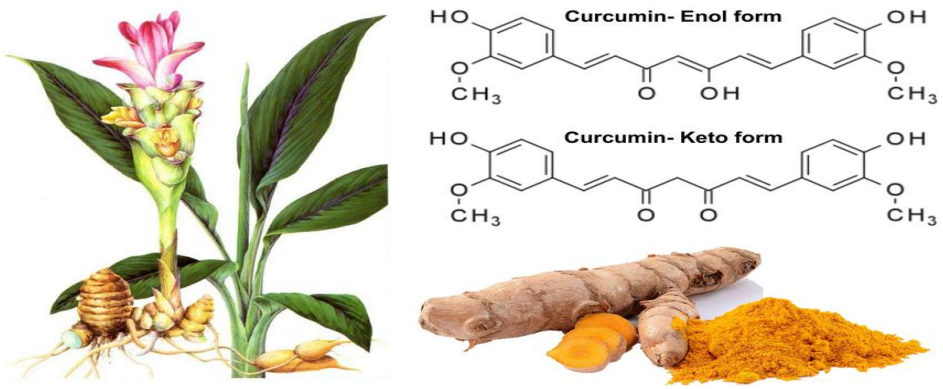

Figure 6: Structure of Curcumin.

Delphinidin-3-glucoside

The bioflavonoid delphinidin-3-glucoside (DPg) has potent antioxidant properties. In addition to lowering ROS generation, p38 MAPK phosphorylation, NF-κB p65 activity, and—most importantly—oxidative stress-induced damage, DPg may also decrease the expression of NOX2/NOX4 and caspase-3 generated by oxidized LDL (oxLDL).[23]

Further, studies reported that DPg could induce autophagy through the AMPK/SIRT1 signaling pathway, thus protecting human umbilical vein endothelial cells (HUVECs) from oxLDL-induced oxidative stress.[24]

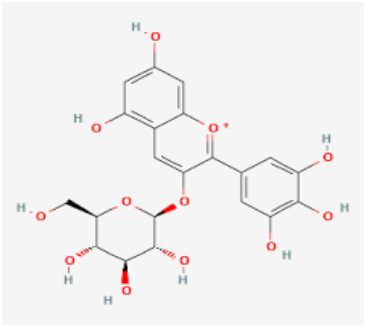

Figure 7: Structure of delphinidin-3-glucoside.

Hawthorn leaf flavonoids

The extract of the dry hawthorn leaves of the Rosaceae family is known as hawthorn leaf flavonoids. It has hypolipidemic, anti-inflammatory, and antioxidant properties. Flavonoids from hawthorn leaves have been shown to improve oxidative stress-induced damage to the rat myocardium via the PKC-alpha signaling pathway, increase the activity of antioxidant enzymes, and prevent the oxidative modification of LDL-C. Additionally, the extract was demonstrated to lower blood triglycerides and control the vascular pathogenic response via activating PPAR-α signalling.[25]

Additionally, it was discovered that by decreasing lipid peroxidation and increasing the activity of antioxidant enzymes and radical scavenging, hawthorn leaf flavonoids might shield vascular endothelial cells from free oxygen radicals.[26] Thus, flavonoids found in hawthorn leaves may be employed to counteract oxidative stress-induced cardiac damage.[26]

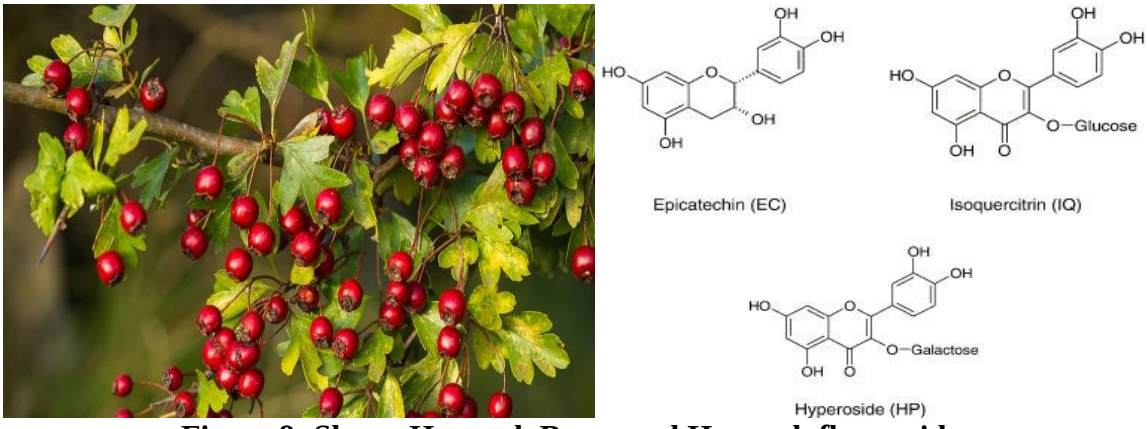

Figure 8: Shows Haworth Berry and Haworth flavonoids.

CONCLUSION

Because of their antioxidant qualities, medicinal plants are utilized to treat cardiovascular disease; impressive results have been documented. The mechanisms of active plant components in the treatment of arrhythmia, ischemia-reperfusion, heart failure, hypertension,

and congestive heart failure were compiled in the current review. More research is needed to determine the appropriate dosage and timing for administering active components. The synergistic effects of several bioactive plant components should be examined in future studies. Large-scale clinical research should also be carried out to verify the safety and therapeutic efficacy of natural medications and their potent active components.

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