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Therapeutic Insights of Picrorhiza kurroa Root in Cardiovascular Diseases: A Review

Subbulakshmi Packirisamy[1], Valli Gunam[2] & Deepa Rajendiran[3]

ABSTRACT

Cardiovascular disease is the common cause of morbidity and mortality worldwide. It is more prevalent in recent days due to life style modifications, change in diet and environmental pollution. Use of herbal plants for the treatment is gradually increasing due to cost effective and low risk of adverse effects. Picrosides is the major compound present in the medicinal plant, Picrorhiza kurroa royle ex benth which accounts for its medicinal properties. It is one of the most important endangered plants which have been reported to exhibit potential cardiovascular activities. Plants with protective effect on heart, contains a variety of bioactive compounds, including diosgenin, isoflavones, sulforaphane, carotinized, catechin, and quercetin. These have been proved to enhance cardioprotection and hence reducing the risk of cardiac abnormalities.

The aim of this review is to highlight the scientific evidence of the rhizome Picrorhiza kurroa and describing the biological mechanisms of cardioprotection.

Keywords: *Cardiovascular diseases, Medicinal plants, Picrorhiza kurroa, Phytochemical, Pharmacology, Cardioprotection.*

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INTRODUCTION

A cardiovascular disease (CVDs) is the disorders of the heart causing the risk to arteries, veins and capillaries. This may lead to various other complications such as heart stroke, systemic hypertension, ischemia, myocardial infarction, angina, atherosclerosis, arrhythmia, and heart failure1. The main causative factors for the CVDs are recent lifestyle modifications and behavioral factors such as cigarette smoking, alcohol consumption, physical inactivity which in turn alters the body weight, blood pressure, blood glucose, and lipids. Various drug treatments are available based on pathological conditions such as organic nitrates, beta-blockers, antiplatelets, ACE inhibitors, pain reliever's cardiotonic, and thrombolytics2.Since most of these drugs have adverse effects that have to be managed by using natural therapies with the help of medicinal plants.

Plants are the major sources of drugs. Research on these traditional herbs attracts the importance in the treatment of CVDs and a related disease because of their diversified structural specificity3. Magnifying importance is need of the hour to study the compounds from natural sources with effects on Myocardial Infarction. This helps in preventing the ischemic reperfusion injury, reduces the damage caused by hypoxia and ischemia condition, and reduces infarcts size4. All parts of medicinal plants (leaves, roots, stem, bark seeds, fruit, flowers, etc.,) are effective in the treatment of diseases and help to discover new kinds of drugs5. Phytochemicals like alkaloids, glycosides, saponins, coumarins, flavonoids, polyphenols, terpenes, carotenoids, carbohydrates, lipids, and proteins, sulfur and nitrogenous compounds, having an important role as cardioprotective agents6. Antioxidants are act against the oxidative stress scavenge the free radicals and protect the body. Vegetables and fruits are rich in antioxidant compounds for example; vitamins C and E, b-carotene, and polyphenolics have been associated with decreased risks of several chronic diseases, such as coronary heart disease and some cancers. There is an inverse relationship between intake of polyphenols and heart diseases7. In Ayurveda, the Indian system of medicine, several cardioprotective plants were mentioned such as Morphine (Papaver somniferum), Digoxin (Digitalis lanata), physostigmine (Physostigma venenosum), quinine/quinidine (Cinchona ledgeriana), reserpine (Rauvolfia serpentine), are some of the examples8,9.Most of the plants and herbs were used traditionally in day to day life as a healthy diet as well as a home remedy.

Bioactive compounds in Picrorhiza kurroa

Picrorhiza kurroa contains various phytochemicals which have been used to cure cardiac and other ailments10. The active compound identified is "Picrosides" or "Kutkin". It is a standardized mixture of two major C9 – iridoid glycosides, i.e. Picroside I (6-O- trans cinnamoylcatalpol) and "Kutkoside" (10-O-vanilloylcatalpol) in 1:2 ratio11. It contains agnusides and negundoside which found to possess various pharmacological properties. Many other active nutrients have been identified such as kutkin, kutkoside, pikuroside, mussaenosidic acid, bartsioside and boschnaloside12 picrosides II, III, V, cucurbitacins, apocynin, drosin,veronicoside, pikuroside, cucurbitacins, and 4-hydroxy-3-methoxy acetophenone, 6-feruloylcatalpol, minecosides, picein, cucurbitacin B, D and R13,14. Curcubitacins are cytotoxic and exhibit anti-tumorous activities. Apocynin belongs to the catechol which fights against inflammation and works to check neutrophil oxidative burst15, 16, 17.

UNDERSTANDING THE CARDIOPROTECTIVE MECHANISM OF PICRORHIZA KURROA

Medicinal herbs have potential therapeutic effects such as inhibiting and regulating the expression of various contractile proteins, regulating calcium levels, and improving mitochondrial function. These herbs decrease the damage to heart muscles, and cardiomyocytes by regulating the K-ATP channel through oxidative stress and apoptosis. Activation of endothelial nitric oxide synthase-nitric oxide (NOS-NO) signaling cascades, Inflammation, oxidative stress, apoptosis, angiogenesis, and endothelial permeability are inhibited by the beneficial effects of medicinal plants/ herbal products.

The cardioprotective role of Picrorhiza kurroa is perhaps due to their antioxidative, anti hypercholesterolemic, anti-ischemic, anti-inflammatory, platelet aggregation inhibition, and anti-angiogenic properties that reduce the risk of cardiovascular disorders. It is reported that the major chemical constituent responsible for biological activities is iridoid glycosides; collectively called "kutkin". Cardiac glycosides are steroidal with attached lactones. It inhibits the membrane-bound Na, K-ATPase resulting in depletion of potassium and an increase in sodium and calcium levels intracellularly. The build-up of intracellular sodium leads to a shift of sodium extracellular through another channel in exchange for calcium ions. Increased intracellular calcium promotes the activation of contractile proteins such as actins and myosin. This result in the decrease of

electrical conductivity in the heart tissue thereby attributes to a decrease in heart rate, and cardiac output. The outcome is to reduce the workload of the myocardium18.

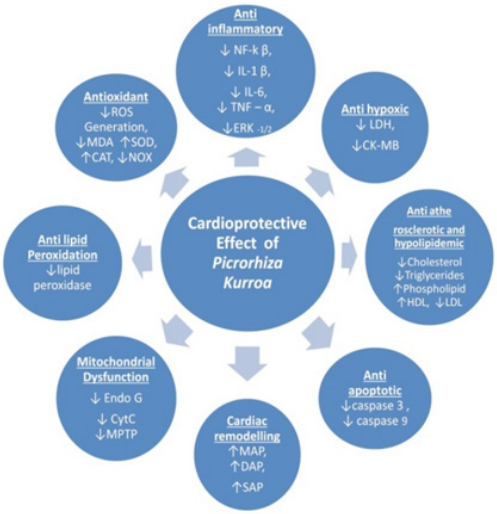

Fig. 1: Cardioprotective Role of Picrorhiza kurroa

ROLE IN ISCHEMIC HEART DISORDERS

Ischemic heart disease (IHD) is a pathological condition, which results in an insufficiency supply of blood and oxygen to the myocardium. Clinical manifestations are due to narrowing of epicardial coronary arteries, atherosclerotic plaque, and micro vascular dysfunction which may seriously damage the myocardium and result in severe ischemia. Once ischemia is triggered, hypoxic condition prevails in the myocytes. Anaerobic glycolysis begins, followed by tissue acidosis from the lactate production, coronary sinus oxygen desaturation, ion pump disturbances causing an increase in Na+ and Ca2+, decrease in pH, and reduction of adenosine triphosphate (ATP) availability are some of the important validates of myocardial ischemia19.

Cardioprotective role of Picrorrhiza kurroa were reported in various studies. In a study, Experimental rats were preconditioned using Picroside I, one of the major bioactive components of Picrorhiza species to study the myocardial damage induced by Isoproterenol. As a result, apoptotic markers, infarct size, cardiac/inflammatory elevations were reversed and improved the antioxidant status and cardiac morphology20

ROLE IN OXIDATIVE STRESS

An imbalance between the oxidants and the antioxidants results in oxidative stress. Increased production and accumulation of reactive oxygen species (ROS)/ reactive oxygen species (RNS) and decreased scavenging activity are attributed to oxidative stress cell damage. Antioxidants help in repairing the cell damage by act against free radicals and ROS. During stress, the myocytes are greatly affected and susceptible to free radical damage due to their low antioxidant enzyme contents, high oxygen requirement, and high levels of polyunsaturated fatty acids. This alters the antioxidant enzymes and influences the lipid peroxidation product; Malondialdehyde21. Free radical scavenging activity and cell membrane stabilizing action show the antioxidant and anti-lipid peroxidation properties. This May be attributed to the cardioprotective role of Picrorhiza kurroa22, 23.

It is reported in a study, that rich contents of polyphenols and flavonoids in the root extracts of Picrorrhiza kurroa show protective action against DNA, protein, and lipids. Presence of these phytoconstituents gives a more power against oxidative stress mediated pathological conditions24.

ROLE IN INFLAMMATION

Inflammation is the body's immune response which promotes healing and reverses the normal physiological functions during injury. It releases mediators such as prostaglandins, TNF α, and Interleukins and activates the inflammatory pathways.

Picrorrhiza kurrora root extracts act against all the inflammatory mediators (TNF-α, IL-6, IL-1β, NF-κB, and p65 subunit) and proinflammatory cells such as neutrophils, macrophages, and mast cells71. Apocynin , a catechol fraction in the Picrorhiza kurrooa has been found to exhibit powerful anti-inflammatory actions against various inflammatory models. It is also found to inhibit neutrophil oxidative burst in vitro without affecting beneficial activities such as chemotaxis, phagocytosis,and intracellular killing of bacteria25.

ROLE IN HYPOXIA

Hypoxia is one of the important factors in the pathophysiology of a variety of cardiovascular disorders26. Abnormal functions lead to the development of hypoxia and its destructive consequences. However, cell develops various adaptive mechanisms and signaling pathways to survive in hypoxic condition.

Picrorrhiza kurrora root extracts acts as a protective agent by reducing the cellular damage caused by hypoxia/reoxygenation-induced injuries. VEGF is the important gene expressed and regulated during hypoxia that is involved in various disorders such as rheumatoid arthritis, tumors, myocardial ischemia, and retinopathies. The potential of protection against the expression of glioma cells, Hep3B cells, VEGF, Protein kinase –C, LDH, and HIF-1 are enhanced and thus reduce the expression of these genes during reoxygenation. Data also added up that rhizomes markedly reduced the membrane damage caused by hypoxia27,28.

ROLE IN MITOCHONDRIAL DYSFUNCTION

Mitochondria are the powerhouse of the cell. It is the membrane-bound organelle present in all the eukaryotic organisms, which involves in the production of ATP using various metabolic pathways such as oxidative phosphorylation, and tricarboxylic acid. Mitochondrial dysfunction is one of the important causes of diabetes, atherosclerosis, cardiac hypertrophy and other valvular heart disorders. Excess accumulation of ROS results in an imbalance of enzymatic and non-enzymatic oxygen free radicals, lipid peroxidation, protein oxidation, and DNA damage, opening the mitochondrial permeability transition pore (mPTP)29 . As a result, an increase in mitochondrial permeability and swelling, the collapse of membrane potential, and cytochrome c release from mitochondria to cytosol, finally end up in cardiomyocyte apoptosis.

The protective role of Picrosides was exhibited in a study conducted in the H9c2 rat cardiomyocyte cell line. It greatly reduced the ROS production, thus mPTP opening is controlled, increases the mitochondrial membrane potential, and inhibits cytochrome c release from mitochondria to cytosol, and downregulates caspase 3 expression and activity. The study concluded that picroside II inhibited H/R-induced cardiomyocyte apoptosis by ameliorating mitochondrial function through a mechanism involving a decrease in ROS production30.

CONCLUSION

Picrorhiza kurroa is a medicinal plant with a great significance in heart-protective action. Both the extract and the active compound have good efficacy which is proved through many research findings. Though it is famous for its many pharmacological properties, it is highly appreciated for its preventive potential for cardiac disorders. Presence and influence of Secondary metabolites like cardiac

glycosides carotenoids, triterpenes, flavonoids, alkaloids saponins, polyphenols, terpenoids, fatty acids etc were responsible for cardio-protective activity helps to use and improve the in the cardiac ailments. Further studies are recommended at the molecular level to understand the elaborate pharmacological actions of the compound.

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