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A Review on Hepatoprotective Activity of Siddha Herbal Formulation Athimathuram and Sangam Verpattai Mathirai

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Abstract

Liver disorders represent a significant global health concern, with chronic liver diseases (CLDs) contributing substantially to morbidity and mortality, particularly in countries like India. While conventional Western medicine often carries risks of adverse effects and accessibility issues, traditional systems like Siddha offer promising alternative therapeutic avenues. This review investigates the hepatoprotective activity of a traditional Siddha herbal formulation, Athimathuram and Sangam Verpattai Mathirai, documented in classical Siddha texts.

The study systematically evaluates scientific evidence supporting the liver-protective effects of its key ingredients: *Glycyrrhiza glabra* (Athimathuram) and *Azima tetracantha* (Sangam Verpattai). Our analysis delves into Siddha principles linking specific tastes (sweet and bitter) to balancing liver-related humors and examines the modern pharmacological actions of these herbs. Findings indicate that *Glycyrrhiza glabra* exhibits robust hepatoprotective properties against drug-induced and alcohol-induced liver injuries, viral hepatitis, cirrhosis, fibrosis, and hepatic cancers, primarily through antioxidant, anti-inflammatory, and antiviral mechanisms. Similarly, *Azima tetracantha* demonstrates significant protective effects against chemical-induced liver damage, iron overload, and possesses anticancer potential.

This compilation of scientific evidence highlights the therapeutic potential of Athimathuram and Sangam Verpattai Mathirai in managing various hepatic conditions. The review suggests this Siddha formulation warrants further pre-clinical and clinical exploration to establish its efficacy and provide an evidence-based alternative for liver disease management, contributing to the development of integrated healthcare solutions.

Keywords: Hepatoprotective activity, Siddha medicine, Herbal formulation, *Glycyrrhiza glabra, Azima tetracantha*.

Introduction

Liver is considered to be the largest digestive organ that is essential for physiological and metabolic functions of body and vulnerable to be impaired by a wide variety of factors, such as toxins, microorganisms, metabolic products, circulatory materials and neoformations [1] Hepatic disorders are fast being recognized as public health priorities in India. Among them cirrhosis is the 11th leading cause of death and 15th leading cause of morbidity, accounting for 2.2% of deaths and 1.5% of disability-adjusted life years worldwide in 2016 [1, 2]. This is reflected in global declines that have been observed in liver disease mortality rates over the past 30 years [2, 3, 4]. Contribution of cirrhosis and its complications, collectively chronic liver diseases (CLDs), has been increasing progressively since 1980, posing an impact on the country's economy and health care resources, apart from being a cause of premature death and disability [5].

Researches on nutraceuticals showed that many natural agents exert protective and therapeutic effects on the liver and are scientifically proven to be beneficial [6] recently there is a tremendous worldwide increase in the usage of natural medicines showing effective and curative action for several liver diseases [7, 8, 9, 10]. There is an emerging need to combine evidence-based medicine and modern scientific research to treat chronic diseases like hepatic disorders. The traditional Siddha system such as finding the root causes of diseases, holistic medicine, personalization, prevention, and treating the mind and the body [8, 11]. This article is a preliminary documentation of Athimathuram Sangam Verpattai mathirai a tablet formulation that has been mentioned in Siddha classical text Gunapaadam Mooligai Vaguppu originally scripted by saint Theraiyar and Saint Agathyar in the texts Theraiyar Gunavagadam and Agathiyar Gunavagam respectively [12].

Study Drug Preparation

Adhimathuram Sangan Verpattaimathirai

Ingredients:

Sangamverpattai–1 part

Adhimathuram-1 part

Both the ingredients are taken in stone ural and pounded into fine powder, then sieved and ground in a kalvam with sufficient amount of lemon juice for three days. Then

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thetrankottai sized balls are made and dried in shade and preserved in air tight container.

Keezhanelli Choornam

Whole plant is collected, cleaned, dried in shade, ground into powder and stored in an air tight container.

Siddha Literature Aspect on Reducing Pitham Based on Taste and Potency

Siddha Basic Concept on Suvai and its Therapeutic Action

Every flavour is made up of the fusion of two fundamental components. Additionally, five elements can be combined in various ways to generate three essential life variables. The six tastes are also used to guide the choice of medications for the treatment of disorders [13].

Table 1: Trihumours and its relationship with suvaigal

Panchabootham (Five Basic Elements) Combination	Suvai (Taste)	Impact on Trihumour (Three Vital Humours)
Earth + Water	Inippu (Sweet)	Increases Kabham, Neutralise Pitham and Vatham
Earth + Heat	Pulippu (Sour)	Increases Pitham and Neutralise Vatham
Water + Heat	Uvarppu (Salt)	Increases Pittam, Kabham and Neutralize Vatham
Air + Space	Kasappu (Bitter)	Increases Vatham, Neutralize Pitham and Kabam
Air + Heat	Karppu (Pungent)	Increases Pittam, Vatham and Neutralise Kabam
Earth + Air	Thuvarppu (Astringent)	Increases and Neutralise Kabham, Increase Vatham, Neutralize Pitham

The composition of the Panchaboothic elements, such as land, air, water, fire, and ether, is the foundation for the three essential powers. The homeostatic ratio for these tridoshas is 1:1/2:1/4. The physiologic activities of the body are disturbed by gradual and chronic changes in this ratio, which eventually results in pathologically disordered disorders known as "Pini" or "noi." The Siddha system states that the tastes change the humours since people are unaware of dietary modifications. Vadham-Rises with rise in astringent and sour flavours. Pitham-Rises as bitter and salty flavours rise. Kabam-Increases when sweet and sour sensations increase [14].

Pitham and its Relationship with Hepatic Disorders

According to Siddha literature, the main complications of kalleralnoigal (Liver disorders) include anaemia, jaundice, and ascites. The consumption of more greasy foods, a lack of physical activity, a bad diet, irregular eating patterns, which are more prevalent in Pitham humors, drinking wine and spirits, and lifestyle changes are common causes of liver disorders, anaemia, and peptic ulcers. Pitham humor was vitiated by these causes and was affected. Liver illnesses are caused by disturbed other *Vali* and *Iyam* humour and affected pitham humour. The physical elements (udal Thadhukkal) are vitiated and impacted by three humours. Senneer and Saaram are among the udal thaathukal are impacted; they cause the tissue system to be depleted and the normal functional pathway of piththuneer (Bile) to be blocked. Additionally, it impacts the two different varieties of vatham, keezhnokkukal and melnokku kaal. These all result in liver disorders [15].

Table 2: Properties of Glycyrrhiza glabra and Azima tetracantha: Taste, Potency, and Trihumour Actions.

S. No	Herb	Taste	Potency	Therapeutic action on Trihumours
1.	Glycyrrhiza glabra (Fabaceae)	Sweet	Hot	Emollient, Demulcent, Mild expectorant, Laxative, Tonic
2.	Azima tetracantha (Salvadoraceae)	Bitter	Hot	Diuretic, Stimulant, Astringent, Tonic, Antiperiodic, Expectorant

The drugs *Sangam Verpattai* and *Athimathuram* possess sweet and bitter taste which balances the deranged *PithaKutram*. In addition to this it also have tonic activity which exert the soothing effect. As per Siddha text *Kaippu Suvai* detoxified the toxins which are the major cause of *Kalleralnoi* (liver disease) and *Inippu suvai* increases *Kabam* which further reduces *Pitham*

Hence administration of the drugs *Sangam Verpattai* and *Athimathuram* can be effective in the management of Kalleralnoi.

Scientific Evidences from Previous Studies

Hepatoprotective Action of Glycyrrhiza Glabra

Botanical Aspects: Glycyrrhiza glabra popularly known as Licorice, sweet wood, glycyrrhiza and has a strong ethnobotanical history. Medicinal plant. It belongs to the family Fabaceae. The species is native to Mediterranean region and cultivated in India, China and Russia. The parts of this plant root and rhizome are used in traditional medicine in Europe and eastern countries. It has a high nutritional value and used in various foods as a sweetener from ancient times [16, 17] [18, 19].

The phytochemical constituents present in Glycyrrhiza glabra are Vitamins, flavonoids, glycosides, triterpenes, saponins, tannins, oestrogens and phytosterols. The major flavonoids reported in the plant are liquiritin, glucoliquiritin, isoliquiritin, licoflavanone, shinflavanone, 1-methoxyphaseolin, Pinocembrin, shinpterocarpin and prenyllicoflavone [20].

Drug Induced Liver Injury

Several experimental studies both *in vitro* and *in vivo*, have reported the role of Glycyrrhiza glabra on drug induced liver injury mainly by reducing the oxidative stress and inhibits the mitochondrial and cell damage. It has been reported that Glycyrrhiza protects the liver cells from azathioprine or t-butyl hydroperoxide (t-BHP)-induced intracellular damage, Glutathione depletion and oxidative stress [21]. Studies also reported the protective mechanism of glycyrrhizin on acute liver injury induced by Carbon Tetrachloride in Mice. It is found to protect the liver cells by inducing the heme oxygenase 1 and downregulate the proinflammatory enzymes [22].

Another study conducted, has analyzed the effect of Glabridin against acetaminophen-induced acute liver injury. It is found to inhibit the proinflammatory cytokine TNF- α, reduce the levels of hepatic marker enzymes like SGPT, SGOT and improved RBC and Hb. Evidence has shown that it inhibits the inflammatory conditions, reduces the oxidative stress markers and prevents apoptosis [23].

Studies suggested 30days herbal treatment with Glycyrrhiza

could most likely reverse the hepatotoxicity by inducing oxidative changes in the liver cells [24]. It is evidenced that Glycyrrhiza can bring pathological changes in the liver cells by downregulating cell tumor antigen, TNF α and interleukin 1β levels. This inhibits oxidative stress, cell death, inflammatory responses and accelerates drug metabolism in Cisplatin-Induced Hepatotoxicity [25].

Alcohol Induced Liver Injury

Progression of Hepatic Fat accumulation to alcoholic hepatitis and damage of the hepatocytes are the important factors to deal with, in alcohol-induced liver injury. The data suggests that Glycyrrhiza has a protective action against alcohol-induced liver injury in mice fed different diet with or without licorice, through its antioxidant defense mechanism and anti-inflammatory properties. The expression of Srebf1 genes and lipid uptake genes is the prominent cause in hepatic fat accumulation and alcoholic liver disease. This Histopathological examination of liver of mice reported that Glycyrrhiza significantly prevented the expression of fat accumulating genes, inhibited TNF-α secretion and restored hepatic glutathione content in the liver cells [26].

Glycycoumarin which is a major bioactive coumarin present in Glycyrrhiza, has proved to possess hepatoprotective activity by activation of nuclear factor erythroid 2-related factor and upregulation of p62 and induction of autophagy. All this together reduced the alcohol-induced hepatotoxicity by removing damaged mitochondria and accumulated lipid droplets [27].

Viral Diseases of Liver (Hepatitis)

Glycyrrhizin is found to have a prominent antiviral activity when compared with antiviral activities of ribavirin, pyrazofurin, 6-azauridine and mycophenolic acid against two clinical isolates of SARS (severe acute respiratory syndrome) virus. Hepatitis enters the cells by receptor mediated endocytosis. Glycyrrhizin is found to be effective not only in controlling viral replication but also inhibits the entry of virus into the cell. This effect by Glycyrrhizin is produced by creating a negative charge on the cell surface decreasing the membrane fluidity. Studies suggest that Glycyrrhizin can be used as a prophylactic and in the treatment HIV-1 and chronic hepatitis C virus [18, 28].

Cirrhosis

Glycyrrhizin is tested to be effective in Cirrhosis of the liver which is apoptosis of hepatocytes. Tumor necrosis factor-alpha (TNF-α) is an important mediator of hepatic apoptosis and necrosis in liver failure. It inhibits the release of cytochrome C from mitochondria into the cytoplasm by inhibiting the translocation of nuclear factor into nuclei, halt the release of TNF-α and inhibit myeloperoxidase activity. Regeneration of liver injury by upregulating the expression of proliferating cell nuclear antigen gives Glycyrrhizin a wider scope to be used in a condition like cirrhosis.[14] Study conducted on the effect of Glycyrrhizin on radiation induced liver injury has shown that it inhibits the production of Kupffer cells and high-mobility group box 1 (HMGB1) production which are involved in ischemia-reperfusion preventing apoptosis [29].

Fibrosis of Liver

Previous studies have found that distribution of Glycyrrhizin isomers in the body is more in the liver tissue and duodenum rather than other organs. This evidenced the protective and anti-inflammatory action of Glycyrrhizin on the liver, which has the ability to reduce the steatosis and necrosis of liver cells. It is found to significantly inhibit the inter-interstitial inflammation and liver fibrosis and promote cell regeneration [30].

Hepatic Cancers

Several studies have reported the anticancer effects of G. glabra especially in the liver. The aqueous extract of G. glabra was tested against *in vivo* and *in vitro* proliferation of Ehrlich ascites tumor cells and found to inhibit the angiogenesis in the liver. The Glycyrrhetic acid works by causing apoptosis to tumor cells by inducing mitochondrial permeability transition. The methanolic extract of Glycyrrhizin also induces Bcl2 phosphorylation and arrests the Growth 2 phase of the cell cycle which resulted in apoptosis of tumor cells monoblastic leukemia U937 cells. Analysis found that the compound licocoumarone is responsible for antioxidant and antimicrobial activity. Experimental study on hydromethanolic root extract of G. glabra showed antimutagenic properties in the bone marrow cells of albino rats by suppression of micronucleus formation and chromosomal aberration. This theory suggests that G. glabra could serve as a model for development of new chemoprotective agents [18].

In a chemotherapeutic study coadministration of G. glabra along with cisplatin has evidenced to promote the accumulation of cisplatin by inhibiting its efflux and proved to reverse cisplatin resistance in hepatocellular carcinoma. Studies also found that GL inhibited hepatic cancer tumor growth in xenograft model by suppressing AKT/mammalian target of rapamycin (mTOR) and ERK1/2 pathways [21].

***Azima tetracantha* Lam (Salvadoraceae)**

Botanical Aspects: A well-known medicinal herb known as "Mulsangu" in Tamil and "Kundali" in Sanskrit is Azima tetracantha (Salvadoraceae). As a rheumatism treatment, diuretic, and stimulant, Azima tetracantha (lam) root, root bark, and leaves are taken with food. Azima tetracantha (lam), a traditional remedy for inflammation, cough, asthma, small pox, and diarrhoea, is used by Indian doctors. Azimine, azecarpin, carpine, isorhamnitine-3-O-rutinoside, friedelin, lupeol, glutinol, and beta-sitosterol are the main phyto-constituents found in Azima tetracantha (lam). Azima tetracantha (lam) is said to have hepatoprotective, antifungal, antitumor, antidiabetic, and antidiarrheal properties.

Azima tetracantha (lam) is a short, spindly, heavily branched shrub with woody undergrowth but young branches that are almost quadrangular in shape and light green in colour. Decussate pairs of opposite to subopposite leaves are present. They have an acute base, are short petiolate, 2x4 cm long, whole, elliptic, acute, and stiff. They are pale green. In the axil of a leaf, there are often two laterally positioned spines. The three cm or so long, roughly triangular-shaped, razor-sharp, and with an indurate apex spine, which morphologically resemble the first pair of leaves of the auxiliary shoot. The plant has two sexes. The axils of the leaves are where the blooms are born. The higher branches, particularly of the male plants, usually have cymes of three blooms in the axil of a leaf, which are significantly or even entirely inhibited [31].

In Siddha medicine, the diuretic root is used to treat dropsy and rheumatism. In the treatment of cough, asthma, and rheumatism, leaves are stimulants and expectorants. Bark has antiperiodic, expectorant, and astringent properties [32].

Action against Drug Induced Liver Injury

A substantial decrease in each of the five biochemical indicators of liver damage caused by carbon tetrachloride (AST, ALT, ALP, ACP, and total bilirubin) was seen in Azima tetracantha Lam. ethanolic leaf extract. Total bilirubin, AST, ALT, and ACP were significantly decreased after receiving this therapy. Due to its active phytoconstituents, which include alkaloids like azimine, azcarpine, and carpine, as well as terpenoids like phytol (Disterpene) and squalene (Triterpene), A. tetracantha has protective effects against liver damage brought on by CCl4. These antioxidants are effective at scavenging free radical species [33].

Chloroform and ethanol extracts of A. tetracantha leaves have hepatoprotective properties against CCl4-induced hepatotoxicity in rats. It was shown that 12 days of oral extract treatment effectively restored normal blood enzyme levels. A. tetracantha leaf powder showed hepatoprotective effect against ferrous sulfate-induced liver damage in albino rats, according to research. A. tetracantha leaf aqueous extract for hepatoprotective efficacy in isolated hepatocytes treated with CCl4 in a test tube. The treatment with a higher concentration of extract led to a considerable restoration in the levels of GOT, GPT, and alkaline phosphatase, which improved hepatocyte survival as evidenced by a rise in cell viability [32].

The normal cellular architecture was maintained in the liver sections of the rats given ethanol extract of Azima tetracantha Lam. root bark extract for 7 days, further demonstrating the extract's powerful hepatoprotective effects. The root bark of Azima tetracantha Lam. provided considerable protection against CCl4-induced hepatocellular damage when extracted in ethanol [34].

Viral Diseases of Liver (Hepatitis)

Cirrhosis, myocardial infarction, viral hepatitis, and other liver diseases all show elevated AST and ALT values. The ethanol extract of Azima tetracantha decreased the raised biochemical markers brought on by hepatotoxin poisoning as well as the production of new proteins and the buildup of triglycerides that result in fatty liver. Reducing elevated bilirubin levels shows that biliary function was stable throughout paracetamol-induced hepatic damage. It was considerably reversed after treatment with Azima tetracantha's ethanolic extract, proving that the phytoconstituents in this extraction had hepatoprotective properties [34].

Cirrhosis & Fibrosis of Liver

The most frequent sign of iron excess is tissue damage, especially in an organ that stores iron like the liver. Chronic iron overload brought on by hereditary disorders and frequent blood transfusions results in cirrhosis and hepatic fibrosis. Necrosis of the periportal regions, the location of hepatic regeneration, is predominantly linked to iron poisoning. The group that had been treated with *A. tetracantha* had very little necrosis visible, and the hepatic cell structure was nearly normal overall. The liver's histopathology results further supported the hydroalcoholic extract of *A. tetracantha's* hepatoprotective properties [35].

Hepatic Cancers

When compared to the stem extract, Azima tetracantha leaf extract exhibits strong anticancer potential against MCF-7 cell lines. The cytotoxicity potential of isolated compounds of *Azima tetracantha LAM* and various concentrations of ethyl acetate extract showed that the cytotoxicity rate increased as the concentration of leaf extract rose [31].

According to *in vivo* research, oral treatment of the extract lengthened survival times, decreased solid tumour volume and the number of viable tumour cells while increasing the number of non-viable tumour cells in Ehrlich ascites carcinoma in mice. *A. tetracantha* leaf solvent extracts have been tested for their cytotoxic effects on *Artemia salina* and *A. fransiscana*. The nauplii of both *Artemia* species could be dose-dependently killed by all extracts, while chloroform extracts had a higher cytotoxic impact. *A. tetracantha* leaves were tested for cytotoxic activity by MTT assay against the cancer cell line HeLa and the normal cell line HPL. It was demonstrated that the extract was cytotoxic to the HeLa cell line [32].

Alcohol Induced Liver Injury

Friedelin, a compound derived from Azima tetracantha Lam., has protective properties against alcohol-induced stomach ulcers in rats. The study's findings demonstrated that the friedelin, which was isolated from Azima tetracantha leaf extracts protected from ethanol, caused significant stomach damage [34].

Conclusion

Chronic hepatic diseases have been recognised as one among the leading health problems worldwide. Treating liver diseases with western medicine carry the risk of adverse effects, limited efficacy and are often not affordable by common man especially for the developing country like India. In this article, we have taken a preliminary effort to compile the scientific value of *Athimathuram Sangam Verpattai mathirai* of Siddha classical text. Through this literature analysis, scientific evidences on their hepatoprotective activity has been meticulously evaluated. The present work may therefore be useful to the health care professionals and scientists to develop evidence-based alternative medicine for hepatic disorders. The formulation may be further explored for its therapeutic effectiveness through pre-clinical and clinical studies.

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