An overview of the Herbs in a Siddha Polyherbal decoction-Pidangunaari Kudineer indicated for Hepatomegaly

V. Thanigavelan, V.Kaliyamurthi, M. Pitchiah Kumar, S. Elansekaran and G. Victor Rajamanickam

ABSTRACT

Handa et al., 1986 noted that in India, more than 87 plants are used in 33 patented and proprietary multi-ingredient plant formulations for liver protection. Siddha Materia Medica illustrates a safer, cheaper, and potential hepatoprotective polyherbal decoction ‘Pidangunaari kudineer’ comprised of three herbal ingredients such as leaves of Premna tomentosa, pericarp of ripe fruits of Terminalia chebula, rhizomes of Curcuma longa. This formulation is very effective against hepatitis in the clinical practice. The goal of this systematic review of the literature was to summarize the literature on the safety and hepatoprotective activity of above herbs. A manual search of bibliographies of papers identified through an Internet search using multiple search engines. Textbooks on herbal medicine and their bibliographies were also searched. Result and Conclusion: A large number of in vitro, in vivo, human clinical studies on those herbs were identified. These included studies on the antioxidant, anti-inflammatory, antihepatic activity induced by acetaminophen and antituberculosis drugs, anticarcinogenicity, antimicrobial properties and also phytochemicals were identified to justify the safety and hepatoprotective efficacy. Ethnic background of these herbs results liver protection make Pidangunaari Kudineer for further screening for hepatoprotection.

Keywords: Hepatoprotective action, Siddha, Herbs, Decoction.

INTRODUCTION

The incidence of hepatic toxicity has been reported to be higher in India. Acetaminophen (Paracetamol), highly active antiretroviral therapy and drugs for Tuberculosis (ATD) are the most commonly reported agents causing drug induced Hepatitis (DH). Many drugs such as NSAID’s, Anabolic steroids, Methotrexate, Erythromycin, Tetracycline, Sulpha drugs, Statins, Methylxypic, Chlorpromazine, Amidarone and Contraceptive pills, etc., exhibit hepatotoxicity on long usage. Among those, the incidence for consuming rate of Paracetamol and ATD are higher. Acetaminophen is a leading cause of acute liver failure because of over dose consumption due to free availability over the counter (OTC). The major problem of this drug is being an OTC product, freely sold and advertised. This leads to unintentional consumption of excessive quantity of acetaminophen when a patient already self medicating with an acetaminophen brand, is prescribed a branded combination product that also contains acetaminophen. Because of the high prevalence of Tuberculosis in India, the administration of first line ATD therapy specifically, Isoniazid (INH) and Rifampicin (RIF) consumption rate is higher.
These ATD produces many metabolic and morphological aberrations in liver. The clinical presentations of ATD induced hepatitis are similar to that of acute viral hepatitis. Commonly, DIH leads to complication of acute fulminant liver failure. Even though, so many drugs have been evaluated for DIH, the clinical results are not so hopeful. Making into account, we select a poly herbal formulation – *Pidangunari kadineer* which has literature background that has already been narrated in Siddha Materi Medica, Part 1 (Murugesh 2008, Kuppusami and Uthamarayan 2006). This formulation comprised of three plants viz: *Pidangunari ilai* (Leaf of *Premna tomentosa* Willd), Kadukkai thol (Pericarp of ripe fruits of *Terminalia chebula* Retz), Karimannal kidangu (Rhizomes of *Curcuma longa* Linn). Many researches have already been done on these plants and evaluated individually for several activities and also reported positive safety profile. In our clinical practice, such combined test formulation gives positive result in the treatment for hepatomegaly by decreasing the elevated level of liver enzymes. We have also observed decreasing viral load in Hepatitis B virus infected patients. So, the results of such clinical studies have motivated us to do general research survey for validating this potential formulation.

**RESEARCH STATUS OF THE PROPOSED HERBS**

*Premna tomentosa* Willd

A moderate sized semi-evergreen tree found in widespread in foot hills to 1400m, India and Sri Lanka. It belongs to the family Verbenaceae also known as *Kolakkatti thekku* and *Malai thekku* as common Southern Indian Name. The leaves of *Premna tomentosa* has essential oil containing d- and dl-limonene, beta-caryophyllene a sesquiterpene hydrocarbon, a diterpene hydrocarbon and a sesquiterpene tertiary alcohol. The leaf has diuretic action used for dropsy. The bark and essential oil of root is used in stomach disorders. The heart wood of this plant has apigenin derivatives (Khare, 2008). Three clerodane diterpenoids, premnones A-C (1-3) were isolated from a chloroform-soluble fraction of leaves of *Premna tomentosa* along with four known flavonoids and three known triterpenoids. Among these isolates, A-C exhibited cytotoxic activity when evaluated against a small panel of tumor cell lines. However, prennone A was found to be inactive when evaluated in a follow-up hollow fiber assay at the highest dose tested (50 mg/kg), using LNCaP, Lul, and MCF-7 cells (Chin et al., 2006). According to Pandima Devi et al., the extract of *Premna tomentosa* at 750 mg/kg, po in Wistar rats has shown good membrane protective effect particularly in acinetominph intoxication. They concluded that the presence of antioxidant compound like limonene in that plant must have provided this membrane protective activity (Pandima Devi et al., 2004).

*Curcuma longa* Linn

*Curcuma longa* Linn. (Zingiberaceae) is commonly known as “Haridra” in Sanskrit, is a persistent plant having a short stem with large oblong leaves. It is normally cultivated in South India, Bengal, Ceylon, Belgium, Indonesia, and in France. *Curcuma longa* has anti inflammatory, antihelmintic, antiseptic, cholagogue, hepatoprotective, blood purifier, antioxidant, detoxifier and regenerator of liver tissue, antiasthmatic, antitumour and antidiabetic actions. The rhizome has several therapeutic benefits and used to treat upper respiratory tract infections, boils due to small pox and mumps, unabated gonorrhea, poison due to beetle biting, swelling and open sore. It protects heart and vessels due to its antiplatelet and antiatherosclerotic activity. It also protects against DNA damage in lymphocytes (Khare 2008). Rhizome posses antiprotozoal, spasmylocytic, CNS active, antiparasitic, antispasmodic, antibacterial and antiarthritic activity (Husain et al., 1992). The rhizomes are also antihelmintic, carminative, antiperiodic, emollient, anodyne, laxative, diuretic, expectorant, alternative, febrifuge, ophthalmic and tonic (Warrier et al., 1994). The Siddha pharmacopoeia of India has indicated the constituents of *C. longa* as Curcumin, desmethoxy curcumin, bisdemethoxy curcumin, dihydrocurcumin, β-turmerone, bisabolane derivatives, ukonan A, B, C & D phytosterols and fatty acids. The rhizomes have given curcuminoids, the mixture consisting of atleast four phenolic dialyl heptanoids including curcumin and monodesmethoxycurcumin; volatile oil (3-5%), containing about 60% of turmerones which are sesqueterpene ketones, and bitter principles, sugars, starch and resin. From *Curcuma longa*, two novel compounds, 4’-(3’ ‘-methoxy-4’ ‘-hydroxyphenyl)-2’ ‘-oxo-3’ ‘-enebutanyl 3-(3’-methoxy-4’-hydroxyphenylpropenoate (calebin-A) and 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,4,6-heptatrien-3,5-dione (curcumin), 1-(4-hydroxy-3-methoxyphenyl)-7(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (demethoxycurcumin), 1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (bisdemethoxycurcumin), 1-hydroxy-4-bis(4-hydroxy-3-methoxyphenyl)-6-heptene-3,5-dione, 1,7-bis(4-hydroxyphenyl)-1-heptene-3,5-dione, 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one and 1,5-bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadien-3-one were isolated following a bioassay-guided fractionation scheme utilizing an assay to detect protection of PC12 cells from β-amyloid insult. Compounds calebin-A, curcumin, demethoxycurcumin, bisdemethoxycurcumin and 1,7-bis(4-hydroxyphenyl)-1-heptene-3,5-dione are found to more effectively protect PC12 cells from βA insult (ED₅₀ = 0.5–10 μg/mL) than Congo red (ED₅₀ = 37–39 μg/mL) (Park et al., 2002). One new quinoline alkaloid and seven known bisabolane sesquiterpenes: 2-((2’-methyl-1’-propenyl)-4, 6-dimethyl-7-hydroxyquinoline (1), 2, 5-dihydroxybisabola-3, 10-diene (2), 4, 5-dihydroxybisabola-2,10-diene (3), turmeronol A (4), bisacurone (5), bisacurone A (6), bisacurone B (7), bisacurone C (8), as well as dehydrozingerone (9) and zingerone (10) were isolated from the root tuber of *Curcuma longa*. 2-(2’-methyl-1’-propenyl)-4, 6-dimethyl-7-hydroxyquinoline (a new compound), bisacurone A,B and C, dehydrozingerone and zingerone were isolated from this plant for the first time (Wang et al., 2008).

Dry rhizomes of *C. longa* yield 5.8% essential oil. A ketone and an alcohol is obtained from the volatile distillate. Fresh
rhizomes yield 0.24% oil containing Zingiberene (Chopra, 1980). The essential oil (5.8%) obtained by steam distillation of dry rhizomes have been reported to contain b-phellandrene, d-sabinene, cineole, borneol, Zingiberene and sesquiterpene ketones (50%). In the recent analysis of the essential oil, turmerone (29.3%), ar-turmerine (23.6%) and abinone (0.6%) have been identified in the ketonic fraction besides p-cymene, isocaryophyllene, trans-b-farnesene, d-curcumene, bbsabolene and b-sesquiphellandrene (Lawrence, 1982). Campesterol, stigmasterol, b-sitosterol, cholesterol and fatty acids were isolated from rhizomes. Fatty acids comprised of saturated straight chain, saturated iso, monoenoic and dienoic acids (Rastogi and Mehrotra, 1991). Ar-turmerone, and Ar-curcumene are the major constituents present in the essential oil of rhizomes and the other compounds are a-and b-pinene, abinone, myrcene, a-terpinene, limonene, p-cymene, perillyl alcohol, turmerene, eugenol, iso-eugenol, eugenol methyl ether and iso-eugenol methyl ether. The essential oil extracted from pulverized rhizome of C. longa obtained from Nigeria by hydrodistillation analysed through GC/GCMS revealed the presence of hydrocarbon monoterpenes (46.9%) constituted the bulk of oil. The other major constituents are myrcene (7.6%), beta-bisabolene (13.9%), trans-ocimen (9.8%), 1,8-cineole (6.9%), alpha-thujene (6.7%) and thymol (6.4%) (Usman et al., 2009).

The successive extraction of C. longa with petroleum ether, alcohol and distilled water yielded extracts, when administered on 1-7 days of pregnancy at dose levels of 100and 200mg/kg have been found to exhibit significant anti-fertility activity (Garg et al., 1978). Essential oil from rhizomes is an antiseptic, anagard and carminative. Effect of the oil on cardiovascular and respiratory systems is not marked, therefore, not of much importance from therapeutic point of view. Chlorotic action of the essential oil is attributed due to p-tolymethyl carbinol. Dye-stuff acts as a chalagogue causing contraction of the gall bladder. Anti-oxidant properties of curcuma powder are due to phenolic character of curcumin (Dey, 1980). Rhizomes are externally effective as insect repellent against houseflies. It is found to inhibit Clostridium botulinum. Essential oil from rhizome has shown fungitoxicity (Asolkar et al., 1992). Essential oil (0.1mg/kg) in rats has shown significantly more marked anti inflammatory effect than cortisone acetate (10mg/kg). The uptake, distribution and excretion of curcumin have also been studied. Clinical trials has exposed that plant definitely has reduced cough distribution and excretion of curcumin have also been studied. However, LNAME (5 mg/kg) pretreatment with curcumin (10 mg/kg, po) has potentiated the protective effect of curcumin as compared to their effect per se. However, L-arginine (100 mg/kg) pretreatment with curcumin (10 mg/kg, po)
has significantly reversed the protective effects of curcumin. This result suggests that nitric oxide mechanism could be involved in the protective effect of curcumin against sciatic nerve ligation induced behavior and biochemical alterations in rats (Anilkumar and Singh 2008).

An extract of the crude drug ‘akon’ containing the rhizomes exhibited intensive preventive activity against carbon tetrachloride induced liver injury invivo and invitro. The liver protecting effects of some analogs of ferulic acid and p-coumaric acid, probable metabolites of the curcuminoids have been also evaluated (Kiso et al, 1983). The rhizome of Curcuma longa Linn has been used for treating various liver disorders caused by Hepatitis B virus in Asia. The extract of this rhizome represses HBV replication through enhancement of the level of p53 protein (Kim et al., 2009). C. longa, a remarkable non toxic plant normalized the concentration of protein, glucose, AMP-deaminase & adenosine deaminase which have been changed by Schistosoma mansoni infection in mice. The extract of rhizome was more potent in reducing egg count and lowered pyruvate kinase level, while Praziquantel treatment induced more elevation of pyruvate kinase (El Ansary et al., 2007). The essential oil is effective against the condition caused by Aspergillus sp, Bacillus subtilis, Corynebacterium diphtheriae, Staphylococcus aureus, Salmonella typhi and Esterechia coli (Garg and Jain 2003).

The ethanolic extract of rhizome at 80-160 mg/kg prevents aspirin induced gastric injuries and haemorrhages in guinea pigs. The same extract exhibits blood sugar lowering activity in alloxan induced diabetic rats (Khare 2008). Turmeric is a promising ingredient of functional food for the prevention and amelioration of type 2 diabetes and that curcumin, demethoxycurcumin, bisdemethoxycurcumin, and artumerone mainly contribute to the effects via PPAR-g activation (Kuroda et al., 2005). Oral administration of tetrahydrocurcumin (THC) isolated from C. longa at 80mg/kg body weight to type 2 diabetic rats for 45 days possesses a significant beneficial effect on erythrocyte membrane bound enzymes and antioxidants defense in addition to its antidiabetic effect (Murugan and Pari 2007). Aggregation and insolubilization of lens proteins due to hyperglycemia is prevented by turmeric and curcumin. Turmeric was more effective than its corresponding levels of curcumin against the development of diabetic cataract in rats. Further, the results from this study imply that turmeric as an ingredient in the dietary sources may be explored for anticitaractogenic agents that prevent or delay the development of cataract (Suryanarayana et al., 2005). The hypolipidemic action of curcumin interferes with more intestinal cholesterol uptake, increasing the conversion of cholesterol into bile acids and increasing the excretion of bile acids via its choleretic effects. Further, the Curcuminoids prevent the increases in liver enzymes and this compound validates the use of Turmeric as a hepatoprotective drug in liver disorders. Crlcone, obtained from the dried rhizome, is used against hepatitis (Khare 2008). Curcumin seems to prevent oxidative damage mediated through selenium and protect the dehydrogenases possibly through its anti-oxidative property. Selenium administration has resulted in a marked decrease in the activity levels of the liver succinate dehydrogenase, malate dehydrogenase, and lactate dehydrogenase while pyruvate dehydrogenase increased significantly (P<0.001) in the wistar rat. The degree of decrease of these enzymes were significantly less (P<0.001) when rats were treated with curcumin, a natural constituent Curcuma longa (Padmaja and Raju, 2008). Oral administration of curcumin from Curcuma longa to rats caused a significant reversal in lipid peroxidation, brain lipids and produced enhancement of glutathione, a non-enzymic antioxidant in ethanol intoxicated rats, revealing the antioxidative and hypolipidaemic action of curcumin responsible for its protective role against ethanol induced brain injury (Rajakrishnan et al., 1999).

Curcumin (diferylolyl methane), the yellow pigment in turmeric (Curcuma longa), is a potent chemopreventive agent that inhibits proliferation of cancer cells by arresting them at various phases of the cell cycle depending upon the cell type. Curcumin-induced apoptosis mainly involves the mitochondria-mediated pathway in various cancer cells of different tissues of origin. In some cell types like thymocytes, curcumin induces apoptosis-like changes whereas in many other normal and primary cells curcumin is either inactive or inhibits proliferation, but does not appear to induce apoptosis. These together with reports that curcumin protects cells against apoptosis induced by other agents (Karunagaran et al., 2005). Curcumin can suppress the growth; induce apoptosis of bladder cancer EJ cell invitro. Its mechanism is related with down-regulations of the expressions of NF-kappaB and Cyclin D1. Curcumin has great potential for the treatment of bladder cancer (Sun et al., 2004).

*Terminalia chebula* Retz

A medium sized deciduous tree found in deciduous forest. It grows large tree in good soil but in one dark rocky place Hills 800-1400m, India. It belongs to the family Combretaceae, it is also known as Kadukkai. The unripe fruits of Terminalia chebula are more purgative than ripe fruits. Due to the presence of tannin 30 – 45% in ripe fruits, it has astringent action. The Siddha pharmacopoeia of India, along with other therapeutic applications, indicated the use of powder of mature fruits in the treatment of jaundice, eye disorders, ascitis, purpura, hypertension, constipation and poisons. The fruits of Terminalia chebula are used in combination with Emblica officinalis, and Terminalia bellerica under the name of formulation Thiripala Choornum in the treatment of liver and kidney dysfunctions. Shikimic, gallic, triacontanoic and palmitic acids, beta-sitosterol, daucosterol, triethyl ester of chebulic acid and ethyl ester of gallic acid; a new ellagitannin, terchebulin along with terchebulin A have been isolated from the fruits of T.chebula. A new triterpene, chebupentol, and arjungenin, termenoic acid and arjunolic acid were also isolated from the fruit. Antioxidant constituents of the plant, phloroglucinol and pyrogallol have been isolated along with ferulic, vanillic, p- coumaric, caffeic and fatty acids. Ether extract showed higher antioxidant activity than BHA and BHT. The acid ester present in phenolic fraction of extract,
were found most effective compound (Khare 2008).

Reddy et al isolated Chebulagic acid from ethanolic extract of the fruits of T.chebula. He has observed that this compound is a potent dual inhibitor of COX-2 and 5-LOX and induces apoptosis in COLO-205 cells (Reddy et al., 2009). Further, Gao et al study results have concluded that the chebulagic acid is a potent alpha-glucosidase inhibitor and it could be used in managing NIDDM (Gao et al., 2008). Moreover, recent studies by Sing et al have displayed that the fruit extract of T. chebula exerts a significant and dose dependent glucose lowering effect in the rat model of metabolic syndrome (Sing et al., 2010). Khazaeli et al have proved T.chebula inhibits tyrosinase activity and DPPH radical (Khazaeli et al., 2009). Kusirisin et al said that due to the presence of polyphenol and tannin in the fruit of T.chebula, it might be used for reducing oxidative stress in diabetes (Kusirisin et al., 2009). The results of Prasad et al suggested T. chebula had a potential protective role from Ferric nitroliatriacetic acid induced oxidative damage and renal tumorigenesis in Wistar rats (Prasad et al., 2007). Murali et al found that the LD 50 of aqueous extract of T. chebula fruit be above 3 g/kg bw and this value was 15 times of ED and also he has concluded this extract has revealed insulin release from Pancreatic islets was two times more than in untreated diabetic animals as in vitro studies. In vivo, at the dose of 200 mg/kg bw, this extract has significantly reduced the elevated blood glucose, HbA1C and also controlled the elevated blood lipids level (Murali et al., 2007). A concentrated aqueous extract of T. chebula is an effective anticaries agent because this extract increases the salivary pH and buffering capacity and decreases the oral microbial count and it could be used as an effective mouth rinse (Carounanidy et al., 2007). Tasduq et al, have chemically characterized 95% ethanolic extract of T.chebula (fruit) on the basis of chebuloside II as a marker and have investigated for hepatoprotective activity against antituberculosis drug induced. TC extract was found to prevent the hepatotoxicity caused by the administration of rifampicin (RIF), isoniazid (INH) and pyrazinamide (PZA) (in combination) in a sub-chronic mode (12 weeks). The hepatoprotective effect of TC extract could be attributed to its prominent anti-oxidative and membrane stabilizing activities (Tasduq et al., 2006). Chebulagic acid (CHE) from the immature seeds of Terminalia chebula is identified as a potent suppressor of T cell activity. CHE significantly suppressed the onset and progression of CIA in mice. Immune suppression via the induction of TGF beta and CD4+, CD25+ T cells may represent a new strategy in the development of therapies for managing rheumatoid arthritis and other inflammatory diseases (Lee et al., 2005).

### RESEARCH STATUS RATHER THAN THESE THREE HERBS

Various active constituents isolated from plants are andrographolide from Andrographis paniculata, picroliv from Picrorhiza kurroa, phyllanthin and hypophyllanthin from Phyllanthus niruri and methoxy benzoic acid from Capparis spinosa, which is reported to be antihepatotoxic (Handa and Sharma 1990, Dwivedi et al., 1990, Thyagarajan et al., 1988, Gadgoli and Mishra 1999, Gupta 2007). These active constituents with antioxidative, antifibrotic, antiviral and other properties may serve as primary compounds for further development as hepatoprotective drugs. Silymarin from Silybum marianum, andrographolide from Andrographis paniculata, curcumin from Curcuma longa, picroside and kutkoside from Picrorhiza kurroa, phyllanthin and hypophyllanthin from Phyllanthus niruri, glycyrrhizin from Glycyrrhiza glabra are traditionally used in the treatment of liver diseases and they represent the phytochemical constituents (Negi et al., 2007). These plants display hepatoprotection due to antioxidant effect but other effects like immunomodulatory, antiviral, anti inflammatory, antifibrotic, membrane stabilizing and antiprotozoal activities were also documented (Koul and Kapil 1994, Fu et al., 2008, Shin et al., 2005, Khang et al., 2006).

Some polyherbal hepatoprotective patent formulations such as Liv 52, Livergen, Livokin, Octogen, Stimuliv and Tefroliv have been studied by Girish et al. Among these formulations, the researchers have concluded that Liv 52 and Livogen are found to be the most effective and safer formulation at normal recommended doses (1x) itself. But, the other formulations were effective only at higher doses (2x) (Girish et al., 2009). So, it is believed that many plant derived natural products have the potential of hepatoprotective. In view of that, these are used to treat acute and chronic liver diseases. Now, the challenge is to identify the most promising compounds and evaluate their protective mechanism. In a recently published article, Wang et al., (2010) have evaluated extracts of the plant Gentiana manshurica kitagawa (GM) in a model of acetaminophen hepatotoxicity. The authors have concluded that GM is a hepatoprotective against acetaminophen induced liver injury due to its antioxidant properties and anti apoptotic capacity (Harmut et al., 2010). Drug induced hepatic injury elicits intra cellular stress that leads to peroxidation of membrane lipids accompanied by alteration of structural and functional characteristics of membrane, which affect the activities of membrane bound ATPases. In an article by Gosh et al., (2007), they identified the 43KDa protein which has been isolated from Cajanus indicus at 2 mg/kg, ip in albino mice as an effective protector of hepatic and renal tissue against oxidative damage induced by over dosage of acetaminophen. In a recent article Ravi et al., (2010), they studied the effect of methanolic extract of flowers of Bombax ceiba Linn against INH+RIF induced hepatotoxicity in rat model. This extract at 150 mg/kg, ip significantly decreased the elevated liver markers and TBARS level and increased the level of decreased GSH.

### CONCLUSION

The inferences gathered from the above research works on these herbs have come to know that these three herbs are effective in protecting liver. Though, these three herbs are screened individually on various pharmacological activities, yet there is no research works are carried out while combining these three as formulation, particularly on drug induced hepatitis. Further, our
classical Siddha literature strongly indicates that the decoction made from these three herbs can exhibit effective and cheaper hepatoprotective action on comparing with other existing patent herbal drugs.

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