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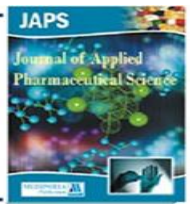

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An overview of the Herbs in a Siddha Polyherbal decoction-*Pidangunaari Kudineer* indicated for Hepatomegaly

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

V. Thanigavelan, V.Kaliyamurthi, G. Victor Rajamanickam
Sairam Advanced Centre for Research, Sri Sairam Medical College, West Tambaram, Chennai-600 044, Tamil Nadu, India.

M. Pitchiah Kumar
PG Department of Gunapadam, Government Siddha Medical College, Arumbakkam, Chennai-600 106, Tamil Nadu, India.

S. Elansekaran
National Institute of Siddha, Tambaram, Chennai – 600 045, Tamilnadu, India.

For Correspondence
Dr. V.Thanigavelan
Assistant Professor,
Sairam Advanced Centre for Research, Sairam Institutions,
West Tambaram, Chennai-600 044, Tamil Nadu, India.

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, cheap 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, antihepatoxicity induced by acetaminophen and antituberculosis drugs, anticarcinogenicity, antimicrobial properties and also phytocompounds 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 (DIH). Many drugs such as NSAID's, Anabolic steroids, Methotrexate, Erythromycin, Tetracycline, Sulpha drugs, Statins, Methyldopa, 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 – *Pidangunnari kudineer* which has literature background that has already been narrated in Siddha Materia Medica, Part 1 (Murugesha 2008, Kuppusami and Uthamarayan 2006). This formulation comprised of three plants viz: *Pidangunaari ilai* (Leaf of *Premna tomentosa* Willd), *Kadukkai thol* (Pericarp of ripe fruits of *Terminalia chebula* Retz), *Karimanjal kizhangu* (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, premnone 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 acetaminophen 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, anthelmintic, 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, spasmolytic, CNS active, antiparasitic, antispasmodic, antibacterial and antiarthritic activity (Husain *et al*, 1992). The rhizomes are also anthelmintic, carminative, antiperiodic, emollient, anodyne, laxative, diuretic, expectorant, alterative, febrifuge, opthalmic 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 diaryl 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‘hydroxyphenyl)propenoate (calebin-A) and 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,4,6-heptatrien-3-one, and seven known compounds, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-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- 1,7-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 (ED_{50} = 0.5−10 μg/mL) than Congo red (ED_{50} = 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 Zingiberine (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 sabinone (0.6%) have been identified in the ketonic fraction besides p-cymene, iso-caryophyllene, trans- b-farnesene, d-curcumene, bbisbolene 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, sabinene, myrcene, a-terpinene, limonene, p-cymene, perillyl alcohol, turmerone, eugenol, iso-eugenol, eugenol methyl ether and iso-eugenol methyl ether. The essential oil extracted from pulverizhed 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-ocimene (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, antacid and carminative. Effect of the oil on cardiovascular and respiratory systems is not marked, therefore, not of much importance from therapeutic point of view. Chloretic action of the essential oil is attributed due to p-tolymethyl carbinol. Dye-stuff acts as a cholagogue 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 and dyspnoea (Rastogi and Mehrotra, 1991). Protective effect of curcuminoids from *C. longa* on epidermal skin cells under free oxygen stress has been analysed by Bonte *et al* (1997). Anti-inflammatory activity volatile oil of *C. longa* leaves has been studied by Iyengar *et al* (1994). A comparative study on the pharmacological properties of natural curcuminoids were carried out by Anto *et al* (1994). A clinical trial of volatile oil of *Curcuma longa* Linn in the cases of Bronchial asthma (Tamaka swasa) is carried out by Jain *et al* (1990). Nematicidal activity of turmeric was studied by Kinchi *et al* (1993). Cytotoxic and tumour reducing properties of curcumin has been analysed by Soudamini and Kuttan (1988). Toxicity studies on *C. longa* are also carried out by Qureshi *et al* (1992).

The main constituents of Curcuma species are curcuminoids and bisabolane-type sesquiterpenes. Curcumin is the most important constituent among natural curcuminoids found in these plants. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is the major bioactive compound in turmeric with antioxidant, antiinflammatory, anticarcinogenic, and antimutagenic effects. Curcumin related phenolics posess antioxidant, anti-inflammatory, gastroprotective and hepatoprotective activities. The antioxidant activity of curcumin is comparable to standard antioxidants – Vit C and E, BHA and BHT (Khare 2008). Curcuminoids has anti inflammatory, antioxidant, anti-HIV, chemoprotective and antiprostate cancer effects. Recent studies on curcuminoids, particularly on curcumin, have discovered not only on the therapeutic activities, but also on mechanisms of molecular biological action and major genomic effects (Itokawa *et al.,* 2008). At low muM concentrations, curcumin modulates many structurally and functionally unrelated proteins, including membrane proteins (Ingolfsson *et al.,* 2007). Curcumin, the colouring agent and major constituent of *C. longa*, is said to possess local as well as systemic antiinflammatory property which has been found to compare favourably with phenylbutazone (Srimal and Dhawan, 1973). The volatile turmeric oil, also curcumin, exhibited anti inflammatory / antiarthritic activity in Wistar rats. The effects were comparable to those of cortisone and phenylbutazone (Ramachandran *et al.,* 2000). On oral administration, Curcumin prevents the release of inflammatory mediators and depletes nerve endings of substance P, the neurotransmitter of pain receptors (Khare 2008). Curcumin, exerts its anti-proliferative action in the synovial fibroblasts obtained from patients with RA. Exposures of the synovial fibroblasts to curcumin have resulted in growth inhibition and the induction of apoptosis, as measured by MTT assay, fluorescent microscopy and Annexin-V-based assay. RT-PCR and immunoblotting showed that treating the cells with curcumin resulted in the down-regulation of anti-apoptotic Bcl-2 and the X-linked inhibitor of the apoptosis protein as well as the up-regulation of pro-apoptotic Bax expression in a concentration-dependent manner. Curcumin-induced apoptosis is also associated with the proteolytic activation of caspase-3 and caspase-9, and the concomitant degradation of poly(ADP-ribose) polymerase protein. Furthermore, curcumin has decreased the expression levels of the cyclooxygenase (COX)-2 mRNA and protein without causing significant changes in the COX-1 levels, which was correlated with the inhibition of prostaglandin E2 synthesis (Park *et al.,* 2007). Chronic administration of curcumin (20 mg/kg, po) in Sciatic nerve ligated Wistar rats, significantly reversed behavioral alteration and attenuated oxidative damage in both sciatic nerve and brain as compared to control. Further, L-NAME (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 diptheriae, 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 arturmerone 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 anticataractogenic 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. Curlone, 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 (diferuloyl 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 *in vitro*. 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 Choornam* 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 terchebin, punicalagin and teaflavin A have been isolated from the fruits of *T.chebula*. A new triterpene, chebupentol, and arjungenin, terminoic 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 nitrilotriacetic 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.

REFERENCES

Anil Kumar., Singh A. Possible nitric oxide modulation in protective effect of *Curcuma longa*, Zingiberaceae against sleep deprivation-induced behavioral alterations and oxidative damage in mice. Phytomedicine. 2008; 15(8): 577-586.

Anto RJ., Kuttan G., Kuttan R., Babu KVO., Rajasekaran KN. A comparative study on the pharmacological properties of Natural Curcuminoids. Amala research Bulletin. 1994; 14: 60-65.

Asolkar LV, Kakkar KK and Chakre OJ. Secondary Supplement to Glossary of Indian Medicinal Plants with active principles. Publications and Information Directorate (CSIR), New Delhi (1992)

Bonte F., Noel Hudson MS., Wepierre J., Meybeck A. Protective effect of curcuminoids from *Curcuma long* L on epidermal skin cells under free oxygen radical stress. Planta Medica. 1997; 63(3): 265-286.

Carounanidy U., Satyanarayanan R., Velmurugan A. Use of an aqueous extract of *Terminalia chebula* as an anticaries agent: A clinical study. Indian J Dent Res. 2007; 18(4): 152-156.

Chin YW., Jones WP., Mi Q., Rachman I., Riswan S., Kardono LBS., Chai HB., Farnsworth NR., Cordell GA., Swanson SM. Cytotoxic clerodane diterpenoids from the leaves of *Premna tomentosa*. Phytochemistry. 2006; 67(12): 1243-1248.

Chopra RN, Nayar SL and Chopra IC. Glossary of Indian Medicinal Plant, CSIR, New Delhi (1980)

Dey AC (ed). Indian Medicinal Plant used in Ayurvedic Preparations. Books and periodicals publication Co, Dehradun, India (1980) 60-75

Dwivedi Y., Rastogi R., Chander R., Sharma SK., Kapoor NK., Garg NK *et al*. Hepatoprotective activity of picroliv against carbontetrachloride induced liver damage in rats. Indian J Med Res. 1990; 92: 195-200.

El-Ansary AK., Ahmed SA., Aly SA. Antischistosomal and liver protective effects of *Curcuma longa* extract in *Schistosoma mansoni* infected mice. Indian Journal of Experimental Biology. 2007; 45(9): 791-801.

Fu Y., Zheng S., Lin J., Ryerse J., Chen A. Curcumin protects the rat liver from CCl_4-caused injury and fibrogenesis by attenuating oxidative stress and suppressing inflammation. Mol Pharmacol. 2008; 73: 399-409.

Gadgoli C., Mishra SH. Antihepatotoxic activity of p-methoxy benzoic acid from *Capparis spinosa*. J Ethnopharmacol. 1999; 66: 187-192.

Gao H, Huang YN, Gao B, Kawabata J. Chebulagic acid is a potent alpha-glucosidase inhibitor. Biosci Biotechnol Biochem 2008; 72(2): 601-603.

Garg SC., Jain RK. Antimicrobial activity of the essential oil of *Curcuma longa* L. Indian Perfumer. 2003: 47(2): 199-202.

Garg SK., Mathur VS., Chaudhury RR. Screening of India plants of antifertility activity. Indian Journal of Experimental Biology. 1978; 16: 1077-1079.

Ghosh A., Sil PC. Anti-oxidative effect of a protein from *Cajanus indicus* L against acetaminophen-induced hepato-nephro toxicity. J Biochem Mol Biol. 2007; 40(6): 1039-1049.

Gupta AK and Sharma M (editors). Reviews on Indian medicinal plants, Vol. 5. Indian Council of Medical Research New Delhi (2007)

Handa SS., Sharma A. Hepatoprotective activity of andrographolide from *Andrographis paniculata* against carbontetrachloride. Indian J Med Res. 1990; 92: 276-283.

Hartmut Jaeschke., David Williams C., Mitchell R McGill., Anwar Farhood. Herbal extracts as hepatoprotectants against acetaminophen hepatotoxicity. World J Gastroenterol. 2010; 16(19): 2448-2450.

Husain A, Virmani OP, Popli SP, Misra LN, Gupta MM, Srivastava GN, Abraham Z and Singh AK. Dictionary of Indian Medicinal Plant. CIMAP. Lucknow, India (1992) 546

Ingolfsson HI., Ii RE., Andersen OS. Curcumin is a Modulator of Bilayer Material Properties. Biochemistry. 2007; 46(36): 10384–10391.

Itokawa H., Shi Q., Akiyama T., Morris-Natschke SL., Lee KH. Recent advances in the investigation of curcuminoids. Chin Med. 2008; 3: 11.

Iyengar MA., Rama Rao MP., Gurumadhava Rao S., Kamath MS. Antiinflammatory activity of volatile oil of *Curcuma longa* L leaves. Indian drugs. 1994; 31(1): 528-531.

Jain JP., Naqui SMA., Sharma KD. A clinical trial of volatile oil of *Curcuma longa* Linn (Haridra) in cases of bronchial asthma (Tamaka swasa). Journal of research in Ayurvedha and Siddha. 1990; 11(1-4): 20-30.

Kang EH., Kown TY., Oh GT., Park WF., Park SI., Park SK *et al*. The flavonoid ellagic acid from a medicinal herb inhibits host immune tolerance induced by the hepatitis B virus-e antigen. Antiviral Res. 2006; 72: 100-106.

Karunagaran D., Rashmi R., Kumar TR. Induction of apoptosis by curcumin and its implications for cancer therapy. Curr Cancer Drug Targets. 2005; 5(2): 117-129.

Khare CP. Indian Medicinal Plants. Springer. New Delhi (2008) 187, 188, 517, 654.

Khazaeli P., Goldoozian R., Sharififar F. An evaluation of extracts of five traditional medicinal plants from Iran on the inhibition of mushroom tyrosinase activity and scavenging of free radicals. Int J cosmet Sci. 2009; 31(5): 375-381.

Kim HJ., Yoo HS., Kim JC., Park CS., Choi MS., Kim M., Choi H., Min JS., Kim YS., Yoon SW., Ahn JK. Antiviral effect of *Curcuma longa* Linn extract against hepatitis B virus replication. J Ethnopharmacol. 2009; 124(2): 189-196.

Kinchi F., Goto Y., Sugimoto N., Akao N., Kondo K., Tsuda Y. Nematicidal activity of turmeric: synergistic action of curcuminoids. Chemical and Pharmaceutical Bulletin. 1993; 41(9): 1040-1043.

Kiso Y., Suzuki Y., Watanabe N., Oshima Y., Hikino H. Antihepatotoxic principles of *Curcuma longa* rhizomes. Planta medica. 1983; 49: 185-187.

Koul IB., Kapil A. Effect of diterpenes from *Andrographis paniculata* on antioxidant defense system and lipid Peroxidation. Indian J Pharmacol. 1994; 26: 296-300.

Kuppusami & Uthamarayan. (2006). Kudineergal. In Siddha Vaidhya Thirattu (pp. 295). Chennai, India: Department of Indian Medicine and Homoeopathy

Kuroda M., Mimaki Y., Nishiyama T., Mae T., Kishida H., Tsukagawa M., Takahashi K., Kawada T., Nakagawa K., Kitahara M. Hypoglycemic effects of turmeric (*Curcuma longa* L. rhizomes) on genetically diabetic KK-Ay mice. Biological & Pharmaceutical Bulletin. 2005; 28(5): 937-939.

Kusirisin W., Srichairatanakool S., Lerttrakarnnon P., Lailerd N., Suttajit M., Jaikang C., Chaiyasut C. Antioxidative activity, polytphenolic content and anti-glycation effect of some Thai medicinal plants traditionally used in diabetic patients. Med Chem. 2009; 5(2): 139-147.

Lawrence BM. Progress in essential oils. Perfumer Flavorist. 1982; 7: 45.

Lee SI., Hyun PM., Kim SH., Kim KS., Lee SK., Kim BS., Maeng PJ., Lim JS. Suppression of the onset and progression of collagen/ induced arthritis by chebulagic acid screened from a natural product library. Arthritis Rheum. 2005; 52(1): 345-353.

Murali YK., Anand P., Tandon V., Singh R., Chandra R., Murthy PS. Long term effects of *Terminalia chebula* Retz on hyperglycemia and associated hyperlipidemia, tissue glycogen content and *in vitro* release of insulin in streptozotocin induced diabetic rats. Exp Clin Endocrinol Diabetes. 2007; 115(10): 641-646.

Murugan P., Pari L. Influence of tetrahydrocurcumin on erythrocyte membrane bound enzymes and antioxidant status in experimental type 2 diabetic rats. J Ethnopharmacol. 2007; 113(3): 479-486.

Murugesha KS. Siddha Materia Medica (Medicinal Plants Division). Department of Indian Medicine and Homoeopathy. Chennai, India (2008) 674-675

Negi AS., Kumar JK., Luqman S., Shanker K., Gupta MM., Khanuja SP. Recent advances in plant hepatoprotectives: a chemical and biological profile of some important leads. Med Res Rev. 2007; 28: 746-772.

Padmaja S., Raju TN. Protective effect of curcumin during selenium induced toxicity on dehydrogenases in hepatic tissue. Indian J Physiol Pharmacol. 2005; 49(1): 111-114.

Pandima Devi K., Sreepriya M., Balakrishna K., Devaki T. Protective effect of *Premna tomentosa* L (Verbenaceae) extract on membrane-bound phosphatases and inorganic cations transport in acetaminophen-induced hepatotoxicity rats. Journal of Ethnopharmacology. 2004; 93: 371-375.

Park C., Moon DO., Choi IW., Choi BT., Nam TJ., Rhu CH., Kwon TK., Lee WH., Kim GY., Choi YH. Curcumin induces apoptosis and inhibits prostaglandin E2 production in synovial fibroblasts of patients with rheumatoid arthritis. Int J Mol Med. 2007; 20(3): 365-372.

Park SY., Kim DSHL. Discovery of natural products from *Curcuma longa* that protect cells from beta-amyloid insult: A drug discovery effort against Alzheimer's disease. Journal of Natural Products. 2002; 65(9): 1227-1231.

Prasad L., Khan TH., Jahangir T., Sultana S. Abrogation of DEN/Fe-NTA induced carcinogenic response, oxidative damage and subsequent cell proliferation response by *Terminalia chebula* in kidney of Wistar rats. Pharmazie. 2007; 62(10): 790-797.

Quereshi S., Shah AH., Ageel MM. Toxicity studies on *Alpinia galanga* and *Curcuma longa*. Planta Medica. 1992; 58(2): 124-127.

Rajakrishnan V., Viswanathan P., Rajasekharan KN., Menon VP. Neuroprotective role of curcumin from Curcuma longa on ethanol-induced brain damage. Phytother Res. 1999; 13: 571-574.

Ramachandran R *et al*. Proceedings of International Congress on "Ayurveda-2000". Chennai. 2000: 199.

Rastogi RP and Mehrotra BN. Compendium of Indian Medicinal Plant Vol I. Central drug research Institute, Lucknow, Publications and Information Directorate, New Delhi (1991) 833

Ravi V., Patel SS., Verma NK., Dutta D., Saleem TS. Hepatoprotective Activity of *Bombax ceiba* Linn against Isoniazid and Rifampicin-induced Toxicity in Experimental Rats. International Journal of Applied Research in Natural Products. 2010; 3(3): 19-26.

Reddy DB., Reddy TC., Jyotsna G., Sharan S., Priya N., Lakshmipathi V., Reddanna P. Chebulagic acid, a COX-LOX dual inhibitor isolated from the fruits of *Terminalia chebula* Retz induces apoptosis in COLO-205 cell line. J Ethnopharmacol. 2009; 124(3): 506-512.

Shin MS., Kang EH., Lee YI. A flavonoid from medicinal plants blocks hepatitis B virus-e antigen secretion in HBV infected hepatocytes. Antiviral Res. 2005; 67: 163-168.

Singh I., Singh PK., Bhansali S., Shafiq N., Malhotra S., Pandhi P., Pal Singh A. Effects of three different doses of a fruit extract of *Terminalia chebula* on metabolic components of metabolic syndrome, in a rat model. Phytother Res. 2010; 24(1): 107-112.

Soudamini KK., Kuttan R. Cytotoxic and tumour reducing properties of curcumin, Indian Journal of pharmacology. 1988; 20(24): 55-101.

Srimal RL., Dhawan N. Pharmacology of diferuloyl methane (curcumin), a non steroidal anti- inflammatory agent. J Pharma Pharmacol. 1973; 25: 447-452.

Sun M., Yang Y., Li H., Su B., Lu Y., Wei Q., Fan T. The effect of curcumin on bladder cancer cell line EJ *in vitro*. Zhong Yao Cai 2004; 27(11): 848-850.

Suryanarayana P., Saraswat M., Mrudula T., Krishna TP., Krishnaswamy K., Reddy GB. Curcumin and turmeric delay streptozotocin-induced diabetic cataract in rats. Invest Ophthalmol Vis Sci. 2005; 46(6): 2092-2099.

Tasduq SA., Singh K., Satti NK., Gupta DK., Suri KA., Johri RK. *Terminalia chebula* (fruit) prevents liver toxicity caused by sub/ chronic administration of rifampicin, isoniazid and pyrazinamide in combination. Hum Exp Toxicol. 2006; 25(3): 111-118.

Thyagarajan SP., Subramanian S., Thirunalasundari T., Venkateswaran PS., Blumberg BS. Effect of *Phyllanthus amarus* on chronic carriers of hepatitis B virus. Lancet. 1988; 2: 764-766.

Usman *et al*. Chemical composition of Rhizome of essential oil of *Curcuma longa* L growing in North Central Nigeria. World Journal of Chemistry. 2009; 4(2): 178-181.

Wang AY., Lian LH., Jiang YZ., Wu YL., Nan JX. *Gentiana manshurica kitagawa* prevents acetaminophen induced acute hepatic injury in mice via inhibiting JNK/ERK MAPK pathway. World J Gastroenterol. 2010; 16: 384-391.

Warrier PK. Indian Medicinal Plant Vol. 2. Orient Longman Ltd, Kottakkal, Kerala, India (1994) 259