Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2021; 10(2): 285-288
Received: 10-01-2021
Accepted: 12-02-2021

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Hepatoprotective medicinal plants traditional knowledge to scientific evidences: A review

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Abstract
Hepatic dysfunction results in inflammation and deposition of fat molecules in the liver. The possible side effects of synthetic drugs arose the need for plant derived liver care products and pharmaceuticals. Phyto resources having potential biologically active hepatoprotective compounds viz., *Tephrosia purpurea* L., *Phyllanthus niruri* L., *Andrographis paniculata* (Burm. F.) Wall. Ex Nees., *Indigofera tinctoria* Linn., *Curcuma longa* L., *Punica granatum* L. and *Nigella sativa* L. are discussed here. Indigenous traditional knowledge and research evidences on *in vitro, in vivo* clinical trials and neutraeuticals possibly capable for hepatic care are reviewed.

Keywords: alcoholism, cirrhosis, indigenous, neutraceutical, traditional

1. Introduction
Hepatic dysfunction is a major health concern resulting in jaundice, hepatitis, abdominal pain, nausea, vomiting and over time resulting in cirrhosis. Liver diseases are steadily increasing over the years and World Health Organisation (WHO) has projected it as the eleventh most important cause of death in the world by 2030 and may be the tenth most common cause of death in India by 2020 [1].

Liver, the largest organ in the human body performs many metabolic functions. Alcoholism is the major cause affecting liver function. Not only alcohol, addiction to junk foods, excessive use of drugs, lack of exercise and some viruses Hepatitis A, B, C, D and E can also causes liver problems. Both alcoholic and non-alcoholic causes results impairment in serum enzyme levels namely, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT). Proteins namely, globulin, albumin, prothrombin and bilirubin pigment levels also gets impaired[2] and results in inflammation and deposition of fat molecules in the liver known as steatosis which may lead to liver cancer.

2. Hepatoprotective medicinal plants
Livercare is a challenge for healthcare professionals and scientists. Traditional health care practice of indigenous people concerning to human health is termed as ethnomedicine. Hence, folkloric herbs with hepatoprotective potentials have gained considerable attention. A few medicinal plants with proven heptoprotective activity viz., the whole plant parts of *Tephrosia purpurea* (L.) Pers. and *Phyllanthus niruri* L., leaves of *Andrographis paniculata* (Burm. F.) Nees. and *Indigofera tinctoria* Linn., rhizomes of *Curcuma longa* L., and fruits of *Punica granatum* L. and *Nigella sativa* L. are discussed below.

2.1. Whole plant
2.1.1. *Tephrosia purpurea* (L.) Pers: Wild Indigo/ Fish poison
Tephrosia purpurea commonly called as wild indigo, belonging to the family fabaceae is an erect annual or short-lived perennial herb. It is a common wasteland weed and in many parts it is cultivated as green manure crop [3]. Indigenously entire plant parts are used for curing hepatic disorders. Its whole plant powder boiled with water or milk, decoction of the whole plant, root juice, root paste along with butter milk and root powder along with black pepper is advised for fatty liver [4].

Methanolic leaf and root extracts of *T. purpurea* was tested *in vitro* in human liver cancer (HepG2) cell lines. Cancer cell growth inhibition property was observed with an increase in concentration [5]. The hepatoprotective activity of methanolic dried stem extract was tested in CCl_4 toxicity induced rats and significant activity was observed at 150 mg/kg concentration [6]. Aqueous whole plant extract proved its hepatoprotective action in CCl_4 hepatic damage induced rats by normalizing the elevated liver enzyme values [7].

Link livecare a polyherbal formulation containing *T. purpurea* was developed by Link Natural Products, Sri Lanka and its *in vivo* hepatoprotective activity was proven in mice [8]

2.1.2. *Phyllanthus niruri* L.: Stone breaker

Phyllanthus niruri commonly called as stone breaker belonging to the family Euphorbiaceae is an erect, annual herb. Leaves are numerous, sub sessile distichous, elliptic oblong, stipulate and paripinnate with small leaflets. Flowers are very minute, numerous and yellowish in colour. Fruit is a capsule [3]. In folkloric medicine, fresh root extract [9], plant juice as well as whole plant powder (5g) [10] and fresh leaves mixed with cow or goat's milk is recommended for jaundice [4].

Phyllanthin, hypophyllanthin and niranthin[11] are the reported hepatoprotective compounds. The hepatoprotective action of epicatechin was proved against D – galactosamine induced hepatitis in rats by lowering the elevated levels of liver enzymes and bilirubin values [12]. Aqueous *Phyllanthus niruri* extract also proved its hepatoprotective action in mice by restoring the elevated liver enzymes levels [13]. In a clinical trial done in patients affected with hepatic steatosis, silymarin/ *Phyllanthus niruri* combination showed significantly better results than silymarin alone, in normalization of the hepatic parameter values [14].

2.2. Leaves

2.2.1. *Andrographis paniculata* (Burm. F.) Wall. Ex Nees.: Kalmegh

Andrographis paniculata commonly called Kalmegh or "King of Bitters" is an erect annual herb with quadrangular stem at the upper part while the lower part of stem is nearly rounded. Leaves are medicinal and is borne opposite, sessile or subsessile, linear lanceolate or lanceolate, 3-8 cm long, acute, glabrous or minutely puberulous beneath with cuneate base and slightly undulated margins [3]. *A. paniculata* leaves are benefited for curing liver ailments in the following ways. In tradition leaf powder added with garlic is recommended along with buttermilk twice daily for curing jaundice [15]. Fresh leaves/ leaf powder is recommended as liver tonic [16]. Leaves and young twigs are smashed and 20-30 g paste is given three times daily for treating jaundice [10]. Kalmegh leaves pasted along with black pepper can be administered by jaundice patients in early morning for better cure [17].

Neo-andrographolide, kalmeghin, andrographoside [11] and andrographolide [18] are the hepatoprotective compounds in kalmegh leaves. In an *in vitro* study andrographolide (30 µmol) treatment provided protection to liver cell against CCl_4 toxicity [19]. In another study, *A. paniculata* aqueous extract (300 mg) proved its hepatoprotective action in rats against D – galactosamine [20]. In a clinical trial done using kalmegh decoction for curing acute viral hepatitis also, reduction in serum enzyme levels and improvement in clinical symptoms (headache, fever, nausea, vomiting, etc.) were noticed [21]. Late in 2017, a polyherbal formulation containing kalmegh marketed in the name Link-livecare was developed by Link Natural Products Limited, Sri Lanka and proven hepatoprotective [8].

2.2.2. *Indigofera tinctoria* Linn.: True Indigo

Indigofera tinctoria, commonly called as true indigo, is the major source of indigo dye. Its leaves are arranged spirally, imparipinnate with 9-13 leaflets and has red/ pinkish papilionaceous flowers in axillary racemes [3]. Its leaves are a major ingredient in Neelibringhadi hair oil. Moreover, palliyar tribes used its leaf infusion along with goat's milk for the treatment of jaundice [22].

The leaves are benefited in curing liver disorders due to the compound indigtone [23]. Its efficiency for damaging human liver carcinoma cells was proved *in vitro* [24]. Liv 52 is proven hepatoprotective drug. The efficiency of clearliv (a polyherbal formulation containing indigo leaves) and Liv 52 was compared and found both are equally good for curing hepatic dysfunction in albino rats [25].

2.3. Rhizome

2.3.1. *Curcuma longa* L.: Turmeric

Curcuma longa commonly called as turmeric is a rhizomatous herbaceous perennial containing anticancerous compound curcumin [3]. For jaundice treatment, rhizome paste (12-15 g) mixed with cow milk [26], rhizome extract mixed with *Piper longum* L. fruits [10] are used in folkloric medicine.

Its the same anticancerous compound curcumin that imparts hepatoprotective function. Fermented turmeric powder capsule consumption was proved clinically good in normalizing the elevated alanine transaminase levels (ALT) [27]. In an *in vitro* study, curcumin showed maximum inhibition of liver cancer cell growth at 50 µM concentration [28].Recently, *in vivo* hepatoprotective potential of curcuminoids was also identified [29].

2.4. Fruits

2.4.1. *Punica granatum* L.: Pomegranate

Punica granatum belonging to the family punicaceae is a small multi-stemmed shrub or tree whose fruits are hepatoprotective [3]. Traditionally it is used for curing hepatic disorder in the following ways. Powdered fruits [10], dry rind powder (2 teaspoons) added in water as well as a mix of *Phyllanthus emblica* and anardana powder [9] are found effective for jaundice.

Gluconorm - 5 a polyherbal formulation containing pomegranate on administration at 300 mg/kg concentration is equally effective for curing diabetes and liver disorders [30]. Pomegranate leaf extract also reported both *in vitro* and *in vivo* hepatoprotective potential[31]. A silver nanoparticle formulation using pomegranate leaf extract was developed that could destruct human liver cancer cells [32].

2.4.2. *Nigella sativa* L.: Black cumin/ Kalonji

Nigella sativa commonly called as kalonji belonging to the family ranunculaceae is an annual herbaceous flowering plant whose fruits are hepatoprotective. The fruits commercially called as kalonji seeds is a large and inflated capsule composed of three to seven united follicles, each containing seeds [3].

Dried and powdered kalonji seeds in milk as well as ajwain extract added with kalonji oil gives quick relief from liver problems and jaundice. The powerful hepatoprotective compound reported is thymoquinone [33]. The cytotoxic potential of *Nigella sativa* seed oil (NSO) was assessed in human liver cancer cell line (HepG2), human breast cancer cell line (MCF-7), human lung cancer cell line (A-549) and human embryonic kidney cell line (HEK293) at different concentrations (50–250 µg/ml). All cancer cells lines are adversely affected by the treatment of *Nigella sativa* seed oil and maximum cytotoxic response was observed in HepG2 cells [34]. In acetaminophen toxicity induced rats elevated levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase could be reduced by kalonji seed extract[35]. Moreover an improvement in liver

steatosis and injury was made possible in patients when *Nigella sativa* seed oil was combined with honey and water [36].

3. Conclusion

A wide treasure of medicinal plants in nature are effective for hepatic care among which only a few medicinal plants are reviewed. Indigenous traditional knowledge base of those hepatoprotective phyto resource are scientifically proved through phytochemical studies *in vitro, in vivo* and clinical trials. Hence scope exists for the identification of new therapeutically active phytochemicals and development of pharmaceuticals, neutraceuticals, nanomedicines, etc. out of those phyto resources.

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