The Pharma Innovation Journal 2022; SP-11(4): 400-406

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2022; SP-11(4): 400-406

www.thepharmajournal.com
Received: 19-02-2022
Accepted: 21-03-2022

Pooja S
Research Scholar, Department of Plantation, Spices, Medicinal and Aromatic crops, College of Horticulture, UHS, Bagalkot, Karnataka, India

Vijaykumar B Narayanapur
Assistant Professor and Head, Department of Plantation, Spices, Medicinal and Aromatic Crops, College of Horticulture, UHS, Bagalkot, Karnataka, India

Corresponding Author
Vijaykumar B Narayanapur
Assistant Professor and Head, Department of Plantation, Spices, Medicinal and Aromatic Crops, College of Horticulture, UHS, Bagalkot, Karnataka, India

Hepatoprotective phyto resources: Traditional knowledge to scholarly evidences

Pooja S and Vijaykumar B Narayanapur

Abstract
Bioprospecting is defined as a systematic and organized search for useful products derived from bioresources including plants, microorganisms, animals, etc., that can be developed further for commercialization and overall benefits of the society. Hepatic dysfunction is a major health concern challenging health care professionals and scientists. It can be a life-threatening condition resulting in jaundice, hepatitis, abdominal pain, nausea, vomiting and over time resulting in cirrhosis. There are several phyto resources with hepatoprotective activity. The whole plant is medicinal, its powder boiled with water or milk is found effective for the treatment of jaundice. Its root along with butter milk and root powder along with black pepper is advised for fatty liver patients. The aqueous extract of *Eclipta alba* in human liver cancer cells at different concentrations (25, 50, 75 µg/ml) and the cell viability was analysed using SRB assay. The liver cancer cell inhibition property was found at very low concentration *i.e.,* at 25 µg/ml maximum liver cells got damaged. Several traditional information documented against each phyto resources and scientific evidences has also been described. Hence it is advisable to focus on productive research by maximum exploitation of traditional knowledge and sustainable utilization of phyto resources for the benefit of the society.

Keywords: Bioprospecting, hepatoprotective, methanolic, *Eclipta alba*, pharmaceutical

Introduction
Hepatic dysfunction is a major health concern challenging health care professionals and scientists. It can be a life-threatening condition 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 (WHO, 2016) [42]. In India about 10 lakh people are diagnosed with liver diseases every year and it affects every one in five Indians (Times of India, 2017) [1].

Liver, the largest organ in the human body performs many functions. It aids in digestion of food by producing bile, stores extra sugar in the body and coverts them back to glucose when the body needs it, helps in the production of amino acids, the basic building blocks for the production of proteins and conversion of waste from human body into urea. There are several causes of chronic liver disease. Alcoholism is the major cause affecting liver function. Not only alcohol, addiction to junk foods, excessive use of drugs and lack of exercise also causes liver problems. Both alcoholic and non-alcoholic causes results in inflammation and deposition of fat molecules in the liver known as steatosis. Steatosis occurs as three stages, Grade 1 (Mild) – Steatosis – 66%, Grade 2 (Moderate)- Steatosis – any degree > 66% and Grade 3 (Severe) – completely inflammated. The symptoms of liver diseases include jaundice, dark urine, extreme fatigue, nausea, vomiting, abdominal pain, etc. (WHO, 2019) [49]. In spite of several advances in modern medicine there are no effective remedies for liver diseases, in contrast a number of traditional medicinal preparations are there in India recommended for the treatment of liver diseases, *i.e.*, several pharmaceutical drugs are available of which the most recommended one is Silymarin which is a plant derived drug from Milk Thistle.

Bioprospecting is defined as a systematic and organized search for useful products derived from bioresources including plants, microorganisms, animals, etc., that can be developed further for commercialization and overall benefits of the society (Oyemitan, 2017) [24]. The first step of bio-prospecting involves traditional knowledge documentation from traditional health practitioners through ethnopharmacological surveys and phytochemicals responsible for the action will be studied. The efficiency of the isolated compounds will be tested for *in vitro* (MTT assay, Trypan Blue exclusion Test, etc.) and *in vivo* analysis (Liver function tests)

followed by the clinical trial in humans finally leading to the pharmaceutical drug or nutraceutical development.

Liver function tests are blood tests done to detect liver damage. These blood tests measure the levels of certain enzymes namely, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT). The normal values of these enzyme are ALT (7 - 55 U/L), AST (8 - 48 U/L), ALP (40 - 129 U/L) and GGT (8 - 61 U/L). Higher values represent liver damage. Proteins namely, globulin, albumin, prothrombin and bilirubin pigment is also measured. The normal values of these proteins and pigments are globulin (2.3 - 3.5 g/dl), albumin (3.5 - 5.0 g/dl), prothrombin (9.4 - 12.5 sec) and bilirubin (0.1 - 1.2 mg/dl). Lower the values of albumin and globulin, higher the time required for blood clotting and higher the values of bilirubin indicate liver damage (ALF, 2016) [4].

Hepatoprotective phyto resources

There are several phyto resources with hepatoprotective activity. A few medicinal plants whose leaves, stem, roots, whole plant, fruits and seeds with proven heptoprotective activity are discussed bel

Whole plant

Tephrosia purpurea (L.) Pers: Wild Indigo/Fish poison

Tephrosia purpurea is an annual belonging to the family Fabaceae (Jain, 2016) [14]. The whole plant is medicinal, its powder boiled with water or milk is found effective for the treatment of jaundice. Its root along with butter milk and root powder along with black pepper is advised for fatty liver patients (Kalaskar *et al.*, 2014) [15].

Tephrorins A and B / Tephrosone are the compounds responsible for its hepatoprotective action (Girish *et al*., 2011) [10]. Padmapriya *et al.* (2017) [25] reported the hepatoprotective activity of both its leaves and roots *i.e.*, when the methanolic extract of leaves and roots was treated with HepG2 (Human liver cancer) cells, liver cancer cell growth inhibition property was observed and the activity increased with the increase in concentration. Verma *et al*. (2017) [40] reported the hepatoprotective activity of methanolic extract of dried stem in CCl4 toxicity induced rats. When toxicity was induced all the biochemical elevated and when *T. purpurea* stem extract 150 mg/kg concentration was given it could lower the elevated biochemical parameters (Table 1).

Table 1: Effect of *T. purpurea* extract on hepatic enzyme activities

Groups	SGPT (IU/L)	SGOT (IU/L)	ALP (IU/L)	Total Bilirubin (mg/dl)
Group 1	26.6 ± 4.63	71.7 ± 5.69	41.9 ± 5.69	0.13 ± 0.002
Group 2 (CCl) 4	207.6 ± 8.10	217.7 ± 7.84	257.2 ± 7.65	0.95 ± 0.05
Group 3 (75 mg/kg)	152.33 ± 5.22	163.2 ± 5.36	162.1 ± 5.69	0.79 ± 0.004
Group 4 (150 mg/kg)	126.2 ± 4.12	98.7 ± 2.36	103.4 ± 4.65	0.31 ± 0.003
Group 5 Silymarin (25mg/kg)	123.8 ± 5.12	101.3 ± 4.56	105.3 ± 5.62	0.32 ± 0.003

(Verma *et al.*, 2017)

Eclipta alba (L.) Hassk: Bhringraj

Eclipta alba is an annual herb belonging to the family Asteraceae. Traditionally whole plant/ leaf juice, 1 teaspooon is given for jaundice patients (Kalaskar *et al.*, 2014) [15]. Also, whole plant paste (20-30 g) mixed with salt is taken to cure jaundice (Sharma *et al.*, 2016) [32].

The compounds responsible for its hepatoprotective action are wedelolactone, luteolin and apigenin (Mismisuraya *et al.*, 2015) [22]. A salient finding was obtained in a cell culture study using aqueous extract of *Eclipta alba* in human liver cancer cells at different concentrations (25, 50,75 µg/ml) and the cell viability was analysed using SRB assay. The liver cancer cell inhibition property was found at very low concentration *i.e.*, at 25 µg/ml maximum liver cells got damaged. (Vyanktesh *et al.*, 2019) [41]. A polyherbal capsule was developed using *Eclipta alba* by Vadivu *et al*. (2013) [39] at Madras Medical College and tested in rats at two different concentrations. When toxicity was induced using CCl4 all the biochemical parameters elevated showing hepatic damage. When polyherbal capsule was given, it could bring down all the biochemical parameters showing significant hepatoprotective activity which is comparable with the standard drug silymarin (Table 2).

Table 2: Effect of polyherbal capsule on biochemical parameters

Group	Treatment	SGOT (IU/L)	SGPT (IU/L)	ALP (IU/L)	Total Bilirubin (mg/dl)
I	Control	23.77 ± 3.08	51.22 ± 2.21	153.31 ± 2.54	0.47 ± 0.05
II	CCl control 4	62.84 ± 2.17*	112.70 ± 1.71*	215.54 ± 2.32*	2.13 ± 0.11*
III	Standard	29.46 ± 1.88**	82.06 ± 2.01**	168.12 ± 2.87**	0.94 ± 0.17**
IV	Test drug (Low dose - 100mg/kg)	38.03 ± 2.19**	84.44 ± 1.45**	186.81 ± 2.03**	1.66 ± 0.28**
V	Test drug (High dose- 200mg/kg)	29.05 ± 3.31**	79.73 ± 3.0**	179.43 ± 2.13**	0.90 ± 0.17**

(Vadivu *et al.*, 2013) [39]

Phyllanthus niruri L.: Stone breaker

Phyllanthus niruri is an annual herb belonging to the family Euphorbiaceae. Traditionally whole plant powder (5g) is recommended for jaundice. Also, fresh roots are crushed and mixed with water. Half cup of the extract is advised for jaundice patients (Abbasi *et al*., 2009) [2].

Mismisuraya *et al.* (2015) [22] reported phyllanthin, hypophyllanthin and niranthin as its hepatoprotective compounds. Shanmugam *et al*. (2017) [31] reported that the compound epicatechin also has hepatoprotective potential and tested in rats. The rats were induced hepatitis by administering D – Galactosamine. When hepatitis was induced all the biochemical parameters, liver enzymes and bilirubin values elevated and albumin value reduced. Epicatechin treatmen recorded reduction in level of liver enzymes and bilirubin, and an increase in albumin values showing the recovery of rats from hepatitis (Table 3).

Table 3: Effect of Epicatechin on biochemical parameters

Group	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	Bilirubin (mg/dl)	Albumin (mg/dl)
I	42.213 ± 4.921	41.843 ± 1.620	151 ± 9.826	1.0 ± 0.2	3.1 ± 0.492
II	47.175 ± 3.428	45.535 ± 3.050	112 ± 11.124	0.5 ± 0.106	2.9 ± 0.21
III (Hepatitis)	206.442* ± 7.642	131.642 ± 11.398	302 ± 12.368	2.7 ± 0.046	1.2 ± 0.0.82
IV (Epicatechin)	72.267* (±2.165)	67.348* (±6.252)	180* (±10.604)	0.9* (±0.049)	2.7* (±0.092)
V	66.731* ± 4.614	51.189* ± 3.092	151* ± 8.814	0.8* ± 0.063	2.2* ± 0.142

(Shanmugam *et al*., 2017) [31]

Balakrishnan and Toms (2018) [7] reported the hepatoprotective activity of *Phyllanthus niruri* aqueous extract by inducing hepatotoxicity in mice using CCl4. Administration of *Phyllanthus niruri* aqueous extract produced significant hepatoprotection against carbon tetrachloride (CCl4) induced hepatotoxicity in mice by restoring the liver enzymes levels. A clinical study was done by combining silymarin / *Phyllanthus niruri* extract and given to patients affected with hepatic steatosis. A similar group of patients were given silymarin alone. Both products were effective in the normalization of liver function, but the combination silymarin / *Phyllanthus niruri* extract showed significantly better results than silymarin alone, considering the normalization of the hepatic parameter values after 3 and 6 months (Mali *et al.*, 2018) [19].

Leaves

***Silybum marianum* L. Gaertn: Milk Thistle**

Silymarin is an erect annual herb growing upto 2.5m. It is an important herbal hepatoprotective drug as well as drug of choice for several hepatic disorders (Praveen *et al*., 2011). Traditionally, its leaf juice and seeds are recommended for jaundice (Abbasi *et al*., 2009) [2].

Silymarin, Silibinin, Silybin and Silydianin are the hepatoprotective compounds isolated from this plant (Mismisuraya *et al*., 2015) [22]. The human hepatocellular carcinoma cell line (HepG2) was utilized and the MTT assay was performed to study the antiproliferative effect of silymarin. Silymarin at different concentrations (50-200 µg/ml) was tested on liver cancer cells. Silymarin proved to inhibit the growth of liver cancer cells showing maximum inhibition at a concentration of 200 µg/ml (Ramakrishnan *et al*., 2009) [28]. A nanoemulsion formulation was developed using silymarin and tested in wistar rats (Praveen *et al*., 2011). For this experiment hepatotoxicity was induced using CCl4. When hepatotoxicity was induced all the enzymes and bilirubin values elevated. When the nanoemulsion formulation was given all these parameters reduced showing its potent hepatoprotective activity. The results indicate an excellent potential of the nanoemulsion formulation for the reversal of CCl4 induced liver toxicity in rats as compared to standard silymarin (Table 4).

Table 4: Effect of nanoemulsion on biochemical parameters

Groups	SGOT (U/ml)	SGPT (U/ml)	ALP (KA units)	Total bilirubin (mg/100 ml)
Control	222.67 ± 1.78	220.17 ± 20.40	25.72 ± 0.49	0.74 ± 0.26
CCl4	250.67 ± 24.04	290.83 ± 21.42	32.07 ± 0.79	4.80 ± 0.77
Silymarin	230.83 ± 1.97**	223.02 ± 21.26**	10.46 ± 0.94**	0.69 ± 0.02**
NEF-1	229.17 ± 1.17**	225.83 ± 20.98**	29.34 ± 0.48**	0.97 ± 0.17**
NEF-2	228.22 ± 1.86**	224.52 ± 20.85**	11.34 ± 0.65**	0.59 ± 0.11**

(Praveen *et al*., 2011)

***Andrographis paniculata* (Burm. F.) Nees.: Kalmegh**

Kalmegh commonly known 'King of Bitters', is an erect annual herb growing 30-90 cm tall. Traditionally fresh leaves/ powder is recommended as liver tonic (Silja *et al*., 2008) [34]. Also, in North Eastern states its leaves and young twigs are used for treating jaundice (Sharma *et al.*, 2016) [32].

Neo-andrographolide, kalmeghin, andrographoside (Mismisuraya *et al.*, 2015) [22] and andrographolide (Thingale *et al*., 2015) [37] are the hepatoprotective compounds identified. Two cell culture studies were done in CCl4 damaged liver cells using kalmegh plant extract an andrographolide compound isolated from it. The cytoprotective role of andrographolide against carbon tetrachloride (CCl4) toxicity in human hepatoma (HepG2) cell line was assessed using trypan blue exclusion test and MTT assay. In both the cell culture assays when toxicity was induced liver cells were damaged. When andrographolide treatment was given the cell viability increased, showing maximum protection at 30µmol concentration (Krithika *et al*., 2012) [17]. A polyherbal formulation Link-livecare was developed using kalmegh by Link Natural Products, Sri Lanka. It was tested by Ureshani *et al.* (2017) [38] at two different concentrations in rats. When hepatic damage was induced using D – galactosamine, all biochemical parameters elevated. When 80 mg formulation was administered, it could bring down all the parameters to the desirable level showing the efficiency of Link-livecare (Table 5).

Table 5: Effect of Link livecare on liver enzyme levels

Treatment	ALT (IU/L)	ALP (lU/L)	Total Bilirubin (mg/dl)
Normal control	139 ± 13	183 ±21	3.4 ± 0.2
Pathological control	287 ± 17[a]	251± 21[a]	4.8 ± 0.5[a]
Treated Group (80 mg/kg)	171 ± 10a,b	182± 19b	3.3 ± 0.3b
Treated Group (160 mg/kg)	169 ± l7[b]	192 ± 8[b]	4.0 ± 0.3[a, b]
Silymarin (50 mg/kg)	165 ± 14[b]	165 ± 11[b]	4.2±0.1[a]

(Ureshani *et al.*, 2017) [38]

***Indigofera tinctoria* Linn.: True Indigo**

Indigofera tinctoria, the source of indigo dye is a perennial plant growing upto 2 m. It has got several health benefits. Traditionally Palliyar tribes used its leaf infusion along with goat's milk for the treatment of jaundice (Maruthupandian *et al*., 2011) [21].

The hepatoprotective activity is attributed to the compound indigtone (Ali *et al*., 2019) [5]. Subhashini *et al.* (2017) [36] used methanolic leaf extract of *Indigofera tinctoria* to study the *in vitro* antihepatotoxic activity of against HepG2 human liver carcinoma cell lines through MTT assay. The plant extract treated carcinoma cells were damaged and the maximum toxicity was reported at 1.6 mg/ml concentration. Clearliv, a polyherbal formulation containing indigo leaves was developed by Apex laboratories, Chennai. Kumar *et al*. (2013) [18] compared the efficiency of clearliv with Liv-52 of Himalaya, by treating with Albino rats. In rats when hepatotoxicity was induced the all-enzyme values were elevated. Clearliv at 1000 mg/kg showed significant reduction in the elevated enzyme levels and it was found equally efficient to Liv 52 on bringing down the enzyme values (Table 6).

Table 6: Effect of Clearliv on biochemical parameters

Treatment	AST (U/L)	ALT (U/L)
Normal control	113.3±4.2	52.3±3.4
GalN control (400 mg/kg)	380.0±68.9	317±60.0
Liv-52 (20 ml/kg)	106.2±25.5***	98.3±5.1***
Clearliv (800 mg/kg)	211.0±17.3**	165.5±19.3**
Clearliv (1000 mg/kg)	136.7±8.63***	111.7±7.4***

(Kumar *et al.*, 2013)

Stem

***Tinospora cordifolia* (Willd.) Hook f. & Thomas: Heart-leaved moonseed**

Tinospora cordifolia is a herbaceous vine indigenous to Indian subcontinent. Traditionally its stem is prepared into juice/extract/ decoction and used for treating jaundice (Sharma *et al.*, 2016) [32].

Recently a study was conducted by preparing silver nanoparticles using aqueous extract of tinospora at different concentrations (200, 400 and 600 µg/ml). Its inhibition potential on HepG2 cells were studied. When 600 µg/ml concentration was given, it showed maximum inhibition of carcinoma cells showing its potent hepatoprotective activity (Priya *et al*., 2020) [27]. Sreshta and Babu (2018) [35] developed a guduchi and black musli herbal formulation and tested in rats by inducing hepatotoxicity using paracetamol. When liver damaged was induced using paracetamol all the biochemical parameters elevated and when treatment was given with the herbal formulation all parameters reduceds howing that the herbal formulationhas significant hepatoprotective effect (Table 7).

Table 7: Effect of herbal formulation on serum biochemical parameters

Group	SGOT (U/L)	SGPT (U/L)	ALP (U/L)	Bilirubin (mg/dl)
Group I (2ml distilled water)	92.23±2.16	73.0±1.72	59.09±.3.95	0.32±0.11
Group II (Paracetamol 2g/kg)	a 151.7±2.16	a 105.6±2.14	a 103.2±6.59	a 2.23±0.25
Group III (Silymarin 100mg/kg)	b 106.3±2.25	b 68.52±1.54	b 56.9±3.19	b 0.65±0.17
Group IV (HF 200mg/kg)	b 132.0±3.54	b 76.48±2.54	b 72.7±3.37	b 0.85±0.08
Group V (HF 400mg/kg)	b 122.3±6.61	b 72.70±1.54	b 62.5±3.92	b 0.78±0.11

(Sreshta and Babu, 2018)

***Curcuma longa* L.: Turmeric**

Curcuma longa is a herbaceous perennial growing 60-90 cm tall. Traditionally rhizome paste (15-25 g) mixed with cow milk is also used for treatment of jaundice (Badgujar and Patil, 2008) [6]. 40-50 g rhizome is pounded, made into extract and mixed with fruits of *Piper longum* L. and consumed for jaundice (Shankar *et al*., 2012) [30].

Mansi *et al*. (2017) [20] reported Curcumin as the hepatoprotective compound in *Curcuma longa*. Curcumin isolated from turmeric rhizomes was treated with HepG2 (human liver cancer) cells at different concentrations (5, 10, 20, 40, 50 µM). Treatment with curcumin reduced the viability of cells, showing maximum cell damage at a higher concentration (50 µM). Recently, a study was conducted by Ibrahim *et al.* (2020) [13]. Two doses of curcuminoids were tested in CCL4 toxicity induced rats. When CCl4 treatment were given to rats, all the biochemical parameters elevated showing hepatic damage. When curcuminods treatment were given, there was a reduction in liver enzyme levels demonstrating that curcuminoids could be considered a novel candidate for the development of a new drug against liver diseases.

Roots

***Glycyrrhiza glabra* L.: Liquorice**

Glycyrrhiza glabra is a herbaceous perennial growing upto 80 cm tall. Traditionally liquorice root is chewed daily morning for liver purification. Liquorice tea/ root decoction is also consumed for curing liver diseases. Hepatoprotective activity is attributed to glycyrrhizin and saponins (Mismisuraya *et al.*, 2015) [22].

In vitro hepatoprotective activity of methanolic extract of *Glycyrrhiza glabra* was tested on HepG2 (human liver cancer) cells using MTT assay. A concentration dependent inhibition in cell growth was observed showing maximum inhibition at 100 µg concentration (Shinde *et al*., 2016) [33].

Goorani *et al.* (2019) [11] proved the hepatoprotective activity of its leaves too. Different concentrations of aqueous leaf extract were treated on rats fed with high-fat diet induced hepatotoxicity. It could significantly decrease the increased enzyme levels showing its significant hepatoprotective action. Also, *G. glabra* reduced the degree of hepatic steatosis as compared to the untreated group. Therefore, *G. glabra* aqueous extract can treat fatty liver disease without any cytotoxic effect.

Fruits and Seeds

***Punica granatum* L.: Pomegranate**

Punica granatum is a small tree belonging to the family Punicaceae. Traditionally dried fruits of *P. emblica* and anardana are grounded along with sugar. Three teaspoons of the powder are dissolved in one cup of water and taken for jaundice. Dried rind is grounded and two teaspoons powder is mixed with sugar and taken with water for curing jaundice (Abbasi *et al.,* 2008). Powder of entire fruit is also recommended for jaundice (Shankar *et al*., 2012) [30].

Pomegranate contains gallic acid, ellajic acid, punicalajin A and B as hepatoprotective compounds (Deepak *et al*., 2012) [8]. Saratale *et al.* (2018) [29] developed a silver nanoparticle formulation using pomegranate leaf extract and tested at different concentrations in human liver cancer cells. Carcinoma cells were destructed in a concentration dependent manner showing maximum destruction at 200 µg/ml concentration. Gluconorm a polyherbal formulation was developed by Gengiah *et al.* (2014) [9]. The antidiabetic and hepatoprotective effect of Gluconorm-

5, was studied insteptozotocin (STZ) induced hyperglycemic rats. The animals that received 300 mg/kg of Gluconorm-5 showed pronounced antidiabetic and hepatoprotective effect which was comparable with glibenclamide, a standard drug (Table 8).

Table 8: Effect of Gluconorm-5 on liver enzymes

Treatment	AST (U/L)	ALT (U/L)	ALP (IU/L)
Control	33.78±4.7	34.23±3.7	76.66±0.53
STZ	a 113.79±4.50	a 115.50±1.08	a 173.16±2.29
STZ + Gluconorm-5 (300 mg/kg)	b 77.30±3.40	b 82.11±2.45	b 126.57±5.82
STZ + Gluconorm-5 (600 mg/kg)	c 76.92±3.60	c 88.75±1.46	c 132.48±2.24
STZ + Glibenclamide (1 mg/kg)	76.92±3.60	79.75±2.06	120.16±3.93

(Gengiah *et al.,* 2014) [9]

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

Nigella sativa is an annual flowering plant belonging to the family Ranunculaceae. The fruits are commercially called kalonji seeds. Traditionally dried powdered seeds with milk is used in the treatment of jaundice. Ajwain extract added with kalonji oil gives quick relief from liver problems and jaundice. The powerful hepatoprotective compound is thymoquinone (Hassan *et al.,* 2010) [12]. The cytotoxic potential of *Nigella sativa* seed oil (NSO) was assessed by MTT assay in HepG2, MCF-7, A-549 and HEK293 cell lines at different concentrations (50–250 µg/ml). The results exhibited significant decrease in the percentage cell viability of HepG2, MCF-7 and A-549 cells in a concentration dependent manner. However, NSO showed higher cytotoxic response in HepG2 cells (Oqail *et al.,* 2014) [23]. Kalonji seed extract reported significant hepatoprotective activity in acetaminophen toxicity induced rats. When toxicity was induced all biochemical parameters elevated. Further on administration of kalonji seed extract it significantly decreased the elevated levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (Adam *et al*., 2016) [3]. The efficacy of *N. sativa* seed oil was proven patients with non-alcoholic fatty liver disease (NAFLD). The patients were divided into two groups where, first group were given *N. sativa* seed oil + Honey + Water and the second group were given Placebo + Honey + Water. Grade of hepatic steatosis was significantly reduced in the oil group compared to the placebo group proving *N. sativa* seed oil to be safe, improve liver steatosis and injury (Khonche *et al*., 2019) [16].

Conclusion

Different phyto resources having hepatoprotective potential have been explored. Several traditional information documented against each phyto resources and scientific evidences has also been described. When a traditional knowledge is obtained scholars will go for *in vitro, in vivo*, clinical trials and finally drug development. Scholars having interest in phytochemistry will explore the compounds responsible for is hepatoprotective activity. Using those compounds studies will be done, but most of the times the study will be carried in an unscientific manner. *i.e.*, after gathering traditional knowledge, they jump into clinical trials or sometimes product development. These unscientific practices are the real constraint with phytochemical research. Sometimes they stop with *in vitro* studies, that means traditional knowledge and phyto resources are not completely utilized. Hence it is advisable to focus on productive research by maximum exploitation of traditional knowledge and sustainable utilization of phyto resources for the benefit of the society.

References

1. [Anonymous]. Is liver disease the next major life disease of India after diabetes and blood pressure, 2017. Times of India, 11 April 2017. Available: https://timesofindia.Indiatimes.com/life-style/health - fitness/health news/is- liver-disease- the-next major lifestyle disease- of -india-after- diabetes and bp/ articleshow/ 58122706.cms [19 Nov. 2020].
2. Abbasi AM, Khan MA, Ahmad M, Zafar M, Khan H, Muhammad N, *et al*. Medicinal plants used for the treatment of jaundice and hepatitis based on socio-economic documentation. Afr. J Biotechnol. 2009;8(8):1643-1650.
3. Adam GO, Rahman MM, Lee SJ, Kim GB, Kang HS, Kim JS, *et al*. Hepatoprotective effects of *Nigella sativa* seed extract against acetaminophen- induced oxidative stress. Asian Pac. J Trop. Med. 2016;9(3):221-227.

4. ALF [American Liver Foundation]. Liver Function Tests, 2016. [Online]. Available: https://liverfoundation.org/wp-content/uploads/2019/11/Liver-Function-Test-Handout-2016.pdf [21 Nov.2020].
5. Ali T, Shah Z, Bashir R, Bader GN. The traditional medicine and phytoconstituents from natural products for liver disease: A review. J Drug Deliv. Ther. 2019;9(2):484-488.
6. Badgujar SB, Patil MB. Ethnomedicines for jaundice used in tribal areas of North Maharashtra. Nat. Prod. Radiance 2008;7(1):79-81.
7. Balakrishnan P, Toms T. Hepatoprotective effect of *Phyllanthus niruri* in CCl4 induced hepatic damage in *Mus musculus*. European J Biomed. Pharm Sci. 2018;5(5):819-824.
8. Deepak HB, Chandrasekaran CV, Dethe S, Deepak M, Pandre MK, Jaya B, *et al*. Hepatoprotective and antioxidant activity of standardized herbal extracts. Pharmacogn. Mag. 2012;8(30):116-123.
9. Gengiah K, Hari R, Anbu J. Antidiabetic antihyperlipidemic and hepatoprotective effect of Gluconorm-5: a polyherbal formulation in steptozotocin induced hyperglycemic rats. Anc. Sci. Life 2014;34(1):23-32.
10. Girish C, Pradhan SC. Indian herbal medicines in the treatment of liver diseases: problems and promises. Fundam. Clin. Pharmacol. 2012;26(2):180-189.
11. Goorani S, Morovvati H, Seydi N, Almasi M, Paryan AA, Nazari F, *et al*. Hepatoprotective and cytotoxicity properties of aqueous extract of *Glycyrrhiza glabra* in wistar rats fed with high-fat diet. Comp. Clin. Path. 2019;28:1305-1312.
12. Hassan SA, Ahmed WA, Galeb FM, Taweel MAE, Bedair FAA. *In vitro* challenge using thymoquinone on hepatocellular carcinoma (HepG2) cell line. Iran. J Pharm. Res. 2010;(4):283-290.
13. Ibrahim J, Kabiru AY, Adeleke TA, Lawal B, Adewuyi AH. Antioxidant and hepatoprotective potentials of curcuminoid isolates from turmeric (*Curcuma longa*) rhizome on CCl4-induced hepatic damage in Wistar rats. J Taibah Univ. Sci. 2020;14(1):908-915.
14. Jain SK. Medicinal Plants (4th Ed.). National Book Trust. New Delhi. 2016, 129p.
15. Kalaskar MG, Surana SJ. Ethnomedicinal plants used against liver diseases among the tribes of India. J Biol. Sci. 2014;14(3):154-168.
16. Khonche A, Huseini HF, Gholamian M, Mohtashami R, Nabati F, Kianbakht S. Standardized *Nigella sativa* seed oil ameliorates hepatic steatosis, aminotransferase and lipid levels in non-alcoholic fatty liver disease: a randomized, double-blind and placebo-controlled clinical trial. J Ethnopharmacol. 2019;234:106-111.
17. Krithika R, Verma RJ, Shrivastav PS. Antioxidative and cytoprotective effects of andrographolide against CCl4-induced hepatotoxicity in HepG2 cells. Hum. Exp. Toxicol. 2013;32(5):530-543.
18. Kumar EP, Rajan VR, Kumar AD, Parasuraman S, Emerson SF. Hepatoprotective activity of Clearliv a polyherbal formulation in Wistar rats. Arch. Med. Health Sci. 2013;1(2):120-125.
19. Mali FN, Negoita IA, Mali DESN, Robu G. The evaluation of hepatoprotective effect of silymarin, *Phyllanthus niruri* extract and choline combination. Med. Surg. J. 2018;122(2):267-275.
20. Mansi AME, Karef AAE, Shishtawy MME, Eissa LA. Hepatoprotective effect of curcumin on hepatocellular carcinoma through autophagic and apoptic pathways. Ann. Hepatol. 2017;16(4):607-618.
21. Maruthupandian A, Mohan VR, Kottaimuthu R. Ethnomedicinal plants used for the treatment of diabetes and jaundice by Palliyartribals in Sirumalai hills, Western Ghats, Tamil Nadu, India. Indian J Nat. Prod. Resour. 2011;2(4):493-497
22. Mismisuraya MA, Alwi SRW, Chua LS, Mustaffa AA. Review of hepatoprotective agents in herbs. J Eng. Sci. Technol. 2015;10:14-24.
23. Oqail MMA, Sheddi ESA, Massarani SMA, Siddiqui MA, Ahmad J, Musarrat J, *et al*. *Nigella sativa* seed oil suppresses cell proliferation and induces ROS dependent mitochondrial apoptosis through p53 pathway in hepatocellular carcinoma cells. S. Afr. J Bot. 2017;112:70-78.
24. Oyemitan IA. African Medicinal Spices of Genus Piper. In: Kuete, V. (ed.), Medicinal Spices and Vegetables from Africa. Academic press, 2017, 581-597. Avialable: https://www.researchgate.net/profile/Opeyemi_Avoseh/publication/312686177_Cymbopogon_citratus/links/5ec284d5299bf1c09ac4e3a8/Cymbopogon-citratus.pdf#page=602[21 Nov. 2020].
25. Padmapriya R, Gayathri L, Ronsard L, Akbarsha MA, Raveendran R. *In vitro* anti-proliferative effect of *Tephrosia purpurea* on human hepatocellular carcinoma cells. Pharmacogn. Mag. 2017;13:16-20.
26. Parveen R, Baboota S, Ali J, Ahuja A, Vasudev SS, Ahmad S. Effects of silymarin nanoemulsion against carbon tetrachloride-induced hepatic damage. Arch. Pharm. Res. 2011;34(5):767-774.
27. Priya SM, Sarathchandra G, Jagadeeswaran A, Preetha SP, Partiban S. Synthesis, characterisation and pharmacological assessment of nanoparticles of *Tinospora cordifolia* for its cytotoxic activity. J Pharmacogn. Phytochem. 2020;9(3):1901-1906.
28. Ramakrishnan G, Muzio LL, Baez CME, Jagan S, Augustine TA, Kamaraj S, *et al*. Silymarin inhibited proliferation and induced apoptosis in hepatic cancer cells. Cell Prolif. 2009;42:229-240.
29. Saratale RG, Shin HS, Kumar G, Benelli G, Kim DS, Saratale GD. Exploiting antidiabetic activity of silver nanoparticles synthesized using *Punica granatum* leaves and anticancer potential against human liver cancer cells (HepG2). Artif. Cells Nanomed. Biotechnol. 2018;46(1):211-222.
30. Shankar R, Rawat MS, Deb S, Sharma BK. Jaundice and its traditional cure in Arunachal Pradesh. J Pharma. Sci. Innov. 2012;1:93-97.
31. Shanmugam B, Shanmugam KR, Ravi S, Subbaiah GV, Ramakrishana C, Mallikarjuna K, *et al*. Exploratory studies of Epicatechin, a bioactive compound of *Phyllanthus niruri*, on the antioxidant enzymes and oxidative stress markers in D- galactosamine-induced hepatitis in rats: A study with reference to clinical prospective. Pharmacogn. Mag. 2017;13:56-62.
32. Sharma BK, Ramashanker, Gosh S, Rahaman L, Nath N, Kaipeng DL. Plant based folk treatments from North East India for jaundice. (An overview). J Med. Plants Stud. 2016;4(5):234-247.
33. Shinde DB, Koratkar SS, Sharma N, Shitole AA.

Antioxidant activity and antiproliferative action of methanolic extract of liquorice (*Glycyrrhiza glabra*) in HepG2 cell line. Int. J Pharm. Pharm. Sci. 2016;8(9):293-298.
34. Silja VP, Varma KS, Mohanan KV. Ethnomedicinal plant knowledge of the Mullukuruma tribe of Wayanad district, Kerala. Indian J. Tradit. Knowl. 2008;7(4):604-612.
35. Sreshta B, Babu SR. Hepatoprotective effect of Poly herbal formulation containing indigenous medicinal plants against various hepatotoxic agents in rats. Asian J Pharm. Pharmacol. 2018;4(2):232-237.
36. Subhashini S, Narayanan S, Rejani K, Kamath AT, Kamak DH, Aravind A. Studies on the *in vitro* antihepatotoxic activity of *Indigofera tinctoria* (Linn.) against HepG2 Human liver carcinoma cell lines. J Pharm. Res. 2017;11(9):1086-1094.
37. Thingale AD, Shaikh KS, Channekar PR, Galgatte UC, Chaudhari PD, Bothiraja C. Enhanced hepatoprotective activity of andrographolide complexed with a biomaterial. Drug Deliv. 2015;22(1):117-124.
38. Ureshani KA, Udumalage C, Chayanika P, Bimalka S, Mahendra AA. Hepatoprotective activity of link livecare in carbon tetrachloride and D-galactosamine induced hepatotoxicity in ICR mice. Int. J Res. Ayurveda Pharm. 2017;8:91-96.
39. Vadivu R, Vidya S, Jayshree N. Standardization and evaluation of hepatoprotective activity of polyherbal capsule. Int. J Pharm. Sci. Rev. Res. 2013;21(1):93-99.
40. Verma N, Neeraj, Singh J. Evaluation of hepatoprotective activity of *Tephrosia purpurea* (Linn.) stem. Int. Educ. Appl. Sci. Res. J. 2017;2(7):5-6.
41. Vyanktesh KD, Suresh TM, Ningappa HS. *In vitro* study of an aqueous extract of *Eclipta alba* (Hassk.) for HepG2 cell line. Int. J Ayurveda Pharma. Res. 2019;35(3):1-6.
42. WHO [World Health Organization]? 2016. Projections of mortality and causes of death, 2015 and 2030. [Online]. Available: https://www.who.int/healthinfo/global_burden_disease/projections/en/ [19 Nov.2020].
43. WHO [World Health Organization]? 2019. Hepatitis. [Online]. Available: https://www.who.int/news-room/q-a-detail/what-is-hepatitis [21 Nov.2020].