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REVIEW

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Bergenia ciliata as a future candidate for liver diseases: a concise review

Uzma Latief[1], Gurleen Kaur Tung[1], Harjeet Singh[2], Tasir Sharief Per[3] and Subheet Kumar Jain[1,2*]

Abstract

Liver cirrhosis, alcoholic liver diseases, non-alcoholic fatty liver and steatohepatitis are the major risk factors for liver damage leading to hepatocellular carcinoma. Oxidative stress and insulin resistance are the main pathogenetic mechanisms leading the hepatic cell injury and damage in these patients. The present review is the first attempt which focuses on the biological activities of *Bergenia ciliata* to explore its benefits and possible applications in the treatment of liver ailments. *Bergenia ciliata* is an evergreen herb belonging to the family saxifragaceae and is regarded as a miracle herb due to its wide medicinal applications. The data published in India and other nations are methodically reviewed and summarized in this article. It covers the facts collected from scientific journals, theses and online bibliographical databases: PubMed, Scopus, Google Scholar and Web of Science from year 1995–2020. The phytochemical studies on *B. ciliata* have shown the presence of many phytochemicals belonging to phenols, flavonoids, fatty acid, glycosides, terpenoids, etc. Due to the presence of a multitude of these bioactives, the whole plant of *B. ciliata* has numerous medicinal applications such as diuretic, antipyretic, α-glucosidase, antiviral, antibacterial, anti-inflammatory and insecticidal activity. Therefore in the present study, we invite the attention of scientists and researchers to carry out further clinical and toxicological studies on this valuable plant in order to discover and develop novel hepatoprotective medicine with fewer side effects on human beings.

Keywords: *Bergenia ciliata*, Hepatoprotective, Liver diseases, Medicinal applications, Phytochemical

Background

Liver diseases continue to be a major health concern over the last few years due to chronic alcohol abuse and modern lifestyle, and cause of morbidity and mortality worldwide (Iqbal et al., 2019). Every year, 3 million deaths occur due to alcohol consumption all over the world (WHO, 2019). At the same time, NAFLD is emerging even larger health problem and is considered to be the most common liver disease. A significant number of individuals are developing non-alcoholic steatohepatitis (NASH) which may progress toward hepatic fibrosis, cirrhosis and ultimately hepatocellular carcinoma (Ahmad & Ahmad, 2012; Page & Harrison, 2009). Approximately one-third of the population in developed countries have NAFLD responsible for liver transplantation (Angulo, 2006; Mikolasevic et al., 2018). Hepatitis B and C virus infections, like ALD and NAFLD, cause chronic liver disease (Raimondo et al., 2005). Due to lack of any effective treatment and increase in the number of cases of cirrhosis and in need of liver transplantation, chronic liver diseases are important health and economic concern. Therefore, there is a need of effective and affordable treatment modalities to reduce the morbidity and mortality associated with CLDs.

Herbal remedies are highly valued all over the world as a rich source of pharmaceutical agents for the prevention of infections and diseases (Kayani et al., 2014; Latief & Ahmad, 2018; Zain-ul-Abidin et al., 2018). In India, there are enormous varieties of medicinal plants; thus, our country has often been referred as 'Medicinal Garden of the world'. These plants have played vital roles in various

*Correspondence: subheetjain@rediffmail.com
[1] Centre for Basic and Translational Research in Health Sciences, Guru Nanak Dev University, Amritsar, India
Full list of author information is available at the end of the article

ancient traditional systems of medication and even today, provide an inexpensive source of drugs for majority of world's population (Sen & Chakraborty, 2017). *Bergenia ciliata* (family Saxifragaceae), a highly valuable plant has been used as a medicine for the treatment of different kinds of human diseases since long. It is commonly called 'Zakhmehayat' or 'Pakhanabhed' and is an evergreen perennial herb, widely distributed in Central and East Asia (Phull et al., 2016; Tiwari et al., 2020). This plant has thick rootstock, and outer surface is dark brown and rough whereas the inner skin is pinkish and smooth. It is covered with dark sheaths of withered leaves. Flowers are arranged in terminal corymbs and may be pink, white or purple. In Himalayan region, people traditionally use *B. ciliata* for the treatment of various ailments (Chowdhary et al., 2009). *Bergenia ciliata* is considered as a miracle herb due to its use in treatment of numerous diseases such as gastrointestinal problems, pulmonary infections, heart diseases, ophthalmic, hemorrhoids, kidney and gall bladder stones. (Hussain et al., 2019; Rajkumar et al., 2011). In addition, it is accredited with antifungal, diuretic, antitussive, anticancer, analgesic, antiviral, antibacterial, anti-inflammatory and antimalarial properties (Rajkumar et al., 2011; Ruby et al., 2012; Timalsena & Lamichhane, 2019; Zafar et al., 2019). In India, an Ayurvedic polyherbal formulation 'Cystone' contains Bergenia in combination with other plants and is used against urolithiasis (Vidyashankar et al., 2010). These virtues of the plant are attributed directly to its phytochemicals composition and account for its utilization in traditional medicine (Fig. 1).

Phytochemical studies on this plant have revealed the presence of gallic acid (3,4,5 trihydroxybenzoic acid), bergenin (C-glycoside of 4-O-methyl Gallic acid), catechin, gallicin, paashaanolactone, arbutin, β-sitosterol, afzelechin, etc. (Dharmender et al., 2010; Kanth et al., 2019). Tannic acid, mucilage, glucose, albumen, metarbin, mineral salts and wax are also reported to be present (Kanth et al., 2019). Extensive examination of medicinal plants for bioactive compounds and biological activities is the foremost and critical step in development of effective novel medications. In view of this, the present review is the first attempt to gather utmost fragmented literature showing the protective effects of various bioactive

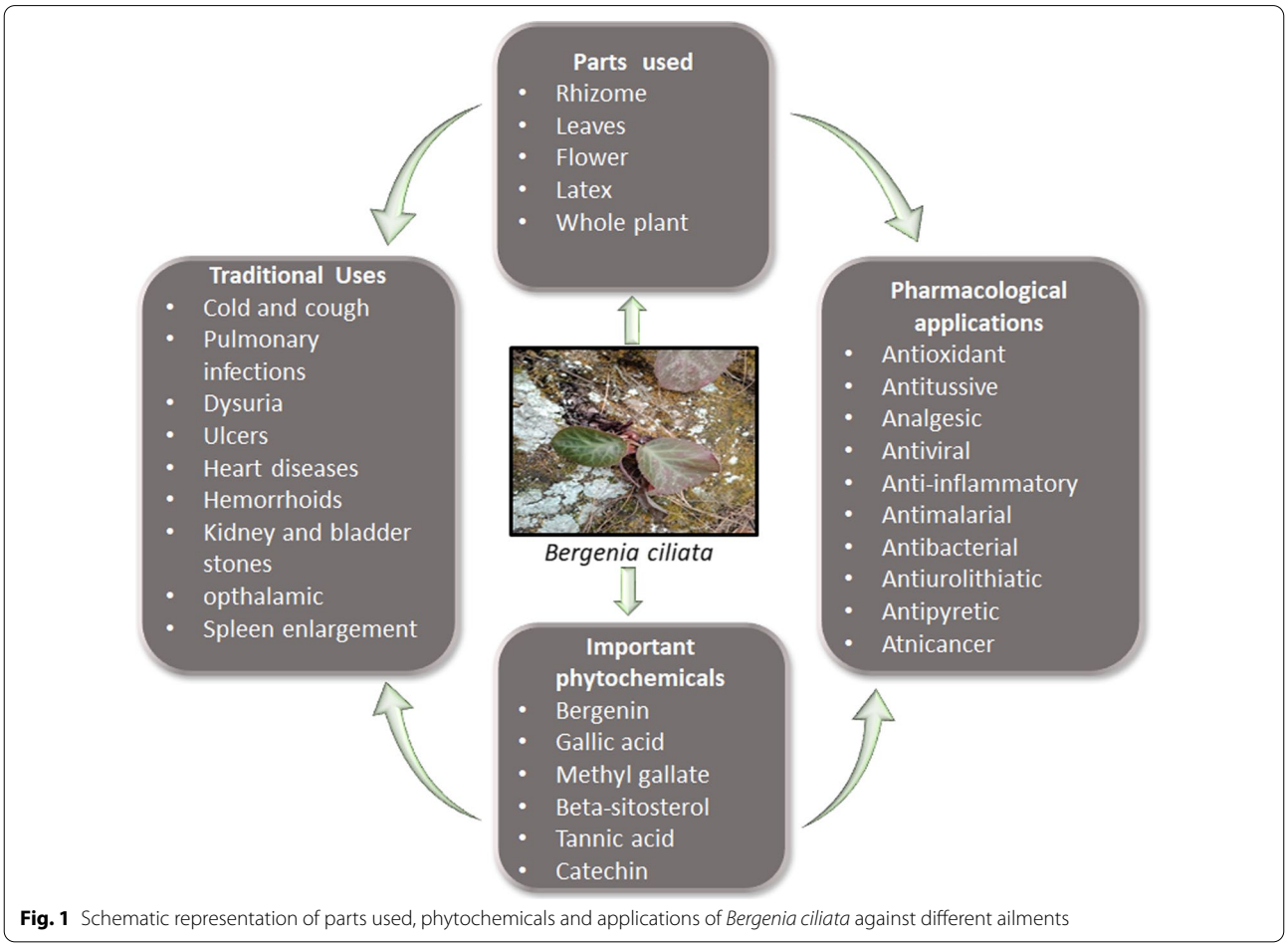

Fig. 1 Schematic representation of parts used, phytochemicals and applications of *Bergenia ciliata* against different ailments

compounds of *B. ciliata* against liver diseases. It will improve the efficacy of this miracle herb against liver infirmities, as well as the active medicinal compounds responsible for them. Furthermore, this article would unfurl logical holes in existing knowledge and make it easier for researchers all over the world to approach studies relating to the discovery of novel compounds and medicines from *B. ciliata.*

Methodology

This review article has been designed by compiling and consulting published papers about the protective efficacy and scientific validation of *Bergenia ciliata* as an anti-hepatotoxic agent. Published papers were retrieved from scientific journals, theses and online bibliographical databases: PubMed, Scopus, Google Scholar and Web of Science. In total, almost 100 research articles on *B. ciliata* plant and its phytochemicals published in English language were reviewed for this article. Inside the databases, we used the keywords including: liver diseases, hepatoprotective activity, *Bergenia ciliata*, pharmacology, phytochemicals, bergenin, gallic acid, arbutin, tannic acid, β-sitosterol, limonene and β-caryophyllene. All the obtained data from previous published literature is summarized in three figures and two table.

Phytochemical constituents

Phytochemical studies include identification and isolation of the chemical compounds, determination of their biological effectiveness through in vitro and in vivo studies in experimental models and through epidemiological and clinical trials in humans. The phytochemical constituents of Bergenia species are summarized in Table 1.

Therapeutic activities of phytochemicals of *Bergenia ciliata* against liver diseases

Gallic acid

Gallic acid (GA) is an important phytochemical of *B. ciliata* and is also found in tea leaves, sumac, oak bark, gallnuts, witch hazel and other kinds of plants (Nabavi et al., 2012). Studies have shown that GA possesses a lot of biological activities such as antiviral antibiotic, anti-inflammatory, antimutagenic and anticancer (Badhani et al., 2015; Kahkeshani et al., 2019). These effects are due to the fact that GA is a potent antioxidant, involved in neutralizing and absorbing free radicals produced by the cells (Badhani et al., 2015).

It is reported that gallic acid has protective activity against hepatotoxicity due to its hydroxyl groups (Anand et al., 1997). Several previous studies have revealed the efficacy of GA on hepatic injury caused by different etiologies, such as cyclophosphamide, paracetamol, diethylnitrosamine, carbon tetrachloride, lindane and methotrexate. (Latief et al., 2016; Oyagbemi et al., 2016; Padma et al., 2011; Safaei et al., 2018; Wang et al., 2014). GA attenuated on hepatic injury and hepatic fibrosis induced by these chemicals in rodent models, which might be due to inhibition of inflammation, oxidative stress and hepatic stellate cell (HSC) activity. The ameliorative effect of GA on hepatic glycoprotein components and lipid peroxidation in the streptozotocin-induced diabetic rats has also been found (Punithavathi et al., 2011). Gallic acid treatment was found to reverse the disturbed metabolism to its normal condition in a mice model with non-alcoholic fatty liver disease (Chao et al., 2014). Results indicated that the potential targets of GA were lipid metabolism and ketogenesis, amino acids metabolism, choline metabolism, glycolysis and gut-microbiota metabolism. GA improved lipid metabolism and glucose tolerance in obese mice, thereby showing evidence of anti-hyperglycemic activity (Bak et al., 2013). This was due to improved triglyceride concentrations and induced PPAR-γ and Akt activations, thus improving the glucose metabolism. Gallic acid was found active on chronic ethanol-induced liver injury in rats by decreasing the serum alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase activities and elevating paraoxonase and arylesterase activity (Kartkaya et al., 2013).

Table 1 Phytochemical constituents of *Bergenia* species

Plant	Phytochemicals	References
Bergenia ciliata	Bergenin, Gallic acid, Gallicin, β-Sitosterol, Arbutin, Catechin, Afzelechin, Linalool, Limonene, Pentanoic acid, α-Terpineol, Hexanoic acid, Hexalactone, Quercetin, Protocatechuic acid	Ahmad et al., (2018a, 2018b, 2018c) and Koul et al. (2020)
Bergenia ligulata	Bergenin, Gallic acid, Tannic acid, Arbutin, Catechin, β-Sitosterol, Stigmasterol, Afzelechin, Methyl gallate), Quercetin, Coumarin	Ahmad et al., (2018a, 2018b, 2018c) and Koul et al. (2020)
Bergenia stracheyi	Bergenin, Gallic acid, Tannic acid, Phytol, Catechin-3-O-gallate Caryophyllene, Damascenone, β-Eudesmol	Ahmad et al., (2018a, 2018b, 2018c) and Koul et al. (2020)
Bergenia crassifolia	Bergenin, Gallic acid, β-Sitosterol, Arbutin, Catechin, Ellagitannins, Caffeoylquinic acid, Quercetin, Linalool, Pentadecanoic acid, Caffeoylquinic acid, Monogalloylquinic acid, Fumaric acid, Stearic acid	Ahmad et al., (2018a, 2018b, 2018c) and Koul et al. (2020)

GA suppressed ethanol-induced necroptosis in hepatocytes by reducing the expression of distinct necroptotic signals receptor-interacting protein 1 (RIP1) and RIP3, as well as the release of high mobility group box protein 1 (Zhou et al., 2019). It also increased the expression of NrF2, which served as a molecular basis for suppressing ethanol-induced hepatocyte necroptosis. Thus, NrF2, a classical antioxidant protein, is a newly identified crucial suppressor for necroptosis. It has been reported that GA attenuated hepatitis C virus infection in hepatoma cells through its antioxidant and antiviral production (Govea-Salas et al., 2016; Hsu et al., 2015). It was also reported that GA decreased DEN-induced HCC by diminishing expression of proliferative marker PCNA and regulating signal transducer and activator of transcription 3 (STAT 3) signaling pathway (Aglan et al., 2017; Jagan et al., 2008). This was due to its high bioactivity, which included antioxidant, anti-inflammatory, apoptotic and antitumor properties. GA was able to inhibit liver metastasis of mastocytoma cells P-815 (Ohno et al., 2001).

Bergenin

Bergenin ($C_{14}H_{16}O_9$) is a natural secondary metabolite isolated from the herb *Bergenia ciliata,* and it is reported that rhizome of *B. ciliata* contains 0.75% bergenin (Ahmad et al., 2018a, 2018b, 2018c). It is an isocoumarin compound extracted from the leaves, roots and bark of many families and genera of plants (Patel et al., 2012). It exhibits anti-inflammatory, antiarrhythmic, antitussive, antifungal, anticancer, antitumor, antiviral, immune enhancement, wound repair, anticoagulant, analgesic, antidiabetic, neuroprotective, antimalarial and antioxidant properties (Aggarwal et al.,; 2016; Ahmed & Urooj, 2012; Bajracharya, 2015; Bessong et al., 2005; Patel et al., 2012). It is reported that there are no side effects of bergenin even in very high dosages (Chauhan et al., 2012).

It was found that liver injury altered the pharmacokinetic behavior of bergenin and enhanced its absorption after given orally (Rong-Hua et al., 2016). These findings provided valuable information for the study of clinical pharmacokinetics of bergenin under hepatic injury condition and guidance for the potential use of bergenin as a hepatoprotective agent. It is reported that bergenin exerted hepatic protection in hepatic ischemia reperfusion (IR) injury model (Xiang et al., 2020). The protective action of bergenin was due to its ability to eliminate reactive oxygen species (ROS), influence the release of inflammatory factors, apoptosis and autophagy-related genes via the PPAR pathway. In a recent study, it was found that bergenin acted as a promising drug candidate for abrogating hepatic fibrosis induced by carbon tetrachloride and bile duct ligation (Xia et al., 2020). Bergenin retarded autophagy and hindered the energy supply required for HSC activation, thereby reducing collagen deposition and hepatocyte damage. Bergenin and metformin helped with hepatic hyperglycemia, insulin sensitivity and glucose uptake (Ambika & Saravanan, 2016). These phytochemicals increased the activity of glycolytic enzymes and significantly decreased the gluconeogenic enzymes in diabetic mice. Under diabetic conditions, this facilitated the release of hepatic glucose into circulation. Bergenin and metformin regulated the activities of these enzymes through metabolic activation or inhibition of glycolysis and gluconeogenesis, respectively. Bergenin improved insulin signalling in the liver of HFD-fed mice by increasing the tyrosine phosphorylation of IR-β and IRS-1, improving PI3K/Akt activation and glucose transporter protein 2 (GLUT 2) translocation. Thus, this phytochemical may be used to treat obesity-related type 2 diabetes mellitus as it enhanced insulin-dependent glucose transport in hepatic tissues by activating and translocating GLUT 2 in a PI3K/phosphorylated protein kinase B (AKT) dependent pathway. Bergenin was also effective against alcohol and tert-butyl hydroperoxide (TBHP)-induced liver injury in hepatoma cells (Sriset et al., 2020). It exhibited hepatoprotective activity via restoration of oxidant-antioxidant system and thus a potential candidate for hepatoprotective treatment.

β-Sitosterol

β-Sitosterol (BSS) is a plant derived natural dietary phytosterol similar to cholesterol. It is present in *B. ciliata* roots and leaves and in many oils from plants and vegetables (Manjunatha, 2010). β-Sitosterol has a wide spectrum of therapeutic effects against various chronic ailments (Yuan et al., 2019). According to reports, this phytosterol shows various types of health benefits against oxidative stress, obesity, anxiety, diabetes, cancer, sedative and prostatauxe effects (Baskar et al., 2012; Berges et al., 1995; Gumede et al., 2020; Jenkins et al., 2003; López-Rubalcava et al., 2006; Normén et al., 2001).

Treatment with BSS showed dose-dependent hepatoprotective effect against CCl_4-induced chronic liver diseases (Devaraj et al., 2020). Its treatment inhibited ROS by causing diminution of intracellular enzymatic antioxidants such as superoxide dismutase and catalase in the rat liver. It also significantly reduced the expression of HSCs activation markers (hydroxyproline, collagen, α-SMA, desmin, vimentin, and MMP 9), thus exhibiting antifibrotic action. BSS has radio-protective effect via regulating the gene expression of PPAR-γ which in turn cause rise in PON-1 and ARE enzymes activities (Moustafa & Thabet, 2017). This action of BSS was due to its antioxidant potential, cholesterol reduction and PPAR-γ agonist properties. Another study indicated that BSS and its derivatives restrained LPS/ GalN-induced

liver injury by inhibiting the oxidation and inflammation in mice (Yin et al., 2018). Their treatment regulated antioxidant status through the Nrf2 activation, heme oxygenase-1 (HO-1) promotion and controlling anti-inflammatory pathway through the toll like receptor 4 (TLR4) inhibition. It is reported that β-sitosterol in combination with stigmasterol acted against high-fat Western diet (HFWD)-induced NAFLD (Feng et al., 2018). Lipidomic analyses conducted in liver samples collected after thirty three weeks of the treatment have revealed the potency of these phytochemicals against NAFLD. Thus, these phytosterols serve as future candidates for human NAFLD by reducing plasma cholesterol levels (Table 2).

Other phytochemicals

Other phytochemicals found in *B. ciliata* are arbutin, tannic acid, fatty acids, terpenes, etc. Arbutin, a glycosylated form of hydroquinone is found in rhizome of *B. ciliata* and other green plants, is often used in various skin diseases (Khanal et al., 2011; Kunwar et al., 2013). It is also effective in repulsion of kidney stones as it possesses antibacterial properties, and heal cystitis and urinary tract infections (Funayama et al., 1995). It was found that arbutin mitigated tert-butyl hydroperoxide-induced toxicity in Hep-G2 cell line (Seyfizadeh et al., 2012). Reports showed that arbutin may protect the liver against cyclosporine and CCl_4-induced oxidative damage in rats (Khadir et al., 2015; Mirshahvalad et al., 2016). This hepatoprotective effect was correlated with the antioxidant, lipoperoxidative and free radical scavenger effects of arbutin. Another finding demonstrated that arbutin is a strong radio-protector for reducing the radiation damage in megavoltage therapeutic x-irradiated mice (Nadi et al., 2019). Thus, arbutin may be used as an antioxidant to protect against oxidative damage induced by toxic chemicals and radiations on liver. Tannic acid (TA) is another polyphenol present in *B. ciliata* and in several fruits and vegetables (Ahmad et al., 2018a, 2018b, 2018c; Fraga-Corral et al., 2020). This compound possesses strong antimicrobial, antioxidant, antiviral, antibacterial and astringent properties, reduces serum cholesterol and triglycerides, and suppresses lipogenesis (Chung et al., 1998; Kaczmarek, 2020). TA exerted significant liver-protective effects against CCl_4- and acetaminophen-induced liver damage and fibrosis in mice (Chu et al., 2016; Zhang et al., 2017). The potential mechanism relied on the inhibition of collagen accumulation, antioxidation, anti-inflammation and antiapoptosis.

Limonene is a monoterpene found in the numerous medicinal plants including rhizome of *B. ciliata* and citrus fruits (Adhikary et al., 2011; Kumar et al., 2010; Peng et al., 2009). It is a colorless liquid and exists in two optical isomers, d- or l-limonene as well as a racemic mixture (Vieira et al., 2018). D-Limonene is reported to have a variety of pharmaceutical applications such as anticancer, antioxidant and anti-inflammatory (Khan et al., 2013; Roberto et al., 2009). It has been reported that D-Limonene is effective against CCl_4-induced hepatic fibrosis in Wistar rats via reducing oxidative stress and inflammation (Ahmad et al., 2018). It boosted the antioxidant status, regulated collagen accumulation and inhibited inflammation through ameliorating NF-κB. Another study demonstrated that D-Limonene reduced the oxidative stress in streptozotocin-induced diabetic rats by decreasing lipid peroxidation and restoring the activities of antioxidant enzymes (Murali et al., 2012). D-Limonene supplementation also ameliorated the NAFLD in rats and thus could serve as a promising complementary therapy against metabolic syndrome associated with NAFLD (Santiago et al., 2012). It is found that limonene inhibited experimental hepatocarcinogenesis in rat model via increased apoptosis and decreased cell proliferation (Kaji et al., 2001). Another terpene found in *B. ciliata* rhizome is β-caryophyllene, a bicyclic sesquiterpene, also a major component of essential oils of food plants such as cinnamon, cloves, black pepper and rosemary (Calleja et al., 2013; Jayaprakasha et al., 2003; Varga et al., 2018). This terpenoid is found to reduce CCl_4-mediated hepatic fibrosis and hepatic cell activation by declining the gene expressions of Collagen-1α1, TGF-β1 and TIMP1 (Calleja et al., 2013). It is reported that β-caryophyllene ameliorated alcoholic and non-alcoholic steatohepatitis in experimental mice by regulating the activities of various inflammatory markers and antioxidant enzymes (Arizuka et al., 2017; Varga et al., 2018) (Fig. 2).

Conclusions

The present review gathers the detailed information about the hepatoprotective potential of *Bergenia ciliata* for the first time. Almost all parts of the plant are used for curing different ailments; the most frequent part used is rhizome followed by root, leaf, flower and latex. The major phytochemical compounds reported in this species are of wide range phenols, flavonoids, fatty acid, glycosides, terpenoids, etc. These phytochemicals exhibit various biological activities including antibacterial, antioxidants, antifungal, antihemolytic and cytotoxic and had been traditionally used among the various communities particularly across the Himalayan region for urinary, gastrointestinal, skin, respiratory, gynecological, inflammatory, kidney disorders and infectious diseases. The techniques of HPLC, NMR, and FTIR can be used to characterize, isolate, and quantify these phytochemicals (Ahmad et al., 2018a, 2018b, 2018c; Majeed et al., 2021). Bergenin, the most abundant phytochemical, may be isolated and studied further in preclinical and clinical

Table 2 Summary of therapeutic activities of different phytochemicals of *Bergenia ciliata*

S. no	Phytochemical	Class	Protective action	Model	References
1	Gallic acid	Phenol	Decreases liver steatosis, body weight and plasma insulin levels. Hepatic steatosis related genes expression show that acetyl-CoA carboxylase and fatty acid synthase mRNA are significantly reduced	HFD-induced steatosis in mice	Sousa et al. (2020)
2	Gallic acid	–	Elevation of liver SOD and CAT activities and reduction of the liver TNF-α expression, MDA and serum protein carbonyl	Fluoxetine-induced liver damage in rats	Karimi-Khouzani et al. (2017)
3	Gallic acid	–	Reduces body weight, liver, adipose tissue, serum parameters (TAG, phospholipid, total cholesterol, LDL, cholesterol, insulin and leptin) and hepatic steatosis. Also decreases oxidative stress (declining GSSG and enhancing GSH, GPx, GRd and GST)	HFD-induced obesity in rats	Hsu and Yen (2007)
4	Gallic acid	–	Diminishes HA, collagen IV, MDA as well as the serum levels of ALT, AST, and γ-GT. Also decrease in MMP-2, TIMP-1 mRNA, and MMP-2 protein levels	CCl_4-induced hepatic fibrosis in mice	Wang et al. (2014)
5	Gallic acid	–	Reduces cellular oxidative stress by decreasing ROS production, which in turn is unfavorable for HCV	Hepatocarcinoma cell lines (Huh7)	Govea-Salas et al. (2016)
6	Gallic acid	–	Reverses HFD-induced disturbances to a wide range of metabolic pathways, including lipid metabolism, glucose metabolism (glycolysis and gluconeogenesis), amino acids metabolism, choline metabolism and gut-microbiota-associated metabolism	NAFLD-induced in mice	Chao et al. (2014)
7	Gallic acid	–	Lessens inflammation, activated HSCs, deposition of collagen. Also decline in COX-2 positive cells in liver	NDEA-induced liver injury	Latief et al. (2016)
8	Gallic acid	–	Limits hepatocyte necroptosis, which was characterized by reduced expression of distinct necroptotic signals RIP1 and RIP3 and release of high mobility group box protein 1. Also induces NRF2 expression in ethanol-incubated hepatocytes	Ethanol-induced hepatocyte necroptosis	Zhou et al. (2019)
9	Gallic acid	–	Inhibitory effect on lipid accumulation through the activation of AMPK in hepatocytes. Also suppresses hepatocyte apoptosis and inflammation	Human hepatoma cell lines (HepG2)	Tanaka et al. (2020)
10	Gallic acid	–	Decreases AST, ALT, LDH activity. Increases paraoxonase and arylesterase activity	Ethanol-induced liver injury in rats	Kartkaya et al. (2013)
11	Gallic acid	–	Decline in AST, ALT, MDA, and elevation of GSH, CAT, SOD and GST	Cyclophosphamid-induced hepatotoxicity in rats	Oyagbemi et al. (2016)
12	Gallic acid	–	Triglyceride and blood glucose concentrations are significantly improved. PPAR-γ expression and the Akt signaling pathway are activated	Diet-induced obesity mice	Bak et al. (2013)

Table 2 (continued)

S. no	Phytochemical	Class	Protective action	Model	References
13	Gallic acid	–	Decreases AST, ALT, ALP acid phosphatase, lactate dehydrogenase, gamma-glutamyltransferase, bilirubin, alpha-fetoprotein, carcinoembryonic antigen, argyophillic nucleolar organizing regions and PCNA	NDEA-induced hepatocellular carcinoma in rats	Jagan et al., (2008
14	Gallic acid	–	Diminishes levels of lipid peroxidation, serum marker enzyme activity with a concomitant increase in GSH, CAT, SOD, GPx and GST	Lindane-induced hepatic and renal toxicity	Padma et al. (2011)
15	Gallic acid	–	Downregulation in the gene expression levels of hepatic gamma-glutamyl transferase and heat shock protein gp96. Regulation of STAT3 signaling pathway via the outstanding bioactivities of gallic acid including antioxidant potential, anti-inflammatory effect, apoptotic action, and antitumor impact	NDEA-induced hepatocellular carcinoma in rats	Aglan et al. (2017)
16	Bergenin	Phenol	Liver injury alters the pharmacokinetic behavior of bergenin and enhances its absorption after an oral dosing, which may promote the therapeutic efficacies of bergenin	CCl_4-induced liver injury in rats	Rong-Hua et al. (2016)
17	Bergenin	–	Reduces the release of ROS, downregulates inflammatory factors, and inhibited apoptosis and autophagy. Additionally, expression of PPAR-γ-related genes is increased and phosphorylation of P38 MAPK, NF-κB p65 and JAK2/STAT1-related proteins is decreased	Hepatic ischemia reperfusion in mice	Xiang et al. (2020)
18	Bergenin	–	Diminishes HA, FN, laminin, type I collagen, α-SMA, matrix metalloproteinases and tissue inhibitors of metalloproteinases. Activates PPAR-γ and inhibits TGF-β and autophagy	CCl_4 and bile duct ligated mice	Xia et al. (2020)
19	Bergenin + metformin	–	Lower body weight gain, plasma glucose and insulin. Whereas the level of Hb and liver glycogen is significantly increased. Gluconeogenic enzymes (glucose-6-phosphatase and fructose-1, 6-bisphosphatase) are significantly decreased and glycolytic enzymes (Hexokinase and glucose-6- phosphate dehydrogenase) are increased	HFD-induced type 2 diabetes in mice	Ambika and Saravanan (2016)
20	Bergenin + Gallic acid	–	Improve cell morphology, elevate cell viability, lower LDH, AST, ALT and MDA levels. Also promote SOD and CAT activities and total GSH content	Ethanol and tert-butyl hydroperoxide-induced oxidative stress in human hepatoma cells (HepG2)	Sriset et al. (2020)
21	β-Sitosterol	Sterol	Inhibits oxidative stress by causing diminution of intracellular enyzmic antioxidants such as SOD and CAT. Significantly reduces expression of HSCs activation markers (hydroxyproline, collagen, α-SMA, desmin, vimentin, and MMP 9)	CCl_4-induced liver injury in rats	Devaraj et al. (2020)

Table 2 (continued)

S. no	Phytochemical	Class	Protective action	Model	References
22	β-Sitosterol	–	Expression of PPAR-γ ligand and PON-1/ARE enzymes activities increases. Also, the activities of SOD, CAT enzymes and HDL-c levels display elevation. Whereas, significant decrease in MDA content, cholesterol, TG and LDL-c levels are revealed	Gamma Irradiated rats	Moustafa and Thabet (2017)
23	β-Sitosterol and its derivatives	–	Decrease the serum activity of AST ALT, TNF-α, IL-1β, IL-6) levels. Improve the activities of antioxidant enzymes such as SOD, GSH and CAT. Meanwhile, the expressions of Nrf2 and HO-1 are enhanced	Lipopolysaccharide/ D-galactosamine-induced acute hepatic injury in mice	Yin et al. (2018)
24	β-Sitosterol + Stigmasterol	–	Decrease in hepatic cholesterol, TGs with polyunsaturated fatty acids and alterations of free hepatic FFA	NAFLD-induced in mice	Feng et al. (2018)
25	Arbutin	Glycoside	TB test and MTT assays reveal the improvement in cell viability	Tert-Butyl hydroperoxide-induced toxicity in Hep-G2 Cell Line	Seyfizadeh et al., (2012
26	Arbutin	–	Raises the levels of serum albumin and lowers the bilirubin and lipid peroxidation	CCl_4-induced hepatotoxicity in rats	Mirshahvalad et al. (2016)
27	Arbutin	–	Decrease in ALP, ALT and AST enzyme	X-irradiated mice	Nadi et al. (2019)
28	Tannic acid	Phenol	Increases activities of SOD, CAT, GSH-Px, eNOS and serum level of NO. Moreover, reduces expression of angiotensin II receptor-1, IL-1β, TNF-α, TGF-β, caspase-3, c-fos, c-jun, the ratio of Bax/bcl-2, TIMP-1. Increases MMP-9 and MMP-1	CCl_4-induced liver injury in mice	Chu et al. (2016)
29	Tannic acid	–	Suppresses overexpression of IL-1β, TNF-α, c-fos, c-jun, NF-κB (p65) and caspase-3, downregulates bax and upregulates bcl-2, Nrf2 and HO-1	Acetaminophen-induced hepatotoxicity in mice	Zhang et al. (2017)
30	D-Limonene	Terpene	Preserves glutathione, SOD, catalase. Decreases hydroxyproline, malondialdehyde content, TNF-α, TGF β, and α-SMA expressions	CCl_4-induced liver toxicity in Wistar rats	Ahmad et al. (2018)
31	D-Limonene	–	Diminishes the levels of plasma glucose and elevates insulin. It also restores the declines the lipid peroxide and restores antioxidant enzyme levels in liver and kidney	Streptozotocin-induced diabetic rats	Murali et al. (2012)
32	D-Limonene	–	Reduces systolic blood pressure, heart rate, fasting blood glucose, plasma insulin, hepatic marker enzymes, hepatic lipids, circulatory lipid peroxidation by-products and hepatic phase I enzyme activities. Increases circulatory nonenzymic antioxidant concentrations and hepatic phase II enzyme activities	HFD and L-NAME-induced NAFLD in Wistar rats	Santiago et al. (2012)
33	D-Limonene	–	Decreases cellular alteration foci, neoplastic nodules and hepatocellular carcinomas and increases apoptotic indices of cellular alteration foci	Hepatocarcinogenesis in Sprague–Dawley rats	Kaji et al. (2001)

Table 2 (continued)

S. no	Phytochemical	Class	Protective action	Model	References
34	β-Caryophyllene	Sesquiterpene	Reduces the gene expressions of Collagen-1α1, TGF-β1 and TIMP1	CCl_4-induced liver fibrosis in Wistar rats	Calleja et al. (2013)
35	β-Caryophyllene	–	Attenuates the pro-inflammatory phenotypic `M1` switch of Kupffer cells and decreases the expression of vascular adhesion molecules intercellular adhesion molecule 1, E-Selectin and P-Selectin as well as the neutrophil infiltration	Alcoholic steatohepatitis-induced in mice	Varga et al. (2018)
36	β-Caryophyllene	–	Lowers hepatic lipid accumulation, TC, LDL and elevates HDL	Hypercholesterolemia-induced in Wistar rats	Harb et al. (2018)

CAT catalase, *SOD* superoxide dismutase, *MDA* malondialdehyde, *TNF-α* tumor necrosis factor alpha, *TAG* triacylglycerols, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *GSSG* glutathione disulfide, *GSH* glutathione, *GST* glutathione S-transferase, *GPx* glutathione peroxidase, *GRd* glutathione reductase, *HA* hyaluronic acid, *TIMP* tissue inhibitor of metalloprotease, *MMP* matrix metalloprotease, *HFD* high-fat diet, *NAFLD* non-alcoholic fatty liver disease, *HCC* hepatocellular carcinoma, *HCV* Hepatitis C virus, *ROS* reactive oxygen species, *HSCs* hepatic stellate cells, *COX-2* cycloxygenase-2, *RIP* receptor-interacting protein, *AST* aspartate transaminase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *γ-GT* Gamma-glutamyl transferase, *LDH* Lactate dehydrogenase, *PPAR* Peroxisome proliferator-activated receptor, *AMPK* AMP-activated protein kinase, *PCNA* Proliferating cell nuclear antigen, *NF-κB* Nuclear factor kappa B, *α-SMA* Alpha smooth muscle actin, *TGF* Transforming growth factor, *FN* Fibronectin, *Nrf2* Nuclear factor 2, *FFA* Free fatty acid, *HO* Heme oxygenase, *IL* Interleukin, *eNOS* Endothelial nitric oxide synthase, *TB* Trypan Blue,*L-NAME* N^{ω}-nitro-L-arginine methyl ester, *TC* Total cholesterol

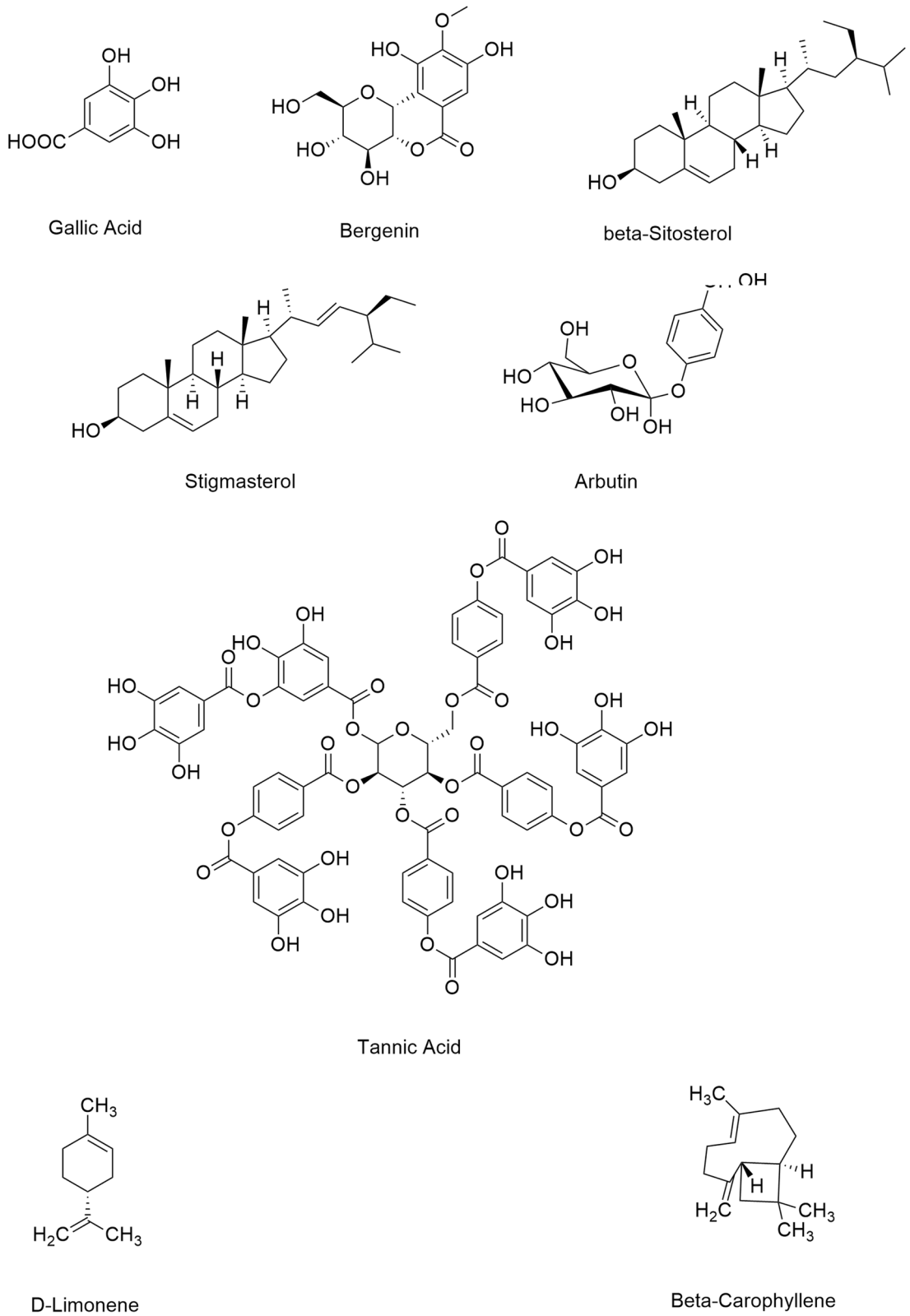

Fig. 2 Chemical structures of phytochemicals of *Bergenia ciliata*

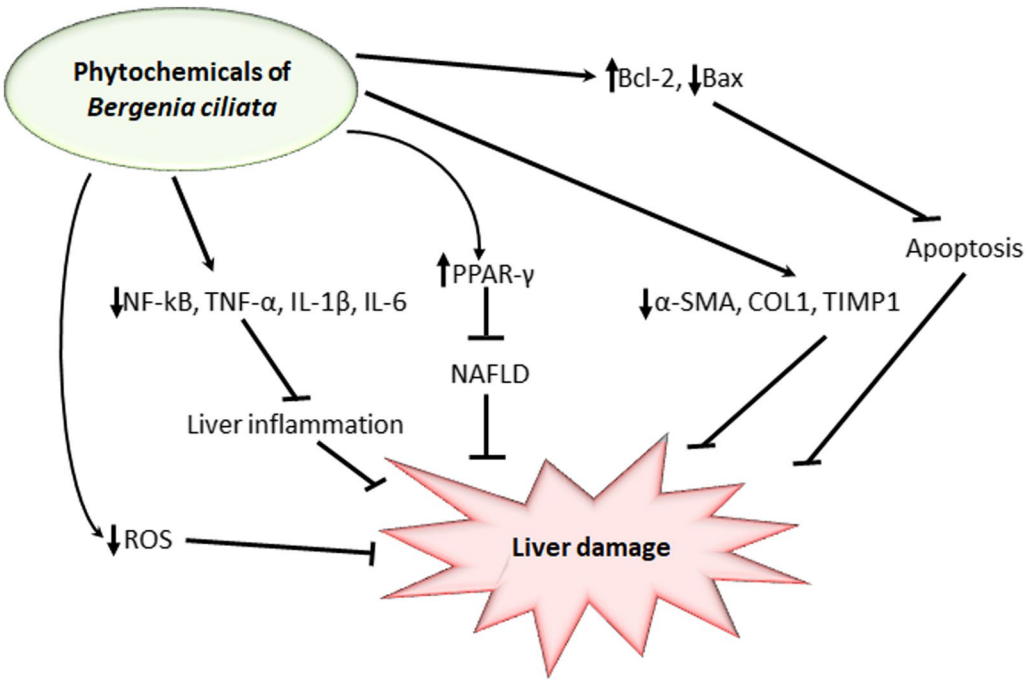

Fig. 3 Mechanism of protective action of *Bergenia ciliata* against liver diseases

studies, allowing researchers to gain a better understanding of its nature and function in order to develop novel treatments for liver illnesses in near future. The antioxidant and hepatoprotective properties of the crude extract and subfractions can also be investigated. Based on the experimental evidences in the current review, *Bergenia ciliata* is considered is one of the most important antihepatotoxic agent which is attributed to its phytochemical constituents. But there is a dire need for further experimental investigations for its use as an antifibrotic and hepatoprotective agents as deficiency in clinical trials has been observed. Therefore, for the future discovery of it as liver medicine, it is necessary to conduct additional clinical studies on this plant. These clinical trials should be conducted to test the efficiency of this plant for its clinical uses along with its safety profit. The outcome of research in these areas will give convincing support for clinical use of *B. ciliata* in modern medicine in near future. Moreover, the plant has also lesser side effects on living organisms as compared to modern medicines (Fig. 3).

Abbreviations

CLDs: Chronic liver diseases; GA: Gallic acid; BSS: β-Sitosterol; LPS: Lipopolysaccharide; GalN: D-Galactosamine; PI3K: Phosphatidylinositol 3-kinase; IR: Insulin receptor.

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Authors' contributions

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Author details

[1]Centre for Basic and Translational Research in Health Sciences, Guru Nanak Dev University, Amritsar, India. [2]Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, India. [3]Department of Botany, Govt. Degree College Doda, Jammu and Kashmir, India.

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