Hepatoprotective plants role in human health: A cross-kingdom review

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Abstract
Liver, being one of the most fundamental and vital organ existing in human body and performing significant role in regulation of enormous number of biological processes including metabolism of biomolecules, secretion, storage, detoxification and excretion of xenobiotics from body. Accomplishment of all these processes leads to acute or chronic hepatic injuries and liver dysfunctions, which sequentially contributes to global health care threat as well as it is a concern for pharmaceutical industry as despite all advancements in medicine there is still a lack of completely assured hepato-protective drugs which stimulate and enhance liver function. However, nature full fills these vacant spaces by providing a number of plant derived hepatoprotective phytochemicals, which are comparatively less toxic and this leads to introduction of an alternative phytotherapeutic approach i.e. introduction of poly herbal formulations for treatment of liver diseases. Throughout the world, herbalists claim the use of a number of remedial plants for treatment of hepatic dysfunctions. Nevertheless, recent research also reveals that not only phytochemicals, but also regulatory microRNAs are being transferred from plant to animal kingdom. Thus, this leads to an alternative concept of cross-kingdom gene regulation by non-coding tiny molecules i.e. orally consumed plant derived xenomiRs play a chief role in human health regulation. The abilities of microRNAs to regulate cross-kingdom gene regulation have prompted the hopes to explore this novel concept in diagnosis, prognosis and treatment as potential therapeutic and dietary supplements. The present review is aimed to compile the available data of promising hepatoprotective plants and introduce the cross-kingdom gene regulation approach as potential therapy for human health care.

Keywords: Cross-kingdom, hepatoprotective plants, liver dysfunctions, microRNAs, phytochemicals

1. Introduction
RNA interference or silencing is a mechanism of sequence specific regulation of gene expression which is prompted by RNA and results in negative regulation of gene expression by non-coding RNAs [1-3]. Based on their origin, effector protein association and mode of processing, these small RNAs are further categorised into microRNAs (miRNAs), small interfering RNA (siRNAs), PIWI-interacting RNA (piRNA) and transfer RNA derived small RNA (tsRNAs) [4]. Lin-4 - the first small RNA was identified and reported in early 90’s. Later, the regulatory properties of small RNA were illuminated when regulation of lin-14 by lin-4 was reported [2-3]. Even after achieving these milestones in RNA world, it took almost a decade to uncover their fundamental role in gene regulation. Today the RNA world is being explored not only for enzymatic properties of RNA but also for regulatory properties. Adding a layer of complexity to many disorders, these small regulatory molecules provide a new horizon of research [5]. Approximately 19-24 mers long, small RNA molecules, having negative regulatory and epigenetic properties, categorised as miRNAs are being identified and reported to be involved almost in every biological process irrespective of plants and animals [6, 7], miRNAs are one such class of small RNAs having big effects in gene regulation, originating from non-protein coding genes, majorly located in intronic regions [2]. Recent advancements in High-throughput sequencing such as small-RNA sequencing and Degradome sequencing have paved new ways in direction of miRNA directed gene regulation [8]. Over the past decade, hundreds of miRNAs have been reported from different species with the aid from advancements in NGS platforms and ever growing bioinformatics tools. After a decade of rigorous research across the globe, today the crucial regulatory role of miRNAs in multiple metabolic processes, developmental cycles, cell proliferation, cell signalling and cell
Recent studies have exploited presence of these miRNAs in various diseases and disorders ranging from Alzheimer’s to diabetes, cancer to neural disorders, liver disorders to anxiety disorders [2, 8]. Till now, number of plant derived miRNAs is reported to play key role in plant development cycles, stress resistance, host-pathogen interaction, increased yield, etc. miRNA induced gene silencing (MIGS) and artificial microRNAs (amiRNAs) are currently being exploited for agro-research and healthcare research [10, 11 & 12]. However, at present scenario health care research is shifting towards Ayurvedonomics. The most ancient record for the use of plants to cure diseases in human race is documented in the ‘Rigveda’ [13]. The focus on Ayurvedic research is accelerated worldwide as 80% of population depends upon the use of traditional medicines, which is pre-dominantly a plant material [14, 15, 16]. Herbalists believe that nature has answers and probably all the cures to treat majority of diseases and this is evident from the key role played by plants in human health care [17, 18]. Tribal communities are known to use their traditional knowledge of medicinal plants, and use it as drugs to treat multiple diseases or disorders. Since decades, this knowledge of ayurvedic drugs is being passed over generations among the tribal communities [19, 20]. Recently the use of herbal plants with Hepatoprotective activities are gaining more attention and are preferred over modern medicine due to the fact that natural medicines are harmless i.e. unlike modern medicine these products do not cause hepato-toxicity [16, 21, 22].

After a lot of research and multiple biochemical assays on plants, some researchers successfully identified active hepatoprotective compounds. Flavonoids are believed to be most important hepatoprotective compounds as they help the system by reducing free radicals [16, 21 & 22]. The isolated compounds also included apigenin, sylimarin, genisten, quercetin, kaempferol and catechins [22, 23]. Some studies also revealed that liver-protective plants have phenols, coumarins, monoterpenes, glycosides, alkaloids and xanthenes [16, 22].

Fig 1: Hepatoprotective plants in cross-talk with Human

Research on Andrographis Paniculata coins andrographolide as the chief liver-protective and anti-liver-toxic constituent [14, 24 & 25]. Phyllanthus amarus is reported to show liver-protective effect by lowering down the content of thiobarbituric acid reactive substances (TBARS) [13, 26, 27]. Oral administration of ethanol (EtOH) extract from the leaves of Cnidoscolus chayamansa demonstrated a protective effect against the hepatotoxicity [28]. Hepatoprotective effect generated against the sub-acute liver damage by the aqueous extract of Allium sativum bulbs, attributes this protection to the flavonoids present in the plant extract [23, 28]. The 95% ethanol extract, aqueous extract and methanol extract of Asteracantha longifolia are also reported for hepato-protective activities against CCI4 and acetaminophen and also accelerate the regeneration of liver cells [28]. 70% acetic extract from Punica granatum is documented to show hepatoprotective effect against hepatotoxicity [28]. Few more documents report hepato-protective effects of methanol extract of Annona squamosa, ethanol extract from the aerial parts of Acanthospermum hispidum, methanol extract of Helminthostachys zeylanica, leaf extract of Alchornea cordifolia, leaf extract of Ziziphus mauritiana, aqueous extracts of fresh tuber roots of Daucus carota andaqueous extract of the roots of Rhoeicissus tridentata against CCI4 and acetaminophen induced liver damage [22, 28].

Even though consumable plants are meant for nutrition and food supply, but an emerging concept of communication across the kingdoms has now reached to the level of gene regulation [29, 30]. A few testimonies favour trans-kingdom gene regulation mediated by plant derived xeno-miRs have aggravated the elation of researchers towards the exploration of these small gene regulators for betterment of human health and therapeutic purposes [31, 32]. Thus cross kingdom gene regulation proves to be a vital key to resolve the regulation communicated by plants on human genes and metabolic pathways.

2. Hepatoprotective plants

By mining a huge amount of available literature we have identified number of plants which have promising hepatoprotective activities (Table 1), and this includes Picrorrhiza kurroa, Andrographis paniculata, Eclipta alba, Silybum marianum, Phyllanthus maderaspatensis, Trichopus zeylanicus, Orthosiphon stamineus, Glycyrrhiza glabra Linn, Saururus chinensis, Cordia macleodii, Arachniodes exilis, Amaranthus spinosus, Aerva lanata Linn, Ocimum sanctum, Cassia roxburghii, and Indigofera tinctoria [19]. The Ayurvedic medicinal system, which has been practiced in Indian Subcontinent by indigenous tribal communities since past 5000 years is based on the mammoth potential of remedial plants which are used orthodoxy and this knowledge is transferred among the generations [19, 20, 33]. The growing popularity of using number of poly-herbal formulations and extracts in treatment of various diseases ranging from cancer to liver injuries is due to the reason that herbal formulations are not harmful, and are effective with minimum reported side-effects as well as easily extracted from natural resources [27, 28]. Furthermore, due to scarcity of safe therapeutic choices and unsatisfactory results, medicines have increased usage of alternative herbal therapeutic options [16, 21]. Even till date, modern pharmaceuticals are reported to contain 25% constituents derived from herbs [22]. In modern day, this approach of using phyto-constituents as drugs is referred as phyto-therapeutic approach. Since time immemorial, indigenous tribal communities have been
practicing this phyto-therapeutic approach to cure various liver disorders including hepatitis, fatty liver and hepatotoxicity induced by multiple agents \[34\]. Derived from a number of phytochemical analyses of hepato-protective plants, it has been reported that these hepato-protective herbs contain like phenols, coumarins, lignans, essential oil, monoterpenes, carotinoids, glycosides, flavanoids, organic acids, lipids, alkaloids and xanthenes, which are responsible for anti-hepatotoxic activities \[15\].

Some of the renowned herbal medicines being consumed by patients suffering from hepatic disorders, are reported to contain Picrorhiza kurroa, Andrographis paniculata, Terminalia chebula, Phyllanthus niruri, Eugenia Jambolana.

### 2.1 Picrorhiza kurroa

Ayurveda mentions Picrorhiza kurroa (family Scrophulariaceae) as a potent herb that has been widely used as an alternative to treat multiple hepatic disorders. It has also been reported as an imperative element in many herbal preparations for hepatic ailments. Phytochemical studies to evaluate hepatoprotective activities of Picrorhiza kurroa identifies and lists picroliv (mixture of picrose I and kutkoxide) as the active phytoconstituent, isolated from roots and rhizomes, used as anti-hepatic-toxic agent in liver diseases such as jaundice. A study concludes picroliv as hepatoprotective constituent against ethanol-induced hepatic injury. These conclusions are drawn from the studies in which P. kurroa extract successfully reduced the activities of SOD and CAT. This study also confirms the dose dependent protective activity of P. kurroa against ethanol-induced hepatic injury. In a study, animals treated with picroliv showed reduction in levels of AST, ALT and ALP, which were earlier increased due to induced hepatic injury, this helps to conclude the hepatoprotective activity of picroliv \[36, 37\].

### 2.2 Terminalia chebula

Terminalia chebula (family Combretaceae), commonly known as chebulic myrobalan, is reported as a potent herbal drug for multiple disorders in Ayurvedic pharmacopoeia, found in abundance in North India. Phytochemical studies identify and report chebuloside II as the active phytoconstituent involved in biological activities of T. chebula. Documents and literature states mature and dried fruit of T. chebula has proven to be functionally effective to treat a number of ailments ranging from urinary tract infections to cardiovascular and hepatic ailments. In a study T. chebula fruit ethanolic extract was assessed and evaluated against induced hepato toxicity by administration of rifampicin (RIF), isoniazid (INH) and pyrazinamide (PZA) and this study reported the result that T. chebula extract was found to be effectively preventing the induced hepato toxicity by notably attenuated the elevated levels of serum AST, ALT, and LDH level in intoxicated animals \[38, 39\].

### 2.3 Andrographis paniculata

Andrographis paniculata (family Acanthaceae), also known as “king of bitters”, is described as Kalmegha in Ayurveda medicine system. This herbaceous plant is mentioned in a number of literatures for its biological properties such as hepato-protective and anti-inflammatory abilities. Literature mining reveals a number of studies which postulate Andrographolide as a major hepato protective phytoconstituent present in this remedial herb, which protects the hepatocytes due to its free radicle scavenging property. Phytochemical studies report Andrographolide as the major active constituent responsible for biological activities such as anti-inflammatory, anti-allergic and hepato-protective. It is also documented that ethanol and aqueous extract of A. paniculata was found to be effective in decreasing blood glucose levels in experimental animals, which signifies its anti-diabetic activity. Experimental studies also conclude that levels of Serum enzymes such as ALT, SGPT and SGOT were found to be decreased but increased levels of proteins were reported after the administration of Ethanolic extract of A. paniculata. A Histology study conducted on liver sections of experimental animals revealed that treatment of animals with extract of A. paniculata resulted in hepatocyte regeneration and leading it to normal histology. Thus it helps to conclude the hepato-protective role of Andrographis paniculata against induced liver toxicities \[40, 41\].

### 2.4 Phyllanthus niruri

Phyllanthus niruri (family Euphorbiaceae), a perennial herb distributed throughout India, is reported to be used to treat various infirmities, predominantly hepatitis. A study done by Shamasundar et al. \[1985\], revealed the chief phytoconstituents present in P. niruri extract such as phyllanthin and hypophyllanthin are responsible for imparting its remedial activity which includes protection against liver toxicity. Experimental study done to evaluate the potential of P. niruri extract against ccl4 induced hepato-toxicity in experimental animals revealed that the changes caused by ccl4 were significantly reversed by the test extract i.e. the elevated levels of serum enzymes GOT and GPT were attenuated back to normal levels, this symbolises the anti hepato-toxic effect of P. niruri extract. In vitro studies conducted on aqueous extract of the plant reveals its potential as a promising hepato protective agent, as it was found as a vigorous inhibitor of lipid peroxidation and also demonstrated anti-oxidant activity. A study concluded that administration of P. niruri aqueous extract in paracetamol intoxicated experimental animals causes a significant reduction in levels of GPT and GOT serum enzymes, which proves it as a hepatoprotective agent against paracetamol \[42, 43\].

### 2.5 Eugenia Jambolana

Eugenia jambolana also known as Syzygium jambolana, (family Myrtaceae), is a large evergreen tree, widely distributed throughout India. Commonly referred as Black plum, is a berry fruit, and is widely used in traditional medicine system such as Ayurveda. Both jamun fruit and seeds are evidenced to retain antioxidant activities due to the presence of alkaloids, flavonoids, glycosides, phytosterols, saponins, tannins and triterpenoids in seeds and existence of raffinose, glucose, fructose, citric acid, anthocyanins, mallic acid and gallic acid in fruit extracts as demonstrated by various phytochemical studies. In experimental studies conducted to estimate hepatoprotective effect of Eugenia jambolana, animals treated with the test extract displayed reduced levels of enzymes (ALT, AST, alkaline phosphatase and total bilirubin) and increased level of total protein and albumin, these results were comparable to standard hepato protective drug Silymarin. Thus it establishes the hepato protective effect of E. jambolana against induces toxicity. In a study jambolana fruit extract treatment also resulted in reduced severity of hepatocellular injury and fibrosis which is indicative of the fact that it contains the remedial compounds with hepatoprotective activity \[44, 45\].
| Plant                | Plant part                  | Plant Extract                  | Hepatic toxicity inducing agents                      | Result                                                                 | References |
|----------------------|-----------------------------|--------------------------------|-------------------------------------------------------|----------------------------------------------------------------------|------------|
| Curcuma longa        | Rhizomes                    | Ethanol                        | Paracetamol, Diethyl nitroamine, CCL4                | Reduced serum levels of ALT, AST and ALP                                 | 46         |
| Foeniculum vulgare    | Leaves                      | Ethanol                        | H2O2, CCL4                                           | Reduced serum levels of ALT, AST and ALP                                 | 47         |
| Allium sativum       | Raw bulblets                | Ethanol                        | Thioacetamide                                        | Reduced AST, ALP, ALT                                                 | 48         |
| Cassia occidentalis  | Leaves                      | Ethanolic extract              | CCL4                                                 | Decreased the elevated levels of ALT, AST, ALP, LDH                      | 49         |
| Mentha piperita      | Leaves                      | Extraction of essential oil, Ethanol extract | CCL4, Paracetamol                                    | Decrease or normalised ALT, AST, ALP and LDH levels                     | 50, 51     |
| Olea europaea        | Leaf                        | Methanol Aqueous               | CCL4, Paracetamol                                     | Decrease in AST, ALT, ALP levels                                       | 52, 53     |
| Agrimonia eupatoria  | Aerial parts                | Water extract                  | Ethanol-induced                                      | Reduced levels of serum enzymes - ALT, AST, ALP, and bilirubin          | 54, 55     |
| Alhagi maurorum      | Whole plant                 | Ethanol                        | Paracetamol                                          | Reduced SGPT, SGOT, ALP and Total Bilirubin level                      | 56, 57     |
| Arctium lappa        | Root                        | Aqueous                        | CCL4, Acetaminophen, Ethanol                         | SGOT, triglyceride levels and SGPT elevations were reduced              | 58, 59     |
| Brassica nigra       | Leaves                      | Methanol                       | D-galn intoxicated rats                              | Increased activities of SGOT, SGPT, LDH. Total protein and albumin were significantly Increased | 60         |
| Caesalpinia cristia  | Leaves and seeds           | Methanol Ethanol               | Iron-overload induced liver injury. CCL4 & Paracetamol | Reduced the elevated levels of serum enzymes - ALT, AST, ALP, and bilirubin | 61, 62     |
| Calotropis procera   | Flowers                     | Hydro-ethanolic extract        | Paracetamol-induced hepatitis                        | Reduced the elevated levels of SGPT, SGOT, ALP, bilirubin, cholesterol. | 63         |
| Cassia occidentalis  | Root                        | Aqueous                        | CCL4                                                 | ALT, AST and GGT decreased                                             | 64         |
| Coriandrum sativum   | Leaves and stem             | Ethanol                        | CCL4                                                 | Decreased ALT, AST, ALP and total bilirubin                            | 65         |
| Crotalaria juncea    | Seed                        | Petroleum ether extract        | Thioacetamide induced acute hepatic damage           | Reduced levels of ALT, AST, and ALP with increasing the level of total protein content | 66, 67     |
| Cuminumcyminum       | Seeds                       | Crude extract                  | Cisplatin CCL4                                       | Decreased the level of ALT, AST, and ALP along with increasing the level of total protein content | 68         |
| Cynodonactylon       | Leaves                      | Phosphate buffered saline      | CCL4                                                 | The activity of SGOT and SGPT was found to be significantly decreased   | 69, 70     |
| Cyperus alternifolius| Aerial parts                | Ethanol                        | CCL4                                                 | AST, ALT and ALP decrease                                             | 71         |
| Daucus carota        | Roots                       | Aqueous                        | Paracetamol, isoniazid and alcohol                   | Restored the elevated enzyme ALT & AST levels to normal and significantly reduced bilirubin | 72         |
| Eupatorium cannabinum| (Stems, flowers, and leaves) | Aqueous                        | CCL4                                                 | Glutamic pyruvic transaminase Cannabinum showed a significant decrease of GPT levels | 73         |
| Foeniculum vulgare   | Seeds                       | Hydroalcoholic extract         | Paracetamol                                          | ALP, ALT and AST decreased                                             | 74         |
| Galium verum         | Aerial parts                | Dry extracts                   | CCL4                                                 | Decrease in serum ALT and AST activity and an increase in serum cholinesterase activity | 75         |
| Glycyrrhiza glabra   | Root                        | Powdered                       | CCL4                                                 | Significant decrease in the activities of LDH, gpt and GOT             | 76         |
| Helianthus annuus    | Seeds and leaves            | Methanolic and Hydromethanolic extract | Paracetamol Acetaminophen                           | Decrease in ALT, AST and ASP                                           | 77         |
| Hibiscus cannabinus  | Leaves                      | Aqueous                        | CCL4 & Paracetamol                                    | Decrease in ALT, AST and bilirubin                                     | 78, 79     |
| Hibiscus rosasinensis| Flowers and aerial parts    | Aqueous and Ethanol            | Hypercholesterolemia induced by feeding pure cholesterol and cholic acid | Decreased the levels of AST, ALT, ALP enzymes                           | 80         |
| Juglans regia        | Leaves                      | Ethanol                        | CCL4                                                 | Serum ALT, AST, ALP and albumin levels decreased                       | 81, 82     |
| Boerhaavia diffusa   | Roots and leaves            | Ethanol                        | Country made liquor and acetaminophoe                | Significant fall in serum ALT, triglycerides cholesterol and lipids and tissue triglycerides and cholesterol. Decreases in the values of serum AST, ALT, ALP, bilirubin and LDH | 83         |
| Plant Name                  | Part Used                      | Extract Type 1 | Extract Type 2 | Extract Type 3 | Extract Type 4 | Effect                                                                 |
|----------------------------|--------------------------------|----------------|----------------|----------------|----------------|----------------------------------------------------------------------|
| Eclipta alba                | Leaves                         | Ethanol        | Paracetamol, CCL4 |                |                | Restored paracetamol induced elevated serum level of ALT, AST and ALP towards normal value |
| Picrorhiza kareora          | Dried rhizomes                 | Aqueous        | Alcohol, Paracetamol, CCL4 |                |                | Alcohol cytotoxicity                                                   |
| Tephrosia purpurea          | Aerial parts                   | Hydro-alcoholic extract | Sodium arsenite | Decreased elevated levels of ALT, AST, ALP |
| Phylianthus amarus          | Aerial part                    | Aqueous extract | Ethanol | Decreased ALT, AST back to normal |
| Mimosa pudica               | Leaves                         | Methanol       | CCL4 | Decrease in the elevated levels of SGPT, SGOT, ALP, TBL, LDH |
| Adhatoda vasica             | Leaf                           | Aqueous        | D-galactosamine-induced liver damage | Decreased SGOT, SGPT and TBARS levels back to normal |
| Morus alba                  | Leaves and Whole plant         | Ethanol        | Paracetamol and CCL4 | Decreased levels of SGOT, SGPT, ALP, LDH |
| Rosa damascena              | Fresh petals and Flowering top | Acetone fraction and ethanol | CCL4 and Paracetamol | Serum ALP, GPT and got activity reduced, AST, ALT and ALP were found to be elevated after the administration of paracetamol, which was significantly reversed by extract |
| Nymphaea alba               | Flowers                        | Ethanol        | Isoniazid | Significant decrease in AST, ALT, ALP |
| Silybum marianum            | Seeds                          | Ethanol        | Thioacetamide | Reduced the level of enzymes activity SGPT, SGOT and ALP and the level of total bilirubin, |
| Flacourtia indica           | Leaves and Aerial parts        | Aqueous extract and Petroleum ether ethyl acetate | CCL4 and Paracetamol | Significant decrease in ALT, AST, ALT and TBARS & significant increase in level of Total protein |
| Annona squamosa             | Dried seeds                    | Ethanol        | Alcohol | Significantly decreased the levels of elevated ALT, AST, ALP, LDH, SB and CHL while significantly increased the reduced levels of total protein and albumin |
| Chamomile capillita         | Dry Chamomile flowers          | Aqueous extract and Aqueous Ethanol extract | 2,4-Dichlorophenoxyacetic Acid and Paracetamol | Reduced the elevated serum levels of ALT and AST, ALP and bilirubin and Decrease in LDH |
| Coccinia grandis            | Leaves                         | Ethanolic      | CCL4 | Significant decrease in levels of SGOT, SGPT, ALKP. |
| Aegle marmelos              | Leaves                         | Ethanolic extract | Alcohol and CCL4 | Lower levels of SGOT, SGPT, ALP and bilirubin |
| Cassia roxburghii           | Seeds                          | Methanol extract | Ethanol and CCL4 | Decrease in SGOT, SGPT and ALP along with a significant increase in tp, albumin. |
| Ficus carica                | Leaves                         | Methanol extract | CCL4 | Lower values of ALP, ALT, AST |
| Lepidium sativum            | Seeds                          | Ethanol extract | D-galactosamine and lipopolysaccharide | Reduction in serum AST, ALT, ALP, and bilirubin level. |
| Solanum nigrum              | Whole plant and Dried fruits   | Methanol and Ethanol | CCL4 | Reduction of the elevated AST, ALT, ALP and serum bilirubin concentration values |

3. miRNAs

miRNAs are a class of small epigenetic regulators, approximately 19-24 nucleotides long single stranded RNA molecules, originating from their precursor molecules[113]. These evolutionarily conserved single stranded small RNAs originate from non – coding genes, majorly located in intergenic regions and few occurring in intronic regions[114]. Though, these miRNAs originate from non-coding genes but manipulate the regulation of protein coding transcripts i.e. miRNAs which originate from coding regions, by predominant target cleavage or translation inhibition, thus mediating gene silencing at post-transcriptional stage hence sometimes these miRNAs are also referred as post-transcription regulators[115]. The production of mature miRNA is a complex multi-step procedure involving nuclear process, transportation, cytoplasmic processing and Argonaute loading. However, the biogenesis procedure varies in animals and plants. Nevertheless, in both the cases, miRNAs are processed from single stranded primary miRNA transcripts called pri-miRNAs. In animal nucleus, pri-miRNAs are processed and cleaved by the activity of multifacetted microprocessor which contains Drosha - RNaseIII enzyme and its co-factor DgGeorge syndrome critical region gene 8 protein - DGCR8, which is also a dsRNA-binding protein, this activity results in transformation of pri-miRNAs into shorter hairpin RNAs of approx 65-100 nt pre-miRNAs[113, 115]. The generated pre-miRNAs are actively transported by exportin 5 to cytoplasm for further processing which involves cleavage activity of Dicer - RNaseIII enzyme and removal of terminal loop resulting in generation of 22-nt miRNA/miRNA* duplex[116]. Subsequently, unwinding of this miRNA/miRNA* duplex by helicase and degradation of one of the strands results in a mature miRNA also known as the guide strand[117]. Conversely, in plants the entire two-step mechanism of generating a mature miRNA occurs only in nucleus by DCL1 - Dicer-like 1 enzyme with the help of hyponastic leaves 1 (hyl1)- a dsRNA binding protein and serrat(e) se[116, 118]. The generated 21 nt mature miRNAs are then incorporated into an Argonaute (AGO1) protein, a central and functional unit of miRNA-induced silencing complex (miRISC) – a complex of proteins that target miRNAs based on sequence complementarity[116,118]. Mature miRNA guides the AGO1 to
identify target miRNAs on the basis of base complementarity and the mechanism for silencing of target mRNA is dependent on the same i.e. perfect complementarity between miRNA-target mRNA results in degradation or cleavage of target mRNA, whereas if the perfect complementarity is lacking among miRNA-mRNA does not results in cleavage but rather it causes translational repression of target mRNA by decapping or exonucleolytic digestion [115, 119, 120].

4. cross-kingdom regulation

In past widespread research has been conducted to enlighten the possible paths by which consumable plants impart their regulatory effects on human health and all these studies are found to suspect the possibility of transferring regulatory miRNAs from plant to animal kingdom [121]. Cross kingdom analysis of plant miRNAs with human genes provides strong evidence for the stable presence of xeno-miRs in human system as well as their potential regulatory effect involved in multiple biological systems [122].

One of the most revolutionary discoveries was marked by researchers at Monsanto Company in 2009 when they found that plentiful endogenous plant miRNAs displayed perfect complementarity to mammalian genes [123]. These findings initiated a wave of research in understanding that exogenous miRNAs can be transferred across species and their role in host species, thus paving a way for cross-kingdom communication through miRNAs was controversial, but for the very first time in 2011 a study by Zhang’s team, confirmed that plant derived miR168a can be absorbed intact from mammalian GI tract and remained stable in human system. From there on it entered circulatory system, after accumulation in liver it binds and targets exon 4 of low-density lipoprotein receptor adapter protein 1 (LDLRAP1) mRNA and regulates its expression [123, 124]. Thus it was evident from this study that exogenous plant miRs can mimic mammalian indigenous miRs and regulate gene expression [123]. This conclusion also revealed that plant miRNAs target not only endogenous genes, but also exogenous genes by crossing the species barrier [123]. Confirmed by another study by Andrew et al. that plant miR159 can be absorbed from sources into human sera and further revealed that mimic of the same can inhibit cell proliferation and it also supressed the xenograft breast tumor growth, if administered orally and this same can inhibit cell proliferation and it also supressed the xenograft breast tumor growth, if administered orally and this concept not only illuminates the active status of the packaged miRNAs but rather it causes translational repression of target mRNA by decapping or exonucleolytic digestion [115, 119, 120]. Hence, these days miRNAs are regarded as new and effective bio-active constituent present in herbal remedies, which can be further exploited for therapeutic effects which are accelerated by technology upgradation in RNA-based therapies which is supported by miRNA interference or silencing. At present, miRNAs are being explored due to their potential to be next generation drugs [130]. Current research on Circulating and cell free miRNAs suggests miRNAs can be used as promising biomarkers for prognosis and diagnosis of various diseases [131]. This provides a controversial but potentially revolutionary concept of miRNA mediated gene silencing and cross kingdom regulation between plants and animals for further research.

5. Conclusion and Outlook

At present descent amount of literature is available which postulates and favours the concept that various kingdoms could exchange or transfer regulatory molecules such as miRNAs across the kingdom as signals for altering gene expression of other kingdom, this indicates the probability of miRNAs emerging as new and unexplored bioactive component available in herbal medicines. However, this potential use of miRNAs in herbal medicines and targeting disease-associated genes in another kingdom with plant derived xeno-miRs is at exploratory stage. Evaluation of stability of herbal miRNAs in human system and the form in which these miRNAs survive as well as to what extent absorption of these miRNAs occur is still questionable. Furthermore studies are wanted to unravel the mechanism of intestinal absorption, bioavailability, tissue recognition, role and influence of secondary metabolites available in herbal extract. In this review we have tried to explore hepatoprotective plants and miRNAs along with the concept of cross kingdom gene silencing. The inevitable question that how medicinal plants are reported to regulate human genome could be answered by identifying the mechanism of cross-kingdom regulation by xeno-mirs and molecular signalling mechanism across the species. Thus this concept not only illuminates the role of plant derived miRNAs in human health, involvement of target genes in various diseases but it also reflects the direction of future studies which might explore miRNA mediated cross – kingdom gene regulation, which could be a promising alternative for prevention and treatment of number of diseases. Future perspectives may include health regulation by herbal miRNAs and in-vitro synthesis of potential therapeutic miRNAs with lower side-effects and discovery of novel target genes. More research in this nascent area will not only help us to understand the role of herbal miRNAs in human health, their importance as food resources, but it will also broaden the way for development of alternative approaches for prevention and treatment of human diseases.

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Conflict of Interest

Authors declare no conflict of interest.
Abbreviations
MIRs: micro RNAs
MIGS: Micro RNA Induced Gene Silencing
AST: ASpartate Transaminase
ALP: ALkaline Phosphatase
ALT: ALanine Transaminase
SGPT: Serum Glutamic Pyruvic Transaminase
SGOT: Serum Glutamic-Oxaloacetic Transaminase
GOT: Glutamate-Oxaloacetate Transaminase
D-GALN: D-Galactosamine
HDL: High Density Lipoprotein
ACP: ACidPhosphatase
TBARS: Thio Barbituric Acid Reactive Substance
SBL: Serine-β-Lactamase
LDH: Lactate Dehydrogenase

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