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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., the use 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 xeno-MIRs 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 silencingis 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

differentiation is well documented for both plant and animal species [3, 5, 7, 9].

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 Ayurgenomics. 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 world-wide 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 hepato-protective compounds. Flavonoids are believed to be most important hepato-protective compounds as they help the system by reducing free radicals [16, 21 & 22]. The isolated compounds also included apigenin, sylimarin, genistein, quercetin, kaempherol and catechins [22, 23]. Some studies also revealed that liver-protective plants have phenols, coumarins, monoterpenes, glycosides, alkaloids and xanthenes [16, 22].

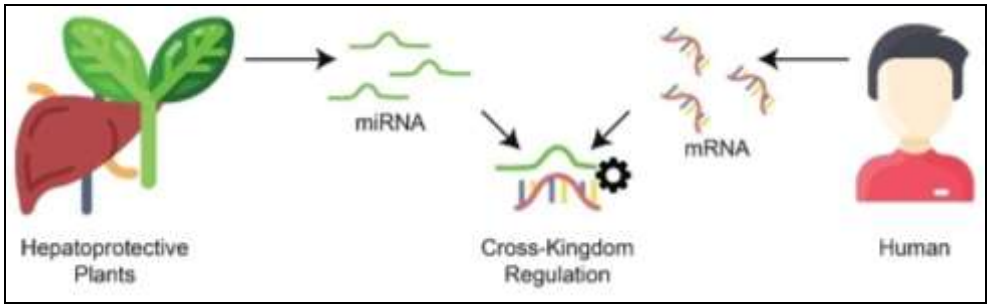

Fig 1: Hepatoprotective plants in cross-talk with Human

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 CCl4 and acetaminophen and also accelerate the regeneration of liver cells [28]. 70% acetonic 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 *Daucos carota* andaqueous extract of the roots of *Rhoicissus tridentata* against CCl4 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, Silibum marianum, Phyllanthus maderaspatensis, Trichopus zeylanicus, Orthosiphon stamineus, Glycyrrhiza glabra Linn, Saururus chinensis, Cordia macleodii, Arachniodes exilis, Amaranthus spinosus, Aerva lanata Linn, Ocimum snctum, 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 orthodoxly 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 hepat-toxic 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 picroside I and kutkoside) as the active phytoconstituent, isolated from roots and rhizomes, used as anti hepato-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 Combetraceae), 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 toxicated 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 *Syzynium 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].

Table 1: Medicinal plants having hepatoprotective potential

Plant	Plant part	Plant Extract	Hepatic toxicity inducing agents	Result	References
Curcuma longa	Rhizomes	Ethanol	Paracetamol, Diethyl nitrosamine, CCL4	Reduced serum levels of ALT, AST and ALP	46
Trigonella foenum-graecum	Leaves	Ethanol	H_20_2, CCL4	Reduced serum levels of ALT, AST and ALP	47
Allium sativum	Raw bulblets	Ethanol	Thioacetamide	Reduced AST, ALP, ALT	48
Petroselinum crispum	Leaves	Ethanolic extract	CCL4	Reduced GOT, GPT, ALP	49
Mentha piperita	Leaves	Extraction of essential oil, Ethanol extract	CCL4	Decreased the elevated levels of ALT, AST, ALP, LDH	50, 51
Olea europaea	Leaf	Methanol Aqueous	CCL4, Paracetamol	Decrease or normalised AST, ALT, ALP and LDHlevels	52, 53
Agrimonia eupatoria	Aerial parts	Water extract	Ethanol-induced	Decrease in AST, ALT, ALP levels	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	Decreased activities of SGOT, SGPT, LDH. Total protein and albumin were significantly Increased	60
Caesalpinia crista	Leaves 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
Crocus sativus	Petals And dried red stigmas	Hydroalcoholic extract, Aqueous and Ethanolic extract	Acetaminophen and Amiodarone-induced	Nearly normal levels of ALT, AST, total bilirubin, total proteins and albumin. Decreased serumALT, AST and LDH	66, 67
Crotalaria juncea	Seed	Petroleum ether extract	Thioacetamide induced acute hepatic damage	Extremely significant Reduction of elevated values such as AST, ALT, ALP and bilirubin	68
Cuminumcyminum	Seeds	Crude extract	Cisplatin CCL4	Decreased the level of ALT, AST, and ALP along with increasing the level of total protein content	69 , 70
Cynodondactylon	Leaves	Phosphate buffered saline	CCL4	The activity of SGOT and SGPT was found to be significantly decreased	71
Cyperus alternifolius	Aerial parts	Ethanol	CCL4	AST, ALT and ALP decrease	72
Daucus carota	Roots	Aqueous	Paracetamol, isoniazid and alcohol	Restored the elevated enzyme ALT & AST levels to normal and significantly reduced bilirubin	73
Eupatorium cannabinum	(Stems, flowers, and leaves)	Aqueous	CCL4	Glutamic pyruvic transaminase Cannabinum showed a significant decrease of GPT levels	74
Foeniculum vulgare	Seeds	Hydroalcoholic extract	Paracetamol	ALP, ALT and AST decreased	75
Galium verum	Aerial parts	Dry extracts	CCL4	Decrease in serum ALT and AST activity and ALP activity and an increase in serum cholinesterase activity	76
Glycyrrhiza glabra	Root	Powdered	CCL4	Significant decrease in the activities of LDH, gpt and GOT	77
Helianthus annuus	Seeds Leaves	Methanolic and Hydromethanol extract	Paracetamol Acetaminophen	Decrease in ALT, AST and ASP	78 , 79
Hibiscus cannabinus	Leaves	Aqueous	CCL4 & Paracetamol	Decrease in ALT, AST and billirubin	80
Hibiscus rosa-sinensis	Flowers and Aerial parts	Aqueous And Ethanol	Hypercholesterolemia induced by feeding pure cholesterol and cholic acid	Decreased the levels of AST, ALT, ALP enzymes	81 , 82
Juglans regia	Leaves	Ethanol	CCL4	Serum ALT, AST, ALP and albumin levels decreased	83
Boerhaavia diffusa	Roots and Leaves	Ethanol	Country made liquor and acetaminophe	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	84 , 85

Eclipta alba	Leaves	Ethanolic Aqueous	Alcohol, Paracetamol, CCL4	Restored paracetamol induced elevated serum level of ALT, AST and ALP towards normal value	86 , 87
Picrorhiza kurroa	Dried rhizomes	Aqueous	Alcohol cytotoxicity	LDH, got and gpt decreased	88
Tephrosia purpurea	Aerial parts	Hydro-alcoholic extract	Sodium arsenite	Decreased elevated levels of ALT, AST, ALP	89
Phyllanthus amarus	Aerial par	Aqueous extract	Ethanol	Decreased ALT, AST back to normal	90
Mimosa pudica	Leaves	Methanol	CCL4	Decrease in the elevated levels of SGPT, SGOT, ALP, TBL	91
Adhatoda vasica	Leaf	Aqueous	D-galactosamine-induced liver damage	Decreased SGOT,SGPT and TBARS levels back to normal	92
Aerva lanata	Leaves and Whole plant	Ethanol	Paracetamol And CCL4	Decreased levels of SGOT, SGPT, ALP, LDH	93 , 94
Morus alba	Leaves	Alcoholic extract and Water extract	CCL4	Decreased SGOT, SGPT, ALP and serum bilirubin	95
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	96, 97
Nymphaea alba	Flowers	Ethanol	Isoniazid	Significant decrease in AST, ALT, ALP	98
Silybum marianum	Seeds	Ethanol	Thioacetamide	Reduced the level of enzymes activity SGPT, SGOT and ALP and the level of total bilirubin,	99
Flacourtia indica	Leaves and Aerial parts	Aqueous extract and Petroleum ether ethyl acetate	CCL4 and Paracetamol	Significant decrease in ALP, AST, ALT and TBARS & significant increase in level of Total protein	100 , 101
Annona squamosal	Dried seeds	Ethanol	Alcohol	Significantly decreased the levels of elevated ALT, AST, ALP, LDH, SBL and CHL while significantly increased the reduced levels of total protein and albumin	102
Chamomile capitula	Dry Chamomile flowers	Aqueous extract and Aqueous Ethanolic extract	2,4-Dichlorophenoxyacetic Acid and Paracetamol	Reduced the elevated serum levels of ALT and AST, ALP and bilirubin and Decrease in LDH	103 , 104
Coccinia grandis	Leaves	Ethanolic Aqueous	CCL4	Significant decrease in levels of SGOT, SGPT, ALKP.	105
Aegle marmelos	Leaves	Ethanolic extract	Alcohol and CCL4	Lower levels of SGOT, SGPT, ALP and bilirubin	106 , 107
Cassia roxburghii	Seeds	Methanolic extract	Ethanol and CCL4	Decrease in SGOT, SGPT and ALP along with a significant increase in tp, albumin.	108
Ficus carica	Leaves	Methanol extract	CCL4	Lower values of ALP, ALT, AST	109
Lepidium sativum	Seeds	Ethanolic extract	D-galactosamine and lipopolysaccharide	Reduction in serum AST, ALT, ALP, and bilirubin level.	110
Solanum nigrum	Whole plant and Dried fruits	Methanolic and Ethanol	CCL4	Reduction of the elevated AST, ALT, ALP and serum bilirubin concentration values	111 , 112

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. mRNAs 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 multifaceted microprocessor which contains Drosha - RNaseIII enzyme and its co-factor DiGeorge 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 serrate (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 mRNAs based on sequence complementarity [116-118]. Mature miRNA guides the AGO1 to

identify target mRNAs 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 Ayurgenomics [124, 125, 126]. Although the concept of 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 became the first evidence for regulation of cancer genes by plant-derived xeno-MIRs [127].

More recent researches helped to identify and report putative miRNAs from *Curcuma longa* which bind with various target genes related to human diseases such as diabetes mellitus type II, cardiovascular disorders, Alzheimer's, cancer, and thalassemia [128]. Anothercross-kingdom regulation evidence by MIR2911 from honeysuckle plant was reported to inhibit viral replication [126, 127]. Naked miRNAs cannot survive harsh conditions of gut, to answer this issue further researchers explained miRNA uptake mechanisms by micro vesicles (MV), shedding vesicles (SV), exosomal vesicles (EV), exosomes and apoptotic bodies, packaging of miRNAs in these vesicles protect it against the activities of RNases as well as natural constituents present in herbal di*et al*so contribute to stability of these miRNAs [125, 129]. In MVs not only miRNAs are packed but along with it RNA induced silencing complex (RISC) components are also packed which ensures the active status of the packaged miRNAs subsequently reaching the destination through circulatory system i.e., the recipient cells wherein it performs its regulatory activity [126]. However, few studies also support the concept of 2'-O-methylated 3' ribose sugar ends of miRNAs being the reason of their stability in mammalian sera, plasma and tissues [127].

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 hepato-protective 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 Transminase
GOT: Glutamate-Oxaloacetate Transaminase
D-GALN: D-Galactoseamine
HDL: High Density Lipoprotein
ACP: ACidPhosphatase
TBARS: Thio Barbituric Acid Reactive Substance
SBL: Serine-β-Lactamase
LDH: Lactate Dehydrogenase

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