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Evaluating hepatoprotective activity of polyherbal formulations - An overview of dietary antioxidants

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Abstract

Chronic liver disease is the foremost cause of morbidity, accounting for 2.2 percent of death. In recent years, excessive attention has been focused on using natural antioxidants as they have the potential to minimize oxidative stress in cells and thus help treat various ailments. Some scientists estimate that two-thirds of plant species have medical applications, and many of these have significant antioxidant potential. Polyherbal formulations (PHFs) have shown therapeutic promise in the treatment of several acute and chronic conditions, including diabetes, wound care, hypertension, cardiovascular disorders, anxiety, neurological imbalances, and disorders of the gastrointestinal, respiratory, and endocrine systems. This article reviews the antioxidant potential of the various PHFs developed to treat hepatic disorders during the past ten years. After preliminary screening, 53 abstracts based on the PHFs selected for hepatoprotection were retrieved from several bibliographical databases. This review provides insight and indicates the gaps presented in the case of PHFs. To conclude, PHFs can activate several physiological processes that quicken the process. Clinical trials should be conducted to further examine these PHFs, and production upscaling will help to open up new markets for PHFs.

Keywords

antioxidants; 2,2-diphenyl-1-picrylhydrazyl; hepatoprotective; liver disease; polyherbal formulation

Introduction

The liver plays a vital role in sustaining numerous physiological processes in the body. It is involved in several functions, such as metabolism, secretion, and storage (1). It regulates the detoxification and excretion of various exogenous and endogenous metabolites. Furthermore, any injuries or damage to the liver showcase the deteriorating health of a person. As per a report, around 2 million people globally die because of liver disease each year (2).

Alternative and complementary systems such as the Indian traditional system, popularly known as the Ayurvedic system, and European and Chinese alternative systems are known to be popular healing systems for locals. Since the beginning of time, plants have been utilized as the mainstay of medicine. Hepatoprotective medications have a substantial source in medicinal plants. Some liver ailments have reportedly been treated with

more than 700 mono- and polyherbal medicines in the form of decoctions, tinctures, and pills. It has been asserted that numerous plants and preparations exhibit hepatoprotective properties. It is said that a total of 160 active components from 101 plants have post-liver protective properties. 33 patented multi-ingredient plant compositions with propitiatory properties contain about 87 plants from India. Despite the enormous progress made, there are no significant and secure hepatoprotective drugs available in contemporary medicine. As a result, the development of mostly plant-based hepatoprotective drugs that are effective against a variety of liver illnesses has received significant attention on a global scale (3).

Polyherbal formulations (PHFs), which have a wide range of indications against numerous illnesses, are affordable and have fewer side effects are created by combining several possible herbs in diverse ratios (4). Approximately 600 PHFs are advertised as liver protectors on the commercial market worldwide (5). Since the vast majority of new polyherbal combinations are not scientifically tested for effectiveness, safety, and health concerns are also growing as they enter the market (6, 7). Oxidative stress, or oxidative damage, has a role in the pathophysiology of several chronic liver disease phenotypes, including alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD) (8), drug-induced liver injury (DILI), and fibrosis (9).

An imbalance between the generation of free radicals (FR) and the antioxidant defenses is referred to as oxidative stress (10). FR are atoms or/and molecules having one or more unpaired and unstable electrons (e^-). FR is understood to be highly reactive. While reducing, an Oxygen (O^-) molecule can generate a reactive oxygen species (ROS) while interacting with transition metals (11). As a result, comparing the antioxidant activity of different PHFs may indicate an antioxidant-rich formulation for treating liver problems (12). To substantiate the therapeutic claims made by the hepatoprotective PHFs formed in the previous ten years, the current study seeks to describe the multiple *in-vitro* antioxidant scientific methodologies used in this regard during 2013-2023.

Methodology

Inclusion and exclusion criteria for the PHFs having hepatoprotective potential

The review is significant of the in-depth literature exploration in various bibliographic databases such as PubMed, Scopus, Google Scholar, etc. with the various keywords “Polyherbal formulations”, “Hepatoprotective”, “liver diseases”, and “antioxidant activity” done as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA guidelines (13). A total of 122 articles were retrieved during the search, however, only 53 relevant papers published in English and having full text were considered to extract the desired information (14, 15). Of which only 154 articles were found inside the inclusion criteria.

Out of the 174 PHFs included in the study, India has contributed the most (n=107), followed by Sri Lanka (2), Korea (22), Taiwan (1), Iran (1), and Pakistan (1) in the past ten years. The year 2015 saw the greatest increase in PHF development. *Boerhavvia diffusa* (n=4) and *Picrorrhiza kurroa* (n=4) were the two plant constituents that were employed the most frequently.

Results

Table 1 enlists the major phytochemicals, such as phenolic and flavonoid content of different hepatoprotective PHFs which are largely responsible for the antioxidant activity. Table 2 indicates the antioxidant activity of different hepatoprotective PHFs evaluated using different test methods. 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was the most common method to evaluate the antioxidant potential of the hepatoprotective PHFs.

Table 1. Total phenolic and flavonoid content of different hepatoprotective PHFs

Sl no	PHF name	Name of the country	Composition	Extract Method	Total Phenolic contents (mg/g)	Total Flavonoid contents (mg/g)	Pharmacological uses	References
1.	PHAF	Sri Lanka	*Cassia fistula*, *Glycyrrhiza glabra*, *Coscinium fenestratum*, *Cyperus rotundus*, *Curcuma longa*, *Azadirachta indica*, and *Stereospermum suaveolens*	Ethanol	327.07±9.65	224.6 ± 8.42	Anti-inflammatory	(34)
				Aqueous	103.65 ± 4.94	76.6 ± 5.83		
2.	LINK LIVECARE™	Sri Lanka	*Andrographis paniculata, Eclipta alba, Phyllanthus amarus, Phyllanthus emblica, Terminalia chebula, Terminalia bellirica, Tinospora cordifolia, Curcuma longa, Glycyrrhiza glabra, Boerhavia diffusa, Osbeckia octandra. Tephrosia purpurea, Piper longum* and *Vernonia cinerea*	Aqueous	1050/7g	-	-	(35)

3.	F1	Korea	*Hovenia dulcis, Oryza sativa* and *Glycine max*		7.30 ± 0.01	-	-	
4.	F2	Korea	*Hovenia dulcis, Oryza sativa* and *Glycine max* extract with powder of *Hovenia dulcis*	Fermented	7.73 ± 0.01	-	-	(36)
5.	L52	India	*Capparis spinosa*, *Cichorium intybus*, *Solanum nigrum*, *Terminalia arjuna*, *Cassia occidentalis*, *Achillea mille-folium*, *Tamarix gallica*, and Mandur Bhasma	Ethanol	5.65 ± 0.17	-	-	
				Aqueous	1.22 ± 0.021			
6.	L38	India	*Phyllanthus niruri*, *Eclipta alba*, *Picrorhiza kurroa*, *Tinospora cordifolia*, *Andrographis paniculata*, *Solanum Nigrum*, *Boerhaavia* diffusa, *Terminalia. Arjuna*, and *Berberis aristata*	Ethanol	3.16 ± 0.09	-	-	(37)
				Aqueous	0.645 ± 0.161			
7.	LST-02	India	*Tinospora cordifolia, Phyllanthus amarus, Emblica officinalis, Terminalia chebula, Terminalia bellerica, Azadirachta indica, Adhatoda vasica, Picrorhiza kurroa, Swertia chirata*, and *Boerhaavia diffusa*	Hydroethanolic	47.9 ± 0.14	-	-	(38)
8.	KGA	Pakistan	*Borago officinalis, Coriandrum sativum, Bombyx mori, Salvia haematodes, Centaurea behen, Santalum album, Melissa parviflora, Lallemantia royleana, Ocimum gratissimum, Lavandula stoechas, Cheiranthus cheiri, Mathiola incana, Ambra grasea, Delphinium denudatum, Paeonia emodi*, and *Pandanus tectorius*	Aqueous metha-nol	27.4 ± 0.2%	36.8 ± 0.2%.	-	(39)
9.	Liv-pro-08	India	*Nigella sativa* (Seed), *Entada pursaetha* (Seed), and *Ficus glomerata* (Fruit)	Aqueous	13.16 ± 0.31	19.71 ± 0.91	Reduces NAFLD	(32,40)
10.	Nannari Mathi-rai	India	*Hemidesmus indicus, Cuminum cyminum, Elettaria cardamomum, Foeniculum vulgare*, and *Sesbania grandiflora*	Aqueous	0.034	0.1720	Antimicrobial	(41)
11.	Qurs-e-Vard	Iran	*Rosa damascene*, *Rhus coriaria*, and *Glycyrrhiza glabra*	Hydroalcoholic	376 ± 0.93	36.27 ± 0.98	-	(27)
				Aqueous	297.6 ± 0.96	17.79 ± 0.86		

12.	PHF tablet	India	*Butea monosperma, Bauhinia variegata*, and *Ocimum gratissimum*	Acetone fraction (*B. Monospera*	452 ± 1.6		-	(28)
				Ethyl acetate (*B. variegata)*	712.4 ± 2.4			
				n-butanol fractions (*B. variegata*)	442.5 ± 1.1			
				Dichloromethane (*O. gratissimum*)	735 ± 2.1			
				Ethyl acetate fractions (*O. gratissimum*)	1365 ± 1.4			
				Quercetin estimation of PHF tablet	0.113155575 mg/ spot			
13.	AEF	Taiwan	*Artemisia capillaris, Lonicera Japonica*, and *Silybum marianum*	Aqueous	52.6	9.6	-	(42)
14.	LivPro	India	*Achillea millefolium, Cichorium intybus*, and *Picrorhiza kurroa*	Ethanolic	396	480	Anti-inflammatory Anti-HCV agent	(43, 44)

Mechanistic perspective of hepatoprotection using poly- herbal formulations

Table 2. *In vitro* antioxidant activity of different hepatoprotective PHFs

S no	PHF name	Name of the country	Composition	Solvent use	*In vitro* antioxidant activity	References
1.	PHAF	Sri Lanka	*Cassia fistula*, *Glycyrrhiza glabra*, *Coscinium fenestratum*, *Cyperus rotundus*, *Curcuma longa*, *Azadirachta indica*, and *Stereospermum suaveolens*	Ethanol	DPPH assay 227.17 ± 6.16 mg Trolox equivalents/g of extract	(34)
				Aqueous	DPPH assay 79.50 ± 4.42 mg Trolox equivalents/g of extract	
				Ethanol	ORAC assay 1481.44 ± 30.20 mg Trolox equivalents/g of extract	
				Aqueous	ORAC assay 481.11 ± 17.30 mg Trolox equivalents/g of extract	
				Ethanol	ABTS assay 577.08 ± 5.48 mg Trolox equivalents/g of extract	
				Aqueous	ABTS assay 198.20 ± 4.55 mg Trolox equivalents/g of extract	
2.	Link Livecare™	Sri Lanka	*Andrographis paniculata, Eclipta alba, Phyllanthus amarus, Phyllanthus emblica, Terminalia chebula, Terminalia bellirica, Tinospora cordifolia, Curcuma longa, Glycyrrhiza glabra, Boerhavia diffusa, Osbekia octandra. Tephrosia purpurea, Piper longum*, and *Vernonia cinerea*	Aqueous	DPPH assay IC_{50} = 50	(35)
				Gallic acid	DPPH assay IC_{50} = 5	
				Gallic acid	DPPH assay IC_{50} = 5	
3.	LST-02	India	*Tinospora cordifolia, Phyllanthus amarus, Emblica officinalis, Terminalia chebula, Terminalia bellerica, Azadirachta indica, Adhatoda vasica, Picrorhiza kurroa, Swertia chirata*, and *Boerhaavia diffusa*	Hydroethanolic	DPPH assay IC_{50} = 164.8 ± 0.10	(38)

4.	KGA	Pakistan	*Borago officinalis, Coriandrum sativum, Bombyx mori, Salvia haematodes, Centaurea behen, Santalum album, Melissa parviflora, Lallemantia royleana, Ocimum gratissimum, Lavandula stoechas, Cheiranthus cheiri, Matthiola incana, Ambra grasea, Delphinium denudatum, Paeonia emodi*, and	Methanolic extract	DPPH assay IC_{50} = 60.8	(39)
				Ascorbic acid	DPPH assay IC_{50} = 64.7	
5.	Livomyn	India	*Andrographis paniculata, Phyllanthus niruri, Boerhaavia diffusa, Amoora rohituka, Cichorium intybus, Adhatoda vasica, Eclipta alba, Zingiber officinale, Berberis aristata, Fumaria officinalis, Embellia ribes, Tephrosia purpurea, Tinospora cordifolia*, *Coriandrum sativum, Aloe barbadensis*, and *Picrorhiza kurroa*	Aqueous	DPPH assay IC_{50} = 61.42	(45)
				Ascorbic acid	DPPH assay IC_{50} = 63.62	
6.	Liv-pro-08	India	*Nigella sativa* (Seed), *Entada pursaetha* (Seed), and *Ficus glomerata* (Fruit)	Aqueous	DPPH assay IC_{50} = 711.00	(40)
7.	Nannari Mathirai	India	*Hemidesmus indicus, Cuminum cyminum, Elettaria cardamomum, Foeniculum vulgare*, and *Sesbania grandiflora*	Aqueous	DPPH scavenging activity	(41)
				Ascorbic acid	DPPH scavenging activity	
8.	PHF	India	*Calotropis procera, Gymnema sylvestre*, and *Lawsonia inermis*	Aqueous methanolic	DPPH assay IC_{50} = 62.76	(26)
				Ascorbic acid	DPPH assay IC_{50} = 42.27	
9.	PHF	India	*Plumeria rubra*, and *Murraya koenigii*	Hydro-methanolic	DPPH assay:	(46)
				Aqueous	DPPH assay:	
10.	Qurs-e-Vard	Iran	*Rosa damascene*, *Rhus coriaria*, and *Glycyrrhiza glabra*	Ascorbic acid	DPPH assay:	(27)
				Hydro-alcoholic	DPPH assay: IC_{50} = 88.14 ± 1.15	
				Aqueous	DPPH assay: IC_{50} = 140.78 ± 2.98	
				Quercetin	DPPH assay: IC_{50} = 78.97 ± 0.25	
				Hydro-alcoholic	Nitric Oxide assays: 59.11 ± 2.15	
				Aqueous	Nitric Oxide assays: 65.08 ± 2.35	
				Quercetin	Nitric Oxide assays: 55.08 ± 2.34	
				Hydroalcoholic	FRAP assay: 255.24±3.45	
				Aqueous	FRAP assay: 134.57±3.45	
				Quercetin	FRAP assay: 16.11 ± 0.45	
11	AEF	Taiwan	*Artemisia capillaris, Lonicera japonica*, and *Silybum marianum*	Aqueous	DPPH scavenging activity = 84.1%	(42)

The mechanistic perspective of hepatoprotection using PHFs necessitates a comprehensive understanding of the distinct molecular and cellular pathways through which these herbal blends exert their safeguarding effects on the liver. Most plant-based hepatoprotective formulas (PHFs) are made up of different plant-based ingredients, each of which has bioactive components that work together to protect the liver (16). The following are some pivotal mechanisms that may play a role:

Antioxidant activity

Numerous PHFs incorporate antioxidant-rich herbs, including flavonoids, polyphenols, and other phytochemicals. These compounds assist in counteracting detrimental free radicals and reactive oxygen species (ROS), which can inflict harm on liver cells and trigger inflammatory responses (1, 17). By becoming oxidized themselves, antioxidants are preventative chemicals that are essential for preventing oxidative harm brought on by reactive oxygen species (ROS) (5, 18-20). Natural antioxidants have attracted more attention in recent years, and the literature indicates clearly that they can replace synthetic antioxidants for some positive reasons. Most studies on natural antioxidants concentrate on phenolic chemicals, especially flavonoids such as Curcumin, as potential sources of these molecules (1, 21, 22). To produce a composition that is both effective and balanced, it is crucial to carefully analyze the antioxidant profiles of each herb. Nearly all experts in the current study collected and evaluated the total phenolic and flavonoid content utilizing aqueous methods. The DPPH scavenging activity was used to determine the antioxidant activity, making it the most popular and trustworthy method. As benchmarks, various synthetic and natural antioxidants were utilized, including ascorbic acid, gallic acid, quercetin, and trolox. To make an overall estimation of the antioxidant potential of PHFs,

the activity of different solvents has been attempted by several researchers.

PHFs mix a variety of herbs or plant extracts to provide a synergistic result that may improve the medicinal effects of each component (17, 18). In general, the discussion over polyherbal ABTS compositions should cover both the possible advantages and drawbacks of using them as antioxidants. It is crucial to approach the subject with a critical perspective, taking into account the existing scientific evidence and the environment in which the formulation would be utilized, just like with any herbal treatment or medicinal product. In the ABTS method, the blue-green chromophore 2,2 -Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS+) is treated with an antioxidant to measure the colour loss that results. The antioxidant decolorizes and transforms ABTS+ to ABTS (23). The hepatoprotective ability of the polyherbal mixture can be completely determined by combining various antioxidant assays. Overall, the available research supports the investigation of polyherbal formulations as an additional strategy for treating oxidative stress-related illnesses and enhancing general health and well-being.

Anti-Inflammatory effects

PHFs contain metabolites like phenols that impede pro-inflammatory pathways and cytokines. By reducing liver inflammation, these blends can provide safeguards for hepatocytes (liver cells) against potential harm (1, 24). Some flavonoids, such as flavonols (quercetin and rutin), flavanones (hesperidin), flavanols (catechin), and anthocyanins (e.g. cyanidin) have been demonstrated for their anti-inflammatory ability (25).

Detoxification support

Certain herbs in polyherbal mixtures may help the liver's natural detoxification processes by making detoxifying enzymes work better and making it easier for the body to get rid of toxins (1, 26).

Stimulation of liver regeneration

A portion of the polyherbal mixtures has the potential to promote the growth and division of hepatocytes, potentially facilitating the regeneration of liver tissue. This mechanism could contribute to the repair of damage caused by various factors, such as toxins or infections (1, 27).

Modulation of cellular signaling

Polyherbal compounds such as flavonoids and terpenoids have the potential to engage with diverse cellular signaling pathways, including those responsible for apoptosis (programmed cell death), cell survival, and proliferation. By modulating these pathways, polyherbs can contribute to the enhancement of liver cell well-being (1, 28). Chen *et al*. (29) indicated that catalpol, a terpenoid, can effectively inhibit the progression of liver disease, and effectively prevent fatty liver by inhibiting inflammation and increasing lipid metabolism.

Anti-fibrotic effects

Excessive accumulation of collagen characterizes liver fibrosis, which can result in cirrhosis and compromised liver function. OS contributes to fibrogenesis, a mechanism often connected to the repair system of a body, by upregulating harmful cytokines such as transforming growth factor-β (TGF-β), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) (30). In addition, TGF-β also leads to ROS production in endothelial and epithelial cells followed by other liver cells such as epithelial cells, and fibroblasts (9). Ingredients within PHFs might possess the ability to impede fibrosis by diminishing collagen synthesis and facilitating its breakdown (24).

Immunomodulation

An array of PHFs might affect the immune response within the liver, aiding in the modulation of immune cells and preventing liver damage caused by immune activity (31).

Cholesterol regulation

The constituents of PHFs may contribute to the regulation of blood cholesterol levels and prevention of fat build-up in the liver, thereby decreasing the likelihood of developing non-alcoholic fatty liver disease (32).

Gut-liver axis modulation

Polyherbal formulations have the potential to affect the gut microbiota and vital gut-liver axis, which hold significant importance in upholding liver well-being. Polyherbals can indirectly provide safeguarding effects to the liver by promoting a harmonious gut microbiome (33).

It is crucial to recognize that the specific mechanisms of liver protection may differ based on the unique herbs and compounds contained in the polyherbal blend. Furthermore, additional research is required to comprehensively understand the mechanisms underlying the hepatoprotective benefits of polyherbal medicines and to ascertain their efficacy and safety in various situations.

Conclusion

In this review, we included various PHFs that were created to safeguard the livers and whose antioxidant activity has been tested. The authors documented several PHFs due to the paucity of scientific validations and the rising number of formulations. Such information revealing their mechanistic method or synergistic system is not readily available. The documented studies were merely pointing out that phenolics and flavonoids, which not only shield cells but also have antioxidant activity, may be responsible for PHFs' protective impact against hepatic damage. Therefore, it can be concluded that PHFs' ability to act as antioxidants themselves in neutralizing harmful metabolites may account for their hepatoprotective properties. Interestingly, none or very little information on these PHFs was discovered. The quality and reproducibility of formulations are not standardised. Although most herbal compounds are thought to be safe, some plants may interact or have negative/allergic effects when mixed. Studies conducted in the preclinical and clinical stages may offer novel insights into the safety profile of these formulations.

In vivo, investigations are necessary to fully comprehend the potential of the PHFs. Before considering their use in clinical settings or as dietary supplements, nevertheless scientific standardization, and safety evaluations are required. To determine the effectiveness of these PHFs to treat hepatic illnesses, investigations on the separation, purification, and characterization of the phytochemicals as well as *in vivo* experiments must be the need of hour and carried out.

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Authors contributions

AKG conceptualized the study. BM, SKM, TU, and BNN performed the literature search, analyzed the data, created a table, and wrote the first draft of the manuscript. AKG and TU performed the English editing and revision along with others. All the authors approved the manuscript for final submission.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interest to declare.

Ethical issues: None.

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