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Therapeutic Efficacy of Flavonoids and Terpenoids an Ongoing Herbal Therapy in the Treatment of Leishmaniasis

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Abstract

Leishmaniasis is an epidemic disease caused by Leishmania parasite. Leishmaniasis is a major disease worldwide many people are affected by this disease. The prevalence of the disease is seen in many countries around the world since many millions are affected by the disease in different countries and thousands of deaths occur every year this is a neglected tropical disease. There are more than 20 species in the world. The parasite develops its life cycle in sand flies. The disease is transmitted by the phlebotomine sand fly which lives in rodents, dogs etc. This parasite uses animals like dogs as a host and develops its life cycle and this disease is carried over to humans through a bite of the insect. This disease is caused due to poor sanitary conditions. The treatments with synthetic drugs have severe side effects and the treatment is very expensive. A major development is seen in developing countries like India in finding new herbal entities to eradicate the disease through herbal remedies. An attempt has been made to review flavonoids and terpenoids their biological role in the treatment of leishmaniasis, these are major secondary metabolite used in the treatment of leishmaniasis by producing therapeutic efficacy against many diseases like visceral leishmaniasis. They are equally potent to marketed antileishmanial drug. This review gives the significance of flavonoids and terpenoids as potent compounds with biological activity present naturally in many plants, fruits, vegetables, as coloured pigments, etc. these compounds can be isolated their therapeutic efficacy can be tested and they can develop promising activities against many diseases.

***Keywords:** Flavonoids; Herbal medicine; Leishmaniasis; Terpenoids; Therapeutic activity*

Introduction

Leishmaniasis called as Kala-Azar in India is a vector borne disease transmitted by sand flies. Leishmaniasis is a parasitic disease caused by more than 20 *Leishmania* protozoan parasite species. Almost 2.5 million people are affected all over the world, 1-1.5 million are affected by cutaneous Leishmaniasis and in India over 90000 are

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affected by visceral Leishmaniasis VL. From 2004-2008 there were an estimated 200,000-400,000 cases and 20,000-40,000 deaths per year globally [1]. WHO is taking preventive measures to eradicate the vector and the disease within 2020 [2]. This parasite starts its life cycle in sand fly (FIG. 1). An epidemic disease caused by leishmania parasite and can be transmitted from a bite of an infected sand fly. It affects either the skin or the internal organs. These parasites are transmitted to humans by the bites of the infected female phlebotomine sandfly. There are three different types of leishmaniasis cutaneous, visceral and mucocutaneous. VL is a serious disorder were internal organs like liver, spleen and lymph node gets affected. The symptoms include fever, enlargement of the liver and spleen, anaemia, weight loss, weakness, decreased production of blood cells, bleeding and swollen lymph nodes. Treatments are given using antimony compound sodium stibogluconate and amphotericin B that causes severe side effects than any other treatment option, but which is very expensive. But the diagnosis and treatment given to patients should be in an affordable price. Both treatments have side effects such as fever, liver and kidney damage or heart disease. A new molecule miltefosine, is available can be given orally and has a lower risk of toxicity. The research on herbal remedies should be given more significance to eradicate the disease and the side effects, so researchers should concentrate more on herbal therapies. The aim of this review was to provide an overview of the ethanobotany of medicinal plants used to treat leishmaniasis in India. This review was to analyze the presentation of herbal therapies for the treatment of leishmaniasis, on the basis of diagnosis, treatment, management and follow up with the objective of highlighting visceral leishmaniasis as an important differential diagnostic tool for the eradication of VL [3,4].

Role of Herbal Medicine in the Treatment of Leishmaniasis

Since time immemorial India is considered to be the land of herbal garden, and the ancient practice in treatment using traditional system of medicine, complementary alternative medicine, like ayurveda, siddha, unani and homeopathy. These Indian systems of medicine have played a vital role in treatment of various diseases including, cancer, Alzheimer's disease, parasitic diseases like, filariasis and leishmaniasis. India is a home for herbal medicine many medicinal plants were used in the form of monoherbal and polyherbal formulation in single and combined dosage forms. In India many herbs are used for leismaniasis, people prefer herbal medicine for treatment since minor or no side effects can be observed and allopathic medicine is the major treatment given but with severe side effects. Varity of medicinal plants have been used by Indian people of different cultures to treat leishmaniasis. Most of the plants were herbs and the commonly used plant part was leaf. Majority of prepared remedies were applied externally to the affected part. There is an urgent need to conduct clinical trials on such plants to support traditional claims and to analyze molecular and cellular mechanisms involved.

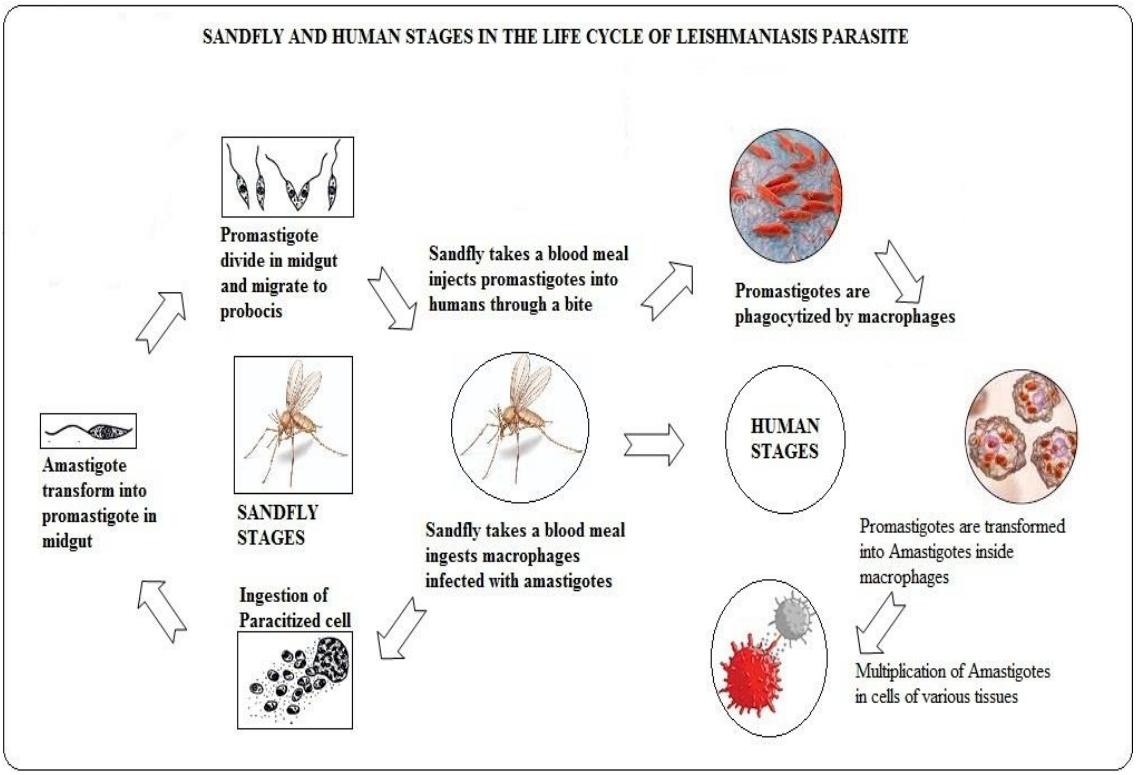


FIG.1. **Life cycle of Leishmaniasis parasite.**

Statistics

The epidemiology of Leishmaniasis is found in 88 countries, of which 72 countries are developing countries and 13 are under developed countries. Cutaneous leishmaniasis is found in the Middle East, Asia and Africa. Visceral leishmaniasis is found in Africa and Asian countries. Also this disease is more in Arabian countries in Iran, Afghanistan saudiarabia and Syria. In India it is mainly found in west Bengal, Bihar and Uttar Pradesh. VL called as Kala-azar is a serious disorder more Indians and African countries like Sudan, Somalia etc. are affected by VL. Hence this is an endemic disease found only in western part of the country. The environmental and climatic condition is suitable for the insect vector to grow. It is also found in epidemic and non-endemic areas of the country (FIG. 2).

FIG. 2. **Statistics of VL worldwide.**

Role of Flavonoids and Terpenoids

Flavonoids and terpenoids are natural occurring secondary metabolites present in plants. Flavonoids are having a polyphenolic structure. They are abundant in plants their biological activity is vast they have high therapeutic value against many diseases which include cardiovascular diseases, anti-cancer, neurological disorders, skin diseases and various other acute and chronic diseases. Flavonoids are therapeutically active and they have antioxidants, free radical scavenging activity. These compounds possess active phytoconstituents, they are potent active constituents found in many plants, fruits and vegetables. They are more efficacious against many diseases and they are potent active constituents present in many plants. They have less side effects and low toxicity. To overcome these side effects and toxicity these natural compounds are used. The isolation of these compounds leads to promising pharmacological activities.

Classification of Flavonoids

Flavonoids are classified into many classes like flavones, flavonols, flavonones, anthocyanins, isoflavonoids, chalcones etc. each classes of flavonoids are subdivided into many subclasses. They also contain phenolic acids like hydroxyl cinnamic acid present in caffeic acid, ferulic acid and gingerol and hydroxyl benzoic acid present in ellagic acid and gallic acid. They contain hydrosable tannins such as chebulic acid and gallo tannins (FIG. 3 and 4).

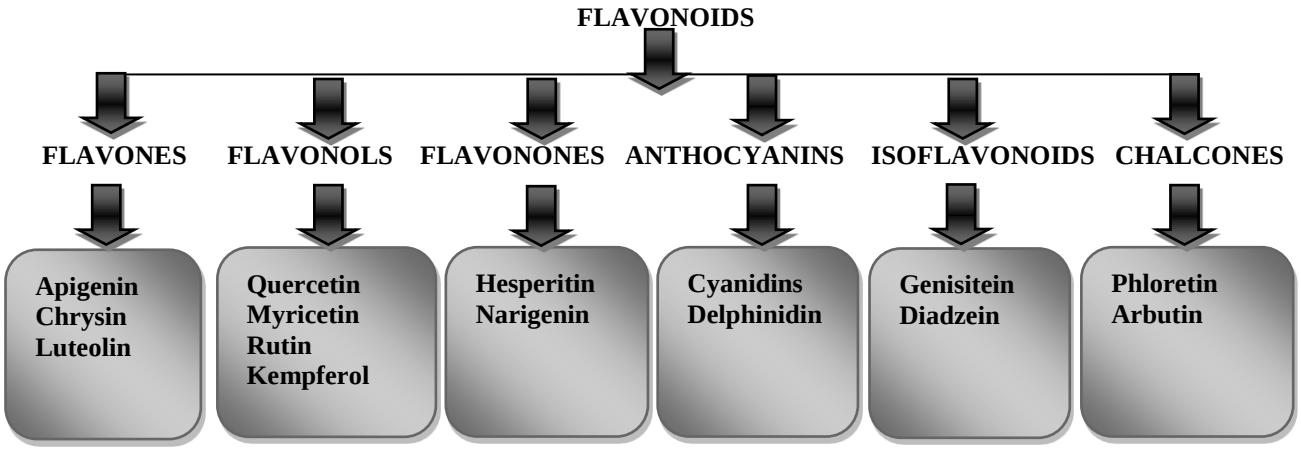


FIG. 3. **Flavonoids.**

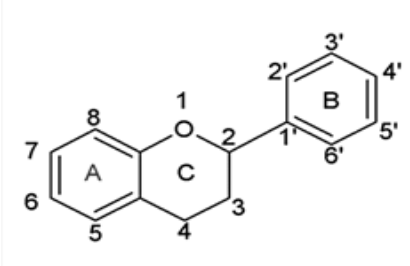


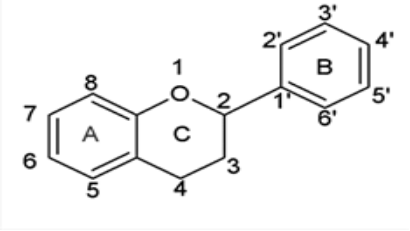
FIG. 4. **Basic Skeleton of Flavonoid**

Chemistry of Flavonoids

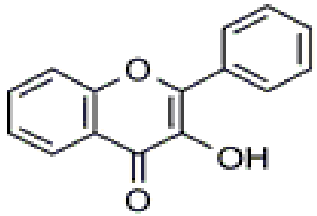
Flavonoid contain C6-C3-C6 compounds, each C6 moiety is a benzene ring. They contain one or more phenolic hydroxyl groups combined with sugar moiety. The hydroxyl groups are found in 5 and 7 position in ring A, ring B contains hydroxyl alkoxyl groups. The aromatic ring A is condensed to heterocyclic ring C attached to a second aromatic ring B. It contains a flavonoid diphenyl propane skeleton. They are divided into two sub classes which include anthocyanins and anthoxanthins. Anthocyanins are water soluble plant pigments containing glycosides. Anthoxanthins are yellow or colorless compounds containing flavones, flavonols, isoflavones and flavonones [5].

- Flavonoids [1]
- The flavanols [2] are a class of flavonoids obtained from 3-hydroxy-2, 3-dihydro-2-phenylchromen-4-one
- Quercetin [3] is a polyphenol from the flavonoid group
- Kaempferol [4] is a type of flavonoid obtained from a natural flavonol
- Myricetin [5] is a polyphenolic compound a member of the flavonoid class, with antioxidant activity
- Galangin [6] is a flavonol type of flavonoid which is found in the rhizome of *Alpinia galanga*.
- Fisetin [7] is a plant polyphenol from the flavonoid group
- Flavones [8] are yellow coloured compounds containing 2-phenylchromen-4-one are a class of flavonoids
- Apigenin [9] is an aglycone of several naturally occurring glycosides found in many plants, is a natural product belonging to the flavone class
- Luteolin [10] is a yellow crystalline compound a flavone type of flavonoid
- Chrysin [11] is also called 5,7-dihydroxyflavone
- Catechin [12] is a plant secondary metabolite a flavan-3-ol, a type of natural phenol and antioxidant. It belongs to the group of flavan-3-ols part of the chemical family of flavon
- Epicatechin [13] is an antioxidant flavonoid, occurring especially in woody plants as both (+)-catechin and (-)-epicatechin (cis) forms
- Epigallocatechin [14] is the most abundant catechin found in tea, it is a polyphenol
- Epigallocatechin gallate [15] is also known as epigallocatechin-3-gallate, is the ester of epigallocatechin and gallic acid, and is a type of catechin
- The flavanones [16] are type of flavonoids, are colorless compounds, aromatic, ketones derived from flavone that often occur in plants as glycosides
- Hesperetin [17] is a 4'-methoxy derivative of eriodictyol, a flavanone. Hesperetin's 7-O-glycoside, hesperidin, is a naturally occurring flavanon-glycoside, a main flavonoid found in lemons and sweet oranges
- Narigenin [18] is a flavanone present in grapefruit
- Anthocyanidins [19] are common plant pigments
- Genistein [20] is an isoflavone that is described as an angiogenesis inhibitor and a phytoestrogen
- Daidzein [21] is a naturally occurring compound found exclusively in soybeans and other legumes and structurally belongs to a class of compounds known as isoflavones

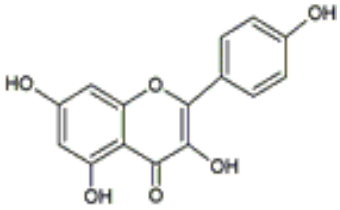
- Isoflavonoids [22] are a class of flavonoid phenolic compounds, many of which are biologically active. Isoflavonoids and their derivatives are sometimes referred to as phytoestrogens, as many isoflavonoid compounds have biological effects via the estrogen receptor
- Cyanidin [23] is a natural organic compound. It is a particular type of anthocyanidin (glycoside called anthocyanins)
- Delphinidin [24] is an anthocyanidin, a primary plant pigment, and also an antioxidant
- Coumarin [25] is an aromatic organic chemical compound in the benzopyrone chemical class, although it may also be seen as a subclass of lactones
- Chalcone [26] is an aromatic ketone and an enone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones or chalconoids
- Dihydrochalcone [27] is a chemical compound related to chalcone (FIG. 5)



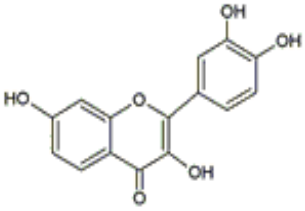
FLAVONOIDS [1]



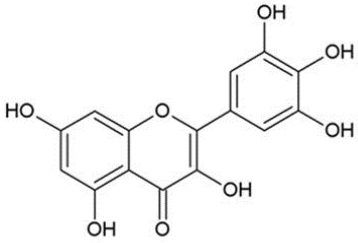
FLAVONOLS [2]



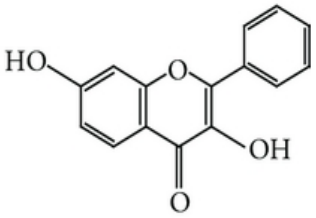
QUERCETIN [3]



KEMPFEROL [4]



MYRICETIN [5]



GALANGIN [6]

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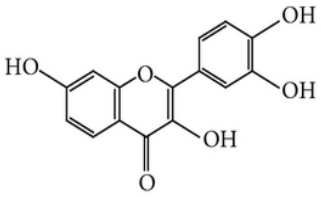
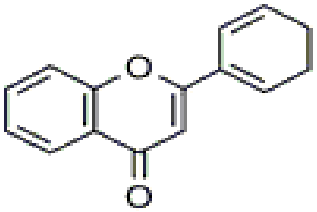
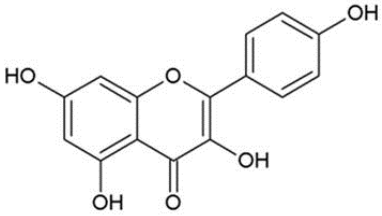


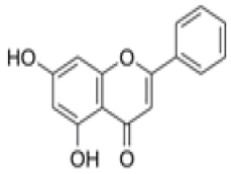
FISETIN [7]



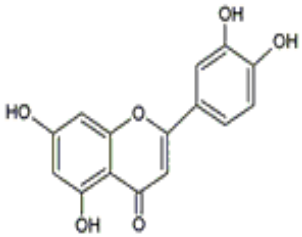
FLAVONES [8]



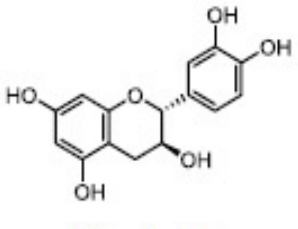
APIGENIN [9]



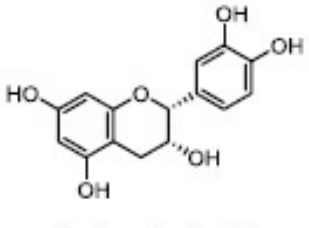
CHRYSIN [10]



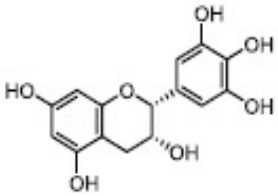
LEUTOLIN [11]



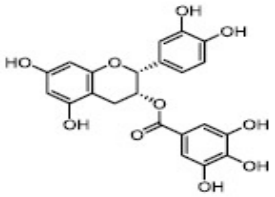
CATECHIN (FLAVONOLS)[12]



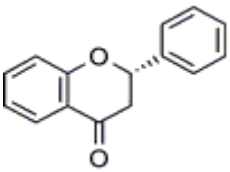
EPICATECHIN [13]



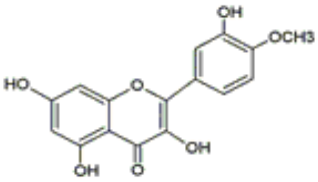
EPIGALLOCATECHIN [14]



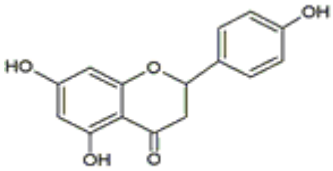
EPIGALLO CATECHIN GALLATE [15]



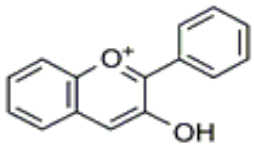
FLAVONONES [16]



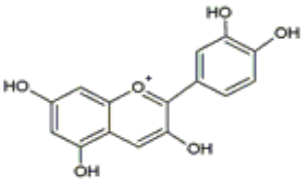
HESPERITIN [17]



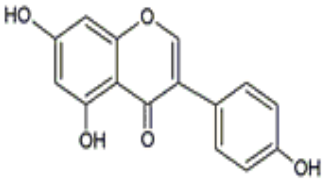
NARIGENIN [18]



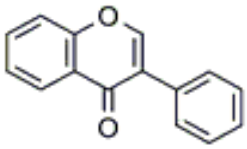
ANTHOCYANIDINS [19]



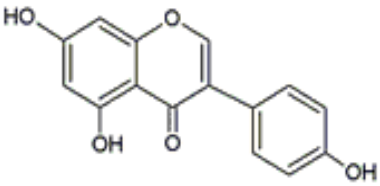
CYANIDINS [20]



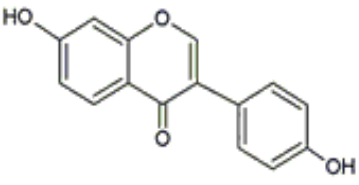
DELPHINIDIN [21]



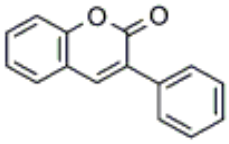
ISOFLAVONOIDS [22]



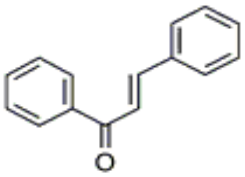
GENISITEIN [23]



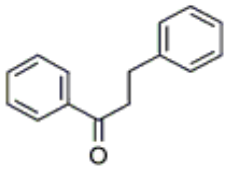
DIADZEIN [24]



COUMARIN [25]



CHALCONE [26]



DIHYDRO CHALCONE [27]

FIG. 5. **Chemistry of Flavonoids.**

Terpenoids

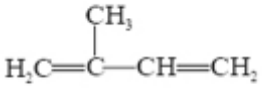
Plant terpenoids are used for their aromatic qualities and play a significant role in traditional herbal remedies. The terpenoids are called isoprenoids, are a large and diverse class of naturally occurring organic chemicals derived from terpenes. Most are multicyclic structures with oxygen-containing functional groups. About 60% of known natural products are terpenoids [6]. Although sometimes used interchangeably with "terpenes" terpenoids contain additional functional groups, usually O-containing [7]. Terpenes are hydrocarbons. Terpenoids at least those containing an alcohol functional group often arise by hydrolysis of carbocationic intermediates produced from geranyl pyrophosphate. Analogously hydrolysis of intermediates from farnesyl pyrophosphate gives sesquiterpenoids, and hydrolysis of intermediates from geranylgeranyl pyrophosphate gives diterpenoids etc.

Terpenoids are natural products whose structures are considered to be divided into several isoperene units therefore, these compounds are termed as isoprenoids. This particular group of compounds is referred as terpenes. The isoprene units come through the biogenetic means starting from acetate mevalonic acid. Each unit consists of five-carbon having two unsaturated bonds and possesses a branched chain. The terpenoids have a number of isoprene units joined together in a head to tail manner.

Terpenoids are classified on the basis of the number of isoprene units (C_5H_8) [28] incorporated into specific unsaturated hydrocarbon terpenoid molecules, such as (FIG. 6):

- Monoterpenes are a class of terpenes that consist of two isoprene units and have the molecular formula $C_{10}H_{16}$ [29]
- Sesquiterpenes are a class of terpenes that consist of three isoprene units and often have the molecular formula $C_{15}H_{24}$ [30]
- Diterpenoids are a class of terpenes that consist of four isoprene units and often have the molecular formula $C_{20}H_{32}$ [31]
- Triterpenes are a class of chemical compounds composed of three terpene units with the molecular formula $C_{30}H_{48}$ [32]

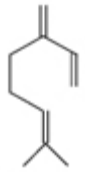
Isoprene rule: The basic concept that terpeniods are essentially built up of several isoprene units is commonly termed as the isoprene rule.

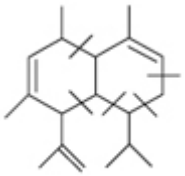


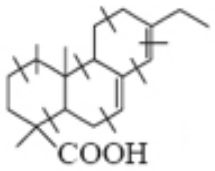
2-methyl-1, 3-butadiene [28]

TERPENOIDS

MONOTERPENOIDS [29] **SESQUTERPENOIDS [30]** **DITERPENOIDS [31]**







TRITERPENOIDS [32]

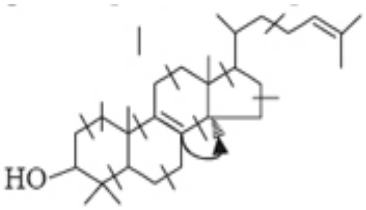


FIG.6. **Terpenoid.**

Medicinal Plants Used in the Treatment of Leishmaniasis (Table 1).

TABLE 1. **The table specifies the plant name, the vectors, different extracts, the isolated compounds and their activity**.

Plant name	Vectors	Extracts and isolated compounds	Activity	Reference
Albizia gummifera Seed	*L. donovani*	n-butanol, aqueous, and chloroform methanolic extract	*in vitro*	[8]
Allium cepa	Leishmania major	Ethyl acetate methanol extract hexane fraction Ether fraction Diethyl ether	*in vitro*	[9]
Allium sativum (garlic) and *Allium cepa* (onion) bulbs	*Trypanosoma brucei* *brucei* and *Leishma*	Sulfur secondary metabolites in garlic and one (zwiebelane) in the onion extract	*In vitro*	[10]

	nia tarentolae			
Allium cepa and *Ixora brachiata*	*L. major*	Root Extract	*In vitro*	[11]
Asparagus racemosus Withania somnifera Tinospora cordifolia	*L. donovani*	Cisplatin induced	*in vivo*	[12]
Annona squamosa leaves Annona muricata seeds	*Leishmania chagasi*	Methanol-water (80:20) alkaloids and Acetogenins annonacinone and corossolone	*in vitro*	[13]
Artemisia annua L. leaf powder	*Leishmania (Viannia) panamensis*	Capsules	*In vitro* and *in vivo*	[14]
Artemisia campestris and *Artemisia herba-alba*	*Leishmania infantum*	Essential oil	*In vitro*	[15]
Artemisinin	*Leishmania donovani*	Artemisinin	*In vitro*	[16]
Asiaticoside	Leishmania donovani	Asiaticoside 50% reduction in liver and spleen	*In vitro & In vivo*	[17]
Azadirachta indica	*Leishmania amazonensis*	Fractionation of ethanolic extracts of leaves and seeds and	*in vitro* activity	[18]
Azadirachta indica leaves (ALE) and seeds (ASE).	*L. donovani*	Hexane, ethanol and water	*in vivo*	[19]
Caesalpinia pulcherrima	*Leishmania major*	Chloroform extract furanocassane diterpenoids,	*in vitro*	[20]
Cassia fistula	Cutaneous Leishmaniasis	Hydroalcoholic extracts	*In vitro*	[21]
Cassia fistula	*L. chagasi*	Hexane extract from the fruits sterol, clerosterol	*In vitro*	[22]
Citrullus colocynthis fruits and leaf	cutaneous Leishmaniasis	Methanol	*In vitro*	[23]
Coccinia grandis leaf	*Leishmania donovani*		*In vitro*	[24]
Coccinia grandis	*Leishmania donovani*	Ethanolic extract	*In vitro*	[25]

Coriandrum sativum, Lippia sidoides and *Copaifera reticulata*	*Leishmania chagasi*	Essential oils oleoresin	*In vitro*	[26]
Copernicia prunifera Arecaceae	*Leishmania infantum*	Triterpenoids	*In vitro*	[27]
Cupressus sempervirens L. Cupressaceae	*Leishmania donovani*	Ethanol extract of the powdered cones fruits	*In vitro*	[28]
Curcuma longa	*Leishmania amazonensis*	Turmerones	*In vitro*	[29]
	Leishmania major, Leishmania tropica and *Leishmania infantum*	Curcumin	*In vitro*	[30]
Eclipta prostate and Gymnema sylvestre	*Leishmania major, Leishmania tropica Leishmania aethiopica*	Saponins, sapogenin, dasyscyphin C, Gymnemagenol	*In vitro*	[31]
Emblica officinalis and Azadirachta Indica	*Leishmania donovani*		*In vivo*	[32]
Euphorbia petiolata extract	*Leishmania major*	Ethanolic percolated and methanolic	*in vivo*	[33]
Juglans Regia, lawsonia inermis and *salvia officinalis*.	*Leishmania major*	Hydroalcoholic extracts	*In vivo*	[34]
Lawsonia inermis L. Leaves	Leishmania tropica	lalioside, luteolin-40-O-b-Dglucopyranoside, apigenin-40-O-b-D-glucopyranoside, luteolin, and apigenin.	*In vitro*	[35]
Lawsonia inermis and *Peganum harmala*	*Leishmania tropica*	Aqueous extracts	on *in vitro*	[36]
peganum harmala seeds	*L major*	Hydroalcoholic extract peganine,	*In vitro* and *in vivo*	[37]
Peganum harmala	*Leishmania major*		*In vitro*	[38]
Mangifera indica leaf extracts	*Leishmania donovani*	Petroleum ether, chloroform and methanol extracts	*In vitro*	[39]

Mangifera indica	*L. amazonensis*	Hydrodistillation terpinolene	*In vitro*	[40]
Melia azedarach Linn fruit	*L. tropica*	Aqueous extract	*In vitro*	[41]
Melia azedarach Linn	*Leishmania tropica*	Methonolic extract	*In vitro*	[42]
Moringa oleifera Lam	*Leishmania donavani*	ethanolic extract of roots and the methanolic extract of leaves and ethyl acetate fraction niazinin, a thiocarbamate glycoside	*In vitro*	[43]
Moringa oleifera leaf extract	*Leishmania major*	Silver nanoparticles Methanolic extract	*In vitro* & *In vivo*	[44]
Moringa oleifera flower	*L. donovani*	Ethyl Acetate	*In vitro* and *in vivo*	[45]
Momordica charantia	*Leishmania donovani*	Momordicatin	*In vitro*	[46]
Nerium oleander L.	*Leishmania major*	Methanolic extract	*In vitro*	[47]
Neem leaf extracts	*L. donovani*	Neem leaf extracts	*In vitro*	[48]
Phyllanthus amarus and *Phyllanthus muellerianus*	*L. major*	Methanolic extracts leaves	*In vitro*	[49]
Phyllanthus amarus	*L. donovani*	Niranthin, a lignin	*In vitro*	[50]
Phyllanthus niruri	*Leishmania donovani*	ethanol extract	*In vitro* and *In vivo*	[51]
Piper betle	*Leishmania donovani*	ethanol extract	*In vitro*	[52]
Piper betle	*Leishmania donovani*	Eugenol	*In vitro*	[53]
Plumbago zeylanica	*Leishmania donovani*		*In vitro*	[54]
Plumeria pudica leaves	*Leishmania donovani*	Petroleum ether, chloroform and methanol extracts	*in vitro*	[55]
Psidium guajava Psidium brownianum	*Leishmania brasiliensis and L. infantum*	Quercetin, myricetin and gallic acid derivatives	*In vitro*	[56]
Psidium guajava L. and *P. brownianum*	*L. infantum Leishmania braziliensis*	Aqueous and hydroethanolic extracts	*In vitro*	[57]

Punica granatum	*L. major*		*in vitro*	[58]
Raphanus sativus		Ethanolic extract	*in vitro*	[59]
Ricinus communis and *Azadirachta indica*	*L. major*	Methanol extract	*in vivo* and *in vitro*	[60]
Solanum lycocarpum	*Leishmania Mexicana*	Solamargine and solasonine,	*in vivo*	[61]
Solanum nigrum	*Leishmania majo*r	Methanolic and aqueous plant extracts	*in vitro*	[62]
Solanum havanense; Solanum myriacanthum; Solanum nudum; Solanum seaforthianum	*L. amazonensis*		*In vitro*	[63]
Sterculia villosa	*Leishmania donovani*	Methanol bark Extract	*In vivo*	[64]
Strychnos pseudoquina	*L. amazonensis*	Ethyl acetate extract flavonoids	*In vitro*	[65]
Syzygium cumini (L.)	*Leishmania amazonensis*	α-pinene	*In vitro*	[66]
Terminalia arjuna	*Leishmania donovani*	Pentacyclic Triterpenoid	*In vivo*	[67]
Tephrosia purpurea	*Leishmania donovani*	*N*-butanol extract	*In vitro*	[68]
Tridax procumbens	*Leishmania Mexicana*	(3S)-16,17-didehydrofalcarinol (1)	*In vivo*	[69]
Withania somnifera and *Asparagus racemosus*	*Leishmania donovani*		*In vivo*	[70]

The different dosage forms and formulations available in the form of nanoparticles, liposomes, neosomes etc. are reported in this study (Table 2).

TABLE 2. **Formulations containing nanoparticles.**

Plant Name	**Vectors**	**Nano Formulation**	**Activity**	**References**
Andrographis paniculata, leaves	*L. donovani*	Andrographolide diterpenoid lactone	*In vitro*	[71]
Liposomal Andrographolide	*L. donovani*	Labdane Diterpenoid andrographolide,	*In vivo*	[72]

Andrographolide Nanoparticle	*L. donovani*	Andrographolide	*In vitro* and *In vivo*	[73]
Terpenoid andrographolide	*L. donovani*	Gold Nanoparticle	*In vitro*	[74]
Nanotized curcumin	*L. donovani*	Curcumin	*In vitro* and *In vivo*	[75]
Swertia chirata amarogentin, a secoiridoid glycoside	*L. donovani*	liposomes and niosomes	*In vivo*	[76]
Quercetin penta-acetylated derivative	*Leishmania amazonensis*	lipid-core nanocapsules	*In vivo*	[77]
Curcumin-loaded mannosylated chitosan nanoparticles	*Leishmania*	mannosylated chitosan nanoparticles	*In vitro*	[78]
Monodispersed gold nanoparticles in kaempferol	*Leishmania donovani*	Kaempferol	*In vitro*	[79]
Nanovaccine chitosan nanoparticles	*L. major*	superoxide dismutase	*In vivo*	[80]

In recent years many pharmacologically active compounds isolated from natural sources have shown promising activities. Many compounds isolated from plants such as chalcones, alkaloids, lignans, sesquiterpenes, triterpenes, saponins, phenols, sterols, coumarins and tannins have shown activity against leishmaniasis (Table 3).

TABLE 3. **Plants containing flavonoids & terpenoids.**

Compound name	**Vectors**	**Isolated compound**	**Activity**	**References**
Apigenin	*Leishmania amazonensis*	Flavonoids, Apigenin	*In vitro* and *In vivo*	[81]
Coumarin Derivatives roots of *Vernonia brachycalyx*	*L.amazonensis Leishmania major*	nanoliposomal formulation coumarin-triazolothiadiazine hybrids triclosan-coumarin hybrids sesquiterpene coumarins	*in-vitro* and *in-vivo*	[82]
Flavonoids fisetin, luteolin	Leishmania (Leishmania) amazonensis	Quercetin, isoquercitrin, quercitrin, luteolin, orientin, isoorientin, fisetin, galangin, kaempferol, 7,8-dihydroxyflavone, apigenin inhibit arginase, a central		[83]

		enzyme		
Flavonols quercetin and quercitrin	*Leishmania amazonensis*	quercetin and quercitrin		[84]
Flavonolignans Silybin milk thistle *Silybum marianum*	*Leishmania infantum and L. donovani*	Flavonolignans Dehydroisosilybin A two diastereoisomers of dehydrosilybin	*In vitro*	[85]
Proanthocyanidins *Khaya senegalensis*	*Leishmania donovani*, *L. major*, *L. infantum*	two dimeric proanthocyanidins, catechin-(4a,6)-catechin (1) and catechin-(4a,8)-catechin)	*In vitro*	[86]
Sesquiterpene lactones from *Smallanthus sonchifolius*	Leishmania mexicana and Trypanosoma cruzi	Germacranolide		[87]
Sesquiterpene lactones *Gaillardia megapotamica Artemisia douglasiana Ambrosia tenuifolia* and *A. scabra*	*Leishmania Mexicana*	mexicanin I (Mxc), dehydroleucodine (DhL), psilostachyin (Psi),		[88]
Sesquiterpene		{pteridine reductase-1 (PTR1), *N*-myristoyl transferase (NMT), cysteine synthase (CS), trypanothione synthetase (TryS)}.		[89]
Tetracyclic iridoids *Morinda lucida*	*Leishmania hertigi*	Molucidin and ML-F52	*In vitro*	[90]
Triterpenoids *Schinus terebinthifolius*	*Leishmania (L.) infantum* and *Trypanosoma cruzi*	Tirucallane		[91]
Mahanine	*Leishmania donovani*	Mahanine	*In vitro* and *In vivo*	[92]

Conclusion

Visceral Leishmaniasis Kala-Azar a killer in the country is a dreadful disease affecting many millions in the world. According to the World health organization the current prespective is that the disease should be eradicated within 2020. WHO is taking preventive measures to eradicate the disease and the parasite vector in spraying of pesticides, protection and prevention against the insect vectors. Since the symptom of the disease are severe with skin lesions which do not disappear for long time in cutaneous leishmaniasis, visceral leishmaniasis where liver and spleen gets damaged and leads to death and mucocutaneous leishmaniasis leads to loss of oral cavity and nasal tract. These symptoms are severe and the diagnosis and treatment given to this disease is too costly. There are many synthetic drugs available with severe side effects. These side effects are toxic to cells and tissues. These drugs may be potent and efficacious but side effects are more. The cost of these drugs is comparatively high but the treatment given to poor patients must be economic and affordable price.

Hence there is a growing demand for herbal medicine and most of the growing population depends on herbal medicine for treatment. India is a hidden treasure of medicinal herbs, these traditional and complementary alternative medicine should be given prime importance in exploring new plants, extraction of phytoconstituents from them, scientist and researchers must come forward isolate phytoconstituents develop them into new lead compounds and formulations to treat various diseases. Even the cultivation of these medicinal plants must be given prime importance. The duration of treatment in alternative system of medicine through ayurveda, siddha, unani and homeopathy may be longer but with no or less side effects and low toxicity to cells and tissue, no damage to internal organs are the advantages of herbal medicine. The drug prepared may be a drug of choice for the poor patients with safety and efficacy and economic and reach patients in an affordable price to treat visceral leismaniasis.

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