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Chapter - 1

Phytochemical and Pharmaceutical Potential of *Tinospora cordifolia*: A Medicinal Plant Review

Babita Kumari, Mona Hamal Thakuri and Akib Ali

Abstract

Tinospora cordifolia (TC), commonly known as Amrita or Guduchi is classified as a very important drug of the Indian Systems of Medicine (ISM). This plant belongs to the family Menispermaceae, which is an evergreen perennial climber, a deciduous and dioecious shrub and TC is distributed throughout the tropical region of South-east Asia. The pharmaceutical significance of this plant mainly resides in its root, stem and leaves which possess antidiabetic, antioxidant, anti-hyperglycemic, anti-neoplastic, immunomodulatory properties as well as hepatoprotective properties; it also constitutes various important photo-active compound such as alkaloids, polysaccharides, steroid and glycosides. This herb is also helpful in the treatment for dyspepsia, diabetes, fever, urinary problems, jaundice, chronic diarrhea, cardiac disease, dysentery, helminthiasis, skin disease, leprosy and so on. TC also promotes longevity, acts as a stress buster and adaptogen which also helps in revitalization. Being such a pharmacologically important plant, this paper aims to explore and establish the current knowledge of the medicinal and pharmaceutical importance of TC. Currently, in-silico approach of the Phyto-compounds of TC using the drug: target interactions and its mechanism of action *in vivo* as an anxiolytic, anti-apoptotic and anti-neuroinflammatory agent have been discussed.

Keywords: *Tinospora cordifolia*, phytochemical and pharmaceutical properties

Introduction

Since time immemorial, a major part of the world has been using traditional health care remedies which are basically plant-derived formulations (Palombo and Semple 2001). According to the World Health Organization (WHO), around 80% of the people rely mainly on traditional therapies consisting of medicinal plants for their treatment of numerous

ailments (Pandey *et al*. 2008). *Tinospora cordifolia* (TC), an evergreen perennial climber, commonly known as Amrita or Guduchi is a deciduous and dioecious shrub (Bhandari and Chandrodaya, 2006) which serves as one of the important drugs of the Indian Systems of medicine (ISM) as reported by Misra and Bhavia, 1969. This plant belongs to the family Menispermaceae which consists of about 70 genus and 450 species, situated in tropical regions (Raghu *et al*., 2006). In Ayurveda, this plant is designated as Rasayana and it possess detoxifying, rejuvenating, and immune boosting properties thereby aiding in health promotion (Tirta 2007). *Tinospora cordifolia* is beneficial in the treatment of numerous diseases including cold, jaundice, fever, diabetes and skin diseases. It also promotes longevity, acts as a stress buster and adaptogen which also helps in revitalization.

Tinospora cordifolia is distributed throughout the tropical region of India as well as the sub-tropical region and is indigenous to some areas of Sri Lanka, China, Myanmar, Thailand, Philippines, Indonesia, Malaysia, Vietnam, Bangladesh and South Africa (Sinha *et al*., 2004 and Sharma *et al*.,2010). Its taxonomic classification is listed below.

Tinospora cordifolia (wild.) Hook. F. & Thomson (Latin) is known by different common names in different parts of India such as Aamoi or Amar Lota (Assamese), Guduchi, Madhuparni, Amrita, Chinnaruha, Vatsaadhani, Tantrika, Kundalini & chakralakshanika (Sanskrit) Giloy, Guduchi (Hindi), Gulancha (Bengali), Tippa teega, Somida (Telugu), Shindilakodi, Sindal (Tamil), Shindilakodi, Gulvel (Marathi) Galo (Gujarathi), Amrita balli, Madhupa (Kannada), Saptamrut (Malayalam) (Abhimanyu Sharma *et al*., 2010).

Taxonomic classification:

Kingdom: Plantae (Plants).

Subkingdom: Tracheophyta (Vascular Plants).

Super-division: Spermatophyta (Seed bearing plants).

Division: Magnoliophyta (Flowering).

Class: Magnoliopsida (Dicotyledons).

Subclass: Polypetalae (Petals are free).

Series: Thalamiflorae (Many stamens and flower hypogynous).

Order: Ranunculales.

Family: Menispermaceae-The Moon See family.

Tribe: Tinospora.

Genus: Tinospora.

Species: Cordifolia.

Various parts of *Tinospora cordifolia* are used in traditional medicine, but its pharmaceutical significance lies chiefly in the root, stem and leaf. Nonetheless, several studies exhibited that the stem contains higher alkaloid content than in leaves making the stem more suitable for approval in pharmacological use.

Table 1: Ethnobotanical uses of *Tinospora Cordifolia*

Sl. No.	Plant part	Ethnobotanical uses	Reference
1	Leaves	Used in the treatment of gout and ulcer.	Premila MS 2006.
2	Stem	Used as stomachic, stimulates bile secretions, as an antidote to snake bite and scorpion sting, stomachic, useful in skin diseases, diuretic, allays thirst, enriches the blood and cures jaundice.	Kirtikar and Basu 1918.
		Stem juice-useful in diabetes, dyspepsia, monkey malaria, vaginal and urethral discharges low fevers and enlarged spleen.	Kirtikar and Basu 1918; Usman, M.R.M *et al*. 2020.
		Stem infusion-used to drunk as a vermifuge, jaundice, against intestinal worms.	Khory, R.N. and Katrak, N.N., 1903; Usman, M.R.M *et al*. 2020.
		Stem decoction-used for washing sore eyes and syphilitic sores, antipyretic, antimalarial.	Khory, R.N. and Katrak, N.N., 1903.
		Starch statue-obtained from stem used for chronic diarrhoea and some form of obstinate chronic dysentery, deal with intestinal problems and improve digestion.	Khory, R.N. and Katrak, N.N., 1903.
3	Stem + Root	Powder of root and stem-To treat cancer Combining with other drugs-as an antidote to snake bite and scorpion sting.	Kirtikar and Basu 1933; Nadkarni KM and Nadkarni AK 1976; Zhaotf *et al*. 1991.
4	Fruit	Dried fruit with ghee or honey used as tonic and treatment of jaundice and rheumatism.	Zhaotf *et al*. 1991; M.R.M *et al*. 2020.
5	Root	As an antidote to snake bite and scorpion sting.	Zhaotf *et al*. 1991.
6	Bark	Anti-allergic, anti-spasmodic, anti-pyretic and anti-leprotic.	Sunanda, S.N., *et al*. 1986; Ikram M *et al*. 1987; Asthana *et al*. 2001.

Tinospora cordifolia is known as a large extensively spreading glabrous, dioecious perennial deciduous climber which grows on wide range of hedges and trees. It is also reported to bear distinct male and female flowers. Its stem, when fresh, have a green succulent bark covered by a thin brown bark and are studded with warty lenticels when dry, the stem shrinks and the bark separate from the wood. Branches are sending down slender pendulous fleshy roots, terete, striate, with tubercled, pale sometimes shining or glabrous bark reported by Kirtikar and Basu 1918. According to the wealth of India 1956, the nutritive composition of T*c* contains high fibre of 15.9%, sufficient protein of 4.5%-11.2%, sufficient carbohydrate of 61.66%, and low fats of 3.1% with the nutritive value of 292.54 calories per 100g. It also has high amount of potassium (0.845%), high chromium (0.006%), sufficient iron (.0.28%) and sufficient calcium of (0.1315%) which plays important role in various regulatory functions by (Nile SH and Khobragade CNN 2009).

Table 2: Active constituents/secondary metabolites of *Tinospora cordifolia*

Class	Chemical constituents	Activity	Plant part	References
Alkaloids	Berberine, Magnoflorine, Choline D, Palmatin, Tembetarine, Tinosporine, Isocolumbin Aporphine alkaloids, Jatrorrhizine, Tetrahydropalmatine, 18-norclerodane glycoside	Anti-viral infections, Neurological disorders, Immunomodulatory, anti-diabetes, anti-cancer	Stem & Root	Khuda M *et al*. 1964; Pachaly P and S chneider C 1981; Bisset NG, N waiwu J 1983; Sarma DNK *et al*. 1998; Kumar S *et al*. 2000; Padhya MA 1986 and Khan MA *et al*. 1989
Steroids	20 δ-Hydroxyecdysone, δ-sitosterol, β–sitosterol, Giloinsterol, Ecdysterone, Makisterone A, columbine, makisterone, jateorine, ecdysterone, g-sitosterol b-hydroxyecdysone,	Inhibits TNF- α, IL-1 β, IL-6 and COX2. Used for inflammatory arthritis, IgA neuropathy	Shoot (Aerial parts)	Pathak A *et al*. 1995; Zhaotf *et al*. 1991; Sunanda, S.N., *et al*. 1986
Glycosides	Tinocordiside, Tinocordifolioside, Cordioside, 18-norclerodane glucoside, Cordifolioside syringin, Syringin apiosyl glucoside, Furanoid diterpene glycoside, Glucoside, Palmatosides, Cordifolioside A, B, C, D and E, Pregnane glycoside, Syringin, palmatoside C31, palmatoside F31,	Anticancer activities, treats neurological disorders like-ALS, Parkinsons, Dementia	Stem	Bhatt RK and Sabata BK1989; Swaminathan K *et al*. 1989; - Khuda M *et al*. 1964; Padhya MA 1986; Sarma DNK *et al*. 1998; Khan MA *et al*. 1989 and Bhatt RK, Sabata BK 1989
Diterpenoid lactones	Furanolactone, Tinosporon, Tinosporides, columbine, Clerodane derivatives, Jateorine	Anti-inflammatory, anti-microbial, anti-viral. Anti-hypertensive, Vasorelaxant. Induce apoptosis in leukemia by activating caspase-3 and BAX, inhibits bcl-2	Whole plant	Ahmad M *et al*. 1978; Hanuman JB *et al*. 1677-1680; Qudrat-I-Khuda M 1966
Sesquiterpenoid	Tinocordifolin	Antiseptic	Stem	Maurya R and Hardass 1998
Aliphatic	Heptacosanol, Octacosanol, Nonacosan-15-one	anti-inflammatory,	Whole plant	Dixit SN and Khosa RL 1971;

compounds	dichloromethane.	Protection against 6-hydroxydopamine induced parkinsonisms in rats		Khaleque A, Miah MAW 1970 and 1971
Miscellaneous compound:	3,(α,4-dihydroxyl-3-methoxybenzyl)-4-(4-compounds hydroxyl-3-methoxy-benzyl) tetrahydrofuran, Giloin, Tinosporic acid, Tinosporidine, Cordifol, Cordileone, Jatrorrhizine, N Trans-feruloyltyramine as diacetate., 6 cordifol, 6 Cordileone, 6 Jatrorrhizine.	Protease inhibitors for HIV and drug resistant HIV.	Whole plant & Root	Khuda M *et al*. 1964; Padhya MA 1986; Sarma DNK *et al*. 1998; Khan MA *et al*. 1989 and Bhatt RK, Sabata BK 1989

Pharmacological properties

Antioxidant

In a study by Praveen *et al.* (2012), the varying degree in the phenolic content and anti-oxidant capacity of several leaf extract of Guduchi was assayed through non-enzymatic *in vitro* models. The phenolic content as well as anti-oxidant ability as determined by DPPH method, reducing power, metal chelating activity and phosphomolybdenum was observed to reduce in the following order: methanolic> ethyl acetate> butanol> water extract. Kumar *et al*., (2018) assessed the hydro-ethanolic extract of TC for its anti-oxidant (DPPH, FRAP, metal chelating, superoxide radical and Nitric Oxide assays), anti-microbial (anti-bacterial, anti-fungal), chemical (Total phenolic content=2.38±0.15 mg/g; total flavonoids content+18.91±0.21 mg), anti-inflammatory and protein-binding characteristics ($1.03\pm0.92\times10^{-5}$ $\mu M^{-1,}$ close to Aspirin). Major phytochemicals detected in the hydro-ethanolic extract include tinocordioside, cordifolide A, etc. (palmatine, quercetin, β-sitosterol, heptacosanol and syringing). Major phytochemicals detected in the hydro-ethanolic extract include tinocordioside, cordifolide A, etc. (palmatine, quercetin, β-sitosterol, heptacosanol and syringing). This extract exhibited low anti-bacterial and anti-fungal capacity, but notable antioxidant activities (60-80%) were observed. Significant linear correlation was noted between the TFC/TPC and antioxidant activities providing empirical evidence of its medicinal importance. Moreover, another study assessed the methanolic extract of the powdered stem and leaves of TC for its total flavonoid and phenolic content in correlation to its anti-oxidative capacity employing DPPH and ABTS assay taking ascorbic acid as standard. Free radical scavenging capacity, however, was found to be higher in ABTS assay as opposed to DPPH assay; the methanolic stem extract presented a more substantial value in its phenolic and flavonoid content as well as free radical scavenging activity when compared to the leave extract (Upadhyay, G *et al*., 2020).

Anti-cancer

In a review, the anti-carcinogenic activities of Guduchi are demonstrated in a range of experimental models. Diverse sets of studies showed the methylene chloride/ hydroalcoholic /hexane extracts of TC increased rate of apoptosis and levels of anti-oxidant enzymes (GSH) as well as inhibited the proliferative property of *in vivo* and *in vitro* cancer cells. (Jagetia *et al*., 1998; Wani *et al*., 2011; Thippeswamy G, Salimath BP 2007). It also has radio-protective property against gamma radiation induced cancers and when

used in combination with drugs like cyclophosphamide, it exhibits an increase in the inhibition rate of tumors and also increase the survival time (Hamsa TP, Kuttan G 2012). Moreover, its secondary metabolites like magnoflorine, palmatine, jatrorrhizine, yangambin etc are effective in the treatment against different types of cancers. Reports suggest that TC is a better alternative to synthetic chemotherapy drugs since it is natural and have an overall minimal side effect comparatively. Most of the synthetic chemotherapeutic agents suffer from toxic side effects. The effect of Guduchi extracts was comparable or better than doxorubicin treatment (G.C Jagetia, V Nayak 1996).

Anti-microbial activity

A study reported that silver nanoparticles synthesized from the stem of *T. cordifolia* possess good antibacterial activity against the bacteria Pseudomonas aeruginosa found in the patient suffering from burn injury (V. Shanthi, R. Nelson 2013 and K. Singh *et al*., 2014). The methanol extracts of *Tinospora cordifolia* have been reported to have potential against microbial infections (R. Jeyachandran *et al*., 2003). Guduchi has also found its importance by decreasing the resistance to different antibiotic therapy by the urinary pathogens and thus check the microbial infectivity. (V. Shanthi, R. Nelson 2013) The anti-bacterial activity of *Tinospora cordifolia* extracts has been assayed against *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Proteus vulgaris, Salmonella typhi, Shigella flexneri, Salmonella paratyphi, Salmonella typhimurium, Pseudomonas aeruginosa, Enterobacter aerogene* and *Serratia marcescens* (Gram-positive bacteria). (Narayanan *et al*., 2011).

A potential anti- SARS-CoV-2 drug

Papia Chowdhury (2020) amidst the Covid-19 pandemic that has created much chaos, scientists are also investigating the efficacy of traditional medicinal herbs against SARS-CoV-2. TC have been used in traditional remedy an in-silico approach using network pharmacology and molecular docking have been employed to explore the drug: target interactions between the available structural components of COVID-19: M^{pro} or $3CL^{pro}$ and main chemical constituents of *Tinospora cordifolia* (e.g. berberine ($C_{20}H_{18}NO_4$), β-sitosterol ($C_{29}H_{50}O$), coline ($C_5H_{14}NO$), tetrahydropalmatine ($C_{21}H_{25}NO_4$) and octacosanol ($C_{28}H_{58}O$). M^{pro}/3 CL^{pro} is a protease that is critically involved in the life cycle of the COVID-19 virus that can probably serve as a drug target. Amongst the major bioactive compounds of TC, it was observed that berberine could inhibit the enzymatic activity of $3CL^{pro}$ and can be fashioned as an anti-SARS-CoV-2 drug.

Thakkar *et al*. 2021 employed molecular docking studies to investigate the efficiency of active secondary metabolites from TC as potential inhibitor(s) against the main protease of SARS-CoV-2 alongside standard drugs (Azithromycin, Chloroquine, Hydroxychloroquine, Favipiravir, Remdesivir) as reference. Based on molecular docking score, they reported Favipiravir and Remdesivir to be highly effective against COVID-19; and amongst other secondary phytomolecules from TC, Columbine, Tinosporide, N-trans-feruloyl-tyramine-diacetate, Amritoside C, Amritoside B, Amritoside A, Tinocordifolin, Palmatoside G, Palmatoside F and Maslinic acids could serve as potential anti-SARS-Cov-2 drug (docking score range from -5.02 to -5.72).

In vivo and *in silico* approach to study potential candidate drugs

The screening of phytochemical compounds by *in vitro* and *in vivo* based testing have revealed many potential candidate drugs again various diseases. Birla *et al*., (2019) studied the ameliorating effects of aqueous extract of TC (TCAE) in 1-methyl-4-phenyl-1, 2, 3, 6-tetra hydropyridine (MPTP)-induced Parkinson's mouse model. This neurodegenerative mouse model exhibited significant behavioral and biochemical abnormalities, up-regulated expression in pro-inflammatory markers, NF-κB, TNF-α, IL-1β, IL-12, ionized calcium binding adaptor molecule 1 and glial fibrillary acidic protein which got significantly reduced by TCAE. They also reported an upregulation in anti-inflammatory marker, IL-10 and Tyrosine hydroxylase with TCAE treatment which suggests that TCAE is beneficial in the maintenance of dopaminergic neuron and also protects against Parkinson's disease mediated neuroinflammation. Singh *et al*., (2020) worked on (female) rat subjects to investigate the therapeutic capacity of Tinospora cordifolia stem powder (TCP) in obesity-related liver and kidney diseases. Rats on high fat diet for 12 weeks reported an increase in body weight, oxidative stress and displayed renal and hepatic disorders in relation to control fed group. Obese rats administered with TCP; however reported better body weight management, improved expression in hepatic lipolysis/lipogenesis markers, reduced oxidative stress and reinstated liver and kidney functionality. In an in silico study by Khanal *et al*. (2019), they attempted to unravel the anti-diabetic mechanism of action from the bioactive phyto-compounds of TC based on their chemical structures using network pharmacology and molecular docking. They found that out of nine bioactive molecules identified for pharmacological efficacy; tembetarine scored highest for drug-likeness hit, shared maximum interaction with diabetic-related pathological proteins and majorly regulated neuroactive

ligand-receptor interaction. Harpal Singh *et al*., (2021) Obesity is correlated to a varied number of chronic diseases like cardiovascular disease, type 2 diabetes mellitus and cognitive disorders. In another study, Singh *et al*., worked on female rat subjects to explore the capacity of Tinospora cordifolia stem powder (TCP) as an anxiolytic, anti-apoptotic and anti-neuro-inflammatory agent. Rats on high fat diet for 12 weeks developed obesity, anxiety, displayed reduced locomotor co-ordination and elevated expression of inflammatory markers (IL-6 and TNF-α) when compared to chow-fed control group. Conversely, obese rats supplemented with TCP were observed to have enhanced synaptic plasticity, finely tuned apoptosis and energy homeostasis, reduced inflammation and better weight management.

Conclusion

The extract of this plant contains numerous phyto-chemical active compounds which possess immunomodulatory and physiological roles that are basically responsible for antibacterial, antidiabetics, anticancer activities etc., for the treatment of several dreadful diseases. This review demonstrate the role of this indigenous drug (TC) for its vast diversity and also reported as a novel candidate used in 'bioprospection' which are used for the treatment of various diseases such as cancer, liver disorder, diabetes, heart disease, ulcers etc., for which still satisfactory cure management is yet unavailable.

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Chapter - 2
Common Plants used in Unani Medicine for Stroke Management

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Chapter - 2

Common Plants used in Unani Medicine for Stroke Management

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Abstract

Unani system of medicine is centuries old time-tested system of medicine which is included in list of WHO under traditional system of medicine. It is originated from Greek and nowadays practiced in most of the parts of Asia. The basic principle and concepts of Unani Medicine are called as *Umoor Tabiyah* which include *Arkan*, *Mizaj*, *Akhlat*, *Aaza*, *Arwah*, *Quwa* and *Afaal*. Apart of these, there is a concept of *Tabiyat* which is considered as supreme planner and ultimate healer of the body and it is believed that role of medicine and physician is to facilitate the action of *Tabiyat.* The Unani system's pharmacopoeia is huge, comprising of more than 2,000 medicines derived from abundant herbal, mineral, and animal sources; majority of these are from herbal origin. Unani medicine has special effect in treating and managing the non-communicable diseases, including diseases of nervous system such as Stroke. Present chapter aims to review some of the important and commonly used drugs of herbal origin used in Unani medicine for the management of Stroke and related disabilities.

Keywords: Unani medicine, stroke, non-communicable diseases, herbal medicine, traditional medicine

Introduction

Stroke is defined as a syndrome of an acute attack of a neurologic scarcity in blood flow that remains on for at least 24 hours; contemplate of focal involvement of the central nervous system and is the consequence of disablement of the cerebral circulation [1]. It is the commonest medical presentation of diseases of the cerebral blood vessels [2].

According to WHO stroke is defined as "swiftly developing clinical signs of focal (sometimes gross) interruption of cerebral function, enduring for more than 24 hours or leading to death with no visual etiology other than that of vascular origin" [3].

Stroke is a common medical casualty with an annual incidence of around 180 to 300 per One lakh. On an average 20 million people diseased with stroke annually and of these 5 million did not survive. Stroke accounts for about 10% of all deaths in most developed countries [2].

Stroke is also a major cause of functional impairments, around 20% of survivals require hospital management even after 3 months of stroke and 15%-30% may lead to permanently disability [4]. All cases of cerebrovascular diseases are exhibit by the abrupt onset of a focal neurologic deficit [5]. The fate of patient and severity of illness often depend upon location and extent of brain injury, the amount of collateral blood flow and early acute care management [6].

Concept of stroke in Unani medicine

In Unani system of Medicine Stroke is mentioned under the name of *Falij* or *Istarkha*. Ancient Unani scholars, from father of medicine, *Buqrat*, to later physicians have narrated *Falij* in detail. *Tabri*, an ancient Unani scholar, described that the obstacle in any portion of the brain may be a cause of *Falij* [7]. According to classical Unani concept, changes in the functions of *Rooh* (pneuma) and *Quwwat* (power) play important role in the pathological process of *Falij* and *Istarkha*. If *Mizaj* (temperament) of any *Azu* (organ) becomes abnormal, this abnormal *Mizaj* combat with the *Quwwat* of *Azu* and, *Quwwat* either reduces or changes its function [8]. The cause behind reduction of motor and sensory functions in patient of stroke (*Falij* or *Istarkha*) is due to interruption of *Roohe Hassas* to penetrate and reach organs thus making the organ weak or paralyzed [9].

The Unani treatment of *Falij/Istarkha* consists of *Tanqia* and *Ta'deel* followed by *Taqwiate As'ab wa Az'a. Tanqia* may be understood as evacuation of *Mawade Raddiyah* (morbid matter) this is achieved with the help of *Munzij Balgham* and *Mushile Balgham* drugs while *Tadeel* which means normalization of *Sue Mizaj* (Abnormal temperament) which may be achieved by internal and external use of Hot temperament drugs [7, 9, 10].

Most of above said medicines are of herbal origin. In fact, unani scholars had mentioned a lot of useful herbal drugs to cure neurological disorders in general and in stroke in particular. All medicines of *Munzij Balgham* and *Mushile Balgham* category are of herbal origin. When some of these drugs are studied on modern scientific parameters using modern tools and techniques either on animal and human models are found to be effective. This chapter will encompass some of the most commonly used herbal medicines described in Unani Medicine for treatment of Stroke.

***Coridothymus capitatus* (L.) Reich**

Synonyms

Arabic: Zahayfy, Za'tar Farisy. English: Wild thyme.

Plant parts

Leaves and flowers.

Active constituents

Carvacrol and thymol [11].

Ethno-botanical use

To treat Paralysis, take a steam bath of the leaves and use it daily for a month.

Scientific reports

Antimicrobial Activity [12].

***Ocimum basilicum* L.**

Synonyms

Arabic: Rayhan. English: Sweet basil, basilica.

Plant parts

Leaves and seeds.

Active constituents

Essential oil, tannin [13]; oil is the active ingredient which consists: thymol, linalol, cineol, eugenol, terpenes, sesquiterpenes and methylchavicol [14, 15, 16].

Ethno-botanical use

Used as a sedative and antispasmodic [17].

Scientific reports

Anti-fungal activity of essential oils *in vitro* [18].

***Origanum vulgare* L.**

Synonyms

Arabic: Mardagush. English: Oregano, wild majorana.

Plant parts

Leaves and whole herb.

Active constituents

Essential oil, tannin, thymol, carvacrol; and vitamin C [19].

Ethno-botanical use

Antispasmodic [13]. Treats pains of facial paralysis [14, 20].

Scientific reports

Antimicrobial Activity [21, 22].

***Anacyclus pyrethrum* L. Link**

Synonyms

Arabic: Oud el-'attas, aqarqarha. English: Spanish pellitory. Hindi: akarkarha [23].

Parts used

Roots.

Active constituents

Anacyclin [24].

Action

Aphrodisiac [23].

Ethno-botanical use

A gargle of its decoction is recommended for partial paralysis of the tongue and lips, relieves neuralgia and palsy [25].

Scientific reports

Emmenagogue, Diuretic [26], Anti-catarrhal, Antibiotic *in vitro* [27].

***Artemisia absinthium* L.**

Synonyms

Arabic: Shih Rumi, Afsantin, Shih, sheeh. Unani: Afsanteen. Hindi: Vilayathi afsanthin. Bengali: Mastaru. Marathi: Sarpana [28]. English: Wormwood.

Plant parts

Leaves, flowers.

Active constituents

Vitamin C [19]. Its active substances include silica, two bitter substances (absinthin and anabsinthine), thujone, tannic and resinous substances, malic

acid and succinic acid. Essential oil, resin, pinene, cadinen, tannin [13, 14]; Santonin, sterols and thujones [14, 29]; it also contains essential oils, sesquiterpene lactones and thymol; leaves and stems contain three nonglycosidic flavonoids [30].

Ethno-botanical uses

To treat nervousness: prepare a sweetened extract from the leaves in glass of water and drink it [11]; to treat paralysis [31].

Scientific reports

Antimalarial Activity, Analgesic and Antipyretic Activity [28].

***Calendula officinalis* L.**

Synonyms

Arabic: Uqhuwan. Unani: Zergul[32]. English: Marigold.

Plant parts

Leaves, flowers and fruit.

Active constituents

Calendulin, essential oil, acids mucilage and carotenoides[13]; Vitamin A and phosphorus [19].

Action

Anti-inflammatory, antiseptic, stimulant, antispasmodic, emmenagogue and anti-hemorrhagic [32].

Ethno-botanical uses

Flowers are used as an antispasmodic [14, 25].

Scientific reports

Wound Healing Property in rat [33], Hepatoprotective Activity in rats [34].

***Carthamus tinctorius* L.**

Synonyms

Arabic: Qurtum. Persian: Qafsha [23] English: Safflower.

Plant parts

Flowers and seeds.

Active constituents

Carthamin, fixed oil, yellow and red coloring matters [13]. Safflower seeds are the source of oil [19]; flowers contain palmitic acid, myristic acid and lauric acid; flavonoids and sterols; seeds contain aphenolic amide [30].

Action

Anti-flatulence [23].

Ethno-botanical use

Boil flowers in water for 15 minutes, filter, and drink five table spoons a day, to treat paralyzed organs [35].

Scientific reports

Analgesic [36], anticoagulant in rat [37].

***Chrysanthemum coronarium* L.**

Synonyms

Arabic: Bisbass. Persian: Gul daudi [23]. English: Chrysanthemum.

Plant parts

Leaves and flowers.

Active constituents

Sesquiterpene lactones.

Ethno-botanical use

Use the leaves in a steam bath to relieve muscle aches, nervousness and contractions of the uterus [11]; sedative and antispasmodic [17].

Scientific reports

Antioxidant Activity [38], Hepato-protective in rats [39, 40].

***Lactuca serriola* L.**

Synonyms

Arabic: Khass Barri. Unani: Kaahusahrai, kaahubarri [32]. English: Oil lettuce, Prickly lettuce.

Plant parts

Leaves, stems and stalks.

Active constituents

Alkaloids, flavonoids and saponin [41].

Action

Mild sedative, diuretic, diaphoretic, expectorant and antiseptic [32].

Ethno-botanical use

Calmative and antispasmodic [25].

Scientific reports

Bronchodilator [42] and vasorelaxant activities in rabbit [43].

***Matricaria recutita* L.**

Synonyms

Arabic: babounaj. Persian: Baboona [23]. English: Wild chamomile.

Plant parts

Flowers, the whole herb.

Active constituents

Essential oil, vitamin C, coumarin, apigenin; potassium; volatile oil; proazulene, flavoles and coumarines; apigenin glycosides.

Ethno-botanical use

Flowers are an antispasmodic and sedative [44].

Scientific reports

Anti-inflammatory in rat, Virucidal agent, Anxiolytic agent [45].

***Silybum marianum* L.**

Synonyms

Arabic: Khurfeish al-jamal, shouk al-jamal. English: Milk thistle, St. Mary's Thistle.

Plant parts

Shoots, the whole herb, seeds.

Active constituents

Tyramine, fixed oil, tannin, resin; seeds contain Silybin, silychristin, and silydianin.

Action

Liver protective, gall bladder protective and antioxidant [32].

Ethno-botanical use

Antispasmodic [44].

Scientific reports

Hypoglycaemic activity, anticancer effects [46].

***Ammi visnage* L.**

Synonyms

Arabic: Khella, Saq al-'Arus. English: Bishop's weed.

Part used

Seeds.

Active constituents

Khellin, visnagin, visnadin [14].

Action

Antispasmodic in renal colic, bronchial asthma and whooping cough [32].

Ethno-botanical use

To prepare a water infusion of the crushed seeds and drink one cup a day, as an antispasmodic and to prevent muscle spasms [44].

Scientific reports

Effects on psoriasis, vitiligo and tinea versicolor [47], prevention of urolithiasis in rats [48].

***Anethum graveolens* L.**

Synonyms

Arabic: Shebet. Unani: Soyaa. Siddha: Sadakuppai, Sanskrit: Sthatpushpi, Hindi: Sowa, Punjabi: Soya. English: Dill [49].

Plant parts

Seeds and flowers, fruit.

Active constituents

Essential oil, terpenes, carvone, fixed oil, tannin; sulfur, seeds contain Anethofuran, carvone and limonene [44].

Action

Anti-inflammatory, diuretic [23].

Ethno-botanical use

Fruit is used as an antispasmodic and sedative [25] and as tranquilizer.

Scientific reports

Antimicrobial effects [50], Anti-inflammatory and analgesic effects in rats [51].

***Apium graveolens* L.**

Synonyms

Arabic: Fitrasaliun. Persian: Karafs [23]. English: Celery.

Part used

Leaves, roots and seeds.

Active constituents

The seeds contain limonene and apiol; Essential oil, apiin, asparagin, limonene [44].

Action

Abortifacient, diuretic [23].

Ethno-botanical uses

Roots are used in the form of infusion for relaxing nervous tension and is antispasmodic [13].

Scientific reports

Anti-inflammatory, hypotensive, carminative, urinary antiseptic, sedative, antirheumatic [52], laxative, stimulant, aphrodisiac, emmenagogue, carminative, antispasmodic and anthelmintic [53].

Conium maculatum

Synonyms

Arabic: Shiqran, Shawkaran. English: Poison-hemlock, Hemlock.

Plant parts

Dried leaves, seeds and roots. Preparation: to prepare the medicine, dried leaves are submersed in water and drunk, a table spoon a day for two weeks.

Active constituents

Essential oil, conhydrine, coniine, conicein; alkaloids: Coniine, being the toxic constituent, found in all parts of the plant; Coniilne and conhydrine.

Ethno-botanical use

Cure nervous excitability, relief paralytic tremors. Ripe fruits are effective as a tranquilizer, analgesic, prophylactic muscle relaxant; neuroleptic, antidepressant, and anticonvulsant. The tincture is prescribed as a neuro muscular sedative and antispasmodic for a paralyzed respiratory organs [44].

Scientific reports

Analgesic and anti-inflammatory activities in rats [54].

***Coriandrum sativum* L.**

Synonyms

Arabic: kuzbarah, kusbara. Hindi: kothmeer. Persian: kishneez [32]. English: Coriander.

Plant parts

Seeds and leaves.

Active constituents

Essential oil, corinadrol and Vitamin C; essential oil from the fruit has high contenct of linalol, leaves are a source of vitamin A and C and coriander oil; fruit and leaves contain: fats, protein, volatile oil [44].

Action

Anti-flatulence [32].

Ethno-botanical use

The distilled essential oil from the fruits relieves muscle pains and acts as a tranquillizer, antispasmodic, sedative and treat nervous disorders [44].

Scientific reports

Antioxidant activity, hypnotic activity, anthelmintic activity and anti-mutagenic [55].

***Cuminum cyminum* L.**

Synonyms

Arabic: Kamun. English: Cumin. Plant parts: Seeds.

Active constituents

Cuminol, carvone, essential oil, cymol, cuminic aldehyde; seeds contain volatile oil.

Ethno-botanical use

Antispasmodic and sedative [44].

Scientific reports

Cumin seed extract is an anti-bacterial agent to kill gram positive &gram-negative bacteria such as Staphylococcus aureus and Escherichia coli *in-vitro* [56].

***Daucus carota* L.**

Synonyms

Arabic: Jazarbarri. English: Wild carrot.

Plant parts

Fruit, roots and seeds.

Active constituents

Vitamin A and B, pytosterine, carotin, asparagine, minerals [13]; Vitamins A, B6, B complex and C; Chloride compounds, magnesium, potassium, sodium and iron; it is a source of carbohydrates; roots contain glucose, sucrose, protein, salts, pectin, carotene, vitamins and asparagine; seeds contain: pinene, limonene, carotol, daucol, isobutyric acid and asarone.

Ethno-botanical use

Fruits are an antispasmodic and sedative [44].

Scientific reports

Gastroprotective and antacid capacity, Nephroprotective and hepatoprotective effects in rats [57].

Pimpinella anisum

Synonyms

Arabic: Yansun. Persian: Badian romi. Hindi: Zandani [23] English: Sweet cumin.

Plant parts

Seeds and flowers.

Active constituents

Essential oil, anethol, fixed oil, choline, mucilage [13]; anisic acid, fats, protein and sugar [30].

Action

Anti-flatulence [23].

Ethno-botanical uses

To treat convulsion, facial paralysis as steam of boiling seeds in water [44].

Scientific reports

Antibacterial activities in rats [58]. Anticonvulsant, Antidiabetic, Antiulcer in rats [59].

Ferula asafetida

Synonyms

Arabic: haltit, Simgh al-Unjadhan, Jiddeh [19]. English: Asafoetida. Urdu: Hitleet. Hindi: Hing, Hingda [60].

Plant parts

Resin: oleo-gum-resin. Active constituents: Sulfur. The oleo-gum-resin, asafetida, is obtained from the plant's rhizome; it consists volatile oil which contain sulphur compounds; the resinous portion include as a resinolferulate and free ferulic acid.

Ethno-botanical use

The oleo-gum-resin is used as an antispasmodic [44].

Scientific reports

Hepatoprotective Activity, Anti hemolytic Activity, Antiulcer Activity, Anti-Diabetic Activity in rats [60].

***Foeniculum vulgare* Mill**

Synonyms

Arabic: Shawmar [61], Razianaj [23]. Urdu name: Badyan and Beekhe Badyan [61]. English: Fennel.

Plant parts

Stems, leaves and seeds.

Active constituents

Essential oil, anethole, anisic acid, acids, fixed oil; Potassium and sulfur; anethole and enol; liquorice and senna; seeds contain volatile oil; phenolic anethole and a ketone fenchone [4]. Action: anti flatulence and analgesic [32].

Ethno-botanical use

The fruit is an antispasmodic and calmative [44].

Scientific reports

Anti-stress, antioxidant and memory-enhancing activities in rats [62].

***Glycyrrhiza glabra* L.**

Synonyms

Arabic: Asal al-sus. Persian: Beekh mahak. Hindi: Chethi [23]. English: Liquorices, licorice.

Plant parts

Leaves, rhizome.

Active constituents

Glycyrrhizin asparagine, liquirtin, coumarin, sugar, tannin and phosphorus; and steroid substances; glycyrrhizin and glycyrrhetic acid; flavonoids, starch, protein and bitter principles.

Ethno-botanical use

To relax uterine muscles, antispasmodic and tranquilizer, sedative, rhizome is used for treating muscle pain [44].

Scientific reports

Anti-bacterial Activity, Antioxidant Activity, Anti-malarial Activity, Anti hyper glycemic Activity [63].

***Vicia faba* L.**

Synonyms

Arabic: Foul. English: broad bean.

Plant parts

Broad bean/brown bean.

Active constituents

Vitamin B1, B complex; potassium, Phosphorus, iron and copper. Ethno-botanical uses: flowers are an antispasmodic [44].

Scientific reports

Antioxidants, antibacterial [64].

***Atropa belladonna* L.**

Synonyms

Arabic: S *et al*. Husn [13], Luffah. Persian: Shabizak [32]. English: Deadly nightshade, Belladona.

Plant parts

Leaves and roots.

Active constituents

Atrosin; atropine, hyoscyamine and hyoscine cocaein.

Action

Anti-inflammatory and diuretic [32].

Ethno-botanical use

Antispasmodic and sedative [44].

Scientific reports

Atropine as antidote in Organophosphate poisoning, Hyoscine can comfort the pain of bowel and stomach cramps by blocking the M1 receptors, hyoscine as cervical antispasmodic agent in labor [65].

***Datura stramonium* L.**

Synonyms

Arabic: Daturah, Jozulmasil [23]. English: Jimsonweed, thorn-apple. Persian: Tatula.

Plant parts

Leaves, seeds and roots.

Active constituents

Atropine, scopolamine and hyoscamine; daturine, hyoscyamine, atropine, scopolamine, hyocine.

Ethno-botanical use

Analgesic, sedative, antispasmodic, useful for asthma and neuralgic pain; acts as a tranquillizer. Tincture of leaves prescribed for spasmodic asthmatic cough; leaves used in fumigations to ease asthma attacks. Its physiological

activity is mainly on the central nervous system. Anti-convulsions effect of the smooth muscles, particularly in the lower part of the body. Leaves acts as an antispasmodic and sedative [44].

Scientific reports

Antibacterial Activity, Antifungal activity, Nematocidal Activity [66].

***Hyoscyamus albus* L.**

Synonyms

Arabic: Bazrul banj. Persian: Bang [23]. English: White henbane.

Part used

Leaves and seeds.

Active constituents

Alkaloids, hyoscyamine, hyoscypicrin, essential oil [13]; atropine and hyoscine [14].

Action

Mucolytic [23].

Ethno-botanical use

plant treats nervous irritation in hysteria; sedative for hysteria and nervousness [44].

Scientific reports

Antibacterial activity against some bacterial strains [67].

***Solanum nigrum* L.**

Synonyms

Arabic: ‘Enb al-Tha’lab. Persian: Rubahtareek [23]. English: Black nightshade. Hindi: Makoi. Telugu: Kachchipandu. Tamil: Munatakali. Marathi: Kamuni [68].

Part used

The whole herb, berries and seeds.

Active constituents

Saponin, solanine; Vitamin C and carotenes; solasodine [44].

Action

Anti-inflammatory [23].

Ethno-botanical use

Sedative, antispasmodic [13]. Leaves to relieve nervous pains: use the leaves as a decoction; the fruit have a narcotic and tranquilizing effect; extracts suppress the activity of the central nervous system and prevent muscle spasms [11].

Scientific reports

The plant is beneficial in preventing liver toxicity & cytotoxicity, improves functions of liver and Kidney. It is useful in abdominal problems, body pain and improves central nervous system and brain functioning [68].

Paeonia emodi

Synonyms

Arabic: Ood Saleeb, Fawania [23]. English: Himalayan peony [61].

Part used

Roots and shoots [23].

Active constituents

Anthraquinones, terpenoids, tannins, carbohydrates, phenolics and tannins, glycosides, paeoniflorin, lactiflorin, oxypaeoniflorin, cycloartenol, sitosterol, campesterol, emodinol, 3-hydroxybenzoic acid, benzoic acid, anthraquinones [69].

Ethno-botanical use

Antiepileptic actions, relief nightmare, diuretics and emmenagogue [23].

Scientific reports

Sedative effect, anti-inflammatory, useful in inflammation, asthma in senile, tumor angiogenesis and cancer [70, 71], spasmolytic activity [61, 72].

Borago officinalis

Synonyms

Arabic: Hajrulbaqr. Persian: singhegao. Hindi: gaoruhan. English: Burrage, bee bread, ox's tongue.

Part used

Leaves, stems [23].

Active constituents

Pyrrolizidine alkaloids, licosamin, intermedin, sopinin, sopindian, yezan, colin [73].

Ethnobotanical use

Aphrodisiac, use in jaundice [23].

Scientific reports

Leaves alkaloid produces a rightward shift in the Ca^{++} concentration-response curves like that caused by verapamil [61, 74].

Discussion & Conclusion

Unani medicine has its own very valid concept of understanding and treating diseases. Most of the diseases of nervous system are considered as *Amraze balghami* in Unani system and they had a number of herbal drugs to treat and cure diseases of nervous system. Some of them are discussed above. The concept behind usage of these herbs are found to be valid when studied on modern parameters as most of drugs are found to have alkaloids which are effective in diseases of nervous system in one or more ways. When these drugs are studied after following proper research protocol are also found effective in alleviating pain [61], spasticity [75], motor weakness [76], gait disability [77] and also found to be effective in improving quality of life of stroke survivors [78], as stated by a number of studies.

Further researches on these herbal medicines are need of hour as they provide better treatment with minimal adverse effects and are also available in rural parts.

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Chapter - 3
Herbal Medicine in the Treatment of Neglected Disease Mycetoma

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Chapter - 3

Herbal Medicine in the Treatment of Neglected Disease Mycetoma

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Abstract

In spite of advancement in mycetoma research and acknowledgement by the World Health Organisation (WHO), a huge awareness gap remains in pathogenesis and epidemiology resulting in the lack of effective control in mycetoma. The main reason behind the delay in the treatment of the disease is the poor knowledge on the etiology of the disease and is initially suspected as malignancy. The isolation of the causative agent requires prolonged bacterial cultures in aerobic and anaerobic conditions at 35°-37 °C for at least 10 days. Early detected localised disease is cured however, as the disease progresses to late stage it leads to by high morbidity. In most of the cases complete treatment of mycetoma is not possible because of the long duration of the treatment, expensive surgery; high dose multiple drugs with many side effects. This has led to people choosing herbal drug as an alternative medicine. The purpose of the review is to focus on the priority of low socioeconomic people in choosing traditional herbs as alternative treatment to mycetoma. The opinion from the studies showed hardly herbal treatment was effective whereas early presentation of the symptoms with medical intervention such as management with antifungal or antibacterial drug and surgical treatment could be promising, Drug distribution and sensitization of the disease can lower the prevalence of a disease and even, eliminate its transmission.

Keywords: Actinomycetoma, eumycetoma, etiology, diagnosis, medicinal plants

Introduction

Neglected tropical diseases are a diverse group of communicable diseases affecting subtropical and tropical countries caused by viruses, bacteria, protozoa and parasitic worms. The WHO incorporated mycetoma to the list of neglected diseases on 28th May 2016, in order to raise awareness

for a better check to fight against the disease. It appears there is a lacuna in proper data on incidence, prevalence, mapping, and mode of transmission and diagnosis of the disease [1]. The disease develops slowly and gradually worsens if left undiagnosed and untreated. It is a chronic mutilating disease that can cause lifelong disabilities and places a burden on the family and society. Mycetoma patients are often considered as a social stigma thus they tend to hide the disease and when they are obligated to seek medical care the condition is in the late stage [2].

A French missionary, Dr. John Gill in 1842, described the first clinical cases of mycetoma in Madurai, southern India, naming it "Madura foot". Mycetoma in Greek means mykes (fungal) and Oma (tumour) [3]. Mycetoma is also known by other names such as fungus disease of India, Godfrey and Eyre's disease, endemic degeneration of the bones of the feet, morbus pedis endophyticus-affection singulière and perforating ulcer of the foot [4]. Though no site is exempt the most common location of the disease is foot and leg [5], hand is the next most common site, trunk, knee joint, perineum, head, lung, neck and other areas other areas such as cervical [6] and breast may be involved [7], abdominal wall involving the bowel [8] and blood-spread eumycetoma though rare, it is reported in Senegal and Sudan [9]. The infected part becomes structurally impaired further leading to loss of body function. The disease affects people of all gender and age particularly its most severe in people who walk barefooted and work outdoors. Apart from these traditional beliefs, fear, drug intolerance, distress and cultural barriers, people are resorting to medicinal plants as alternative treatment without much benefit.

Geographical distributions

Actinomycetoma (bacteria) is more rampant in dry areas while eumycetoma (fungi) is more prevalent in regions of rainfall. 'Mycetoma belt' is a region between latitude 15°S and 30°N where most of the disease cases have been reported. The most endemic countries include India to Yemen, Saudi Arabia to Sudan, Senegal to South America and Mexico [5]. Latin American countries include Argentina, Colombia, Mexico, Venezuela, and Brazil, Comoro Islands. Mycetoma is reported in Laos, Singapore, Malaysia, Philippines, Indonesia, Cambodia, Thailand and Vietnam. In Africa, cases are seen in Sudan, Nigeria, Mauritania, Ethiopia, Chad, Kenya, Djibouti, Cameroon, Somalia, Tunisia, Niger. Senegal alone contributes to 74.1% cases. European countries include Germany, Albania, Bulgaria, Greece, Italy, and Turkey particularly these people were immigrants from Africa [10].

Causative organisms

More than 50-70 bacterial or fungal organisms are involved in causing mycetoma. Mycetoma is a tropical chronic subcutaneous inflammatory disease commonly caused by the fungus (eumycotic) or bacteria (actinomycotic). *Madurella mycetomatis*, *Madurella grisea* and *Scedosporium apiospermum* are the most common causative fungus. Common actinomycotic species include *Streptomyces somaliensis*, *Actinomadura madurae*, *Actinomadura pelletieri*, *Nocardia brasiliensis* and *Nocardia asteroids* [5]. Other causative agents include *Acremonium falciforme*, *A. kiliense*, *A. recipe*, *Cylindrocarpon nescens*, *C. destructans*, *Exophiala jeanselmei*, *Scytalidium dimidiatum*, *Aspergillus nidulans*, *Neotestudina rosatii*, *Leptosphaeria senegalensis*, *Pyrenochaeta romeroi* and *Phialophora verrucosa* [11].

With the advent of molecular biology techniques identification of the genera and species of the organism has been simplified. For example, a first case of white grain eumycetoma caused by the fungus *Microascus gracilis* was identified and successfully treated with surgery and drug itraconazole. Thus emphasizing the importance of molecular tools and renaming of various mycetoma causative agents. The identified organism is archived in the collections of the Westerdijk Fungal Biodiversity Institute, the UK National Mycology Reference Laboratory (NCPF; National Collection of Pathogenic Fungi; Bristol, UK) and the Institute Pasteur (UMIP; Collection de Champignons et Actinomycetes Pathogens; Paris, France) [12].

Mode of transmission

The incubation period of the disease varies; sometime it takes months to years for the symptoms to be blown up but still remain unspecified. Mycetoma is commonly seen particularly among the poorest and vulnerable communities and the initial cause of the disease is deficiency in nutrition, lack of sanitation and hygiene. The warm climate and unprotected clothing and foot ware are postulated to be easy route of transmission [13]. Apart from the diverse climatic condition, ecological niche too play an important role such as populations living in close vicinity to animals and their waste. The exact mode of transmission of the causative organisms is still a paradox [14]. The organism is soil inhabitant and is transmitted into the subcutaneous tissue when an individual with injury or trivial trauma comes in contact with the infectious agent. It is believed there is a close association between the shrub acacia and mycetoma. There are reports citing thorn pricks of the acacia plant severing as a route to the infection [15]. Survey reports show

outdoor workers are more affected. Women too are prone to infection because of hormonal imbalance and weak immune system during pregnancy [16]. A recent study has attributed to the possible cause of ticks in the transmission of eumycetoma, Though the exact role is uncertain the study reported the presence of *M. mycetomatis* DNA in ticks present on the animals in the shelter houses as the statistics provided by recombinant RNA genes [17].

Etiology of the disease

The hallmark characteristic of mycetoma is the presence of grain in the infected area which appear as a discharge in blood or pus. Bacterial grains are delicate and brittle, with a fine substructure and with colors varying from off-white to pinkish, whereas fungal grains are firm and are composed of microscopically visible hyphae that are either black or whitish in colour [18]. The grains are believed to protect these microorganisms against host defence mechanisms and antimicrobials [19]. In eumycetoma, the lesion grows slowly with clearly defined margins and remains encapsulated for a long period whereas, in actinomycetoma, the lesion is more inflammatory, destructive and invade the bone at an earlier period; as evident in *A. pelletier* actinomycetoma [20]. The infection normally spreads to the skin, deep tissues, and eventually the bone, resulting in severe deformities, distortions, and disabilities. Owing to the painless nature of the disease patients usually are unaware of injury, therefore late disease presentation of the disease makes the treatment difficult [21]. The disease is known to spread via the lymphatics and blood leading to distant secondary nodule associated with high morbidity and mortality. As the mycetoma granuloma increases in size, the skin over it becomes attached and stretched [22, 23]. In eumycetoma the melanin pigment is deposited in the cell walls, the skin may become smooth, shiny and areas of hypo or hyperpigmentation develop. The fungi produce superficial to subcutaneous to deep hyphae [24]. Melanin are known to contribute to virulence of the pathogen and play a pivotal role in the protection of the microorganism thus having more relapses compared to non-melanised fungi [25].

The infection spreads the nerves and tendons only during later stage due to this neurological and trophic change are not observed in patient with long-standing mycetomas [23]. Cystic form of mycetoma though are rare, a recent study by Bellalah *et al*. [26] reported cystic mass measuring 4.5×4.5×3cm in an old Tunisia patient with a thick capsule and heterogeneous synovial fluid cyst. The patient was however satisfactorily treated with streptomycin and co-trimoxazole.

Diagnosis

Diagnosis in suspected lesions are made with the aid of grain examination, various imaging techniques such as X-ray, ultrasound, MRI (magnetic resonance imaging), CT scans (Computed Tomography). These diagnostic techniques are essential to determine the disease spread along various body planes, their precise location, size or the extent of the lesions, including involvement of deeper bony or muscular structures [27]. Gram stain examinations of tissue biopsies, as well as molecular diagnostic techniques, are used to identify the causative fungal and bacterial species [28]. Grains can be obtained by fine needle aspiration for cytology (FNAC) and can be examined by cytological and histopathological using cell block technique [29].

Dot-in-circle sign is an image-based diagnosis, developed with ultrasound and MRI allow early diagnosis when clinical features such as sinuses and grains are undefined or histopathological diagnosis and aspiration cytology are negative [29]. Grading system is used in MRI to describe and grade disease as mild, moderate, and severe based on a score from 1 to 10 [30]. Stages 0 to VI range from simple soft-tissue swelling (Stage 0), to cortical erosion and central cavitation (Stage III), to multidirectional spread due to uncontrolled infection (Stage VI) [31]. Molecular sequencing is particularly important in cases of negative culture and is used in accurately in distinguishing between fungi and bacteria taxonomy and phylogeny [32]. Three isothermal amplification techniques for the determination of *M. mycetomatis* have been developed, namely, Recombinase Polymerase Amplification (RPA), Loop-mediated isothermal Amplification (LAMP) and Rolling Circle Amplification (RCA). As reported by Ahmed *et al*. [33], RPA and LAMP do not require thermo-cycler. Table 1 shows the merits and demerits of techniques used. Nyuykonge and co-workers [34] have demonstrated the use of short-tandem-repeat assay (*Mmy*STR) for genotyping of *M. mycetomatis* in particular. Phylogenetic markers must be sequenced for an accurate identification and taxonomical placement of the isolates. *Mmy*STR markers showed a large genotypic heterogeneity, high stability, reproducibility, and specificity. The authors further concluded *Mmy*STR assay to be used to establish a global reference database *mycetomatis* isolates.

Table 1: Merits and demerits of various diagnostic methods

Diagnostic methods	Merits	Demerits
Clinical	A commonly available preliminary technique used as referral to identify the disease	It cannot distinguish the etiologic of the causative agent.
Microscopy [45]	Microscopic examination is easy and cheap. The specimen is visualized by staining with Lactophenol Cotton blue, Periodic acid-Schiff (PAS), Grocott's methenamine silver (GMS) and hematoxylin and eosin (H&E) staining.	Not available in endemic area. Technical expert is needed.
Culture [10]	Best method for aetiology identification Organism are cultured on both Sabouraud dextrose agar with chloramphenicol and Lowenstein-Jensen agar.	Time consuming, delay by at least by 4-week contamination is the major drawback, technical expertise is needed Available in tertiary health care centers.
Histopathology/ FNAC [66]	Simple, easy, painless, cost-effective, quick diagnostic method helps in complete excision and prevents recurrences.	Bone lesions are difficult to aspirate. FNAC should be coupled with other radiology and biopsy.
Serology Test [67]	Detection of circulating antibodies. Less invasive procedure. Cheap and relatively fast. Useful for measuring therapeutic response.	Not reliable for all causative agent. Standardization and pure antigens is needed. Cross reactivity in some cases.
Radiography [31]	Reveals bone irritation, invasion and spread involving metatarsal bone and intrusion into tendons, blood vessel and nerve.	Sensitivity is 50%. Early soft-tissue reaction and tiny cortical erosion can be missed.
Molecular-PCR [68]	Generating accurate therapeutic data of mycetoma agents to species level.	The approach is time consuming and expensive, not readily available in endemic areas.
Molecular-LAMP [67]	Reliable identification of causative agents can be used in resource-limited settings cheaper and easier compared to PCR.	Less specific than PCR in identifying etiologic agents.
Ultrasonography [69]	distinguishes between eumycetoma (produces multiwalled cavities) and actinomycetoma (produces fine echoes)	Requires high frequency resolution

	Provides higher axial resolution.	
Computerized tomography (CT) [70]	Optimal imaging technique for detecting fungus ball preoperatively. It is fast and non-invasive method.	Provide only limited evaluation due to poor soft tissue contrast. Not specific for early bony involvement.
Magnetic Resonance Imaging [71]	Most comprehensive method to distinguish mycetoma from other etiologies such as a sarcoma or benign lesions. A dot-in-circle sign with central low-signal “dots” surrounded by bright signal intensity, is specific diagnostic seen in MRI for mycetoma.	Requires highly expert persons. Available in specialized health care.
Dermoscopy or Dermoscopy [72]	Evaluates pigmented skin lesion Mycetoma are viewed as yellow globules, white structureless areas, structureless blue-white areas mixed with neutrophils, dermal fibrosis, with subcutaneous pigmentation.	Experienced hands is critical factor

Pathogenesis and host defense

Immunology and genetics along with external environment play a knee role in increasing the susceptibility to the disease. Two types of tissue reaction are involved, initially the host neutrophil adheres to the microorganism and enclose it resulting in degranulation and disintegration of the grains forming fibrous tissue. The chemokine CCL5 and the cytokine IL-10 play important roles in granuloma formation and antigen-specific immunosuppression [19]. In type II reaction, the host macrophages clear the debris resulting in formation of epithelioid granuloma that results in inflammation. Finally, a well-developed epithelioid granuloma is formed in type III reactions. IL-10, a cytokine down regulates Th1-activity [35, 36]. Nasr *et al.* [19] have reported higher levels of the Th-1 cytokines (IFN-γ, TNF-α, IL-1β and IL-2) in patients treated with surgical excision, than without surgery. While in patients treated with surgical excision, Th-2 cytokines (IL-4, IL-5, IL-6 and IL-10) were significantly lower than in those treated without surgical excision. The results indicated the importance of cell mediated immunity in tackling the pathogenesis and complement dependent innate immunity being the first line of defense against the infection. Musa *et al*. [37] have reported Toll like receptors (TLRs) polymorphism (Asp299Gly) to play a key role in the innate immune response, immune-surveillance and inflammation in mycetoma infected patient.

Treatments

Treatment of mycetoma is determined mainly by the causative organism through fine-needle aspiration (FNA) cytology. The treatment procedure is long and requires a pragmatic approach comprising combination of antimicrobials, surgery and rehabilitation. Combating actinomycetoma is more successful while in eumycetoma it is disappointing as only a few patients respond to therapy. In such unresponsive cases, surgery is the only option [38]. For small, well-circumscribed lesions, surgery is a viable alternative whereas wide surgical excision plus flap is chosen for big lesions when primary closure is not relevant [39]. Identifying pathogen species is difficult since many isolates fail to sporulate and remain sterile in growth culture and grains fail to form *in vitro* condition. Sterility can make the morphological description of the reproductive structures impossible [40]. Amputation could be done for toes, fingers, or complicated limbs such as hand or foot depending on the bone involvement and infection. Treatment may last at least for one year for minor lesions to resolve and several years for large lesions [41]. Even after full recovery, patients need to be followed up as it is the crucial step for the patient and health care professional to make sure there is no evidence of recurrence. Finally, support and adaptation for individuals with disability is a prerequisite. The Mycetoma Research Centre (MRC) at the University of Khartoum, a WHO Collaborating Centre is presently conducting the first double blind clinical trial on a new drug called Fosravuconazole having active compound ravuconazole sponsored by the Drugs for Neglected Diseases initiative, Geneva. The drug is available both intravenous and oral formulations [42]. In another study olorofim, the lead candidate of the orotomide is proven to be highly susceptible to Madurella mycetomatis and is, *in vitro* phase II trials [43]. Emulgels loaded with 0.77% amikacin sulfate is demonstrated to be a potent drug for treating mycetoma preferably *Actinomadura madurae* and *Nocardia brasiliensis* [44]. Although the most successful drug currently in use is itraconazole, 500 mg terbinafine twice daily also has been reported alternative to former drug [45]. Or both the drugs are used in combination as in case of cutaneous mycetoma caused by *Paecilomyces variotii* along with resection surgeries [46]. Linezolid an oxazolidinone antibiotic showed favorable result against *Actinomadura madurae* [47]. A study documented in Pakistan showed voriconazole as a likely drug of choice for treatment of eumycetomas caused by Aspergillus species as it was safe and efficacious and well tolerated among the five of the six-patient treated [48].

A first case of *Actinomadura pelletieri* with urethral complication and discharge of small grains in the urine was reported to mycetoma research center initially the patient was treated with 1g of amoxicillin and clavulanic acid (Augmentin) twice daily and 80 mg of trimethoprim and 400 mg of sulfamethoxazole (co-trimoxazole) twice daily. The patient showed an excellent response to medical treatment and surgery but was still in follow up due urinary dribbling [49]. *Phellinus* spp. is another rarely reported mycetoma causing agent which is also treated by amphotericin B and voriconazole [50]. In another model experimental study *G. mellonella* larvae were infected with M. *mycetomatis*. The study showed amphotericin B and terbinafine were able to enhance the larval survival but not the azoles. Such types of typical studies can serve as a tool to drug discovery although correlation should be achieved in laboratory model and clinical outcome [51].

As reported earlier melanin producing fungi showed more virulence, hence it is ideal to inhibit the melanin production pathway. The authors Lim *et al*. have reported DHN-melanin (1,8-dihydroxynaphthalene) is the most predominant type of melanin in all fungi so this could be a potential target for the drugs. The authors observed enhanced efficacy of azole drug decreased the melanin production indicating melanin inhibitors to be hopeful drug as it increased the fungi susceptibility [25]. Also MycetOS an open-source-drug-discovery library aimed at screening potential drugs against mycetoma has reported 287 compounds to be promising candidate for eumycetoma with active ingredient being fenarimols [52]. Fig, 1 shows the future prospective in mycetoma research.

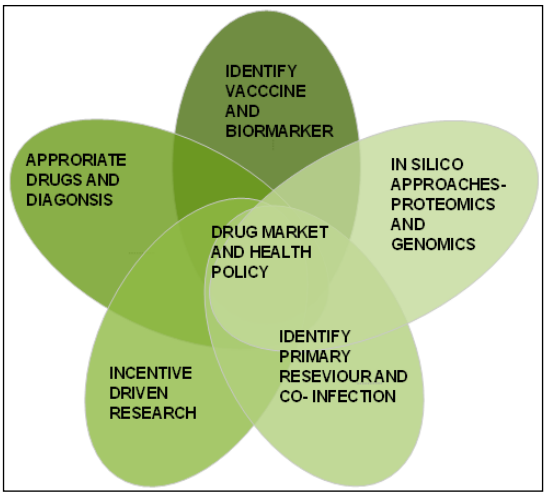

Fig 1: Future Prospective in Mycetoma Research

Herbal drugs in treatment of mycetoma

As most affected individuals are from low social economic class, living in remote endemic area with low health care facility serve as a hindrance to the treatment. By the time the patients come to the health center the disease presentation state is in the latter stage. Poor treatment outcome, wrong diagnosis, surgical treatments with high amputation rate and cost are disappointing for the patients. Pharma Companies are unwilling to invest in NTDs because return on the investment cannot be assured which is a risky business for the investors [53]. Due to these multifactorial reasons patients prefer herbal treatment with local medicinal plants as an alternative [54]. Herbs are consumed in form of decoction, chewed or the active constituent is applied topically. Elfadil *et al*. [55] determined the antifungal activity of chemical extractions of *Acacia nubica, Boswellia papyrifera* and *Nigella sativa* against *M. mycetomatis.* A number of clinical studies have supported the anti-inflammatory, wound healing and anti-arthritic properties of these plants. All these plants showed some antifungal activity, of these *Boswellia papyrifera*, had the highest antifungal activity (MIC_{50} of 1 µg/ml). Analysis of *B. papyrifera* fractions by gas chromatography-mass spectrometry (GC-MS) showed the presence of active component beta-amyrin, beta-amyrone, beta-sitosterol and stigmatize. Stigmatize showed best antifungal activity, compared to other three phytoconstituents, with a MIC-50 of 32 µg/ml. The authors concluded, the antifungal activity of the identified phytoconstituents was only narrow, when compared to the complete extracts indicating synergism.

In another study 311 patients of different age groups, occupations, educational levels with eumycetoma were invited to participate and give their consent on herbal medicine. The study showed that 42.4% of the patients used herbal medicine for the treatment of eumycetoma. Generally used herbs were *Moringa oleifera*, *Acacia nilotica*, *Citrullus colocynthis* and *Cuminum cyminum*. *Moringa oleifera* consumption was reported in 25 patients (18.9%). It was used as a hot drink, applied topically on the lesions or the leaves or other parts of the tree were consumed. Most of the patients claimed no benefits from the herbal treatment. 91 patients out of 132 patients (29.3%) had encountered complications like infection, burn and skin necrosis. The patient's acquaintance on the various aspects of mycetoma showed, most of them 177 (56.9%) had only moderate knowledge [56] as traditional treatment is a popular culture.

AbdElGaffar *et al*., [57] have attempted to explore the possible antimicrosomal activity of the root of *Tinospora bakis* and the rhizome of *Curcuma longa* (Zingiberaceae). The woody part of the root of *Tinospora bakis* is well known in West Africa as a diuretic and febrifuge, the root is used against jaundice, hematuria, bilious fever, yellow fever, malaria and schistosomiasis [58]. Curcumin, a polyphenolic compound, present in the *Curcuma longa* plant has a very long history of medicinal use, dating back nearly 4000 years. In Southeast Asian countries, turmeric is used as a chief spice and as complementary medicine [59]. *Tinospora bakis* was extracted with chloroform and a mixture of methanol-acetone, whereas the rhizome of *C. longa* was extracted with 70% ethanol followed by concentration and fractionation with ethyl acetate. All the extracts were examined through *invitro* screening against *Madurella mycetomatis*. *T. bakis* extracts exhibited MICs of 78.1 (chloroform) and 39.1 µg/mL (methanol-acetone, respectively. The extract of *C. longa* showed a MIC of 39.1 (crude ethanol) and MIC of 156 µg/mL (ethyl acetate fraction). The microbial activity was attributed to the presence of alkaloid berberine and the diarylheptanoid curcumin in *T. bakis* and *C. longa* respectively.

Essential oil of many plants is document to have antimicrobial property and one such plant is tea tree oil, also known as melaleuca oil, it is an essential oil distilled from the leaves of the Australian Plant *Melaleuca alternifolia*. The medicinal uses of tea tree oil relate principally to the anti-inflammatory and antimicrobial [60]. Studies on the antifungal activity of tea tree oil (TTO) demonstrated, at a concentration below 0.25% (v/v) was effective against *M. mycetomatis.* Artemisinin, isolated from the plant *Artemisia annua* a well-known antimalarial component showed no inhibition against *M. mycetomatis* [61].

Eltayeb and colleagues [62] have reported the antifungal activity in the chloroform extract of the bark of *Anogeissus leiocarpus* against *M. mycetomatis* at a concentration of 10 mg/mL. The active fraction present in the extract was found to be ellagic acid and flavellagic acid derivatives. In another study, the antimicrosomal activity of the leaves of *Terminalia brownii* (Combretaceae) was investigated. This plant is found mainly in Africa and the various parts of the plant is used to treat jaundice, cystitis, leucorrhoea, syphilis, hepatitis, liver cirrhosis, yellow fever and skin disease [63]. The results showed methanolic crude extract with a MIC of 78.1 µg/mL while the chloroform and ethyl acetate fractions exhibited activity with MIC<39.1 µg/mL. The active compounds identified in the extracts were tetrahydro chalcone, p-coumaryl glucoside and catechin 3-*O* gallate C-

glycosylated flavone, isoorientin and myricetin 3-*O*-hexose gallate, Combretastatin B5 *O*-hexose gallate stilbene. Ellagic acid, hydroxylated flavan-3-ol gallocatechin was the major compound in the chloroform fraction [64].

Nauclea latifolia Smith, a shrub belonging to the family Rubiaceae is well known African traditional medicine it is used to treat jaundice, yellow fever, rheumatism, abdominal pains, hepatitis, diarrhea, dysentery, hypertension, as well as diabetes [65]. N. *latifolia* crude extract inhibited *M. mycetomatis* at a concentration ranging between 625 and 39.1 µg/mL. The active compound in the extract was identified as β-carboline alkaloid, strictosamide, which exhibited a MIC of 3.91 µg/mL while the positive control ketoconazole, showed MIC of 0.25 µg/mL [57].

Conclusions

Effective control of mycetoma can be achieved by early detection and management of the disease this should involve early diagnosis. Presently there is no vaccination for mycetoma infection. A combination of drugs and surgical removal of the lesions, timely mobilization and physiotherapy are mandatory for better surgical outcomes to avoid the joint stiffness and reduce deformities and disabilities. At present amphotericin B, itraconazole, voriconazole, posaconazole, terbinafine, and micafungin are the drugs used against mycetoma. Accurate diagnosis and teamwork consultations are needed to identify the causative agent and disease management. Herbal medicines are, regarded as an approach to healing because of the fear of possible misdiagnosis and wrong treatment. People in the endemic area prone to mycetoma infection should wear protective covering like shoes, the body should be fully covered with cloth and proper hygiene is to be maintained. People should be educated and sensitised about the disease and total global coverage of the disease is required. Safety concerns arising from the use of herbal medicinal products should be strictly monitored. Countries where the disease is prevalent; planning, implementation and documentation becomes paramount important.

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Chapter - 4
Medicinal Plants from Northeast India having Hepatoprotective Properties and Their Future Prospects

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Chapter - 4

Medicinal Plants from Northeast India having Hepatoprotective Properties and Their Future Prospects

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Abstract

Liver disease is rising at an alarming rate and affecting larger proportion of the world's entire population. There are various types of liver diseases that can be caused by many reasons such as virus, damage due to drugs or chemicals, obesity, diabetes or due to autoimmune diseases. When the condition is left untreated, it can become life threatening and can permanently damage the liver or the bile duct. This damage leads to malignancy and cause liver cancer. Hepatoprotective drugs such as Liv52, Silymarin, Silybon 140 are extensively used in the treatment of liver disease. But these drugs have lots of side effects on human health. In the last few decades, there has been a rapid growth in the use of medicinal plants with different formulations gaining popularity all over the world as it possesses minimal side effects. The present review focuses mainly on the types of liver disease, causes, clinical manifestations and the importance of 30 herbal plants belonging to different families in the treatment of liver disease.

Keywords: Liver disease, hepatoprotective, hepatotoxic, cirrhosis, medicinal plants, secondary metabolites

Introduction

Liver diseases are now becoming a major health problem and about 2 million peoples lose their lives every year due to cirrhosis, hepatitis and hepatocellular carcinoma globally [1]. About 10% of the world population is affected by various liver diseases [2]. Exact statistics are not always available because cause-specific mortality data are sparse for many regions where liver disease is highly prevalent, particularly in Africa. Besides, approximately one-third of all countries worldwide do not have accurate mortality data. Even in developed countries, clear separation of liver disease burden according to aetiology and stage of the disease is not possible. The incidence and prevalence of the chronic liver disease is not well established

even in the available population-based studies. Therefore, there are some differences in liver disease burden based upon geographic region, race, gender, ethnicity and socioeconomic strata. In some studies, an outsized proportion of patients have liver disease on presentation, probably biasing the estimate towards patients with advanced pathology. Correct mortality information is additionally hampered as official death records underestimate liver diseases and liver disease because the main reason for death. With the aforesaid caveats, current information recommends that each acute and chronic liver diseases square measure current worldwide, inflicting important morbidity and mortality. Further, the world burden of each acute and chronic disease is predicted to extend. In human body, liver has over 5000 separate bodily functions as well as serving to blood to clot, cleansing the blood of poisons to changing food into nutrients to regulate secretion levels, fighting infections and malady, make back when injury and metabolizing steroid alcohol, glucose, iron and dominant their levels. There are several types of liver diseases caused due to several reasons like viruses, damage from drugs or chemicals, obesity, diabetes or an attack from own immune system, when this condition is not treated at proper time it may turn into malignancy and lead to death [3]. Numerous phytomedicines or polyherbal formulations are being used for the prevention and treatment of various liver disorders or hepatotoxicity in all over the world. The medicinal plants contain several phytochemicals, which possess strong antioxidant activities. These antioxidant phytochemicals may be flavonoids (flavones, isoflavones, flavonoids, anthocyanins, catechins, iso catechins, quercetin), terpenoids, polyphenols (ellagic acid, gallic acid, tannins), alkaloids, saponins, vitamins (A, C, E, K), carotenoids, minerals (selenium, copper, manganese, zinc, chromium, iodine), enzymes (superoxide dismutase, catalase, glutathione peroxidase), polysaccharides, saponins, lignins, xanthones and pigments, etc. The antioxidants may cure different diseases by protecting the cells from damage caused by 'free radicals'-the highly reactive oxygen compounds [4].

Northeast India is very rich in biodiversity and so many medicinal plants are found. Ethno-medicines are those alternative medicines, practices by ethnic communities and tribes in a particular geographical area or region with biotic and abiotic components of nature for prevention and control of diseases and illness of human, animals, cultured crops and other purposes. Such practices are inherent linked with folk-culture and tradition. The chief source of ethnomedicines is plants and its different parts and products. Medicinal plant bio-resources have played a significant role in ethno-medicinal health care system. It fulfilled the basic health care needs of large

section of rural masses of the world with providing vitamins, minerals, antioxidants and other essential phytomolecules. It is one of the many service systems that have emerged to facilitate fulfillment of individual as well as social goals. In this article, we discussed the liver disease and the medicinal plants of Northeast India having hepatoprotective activity [5].

Liver diseases

When high levels of Bilirubin is produced and dead RBC's are not excreted by liver as bile leads to the onset of different liver diseases occur associated with jaundice. Some common liver disease such as Hepatitis, is a condition with swelling of liver caused by virus, autoimmune diseases; late-stage Liver cirrhosis associated with killing of hepatocytes by fibrous tissue in liver; inherited liver disorder such as Hemochromatosis causes liver damage by accumulated iron content in body, Wilson disease due to copper accumulation, Gilbert's syndrome, a genetic disorder affecting the normal ability of body to process bilirubin. Special clinical studies measuring the level of specific enzymes, metabolites, or substances can help us to identify the proper functioning of liver.

Acute liver failure

Acute liver failure (ALF) also called fulminant hepatic failure, is a liver disease caused when liver quickly loses its ability to function which can cause excessive bleeding and increased pressure in brain. Acute liver failure can be treated through hospitalization but a critical condition requires a liver transplant.

Within 26 weeks of the onset of this illness, there is formation of abnormal liver synthetic function (international normalized ratio; INR > 1.5) and altered mental status (hepatic encephalopathy). Hyperacute form of this disease has better prognosis but with a higher cerebral oedema. Acute and subacute form shows worse prognosis but with a low cerebral oedema [6].

Hepatitis

Hepatitis is a viral infection of liver caused by viruses (such as Hepatitis A, B, C), bacteria or parasites, via immune cells causing autoimmune hepatitis and from consuming alcohol, poisonous mushrooms, overdose of drugs such as acetaminophen. It is associated with swelling of liver and can also be inherited such as cystic fibrosis, a condition of excess iron deposit in liver. Jaundice, dark urine, abdominal pain, fatigue, low grade fever, nausea, vomiting are some symptoms of this disease [3]. Grover and Keays, 2010 state that Hepatitis can be caused by non-infective such as alcohols, drugs,

metabolic such as Wilson's disease but major cases occur from infective causes such as viruses (cytomegalovirus (CMV), Epstein Barr virus (EBV) and Herpes Simplex Virus (HSV) [7]. New Drug treatments can reduce the risk for patients suffering from chronic viral hepatitis causing cirrhosis and chronic liver failure or hepatocellular carcinoma.

Hepatitis A

Hepatitis A, a liver disease is associated with inflammation of the liver caused by Hepatitis A virus (HAV) mostly found in stools and blood of an infected person within 15-45 days during first week of illness. Symptoms such as dark urine, fatigue, itching, loss of appetite, low-grade fever, vomiting, nausea, colored stools and yellow skins occur after 2-6 weeks of HAV infection.

The most common route of HAV is the faecal-oral route with poor sanitation areas mostly in developing world and in civil disruptive countries. HAV is a 27 nm RNA virus whose symptoms begins after a fortnight infection causing increase transaminase levels, IgM and IgG anti-HAV titres and faecal viral shedding. Combination of IgM antibody and HAV antigen detection in blood clinically is used for diagnosis. Adults, pregnant women and children above the age of 2 are provided active immunity to HAV whereas people travelling to high-risk areas are given passive immunity to HAV by injection of immunoglobulin [7].

Hepatitis B

Hepatitis B is caused by hepatitis B virus (HBV) is associated with inflammation of liver where the virus is spread by infected person's blood or body fluids (such as semen, vaginal fluids and saliva). Symptoms may appear after 6 months which include loss of appetite, fatigue, low fever, muscle, joint aches, nausea, vomiting, dark urine, jaundice. HBV is a 42 nm DNA virus with an outer and inner protein layer covering the genome and DNA polymerase enzyme. Hepatitis is associated with significant increase in ALT (Alanine aminotransferase) levels. Acute HBV infection indicated by IgM anti-HBc levels shows symptoms after 2 months. Vaccination has shown to be effective against the disease with neonate given immunoglobulin to prevent infection.

Hepatitis C

Hepatitis C is a liver disorder caused by Hepatitis C virus which causes swelling of the liver. The virus is spread by an infected person's blood whose symptoms includes pain in upper right abdomen, abdominal swelling

due to fluid (ascites), clay-colored or pale stools, dark urine, fatigue, fever, itching, jaundice, loss of appetite, nausea and vomiting [3].

Initially known as “non-A non-B virus”, the RNA has infected approximately 170 million people by parenteral spread. The route of parenteral transmission can occur through blood transfusion or via needlestick (intravenous drug abuse or occupational exposure in healthcare workers), sexual route. After one month of exposure, HCV RNA appears in the serum with transaminitis developing after a week or two later. Anti-HCV antibodies develop after 1-6 months.

Hepatitis D (Delta agent)

Hepatitis D is a viral liver disease caused by hepatitis D virus (HDV) that causes symptoms such as abdominal pain, dark- colored urine, fatigue, jaundice, joint pain, loss of appetite, nausea and vomiting in people carrying hepatitis B virus who never had symptoms. The transmission factors includes abusing intravenous (IV) or injection drugs, passing the virus to the baby during pregnancy by hepatitis B carrier mother, men having sexual intercourse with other men, receiving many blood transfusions.

HDV is a RNA virus that causes co-infection only in presence of HBV that acts as a helper virus with super-infection causing cirrhosis and hepatocellular carcinoma. Ribozymic property of HDV RNA virus may be a tool to reduce the risk of HDV infection in future.

Hepatitis E

Hepatitis E is caused by hepatitis E virus (HEV) which is associated with inflammation of the liver. The major factor of HEV transmission is faecal contamination of drinking water due to poor sanitation, other transmission includes consumption of contaminated food, such as raw or undercooked meat (e.g.: pork and shellfish) from infected animals and through transfusion of infected blood products. Jaundice, malaise, anorexia nausea, vomiting, abdominal pain, hepatomegaly, pruritis and arthralgia are the symptoms of this disease. HEV is a positive sense, single stranded non-enveloped RNA icosahedral virus causing hepatitis in pregnant women in third trimester and chronic infection in immunosuppressed patients. Anti-HEV antibody measurement and exclusion of other hepatitides clinically are present diagnosis for this disease with no vaccine currently available.

Alagille syndrome

Alagille syndrome is an autosomal dominant disorder causing liver damage due to failure of bile drainage deposit in liver. It is a spontaneously

developed gene mutation in which neither of the parents are the carriers but a child with Alagille syndrome parent has 50% chance of developing the disorder. Mutations in the *Jagged1 (JAG1)* gene and NOTCH2 gene are seen in people with Alagille syndrome. Symptoms include various liver diseases in infants and adults with infants showing poor bile drainage from the liver in the first few weeks.

Alcohol related liver disease

Alcohol is broken down in the liver so as to remove from our body. Over consumption of alcohol can have serious effects by destroying liver cells. Three main types of alcohol-related liver disease are: fatty liver disease, alcoholic hepatitis and alcoholic cirrhosis.

Fatty liver

Fatty liver is a common condition of too much fat build up in liver which is an early stage of alcohol related liver disease. Most heavy drinkers have fatty liver disease with symptoms such as fatigue, weakness, and weight loss. With minimize or total cease of drinking, can reduce the fatty liver disease.

Alcoholic hepatitis

Alcoholic hepatitis is a condition of liver swelling with mild and severe condition causing liver damaged. Loss of appetite, nausea, vomiting, abdominal pain, fever and jaundice are some symptoms of this disease. Mild form of this disease can be treated but severe form includes liver failure and death with 35 percent of heavy drinkers developing alcoholic hepatitis.

Alcoholic cirrhosis

Alcoholic Cirrhosis is the most serious type of alcohol-related liver disease associated with scarring of the liver. Symptoms are similar to those of alcoholic hepatitis and 10 to 20 percent of heavy drinkers are affected by Alcoholic cirrhosis. It cannot be reversed causing liver damage.

Enlarged liver

Hepatomegaly (hep-uh-to-MEG-uh-le) is a medical term of enlarged liver in which size of liver is bigger than normal condition. Enlarged liver is not a disease but associated with liver issue such as liver disease, congestive heart failure or cancer which can be treated by identifying and controlling the caused condition. Various liver disease conditions are responsible for Enlarged liver such as Cirrhosis, Hepatitis caused by virus (including hepatitis A, B and C), Non-Alcoholic fatty liver disease, Alcoholic fatty liver

disease, Wilson's disease, hemochromatosis, Gaucher's disease, liver cysts, Noncancerous liver tumors, including hemangioma and adenoma, Obstruction of the gallbladder or bile ducts and toxic hepatitis.

Nonalcoholic fatty liver disease-(NAFLD)

NAFLD is a common disorder of fat builds up in liver associated with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia, and metabolic syndrome. The risk of NAFLD increases with obesity. Non-alcoholic steatohepatitis (NASH), a subtype of NAFLD leads to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation [8].

Alpha-1 Antitrypsin deficiency

Alpha-1 antitrypsin deficiency (Alpha-1) is a genetic disorder associated with lung and/or liver disease with most common in children and sometimes in adults with lung conditions such as emphysema as well as liver problems. Persons with Alpha-1 however never develop any of the associated diseases.

Budd-Chiari syndrome

Budd-Chiari, is a syndrome caused by complete or partial blood clots blocking large veins carrying blood from liver into inferior vena cava. This syndrome causes polycythemia, sickle cell disease, inflammatory bowel diseases and connective tissue disorders.

Gilbert's syndrome

Also known as constitutional hepatic dysfunction and familiar non-hemolytic jaundice, Gilbert’s syndrome is a mild liver condition which occurs when liver is unable to process Bilirubin properly. This syndrome is caused by an inherited gene mutation requiring no treatment due to its harmless condition. It can be detected from blood test with increase bilirubin levels.

Liver-hemangioma

It is a noncancerous mass made up of tangle of blood vessels occurring in liver with no signs and symptoms. It does not require any treatment and no information have been reported about untreated liver hemangioma causing liver cancer.

Nonalcoholic steatohepatitis-NASH

NASH often called “silent” liver disease is a common liver disease associated with inflammation and liver damage that occurs in people who

consume little alcohol or no alcohol. Severe NASH can lead to cirrhosis with permanent liver damage. Nonalcoholic fatty liver disease (NAFLD) can be detected by analyzing the fat levels by blood test or scans of the liver.

Portal hypertension

It is a condition of increase high blood pressure in portal vein and its branches caused commonly by Cirrhosis. Swollen abdomen, abdominal discomfort, confusion and bleeding in the digestive tract are some symptoms.

Hepatic encephalopathy

Hepatic encephalopathy (portosystemic encephalopathy, liver encephalopathy or hepatic coma), is a liver disease caused by bleeding in the digestive tract, an infection, failure to take prescribe drugs, stress in liver disorder people. It is associated with worsening of brain function due to accumulation of toxic substances in blood reaching brain, usually removed by the liver. Changes in personality, behavior, mood accompanied by drowsy, confusion are some symptoms of this disease.

Ascites

It is the abnormal buildup of protein containing (ascitic) fluid in abdomen causing sudden weight gain, distended abdomen, abdominal pain, heart burn, nausea, vomiting, short of breath and uncomfortable. Intake of low-sodium diet and diuretics helps to eliminate the excess fluid.

Cholestasis

Cholestasis is a condition of decrease bile flow when there is damage in between liver cells and duodenum causing skin and sclera of the eyes look yellow, itching of skin, dark colored urine, light-colored and foul-smelling stool. Usually, bile is eliminated from the body via stool when it binds with bilirubin in the liver.

Jaundice

It is a condition of excess bilirubin (a yellow pigment) in blood and associated with yellowing of skin and sclera of the eyes. Normally, bilirubin formed by hemoglobin is broken down by recycling old or damaged red blood cells. Nausea, vomiting, abdominal pain, and small spider like blood vessels that are visible in the skin, enlarged breasts in male, shrunken testes are some symptoms of this disease.

Primary Sclerosing Cholangitis (PSC)

PSC is a chronic liver disease characterized by inflammation of the bile ducts leading to scar formation and narrowing of the ducts in due time causing bile builds up in the liver and damages liver cells. PSC can lead to cirrhosis and liver failure with scar tissue spread throughout the liver.

Biliary atresia

Biliary atresia is a condition of blockage in the bile ducts occurring in infants having life threatening implication. Fetal and perinatal are two types of biliary atresia with former affecting baby in womb causing birth defect in heart, spleen or intestines and the latter being more common not visible up to 2-4 weeks after birth. Weight loss, irritability, jaundice, hardened of liver with distended abdomen; pale grey stools and dark urine are symptoms of this disease.

Test for liver diseases

A number of liver function test are available to test the proper function of the liver, serum proteins, serum albumin, bilirubin (direct and indirect), alanine aminotransferase (ALT), AST, GGT, ALP, PT and PTT). Liver tissue and bile ducts can be studied by various techniques. Common techniques are imaging tests includes transient elastography, ultrasound and magnetic resonance imaging, liver biopsy etc.

ALT and AST test

ALT and AST are sensitive indicators of hepatocellular injury, but since these two are also present in muscle (cardiac and skeletal), kidney, and RBCs, they have limited specificity. The aspartate aminotransferase (AST) test is a blood test. AST is an enzyme produced by liver. In normal condition the AST level is low, but when any liver damage takes place, it secretes more AST to blood in cytoplasm of hepatocyte abundance of AST is more than ALT. The diagnosis for alcoholic hepatitis is supported by the finding of a ratio of AST to ALT of at least 2:1 and gamma-glutamyl-transpeptidase (GGT) that is twice the normal level. Based on AST: ALT ratio we can differentiate different conditions: high ratio in hepatitis C with cirrhosis, liver metastases and HCV with cirrhosis versus low ratio in acute inflammation and cholestasis [9].

Alkaline phosphatase (ALP) test

This enzyme is primarily found in liver, besides liver it is also found in many parts of the body such as liver, bones, intestine and kidneys, placenta. Serum ALP is thus a mixture of different ALP isoenzymes and can be

fractionated by electrophoresis. Normal level of ALP varies from person to person, age, gender, and blood type but abnormal level of ALP in blood indicates problems in liver, gallbladder, pancreas, kidney or bones.

Bilirubin test

Bilirubin test is used to determine the amount of bilirubin in blood. Serum bilirubin is a mixture of α, β, γ and δ fragments. Based on the bilirubin amount in blood it can be predict heath condition of a person, whether the person is suffering from jaundice, anemia or liver disease like cirrhosis, hepatitis, gallstone etc. If the bilirubin levels are higher than normal, it indicate that either your red blood cells are breaking down at an unusual rate or that waste products are not properly degraded by liver and clearing the bilirubin from your blood.

Albumin test

It is another type of blood test for liver function, based on measurement of different enzymes and proteins in the liver including albumin. The protein albumin is synthesized by liver and very useful in detecting liver diseases. Changed in the level of albumin indicate various liver diseases, such as low albumin level in patients with hepatitis C can be a sign of cirrhosis.

Table 1: List of plants having hepatoprotective properties

Sl. No.	Botanical Name	Family	Parts used for Treatment	References
1.	*Achyranthes aspera*	Amaranthaceae	Leaves	[10]
2.	*Alternanthera sessilis*	Amaranthaceae	Whole plant	[11]
3.	*Amaranthus spinosus*	Amaranthaceae	Whole plant	[12]
4.	*Amaranthus tricolor*	Amaranthaceae	Root	[13]
5.	*Aloe vera*	Asphodelaceae	Leaves	[14]
6.	*Alpinia nigra*	Zingiberaceae	Leaves	[15]
7.	*Amaranthus viridis*	Amaranthaceae	Whole plant	[16]
8.	*Andrographis paniculata*	Acanthaceae	Aerial part	[17]
9.	*Argemone Mexicana*	Papaveraceae	Aerial part	[18]
10	*Brassica juncea*	Brassica	Leaves	[19]
11	*Boerhavia diffusa*	Nyctaginaceae	Root	[20]
12	*Cassia tora*	Leguminosae	Leaves	[21]
13	*Chenopodium album*	Chenopodiaceae	Leaves	[22]
14	*Colocasia esculenta*	Araceae	Leaves	[23]
15	*Commelina benghalensis*	Commelinaceae	Leaves	[24]
16	*Curcuma amada*	Zingiberaceae	Rhizomes	[25]

17	*Eclipta alba*	Asteraceae	Leaves	[26]
18	*Eleusine indica*	Poaceae	Leaves	[27]
19	*Enhydra fluctuans*	*Asteraceae*	Aerial part	[28]
20	*Euphorbia hirta*	Euphorbiaceae	Whole plant	[29]
21	*Hedyotis corymbosa*	Rubiaceae	Whole plant	[30]
22	*Houttuynia cordata*	Saururaceae	Whole plant	[31]
23	*Leucas aspera*	Lamiaceae	Whole plant	[32]
24	*Mimosa pudica*	Leguminosae	Leaves	[33]
25	*Musa paradisiacal*	Musaceae	Stem	[34]
26	*Ocimum sanctum*	Lamiaceae	Leaves	[35]
27	*Oxalis corniculata*	Oxalidaceae	Whole plant	[36]
28	*Phyllanthus fraternus*	Euphorbiaceae	Aerial part	[37]
29	*Raphanus sativus*	Brassicaceae	Leaves	[38]
30	*Rumex vesicarius*	Polygonaceae	Whole plant	[39]

Conclusion

A large proportion of population across the Globe is affected by liver diseases and is rising at an alarming rate. Liver diseases can be inherited or caused by a variety of factors that damage the liver (virus, drugs or chemicals, obesity, diabetes or an attack from own immune system), if liver diseases are not treated at right time the situation may become life threatening and sometimes it leads to permanent liver damage or the damage of the bile duct. This damage can then become malignant. The liver disease prognosis depends on how quickly the condition was diagnosed and treated. In beginning stages, liver disease usually responds to treatment, but in advanced liver disease, the damage done by fibrosis, cirrhosis and liver failure cannot be reversed. This advanced stage leads to eventual death. While diagnosing liver disease, the condition causing the disease must be treated. If caught early, and are treated correctly, the damage to the liver may heal. In the middle stages of disease, treatment may work to help heal the damage, but as the disease progresses, treatments focus on managing the disease and prolonging the diagnosis. Treating liver disease with plant derived compounds which are attainable and requires moderate laborious pharmaceutical synthesis seems highly feasible. Standard plant products can be manufactured from standard plant extracts by using modern analytical methods and pharmaceutical techniques.

The study revealed the hepatoprotective activity of 30 plant species which are found in the northeastern regions of India and are used in the treatment of liver disease. The majority of the studies confirmed the

hepatoprotective effect of the medicinal plants in the management of hepatic disease. The detailed medicinal plants not only used for the treatment of liver, but also for the management of other diseases and ailments. Various anatomical parts (leaves, flowers, roots, barks, and whole plant) were useful for the treatment. However, the hepatoprotective model that was most commonly used was the drug (Carbon tetrachloride, paracetamol, ethanol, Thioacetamide) induced mice or rats. Active constituents such as flavonoids, alkaloids, tannins, saponins, and phenolic compounds were reported. The potency of plant-based drugs is significant as they have less adverse effects than the synthetic drugs. There is increasing demand of natural product with hepatoprotective activity. Hence, all the medicinal plants discussed in this review have significant hepatoprotective activity. The bioactive constituents are responsible for the hepatoprotective action. However, many other active agents and chemicals extracted from the plants have not been well characterized. Further studies will be necessary to find out the exact mechanism of action of the plants having hepatoprotective activity.

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Chapter - 5
Medicinal and Aromatic Plants in Phytoremediation

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Chapter - 5

Medicinal and Aromatic Plants in Phytoremediation

Macherla Chandana and Sudati Akshitha

Abstract

Accumulation of heavy metals in environment and particularly in soil is a serious environmental concern, as the accumulated heavy metal ions can find their way into living organisms via contamination of ground water or food chain. Phytoremediation is a plant-based approach for controlling pollution, an alternative to the conventional physical and chemical remediation techniques. Medicinal and aromatic plants have been used as herbal remedies and affordable health care products worldwide. Currently, their importance in conservation of vital biodiversity is detected and researches on this subject gained ground. Environmental contamination by heavy metals such as mercury, cadmium and lead is a serious problem throughout the world. Heavy or toxic metals are trace metals that are at least five times denser than water. They are also stable elements and cannot be metabolized by the body or bio-accumulative and they passed up the food chain to humans. Toxic industrial wastes mixing with liquid agricultural fertilizers disperse farmlands. Reclamation of agricultural soil and transition of the metal ions into insoluble forms may be quite expensive and can hardly be applied to huge areas. Heavy metal accumulator plants can be used as alternative solution for solving the problem. Medicinal plants exhibit therapeutic properties due to the presence of bioactive compounds derived from secondary metabolites such as phenolics, terpenoids and compounds containing sulphur and nitrogen. Depending on plant species and existing environmental factors, bioactive compounds from medicinal plants have the potential for remediating specific pollutants.

Keywords: Phytoremediation, medicinal plant, therapeutic, secondary metabolites

Introduction

Some metals are naturally found in the body and are essential to human health (iron, zinc, magnesium and copper), however, most of the heavy

metals such as mercury, nickel, lead, arsenic, cadmium, aluminium, platinum and copper (Metalic form versus ionic form) act as poisonous and interference to the enzyme systems and metabolism of the body. On the other hand, some types of metal such as Cu, Mn and Zn are the natural essential components of coenzymes and they are important for growing, photosynthesis and respiration (Sovljanski *et al*. 1989).

Environmental contamination with heavy metals is a serious growing problem throughout the world. In today's industrial society, there is no way to avoid the exposure to toxic chemicals and metals. Heavy metals are enriched in the environment by human activities of different kinds (Dean *et al*. 1972). Results of these activities end up in outlets and wastes where they are transported to the environment by air, water or deposits, thereby increasing the metal concentrations in the environment (Greger 2004). In general, heavy metals (HM) are systemic toxins with specific neurotoxic, nephrotoxic, fetotoxic and teratogenic effects (Nordberg 1999). HM can directly affect on human behaviour by impairing mental and neurological functions and they can cross the placental barrier and they can be found in breast milk, intellect and the developing nervous system in children (Tong *et al*. 2000, WHO, 2003). From plant nutrition studies, it is known that plants require a certain amount of trace elements that they respond differently to an enhanced or lowered trace element supply, and that, in some cases agricultural products may be contaminated with toxic heavy metals. Bioremediation has gained a lot of importance recently as an alternate technology for removal of elemental pollutants in soil and water, which require effective methods of decontamination. Phytoremediation; the use of green plants to remove, contain or render harmless environmental pollutants, may offer an effective, environmentally non-destructive and cheap remediation method. Remediation of HM contaminated sites using hyperaccumulators also presents a promising alternative to current environmental methodologies (Eapen and D' Souza, 2005). The aim of this article is to review, the response of medicinal and aromatic plants to heavy metals and their roles in phytoremediation as hyper accumulators.

Heavy metal accumulation in some medicinal plants

Heavy metal is the generic name given to the group of elements with an atomic density greater than 6 g cm^{-3}. While these elements are ubiquitous in the Earth's crust, their concentration and availability in soil and water varies from less than 1000 parts per million (ppm = mg kg^{-1} = mg L^{-1}) to a few parts per billion (ppb = µg kg^{-1} = µg L^{-1}), with the exception of manganese, which is found in soils in concentrations ranging from 20 to 10,000 ppm (Alloway 1995).

Heavy metal contents in spices and medicinal plants depend on climatic factors, plant species, air pollution and other environmental factors (Sovljanski *et al*. 1989). Medicinal plants may carry residuals of environmentally persistent pesticides or assimilate heavy metals in varying degrees. Several factors may influence accumulation of contaminants, including species, level and duration of exposure to contaminant, and topography. There are some researches reported from different areas which were conducted to search of the accumulation certain medicinal plants.

The research on 'the heavy metal in Egyptian spices and medicinal plants and the effect of processing on their levels' was conducted by Arab and Donia (2000). They showed that 20 different types of spices and medicinal plants with different growing seasons and each with its own agricultural practices, collected from different sources of exportation in Egypt were tested. They recorded the highest Sn and Mn levels from the tea samples (0.1 and 343 µg g^{-1} respectively), Ni and Zn from the (2.85 and 35.5 µg g^{-1} respectively) basil and Pb (14.4 µg g^{-1}) from marjoram. The results also proved that celery, parsley and spearmint contained the highest mean levels of Cd (2.44 µg g^{-1}), Cu (11 µg g^{-1}) and Fe (1046 µg g^{-1}). It was observed that the lowest mean levels of Pb, Cd, Ni, Sn and Mn were detected in Jew's Mallow with 1.14, 1.06, 0.61, 0.01 and 22.4 µg g^{-1} respectively. The lowest mean levels of Zn (8 µg g^{-1}), Cu (1.8 µg g^{-1}) and Fe (145 µg g^{-1}) were scored in tea.

The role of medicinal plants in phytoremediation

The process of removing contamination from soil or water using plants is known as phytoremediation. It is a name for the expansion of an old process that occurs naturally in ecosystems as both inorganic and organic constituents cycle through plants. Plant physiology, agronomy, microbiology, hydrogeology and engineering are combined to select the proper plant and conditions for a specific site. Phytoremediation is an aesthetically pleasing mechanism that can reduce remedial costs, restore habitat, and clean up contamination in place rather than entombing it in place or transporting the problem to another site (Zynda 2001). Phytoremediation consists of mitigating pollutant concentrations in contaminated soils, water, or air with plants able to degrade or eliminate metals, pesticides, solvents and its derivatives from the media that contain them. Many plant species have their own adaptation mechanisms that allow them to survive under a highly polluted environment. Indeed, some plants known as hyper accumulators are able to survive or thrive on heavy-metal-polluted soils despite high levels of metals in their tissues.

I. How does phytoremediation work?

Plant roots take contaminants from the ground into the body of the plant. The plant root zone is referred to as the rhizosphere, this is where the action occurs. This soil supports large populations of diverse microorganisms. This is due to chemicals exuded by plant roots which provide carbon and energy for microbial growth. This combination of plants and microorganisms appears to increase the biodegradation of compounds.

II. What are the pollutants of phytoremediation?

Plants can be used to extract, detoxify, and toxic pollutants from soil, water, and air in a process called phytoremediation.

Phytoremediation need to distinguish between,

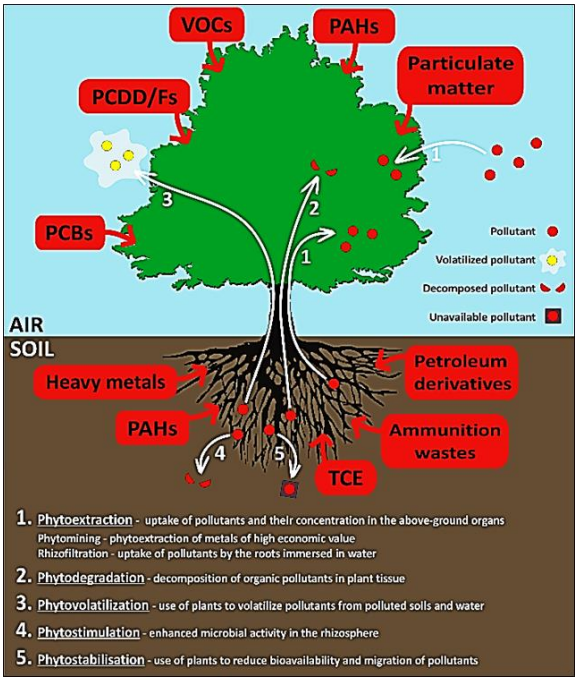
1) The remediation of elemental pollutants.
2) The remediation of organic pollutants.

- Elemental pollutants are heavy metals and metalloids.

e.g.- Hg, pb, cd, As

- Organic pollutants are toxic chemicals such as,

e.g.- formaldehyde, benzene



III. Properties and criteria of medicinal plants in relation to phytoremediation

Besides their traditional uses, medicinal and aromatic plants have important economic values in many industries such as pharmaceuticals, food, cosmetics and ornaments. Medicinal plants exhibit therapeutic properties due to the presence of bioactive compounds derived from secondary metabolites such as phenolics, terpenoids and compounds containing sulphur and nitrogen. Phenolic compounds, for example, are good solubilizers and metal chelators for plants in contaminated areas. phenolic compounds can be released as plant root exudates containing organic acids such as lactates and acetates. These compounds can facilitate bioremediation of pollutants, provided that other environmental factors such as pH, temperature and soil conditions are also suitable for the process to happen. Secondary metabolites could contribute to the protection of plant against toxin stress and could be involved in the detoxification of some toxic metals. The mechanism of pollutant uptake and accumulation varies depending on the type of plant tissues. Pollutants normally enter plants through foliage or root system prior to undergoing oxidation or storage in other compartments such as vacuoles. In response to pollutants, plants usually increase the production of reactive oxygen species. However, high levels of these species are harmful thus, antioxidants are produced to alleviate the cellular oxidative stress.

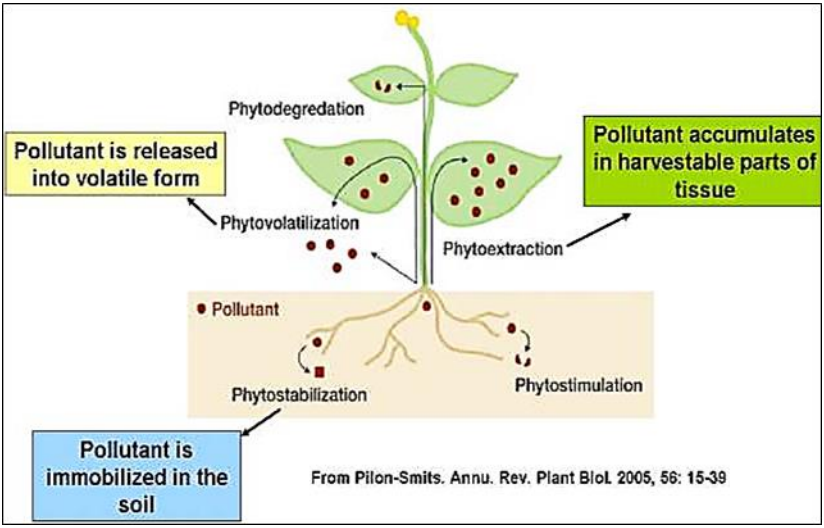
Since secondary metabolites produced by medicinal plants normally contribute to various biological roles, this could be a way for plants to adapt to the polluted environment. Secondary metabolites could contribute to the protection of plant against toxin stress and could be involved in the detoxification of some toxic metals. The ability of certain plants to survive in a contaminated area suggests that they may be able to tolerate or even hyperaccumulate pollutants.

Apart from the roles of secondary metabolites, plant species and environmental conditions are important factors to ensure the success of phytoremediation process. For some susceptible plants, their medicinal properties may be affected due to exaggerated growth and development and alteration of their chemical composition under polluted conditions. Normally, plants for bioremediation have to be robust and able to survive under a stressful environment. In addition, their ability to take up pollutants in a reasonable time frame is also important. Such characteristics as rapid growth and development resulting in height and abundant branches and leaves that lead to the production of high plant biomass under polluted conditions indicate the fitness or suitability of the plants for bioremediation.

Medicinal plants such as *Helianthus annuus* and *Pteris vittata* are good phytoremediators as they are fast-growing species, less prone to diseases and have the ability to accumulate heavy metals in plant tissues.

IV. Various processes of phytoremediation

- Phytoextraction
- Rhizofiltration
- Phytostabilization
- Phytotransformation
- Rhizosphere Bioremediation
- Phytovolatilization



1. Phytoextraction

Phytoextraction is the uptake/absorption and translocation of contaminants by plant roots into the above ground portions of the plants (shoots) that can be harvested and burned gaining energy and recycling the metal from the ash.

ex: Lavender, *Catharanthus roseus, Bacopa monnieri, Mentha spicata.*

Advantages

- The main advantage of phytoextraction is environmental friendliness.

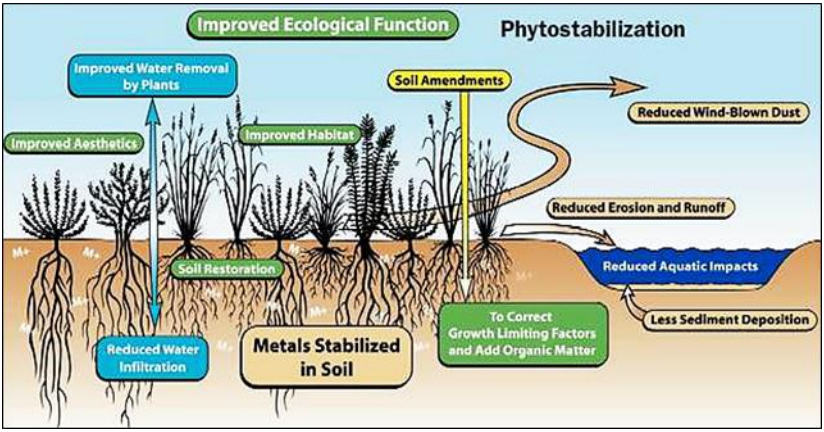
- Traditional methods which are used for cleaning up heavy metal contaminated soil disrupt soil structure and reduce soil productivity, whereas phytoextraction can clean up the soil without causing any kind of harm to soil quality.
- Another benefit of phytoextraction is that it is less expensive than any other clean-up process.

Disadvantages

- As this process is controlled by plants, it takes more time than traditional soil clean-up methods.

2. Phytostabilization

Phytostabilization is the use of plants to prevent the migration of contaminants through control of the hydraulic gradient or by reinforcing the soil structure.



Advantages

- No disposal of biomass is required.
- Very effective when rapid immobilization is needed to preserve ground and surface waters.

Disadvantages

- Contaminant remain in soil.
- Application of extensive fertilisation/soil amendments.
- Mandatory monitoring required.

3. Phyto transformation

Chemical modification of environmental substances as a result of plant metabolism resulting in their inactivation, degradation (phytodegradation) or immobilization (phytostabilization).

Advantage

- Both economically and environmentally friendly

Disadvantages

- Requires more than one growing season to be efficient.
- Soil must be less than 3 ft in depth and groundwater within 10 ft of the surface.
- Contaminants may still re enter the food chain through animals or insects that eat plant material.

4. Rhizofiltration

Filtering water through a mass of roots to remove toxic substances or excess nutrients. The pollutants remain absorbed in or adsorbed to the roots.

ex: Vetiver, lemon grass, palmarosa.

Advantages

- Ability to use both terrestrial and aquatic plants for either *in situ* and *ex situ applications.*
- Contaminants do not have to be translocated into shoots.

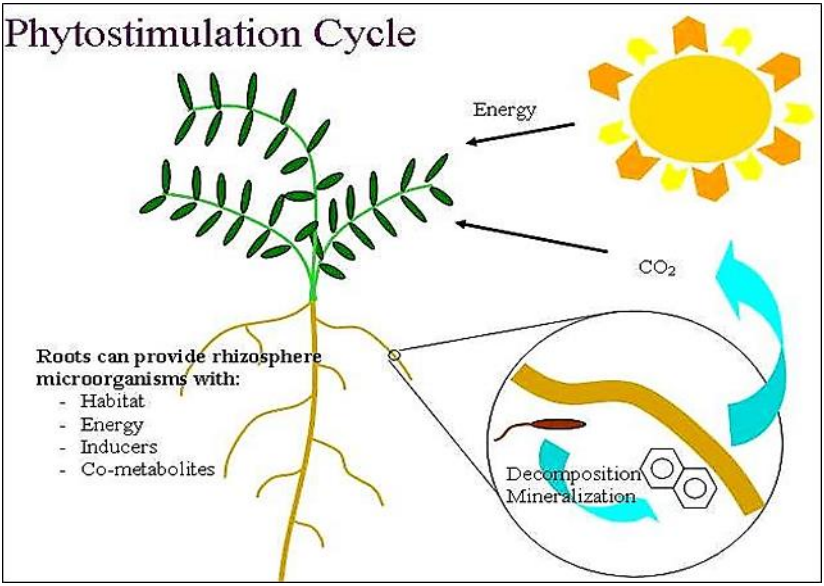
Disadvantages

- Constant need to adjust pH.
- Plants may first need to be grown in greenhouse/nursery.
- There is periodic harvesting and plant disposal.
- Tank design should be well engineered.

5. Rhizosphere bioremediation

Enhancement of soil microbial activity for the degradation of contaminants, typically by organisms that associate with roots.

- Rhizosphere = soil + root + microbes.
- Also known as Phytostimulation.



Advantages

- *In situ* practice resulting in no disturbance.
- No removal of contaminated materials.
- Complete mineralisation of the contaminant can occur.
- Low installation and maintenance cost.

Disadvantages

- Development of extensive root zone required-takes time.
- Root depth limited due to physical structure of soil.

6. Phytovolatilization

Definition: Involves plants taking up contaminants from soil, transforming them into volatile forms and transpiring them into atmosphere.

- Works on organic compounds and heavy metal contaminants, TCE as well.
- Mercury is the primary metal contaminant that this process has been used for.

Advantage

- The contaminant, mercuric ion, may be transformed into a less toxic substance (*i.e.*, elemental Hg).

Disadvantage

- The mercury released into the atmosphere is likely to be recycled by precipitation and then re-deposited back into lakes and oceans, repeating the production of methyl-mercury by anaerobic bacteria.

V. Basic characteristics of hyper accumulator

1. Translocation factor (TF)

- Used to evaluate the potential of plants for phytoextraction.
- It is the ratio is an indication of the ability of the plant to translocate metals from the roots to the aerial parts of the plant.

$$TF = \frac{\text{Metal concentration (stems + leaves)}}{\text{Metal concentration (roots)}}$$

2. Bio Concentration Factor (BCF)

- Determine the quantity of heavy metals that is absorbed by the plant from the soil.
- This is an index of the ability of the plant to accumulate a particular metal with respect to its concentration in the soil

$$BCF = \frac{\text{Metal concentration in plant tissue}}{\text{Initial concentration of metal in substrate (soil)}}$$

VI. Species of medicinal plants accumulators

Species	The accumulated toxic substance	The accumulator vegetative organ	Extracted contaminant/ substrate	
Thlaspi caerulescens	Zn, Cd	Shoots	Heavy metals, mining wastes	
Catharanthus roseus	Cr	Roots, leaves	Chromium, sludges derived from tanneries	

Brassica juncea (Indian mustard)	Atrazine Cd	Roots, shoots	Pesticides cadmium	
Hypericum perforatum	Cu, Cd	Roots, shoots, leaves	Heavy metals	
Matricaria recutita	Cd, Zn	Roots, shoots, leaves	Heavy metals	
Bacopa monnieri	Hg, Cd	Roots, shoots	Sewerage wastes, chlorosodical industrial wastes	
Achillea millefolium	Cu	Roots	heavy metals, mining wastes	
Salvia officinalis	Cd	Shoots	Cadmium	
Centaurea cyanus	Zn	Roots	heavy metals, mining wastes	

Echinophora platyloba	Zn	Roots	Heavy metals, mining wastes	
Ocimum basilicum	Cd	Roots, shoots, leaves	Organic and inorganic additives	
Artemisia vulgaris	Zn, Cu, Pb, Cd, Ni	Roots, shoots, leaves	Sludges, compost, waste paper and from retteries	
Alyssum bertolonii	Ni	Roots	Mining wastes	
Mentha spicata	Cr, Cu	Roots, shoots, leaves	Heavy metals arising from exploitation and burning of fossil fuels	
Hippophae rhamnoides	Fe, Zn, Mn, Cu	Leaves, fruits	Mining wastes	
Rinorea niccolifera	Ni	Leaves	Heavy metals	

Aloe vera	Cd, Cr, Pb, Co, Ag, Se, Hg	Leaves	Heavy metals	
Cannabis sativa	Pb, Cu, Zn, Cd, Ni	Shoots, roots, leaves	Heavy metals	
Urtica dioica	Cr	Shoots, roots, leaves	Chromium	
Taraxacum officinale	Cd, Cu, Zn	Leaves		
Astragalus racemosus	Se	shoots, roots	Naturally Seleniferous soil	

Hussain *et al*. (2011) conducted an experiment on Heavy metal accumulation potential and medicinal property of *Bacopa monnieri*-a paradox. Bioaccumulation potential of *B. monnieri* is more towards Cd than Hg. Absorption and translocation of Hg (400µg) and Cd (224µg) are proportional to the availability of the metal in the growth media and period of growth. Effect of acidic pH showed enhanced accumulation while basic pH resulted in significant reduction in the accumulation of Hg and exorbitant reduction of Cd.

Rumana Ahmad and Neelam Misra *et al*. (2014) conducted an experiment on Evaluation of Phytoremediation Potential of *Catharanthus roseus* with Respect to Chromium Contamination. *C. roseus* was shown to absorb up to about 38% of the amount of Cr present in primary and

secondary sludge amended soil through roots and accumulate it to about 22% in leaves. Increased expressions of antioxidant enzyme peroxidase (POD) and detoxification enzyme glutathione-S-transferase (GST) were observed under stress conditions as compared to control.

Mini Mathew *et al*. (2015) studied the Effectiveness of vetiver System for the Treatment of waste water from an Institutional Kitchen. It is observed that the waste water treatment using VS has significant potential to reclaim the wastewater. The VS is able to remove 80 to 85% of BOD, 85 to 90% of COD and 85% of total Coliform. Most of the water quality parameters are within permissible limits as per IS 10550, 2012 and IS 2292, 1992.

Violina *et al*. (2015) conducted an experiment to study Potential of Lavender (*Lavandula vera* L.) for Phytoremediation of Soils Contaminated with Heavy Metals. Lavender is a plant which is tolerant to heavy metals and can be grown on contaminated soils, and which can be referred to the hyperaccumulators of lead and the accumulators of cadmium and zinc, and can be successfully used in the phytoremediation of heavy metal contaminated soils. Favorable is also the fact that heavy metals do not influence the development of the lavender, as well as on the quality and quantity of the essential oil.

Sharifah Nur Munirah Syed Hasan *et al*. (2017) evaluated the Performance of Vetiver Grass (*Vetiveria zizanioides*) for phytoremediation of contaminated water. Findings indicated that the removal of heavy metal was decreased in seven days of the experiment where iron shows the highest percentage (96%; 0.42 ppm) of removal due to iron is highly required for growth of vetiver grass. Removal rate of heavy metals in water by vetiver grass is ranked in the order of Fe>Zn>Pb>Mn>Cu. The accumulation of heavy metals in plant biomass was higher in vetiver shoot than in root due to metal translocation from root to the shoot.

VII. Advantages

- The cost of the phytoremediation is lower than that of traditional processes both *in situ and ex situ*.
- The plants can be easily monitored.
- The possibility of the recovery and re-use of valuable metals (by companies specializing in “phyto mining”).
- It is potentially the least harmful method because it uses naturally occurring organisms and preserves the environment in a more natural state.

VIII. Limitations

- Phytoremediation is limited to the surface area and depth occupied by the roots.
- Slow growth and low biomass require a long-term commitment.
- With plant-based systems of remediation, it is not possible to completely prevent the leaching of contaminants into the groundwater.
- The survival of the plants is affected by the toxicity of the contaminated land and the general condition of the soil.
- Bio-accumulation of contaminants, especially metals, into the plants which then pass into the food chain, from primary level consumers upwards and/or requires the safe disposal of the affected plant material.

IX. Future prospects

- Studies on phytoremediation using medicinal plants should be planned by researchers for carrying out more analysis for finding out the capability of these weeds, so as to remove the metallic component in industrial and municipal level waste waters.
- The possibility of using biotechnology to improve the efficiency of phytoremediation processes makes even better than any other existing methods.

X. Conclusion

- This technology can be applied “in situ” to remediate shallow soil, ground water and surface water bodies.
- Phytoremediation has been perceived to be a more environmentally-friendly “green” and low-tech alternative to more active and intrusive remedial methods.
- Phytoremediation is a new cleanup concept that involves the use of plants to clean or stabilize contaminated environments.
- The high cost of existing cleanup technologies led to the search for new cleanup strategies that have the potential to be low-cost, low-impact, visually benign, and environmentally sound.
- By phyto remediation, the physical structure and the biological properties of the soil are maintained and the fertility and biodiversity can be improved.

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Chapter - 6
A Review on the Traditional uses and Phytochemistry of Two Important Medicinal Plants of North East India

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Chapter - 6

A Review on the Traditional uses and Phytochemistry of Two Important Medicinal Plants of North East India

Punam Jyoti Borah

Abstract

The North Eastern region of India is known for its bioresources is comprised of half of the total biodiversity of the country and among them thousands of plants are of medicinal value. Ethnic communities have been using folk medicine based on plant parts according to their traditional knowledges from years ago. People from this region are utilizing herbs like *Centella asiatica* (L), *Paederia foetida* Linn., *Houttuynia cordata* Thunb., *Oxalis corniculata* Linn. etc. as their nutrient diet which are used in Indian medicinal system. The increasing demand of the herbal medicine throughout the world in modern days brings consequences of exposing the treasures to the globe as well as the conservation of the jewels from illogical collection. For the discovery and designing of novel drugs, the traditional medicinal plants that contain potent phytocompounds may have played the leading role if it will be prioritized.

Keywords: Phytochemistry, medicinal plants, *Mesua ferrea*, *Gnetum gnemon*

Introduction

There is a strong interrelationship between plants and humans and it traces to the survival of the primitive man through close association with nature which made the human race on earth acquire the knowledge through traditions of using plants and plant products [1, 2]. The indigenous communities from regions rich in biodiversity have developed the traditional knowledge systems of using more than three thousand medicinal plants [3, 4, 5]. The North East region of India constitutes eight states (Assam, Arunachal Pradesh, Mizoram, Manipur, Nagaland, Meghalaya, Tripura, Sikkim) is a heritage for biodiversity, cultures and traditional knowledges. Occupied by tropical, subtropical, temperate and alpine climatic conditions, this region is the heaven for growing diverse type of medicinal plants. Meghalaya hosts 850 medicinal plants, while Sikkim is rich with 420 plants used for primary to deadly health

care needs by the indigenous people of the states. A total of 900 therapeutic herbs exist abundantly in the hills and forests of Assam. Assamese people for various ailments like diabetes, cold and cough, dysentery, diarrhoea, jaundice, pneumonia, fever, malaria, piles etc. formulate plant materials of *Rauvolfia serpentina* (Benth) ex. Kurz.), *Piper longum* Linn, *Asparagus racemosus* Wild., *Terminalia arjuna* Wight & Arn., *Eclipta alba* (Linn.) Hassk., *Garcinia cowa* Roxb. Ex D.C., *Phlogacanthus thyrsiflorus* Nees., *Gnetum gnemon* Linn., *Coccinia grandis* (L.) J. Voigt, *Cissus quadrangularis* L. etc [6].

Ethnic tribes live in the remote areas of this regions are treasures for herbal remedies and they rely on those mostly for the socio-cultural preferences and somewhere for the lacking modern healthcare alternatives and effectiveness [6, 7].

Scientists are often attracted by the pleasant source of innumerable medicinal plants of the North East Indian region. A diverse group of phytochemicals i.e. the secondary metabolites like alkaloids, tannins, phenolic compounds, glycosides represent immense use in pharmaceutical industries [8]. Till date, countless numbers medicinal plants indigenous to this region have been explored and their phytoconstituents have been reported. A potent medicinal plant of Arunachal Pradesh, *Coptis teeta* has found to be a house of alkaloids like Berberine, Palmatine, Coptisine, Columbamine, Jatrorrhizine etc [9]. The aerial parts of *Gynura cusimbua* contains essential oil which constitutes myrcene, β-Phellandrene, eugenol [10]. The phytochemical studies on *Houttuynia cordata* have revealed the presence of Houttuynamide A, quercetin, catechin, procyanidin B etc. that possess various pharmacological activities [11].

Discussion

The plants utilized for therapeutics are not only the pleasant source of medicine but also as an agent of flavoring, dyeing and conservation of foods. The bioactive compounds accumulated in different parts of the plants offer various pharmacological properties such as antioxidant, antimicrobial, antiallergic, antibiotic, hypoglycaemic and anti-carcinogenic activity etc [12, 13]. A kind attempt has made through this article to focus the ethnic uses and phytochemical compounds of two important medicinal plants i.e. *Mesua ferrea* and *Gnetum gnemon* from available published literatures.

Mesua ferrea

***Traditional uses*:** Both in Ayurvedic and Unani system, this plant is used in several formulations as immunity booster and an ingredient in various kind of recipes like “Jawarish Shehryaran” “Hab Pachaluna” and “Halwa-isupari

pack" as tonic for healthy stomach and liver. In the review paper of Chahar *et al.* 2013 and Asif *et al.* 2017, listed the ethnomedicinal values of this plant all over the world [14, 15]. The plant parts are used in inflammation, gastritis, bronchitis, as antiseptic, purgative, blood purifier, carminative, expectorant, cardiotonic, diuretic, tonic and antipyretic agent for worm control, to treat fever, cold, asthma, bleeding piles, cardiovascular disorders, excessive thirst, headache, hiccup, itching, sweating, scabies, skin problems, small tumors and vomiting etc. Leaf and flower part have antivenom properties and traditionally used as antidotes for snake and scorpion bite. In the treatment of sore eyes ashes of leaves of this plant are used. Flowers of *M. ferrea* used for the treatment of dysentery and cough and also used as stomachic, expectorant and astringent [16]. Abortifient properties of this plant are also reported to use by the people of India [17]. Seeds of *M. ferrea* also have particular significant uses in household, they can be brunt like candles and may use as fuel. Seed oils are used as resins. The wood is also used for golf club heads whereas flowers and stamens are used for stuffing pillows for the bridles bed [14].

Table 1: Phytocompounds of M. ferrea

No.	Plant parts	Phytoconstituents
1	Root bark	Mesuaferrin A, Mesuaferrin B, Caloxanthone C, 1,8-Dihydro-3-methoxy-6-methylanthraquinone, β-Sitosterol, Friedelin, Betulinic acid [18]
2	Blossom	Mesuol, Mammea A/AB, Mammeisin, Mammea A/AA, Isomammeisin, Mammea A/BB, Mammea A/BA, Mammea A/AD cycloF, Mammea A/AB cycloF, Mammea A/AA cycloF, Mammea A/AD cycloD, Mesuagin, Mammea A/AB cycloD, Mammeigin, Mammea A/AA cycloD, Assamene, Surangin C [19]
3	Heartwood	Mesuaxanthone A, Mesuaxanthone B, Euxanthone [20]
4	Flowering bud	5,7-dihydroxy-8-(2-methylbutanoyl)-6-[3,7-dimethylocta-2,6-dienyl]-4-phenyl-2Hchromen-2-one, 5,7-dihydroxy-4-(1-hydroxypropyl)-8-(2-methylbutanoyl)-6-[3,7-dimethylocta-2,6-dienyl]-2H-chromen-2-one, 5-hydroxy-8,8-dimethyl-6-(2-methylbutanoyl)-4-phen yl-2H-pyrano[2,3-h]chromen-2-one, 5,7-dihydroxy-6-(2-methylbutanoyl)-8-(3-methylbut-2- enyl)-4-phenyl-2H-chromen-2-one, 5,7-dihydroxy-8-(2-methylbutanoyl)-6-(3-methylbut-2-en yl)-4-phenyl-2H-chromen-2-one, 5,7-dihydroxy-6-(2-methylbutanoyl)-4-phenyl-2H-chromen -2-one, 8,9-Dihydro-5-hydroxy-8-(2-hydroxypropan-2-yl)-6-(2-methylbutanoyl)-4-phenyl furo[2,3-h]chromen-2-one [21]
5	Seed	Mesuol [22]
6	Root bark	Mesuaferrin A, Mesuaferrin C, Caloxanthone C, Macluraxanthone, Mesuaferrin B, 1,5-Dihydroxyxanthone, Tovopyrifolin C [23]
7	Seed	Mesuagin, Mammeigin, Mammeisin, 4-Phenyl-5′7-dihydroxy-6-isovaleryl Coumarin, Mesuol [24]

8	Stamen	α-amyrin, β-amyrin, β-sitosterol, mesuanic acid, Mesuaferrone-B, Mesuaferrone-A [25]
9	Wood	1,5-dihydroxy-3-methoxyxanthone, 1,5-dihydroxyxanthone, Euxanthone, euxanthone-7-methyl ether, β-sitosterol [26]
10	Bark	Ferruol A, Ferruol B, Mammea B/BB, mammea C/BB [27]
11	Stamen	Mesuaferrone-A, Mesuaferrone-B, Mesuaferrol, Mesuanic acid, α and β-amyrin [14]
12	Leaves	(Z)3-Hexanol, Linalool, Edulan I, α-Cubebene, α –Ylangene, α-Copaene, β-Bourbonene, β-Elemene, (cis)-Caryophyllene, (trans)-Caryophyllene, (+) Aromadendrene, α-Humulene, (-) Alloaromadendrene, γ-Muurolene, Germacrene D, β –Selinene, Valencene, α-Selinene, α-Muurolene, β-Bisabolene, γ-Cadinene, δ-Cadinene, (cis)-Calamenene, α-Calacorene, Caryophyllenyl alcohol, β-Caryophyllene oxide, T-muurolol, Hexahydrofarnesyl acetone, n-Hexadecanoic acid, Phytol, 4,8,12,16-Tetramethyl heptadecan-4-olide, Hexanedioic acid, bis (2ethylhexyl) ester, Heptacosane, Squalene, Nonacosane, Sesquiterpene, Diterpene and triterpenes, Carboxylic acids [28]
13	Seed	Myristic acid, Palmitic acid, Linoleic acid, Oleic acid, Stearic acid, Arachidic acid [29]
14	Bark, Leaves, Flower, Bud	(E)-α-bisabolene, α-selinene, α-copaene, β-caryophyllene, Germacrene D [30]
15	Seed	Stearic acid, Palmitic acid, Linoleic acid, Oleic acid [31]
16	Stem Bark	Betulinic acid, Pyranojacareubin, Mesuabixanthone-A, Mesuabixanthone-B, 1,6-Dihydroxyxanthone, (-)-Epicatechin [32]
17	Heartwood	1,3-Dimethoxy-5,6-dihydroxyxanthone, 1,3,5,6-Tetramethoxyxanthone, 1,3,6-Trimethoxy-5-hydroxyxanthone, 1,3-Dimethoxy-5,6-diacetoxyxanthone [33]
18	Timber	β-sitosterol, 2-hydroxyxanthone, 2-methoxyxanthone, 4-hydroxyxanthone, 1,5-dihydroxyxanthone, 1,7-dihydroxyxanthone, 1-hydroxy-5-methoxyxanthone, 1-hydroxy-7-methoxyxanthone, 3-hydroxy-4-methoxyxanthone, and 1,5,6-trihydroxyxanthone, 1,3,6-trihydroxy-7,8-dimethoxyxanthone, 3,6-dihydroxy-1,7,8-trimethoxyxanthone [34]
19	Bark	Mesuferrols A, Mesuferrols B, 1,7-dihydroxy- and 5-hydroxy-1-methoxyxanthone, (-)-epicatechin [35]
20	Stem Bark	Friedelin, 3β-friedelanol, Lupeol, 3-Oxo-betulin, Spinasterol [36]
21	Root Bark	mesuaferrin C, macluraxanthone, caloxanthone C, β-sitosterol, Friedelin, Betulinic acid [37]
22		Coumaric acid, Ellagic acid, Gallic acid, Kaempferol, Myricetin, Rutin, Quercetin, Vanillic acid [38]
23	Flowers	Kaempferol-3-O-rhamnoside, Quercitrin, Quercetin, Rhusflavanone, Mesuaferrone B, 5,6,6'-trihydroxy [1.1'-biphenyl]-3,3'-dicarboxylic acid, 3-amino-4-hydroxybenzoic acid, Procatechuic acid, Gallic acid, Procatechuic acid ethyl ester [39]

24		Mesuol [40]
25	Seed	Mesuagin, Mammeigin [41]
26		Mesuol [42]
27	Seed	Mesuol, Mammeisin, Mesuagin, 4-Phenyl-5 ‘7-dihydroxy-6-isovaleryl Coumarin, Mammeigin [43]
28	Stem bark	Friedelin, Stigmasterol [44]
29	Stamen	Gallic acid [45]
30	Leaves	12,13-Furano-8-hydroxynapthyl-6-0-b2′,3′,4′,6′-tetrahydroxy-5′5′dimethyl cyclohexyl ether [46]
31	Stem bark	α-amyrin, Globulol, Phthalic acid, mono-2-ethylhexyl ester, n-hexadecanoic acid, (-)-aromadendrene, (+)-aromadendrene, (-)-aristolone, 2,4-di-tert-butylphenol, Epiglobulol [47]
32	Petal, Flower	alpha-copaene, trans-alpha-bergamotene, benzoate geranyle-1, dioctyl Phtalate, dicotyl terephthalate, beta-caryophyllene, trans-betafarnesene, alpha-bisabolene, β-selinene [48]
33	Stamen	β-amyrin, β-sitosterol, Mesuaferrol [49]
34	Fruit	4-phenyl coumarins, Mesuol, Mesuone, Mesuarin, Mesuein [50]
35		Isoledene [51]
36	Stamens	Rhusflavanone, mesuaferrone B, Lupeol, Benzyl-b-D-glucopyranoside, Protocatechuic acid, Protocatechuic acid methyl ester, p-Hydroxybenzoic acid, Apigenin 8-C-glucoside, Quercetin 3-O-rhamnoside, Kaempferol 3-O-rhamnoside, Kaempferol 3-O-glucoside, Luteolin 8-C-glucoside [52]
37	Flower	Mesuaferroic acid H, Mesuaferroic acid I, Mesuaferroic acid J, Mesuaferroic acid K, Mesuaferroic acid L, Mesuaferroic acid C, Laxifloranone [53]
38	Flower	Ferroxanthone [54]
39	Flower bud	Mesuaferols D, Mesuaferols E, Mesuaferols F, iso-Mesuaferol F [55]
40	Flower	Friedelin, Stigmasterol, Germacrene D [56]
41	Leaves	12- 13-furano-8-hydroxy napthyl-6-O-β-2'-3', 4'-6' tetrahydroxy 5'-5'-dimethylcyclohexyl ether [57]
42	Flower bud	Cinnamaldehyde, Eugenol, Caryophyllene, 2-Methoxycinnamaldehyde, n-Hexadecanoic acid, 2H-1-Benzopyran, Terpinyl acetate [58]
43	Flower Bud	Mesuaferol G, Mesuaferol H, Mesuaferol I, Mesuaferol J, Mesuaferol K, Surangin D, Surangin C, Theraphin C, Theraphin B [59]
46	Bark	Mesuaferroic acid A, Mesuaferroic acid B, Mesuaferroic acid C, Mesuaferroic acid E, Mesuaferroic acid F [60]
47	Seeds	Palmitic acid, Linoleic acid, Oleic acid, Stearic acid, Arachidic acid [61]
48	Bark	Mesuaferrin-A [62]

49	Stem bark, Flower	Betulinic acid and 1,8-dihydroxy-3-methoxy-6-methyl-anthraquinone, Stigmasterol, Sitosterol, Lup-20(29)-en-3β-ol [63]
50	Seed	Oleic acid, Linoleic acid, Stearic acid, Palmitic acid, Myristic acid, Arachidic acid [64]

Gnetum gnemon

Traditional uses: Various parts of this plant are consumed by people and is being a promising wild edible plant. Young leaves, inflorescences and tender tips, shoot as vegetables and ripe fruits eaten as raw [65, 66, 67]. Leaves of this plant are extremely popular among the tribal populations of North East India. The tribal people of Manipur, Nagaland and Karbi Anglang districts of Assam consider the vegetable as usual part of diet as food stuff for curry, soup and spice. The Mizo people of Mizoram consume boiled leaves of this plant while the people of Indonesia use the seeds to make Pakodas [68, 69]. Integral uses of this plant reported from the Karbi tribe of Assam, India. They consume leaves and roasted seeds in their traditional cuisines [70, 71, 72]. Hanthu (*G. gnemon*) has a long association with the culture and tradition of the Karbi people. There was a myth that the Hanthu was used for preparation of the first cuisine (popularly known as Kangmoi) by the Karbis. They also offered the plant to local deities, particularly in Chojun ritual where the leaves of the plant used to make a sacred dish called Hanmi Hanmoi [73]. The surprising ethnomedicinal value of this plant reported using in the treatments of arthritis, bronchitis and asthma. For irregular menstrual cycle boiled leaves of *G. gnemon* are taken as medicine [70, 71]. Leaf saps are used in cure of eye disorder [66].

Seeds have significant value in the home industry used by people in Java. The seeds are being heated and the hot kernel is pounded into a flat cake which are dried under the sun, graded and packed for sale. A kind of snack is prepared by soaking up the cakes in boiling water. Phangchopi *et al.* in 2014 reported the ritual uses of seeds and leaves and mentioned cash generating value of this plant [74]. *G. gnemon* can be considered as soft timber plant as its wood, bark fibers are used in making boxes, tool handles, rope making, fishing net and paper products. The famous Sumba bow string is prepared by using inner bark of this plant.

Some other ecological significant values were also reported for this plant. Manner and Elevitch 2006 and Barua *et al.* 2015, in their research paper stated the beneficial association of mycorrhizae with this plant that makes the soil rich in mineral nutrients like phosphorus and other micro nutrients required for plant growth and development [66, 71].

Table 1: Phytocompounds of *G. gnemon*

No	Parts used	Phytoconstituents
1	Seed	Gnemonoside A, Gnemonoside D, Gnetin C, Resveratrol, Gnemonoside C, Gnetin L [75]
2	Root	Gnemonol K, Gnemonol L, Gnemonol M, Gnemonoside K [76]
3	Fruit	Resveratrol, Isorhapontigenin, Gnemonoside D, Gnetins C, Gnetins E, Gnemonoside L, Gnemonoside M [77]
4	Seed	Gnemonoside C, Gnemonoside D, trans-resveratrol [78]
5	Root	Gnetoflavanols A, Gnetoflavanols B, Gnetoflavanols C, Gnetoflavanols D, Gnetoflavanols E, Gnetoflavanols F [79]
6	Seed	Gnetin C, Gnemonosides A, Gnemonosides C, Gnemonosides D, trans-resveratrol [80]
7	Leaves, seed	α-tocopherol, β-tocopherol, δ-tocopherol, γ-tocopherol [81]
8	Leaves, seed	Cyclopropane fatty acids [82]
9	Seed	Gnetin C, Gnemonoside A, Gnemonoside D, Resveratrol, Gnetin L, Gnemonoside C [83]
10	Root	Gnemonol D, Gnemonol E, Gnemonol F [84]

Conclusion

The Northeastern part of India consist of rich varieties of medicinal plants though many of those plants and their uses are known only to the ethnic tribes. The pharmaceutical formulations of these medicinal plants in different diseases are gaining utmost importance now a days as for the increasing demand of herbal medicine all over the world. Discoveries of new drugs derived of these plants may clear the route of alternative medicines against the allopathic medicines. Protection from nonscientific collection from nature and conservation of these medicinal plants and the traditional knowledges is a serious matter not only for conservation of mother nature as well as for the sociocultural upliftment of the traditional societies.

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