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Preface

The purpose of distributing this book to undergraduate, graduate, and research scholars is to give them authentic and understandable information on Indian medicinal herbs. Herbal medicine has a long history in India. With more than 45,000 plants, India is one of the 12 mega diversity hubs. 800 plants have been utilised in traditional medicine, while around 1500 plants having therapeutic benefits are referenced in ancient books.

Rural people are quite knowledgeable about various plant-based remedies. Because nature is a part of who we are as humans, we are a part of nature. Therefore, rather than using nature for profit, it is founded on the idea of relationships. More than 80% of the world's population still receives health care from traditional medicine, particularly in underdeveloped nations. Living instances of medication discovery from the past and present are abundant, treating everything from simple illnesses to cancer, diabetes, hypertension, and asthma.

In light of this, the considerable research done in this area by experts has greatly expanded our understanding of Indian medicinal plants and sustainable development. The goal of the book is to present the potential of traditional medicine and medicinal plants in general as a powerful source of new medications, currently accounting for about 90% of all recently discovered pharmaceutical products, as well as their importance, strategies, and initiatives that can be used to solve problems.

The chapters cover many facets of medicinal plants and how they relate to conventional medicine. As a result, a concise and thorough summary has been created in light of recent work and the most recent information accessible from various sources.

The author would like to express her gratitude to her colleagues at various institutions and universities around the nation who have provided excellent advice that has greatly aided in preparing for this endeavour. I sincerely thank every one of the authors who contributed to this book. This publication would not be feasible without their help.

Comments on how to make the book better are not just welcome but greatly valued.

Mrs. Bhanumati Sarkar

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Anticancer and antidiabetic potential of phytochemicals derived from *Catharanthus roseus*: a key emphasis to vinca alkaloids

Aloke Saha, Susmita Moitra and Tanmay Sanyal*

Keywords: Diabetes, Cancer, Phytomedicine, *Catharanthus roseus*, Ethnobotany.

Abstract:

Catharanthus roseus is a widely used medicinal herb in several regions of the world. It has already gained popularity because of the discovery of numerous phytoconstituents with diverse biological properties like anti-oxidant, antimicrobial, antifungal, hypoglycaemic, and anticancer properties. Cancer treatments involve surgical intervention, chemotherapy, radiotherapy, as well as pharmacotherapy, among other things, that not just have a significant financial impact on the patients. Still, it also leads to chronic drug resistance in patients over time. Plant-based drugs have emerged as effective precautionary chemotherapies in both developing and advanced nations. Surprisingly, the plant-derived anticancer agent vinblastine as well as vincristine were the first phytoconstituents to be utilised for drug development. In vitro suppression of human breast cancer cell lines was successfully demonstrated by new isolated biologically active compounds from this plant, such as catharoseumine, 17-deacetoxy-cyclovinblastine etc. Furthermore, vindoline, vindolicine, vindolinine and vindolidine extracted from *Catharanthus roseus* plant displayed anti-diabetic or anti-hyperglycaemic activity in vitro. Such findings strongly suggest how this plant has become a viable source of biologically active compounds and needs to be analysed further. This article highlights the function and sources of bioactive compounds derived from *Catharanthus roseus*, as well as the traditional uses and characteristics of phytoconstituents of this plant. Furthermore, the potential advantages of bioactive components found in *Catharanthus roseus* were reviewed in order to promote their potential as therapeutics.

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Introduction:

India obtains a priceless herbal heritage (Bhattacharjee, 2021; Sarkar et al., 2016; Sarkar, 2017). In India, the traditional medical system continues to be crucial to the country's overall healthcare system, along with homoeopathy and folk medicine (Sanyal et al., 2018; Kundu, 2022). Since the beginning of time, humans have used medicinal plants as necessary ingredients in foods, drinks, and treatments. The nutritional, pharmacological, biological, and toxicological properties of medicinal plants have extensive industrial applications (Erfani, 2021; Kar et al., 2022).

Diabetes and cancer are two diseases that are diversified, multi-factorial, serious, and chronic. Due to their recurrence, reciprocal influence, sometimes minor ones, can have a massive effect (Onitilo et al., 2012). Diabetes mellitus is a serious and rising health issue throughout the world. It is associated with significant acute and persistent health problems that have a detrimental effect on the lifestyle quality and the survival of those who have it. Diabetes affects 537 million individuals worldwide, which is expected to rise to 783 million in the next twenty years. It is a chronic metabolic disorder that develops when the pancreatic beta cells stop producing sufficient insulin or when cells continue to fail to use the insulin produced effectively. Several genetic, environmental, and other variables also contribute to it (WHO, 2022). It is categorized mainly into two types such as T1DM & T2DM.

Over the next twenty years, the global cancer burden is predicted to rise at a rate of 22 million cases per year, requiring rapid advances in chemo-, targeted-, and immune-therapy investigations to encounter this increasing epidemic head-on (Thun et al., 2009). Cancer is currently the world's second most common cause of death, and several research works over the last decade have concentrated on finding therapeutic approaches to decrease the side consequences of existing treatments (Wang et al., 2019). Cancer is a broad term for a group of disorders characterised by the unregulated proliferation of malignant cells with the capability to invade and destroy normal human tissue. It has the potential to spread all throughout the body (Mathur et al., 2015). Genetic alterations inside cells trigger cancer. Within a cell, DNA is organized into many specific genes, each of which consists a set of commands informing the cell what activities to perform and how it should grow and split. Mistakes in the commands could really lead the cell to cease to function normally and even end up causing it to develop into cancer cells. Tumours become extremely heterogeneous as they advance, resulting in a mixed group of cells with specific biochemical characteristics and widely different responsiveness to therapies. Notwithstanding, studies have discovered that cancer treatment is far more complicated than previously thought, with a confounded system of biochemical abnormalities and a rigorous tumour microenvironment (TME) making a contribution to the issue (Hassanpour & Dehghani, 2017). Most cancer therapeutic strategies currently rely on a specific target and genotoxic agents explored using one gene, one target, and one disease strategy. Whereas this framework has contributed to many developments in cancer pharmacognosy, specific target drug discovery, and a greater understanding of cancer pathogenesis and progression, it has significant attrition rates as well as slow clinical translation, denoting that it is unsatisfactory to meet the increasing requirements for cancer therapies and prevention (Pucci et al., 2019). Recent reports and studies indicate that traditional phytomedicines or their separated bioactive constituents are increasingly being used as adjuvants or supplementary chemotherapeutics agents in cancer sufferers to ameliorate disease manifestations or promote healthy lifestyles (Yin et al., 2013). Whilst also circumstantial evidence is used to support years of ethnobotanical use of phytomedicines, evidence-based information obtained from omics technology platforms, such as genomics, proteomics, and metabolomics, assists scientists and clinicians in evaluating the worth of biochemical pharmacodynamic systems targeted by bioactive substances or pharmacological medicinal herbs that might be advantageous in treating cancer (Choudhari et al., 2020). Furthermore, these methods ensure quality and assess systemic side effects such as carcinogenicity and safety.

Epidemiological research shows that individuals with diabetes have an elevated incidence of many kinds of cancers (such as pancreatic, hepatic, ovarian, colorectal and urogenital). Morbidity is also slightly higher. As a result, if hyperglycaemia is linked to even a minor increase in the chance of cancer, the population-wide implications could be significant (Onitilo et al., 2012). Numerous general and site-specific predisposing variables start making appropriately analysing the chance of developing cancer in diabetic individuals challenging. Diabetes timeframe, widely different levels of glycaemic control, types of drugs used for treatment, and long-term side effects are among these variables (Shahid et al., 2021). Hyperinsulinemia most probably promotes cancer in individuals with diabetes because insulin is indeed a growth factor both with metabolic as well as oncogenic impacts, and thus its activity in tumour tissues is aided by processes that act both at the receptor as well as post-receptor levels. Overweight, hyperglycaemia, and enhanced reactive oxygen species may all play a role in diabetes-related cancer incidence (Wang et al., 2020). Whereas anti-hyperglycaemic pharmaceuticals have a slight effect on cancer threat, chemotherapeutic pharmaceuticals might very well lead to diabetes or aggravate pre-existing metabolic syndrome (Gristina et al., 2014). Aside from the well-studied hyperglycaemic effects of steroid hormones and anti-androgens, an overwhelming amount of directed anti-cancer compounds may interact with glucose homeostasis by intervening at differing stages on the signalling substances shared by IGF-I and insulin receptors (Novosyadlyy & LeRoith, 2012). As a result, diabetes mellitus and cancer have a complicated relationship that necessitates too much immediate medical attention and effective studies.

Natural resources, such as medicinal herbs, that consist of a wide range of phyto-constituents appealing as traditional medication to cure prolonged and potentially life-threatening diseases, are thought to really be safer and more efficient than chemically synthesized agents (Ekor, 2014). Among some of the various medicinal herbs discovered, *Catharanthus roseus* has indeed been extensively utilized in different regions throughout the globe for treating different diseases (Kumar et al., 2022).

Vinca alkaloids are a form of organic compound which are frequently extracted from different plants. Even though the term suggests alkali, a few do not have alkaline characteristics. Several more alkaloids that really are toxic also have pharmacological effects that render them helpful as medications. The vinca alkaloids are the ancient group of plant-derived metabolites used to fight testicular and breast and lung cancers. The *Catharanthus roseus* plant yields vinca alkaloids. These vinca alkaloids may be naturally occurring or semi-synthetic also (Moudi et al., 2013). Too many factual studies have shown that specific phyto-constituents derived from this plant may well have therapeutic effects. Pharmacological uses of this kind of plant necessitate the assessment of these substances for antidiabetic activity, which would be minor in comparison to their cytotoxic characteristics. They are being used to treat diabetes, hypertension, and also being used as antibacterial agents (Al-Shaqha et al., 2015). Nonetheless, the vinca alkaloids are critical cancer fighters. Four main pharmacologically active vinca alkaloids are vinblastine, vincristine, vindesine and vinorelbine (Dhyani et al., 2022).

This review focuses on various antidiabetic and anti-cancer alkaloid bioactive compounds, including vincristine, vindesine, vinorelbine and vinblastine within diverse aspects of existing knowledge on all these compounds, including such their clinical applications (modern/traditional), method of antineoplastic activity, and prospective scale-up biopharmaceutical research on in-vitro experiments. This review will be a useful factor contributing to the growth of plant-based anticancer agents containing various secondary metabolites.

Taxonomic description & Traditional Uses of *Catharanthus roseus*:

Catharanthus roseus belongs to the Order: Gentianales, Family: Apocynaceae and Genus: *Catharanthus*. It is currently being grown in several countries and has become a popular decorative, easy-to-grow, and spreading evergreen herb. *C. roseus* grows to be 0.5-1.0 m in height, with young pubescent branches (Marles & Farnsworth, 1995). It has oval or oblong leaves that are membranous, greenish, glossy, hairless, obtuse, narrow petioles about 1-1.8 cm, and are organised in opposing pairs. The inflorescence is axillary, and the colour of flowers range from whitish to dark pink according to variety. The corolla tube is about 2-5 cm in diameter, pubescent above, and hairy beneath the stamens, however the calyx is small. The ovary is long and has pentagonal stigmata. It has two follicles and fruits (Mishra & Verma, 2017; Swanston-Flatt et al., 1989).

This herb is used as an ethnomedicine throughout many countries around the world. In North-east India, Australia, England, Philippines, Europe, and Taiwan, the dried plant parts are boiled in water and extract are taken as a drink to alleviate hyperglycaemia (Holdsworth, 1990; Khan, 2010). Vietnamese people use the extract of plant parts or entire plants as an alternative and complementary medicine for different kinds of cancer, including mouth, abdomen, and gastrointestinal cancers (Ochwang'I et al., 2014). Powder of the entire plant is mixed with regular milk in the Kancheepuram District of Tamilnadu, India, and taken as a drink to control hyperglycaemia (Muthu et al., 2006). Dehydrated root is crushed and mixed with water for treatment of urinogenital infections in South Africa, and abdominal swelling in Zimbabwe (Fernandes et al., 2008; Semenya & Potgieter, 2013; Chigora et al., 2007).

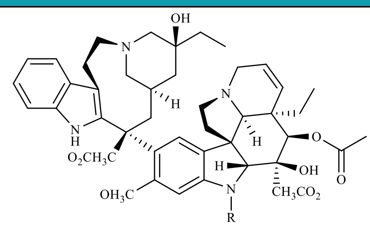
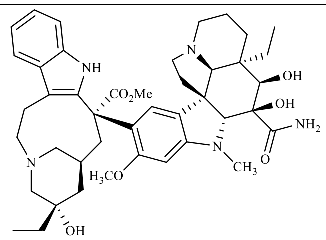
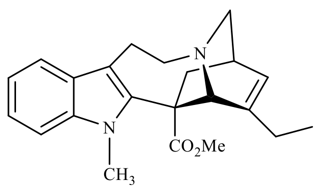
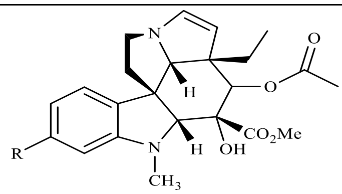
Table 1. Traditional utilization of *Catharanthus roseus* throughout the world.

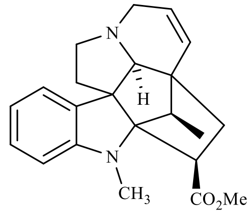
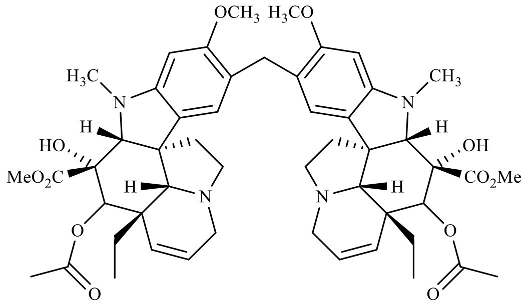
Plant Components	Preparation	Diseases	Country	Ref.
Whole plant	Soaked and steamed in water	Diabetes, Hypertension, Dysentry	Vietnam	Pham et al., 2020
		Diabetes Mellitus (DM)	Pakistan	Nisar et al., 2016
		Cancer	India	Kumar et al., 2022
		Throat, stomach, oesophageal cancer	Kenya	Vo, 2012
	Dried, soaked and steamed in water	DM	England	Kumar et al., 2022
	Dried, ground into a fine powder and diluted in regular cow milk	DM	Tamilnadu, India	Muthu et al., 2006
	Dried and prepared an extract by decoction	DM	Taiwan	Hsu & Cheng, 1992
Leaf	Dried and prepared an extract by decoction	DM	Northern European countries	Swanston-Flatt et al., 1989
	Soaked and steamed in water	DM, Menorrhagia	Australia	Webb, 1948
Roots	Crushed and added with water	Stomach pain	Zimbabwe	Chigora et al., 2007
	Dried and crushed	Urogenital infection	South Africa	Pham et al., 2020
	Boiled in water	Gonorrhoea	South Africa	Semenya & Potgieter, 2013
Upper part	Boiled in water	Menstrual regulation	China	Virmani et al., 1978
Stem	Boiled in water	DM	North America	Aslam et al., 2010

Some major bioactive compounds obtained from Catharanthus roseus:

Catharanthus roseus contains a variety of metabolites (nitrogen-containing organic substances apart from amino acid residues, peptides, pyrimidines and derivative products, and antimicrobials). Based on their chemical structure, alkaloids are categorised as either heterocyclic or non-heterocyclic. Heterocyclic alkaloids have a nitrogen atom inside the ring structure, and based on their size, they are classified as pyridine, quinoline, piperidine, pyrrole, pyrrolizidine, isoquinoline, or indole alkaloids. Non-heterocyclic alkaloids are less prevalent in nature. Such molecules contain a nitrogen atom that does not belong to any ring structure, unlike colchicine (Wansi et al., 2013). This plant contains a numerous pharmacological bioactive compounds that contribute significantly to the ethnomedicinal sector; even so, the quantities observed there in the plant seem to be frequently lesser. It is worth noting that both biotic and abiotic variables influence the metabolic pathways of phytoconstituents. Due to plant's protective role, environmental constraints have indeed been discovered to enhance the yield of biologically active compounds, including alkaloids. As a result, more experiments are being initiated to increase the quantities of these substances by altering environmental factors such as illumination, alkalinity, soil composition and microelements, drought, and metal stress (Pham et al., 2020).

Table 2. Some important bioactive compounds derived from *Catharanthus roseus*.

Bioactive Compound	Plant Part	Chemical Structure	Ref
Vincristine	Leaf, Stem, Root	 Vincristine: R = CHO Vinblastine: R = CH_3	Alam et al., 2017
Vinblastine	Leaf, Stem, Root		
Vindesine	Leaf, Stem, Root		Arora et al., 2010
Catharanthine	Leaf		Jair Barrales-Cureño et al., 2019
Vindolidine	Leaf	 Vindolidine: R = H Vindoline: R = OCH_3	Jair Barrales-Cureño et al., 2019
Vindoline	Leaf, Stem, Root		

Vindolinine	Leaf		Eng et al., 2022
Vindolicine	Leaf		Jair Barrales-Cureño et al., 2019

Mode of synthesis of Terpenoid Indole Alkaloids (TIA) in Madagascar Periwinkle: *Catharanthus roseus*:

Alkaloids are types of naturally occurring plant-derived products containing nitrogen. Amongst various terpenoids, Terpenoid indole alkaloids are the major ones with nearly 3000 diversities. *Catharanthus roseus* which belongs to Apocynaceae family, is a widely studied plant from which more than 130 alkaloids are found and characterized (Heijden et al., 2004). *Catharanthus roseus* became the potential model system to study the biosynthesis of TIA which include more than 50 complicated biosynthetic pathway involving various kinds of genes, enzymes, transcription factors etc. (Zhao et al., 2013). These TIAs have strong pharmacological activities and are considered to treat various diseases (Heijden et al., 2004). The principal vinca alkaloids found in *Catharanthus roseus* are vincristine, anhydrovinblastine, vinblastine, vinorelbine, ajmalicine, vindolicine, vindolinine etc. Among all these, the vinblastine and vincristine are the most potent naturally derived anti cancerous drug and ajmalicine and serpentine are the naturally synthesized strong antihypertensive drug and the two are very much useful in treating various cardiac diseases (Jair Barrales-Cureño et al., 2019).

Three steps involved in achieving the synthesis of bisindole alkaloids are – **1)** Very first step involved in the biosynthetic pathway includes the genesis of tryptamine from L-tryptophane amino acid, which was catalysed by tryptophan decarboxylase (TDC) enzyme in the shikimate pathway and formation of secologanin, last product of the iridoid biosynthesis in the terpenoid pathway catalysed by Strictosidine synthase (STR) enzyme. **2)** Formation of strictosidine, the precursor of all monomeric alkaloids, by tryptamine and secologanin pairing takes place under catalysis of the enzyme STR. **3)** Metabolism of strictosidine takes place through various enzymes including D4H and DAT with the formation of two monomeric alkaloid vindoline along with catharanthine, two monoterpene precursors of vinblastine and vincristine (Goddijn et al., 1995; Yu et al., 2015; De Luca et al., 1988).

Shikimate Pathway of TIA:

Initiation of the TIA's shikimate pathway involves the production of anthranilate from chorismite by the activity of the enzyme anthranilate synthase (AS). Then the anthranilate is converted to tryptophan, which is turned into tryptamine with the enzyme tryptophan decarboxylase (TDC) (Li & Last, 1996; Noé et al., 1984).

Mevalonate (MVA) Pathway and Methyl Erythritol Phosphate (MEP) Pathway:

The MVA and MEP pathway leads to the formation of Isopentenyl pyrophosphate. The MVA pathway involves the production of triterpenes and sesquiterpenes. At the beginning, under the catalysis of hydroxymethyglutaryl synthase (HMGS) one molecule of acetyl-coA binds with one molecule of acetoacyl-coA to form 3-hydroxy-3-methyglutaryl-coA (HMG-coA). Then mevalonate is formed by the effort of the enzyme HMG-coA reductase (HMGR). Thereafter, mevalonate is phosphorylated to form mevalonate 5-diphosphate (MVAPP)by mevalonate kinase followed by the synthesis of isopentenyl pyrophosphate (IPP) by the function of the enzyme mevalonate 5-diphosphate decarboxylase. Then IPP is converted into dimethylallyl diphosphate(DMAPP) by the catalysis of the enzyme IPP isomerase(IDI) (Lange & Croteau, 1999).

Formation of geranyl diphosphate (GPP), the predecessor of secologanin, has occurred in the iridoid pathway by the fusion of DMAPP and IPP under the catalysis of geranyl diphosphate synthase. The iridoid pathway comprises nine steps by which geraniol is constructed via conversion of GPP by an enzyme geraniol synthase. At last secologanin is formed through the modification of geraniol to 10-hydrxygenaniol, iridodial, 7-deoxylaganic acid, loganic acid, loganin (Collu et al., 2001; Geu-Flores et al., 2012; Asada et al., 2013).

Formation of Strictosidine:

Synthesis of Strictosidine occurs via the conjugation of tryptamine and iridoid glycoside secologanin under the activity of the enzyme strictosidine synthase (STR). It is a predecessor in the TIA biosynthesis pathway (Treimer & Zenk, 1979).

Formation of Catharanthine and Vindoline:

Strictosidine-β-D-glucosidase (SGD) plays a major role in converting strictosidine into a highly reactive 4,21-dehydrogeissoschizine by removing a glucose moiety from strictosidine. This step is followed by the formation of cathenamine by cathenamine synthase and then cathenamine to tabersonine to vindoline. Many enzymes play crucial role in the formation of vindoline from taberosine, includes- tabersonine16- hydroxylase (T16H), N-methyltransferase (NMT), O-methyl transferase (OMT), deacetylvindoline-4-O-acetyltransferase (DAT) and deacetoxyvindoline-4-hydroxylase (D4H) by various modifications like – hydroxylation of aromatic residues, hydration of 2,3-double bonds, O-methylation, 4-O-acetylation, N(1)-methylation (El-Sayed & Verpoorte, 2007).

There is very limited information regarding catharanthine biosynthesis. Somehow catharanthine is synthesized by 4,21-dehydrogeissoschizine (El-Sayed & Verpoorte, 2007).

Construction of Vinblastine and Vincristine in the TIA biosynthesis pathway:

Synthesis of two naturally synthesized anticancer drug vinblastine and vincristine, is essential and possesses great importance. The pairing of vindoline and catharanthine forms these two. At first, α-3′-4′-anhydrovinblastine is formed thereafter, it is turned to vinblastine and then to vincristine by the activity of the enzyme anhydrovinblastine synthase (AVLBS) (Costa et al., 2007).

Anticancer Activity of Vinca Alkaloids:

Catharanthus roseus is regarded as an ornamental as well as the most medically important plant throughout the world. This plant contains near about 130 various types of Terpenoid indole alkaloids (TIA), which have potential pharmacological significance. These alkaloids have been used for years after years against various diseases like cancer, diabetes, heart related problems etc. Vinblastine and Vincristine, two dimeric alkaloids, are famous for their anticancer properties and they are the first naturally synthesized anticancer drugs. Some semi-synthetic drugs like vinorelbine, vinflunine also contain antitumor properties (Noble, 1990). These TIAs are now used progressively in medicine and serve as immunosuppressive or antitumor agents. All these vinca alkaloids can be employed singly or in association with other natural substances or synthetic medication. After administering intravenously, these alkaloids are readily metabolized by the liver and excreted quickly (Bennouna et al., 2006; Almagro et al., 2015).

Vinblastine (VLB):

The official name of vinblastine is vincaleukoblastine. It is a sulphur derivative and mostly a colourless crystalline compound produced from the shoot of the plant. The construction of vinblastine can be established by X-ray crystallography. This dimeric alkaloid is soluble in water as well as in methanol. Plants produce more amount of vinblastine than vincristine. Sometimes vinblastine can be converted to vincristine chemicallyor by using microbes. Vindoline occupies fifty percent constituents of vinblastine. Vinblastine serves as a panacea for various kinds of cancer like- non-small cell lung cancer, cancer of head and neck, testicular cancer, Hodgkin’s lymphoma, and breast cancer (Silvestri, 2013).

Mode of Action:

Vinblastine is widely regarded as the first naturally synthesized anticancer drug worldwide. It was first discovered in Madagascar periwinkle plant and its’ utility came into force when it was crushed into tea, leading to a decrease in the amount of white blood cells. Since it was postulated that vinblastine bears anticancer properties in opposition to white blood cells. Vinblastine is an antimitotic agent and it prevents cell cycle by binding with tubulin protein leading to the disassembly of the microtubules at the cell cycle M-phase. It also evokes programmed cell death by changing dynamics of the microtubules, components of cytoskeleton. The microtubules are the mitotic spindles' core components, which induces separation of chromosomes and properly maintains cellular structure during meiosis and mitosis. Microtubules are constructed with α-tubulin and β-tubulin by creating polymerisation and depolymerisation dynamics at their terminal. This assembly and disassembly are regarded as "treadmilling" and "dynamic instability" sequentially. Interruption in the dynamics of these microtubules leads to halt of the cell cycle and induces apoptosis that is programmed cell death. This phenomenon is used in tumour cells to arrest them during the mitosis phase when these vinca alkaloids bind at the surface between tubulin heterodimers and GTP- binding sites (Wilson et al., 1999). Vinblastine binds slowly or rapidly to the two existing alkaloid binding sites of each tubulin dimer. Binding of vinblastine prevents the assembly of microtubules leading to stop the process of metaphase. Vinblastine do not interfere the action of any drugs that alkylate DNA. Recent study displays that these alkaloids can also bind with calmodulin and many microtubules associated protein and inhibit the metabolism of amino acids (Jordan et al., 1991; Gigant et al., 2005).

Side Effects:

Vinblastine is a mutagenic agent and also toxic for embryos, so it is not prescribed during pregnancy. Vinblastine also induces bone marrow suppression, causes gastrointestinal toxicity, extravasation injury. When patients are infected with viruses this drug is not prescribed. It also causes laryngeal paralysis. Thrombocytopenia, anaemia can be seen by using vinblastine. It also gives rise to acute cardiac ischemia, chest pain, fever etc. (Arora et al., 2010b).

Vincristine (VCR):

It is also known as leurocristine. Vincristine is a colourless fluid and act as mitotic inhibitor thus used in chemotherapy. It is a dimeric alkaloid made by paring of vindoline and catharanthine. Vincristine is widely adopted for the prevention of various diseases like- acute leukaemia, neuroblastoma, Wilm's tumor, Hodgkin's lymphoma etc. (Arora et al., 2010b).

Mechanism of Action:

Vincristine prevents polymerization of microtubules by binding with tubulin dimer. Thus, mitosis is arrested at the metaphase stage and cell cycle can't proceed further. This phenomenon is used in cancer cells and makes the growing cancer cells stop at metaphase. This drug binds at the end of these microtubules forming 'end-capping' or 'poisoning' effect. Vincristine performs its' function under micromolar concentration ranging from 10nM to 1µM. At higher concentrations (>10µM), vincristine forms tubulin paracrystals causing tubulin polymerization (Arora et al., 2010b).

Side Effects and Toxicity:

Major side effects regarding the use of vincristine is – hyponatremia, loss of hair, constipation, peripheral neuropathy. If vincristine is used along with other anticancer drugs secondary cancer will form as then vincristine will act as a carcinogen. Besides vincristine also causes leukopenia, weakness of motor neurons, neuromyopathy, psychoses, depression, nausea, vomiting, peripheral neuritis etc. In some patients, breathing problem also occurs (Arora et al., 2010b).

Vindesine (VDS):

The marketed name of vindesine is Eldisine and Fildesin. The commercial availability of vindesine is in a powdered form and when it is dissolved into water it seems to be a colourless fluid. Vindesine is an antimitotic inhibitor and are popularly used in the treatment of several kinds of cancer such as -leukaemia, breast cancer, melanoma, lymphoma lung cancer etc. The side effects of vindesine is same as vinblastine (González-Burgos & Gómez-Serranillos, 2021).

Vinorelbine (VNLB, VRL):

This drug is created semi-synthetically from the monomeric alkaloid vindoline and catharanthine. It is regarded as the earliest and foremost 5′-NOR semi-synthetic alkaloid of *Catharanthus roseus*. It has a very wide range of antitumor activity in relation to other vinca alkaloids. It being an antimitotic agent also used as the remedy of various types of cancers. Neurotoxicity of vinorelbine is less compared to other alkaloids. Vinorelbine displays antitumor activity against MX-1 breast cancer and LC-6 non-small cell lung cancer. Vinorelbine accompanied with Cisplatin (CDDP) shows greater effect in chemotherapy (Okouneva et al., 2003).

Side Effects:

Vinorelbine shows potential side effects like- constipation, bleeding, nausea, anaemia, vomiting, diarrhoea, inflammation of the vein in which vinorelbine is injected (Arora et al., 2010b; Ngan et al., 2000; Nazir et al., 2016).

Vinflunine (VFL):

Vinflunine is made synthetically from vinorelbine with the addition of two fluorine molecules through chemistry in association with super acid in a tiny exploited region of catharanthine moiety. It became known as the fluorinated mitotic inhibitor amongst vinca alkaloids. It is extensively regarded as a remedy for breast cancer, translational cell carcinoma, non-small cell lung cancer. It performs by declining the metaphase to anaphase transition thereby obstructing cancer cells at metaphase-inducing apoptosis. Vinflunine is currently under phase three trials. Phase one trial of vinflunine activity shows prolonged inhibitory effect on the growth of tumour. Vinflunine has unique 3-16 folds weaker binding activity with tubulin. Vinflunine imparts differences in the inhibitory effects on microtubule dynamics. Vinflunine produces a much stronger effect in combination with compounds like Cisplatin, doxorubicin, or 5-fluorouracil. Vinflunine also expresses antiangiogenic and anti-vascular activity when administered in non-toxic concentration (Kruczynski & Hill, 2001).

Antidiabetic Activity of Vinca Alkaloids:

Catharanthus roseus has historically been utilized to control diabetes throughout many countries all over the world. Extract from the leaf of *Catharanthus roseus* has been shown to increase glycemic control both in diabetic and healthy rabbits (Nammi et al., 2003). In diabetic mice, *Catharanthus roseus* methanol extracts demonstrated excellent antidiabetic activity, which was associated with improved body mass, serum lipids, and pancreatic cell regeneration (Ahmed et al., 2010). Scientists investigated the in vitro anti-diabetic effects of four different bioactive compounds separated from *Catharanthus roseus* leaves, which include vindolidine, vindolinine, vindolicine and vindoline using 2-NBDG glucose uptake as well as downregulation of PTP-1B which inhibit the insulin signalling pathway (Tiong et al., 2013). Boosting glucose absorption in pancreatic cells can improve glycemic control in T2DM individuals. Four alkaloids were reported to boost glucose absorption in mouse -TC6 pancreatic and myoblast C2C12 cells while inhibiting PTP-1B. Vindolicine was the most active among the four alkaloids (Muhammad et al., 2021). The results demonstrated the conventional use of *Catharanthus roseus* for therapeutic applications in diabetic patients, emphasising *Catharanthus roseus* as a promising source for further research into anti-diabetic agents (Pham et al., 2020; Tandon et al., 2022).

Conclusion:

Since ancient, *Catharanthus roseus* has been serving as a cure-all for various types of diseases far and wide. It has come to light as one of the most potent plants worldwide. This study shows that the vinca alkaloids found in the plant have strong anticancer, and anti-proliferative qualities. In no time, the vinca alkaloids became so popular over various synthetic anticancer drugs as they can cure the disease naturally. But surprisingly the vinca alkaloids are produced in very low quantity. So, keeping in mind about the vast process of synthesis of these vinca alkaloids they should be produced synthetically in vitro. Besides the anticancer properties of vinblastine, vincristine, vinorelbine, vindoline, vindolinine, vindolicine exerts antidiabetic activity. Till now little is known about their role in immunology, so there is hope that we will get important updates on this matter in the impending future. Besides all these good qualities, it should not forget that these phytomedicines also cause various significant side effects such as it is found that vincristine can cause male infertility, however, the exact mechanism is not known. So, precautions must be taken before using these phytomedicines. Furthermore, characterization and separation of novel phytoconstituents from this plant should go on. The bioactive components obtained from this plant must be examined further before using in the pharmaceutical and biomedical industries.

Conflicts of Interest:

None

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Chapter- 2

A comprehensive analysis of ethnopharmacological and pharmacotherapeutics of *Withania somnifera* (L.) Dunal (Ashwagandha)

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Keywords: *Withania somnifera*, Ethno-botanical, Phytochemicals, Ayurveda, Therapeutics.

Abstract:

Ashwagandha [*Withania somnifera* (L.) Dunal] has been used as an Indian traditional medicine for a long time. Traditional uses of this plant include a plethora of medical conditions like hypertension, diabetes, stress, asthma, cancer, bronchitis, ulcers, conjunctivitis, epilepsy, insomnia, senile dementia, Parkinson's disease, nervous disorders, arthritis, intestinal infections, impotency etc. Different parts of this plant, specifically the roots, have been used as a traditional Rasayana herb to treat various ailments. The plant also possesses sedative, diuretic, anti-inflammatory properties and demonstrates strong immunostimulatory activity. According to Ayurveda, Ashwagandha is considered one of the most important medicinal herbs with varied functions. The multipurpose uses of Ashwagandha have numerous other beneficial health effects that are relevant in light of pharmaceutical perspectives. In this chapter, we present a comprehensive sketch of geographical distribution, description, phytochemistry and pharmacological activities of *W. somnifera* along with its active constituents. A brief description of the uses of *W. somnifera* against various cancer and its relevant signaling pathways are also descried. Preclinical studies with the extracts of various parts of Ashwagandha are also elucidated in this chapter. However, more detailed studies are required on the clinical use of Ashwagandha (*W. somnifera*) against human diseases.

Introduction:

Plants are great sources of food, medicine, oxygen, aromas, flavours and many essential ingredients that are widely used in our daily life (Maiti et al., 2010; Maiti et al., 2013; Kar et al.,

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2022). In ancient India, treatment was based upon plant derivatives. Ayurveda, Unani, Siddha, Chinese all these are traditional treatment methods relied upon plant extracts or phytochemicals (Sarkar et al., 2016; Sarkar, 2017; Sanyal et al., 2018; Bhattacharjee, 2021). The father of medicine, Hippocrates (440 BC), stated that "Let food be thy medicine and medicine be thy food". At present, multiple lifesaving drugs derived from plants are used widely (Bhandari et al., 2012; Banerjee et al., 2014; Acharya, 2016; Acharya et al., 2021). According to World Health Organization (WHO), 80% of people in new-age countries use conventional plant-based treatments. India houses about 47000 plant species among which 7500 plants have known medicinal importance. Many more are still to be discovered (Gahlawat et al., 2014; Sarkar, 2016; Sanyal et al., 2016).

Study of the inter-relationship between people and plants, the practical uses of these plants or their various parts through the traditional knowledge of local culture and people is known as ethnobotany (Erfani, 2021). Ethno-botanical knowledge can conduct the discovery of many new bioactive compounds (Gahlawat et al., 2014; Chakraborty et al., 2019; Kundu, 2022). Indian subcontinent is known as "the botanical garden of the world" and it consists of four major biodiversity hotspots. India has a large expansion of plants with novel phytochemicals and with ethnobotanical importance. Among these phyto-chemicals multiple has demonstrated promising medicinal outcomes. The classical texts of Ayurveda, Sushruta Samhita and Charaka Samhita, Ayurvedic Materia Medica demonstrated medicinal plants along with their therapeutic potential. *Withania somnifera* (Ashwagandha), a well-known medicinal plant in India, is also known as Indian ginseng or Indian Winter Cherry. It is an important ancient plant and its roots are used in traditional Indian medicine Ayurveda and Unani.

Withania somnifera (L.) Dunal (*W. somnifera*) belongs to the Solanaceae family and is commonly named as Ashwagandha. It's an evergreen shrub or woody herb distributed almost all over the Indian subcontinent. Ashwagandha has both ecological and economic importance. The roots of *Withania* have been used for over 3000 years in various clinical treatments of different ailments. The roots of these plants are the major ingredient of more than 200 formulations used in Indian folk medicine. It can be used in stress release, increasing vitality, blood sugar regulation, cognitive health improvement etc. It can also treat anxiety and depression (Afewerky et al., 2021). Additionally, reports have also demonstrated the use of root extract to treat asthma, inflammation, insomnia, psoriasis, constipation, fatigue, weakness, ulcers etc. (Pandian et al., 2020).

Distribution of Ashwagandha in India:

Ashwagandha or *Withania somnifera* is an Indian native plant species commonly distributed in a different states of India, including Rajasthan, Uttar Pradesh, Punjab, Maharashtra, Haryana, Kerala, West Bengal, Gujarat, Madhya Pradesh etc. It is also found in other tropical and subtropical areas (Gill et al., 2019). This plant species generally grows well in dry condition. They are highly cultivated in sandy loam, black, light red soil at suitable pH 7.5 to 8.0 (Devi et al., 2020; Gill et al., 2019).

Description of the plant:

Withania somnifera is an evergreen shrub about 2 feet long and covered with woolly pubescence. It consists of a short stem, long roots and simple green leaves. Root of this plant is whitish brown, fleshy and stout with strong medicinal values. Leaves are very simple, opposite and ovate type. Flowers are yellowish or greenish with orange-red berries and yellow seeds. The ripe fruit is orange-red and has milk-coagulating properties. Fruits are harvested in the late fall. Seeds are dried and stored for further plantation in the following Spring (Gupta et al., 2007).

Parts of plant with therapeutic values:

Roots are the most important parts of this plant with strong therapeutic properties. Leaves, fruits, stems, green berries, bark and seeds are also used for the same (Gupta et al., 2007). Till date 29 common metabolites are extracted from the plant leaves and roots. These are found to have anti-oxidant, anti-inflammatory, anti-arthritic, anti-cancer, anti-diabetic, anti-epileptic, anti-pyretic and anti-coagulant properties along with efficacies of regenerating, rejuvenating, analgesic and growth-promoting attributes (Dutta et al., 2019).

Bioactive compounds extracted from Withania are abundant with macro and micro-nutrients like copper, iron, zinc, phosphorous and magnesium. Different parts of Ashwagandha are being widely used for different treatments strategies like, severe cuts and wounds and the extracts of fruits, leaves, root can be applied to reduce anxiety, stress, in regulating cardiac issues, swelling, maintaining cholesterol, diabetes, asthma, cancer, bronchitis, ulcers, conjunctivitis, epilepsy, insomnia, senile dementia and preventing hair loss. It can also act as a potent antioxidant (Afewerky et al., 2021). Among all parts of *W. somnifera*, roots are the most potent one to exert pharmaceutical properties. *W. somnifera* may also demonstrate some adverse side effects like abdominal irritation and loose motion in few cases (Afewerky et al., 2021).

Biochemical compositions:

Roots of *W. somnifera* consist of various valuable phytochemicals like alkaloids, steroidal lactones, withanoloides and saponins. The leaves of this plant are mainly composed of withanolides, a steroidal lactone compound having C28 steroidal nucleus. According to study reports 35 withanolides, 12 alkaloids and many sitoindosides chemical constituents are isolated from this herbal plant species. It is an important source of iron. Withaferin A, Withanolide D are the two most common pharmacologically active withanolides used to treatvarious diseases (Narinderpal et al., 2013). *W. somnifera* also contains various amino acids including aspartic acid, glycine, glutamic acid, proline, cysteine, tyrosine, alanine and tryptophan. This plant exhibits three chemotypes till date having the same chemical nature but with different withanolide contents (Gupta et al., 2007).

List of major bioactive compounds of Ashwagandha (*W. somnifera*) that are isolated from different parts of the plant is summarized in Table 1 (Narinderpal et al., 2013; Dar et al., 2016; Gupta et al., 2007).

Table 1.List of major bioactive compounds extracted from Ashwagandha (*W. somnifera*)

Groups	Name of bioactive compound
Steroidal lactones	Withaferin A, Withanolide A to Y, Withasomniferols A to C, Ashwagandhanolide, Withasomniferin, Withanone, Asomnidienone, Withasomidienon.
Alkaloids	Somniferinine, Somniferin, Somnine, tropine, Withanine, Anaferine, Pseudo-withanine, Isopelletierine, Ashwagandhine, Cuscohygrine, Anahygrine and Tropine.
Other chemical compounds	Glycosides, Scopoletin, Chlorogenic acid, Dulcitol, Saponins, Acylsteryl glucosides, Withaniol, starch, hantreacotane, reducing sugars and amino acids.

Pharmaceutical properties of *Withania somnifera* (Ashwagandha):

Anti-oxidant properties:

Our brain and nerves are lipid and iron-rich portions and are prone to oxidative damage. This damage may lead to ageing and neural diseases like schizophrenia, Alzheimer's, Parkinson's, epilepsy and other diseases. It is experimentally established that, Withaferin A is a steroidal lactone, derived from *W. somnifera* can increase the concentration of superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT) and ascorbic acid and can decrease lipid peroxidation in rat and mice models (Singh et al., 2019). In vivo experiments in a rat model showed that *W. Somnifera* has antioxidant effect on the brain and a protective effect on neuronal tissues. It also exhibited the prevention of lipid peroxidation in mice and rabbit models (Gupta et al., 2007). Root extract (aqueous) of W. somnifera prevented the increase of stress-induced lipid peroxidation in mice and rabbits following certain bacterial infections (Gupta et al., 2007).

Anti-inflammatory properties:

NF-κB activation plays a major role in inflammation. Evidence suggests that withanolides can suppress the activation of NF-κB and also the NF-κB regulated gene expressions and promote apoptosis (Gupta et al., 2007). Reports demonstrated that Withaferin A can also inhibit the binding of NF-κB and exert anti-inflammatory capacity both *in vitro* as well as *in vivo* (Heyninck et al., 2014). Leaf extract of *W. somnifera* can inhibit microglial activation and may have the potency to suppress neuro-inflammation (Gupta et al., 2016). Mitochondrial oxidative stress release is one of the important roles of withanolides (Wei et al., 2020). The root extract of Ashwagandha, with a few other herb's mineral-based formulation is an effective anti-inflammatory agent and can be used as a complementary and alternative treatment (Trivedi et al., 2017). Withaferin A also showed promising antibacterial, antitumoral, immune-modulating and anti-inflammatory properties in animal models (Singh et al., 2011). Root extract of *W. somnifera* showed an anti-inflammatory role in different rheumatologic conditions. Inhibition of cyclooxygenase (COX) may be involved in such mechanism of action (Gupta et al., 2007).

Ashwagandha extract produced significant analgesic activity in the rat model. The involvement of pain mediators, namely prostaglandin and 5-hydroxytryptamine, in the analgesic activity of Ashwagandha was studied thoroughly. The analgesic activity of Ashwagandha was potentiated significantly by cyproheptadine, suggesting the involvement of serotonin but not prostaglandins in the analgesic activity of Ashwagandha (Singh et al., 2011).

Anti-stress and analgesic effects:

Ashwagandha has been known to reduce stress in humans and other animals. Researchers investigated that *W. somnifera* can reduce the frequency of stress-induced ulcers, induce male sexual behaviour and reduce chronic stress (Jana et al., 2018). Experimentally it has been established that, Withania can increase pain threshold time and act as an analgesic agent (Krutika et al., 2016).

It is reported that root extract powder of *W. somnifera* prevented stress-induced neuronal degeneration in the hippocampal Cornu Ammonis-2 (CA2) and CA3 areas compared to control or non-stressed animals. It has been further documented to provide significant protection against stress-induced gastric ulcers and other stress-related disorders in animal models. Experimental studies revealed that the root extract reduced stress significantly without any side effects in adults (Paul et al., 2021). Experimentally, *Withania* can increase pain threshold time and act as a potent analgesic agent (Krutika et al., 2016).

Anti-anxiety and anti-depressive properties:

Ashwagandha is known to have anti-anxiety properties. Experimental studies showed that *W. somnifera* bears GABA-like activity and delivers anti-anxiety and calming effects. GABA inhibits excess neuronal activities and gives sedative effects, reducing anxiety and mood regulation. It can also reduce depression (Jana et al., 2018).

Glycowithanolides have potent anxiolytic effects compared with many prominent anti-anxiety drugs and can effectively reduce rat brain levels of tribulin, a marker of clinical anxiety. It has also exhibited an antidepressant effect. Root extract of *Withania* may act as a mood stabilizer in the rat model's clinical conditions of anxiety and depression (Bhattacharya et al., 2000).

Anti-microbial Activity:

Anti-microbial properties of Ashwagandha are well known in the literatures. It’s a potent anti-fungal agent and can act against fungal species namely *Radicis lycopersici* and *Fusarium oxysporum* (Nefzi et al., 2016). *W. somnifera* can inhibit *E. coli* population and is reported as a potent anti-herpetic drug (Vinod et al., 2021). It can reduce the growth of different acid-fast, gram positive bacteria, and aerobic bacilli. Ranikhet virus, vaccinia virus and *Entamoeba histolytic* are inhibited by *W. somnifera* plants extracts. The antibiotic property of Withaferin A relies upon the presence of unsaturated lactone ring (Jana et al., 2017). Aqueous and alcoholic extracts of Ashwagandha (both root and leaves) were found to exhibit anti-bacterial property against various kinds of bacterial species. Synergistic increase in the antibacterial effect of these extracts along with other antibiotics, are also reported in the literature (Gupta et al., 2007).

Anti-diabetic Activity:

Jonathan et al. (2015) reported that among all withanolides, withaferin A is more efficient in glucose uptake by skeletal myotubes. On the other hand, it was also proved that leaf extract is more efficient than root extract in glucose uptake. The study revealed the potent anti-diabetic nature of withaferin extracts (Jonathan et al., 2015; Vinod et al., 2021). Root powder of *W. somnifera* showed excellent results in diabetic patients with associated metabolic disturbances. These extracts are also effective and safe herbal therapeutic alternatives against diabetes-associated hyperlipidemia. It is well tolerated without any severe adverse effects and the bioactive metabolites of the plant showed anti-hyperlipidemic and Hb1Ac level suppressing effects. All these data established *W. somnifera* as an anti-diabetic plant. It's extracts could eventually lead to novel therapeutics and strategies are needed for preventing and curing diabetes with this plant (Kumar et al., 2017).

Immuno-modulation and hematopoiesis by *Withaferin*:

The role of the root extract of *W. somnifera* as an immune-modulator has been extensively studied. The root extract has been reported to enhance white blood cell count and increase phagocytic activity of macrophages in mice (Davis et al., 2000). Increased cytotoxic effect and enhanced phagocytic activity of macrophages exposed to *Withaferin* extracts have also been reported. These results confirmed the immunomodulatory activity of *Withaferin* extract in indigenous medicine. The report displayed that immunosuppressive effect of root powder could be a potential candidate for developing an immunosuppressive drug for inflammatory diseases (Gupta et al., 2007). Ashwagandha treatment can also enhance body weight increase RBC number and platelet number and haemoglobin concentration. Cyclophosphamide (CTX) treated patients with leucopenia have shown low pathological effects after administration of Ashwagandha. Withaferin A and withaferin E have an immune-suppressive effect on human B and T lymphocytes. Withanolide E is specified for T lymphocytes and withaferin A is specified for both B and T lymphocytes (Narinderpal et al., 2013).

Anti-ageing activity:

Ashwagandha is known for its anti-ageing properties. It has shown excellent results in the improvement of haemoglobin and RBC cell count, calcium retention and decrease in serum cholesterol by withaferin treatment have been shown by in-vivo experiments (Narinderpal et al., 2013).

Effects on sexual behaviour and reproduction:

Withaferin extract preparation, including ghee, sugar and honey, is used in ayurvedic treatment to improve semen quantity, quality and sperm motility. It can treat erectile dysfunction and early ejaculation and induce libido (Umadevi et al., 2012). Ashwagandha root powder with boiled milk can cure female sterility. Traditional use of Ashwagandha roots to induce vigour, vitality, youth and physical strength is very well-known (Pandian et al., 2020).

Ashwagandha can treat spermatopathia, impotence and seminal depletion and increase vigour and vitality in men. Root extract with boiled milk can cure sterility in women (Singh et al., 2019). Ashwagandha has been known to reduce stress in humans and other animals. Researchers investigated that *W. somnifera* can reduce the frequency of stress-induced ulcers, induce male sexual behaviour and reduce chronic stress (Jana et al., 2018).

Act as an antivenom:

In India, snake charmers' ethnomedicinal practice in rural locations is still present. Snake bite victims can be treated with plant extracts externally as an antidote. Cobra (*Naja naja*) and viper (*Daboia russelii*) venoms having hyaluronidase, destroy extra-cellular matrix integrity and help rapidly spread the venom. Withaferin extracts bear hyaluronidase inhibitors and can somewhat inhibit venom spreading (Gupta et al., 2007).

Hypoglycemic, hypocholesterolemic and hypolipidemic effects:

A formulation with Ashwagandha extracts and other ingredients was administrated into streptozocin (STZ)-induced hyperglycaemic rats (Narinderpal et al., 2013). In this model, pathogenicity was caused by decreased superoxide dismutase (SOD) activity in pancreatic islet cells. This incident leads to the aggregation of reactive oxygen species (ROS). After the treatment hyperglycaemia was found to be decreased. This anti-hyperglycaemic effect might be exerted by pancreatic islets' free radicle scavenging activities (Narinderpal et al., 2013).

Ashwagandha is commonly used as an ayurvedic herb for weight loss. Hypolipidemic effect of withaferin is practised to reduce body fats. Withaferin root powder can reduce total lipids, triglycerides and cholesterol in hyper-cholesteremic animals. But it increases plasma HDL-cholesterol, neutral sterol and bile acid content in liver. Significant decreases in lipid-peroxidation rate and lipid profile are also important effects of Ashwagandha root extracts. Ashwagandha fruits also show similar properties. In humans, withaferin roots exhibit hypo-glycemic, diuretic and hypocholesterolemic effects. It can increase urine volume and urine sodium level and reduce serum cholesterol, LDL, VLDL and triglycerides level (Narinderpal et al., 2013).

Neural improvement and cognitive effect:

Sitoindosides VII to X and withaferin were isolated from aqueous methanolic extract of Ashwagandha roots and were studied upon brain glutamatergic, cholinergic and GABAergic receptors of rats. This treatment was reported to modulate basal forebrain and cortical cholinergic-signal transduction cascade. Withaferin extracts can enhance cognitive behaviour and improve memory in humans and other animals. In an experimental study, it was reported that withanolides could inhibit neuronal damage and increase neurite outgrowth. Withanosides can also exert positive effectsin Alzheimer’s patients with neuronal dysfunction. Ashwagandha exhibit a nootropic effect in naïve and amnesic mice (Narinderpal et al., 2013). Figure 1 presents the pharmaceutical properties of Ashwagandha (*Withania somnifera*).

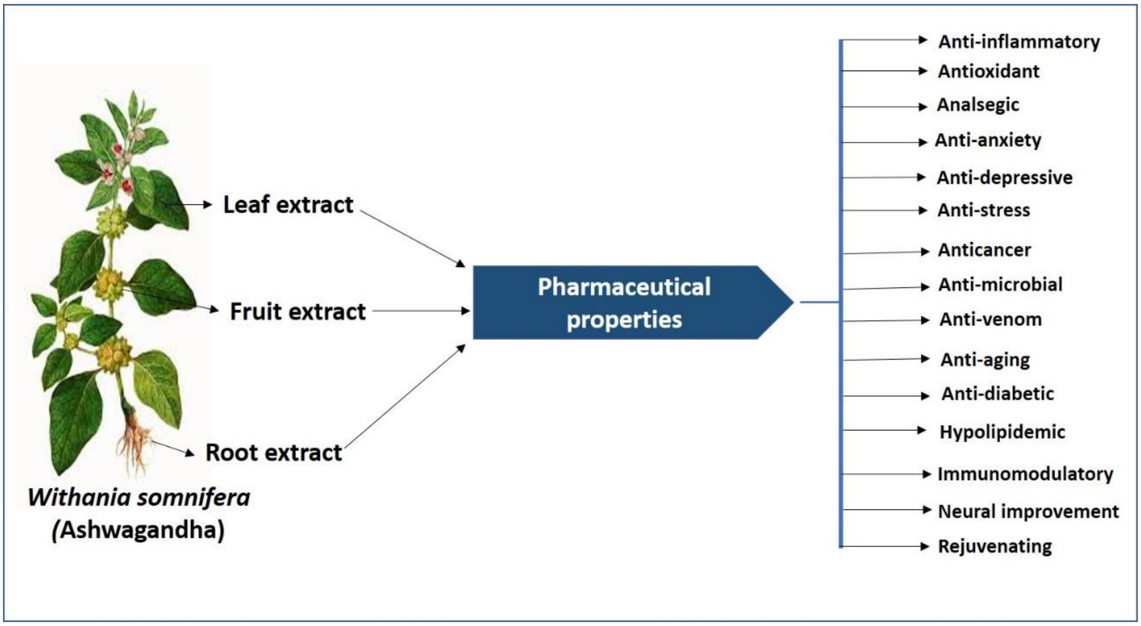

Figure 1. Pharmaceutical properties of different parts of *Withania somnifera* (Ashwagandha)(The Plant figure has been taken from Botanistry.com)

Pharmacological importance of Withania somnifera (Ashwagandha) against few diseases:

Cancer:

W. somnifera (Ashwagandha) and its bioactive secondary metabolites exhibitedanti-cancer properties in various ways such as inducing DNA damage, increasing ROS production, regulating cancer progression pathways etc. (**Figure 2**). Dysregulation of tumor suppressor genes with significant upregulation of oncogenes are commonly found in many cancers (Saggama et al., 2020). Leaf extract of Ashwagandha potentially activated the function of tumor suppressor gene p53 which acts as a growth suppressor by blocking unregulated cell cycle and inhibiting tumour cell growth (Saggama et al., 2020). Withaferin A (WA) is one of the strong bioactive phytochemicals that significantly increase the function of PP2A (protein phosphatase 2A) and reduce cancer cell proliferation. PP2A is a tumour suppressor that can decrease phosphatase activity in several cancers (Saggama et al., 2020). Beside the excessive proliferation capacity, cancer cells also have an ability to avoid apoptosis by inhibiting apoptotic signalling with increasing expression of several anti-apoptotic factors like Bcl-2 (B-cell lymphoma 2) (Kim et al., 2017). Ashwagandha and its other phytochemicals can upregulate extrinsic (via death receptor) and intrinsic (via mitochondrial caspase) apoptosis signalling. WA enhances PARP (poly adenosine diphosphate-ribose polymerase) cleavage and increases pro-apoptotic factors Par4 (protease-activated receptor 4), and caspase expression (Saggama et al., 2020). Additionally, WA also interferes with replicative immortality by suppressing the Alternative Lengthening of the Telomeres process (ALT) and its associated factors. High amounts of nutrition & O2 requirements are essential for tumor expansion. Tumor microenvironment creates a hypoxic condition to induce angiogenesis by upregulation of various angiogenic factors like vascular endothelial growth factor (VEGF) (Saggama et al., 2020). Angiogenesis is the procedure of establishing a new vascular network around the tumor that fulfils the necessary environment for tumor growth. WA has also been shown to effectively suppress factors involved in angiogenesis. Additionally, phytochemicals of Ashwagandha also act as anti-metastatic agent by downregulating metastasis responsible molecules including MMPs (matrix metallop-roteinases), vimentin, pro-inflammatory cytokine (IL-8), chemokineetc. WA attenuates the expression of metastasis inducible signalling pathways like NF-kβ (nuclear receptor kappa β), cox-2 (cyclooxygenase-2), STATs in many cancer cells (Saggama et al., 2020). The mechanical action of *W. somnifera* and its phytochemicals in different cancer are listed in **table 2**.

Table 2. Anticancer effect of *W. Somnifera* (Ashwagandha) by targeting multiple signaling pathways in various cancer.

Sl No.	Types of Cancer	Molecular mechanism of action by *W. somnifera*	Reference
1.	Breast	Upregulates p53, PP2A function, inhibit cell growth and enhance cytotoxicity by ROS production in breast cancer cell line. Downregulates Bcl-2 and Survivin expression.	Saggama et al., 2020; Dutta et al., 2019.
2.	Cervical	Upregulates caspase-3, PARP cleavage and p53 function. Downregulates E6/E7 oncogenes expressed by human papilloma virus (HPV).	Dutta et al., 2019
3.	Colorectal	Increases caspase-mediated apoptosis of cancer cells Decrease proliferation, metastasis in colorectal cancer cell line. Inhibits STAT3, Notch, NF-kβ, mTOR signalling. Supress pro-inflammatory cytokines expression TNF-α, IL-6.	Dutta et al., 2019
4.	Glioblastoma	Block cell cycle (G2-M phase), suppress the expression of Heat shock protein (Hsp) 70, VEGF and matrixmetallo proteinases (MMPs). Increase expression of NCAM (neuronal cell adhesion molecules).	Halder et al., 2017; Lee et al., 2016.
5.	Lung	Enhances Bax, caspase activity and ROS production. Reducesepithelial mesenchymal transition (EMT) and lung cancer cell migration. Downregulates PI3/Akt signalling.	Dutta et al., 2019

6.	Lymphoma	Downregulates Hsp 90, Bcl-2, MAPKs expression and inhibits cell proliferation. Upregulates caspase-3 mediated cell death with significantly increased PARP cleavage.	Halder et al., 2017.
7.	Melanoma	Improves mitochondrial translocation, upregulates the apoptosis pathway by increasing the activity of both caspases 9 and caspase 3, promotes tumor regression.	Bungau et al., 2021; Saggama et al.,2020
8.	Ovarian	Reduces the number of ALDH-positive ovarian cancer stem cells (CSCs), and inhibits cancer progression.	Dutta et al., 2019
9.	Prostate	Downregulates Chk1 and Chk2 in prostate cancer cells line. Upregulates the expression of apoptosis-associated factors Bax, caspase-3 and increase p27 function.	Halder et al., 2017; Saggama et al., 2020
10.	Pancreatic	Upregulating apoptosis pathway by significantly inhibiting the activity of PI3K/AKT signalling activity. Block cell cycle mediated cancer cell proliferation in the different pancreatic cancer cell lines.	Halder et al., 2017

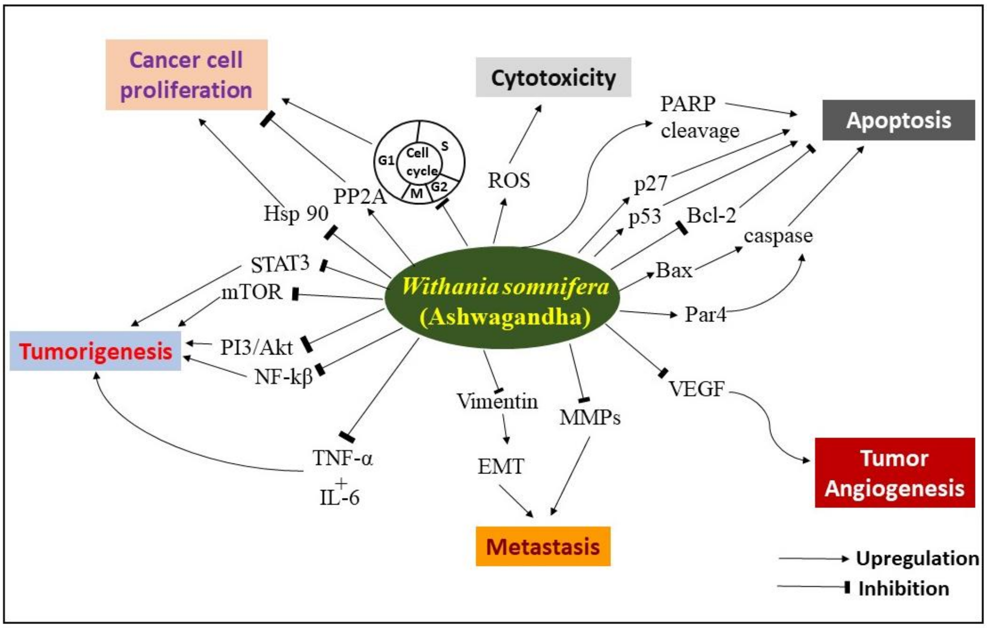

Figure 2. The major signaling pathway(s) regulated by *W. somnifera* (Ashwagandha) in the pathogenicity of cancer.

Cardiovascular disorder:

W. somnifera (WS) is largely used as herbal medicine (mostly in Ayurveda and Unani) to treat various cardiovascular disorders. It is a cardio-protector that reduces myocardial infarction and ischaemia-reperfusion injury in cardiac system (Afewerky et al., 2021). *W. somnifera* significantly reduces cardiac damage caused by doxorubicin in *in-vivo* system. It elevates the expression of detoxification genes by enhancing the activity of nuclear factor-erythroid-2 (Nrf–2) in cardiomyocytes (Paul et al., 2021). Withaferin A has been emphasized as cardio-protector in cardiorespiratory damage caused by corona virus infection (COVID-19). Root extract of Ashwagandha has been reported to reduce hypertension via lowering the systolic blood pressure considerably (Afewerky et al., 2021). Histopathological studies exhibited that *W. somnifera* minimize cardiac cell death (apoptosis) and improves overall cardiac function due to its antioxidant and anti-lipoperoxidation properties (Afewerky et al., 2021). The extracts of *W. somnifera* showed a strong cardio-protective effect against isoprenaline-induced myonecrosis in rat models (Narinderpal et al., 2013).

Neurodegenerative diseases:

Several clinical reports suggest that different phytochemicals derived from *W. somnifera* act as neuro-protector. The toxic effects of scopolamine (atoxic agent) in neurons and glial cell can bereversed by Withanone, a leaf-extracted phytochemical of *W. Somnifera* (Paul et al., 2021). It also reduces the harmful toxic effects of lead in glial cells by maintaining the normal expression of different proteins, including Heat shock protein 70, GFAP (Glial fibrillary acidic protein), mortalin and NCAM (neural cell adhesion molecule). Glycowithanolides is another phytochemical of *W. somnifera*, exhibited strong antioxidant effect by downregulating the oxidative stress markers and significantly upregulated the expression of a different antioxidant enzyme such as SOD, glutathione peroxidase etc. (Paul et al., 2021). Root extraction of *W. somnifera* exhibited its neuroprotector properties by regulating the activity of Bcl-2/Bax axis and can maintain the balance between apoptosis and anti-apoptosis pathway (Prakash et al., 2014).

Since the last few decades, the occurrence of neurodegenerative disorders have increased day by day. Parkinson's, Alzheimer's, a Huntington's are the most harmful, complicated, irreversible neurodegenerative diseases. Till now, no specific effective treatments are available for neurodegenerative diseases (Afewerky et al., 2021). Pharmacological investigations suggested that intake of antioxidant rich *W. Somnifera* may lead the way-out of several brain disorders such as bipolar disorder, loss of memory and locomotor disability etc. Additionally, in neuron-like cells, the Amyloid-beta (Aβ)-triggered ROS production, which is relatively alleviated by the root-extracted compounds of *W. somnifera*. This root extract also increased the neuron integrity and maintained the unimpaired neuronal transmission in Alzheimer animal model after the treatment with the extract (Afewerky et al., 2021). Reports also exhibited that *W. somnifera* has been used to treat Parkinson's disease by enhancing dopamine levels and restoring normal coordinated movements (Afewerky et al., 2021). In addition, it can alleviate the NO level by reducing the iNOS activity. Furthermore, in Parkinson's disease-affected brain, this herbal plant extract modulates the expression of Glial fibrillary acidic protein (Paul et al., 2021). *W. somnifera* is also documented for treating Huntington's disease by protecting the basal ganglia from the damage caused by huntingtin protein (in animal model)(Afewerky et al., 2021). GABAergic signalling and the level of different antioxidant molecules in Huntington's disease-affected brain, could be restored significantly by *W. somnifera* extract. The plant extract also improved mental apprehension and locomotor coordination (Afewerky et al., 2021).

Arthritis:

Ashwagandha is an anti-inflammatory and analgesic used to reduce many inflammatory diseases and their related symptoms. Among the inflammatory diseases, arthritis is a common inflammatory disorder characterized by excessive pain and swelling around the joint area. Few reports suggested that Ashwagandha (root) is an effective treatment in arthritis as it can significantly reduce the arthritis-related pain and recover joint flexibility in animal models (Khan et al., 2015; Elgaret al., 2021). It has been found that root extract of *W. somnifera* can decrease the ROS level and decrease the biomarker of rheumatoid arthritis, such as rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (Khan et al., 2015). Withaferin A is a potent analgesic phytochemical compound which can regulate COX pathway down and also deliver relief from prostaglandin-induced pain (Elgar et al., 2021).

Thyroid disorder:

Several clinical studies reported that *W. somnifera* could significantly increase the thyroxine hormone level and reverse the thyroid's dysregulation by regulating (hypothalamus−pituitary−thyroid) HPT axis activity. Additionally, it also interacts with metabolism of thyroid hormone. *W. somnifera* is a beneficial therapeutic effect against hypothyroidism (Elgar et al., 2021).

Conclusion:

Withania somnifera or Ashwagandha is a natural medicinal herb used in various disease treatments. It greatly contributes to Indian ayurvedic practices because of its renowned pharmaceutical activities. Phytochemical composition may vary in terms of geographical distribution. Roots, leaves and fruits are the main parts to extract phytochemicals, including alkaloids, steroids and other bioactive compounds. Various scientists have reported anticancer, anti-oxidant, antibiotic, anti-ageing, anti-stress, anti-inflammatory and other important activities with Ashwagandha's extracts. This evergreen herb also regulates rejuvenation, sexual behaviour and Alzheimer, Parkinson, Huntington disease treatment. A wide variety of this plant's secondary metabolites have been isolated to date. Many more are waiting to be explored. Recognition and cultivation of these ethnomedicinal plants are growing day to day. *Withania somnifera* should be studied more extensively, and clinical trials are in demand to uncover its other pharmaceutical properties.

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The authors declare no conflict of interest.

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Chapter- 3

Heliotropium indicum L: An Ethnomedicinally Important plant of India

Rupam Mandal

Keywords: Ethnomedicinally Important, *Heliotropium indicum*, phytopharmacological activities, Medicinal Value.

Abstract:

This study attempted to summarise the existing data on the ethnomedicinal and phytopharmacological activities of *Heliotropium indicum* L., and it did so by using database reports as its primary source of information. In order to accomplish this goal, a search of the most recent relevant literature was carried out. Based on the data, it appears that the plant possesses a significant quantity of essential phytochemicals. In the plant family known as the Boraginaceae, *Heliotropium* is a sizable genus that spans both the tropical and temperate regions of the world. Because most of the alkaloids that can be isolated from *Heliotropium indicum* are toxic, this plant's use in treating internal conditions is not suggested. In order to provide light on potential directions for future research, the purpose of this review is to summarise the phytochemistry and pharmacological activity of the many species of *Heliotropium*.

Introduction:

New medicinal agents are frequently discovered using natural products. Traditional medicine has been the most logical and cost-effective form of care. From ancient time plant have been used as a source of therapy (Maiti et al., 2013; Sanyal, 2016). The medicinal plant plays a vital role in discovering new therapeutic agents (Banerjee et al., 2014; Bhattacharjee and Manna, 2016). Various phytochemicals like alkaloids, flavonoids, tannins, and phenols contribute to the medicinal property of medicinal plants. The medicinal use of herbs is deeply rooted in Indian culture (Maiti et al., 2010; Sarkar et al., 2016; Sarkar, 2017; Bhattacharjee, 2021). Traditional systems of medicine, along with homoeopathy and folklore medicine, both of which are practised in India, continue to play an essential part in the country's overall healthcare system for the general people (Sanyal et al., 2018; Erfani, 2021; Kundu, 2022; Kar et al., 2022).

Heliotropium indicum is locally known as Hatisur and gets its name from the Greek word "helios" meaning sun and "tropein" meaning to turn indicating that its flower turn towards the sun. This plant is distributed throughout Bangladesh, Sri Lanka, Thiland, Nepal, India, tropical

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Asia, and some parts of Africa. This plant is traditionally used against many pathological diseases (Sarkar, 2016; Chakraborty et al., 2019). In this chapter, the ethnomedicinal, phytochemical, and pharmacological profiles of *Heliotropium indicum* are intended to be reflected in the current context.

Plant Taxonomy:

Heliotropium indicum belongs to-

Domain: Eukaryota

Kingdom: Plantae

Phylum: Spermatophyta

Subphylum: Angiospermae

Class: Dicotyledonae

Order: Boraginales

Family: Boraginaceae

Genus: Heliotropium

Species: indicum

Plant Morphology:

Heliotropium indicum is an annual, perennial herb reaching a height of 20 to 50 cm (Dash and Abdullah, 2012). The stem is widely distributed, branched or unbranched. Long and heavily branched tap-roots make up the root system. The leaves are oval or ovate-oblong, simple alternate or sub-alternate, and have an undulate border. The undersides of the leaves are visibly covered in hair and nerve, which are found on both sides of the serrulate or cordate leaves. Heliotropium indica blooms all year long. Within the cymose, the flower grows apically. The fruit is referred to as a nutlet. They are 4-6 mm long, 2-4 lobed, and indehiscent. There are two cells and a beak on each nutlet. At the base of the flower, mature nutlets are visible. The flower is sessile, two-ranked pentamerous, and white or violet in colour. The sepals are five, evenly spaced with the hair outside, deep green in colour, irregular, and between three and five millimetres long.

Traditional and folk values:

Different traditional and folkloric medical systems have employed *Heliotropium indicum* to treat various ailments. *Heliotropium indicum* is a medication used to treat neurological problems, poison ivy, and skin conditions in Tamil Nadu, India. According to legend, the Malasar tribe used coconut oil and leaf juice boiled together to treat dandruff (Rahman et al., 2011). The root juice of *Heliotropium indicum* is used by some tribes in Assam, India, to treat ophthalmia.

When consumed orally, the dried flower is said to sterilize females permanently. Thailand is home to this practice. *Heliotropium indicum* is thought to be beneficial in treating dermatitis, stomach pain, and malaria in various African nations (Rahman et al., 2011). The flower is also infused and used to treat menorrhagia in Jamaica.

Several ailments have been treated using the entire plant in various traditional systems. In Bangladesh, the extract of *Heliotropium indicum* is used to cure chicken pox, allergies, knee swelling, and poisoning (Nawaz, 2009).

In the Philippines, dried root decoction is used to promote menstruation, flower infusion is used to cure kidney stones, and seeds are used to heal wounds, cholera, and malaria (Wiart, 2006). In Malaysia, the whole plant decoction is used to treat ringworm infection, whereas it is used to treat gonorrhoea in Burma (Wiart, 2006). Table 1 includes a list of the regional names and traditional uses of *Heliotropium indicum* in several nations.

Table 1. The use of H.indicum in traditional medicine

Country	Local name	Traditional use for	Plant parts used	Reference
Bangladesh	Hatisur	Antidote to poisoning	Leaves and stem	Nawaz, 2009
		Swelling of Knee, joint pain	Root	Nawaz, 2009
		Chicken pox, Allergy	leaves	Shahnaj et al., 2015
		Blood purification	Root	Akhter et al., 2021
Benin	Koklosouden	Psychosis	Leaf and root	Adjanohoun, 2011
		Leucorrhoea	Whole plant	Adjanohoun, 2011
Ghana	Komfemtikoro	Eye infection	leaves	Komlaga, 2017
India	Nakipoo	Snake and scorpion bite	leaves	Alagesaboopathi, 2009
	Indian heliotrope & Hatisur	Wound and skin infection	Whole plant	Muthu, 2006
		ophthalmia	root	Das et al., 2008
Indonasia	Bandotanlombok	Herpes & rheumatism	leaves	Togola, 2005
Jamaica	Turnsoles	Menorrhagia	flower	Asprey and Thornton, 1955
		Fever, ulcer, sore throat, Induced abortion, rectal sores	Whole plant	Asprey and Thornton, 1955
Mauritius	Herbepapillon	Renal colic	leaves	Suroowan and Mahomoodally, 2019
Mali	Bambara	Nausea & vomit-ing, high blood pressure	leaves	Nordeng et al., 2005

Nigeria	Akuko	Hepatitis and fever	leaves	Adjanohoun, 2014
		Gonorrhea	leaves	Ainslie et al., 1981
Philippines	Buntot-leon	Diuretic & kidney stone	Whole plant	Quisumbing, 1951
Senegal	Mandingbambaranagiku	Dermatitis	leaves	Kerharo and Adam, 1974
Taiwan	Gou Wei chungtsan	Hepatitis	Leaves and root	Lin and Kan,1990
West Indies		Head lice	Whole plant	Ayensu, 1981

Phytochemical Constituent

As *Heliotropium indicum* has been widely used in traditional and folk medicine since ancient times, researchers have made many efforts to identify the different phytochemicals and pharmacologically active compounds that contribute to the wide use of this plant in herbal medicine. Reports suggest that the areal part of *Heliotropium indicum* contains different alkaloids like helindicine, echinitine, europine, indicinine, heliotrine-Noxide. The roots contains a high level of estradiol. *Helindicine* is a new pyrrolizidine alkaloid that has been isolated from the roots of Heliotropium indicum (Souza et al., 2005).The plant is reported to contain triterpenes like lupeol, rapone, rapanone, amines like putrescine, spermidine, spermine and sterols like astradiol, campesterol etc. (Wiart, 2006 ; Coe and Anderson,1996; Lin and Kan,1990). *Heliotropium indicum* also yields an essential oil that consists mainly of phytol, 1-dodecanol and beta-linalool. The different chemical compounds isolated from the plant are listed in **table 2**.

Table 2. Different Phytochemicals present *Heliotropium indicum*

Plant part	Phytochemicals	References
Seed	**Alkaloids:** Cynoglossine, Europine N-oxide, Heleurine N-oxide, Heliotridine N-oxide, Heliotrine N-oxide	Williaman and Schubert, 1962
Aerial part	**Alkaloids:** Echinatine, Heleurine, Heliotrine, Heliotridine, Indicine Aerial, Indicine N-oxide, Lasiocarpine,	Duke, 1994; Coe and Anderson,1996; Pandey et al.,1996
Leaves	**Alkaloid:** Trachelanth-amidine **Amines:** Putrescine, Spermidine, Spermine	Birecka et al., 1984
Whole plant	**Sterols:** β-Sitosterol, Estradiol, Chalinasterol, Campesterol ,Hexacosane-1-ol, Stigmasterol Volatile oils:1-Dodecanol, β-Linalool, Phytol	Andhiwal, 2013; Machan et al., 2005

Medicinal Importance:

Based on the data available on the presence of various phytochemicals in the different solvent extracts of Heliotropium indicum and its enormous use in folk medicine, many investigations have been conducted to look into the medicinal importance of the plant. The results have shown diverse biological effects described in this section.

Anti-microbial Activity:

The alcoholic extracts of the whole plant exhibited a dose-dependent anti-bacterial property. The extracts were effective against Bacillus subtilis, Bacillus pumilus, Staphylococcus aureus, Pseudomonous aeruginosa, Escherichia coli, Proteus vulgaris (Osungunna and Adedeji, 2016; Rao et al., 2002). In another study, the petroleum ether, chloroform, aqueous and methanolic leaf extract of *Heliotropiumindicumhas* shown antibacterial effects against *Bacillus subtilis, Escherichia coli, Pseudomonous aeruginosa and Staphylococcus aureus.* (Oluwatoyin et al., 2011; Dash and Murthy, 2011). It has also been reported that the methanolic and aqueous leaf extracts mixed with simple ointment give promising results in *Staphylococcus aureus* induced wound infection model (Dash and Murthy, 2011). The volatile oils isolated from the aerial parts of the plant showed antituberculosis activity against *Mycobacterum tuberculosis* (Machan et al., 2005). The alcoholic extracts also possessed anti-fungal activity as tested against *Aspergillus niger, Aspergillus wentii, Rhizopus oryzae, Candida albicans* (Osungunna and Adedeji, 2016; Rao et al., 2002). However, the anti-bacterial and antifungal effect of *Heliotropium indicum* high extract concentration is required. Therefore, the isolation and characterization of the active components and formulation based on those active components would increase the efficiency of this plant's antimicrobial properties.

Anti-inflammatory Activity:

The leaf extract of *Heliotropium indicum* has exhibited anti-inflammatory activity carrageenan-induced hind paw oedema and cotton pellet granulosa model of inflammation. The methanolic root extract of *Heliotropium indicum* showed a significant anti-inflammatory effect, with a 49% reduction in paw edema and a 55% reduction in granuloma formation (Srinivas et al., 2000). The ethanolic and petroleum ether extracts of *Heliotropium indicum* could successfully reduce the inflammation in egg white and induce acute paw oedema in a rat model (Shalini et al., 2010). Aqueous whole plant extract of *Heliotropium indicum* has also been reported to show anti-inflammatory effects in lipopolysaccharide-induced rabbit models. The extracts reduce inflammation and inflammatory cell infiltration (Kyeiet et al., 2016). It is noted that an oral pharmaceutical product obtained from *Heliotropium indicum* is used against inflammation, particularly against inflammatory diseases of the intestine (Pianowski et al., 2011).

Wound healing capacity:

Different *Heliotropium indicum* extracts have been shown to have wound-healing properties. In a rat model, the alcoholic extract of *Heliotropium indicum* demonstrated wound-healing efficacy. Topically, rats who received an extract demonstrated full wound healing (Reddy et al., 2002). The alkaloids extracted from n-butanol crude extract display remarkable wound healing activity in human lung cell line H292.

Anticancer activity:

Heliotropium indicum possesses anticancer properties, as is evident from a study on HeLa cells using stem and leaf methanolic extract. Within 48 hours of treatment, both extracts demonstrated anti-proliferative effects (Sivajothi et al., 2015). On the SKBR3 human breast cancer cell line, an ethanolic extract of *Heliotropium indicum* demonstrated an anti-proliferative activity (Goyal and Sharma, 2014). The brine shrimp nauplii were cytotoxic to the *Heliotropium indicum* methanolic root extract, with an LC50 value ranging from 2.57 to 31.44 ug/ml (Rahman et al., 2011). Interestingly, the main pyrrolizidine alkaloid derived from the plant, indicine N-oxide, has entered phase-I clinical trials in patients with advanced cancer (Ohnuma et al.,1982).

Antifertility activity:

The ethnomedicinal use of *Heliotropium indicum* as an antifertility agent is supported by the plant's substantial antifertility and abortifacient action in the petroleum ether extract (Andhiwal et al., 2013). A study discovered that the n-hexane and benzene fractions of *Heliotropium indicum*'s ethanol extracts displayed antifertility effects in rat anti-implantation and abortifacient models (Savadi et al., 2009). The unfavourable impact of *Heliotropium indicum* extracts on sperm mortality was also demonstrated in the in-vitro study.

Anticataract effect:

Rats exhibit anticataract behaviour in response to the ethanolic leaf extract. According to the study, rats given extract treatment had much more water, soluble protein, and glutathione in their lenses (Veda et al., 2016). The aqueous extract of the entire plant *Heliotropium indicum* greatly reduced the occurrence of selenite-induced cataract (Kyei et al., 2015).

Anti helmintic effect:

On Indian adult earthworms, the leaf extracts of *Heliotropium indicum* in both methanol and water demonstrated an anti-helminthic activity. The effect of the methanolic extract was comparable to that of the reference medication, mebendazole. On the other hand, the aqueous extract had a significantly smaller and less potent effect on earthworms (Mahato et al., 2014).

Conclusion:

The conventional medical system makes extensive use of *Heliotropium indicum*. Numerous compounds with promising biological action may be obtained from the plant. Modern society is concerned about the overuse of medicinal plants for pharmacological purposes. According to reports, approximately 15000 plant species may go extinct as a result of overharvesting and habitat damage brought on by human activity. This should be considered while employing plants with medicinal value.

The use of herbal medicine has gained popularity recently, although there are still some questions about its effectiveness and safety. According to the article, *Heliotropium indicum* is used in several nations, but additional research is needed to identify the phytochemicals and therapeutic properties. The use of this plant in clinical practice is constrained because there have been relatively few investigations on its isolated ingredient, despite the fact that it can significantly progress medical treatment. Animal models for the toxicity of the extracts show contributions from heliotrine, lasiocarpine, and retrogressive presence. As a result, it is crucial to solve this issue. These problems can be solved with enough research, opening the door for this plant as a secure, efficient, and reasonably priced healthcare option.

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Chapter- 4

Aquatic Macrophytes: An Untold and Valuable Panoramic Resource of Ethnomedicine

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Keywords: Ethnomedicine, Ethnopharmacology, Ethnobotany, Macrophytes.

Abstract:

Medicinal plants have been used in healthcare since ancient times by different societies, tribes and communities worldwide. From ancient times human beings started to acquire knowledge about medicinal plants that helped to improve health conditions through observation and experiments. Phytomedicines and herbal drugs obtained from medicinal plants are a primary source for treating several diseases. These medicinal plants contain several secondary metabolites and bioactive compounds that are the main source of the plant's therapeutic properties. Several products from ethnomedicinal plants are cost-effective, safe, and have fewer side effects. Therefore, they are becoming the main targets for the production of herbal drugs in the pharmaceutical industry. Moreover, aquatic macrophytes are also being considered as a source of medicine nowadays and are used by several tribes for medicinal purposes. This review deals with the aquatic macrophytes that are usually used by different tribes worldwide for treating several diseases and their bioactive compound present in plants and provide protection against diseases.

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Introduction:

J. W. Harshberger first used the term "Ethnobotany" in 1895. This term is derived from two words, "ethno" which means the study of people and "botany" that means study of plants. So, ethnobotany deals with the study and evaluation of the direct relationship between plants and humans and the effects of plants on human society (Prance, 1991; Himanshu & Ashwani, 2011; Sanyal et al., 2018; Kundu, 2022). The term Ethnobotany is often used as a synonym for traditional medicine and economic botany. The use of processed plant parts or whole plant for business purposes is called economic botany. But traditional medicine is not synonymous with ethnobotany. Earlier, at the time of the origin of traditional medicine there were some roots of ethnobotanical folklore, but nowadays traditional medicine includes several systems that are well organized and have undergone different diagnostic tests (Prance, 1991).

According to the WHO, over 80% of the total world's population depends on plants to cure primary health issues. Plants are a great source of medicines and have been used from prehistoric times (Bhattacharjee, 2021; Sarkar et al., 2016; Sarkar, 2017; Maiti et al., 2010; Maity et al., 2013). The earliest record of the healing properties of plants was found in Rig-veda in India (Mazid et al., 2012).

Many folk medicinal practices are verbally transmitted from one generation to another and sometimes confined to a particular region or within a group of tribal people (Mazid et al., 2012; Erfani, 2021; Kar et al., 2022). But nowadays due to industrialization and life-style, this process has become faded. For this reason, many ethnobotanical and ethnopharmacological research works and documentation processes have been undertaken to conserve the native information (Banerjee et al., 2014; Bouasla & Bouasla, 2017; Acharya, 2016; Acharya et al., 2021).

Aquatic macrophytes normally herbaceous, are one of the most important parts of the aquatic ecosystem. Aquatic macrophytes include some macroalgae, several bryophytes such as mosses, ferns and many angiosperms that are found either particularly in one or some seasons or throughout the entire year in wetlands, streams, ponds or lakes. These are highly productive with a fast growth rate. These plants are being used as phytomedicine throughout the world. In India, Russia, and China, these are also used as ethnomedicine for respiratory problems, kidney disease, and some other diseases such as gastrointestinal, liver, and skin diseases. These medicines show remarkable positive effects on cancer and diabetic patients (Unadkat & Parikh, 2021). Different parts of aquatic macrophytes such as leaves, roots and stems, possess medicinal properties. For example, the leaves are thought to have diuretic, blood purifying properties. Different plants are different in their effectiveness against any one kind of disease like Brahmi is more effective than Madukparni as brain tonic (Mazid et al., 2012). Moreover, aquatic macrophytes protect against diseases as they have different and diverse phytochemicals such as alkaloids, flavonoids, terpenoids, carotenoids, proteins, steroids and minerals. These compounds have several biological properties like antioxidant, antidiabetic and anticancerous properties. From ancient times, these aquatic plants have been used in the treatment of various diseases on the basis of their availability, low cost, compatibility etc. (Poddar et al., 2020).

Classification of Aquatic Weeds According to Zonation:

The aquatic weeds can be categorized according to different pond zones: Floating, Emergent, Marginal and Submerged (Sanyal, 2017).

Floating:

There are several families found in this category such as Pontideriaceae, Araceae, Salviniaceae, Lemnaceae etc.

Pontederiaceae:

Various plants of Pontederiaceae family play an important role in the sector of ethnomedicine. *Monochoria vaginalis* (Pond weed) is native to Sri Lanka and also found in Philippines, China, Korea, Vietnam, Bhutan, Cambodia, India, Indonesia, Malaysia, Myanmar, Nepal, Pakistan and Taiwan. Neelyaadi oil, made from *Monochoria vaginalis*, is used as wound and fracture healing component and helps lower blood pressure and headache, curing skin disease. This plant's leaf extract helps cure many diseases such as cough, asthma, toothache, and stomach and liver problems. The root extract of this plant is also used as anti-inflammatory and anti-nephrotoxic agent (Narathota et al., 2020). *Monochoria hastata* is another plant of this family which has some pharmacological properties such as diuretics, blood cleaning, and anti-gingivitis activity. It also exhibits anti-asthmatic anti-inflammatory, anti-nephrotoxic, analgesic, fever suppressing properties, as well as toothache relief action (Haq et al., 2021). *Pontederia crassipes* (water hyacinth), a representative plant of this family, also have some medicinal value. The extraction of this plant prevents the growth of gram-negative and gram-positive bacteria. This plant is also used in the textile industry (Abe et al., 2014).

Araceae:

Caladium bicolor is a member of Araceae family. It has antidiarrheal, antiseptic, emetic and insecticidal properties. This plant's leaf extract greatly affects gastrointestinal disorders (Salako et al., 2015). *Amorphophallus konjac* is another medicinal herb of Araceae family that acts as analgesic and antihemorrhagic and exhibits anti-tumor activity (Liu et al., 2019).

Salviniaceae:

Azolla pinnata is a very popular species of this family. Plant extract of this plant is used to treat sore throat and cough (Kumar et al., 2022). The mixture of leaf extract of *Salvinia natans* (floating fern) and ethanol or acetone exhibit antibacterial activity on *Escherichia coli*, *Vibrio sp*., *Staphylococcus aureus* (Al-Maliki et al., 2017). Methanolic extract of *Salvinia minima* (Water spangles) shows antimicrobial activity on *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Achromobacter spp*., *Candida albicans*, *Aspergillus niger*, *Aspergillus flavus* and chloroform extract of this plant act as an anti-growth factor against *Salmonella Typhi*, *Proteus mirabilis*, *Candida albicans* (Panda et al., 2014).

Lemnaceae:

Spirodela polyrhiza is an aquatic weed of this family. It contains fibrinolytic protease which hydrolyze fibrin and fibrinogen that ultimately helps in blood coagulation (Cho & Choi, 2003). This plant act as an oriental drug and is used for many diseases such as nephritis, oedema, urticarial. This plant has anticoagulant activity and acts as immunomodulatory, gastroprotective and anti-hypersensitive (Jeon, 2010).

Emergent:

Many emergent plants are found in the aquatic ecosystem, but the most important family is Nymphaeaceae. *Nymphaea* is an important member of this family which comprises many species such as *Nymphaea rubra* (Red water lily), *Nymphaea thermarum* (Extinct), *Nymphaea nouchali*, *Nymphaea alba* (White water lily), *Nymphaea tetragona*, *Nymphaea candida* and *Nelumbo nucifera*. These plants exhibit various medicinal properties. Rhizome of *Nymphaea nouchali* has pharmacological effect on dysentery, dyspepsia. Extraction of root and rhizome of *Nymphaea nouchali* is used for treatment of diabetes and cutaneous disease. Seed extract, flower extract of this plant, is used as astringent, cardiotonic agent and acts as an antibiotic against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Shigella dysenteriae* and *Escherichia coli* and also inhibit fungal (Candida albicans, Trichophyton mentagrophytes) growth. *Nymphaea alba* is used in the case of anxiety disorder and it also acts as an anti-carcinogenic agent (Al-Maliki et al., 2017; Pareek & Kumar, 2016).

Marginal:

Cyperus rotundus is a type of marginal plant of the family Cyperaceae. This plant shows immunomodulatory properties and it also exhibits a positive effect on lactating mothers for milk secretion as well as it reduces menstrual cycle irregularity. Methanol, chloroform and acetate extract of rhizome of this plant acts as an antibiotic against *Staphylococcus aureus*, *Aspergillus niger*, *Klebsiella pneumonia*, *Candida albicans* and *Escherichia coli*. Ethyl acetate or methanolic extract of rhizome shows antifungal activity against *Aspergillus flavus* and *Aspergillus niger* (Aeganathan et al., 2015).

Submerged:

Hydrilla sp. is a type of submerged plant of Hydrocharitaceae family. It is used in case of neurological diseases and gastrointestinal diseases and helps improve blood circulation and cardiovascular complications. Otteliones A and B present in this plant show antitubercular and anticancer properties (Unadkat & Parikh, 2021).

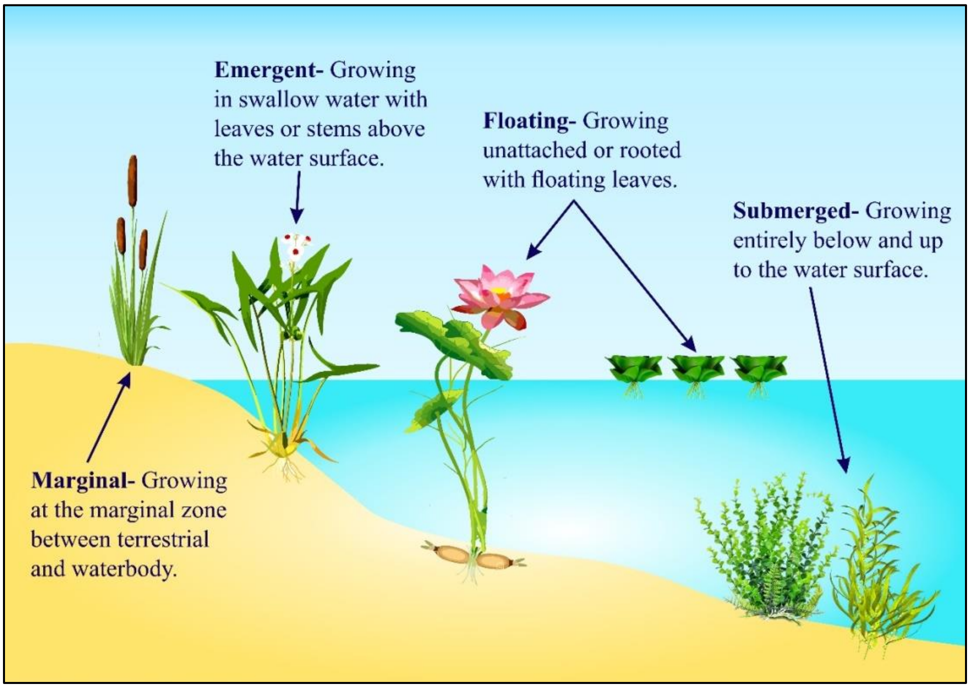

Figure 1. Different types of aquatic macrophytes are distributed at different zones of aquatic ecosystems.

Utilization of Aquatic Macrophytes by Various Tribal Communities:

Many aquatic macrophytes are distributed throughout the world and are being used by several tribes across the globe. *Enhydra fluctuans* is used by the Shan tribe of Assam and the Meitei-pangal community to treat diabetes. In Meghalaya, this plant is used by the Jaintia tribe for treating skin diseases and liver problems. Muslim herbalists use this as a cure for kidney diseases (Sarma et al., 2014, Saha & Paul, 2019). *Anagallis arvensis* is mainly found in rural areas of Egypt, Palestine, South America, Taiwan and this plant is generally used for treating different types of kidney problems (Yasmeen et al., 2020). *Bacopa monnieri* is generally used by many tribal communities in Rajasthan to treat many diseases. The tribals of eastern Rajasthan and Kathodias (a monkey-eating tribe) use this plant for its medicinal value (Verma, 2014). Tribes of Himachal Pradesh like, Gaddis, Pangwal, Kinnayris, Lahaulis, Bhots, Gujjars use *Chenopodium album* as a medicinal source (Radha, 2022). *Commelina benghalensis* is used by the Jawhar tribes in Rajasthan for treating various diseases (Deshpande et al., 2019). *Eclipta alba* is used by tribes of Manipur, Tamil Nadu and Sagar tribes of Madhya Pradesh (Kumari et al., 2021). *Heliotropium indicum* plant is mainly used by twelve clans of Santals such as the Soren clan in Rajshahi of Bangladesh (Rahmatullah et al., 2012). *Homonoia riparia* is used by the Irula tribes of Tamil Nadu (Binu et al., 2003). *Portulaca oleracea* is mainly used by Turi tribe of north-west Pakistan (Abbas et al., 2020). *Rungia repens*, is used as medicine for various purposes by different communities such as Dimasa, Vaiphei, Biate, Hamar, Mizo, Kukis of Dima Hasao District of Assam (Roy & Nath, 2019). *Ammannia baccifera* is used in several parts of India by different tribes such as Jhara, Keura, Dhivara tribe of Orissa, Sugali tribe of Andra Pradesh, Muthuvas tribe of Kerala, Gujjars, Bhotiyas tribe of North-west Himalaya, Maher tribe of Gujrat, Santal- Kantabania tribe of Jaipur, Kanikkars tribe of Western ghat etc. (Poornima et al., 2014).

Table 1. Some ethnomedicinal plants along with their medicinal uses, parts which are responsible for medicinal use, major bioactive compound, pharmacological activity.

Name	Family	Common Name	Parts Used	Medicinal Uses	Major Bioactive Compounds	Pharmacological Properties	Ref.
Ammania baccifera L.	Lythraceae	Dadmari	Leaf, whole plant	Leaves have purgative, stomachic and aphrodisiac activities. Used for treating rheumatic pains, leukorrhea, snake-bites and ulcers.	Isoquercitrin, Luteolin 7-O-β-D-glucoside, Isorhamnetin 3-rutinoside, Apigenin-7-O-β-D-glucopyranoside, Kaempferol-3-rhamnoglucoside.	Anti-oxidant, anti-inflammatory, antimicrobial.	Verma & Singh, 2008
Anagallis arvensis L.	Primulaceae	Krishna neel	Whole plant, seed, leaf.	Treatment of liver complications, skin problems, conjunctivitis, rabies.	Kaempferol-3-rhamnoglucoside, Cucurbitacin, α-Spinasterol, ß-sitosterol, Linoleic acid.	Antimicrobial, anti-oxidant, anti-inflammatory, cytotoxic, antiviral.	Verma & Singh, 2008
Bacopa monnieri (L.) Wettst.	Scrophulariaceae	Brahmi	Whole plant, leaf, roots.	Used as memory booster and to treat asthma, bronchitis, piles, dysentery etc.	Anthraquinone glycosides, saponins, flavonoids, steroids, tenins.	Antimicrobial activities.	Jeyasri et al., 2020

Chenopodium album L.	Chenopodiaceae	Bathua saag	Whole plant, leaves, roots, seeds.	To treat fever, influenza, gastroenteritis, skin dieases, venereal diseases and rheumatic disorders	Phenolics (Gallic acid, Benzoic acid, Caffeic acid), Flavonoids (Querectin, Apigenin), Terpenoids (Linalool, limonene).	Antibacterial, antifungal, antiviral, antiparasitic, anticancer, antidiabetic, antioxidant, anti-inflammatory activities.	Verma & Singh, 2008
Commelina benghalensis L.	Commelinaceae	Dholpata	Whole plant, stem	Used for curing several eye diseases like night blindness, conjunctivitis, skin diseases like eczema, acne and to treat infertility in women.	Salicylic acid, p-Coumaric acid, 8-Hydroxyquinoline, Caffeic acid, Ascorbic Acid, α-carotene, β-carotene, β-sitosterol.	Anti-inflammatory, anti-microbial, larvicidal, anti- diarrheal, anti-helminthic activities.	Jeyasri et al., 2020
Commelina diffusa Burm. F.	Commelinaceae	Kanshira	Whole plant, leaf, stem.	Used to treat high blood pressure, frequent urination, diarrhoea.	Anthocyanins, stigmasterol, n-octacosanol, n-triacontanol, campesterol.	Anti-proliferative, anti-microbial, antioxidant activity.	Verma & Singh, 2008

Cyperus rotundus L.	Cyperaceae	Motha	Rhizome	Used to treat vomiting, indigestion, stomach disorders, irritation of bowl, dysentery, fever, cough, bronchitis	β-patchoulene, Rotundone, β-caryophyllene, Isorhamnetin, Salicylic acid, Caffeic acid, β -Sitosterol 3-O-beta-D-galactopyranoside.	Anti-inflammatory antipyretic, hypolipidaemic, antidiarrheal, antimicrobial, antioxidant, antidiabetic activity.	Seethapathy et al., 2014
Eclipta alba (L.) Hassk	Asteraceae	Bhringraj	Whole plant, leaf.	Used to treat jaundice and skin diseases, cirrhosis of liver and gall bladder, minor cuts, hepatic and spleen enlargement etc.	Desmethylwedelolactone glucoside, 20-epi-3-dehydroxy-3-O-5,6-dihydro-4,5-dehydroverazine, Ecliptalbine, Ursolic acid.	Anti-hepatotoxic, antioxidant, immunomodulatory, analgesic, antidiabetic, anticancer activities.	Verma & Singh, 2008
Enhydra fluctuans Lour	Asteraceae	Helencha saag	Leaf, stem, whole plant	Used to treat gastric ulcers, constipation, diabetes, pimples, kidney stones and nervous problems.	β-carotenes, Stigmasterol, Enhydrin, Farnesyl acetate, Baicalein-7-O-glucoside.	Antidiabetic, antimicrobial, anti-inflammatory , antioxidant, anti-cancer, neuroprotective activity.	Jeyasri et al., 2020
Heliotropium indicum L.	Boraginaceae	Hanthi sur	Entire plant, flower, stem, leaves and roots.	Used in treatment of fever, ulcers, sore throat, menorrhagia, herpes, whooping cough, dysmenorrhea.	Lasiocarpine, Retronecine, Cynoglossine, Heliotrine N-oxide, β-amyrin, β-sitosterol, stigmasterol and campesterol.	Antifungal, antibacterial, anti-tumor, anti-inflammatory, antipyretic, diuretic, antioxidant activity.	Verma & Singh, 2008

Homonoia riparia Lour.	Euphorbiaceae	Willow-leaved water croton	Leaves, root, flower, fruit	Inhibitory effects on advanced glycation end product (AGE) formation that cause diabetic complications. It is also used to treat ulcer , skin disease etc.	Amentoflavone, Astragalin, quercitrin, Myricetin-3-O-glucoside, Desmanthin-1, corilagin, (-)-Epigallocatechin-3-O-gallate and (-)-Epicatechin-3-O-gallate	Angiogenesis inhibitory activity, antioxidant, nephroprotective, antifungal, anticancer activity.	Jeyasri et al., 2020
Hygrophila auriculata (K. Schum.) Heine.	Acanthaceae	Kulekhara	Seed, root, stem, leaves, whole plant	To treat diarrhea, cancer, body pain, jaundice, tuberculosis, fistula, urinogenital complications and liver diseases.	Apigenin-7-O-β-D-glucuronide, Luteolin 7-rutinoside, Ellagic acid, Gallic acid, Lupenone, Hentriacontane, Stigmasterol.	Antimicrobial, anticancer, antidiabetic, antioxidant, diuretic, anti-inflammatory, antipyretic activity.	Verma & Singh, 2008
Nymphoides indica (L.) Kuntze	Menyanthaceae	Chandmala	Roots and leaves	Used to treat skin infections, sunstroke, vomiting, fever, diarrhea etc.	-	-	Verma & Singh 2008

Oldenlandia corymbosa Linn.	Rubiaceae	Diamond flower	Whole plant, leaves, root.	Used to treat sore eyes, stomach problems and high fever.	Geniposide, 6-α-Hydroxygeniposide, Scandoside methyl ester, Asperuloside, Lyoniresinol 3α-O-β-D-Glucopyranoside, bifloron and biflorin.	Antibacterial, hepato-protective, antimalarial, antioxidant, antidiabetic activity.	Verma & Singh 2008
Portulaca oleracea L.	Portulacaceae	Golgola saag	Whole plant, leaves, seeds	Used to treat lung, liver, kidney diseases, asthma, urogenital infections and inflammation, dysentery, skin rash, fever, mouth ulcers, toothache, excessive menstrual flow.	1,5-dimethyl-6-phenyl-1,2-dihydro-1,2,4-triazin-3(2H)-one, Aurantiamide acetate, Portulacanones A-D, Kaempferol, Apigenin, Myricetin, Portuloside A, Portuloside B, Pyridoxine, Quercetin, Portulene.	Antioxidant, hepatoprotective, analgesic, anti-inflammatory, hypocholesterolemic.	Verma & Singh 2008

Rungia repens (L.) Nees	Acanthaceae	Creeping rungia	All parts	Used in treatment of snake bite, fever, cough. Fresh leaves are crashed and mixed with castor oil and used to remove *Tinea capitis* (Ringworm of the scalp).	Luteolin 7-glucoside, delphinidin, chrysoeriol.	-	Seethapathy et al., 2014
Saccharum spontaneum L.	Poaceae	Kaash	Stem, whole plant, roots, leaf	To treat mental illness, vomiting, anaemia, burning sensation, gynecological troubles, respiratory problems	Coumarins, 3',4',5,7-Tetrahydroxy-3,8-dimethoxyflavone, 3,5-Dihydroxy-4'-methoxy-7-oxyglucopyronoside flavone.	Antioxidant, antifungal, cytotoxic, antibacterial activities.	Verma & Singh, 2008
Scirpus grossus L.	Cyperaceae	Kasheruka	Leaf	Used to treat constipation, respiratory problems, eye diseases, leucorrhea, burning sensation etc.	Alkaloids, phenols, flavonoids, terpenoids, saponin, steroids.	Anti-oxidant activity.	Verma & Singh, 2008
Sphaeranthus indicus L.	Asteraceae	Gorakmundi	Leaf, stem, root, bark, flower etc.	Used to treat piles, cough, jaundice, dysentery, rheumatic pains, mouth ulcer, leucorrhoea.	Sparteine, β-sitosterol, 7α-Hydroxyeudesm-4-en-6-one, 5-Hydroxy-3',4',6,7-tetramethoxyflavone.	Ovicidal, analgesic, anti-helminthic, anti-diabetic, antimicrobial activities.	Verma & Singh, 2008

Spilanthes acmella	Asteraceae	Toothache plant	Leaf, flower, whole plant	Used to treat rheumatism, fever, cough, tuberculosis, skin diseases, toothache etc.	Spilanthol, Ferulic acid, Vanillic acid, Coumarin, Stigmasterol, α-Amyrin	Antipyretic, anti-inflammtory, diuretic, antioxidant.	Verma, 2014
Vallisneria spiralis L.	Hydrocharitaceae	Eel weed	Leaf, whole plant.	The leaves are used to cure stomach pain and leucorrhoea.	-	-	Jeyasri et al., 2020

Conclusion:

This study focuses mainly on the medicinal uses of aquatic macrophytes in folklore which usually deals with the primary healthcare needs used by most of the world's population. The medicines obtained from these plants are cost-effective, easy to use, and have no serious side effects. They have been the source of various phytochemicals since ancient times. The plant derived medicines are well acknowledged as an origin of therapeutic agents. The worth and demand of plant-derived ethnobotanical and traditional medicine are gradually increasing for curing diseases. But, many aquatic macrophytes' medicinal practices by different tribes have not been properly studied. Therefore, detailed screening and surveys have to be made and the tribal uses must be verified through scientific experiments so that it would be beneficial in future drug discovery and combating different fatal diseases.

Conflicts of Interest:

None

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Chapter- 5

Role of mangroves in pharmacotherapy

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Keywords: Mangrove, traditional medicines, antibiotics, plant metabolites, bioactive compounds.

Abstract:

Mangroves are very unique, bridging salt and freshwater ecosystems and exhibiting a wide variety of flora exclusive to halophytic conditions. Local populations have relied upon the medicinal benefits of multiple parts of various trees and plants for the treatment of diseases and infections like nausea, asthma, leprosy, rheumatic pain, arthritis, skin infections etc. These bioactive and medicinal properties have developed in the plants from secondary metabolites and chemicals present in them, like saponins, tannins, flavonoids, polyphenols, glucosides etc. The essential properties of these chemicals have made them viable alternatives to chemical pharmaceutics. Although chemically manufactured medicines are more suitable for treating multiple diseases at a lower cost of production, large-scale mismanaged applications have given rise to bacterial populations which are unsusceptible to their effects and the development of antibacterial resistance in the human body. Traditional medicines have emerged as an answer to this problem by not showing any side effects of application, and with newer natural molecules being discovered progressively, they might have a big role to play in the pharmaceuticals of tomorrow.

Introduction:

The word "mangrove" originates from the Portuguese words "*mangue*" meaning tree and "grove" meaning garden. As of now, 16 families and 70 species of mangrove plants have been identified (Sengupta, 2010), and all of them generally refer to a group of salt-tolerant, evergreen woody plants which are genetically, morphologically and physiologically adapted to the extreme salt concentrations of the mangrove ecosystem (Abdel-Aziz et al., 2016). Because of the rampant use of antibiotics and the resulting development of resistance in the human body to these

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pharmaceuticals, alternative sources of medicine, such as plant extracts, have come to the forefront of medical research. Because of their application versatility, plant extracts have been used for years among the traditional folk to treat injuries and heal ailments without suffering side effects or increased resistance to antibiotic drugs. The medicinal property of mangroves is a result of high concentrations of phytochemicals like terpenoids, tannins, flavonoids, alkaloids, saponins and antimicrobial peptides, which have all been found to have antimicrobial and antifungal properties along with therapeutic properties (Panda et al., 2012) Phytochemicals are non-nutritive chemicals found in plants which are produced by the system for protection and disease prevention and sometimes even have a protective effect on the user against said diseases. Rheumatism, ulcers, smallpox, leprosy, hepatitis, asthma, toothache and other ailments can be treated with extracts from these plants (Ravindran et al., 2005), while some extracts can be used for anti-diabetic effects and even as mosquito larvicides (Thangam and Kathiresan, 1991).

Mangroves are very special in their adaptation because they are found in areas of extreme salt concentrations and unique soil-water dynamics. The high concentrations of moisture, salt, salt-tolerant microbes and low tides make them capable of growing in areas other vascular plants will be unable to thrive and as a result, they are ideal representatives of ecotonal species between fresh and marine water ecosystems (Smith et al., 2013). The most diverse mangroves are found in the region between Malaysia and New Guinea, with 80% of the total mangroves found in the Indo-pacific region, 9% in east Africa, 6% in west Africa, 5% in the Caribbean and South Americas respectively (Michel, 2014). Mangroves can be classified into three categories:

- The true mangroves, which are restricted to intertidal areas between high water levels and neap tides. Around 20 different families of plants are found here, with 80 species already recognized.
- Minor species are those which are distinguished by their inability to form conspicuous elements of vegetation and rarely form communities.
- The mangal associates are salt tolerant but not located exclusively in the mangrove regions of backwaters but can also appear in transitional zones (Bandaranayake, 2002).

Collectively, mangroves, minor mangroves and associates are very productive both economically and environmentally. In addition to providing benefits to humans by providing alternatives to therapeutics (Rangasamy et al., 2019), they provide ecological functions like controlling the coastline (Gijsman et al., 2021), stabilizing the sediments and soil structure (Völkel et al., 2018), purification of the coastal waters by phytoremediation (Moreira et al., 2011) and providing a habitat for crabs, shrimps, oysters, fishes etc. (Situmorang and Barus, 2015). As a buffer, it reduces soil erosion and maintains water quality. Because it is situated between a terrestrial and a marine ecosystem, it effectively traps sediments, nutrients and contaminated runoff which maintains the overall health of the marine ecosystem (Wagabi, 2015). In reverse, mangroves protect the land cover by absorbing the energy from tidal waves and currents directed at the land mass by creating a natural windbreak against the direction of strong winds, which has protected the in-lands of West Bengal in many instances within a very short period (Daniary, 2020).

Medicinal importance of mangrove plants:

Widespread use of antibiotics has given rise to multidrug-resistant diseases, like those caused by *Clostridium difficile*, the treatment of which has become increasingly difficult on account of the side effects of antibiotic use. Allergies have been a common side effect from the very start of application in human communities, and even when sulfonamides were considered to be very effective, the risk of skin infections was always present from the use of the drug. Chloramphenicol was widely used because of its ability to penetrate the blood-brain barrier but at the expense of a serious risk of developing aplastic anaemia (Mohsen et al., 2020). It is to be noted that the development of resistance is not only on a community level but also on an individual level. As reported quite recently, individuals prone to taking high amounts of antibiotics are also prone to developing other infections and have more resistant bacterial flora by the time they are on the verge of taking their next dosage (Malik et al., 2018). Adverse effects of use are dependent on the dose applied to the body and the duration of application or the presence of the chemical in the system. Common effects of use, like nausea or vomiting, are often masked by the original illness and often go undetected in the patient. Furthermore, because many adverse effects occur at relatively low rates and are identified in large trials, it becomes difficult to recognize them early and attribute their occurrence directly to a drug (U.S Food and Drug Administration, 2019). In response to this rapid development of antibiotic ineffectiveness, mangrove plants have been suggested as an alternative because of their efficacy among traditional folk for hundreds of years (Abeysinghe, 2010). Mangroves are the richest source of phytochemicals, and of the plants' carbohydrate, amino acid, fatty acid, lipids, phenols, sterols etc content. Steroids, saponins, flavonoids, alkaloids, and tannins are abundantly found in vegetation, functioning as their secondary metabolites. A study of only 5 species of plants revealed an abundance of the useful chemicals present, some of which have pharmacological and economic importance (Abeysinghe, 2010) (*Table 1*).

Table 1. Chemical composition of some mangrove plants (Abeysinghe, 2010).

Specie	Chemicals present
Acanthus ilicifolius	Long-chain alcohols, benzoxazoline, triterpenes, steroids, acanthicofolin, triterpenoidal saponinsalkaloid,
Aegiceras corniculatum	Carotenoids, coumarins, benzoquinones, flavonoids, saponins, triterpenes, tannins, polyphenols,
Avicennia marina	Terpenoids, flavones, glucosides, steroidsnaphthalene derivatives,
Excoecaria agallocha	Phorbol ester, lignin, tannins, pentosan, phenols, flavanone, glycoside,
Rhizophora apiculata	Triterpenes, steroids, esters

Phytochemicals such as triterpenoids, alkaloids, and flavonoids mentioned here are the major classes of antimicrobials and antioxidants found in plants and are indicative of their use beyond the scope of ecological stability and self-sustainability (Shamsuzzaman et al., 2021). The medicinal effect of the materials arises from the synergistic effect of the various phytochemicals and as such, the isolated effectiveness of each chemical is comparatively much less potent. These products also play a major role in maintaining the plant's defence system against foreign pathogens through cytotoxicity against microbial invaders (Sarkar et al., 2016; Patra and Mohanta, 2014) (*Table 2*).

Table 2. Biological role of phytochemicals.

Phytochemical	Biological role
Phenolic-flavonoids	Reaction with free radicals for prevention or treatment of skin ageing (Podda and Grundmann-Kollmann, 2001).
Alkaloids	Antitumor, antihypertensive, muscle relaxant, antiprotozoal (von Linné, 2007).
Steroids	Antioxidants and maintaining hormonal balance (Moss, 1989)
Flavonoids	Antioxidants (Toudert et al., 2009)
Tannins	Metal ion chelating property enables it to function as an antioxidant and antimicrobial agent (Tukiran, 2013).
Terpenoids	Purgative for cough treatment and asthma (Edeoga et al., 2005)
Cardiac glycosides	Used in the treatment of arrhythmia and congestive heart failure (McMurray and Pfeffer, 2005)

A study of a few more species reveal the multitudes of therapeutic properties of these plants (Rangasamy et al., 2019) (*Table 3*).

Table 3. Therapeutic use of mangrove plants.

Specie	Therapeutic use
Acanthus ilicifolius	Treatment of asthma, paralysis, hepatitis, dyspepsia, leprosy, rheumatic pain and is leishmanicidal
Aegiceras corniculatum	Asthma, hepatitis, diabetes, rheumatism and fish poison
Avicennia marina	Skin diseases

Avicennia officinalis	Aphrodisiac, leprosy, diuretic, hepatitis
Bruguiera gymnorhiza	Eye diseases
Bruguiera parviflora	Antitumor
Bruguiera cylindrical	Stopping haemorrhage, applied to malignant ulcers, antioxidants
Ceriops decandra	Hepatitis, ulcer
Lumnitzera racemosa	Antifertility, asthma, diabetes, treatment of snake bite
Rhizophora mangle	Angina, boils, many antifungal infections, malaria, diarrhoea, dysentery, elephantiasis, fever, leprosy, tuberculosis and is antisceptic
Rhizophora mucronata	Elephantiasis, febrifuge, haematoma, hepatitis, ulcers
Salicornia brachiate	Hepatitis
Sesuvium portulacastrum	Hepatitis
Sueda maritima	Hepatitis
Sueda monoica	Hepatitis

Anti-diabetic property:

For a long time, *Excoecaria agallocha* has been traditionally used for the treatment of epilepsy, conjunctivitis, hematuria, dermatitis, toothache, leprosy etc because of the presence of phorbol esters, flavanone, glycoside, dichloromethane, lignin, pentosan, saponins, tannins and phenols as confirmed by phytochemical screening. Pharmacological investigation of the various extracts containing these phytochemicals has shown that they are capable of being used as anti-diabetics, antioxidants and antibacterial effectively without showing any signs of development of resistance in the user (Zou et al., 2006; Kar et al., 2022). The edible viviparous seeds of *Rhizophora apiculata* are useful for the treatment of diarrhoea, nausea and vomiting, while the wood is a source of tannin and used as a substitute for petroleum coke, mosquito repellent, cure for typhoid fever and phytochemical screening showed the availability of triterpenes, steroids and novel triterpenoid esters which are effective against diabetes too (Rangasamy et al., 2019).

Antioxidant property:

The barks of *Bruguiera cylindrical* and *Ceriops decandra* have been shown to possess an appreciable quantity of polyphenols, with *C. decandra* showing a higher content when compared to other species. Already shown to possess tannins previously (Ravi and Kathiresan, 1990), newer tests show elevated levels of polyphenols which are the most active radical scavengers and hence a better option as antioxidants. There is also strong evidence which shows phenolics to be useful in age-related chronic diseases (Kroon and Williamson, 2005). DPPH assay (2,2-Diphenyl-1-picrylhydrazyl), which is the most commonly used test for antioxidant properties of plant extracts (Nagarajan et al., 2017), showed both these plants to possess a concentration-dependent antiradical activity. The scavenging activity of the extracts from both barks was high and decolourization of $ABTS^+$ cation reflected the capacity of the extracts to act as electron donors, which made it evident they act as antioxidants (Krishnamoorthy et al., 2011).

Anticancer activity:

Bioactive compounds have been isolated from mangrove plants, like *Xylocarpus granatum*, which show cytotoxic effects against cancer cell lines like tetranor triterpenoids, while limonoids granaxylocarpins A and B are cytotoxic against P-388 leukaemia cells (Yin et al., 2006). Naphtoquinones 3-chlorodeoxylapachol and stenocarpoquinone B isolated from *Avicennia germinans* and *A.* marina respectively have shown strong cytotoxic activity against cancer cell lines K562 and HeLa (Jones et al., 2005) (Table 4).

Antibacterial activity:

Plant extracts have been used for treating common diseases for centuries and were the first medicines to be used by humans (Petrovska, 2012). With the increasing complexity and virulence of diseases, chemical pharmaceutics started being used as more clinically efficient alternatives, cheaper to manufacture and could be administered orally and thus improving patient compliance (Wang et al., 2022). However, with increasing self-diagnosis and heightened use of these chemical therapeutics, the development of resistance has become rapid in human systems (Rather et al., 2017), giving rise to The Antibiotic Resistance Crisis (Ventola, 2015). Although chemically manufactured therapeutics possess greater efficacy against diseases because of their specificity, better membrane permeability and stability (Wang et al., 2022), the world is being forced to look at alternatives to stop the development of resistance which can be passed on to the future generations and thereby bringing about a global crisis (MacLean et al., 2010). One of the earlier research into medicinal properties of mangrove plants revealed that *A. ilicifolius*, *A. marina* and *E. agallocha* possess significant analgesic activity (Kokpol et al., 2004). Later, seventy-five extracts from various mangrove plants in various solvents like chloroform, ethyl acetate, petroleum ether, ethanol and water reveled that they inhibit the growth of *S. aureus* and *S. proteus* (Abeysinghe, 2010), the former being the most widely used bacterial strain for testing antibacterial activities (Chassagne et al., 2021). Increasing scientific developments lead to the World Health Organisation acknowledging mangroves have sufficient ability to combat disease, having proven antimicrobial, antifungal and antiviral properties (Nascimento et al., 2000). Research has already revealed the multitudes of bioactive compounds found in many mangrove plants and their pharmaceutical importance (Bandaranayake, 2002) and it is now about optimizing their yields and overcoming drawbacks such as the stability of organic peptides (Wang et al., 2022), specificity of organic molecules and standardizing synergism between antibiotics and natural compounds which is holding back large-scale production of natural medicines for the diseased.

Table 4. Mangrove plants and anticancer compounds.

Plant	Isolated compound	Effective against
Acanthus ilicifolius	Benzoxazoline	Anticancer and antiviral activities, tumours
Agiceras corniculatum	Hydroquinone	Antiproliferative activity against human tumour cell lines
Avicennia alba	Naphthoquinolines, avicequinone	Anticancer
Avicennia marina	Naphthoquinones, avicequinone, stenocarpoquinone, iridoid, glycosides	Used for cytotoxicity against tumour cells
Avicennia officinalis	Triterpine, betulinic acid	Ehrlich ascites carcinoma cells, human leukaemia cell line HL-60
Bauhinia variegate	Steroids, triterpenoids, flavonoids	Ehlrich ascites carcinoma cells
Bruguiera gymnorrhiza	Brugine	Anti-tumour activity against Sarcoma 180 and Lewis
Bruguiera sexangula	Tropine, isobutyric, benzoic acid, brugine	Sacroma 180, Lexis lung carcinoma
Calophylum inophylum	Biflavonoids, neoflavonoids, xanthone, benzophenones	Antitumor, anticancer and lipid peroxidation
Ceriops decandra	Quinine	Malignant ulcers, buccal pouch carcinogenesis
Excoecaria agallocha	Diterpenes, tannins, excoecarin	Enhancing antitumor activity
Heritieria fomes	Phenolic compounds	Cytotoxicity against cancer cells
Pongamia pinnata	Lanceolatin B, chalcone, flavonoid, polyhydroxylates	Development of cancer
Xylocarpus mekongenesis	Xylomolin, xyloccensin	Cytotoxic activity

Conclusion:

Traditionally, mangroves have always been a source of necessities for the area's local population. Apart from providing materials for living and food for sustenance, plants have been known to be a source of ethnobotanical medicines which do not possess the negative side effects of antibiotic use over a sustained period. With the progress of scientific research, phytochemical compounds began to be newly discovered, found and identified from various parts of these plants, many of which are responsible for imparting medicinal properties to the plants associated with them. Classes of flavonoids, polyphenols, tannins, essential oils, alkaloids, phorbol esters, terpenoids, derivatives of quinones, and steroids have all been discovered from various plants and identified as agents of pharmacological importance. Antimicrobial properties were among the first uses of these plant extracts as populations in and around mangrove areas have always been of the lower economic class for whom the availability of commercial medicines has always been a cause for concern. Other common uses like cures for nausea, vomiting, haemorrhage or snake bite have been met by selecting appropriate plant varieties and extracting its metabolites or using the biomass directly on the skin or consuming it in concentrated proportions to aid the natural immunity of the body. As mangroves started being recognised as a very unique ecosystem possessing ecotonal varieties of flora with adaptations to the extreme conditions of salinity, humidity, temperature and microbial population of the soil, exploring other applications of the flora became a scientific endeavour which is being proven to be successful, with advanced medical issues like diabetes, development of tumour, cytotoxicity of cells, cancer started coming within the scope of application of mangrove extracts. However, plant extracts cannot be substitutes for pharmaceuticals as the potency of activity is yet to be equated fully against established medications. Certain activities are less than effective compared to their chemical counterparts. When used on a wide scale, systemic and local toxicity have emerged as problems which need addressing, along with modifications to drug design, predicting biological activity and calculating the stability of peptides when antimicrobial peptides are in question. The biggest problem with establishing natural medicines as permanent alternatives to pharmaceuticals, especially when mangrove plants are considered, is the global distribution of these plants, which is extremely localized and adapted to a very unique and extreme set of abiotic conditions. The cost of production of such medication will go up unless an alternative to the lack of widespread availability is found.

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Conflicts of Interest:

The authors Chiradeep Basu, Subarna Bhattacharyya, Punarbasu Chaudhuri have no financial, commercial, legal or professional conflict of interest with any other parties with the submission of this manuscript.

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Chapter- 6

Traditional practices of ethnomedicinal plants among forest-dependent communities of Paschim Medinipur, West Bengal

Dr. Rupa Sanyal

Keywords: Indigenous knowledge, Ethnic community, Medicinal plants, Ailments.

Abstract:

Since ancient times, people have used plants to treat illnesses and soothe physical suffering. Plant-based medicines have a special place in the world, even though allopathic pharmaceuticals have sparked a revolution. Due to illiteracy, traditional applications of plants as medicine have not been fully documented and have instead been passed down through families as a domestic custom. This study aims to retrieve the indigenous knowledge of herbal plants from tribals of West Medinipur district by conducting focus group discussions in 'Jabola, Amlasol, Daldali, Kakrajhore, Jujardhara and Mayurjharna villages' and exercising semi-structured questionnaire to the traditional herbal practitioners. The common ailments/diseases the locals face include Jaundice, Typhoid, Dysentery, Digestive disorder, Leucorrhoea, Malaria, Snake bite, Headache, Body pain etc. Through extensive interviews with the traditional practitioner (*Vaidya and Ojha*s), it was revealed that the most frequently used medicinal plants for the treatment of various diseases-*Uraria lagopoides*, *Smilex ovalifolia*, *Emblica officinalis*, *Asparagus racemosus*, *Curculigo orchioides*, *Dregea volubilis*, *Ziziphus nummularia*, *Cisssus adnata*. Among these plants, the first two are highly exploited commercial plants with high medicinal values of multipurpose usage. Different parts of *Uraria lagopoides* are used for the treatment of various ailments like leprosy, wound healing, cough and cold, mental disorder, and *harhiya*, as reported by the respondents. The traditional uses of *Asperagus racemosus* roots are used to cure bloody urine and blood diarrhoea. Additionally, they treat piles with rhizomes and utilise leaves to treat night blindness. The area's Santhal, Munda, and Lodha populations indicated that the additional uses included treating general discomfort, stomach pain, waist pain, leucorrhoea, and constipation. Learning is made feasible by recalling the lifetime experiences of the ethnic community and herbal practitioners. Exploration and rigorous documenting of indigenous knowledge of medicinal plants are necessary.

Introduction:

Plants have been used for medicinal purposes long before the prehistoric period. There is evidence that people in European and Mediterranean cultures, as well as Indian Vaids and Unani Hakims, have been using plants as medicine for almost 4000 years. Herbal medicine was practised in indigenous societies throughout history, including Rome, Egypt, Iran, Africa, and

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the Americas. On the other hand, others built traditional medical systems such as Unani, Ayurveda, and Chinese Medicine, all of which make systematic use of herbal remedies.

The Indian forest is the primary reservoir of a huge number of plants with medicinal and aromatic properties. These plants are primarily collected as raw materials for use in the production of pharmaceuticals and aromatic products. The AYUSH medical systems in India have documented around 8,000 different herbal treatments. According to a recent estimate by the World Health Organization (WHO), over eighty percent of people all over the world rely on herbal medicines for some part of their primary health care need. The World Health Organization estimates that there are around 21,000 plant species that have the potential to be used in therapeutic applications.

According to the currently available data, more than three quarters of the globe's population relies mostly on plants and extracts from plants for their healthcare requirements. More than thirty percent of all plant species have been utilised to prepare therapeutic remedies (Erfani, 2021; Kar et al., 2022). It is predicted that plant pharmaceuticals make up as much as 25% of the total drugs in established countries like the United States but that their share can reach as high as 80% in rapidly emerging countries like India and China. Therefore, the economic significance of medicinal plants is significantly higher for some nations, like India, than for the rest of the world (Banerjee et al., 2014; Sarkar, 2017; Sanyal et al., 2018; Kundu, 2022). These nations supply approximately one-third of the plants utilised in contemporary medical practices, and the indigenous medical practises of these nations are crucial to the functioning of the healthcare infrastructure serving rural areas.

It is generally agreed that treatment with medicinal plants is relatively safe because there are either none or very few adverse effects. Herbal remedies are safe and effective for people of any age or gender, which is one of their most appealing qualities (Maiti et al., 2010, 2013; Acharya et al., 2021). Traditional medicine practitioners can provide highly effective recipes for treating common ailments such as diarrhoea, constipation, hypertension, low sperm count, dysentery and weak penile erection, piles, coated tongue, menstrual disorders, bronchial asthma, leucorrhoea, and fevers (Acharya, 2016; Sarkar et al., 2017; Bhattacharjee, 2021;.

Objectives:

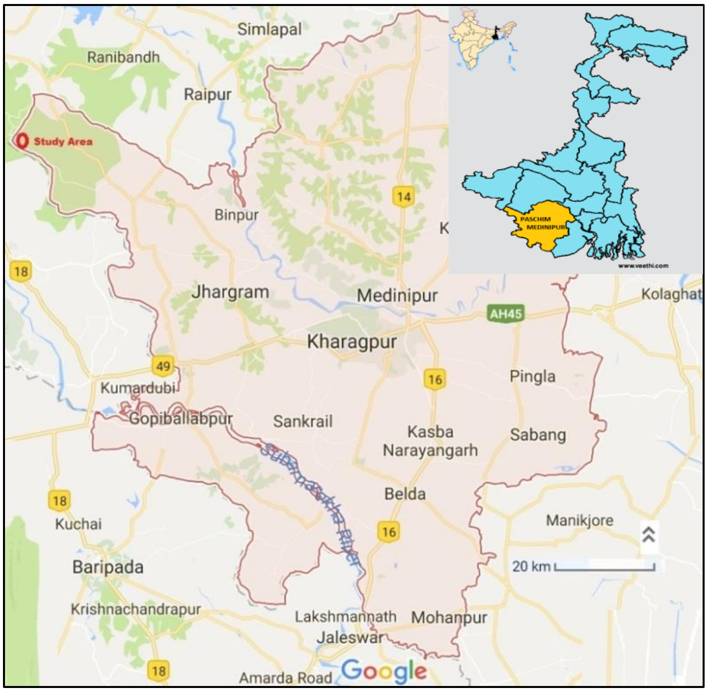
The major objectives of this paper include

- Listing of most common ailments and the surrounding tribes commonly employ therapeutic plants
- Identification of traditional herbal practitioners in the locality

Exploration of inherited knowledge on the usage of medicinal plants, especially on *Asperagus racemosus* and *Uraria lagopoides*

Study Area:

The study area was selected based on the availability of multiple ethnic communities who still practice inherited traditional treatment of various ailments or diseases as primary treatment methods. The access to the natural treasure of medicinal plants i.e., proximity to natural forests was another criterion. For the purpose of gathering ethnomedical data, six villages in the West Medinipur district of Amlasol—Daldali, Kakrajhore, Jabola, Jujardhara, and Mayurjharna—were chosen.



Map 1: Map of study area, West Bengal

Methodology:

A series of Focused Group Discussions (FGD) meetings were held in the villages of Kakrajhore, Amlasol, Daldali, Jabola, Jujardhara, and Mayurjharna to list common illnesses and frequently used medicinal plants by the local tribes, which included the Santhal, Munda, and Lodha tribal communities.

The organised meeting's participants were used to identify local herbalists such vaidyas and ojhas, as well as by asking for referrals from them and the nearby peasants. To elicit hereditary knowledge on the use of medicinal plants from the respondents, personal interviews were conducted while utilising a semi-structured questionnaire. While conducting in-person interviews, the focus was placed on learning as much as possible on the use of Asperagus racemosus (Satamul) and Uraria lagopoides (Shiv-Jata).

PASW Statistics 18.0, a statistical programme, was used to analyse both qualitative and quantitative data. According to the following formula (Phillips and Gentry, 1993), the usage value was employed to assess the relative significance of the plant species that were utilised:

$$UVi=\Sigma Ui/Ni$$

UVi is the use value of a given species; Ui denotes the quantity of use reports submitted by each informant for a certain plant species; and Ni denotes the total number of informants. A plant with a high use value has a lot of relevant reports, which suggests that it is significant, whereas a plant with a low use value (which is close to zero) has few reports concerning its usage (Suleiman, 2015).

Eighty percent of respondents were male and twenty percent were female, and the respondents were separated into two age groups: those under 50 years old (17%) and those over

50 years old (83%). Older people were better informed as the number of followers in the current generation is declining. There is masculine domination as well. However, women were more involved in gynaecological and obstetrical disorders since information flow was a problem.

Table 1. Composition of respondents.

Informants	Age Group		Total Informants
	≤ 50 Years	> 50 Years	
Male	30	135	**165**
Female	5	36	**41**
Total	**35**	**171**	**206**

Malaria, diarrhoea, jaundice, typhoid, dysentery, digestive trouble, leucorrhoea, snake bite, headache, body discomfort, etc. are some of the prevalent illnesses/diseases experienced by the locals. More than 80% of families in the study region live in poverty. Malnutrition makes the local population more vulnerable to several illnesses, particularly those spread by vectors. Snake bite is another significant issue because the majority of victims occur while harvesting Babui grass, a significant cash crop used to make rope. According to the FGD, locals were able to identify some of the plants used to treat the most prevalent diseases, as shown in the accompanying table.

Table 2. Major ailments and associated medicinal plants

Sl. No.	Diseases/ ailments	Medicinal plants used against the disease/ ailments		
		Primary findings	Standard literature	In Ayurveda
1.	Malaria	Kalmegh (*Andrographis paniculata* Burm.F.Wall. ex Nees, Kurchi (*Holarrhena pubescens* Buch.-Ham.Wall. Ex G. Don.)	*Cassia abbreviata* Oliv., *Aristolochia albida* Duch., *Toddalia asiatica* (L.) Lam.	*Alstonia scholaris*, *Coptis teeta*, *Crotolaria occulta*, *Ocimum sanctum*, *Polygala persicariaefolia*, *Vitex peduncularis*
2.	Diarrhoea	Aam (*Mangifera indica* L.), Jam (*Syzygium cumini (L.) Skeels.)*, Sal (*Shorea robusta* Roth.)	*Helicteres isora* Linn., *Woodfordia fruticosa* Kurz.	*Emblica officinalis* Gaertn., *Terminalia bellirica* (Gaertn.) Roxb., *Woodfordia fruticosa* Kurz.
3.	Jaundice	Arhar leaf [Cajanus cajan (L.) Millsp.]	*Flacourtia indica* (Burm.f.) Merr	*Flacourtia indica* (Burm.f.) Merr., *Curculigo orchioides* Gaertn.

4.	Typhoid	Gurman (*Ceriscoides turgid* Roxb.)	*Ceriscoides turgida* Roxb.	*Holarrhena pubescens* (Buch.-Ham.) Wall. Ex G. Don.
5.	Dysentery	Satamul (*Asperagus racemosus*)	*Helicteres isora* Linn., *Woodfordia fruticosa* Kurz	*Emblica officinalis* Gaertn, *Azanza lampas* (Cav.) Alef, *Helicteres isora* Linn. *Woodfordia fruticosa* Kurz
6.	Wound healing	Mahadevjata/Shivjata [*Uraria lagopodoides* (L.) Dc.]	*Uraria lagopodoides*	*Vernonia anthelmintica* (L.) Willd.
7.	Leucorrhoea	Satamul (*Asperagus racemosus)* , Ramdatan (*Smilex ovalifolia),*	*Smilax ovalifolia* Roxb.	*Azanza lampas* (Cav.) Alef
8.	Snake bite	Sarpagandha (*Rauvolfia serpentine (L.) Benth. Ex Kurz).*	*Croton roxburghii* Balakr	*Rauvolfia serpentine*
9.	Headache	Kundri (Coccinia indica), Bichuti fruit (Tragia involucrate L.), Mahadevjata/shivjata (Uraria lagopodoides (L.) DC.)	*Ceriscoides turgida* (Roxb.) Tirvengadum	*Ceriscoides turgida* (Roxb.) Tirvengadum
10.	Body pain	Satamul (*Asperagus racemosus*), Putla (*Croton roxburghii* Balakr), Lodh bark (*Symplocos racemosa* Roxb.)	*Meyna laxiflora* Robyns, *Dioscorea esculenta* Burkill	*Grewia helicterifolia* Wall. Ex G. Don. The findings from books and journals are presented under the heading "Standard Literature" in the second column of the above table, while the FGD results are shown in the first column under the heading "Primary Findings," with an Ayurvedic reference in the last column. Similar

				approaches can be employed to treat many illnesses, and a few novel species have also been discovered and are being used locally.

Table 3. List of Medicinal Plant Species Inventorized with their Use Value (UV)

Sl. No.	Local Name	Scientific Name	Family	Habit	Parts Used and Uses	UV
1.	Amloki	*Emblica officinalis* Gaertn.	Phyllanthaceae	Medium Sized Tree	Fruits: Constipation and dyspepsia	1.74
2.	Bhui kul	*Ziziphus nummularia* (Burm.f.) Wight & Walk.-Arn.	Rhamnaceae	Bushy Shrub	Leaves: Used in bleeding gums. Fruits: Used as appetizer	1.49
3.	Chitpunji	*Dregea volubilis* (L. f.) Benth.	Asclepiadaceae	Vine	Root and tender stalks— Used in colds, sinusitis and biliousness.	1.61

4.	Dudhilata	*Ichnocarpus frutescens* R. Br..	Apocynaceae	Twining Shrub	Leaves: Paste applied to sore in between fingers; fresh latex applied to treat nail disease; with mustard oil used to treat scabies.	1.29
5.	Paniya Lata	*Cisssus adnata* Roxb.	Vitaceae	Climber	Tubers: Used for blood purifying. Roots: Powdered and heated root applied to cuts and fractures	1.18
6.	Putla	*Croton roxburghii* Balakr.	Euphorbiaceae	Medium Sized Tree	Root: In snake bite Fruit/Seed: purgative in snake bite.	1.68
7.	Ram Datan	*Smilex ovalifolia* Roxb.	Smilaceae	Climbing Shrub	Roots: Used to treat abnormal discharges of semen and white discharge of semen.	1.84

8.	Satamul	*Asparagus racemosus* Wild.	Asparagaceae	Shrub	Tuber roots: Used in blood dysentery, bloody urine, white discharge of female Leaves: Used to treat night	1.82
9.	Shivjata	*Uraria lagopoides* (L.) Dc.	Fabaceae	Shrub	Tuber roots: Used to treat intermittent fever, chest inflammation, treatment of dysentery and diarrhoea	1.85
10.	Talmuli	*Curculigo orchioides* Gaertn.	Amaryllidaceae	Herb	Rhizomes: Used to treat piles and in body-cooling	1.74

The tribal society uses the entire Mahadevjata plant (*Uraria lagopoides*) to treat a variety of illnesses. They use the root of this plant to make hariya, a beverage they consume to keep their bodies cool, especially during the summer. The root and leaf of this plant have wound-healing properties. The root is also used to treat leucorrhoea and is given to patients with mental disorders to help them. The entire plant is also used to treat cough and colds.

Conclusion:

Results show that people living around the Kakrajhore forest area of West Medinipur District hold valuable knowledge of the uses of plant resources and that some plants represent an important component of the local livelihood strategies. However, more in-depth investigations are required for some plants on their possible pharmacological activity. Though the Kakrajhore Forest area is rich in medicinal plant resources but the habitat of most of the plant species have shrunk and are becoming endangered due to the expansion of the human population and environmental degradation primarily due to heavy live stock grazing, uncontrolled and unscientific harvest of species etc. The better conservation of natural recourses can be done by inclusion of section on the plant conservation especially of rare and endangered plants, in the wildlife protection act, promotion of community based conservation, *in-situ* conservation through the establishments of nature reserves, *ex-situ* conservation through tissue culture, developing cultivation technologies and nurseries of medicinal plants and conducting of regular training on the procedure of medicinal plants collection, awareness among the local people, traders and real stake holders. Therefore a sustainable management approach and proper conservation strategy for the area is recommended by local communities and administration involvement.

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Chapter- 7

Ethno-medicinal properties of some selected holy plants of West Bengal, India

Biplab Bhowmik, Bipasa Dey, Riya Mondal and Priya Roy*

Keywords: Holy plants, Medicinal value, Bioactive compounds, Ethno-medicine.

Abstract:

Worship of nature has been an integral part of human culture. The different religious communities of India have worshipped many plants since time immemorial. Our ancient scriptures have also enlisted the names of many plants which hold religious importance. These plants are considered very precious gifts to mankind. Some of these sacred plants include neem, mango, babool, turmeric, night flowering jasmine, lotus, tulsi, doob grass, etc. Many of these plants or their parts are used for their medicinal properties. Different parts of these plants, like flowers, fruits, seeds, leaves, barks and roots, are used to treat several types of health-related issues like cough and cold, anxiety, oral problems, digestive disorders, cardiovascular problems, skin ailments and various other health issues. These plants contain various bioactive compounds, which generally play vital roles in reducing the physical manifestations of those diseases and may help to control them. Still, we lack detailed information and knowledge about the medicinal benefits of those holy plants in order to pave the way to establish them as commercial medicine, so that one can obtain the advantages from them. It can be revealed only through proper studies and experimental research.

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Introduction:

India is the second largest country in the world in terms of population and seventh largest in terms of area. India is known for its rich diversity in geographical landscapes, climatic conditions, culture and traditions of people, languages, food and religious beliefs. Different religious communities have different ways of worship. India is also rich in floral and faunal diversity. The Botanical Survey of India has described over 46,000 species of plants and over 1.03 lakh species of fauna have been described by the Zoological Survey of India. Many of the plant species are considered sacred among different religious sects and are worshipped as a part of their tradition. Common plants considered sacred include tulsi, turmeric, mango, banyan, peepal, bael, kadambh, neem, lotus, etc. These plants are often believed to be incarnations of God and Goddess. Many sacred rituals are considered to be incomplete without the use of these sacred plants (Pandey and Pandey, 2016). A wide range of these plants also has other benefits. Some of them have ornamental flowers used for decoration during different festivals while many are used in the preparation of essential oil. Some plants like neem, turmeric and tulsi act as insecticides (Sarkar, 2017). Many of these plants have been used as ethno-medicine for years (Sarkar et al., 2016; Bhattacharjee, 2021). The Unnani, Ayurveda and Tibbia have enlisted around 2000 different species of plants which are considered beneficial to humans (Gadgil and Varkala, 1976). For a long time, indigenous people have used different parts of these plants like their flowers, seeds, stems, leaves, roots etc., for their medicinal advantages (Maiti et al., 2010; Maiti et a., 2013; Acharya, 2016; Sarkar, 2016; Sanyal et al., 2017). These properties generally include analgesic, anti-diabetic, antimicrobial, antiseptic, anti-inflammatory and many other activities that greatly benefit human health (Erfani, 2021; Kar et al., 2022). Proper studies on the medicinal advantages of these plants can reveal more unknown beneficial properties and help us learn their mode of action better (Banerjee et al., 2014; Sanyal et al., 2016). Some common holy plants of the Indian subcontinent and their medicinal values are discussed here.

Practices of medicinal plants in tribal communities:

India consists of half of the tribal population of the total of the world (Prakash, 2015). They are enriched in the knowledge of different medicinal plants and their benefits in regular life to survive in the remote and challenging environment of the different geographic location of India. Their traditional knowledge about the application of medicinal properties of various local plants is the base of various scientific researches in the healthcare system. The greater biodiversity of India also supports this practice. The Indigenous people of India have strong faith on the medicinal plants as a part of their many religious practices. Few medicinal plants like *Ocimum sanctum*, *Aeglemarmelos*, *Cedrusdeodara*, *Musa paradissica*, *Azadiractha indica*, *Ficus religiosa* etc are used for common treatments and worship (Prakash, 2015), but different anthropogenic disturbance negatively effects on those communities which lead to diminishing their precious knowledge of medicinal plants. It is important to conserve those biological resources for the greater benefit of mankind.

Azadirachta indica (Neem):

Azadirachta indica is commonly known as Neem in India. It is a large tree of the Lamiaceae family which can grow upto almost 30 meters. This medicinal plant is generally found in the tropical and subtropical regions. It has widespread branches and pinnate leaves which range from medium to dark green in color. The flowers are white and fragrant.

Neem as a holy plant:

This tree is considered sacred and is worshiped in some parts of Odisha and Southern Asia. According to the Hindu mythology, it is believed that neem tree is the reincarnation of Goddess Durga (Sikarwar, 2016).

Bioactive components of Neem:

The neem plant has two main bioactive chemicals. They are Limonoids and Terpene (Ogbewu, 2008). Other bioactive compounds include Nimbin, which has spermicidal activity and Gedunin- which is antimicrobial in action. It also contains certain polysaccharides which show anti-inflammatory activities (Kudoma et al., 2011; Chopra et al., 1958).

Medicinal properties of Neem:

As an immunostimulant:

When the leaves of Neem plant were administered orally for three weeks, it was seen that there was an increase in the amount of IgM and IgG antibodies. The amount of anti-ovalbumin had also increased with the intake of Neem leaves (Kraus, 1995).

Reduction of ulcer:

Neem contains a bioactive compound called glycoside which has antiulcer and antacid properties (Sharma and Saksena, 1959).

Antimicrobial properties:

Neem can prevent the occurrence of fowlpox, chickenpox and smallpox (Bhowmik et al., 2010). It also halts the replication process of Dengue type 2 viruses (Rao et al., 1969). Ethanolic extraction of Neem leaves is effective against *Aspergillus* and *Rhizopus* (Mondali et al., 2009).

As an analgesic:

Oil produced from the seeds of neem plants has been shown to have analgesic properties.

Antimalarial activity:

Spraying purified neem extracts on stagnant water bodies reduces the growth of Plasmodium falciparum larva, the causative agent of the deadliest falciparum malaria (Rojanapo et al., 1985).

Anthelminthic property:

The anthelmintic properties of Neem have been reported repeatedly. It inhibits the larval hatching of *Haemonchus contortus*. Neem extract also possesses anti-filarial activity against bovine filarial parasites *Setaria cervi* (Mukherjee et al., 2018).

Uses of neem as a medicinal plant:

In traditional medicine, almost all parts of the neem plant, including its leaves, flowers, seeds, bark, and stem, have been used (Locke, 1990). Several ways of using different parts of neem plant and their benefits are:

- Oral ingestion of the neem leaves is helpful in purifying blood and in regulating blood glucose levels.
- Chewing neem sticks are considered extremely beneficial for oral hygiene.
- Neem seed oil is helpful in curing several skin infections.
- Neem leaves have also been shown to cure intestinal worm infections and cause other digestive tract infections.
- The application of neem tree bark can prevent the spread of microbial infections on the skin. It has also been shown to have wound-healing properties.
- Neem tree bark is also beneficial for conditions like excessive thirst and nausea.

Ocimum sanctum (Tulsi):

Ocimum sanctum is the scientific name given to Tulsi. The Tulsi plant is also called holy basil. Tulsi plant grows up to 2 meters in length. It has many erect branches and sub-branches. The stems are hairy and the leaves are petiolar and oval-shaped (Warrier 1995). It is distinguished into two types- Rama Tulsi; which has bright green stems and Krishna Tulsi; which has dark reddish purple stems (Staples and Kristianerran, 1999). Tulsi plants grow both in the home (GramyaTulsi) as well as in the forest (VanyaTulsi ; Kumar, 2012).

Tulsi as a holy plant:

The Tulsi plant is considered sacred among the Hindu community and leaves of this plant are used to worship many gods and goddesses (Robinson and Cush, 1997). Some communities also wear the tulsi beads around their neck. In several cultures, tulsi is grown at home in the centre of the lawn and water is offered to the plant regularly.

Bioactive components of Tulsi:

Tulsi leaves contain a volatile oil which has methyl eugenol (20%) and eugenol (71%). The stem of Tulsi plant has phenolic compounds and antioxidants like rosameric acid, apigenin, cirsimaritin, cirsilineol and isothymusin (Yanpallewar et al., 2004).

Medicinal properties of Tulsi plant:

Antimicrobial properties:

The oil from tulsi plants is effective against bacteria like *Pseudomonas* sp. and *Bacillus* sp. Extracts of Tulsi plant can inhibit the growth of *Staphylococcus* sp. and *Proteus* sp. (Kumar et al., 2012).

Anti-inflammatory activity:

Extract of methanol prepared from tulsi leaves has anti-inflammatory activity on acute and chronic inflammation (Singh and Majumdar, 1997). It has also shown a reduction in inflammatory symptoms in rats (Singh and Agarwal, 1991).

Anti-diabetic property:

An experiment was carried out in the hyperglycemic rats in which extraction of tulsi plant was administered orally to them. It was found that their glucose levels got restored to normal after continuous administration for several days.

Anthelmintic activity:

Antihelminic efficacy of Tulsi against earthworms has been reported previously by Buchineni et al. (2015). Aqueous extract of leaves of Tulsi causes paralysis and consequent death of earthworms (Buchineni et al., 2015).

Use of Tulsi as medicinal plant:

Tulsi plant is considered of great medicinal value. It is used in the treatment of cough and cold, influenza, bronchitis, asthma and a number of other therapeutic conditions like vomiting, catarrhal fever, diarrhea, dysentery, skin rash, eczema and allergies (Prakash and Gupta, 2005).

- Tulsi plants can give several health benefits. Some of them include treatment for sore throat, kidney stones, coughs and colds, eye problems, oral infections and skin ailments.
- In order to cure sore throat, tulsi leaves are boiled and gargled.
- If tulsi leaf juice is consumed with honey regularly for several months, it can help expel kidney stones through the urinary tract.
- Tulsi leaves are chewed raw in order to provide relief for cough and cold.
- Pouring a few drops of Tulsi oil into the eyes can cure eye problems.
- Chewing a few basil leaves regularly is known to cure oral infections.
- The application of basil leaf paste helps to cure a skin infection.

Circumin sp. (Turmeric):

Turmeric plant is known as *Circumin* sp. in Latin. It belongs to the family Zingiberaceae. It is mainly found in India and some parts of South East Asia (Gupta et al., 2013). It is 3 to 5 feet tall and has yellow-coloured flowers. The rhizome stem is underground. It is thick and fleshy.

Turmeric as a holy plant:

Turmeric plant is worshiped in several parts of India, especially in the states of Bihar and Jharkhand. Young saplings of turmeric plants are immersed in the river water during the festival of Chhath as a part of worship.

Bioactive components of turmeric:

Phytochemicals present in turmeric include Circumin (70-75%), demethoxycircumin (5-10%) and bisdemetoxicicumin (5-10%) (Kocaadam and Sanlier, 2017; Soleimani et al., 2018).

Medicinal properties of turmeric:

Prevention of heart disease:

Adding turmeric to food has decreased bad cholesterol levels, which helps prevent heart disease (Patil et al., 1971).

Effect of turmeric on arthritis:

Using turmeric can provide benefits to patients who have arthritis since it is known to have antioxidant and anti-inflammatory properties.

Anti-carcinogenic properties:

Circumin, the main bioactive turmeric compound, plays an important role in the induction of apoptosis and promotes proper regulation of the cell cycle (Gautam et al., 1998).

Antimicrobial properties:

Aqueous solutions made from the extracts of turmeric have shown to kill bacteria. But these tests are performed only in animals (Kumar et al., 2001).

Anthelmintic property:

Ethanolic extract of *Curcuma longa* was reported for their anthelmintic activity towards third-stage Haemonchus larvae (L3) (Nasai et al., 2016). Rhizome extracts of Curcuma longa act as a biological nematicide against the Indian earthworm *Pheretima posthuma* (Singh et al., 2011).

Use of turmeric as a medicinal plant:

- Uses of turmeric in food as a spice aid in digestion. It also burns low-density lipoproteins and is effective for cardiovascular health.
- Milk mixed with turmeric powder is effective against cough and cold.
- Leaves of turmeric plants are believed to have antiseptic properties. It can also reduce symptoms of jaundice common cold and can also prevent intestinal worm infections.
- The application of turmeric paste to the joint can cause a reduction in joint pain. In addition, turmeric is very effective against microbial infections.

Nyctanthes arbor tristis (Night jasmine):

It is commonly called Parijat or night jasmine. Night jasmine belongs to the family Oleaceae. It grows in deciduous forests and semi-arid regions (Chopra et al., 1956).

Night jasmine as a holy plant:

The flowers of night jasmine are offered to Goddess Durga during Navratri. Hindu scriptures state that Lord Krishna had brought this plant for his wife Satyabhama. This plant is considered the combined form of the five wish-fulfilling plants of Devlok (Mesharan et al., 2012).

Phytochemicals of Night jasmine plant:

Some important phytoconstituents of Night jasmine include voatie oil, carotene, lupeol, fructose, benzoic acid, carotenoid, glycosides, alpha-carotene, oleic acid, lignoceric acid, palmitic acid, myristic acid, alkaloids etc.

Medicinal properties of night jasmine:

Antimalarial activity:

A test was carried out on one hundred and twenty patients who were infected by the malarial parasite, *Plasmodium vivax*. In this experiment, the paste made from five medium sized leaves was administered three times daily for seven to ten days. It was seen that ninety patients got cured within seven days, while the rest of the patients recovered within ten days (Shah and Verma, 2012).

Anti-anemic property:

The extracts obtained from different parts (flowers, leaves, barks etc.) of the plant have been shown to increase the haemoglobin count and the number of red blood cells in rats (Jain and Mittal, 2011).

Anti-filarial property:

The flowers of the night jasmine plant can be used to extract a type of chloroform which is capable of killing the mosquito larvae which act as vectors of filaria-causing parasites (Khatune et al., 2001).

Anti-inflammatory properties:

Extracts of night jasmine are rich in flavonoids that cause a reduction in the inflammatory response (Omkar et al., 2006).

Conclusion:

The medicinal values of sacred plants have been known to human knowledge since ancient times. Many indigenous communities of India utilize different parts of these plants regularly to treat certain ailments like cough and cold, skin problems, oral disorders, etc. Plants contain bioactive compounds which play crucial roles in reducing the symptoms of certain diseases and infections. These phytochemicals have lesser side effects compared to the medicines manufactured by the use of strong synthetic chemicals. So, proper study on the benefits of those medicinal plants can help to establish phytochemical based therapeutics for the treatment of various acute and chronic diseases with lesser side effects in low cost sustainable manner. Some of these plants like neem, babool, turmeric etc. have excellent insecticidal properties. Planting tulsi on the house can prevent mosquitoes from entering the house. Neem also prevents the entry of many harmful and poisonous insects. So extracts from these plants can be used to make plant-based insecticides and mosquito repellents less harmful than synthetic ones. Proper studies and detailed research can reveal much more about the medicinal advantages of holy plants.

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Chapter- 8

Phytosomes: a cutting-edge technique for herbal drug delivery and its clinical applications

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Keywords: Phytoconstituents, Drug delivery, Phytochemicals, Phytosomes, Bioavailability.

Abstract:

In past few decades extensive research has been conducted worldwide to explore the therapeutic potential of various medicinal herbs and their active phytoconstituents. Although plant extracts or phytochemicals purified from plant parts, show robust pharmacological efficiency in vitro but poor bioavailability, low absorption rate and selectivity might limit the clinical application of these phytochemicals in the practical field. Different techniques have been employed to manufacture effective vehicle systems to overcome these obstacles. Among them, phytosome technology appears to be a promising one to enhance bioavailability and other impediments. Phytosomes are novel drug delivery techniques synthesized by conjugating phospholipids with water-soluble herbal compounds or bioactive phytochemicals. This novel approach ultimately improves the availability and absorption of these phytoconstituents and greatly enhances their clinical efficacy which can be employed in the treatment of several diseases. This chapter is designed to provide a piece of updated information on the structure, and characterization of phytosomes and its clinical application for the management of various ailments.

Introduction:

From ancient times, different parts of the plant and their active components have been utilized to treat different ailments. Modern drugs with several side effects are unable to cure all diseases. Natural products have been used to treat several diseases without any undesirable outcomes.

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However, due to poor bioavailability, less aqueous as well as lipid solubility, absorption rate, improper molecular size, destruction in the gut, highly distributed throughout the body, less plasma half-life, poor stability, the clinical application of numerous phytoconstituents is still questionable. To overcome all these obstacles several novel drug delivery systems have emerged to deliver phytochemicals. It includes novel herbal formulations like niosomes, transferosomes, liposome, ethosomes, proniosomes, and nano capsules. Amongst all these approaches, phytophospholipid complexes, popularly known as phytosomes, appeared to be a great technique for enhanced bioavailability (Anjana et al., 2017).

The term "Phyto" means plant, while "some" refers to cell-like. Phytosomes or Herbosomes are the cell-like vesicular drug delivery system; with enhanced absorption rate and improved bioavailability of drugs, phytosomes overcome the limitations of traditional drug delivery systems (Bhattacharya et al., 2009; Nagar et al., 2019). Phytosomes are complexes made up of bioactive plant extract or phytochemicals (like flavonoids, terpenoids and tannin, etc) surrounded and bounded by lipids. Phytosomes are developed via molecular association in which a hybrid bond formation occurs between plant extract or water-soluble phytoconstituents and phospholipids, producing a lipid-miscible molecular complex with reduced polarity having the capability to cross the plasma membrane. In a nutshell, phytosomes are active hydrophilic phytoconstituents covered by lipid-soluble phospholipid, having better drug encapsulation efficiency, enhanced bioavailability, absorption rate and high stability.

Phytosome Structure:

Phytosomes are formed by the interaction between active phytoconstituents and the polar head of phospholipids (Fig. 1.) (Khan et al., 2013). Interactions between phospholipids and bioactive phytoconstituents enable the phospholipid complexes to be an essential integrated part, involving the anchorage of phospholipid head groups but the long fatty acid chains do not take part in complex formation. The two long-moving fatty acid chains encapsulate the polar part of complexes to form a lipophilic outer layer. For the production of Phytosomes 2-3 moles or 1 mole of phospholipid such as phosphatidylcholine, phosphatidyl- ethanolamine or phosphatidyl-serine combined with 1 mole of bioactive component (flavonoids or terpenoids) in an aprotic solvent (dioxane, acetone, methylene chloride, ethyl acetate). The phyto-phospholipid complex formed agglomerates when diluted in water (Ghanbarzadeh et al., 2016).

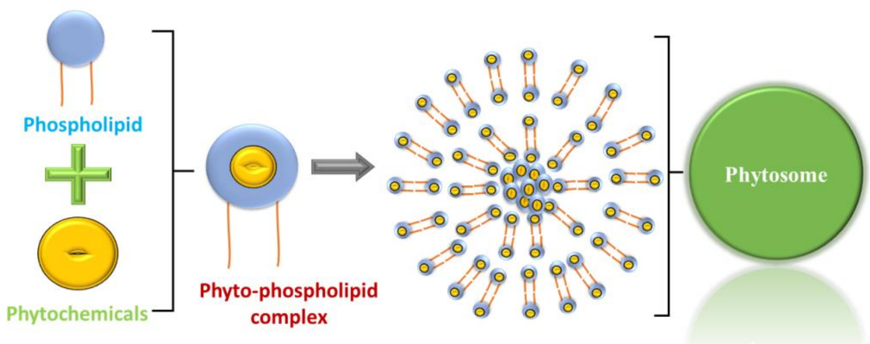

Figure 1. Diagram Representing Basic Principle of Phytosome Formulation

Phyto-active Components:

Phytochemicals or plant chemicals are a wide range of naturally occurring bioactive compounds of plant origin. Bioactive phytochemicals can interact with different types of components of living organisms, hence, exerting their beneficial effects. Alkaloids, phenolics, terpenoids, carbohydrates, lipids and other nitrogen-containing molecules are the key categories of phytochemicals. Among all these phytochemical compounds, molecules with an active hydrogen atom (-COOH, -NH, -NH_2, etc.), like polyphenols, has been selected as the suitable one to synthesize phytosome. A hydrogen bond can be formed between herbal derivatives and the hydrophilic parts of amphiphile molecules by an active hydrogen atom. Polyphenols are the most frequently found phytochemicals in plant-based foods. Many researchers reported that Polyphenols have potential health benefits in a variety of diseases, including inflammation, neurodegenerative disease, cancer, cardiovascular diseases, type 2 diabetes, and obesity (Kondratyuk et al., 2004; Tsao et al., 2010; Barani et al., 2021).

Phospholipids:

Phospholipids help in digestion and also have nutritional properties such as giving nutrition to brain cells, helping in liver cell regeneration and also can act as a carrier molecule for both polar and non-polar molecules (Singh et al., 2011). Different kinds of phospholipids obtained from various sources can be used such as soy lecithin, phosphatidylserine, and 1,2- distearoyl-Sn-glycero-3- phosphatidylcholine. Egg yolk and plant seeds are both rich sources of phospholipids and are classified depending on backbone *viz* sphingomyelins and glycerophospholipids. Amongst glycerophos-pholipids, phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylserine (PS) and phosphatidylinositol (PI) are the key compounds (Li et al., 2015). PC, PS and PE are the main phospholipids used in phytosome synthesis. PC is frequently used for synthesizing phospholipid complexes. PC is an amphipathic molecule that enables its solubility in both water and lipid. Moreover, being an essential component of the plasma membrane, PC has strong biocompatibility and minimal toxicity (Suriyakala et al., 2014; Lu et al., 2019).

Solvents:

Researchers have produced phyto-phospholipid compounds using a range of solvents. Presently, protic solvents like ethanol and methanol were used to synthesize phyto-phospholipid complexes instead of aprotic solvents like methylene chloride, cyclic ethers, halogen derivatives, ethyl acetate, and hydrocarbons because of their higher success rates (Khan et al., 2013; Suryakala et al., 2014). Various solvents have been successfully investigated. Ethanol can be a beneficial and popular solvent that leaves minimum residue and cause minimum harm when the yield of phospholipid complexes is high enough (Lu et al., 2019). Many research studies have recently used the supercritical fluid (SCF) process to manipulate the size, shape, and morphology of the material of interest. Supercritical anti-solvent process (SAS), one of the SCF technologies, becoming a promising technique for producing micronic and submicronic particles with controlled size and size distribution (Semalty et al., 2014).

Stoichiometric Ratio of Phospholipids and Active Phyto-Constituents:

Normally, phytosomes are developed by reacting phytoactive constituents with natural or synthetic phospholipids in the 0.5-2.0 molar ratio range. A stoichiometric ratio of 1:1, on the other hand, is thought to be the most efficient ratio for preparing phospholipid complexes, e.g., quercetin-phospholipid complexes have been produced through combining Lipoid S 100 and quercetin at a molar ratio of 1:1, curcumin phytosomal softgel and phytosomes have been developed by incorporating curcumin and SPC Lipoid® S 100 in molar ratio of 1:1. However, different stoichiometric ratios of phytoconstituents and phospholipids have also been used. Silymarin-phospholipid complexes have been synthesized with different stoichiometric ratios such as 1:5, 1:10 and 1:15 and the results indicate that phytosome complexes produced with a stoichiometric ratio of 1:5 showed the best physical properties and the highest loading capacity.

Properties of Phytosomes:

Chemical properties:

Phytosomes are made by reacting a stoichiometric amount of phospholipid with standardized plant extracts as the substrate. According to the spectroscopic data, the phospholipid substrate interaction is caused by the formation of a hydrogen bond between the polar head (i.e., phosphate and ammonium group) and the polar functionalities of the substrate (Chauhan et al., 2009). The size of Phytosomes varies from 50 nm to a few hundred µm (Tripathy et al., 2013). Phytosome, after treating with water, changed their shape to a micellar-like structure and looks like liposomes when observed under photon correlation spectroscopy (PCS). The data gathered from H1 NMR and C13 NMR indicates, the fatty chain gives unchanged signals both in free phospholipid and in the complex, which indicates that long aliphatic chains are wrapped around the active principle producing lipophilic envelope (Patel et al., 2013; Jain et al., 2005; Dayan et al., 2000). The complexes are usually soluble in aprotic solvents, less soluble in lipids and insoluble in water (Maffei et al., 1994)

Biological properties:

In comparison to traditional herbal extracts, phytosomes are more advanced herbal products that are better absorbed, utilized, and subsequently yield better results. The increased bioavailability of phytosomes over non-complexed botanical derivatives has been demonstrated by pharmacokinetics experiments or by pharmacodynamic tests in laboratory models and human subjects. (Franco and Bombardelli, 1998).

Preparation Method:

Several methods for preparing phytosomes have been proposed, including the rotary evaporator method, anti-solvent precipitation technique, freeze-drying co-solvency, and salting-out technique. The evaporator approach and solvent evaporation are popular and widely used techniques for producing phyto-phospholipid complexes. Shan et al. (2012) applied the solvent evaporation method to synthesize oleanolic acid-phospholipid complexes whereas, berberine-phospholipid complexes (P-BER) prepared by rapid solvent evaporation method followed by a self-assembly procedure to develop more efficient berberine drug delivery system. In the solvent evaporation process, lipid components were combined with an organic solvent and then the solvent was pulled out by vacuum rotary evaporation (Yu et al., 2016). By using the solvent evaporation method, recently Telange et al. (2019) developed an apigenin-phospholipid phytosome to increase the bioavailability, solubility, and antioxidant activity of the compound in vivo. To increase the bioavailability of dihydromyricetin, which has the potential for antibacterial, antioxidant, hypoglycemic, anti-inflammatory, and hypolipidemic effects, Zhao et al. (2017) developed the dihydromyricetin-phospholipid complex via solvent evaporation approach. Singh et al. reported the synthesis of lawsone-loaded phytosome by using the anti-solvent precipitation method; during this process, lawsone and soy lecithin were refluxed with dichloromethane at a temperature not exceeding 60 °C and then, to get the precipitation, N-hexane was added and stored overnight in vacuum desiccators (Singh et al., 2015). Karole et al. (2019) employed an anti-solvent precipitation method to construct phytosomes utilizing *Bombax ceiba* extract. In addition to the above-mentioned methods, anhydrous co-solvent lyophilization is another method to produce phyto-phospholipid complexes. For example, Diosmin was first dissolved in DMSO, added to the SPC solution, and stirred for three hours for complex formation. Kaempferol-phospholipid complexes were also produced by using the lyophilization process (He et al., 2010; Al SJE et al., 2012; Freag et al., 2013; Telange et al., 2016). Li et al. devised supercritical anti-solvent precipitation to make puerarin phospholipid complexes, and they suggested that this method was better than other ones for making drug phospholipid complexes. The phyto-phospholipid complex was also developed by using the salting-out method and the film formation method (Lu et al.,2019).

Characterization of Phytosomes:

Solubility and partition coefficient:

Determining solubility in both water or natural solvents and the n-octanol/water partition coefficient (P) is critical to represent active constituents, active constituent phytophospholipid complexes and physical mixtures and generally, phyto-phospholipid complexes have higher lipophilicity and hydrophilicity than active constituents, and exhibit better lipophilicity (Pathan et al., 2011).

Surface Charge:

Zeta potential (total charge produced by medium) is defined as the electrical charge carried by the phytosomes in emulsions. Depending on the composition of phytosome, Zeta potential may be negative, positive, or neutral (Chibowski et al., 2016; Smith et al., 2017). The stability of phytosome in a medium is reflected by the value of Zeta potential. A stable phytosome emulsion represents a zeta potential greater than or less than 30 mV (Ojha, 2018). The electrostatic characteristics of phytosomes can be measured using Doppler velocimetry, zeta sizer, fluorophores, high-performance capillary electrophoresis, and DLS instruments (Barani et al., 2021).

Surface Tension:

The surface tension of phyto-active constituents in aqueous solution can be measured utilizing ring method in a Du Nouy ring tensiometer (Pal et al., 2021).

Transition Temperature:

Differential scanning calorimetry (DSC) is frequently used to quantify the enthalpy and transition temperature of phospholipid complexes.

Drug content:

The volume of the drug can be measured through modified high performance liquid chromatographic method or any suitable spectroscopic technique.

Lamellarity and Stability:

The term "lamellarity" refers to the number of lipid bilayers in phytosomes. The most popular techniques for determining lamellarity include small-angle X-ray scattering, 31P nuclear magnetic resonance, and electron microscopy techniques. One of the most accurate and frequently used technique for figuring out lamellarity is 31P NMR. This method's drawback is that it is susceptible to experimental factors such as reagent concentration, vesicle type, and buffer concentration. Cryo-microscopy, freeze-fracture, and negative staining electron microscopy are further modern visualization techniques. Phytosomal stability is also an essential aspect in the development of an effective carrier. To investigate the phytochemical alterations of phytosomes during storage and general circulation, stability studies are carried out. By evaluating the mean vesicle size, zeta potential, size distribution, and trapping efficiency, stability can be assessed over several months. Rhamnolipids (RL) modified curcumin liposomes were evaluated for their thermal and photochemical stability, and the results revealed improved stability of the loaded liposomes under varying pH, ionic, and heat conditions (Gurunathan et al., 2018; Cheng et al., 2019)

Encapsulation Efficiency and Release Behaviour:

The amount of phytochemical that is encapsulated in the phytosomes is evaluated by encapsulation efficiency (EE percent). The Equation given below can be used to describe EE percent:

where EE% is for encapsulation efficiency, EP stands for encapsulated phytochemical, and IP stands for initial phytochemical content.

$$EE\% = \{(IP - EP) \div IP\} \times 100$$

The Encapsulation efficiency of phytoactive constituents in phospholipid complexes can be measured by utilizing ultracentrifugation method. The ultracentrifugation is conducted either at high rpm for shorter periods or low rpm for longer periods to find out % entrapment efficiency (Barani et al., 2021; Pal et al., 2021).

Since the release rate achieved in vitro may serve as an indicator of the efficacy of the carrier in vivo, the drug release behaviour of vesicle carriers has been the focus of intensive investigation over the past few years. The most popular conventional methods for determining the release rate of active substances are sample and separate strategy, in situ process, continuous flow, membrane diffusion techniques (dialysis, micro-dialysis, fractional dialysis, and reverse dialysis), and membrane diffusion strategies (Barani et al., 2021).

Phytosomes & Disease Management:

Several research works have revealed the importance of phytosomes in disease control (Fig. 2) and management. Natural herbal extracts with potential therapeutic values are being retarded from its optimized clinical application due to poor gastrointestinal absorbance followed by low bioavailability. To overcome this problem scientists have been formulating different types of phytosomes encapsulated phyto-active components of plant extracts as one of the easiest ways of drug delivery system with increased structural stability and bioavailability with minimum/no side effects. Table.1 showing some popular phytosomes, their active components and the utilization of these drugs.

Phytosomes in Diabetes Management:

Allium cepa–phospholipid (ACP) complex has been prepared using one mole each of *Allium cepa* standard extract (ACE) and hydrogenated soya phosphatidylcholine (HSPC) in dichloromethane and tested for antidiabetic potentiality in streptozocin induced diabetic rats. Characterization of prepared phytosomes was done using DSC, SEM, and FT-IR studies. ACP showed high radical scavenging activity. ACE and ACP resulted in reduced hyperglycemia in two different treatment regimens (one dose one-day and multiple-dose fifteen-day) in diabetic studies. Also decreased STG, STC, VLDL-c, and LDL-c suggested low levels of lipolysis. Thus, ACP accelerated hypolipidemia, and showed antidiabetic activity along with antioxidation activity (Habbu et al., 2015). In another study, Yu et al. (2016) first developed the BER-SPC complex by mixing Berberine (an isoquinoline alkaloid with antidiabetic potentiality) and Soybean phosphatidylcholine (SPC) in a ratio of 1:5 using the rapid solvent evaporation method then BER-SPC complex was formulated into the P-BER by a self-assembly technique for preparing a better BER drug delivery system. 85% entrapment efficiency, nanoscale particle size, and negative surface charge highly suggested the stability of formulated phytosome. The oral bioavailability of the P-BER was found to increase 3-fold than normal orally administered BER. 9 weeks old, db/db mice were treated with BER (100 mg/kg, suspended in 0.5% CMC-Na) and P-BER (100 mg/kg) for 4 weeks respectively. End of the experiment, fasting glucose level showed a significant hypoglycemic effect, indicating glucose metabolism had been improved in

P-BER treated mice compared to only BER. Also found to decrease triglyceride (TG) levels in liver of db/db mice to near control value. Altogether suggesting anti-diabetic efficiency along with diabetogenic hyperlipidemia management. Improvement in the pharmacological activity of conventional herbal extracts, containing quercetin (a major flavonoid) from three fruit plants *Mamordica balsamina*, *Citrullus colocynthis*, and *Mamordica dioica* were loaded in phytosomes to formulate antidiabetic phytosomes, had been evaluated for enhanced efficacy. The particle size of vesicles ranged between 300-675 nm and entrapment efficiency was measured between 70% to 88%. Suggesting good stability of phytosomes with -22.7mV zeta potential. Phytosomes prepared with fruit plant extracts exhibited anti-diabetic activity at low doses equivalent to the conventional drug metformin (Rathee & Kamboj, 2018). Phytosomes loaded with *Casuarina equestifolia* extract have been successfully synthesized following the antisolvent precipitation method with average particle size, entrapment efficiency, and Span value of 295 ± 0.53nm, 82.43 ± 1.65% and 0.34 ± 0.14 respectively. 19.35mv zeta potential suggested the stability of the particle. While *in vitro* study depicted that the drug has been successfully released following Korsmeyer- Peppas kinetic model, *in vivo* experimental results suggested its antidiabetic efficacy compared to crude *Casuarina equestifolia* extract (Rani et al., 2019).

Table 1. Major Phytosome Formulations and Their therapeutic Applications:

Sl. No.	Common Name/ Trade Name	Composition	Disease Management	References
1.	18 ß-glycyrrhetinic acid Phytosome	18 ß-glycyrrhetinic acid from the rhizome of Licorice	Soothing, Anti-inflammatory activity	Bombardelli et al., 1989
2.	Berberine-phospholipid complex- based phytosomes	Berberine	Antidiabetic, anti hyperlipidemia	Yu et al., 2016
3.	Casperome® Phytosome	*Boswellia serrata* Roxb. ex Colebr. – Resin	Anti-inflammatory response, pain reliever, Joint health, promote tissue regeneration, anti-psoriasis and erythematous eczema	Riva et al., 2017; Togni et al., 2014
4.	Centevita®	Asiatic acid, madecassic acid from *Centella asiatica*	Anti-inflammatory, Cognitive improvement, skin disorders, antiulcer, wound healing, hair falling	Ju et al., 2018; Sbrini et al., 2020
5.	Crataegus Phytosome®		Antioxidant	Lu et al., 2019
6.	Cucurbita Phytosome/ Tocopherol, carotenoids Phytosome	*Cucurbita pepo*	Anti-inflammatory, Prostatic hyperplasia	Huang et al., 2020

7.	Curcumin Phytosome/ Meriva®	*Curcuma longa* L.- Rhizome	Antioxidant & anti-inflammatory, muscle injury recovery, pain reliever,	Zhang et al., 2013; Drobnic et al., 2014
8.	Escin β sitosterol Phytosome	Escin β-sitosterol of horse Chestnut fruit	Antihyperalgesic	Djekic et al., 2019
9.	Evodiamine phospholipids complex	Evodiamine	Anti-tumor	Liu et al., 2012
10.	Ginkgoselect® Phytosome	Flavonoids of *Ginkgo biloba*	Anti-aging & cognitive improvement	Naik et al., 2006
11.	Ginseng Phytosome	Ginsenosides of *Panax ginseng*	anti-inflammatory, antioxidant, and anticancer	Kiefer & Pantuso, 2003
12.	Ginseng Phytosome	*Panax ginseng*	Nutraceutical, immunomodulatory	Chen at al., 2011
13.	Greenselect®/ Green Tea Phytosome	*Camellia sinensis* (L.) O. Kuntze – Leaf	Bodyweight maintenance after intentional weight loss, Anti-obesity, Antioxidant activity, Anti-Cancer	Di Pierro et al., 2009; Gilardini et al., 2016
14	Gingerol	*Zingiber officinale*	Anti-bacterial, anti-inflammatory And antioxidant activity.	Singh et al., 2018
15.	Hawthorn Phytosome	Flavonoids of *Crataegus* species	Anti-hypertensive and Cardioprotective	Ja, 2011
16.	Leucoselect®/ Grape Seed Phytosome	*Vitis vinifera* L. – Seed	Cardiovascular protection and Anti-oxidant activities Effective against chronic allergic disorders	Nuttall et al., 1998; Magrone et al., 2014; Vigna et al., 2003
17.	Lymphaselect	*Melilotus officinalis*	Used for chronic venous insufficiency of the lower limbs	Albrigo et al., 2019
18.	Mirtoselect®/Anthocyanose Phytosome	*Vaccinium myrtillus*	Antioxidant, anti-inflammatory, diabetic retinopathy	Liu et al., 2013
19.	Naringenin Phytosome	*Citrus aurantium*	Suppress Oxidative stress, Prevent acute lung injury	Yu et al., 2020
20.	OleaselectTM Phytosome	Polyphenols of	Anti-inflammatory	Shivanand &

		Olea europaea	and Antihyperlipidemic	Kinjal, 2010
21.	Polinacea Phytosome	*Echinacea angustifolia* Root	Improve immune system, Counteract increased cortisol response	Sgorlon et al., 2012
22.	PolinaceaTM Phytosome	Echinacosides of *Echinacea angustifolia*	Immunomodulation and Nutraceuticals	Li et al., 2015
23.	Phytosome®	Proanthocyanidin A2 obtained from *Aeschylus hippocastanum*	vasokinetic activity, antiwrinkle, antioxidative, UV protection	Lu et al., 2019
24.	Quercefit™ Phytosome	Quercetin found mostly in citrus fruits, apples, onions, parsley, tea, grapes etc.	Antiasthma, Sports suppliment, suppress oxidative stress,	Cesarone et al., 2019
25.	Rhizoma paridis Phytosome	Rhizoma paridis from *Paris polyphylla*, steroidal saponins	Anticancer activity, immunity adjustment, antiviral and anti-inflammation	Liu et al., 2013
26.	Siliphos®	Silybin of *Silybum marianum*	Liver protection, antioxidant	Kidd & Head, 2005; Tedesco et al., 2003; Haddad et al., 2011
27.	Soyselect®/ Soybean extract Phytosome	*Glycine max* extract	Anti-obesity, Anti-angiogenic, anti-cancer, cardioprotective, and anti- hyperlipidemic	El-Menshawe et al., 2018
28.	Ubiqsome® Phytosome	CoQ10	Suppress oxidative stress in cardiac & skeletal muscle, Antiinflammation	Petrangolini et al., 2019
29.	Vazguard™ Phytosome	Citrus x bergamia Risso & Poit. - Fruit juice	Extremely effective in supporting healthy blood levels through the optimization of total cholesterol, c-LDL, c-HDL,	Riva et al., 2020

			triglycerides, and glucose levels	
30.	Vazguard™/Naringin Phytosome	*Bergamot extract*	Protection to cardiometabolic disorders, balance lipid profile & glucose level	Mollace et al., 2019
31.	Virtiva®/ Ginkgo biloba Phytosome	Ginkgo flavonglycosides like ginkgolides, bilobalide	UV protection, Improve cerebral insufficiency, vasokinetic activity, antiwrinkle, antioxidative,	Di Pierro et al., 2016; Lu et al., 2019
32.	Visnadex Phytosome	Visnadin from *Amni visnaga*	Microcirculation improvement	Alam et al., 2013
33.	Xanthones Phytosome	*Swertia alternifolia*	Suppress oxidative stress	Kalita et al., 2013

Phytosomes in Respiratory Disease Management:

The patients treated with *Boswellia serrata* phytosome as supplementation with the normal treatment (inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs) required lower number of inhalations/days compared to other group of asthma patients that had not received supplementation (Ferrara et al., 2015). Gingerol, the antibacterial drug blended with soya lecithin to formulate phytosome (GP), was further loaded in chitosan (polysaccharide derived from chitin) solution to prepare phytosome complexed with chitosan (GLPC) and studied for its efficacy against respiratory infection. *In vitro* study results showed antioxidant activity, susceptible antibacterial activity and effective anti-inflammatory activity as well as *in vivo* results exhibited increased bioavailability, and sustained-release of gingerol as compared to GP in respiratory infection disease (Singh et al., 2018). A preliminary study by Cesarone et al. (2019) with patients (healthy but with mild-moderate asthmatic attacks and rhinitis) were given quercetin phytosome in addition to standard management (SM) for 30 days, showed better results compared to only SM treatment strategy in controlling, preventing and decreasing daily and night symptoms. Also found to reduce the use of inhalers, nasal drops, and rescue medications with improved rhinitis score. In a recent investigation Yu et al. (2020) prepared a unique naringenin (NG) loaded Dipalmitoylphosphatidylcholine (DPPC) phytosomes and evaluated its efficacy in rat with acute lung injury. Parameters of *in vitro* study showed superior drug delivery ability. *In vivo* data suggested inhibition of the phosphorylation of P38 in the MAPK pathway and suppression of oxidative stress following dry powder inhalation (NPDPIs).

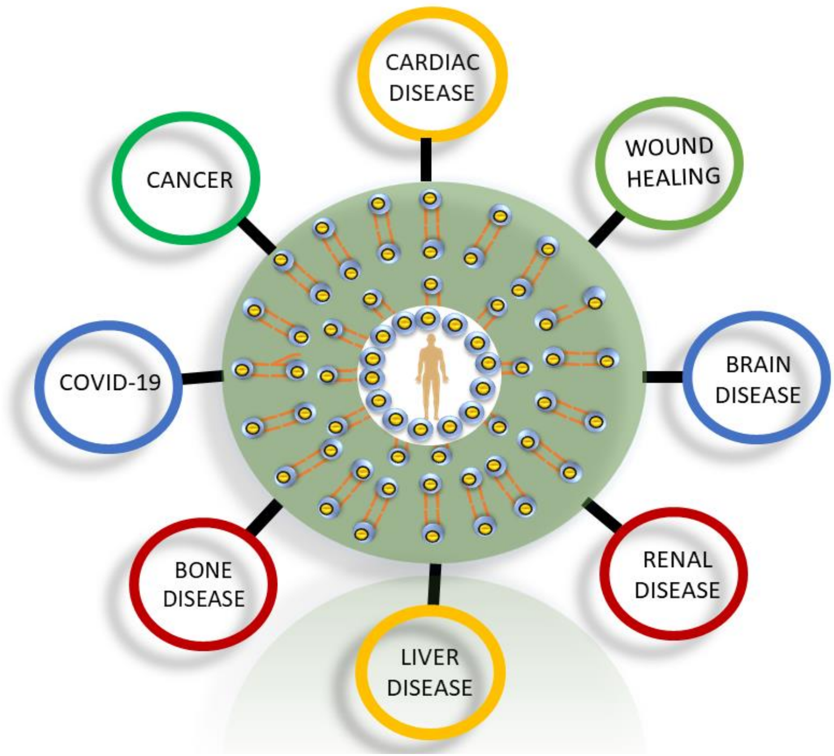

Figure 2. Human Diseases Controlled by Phytosome Based Therapeutic Approaches

Phytosomes in Wound Healing Management:

Sinigrin-phytosome complex was prepared to evaluate its cytotoxic as well as wound healing capability on Human immortalised keratinocyte (HaCaT) cells and A- 375 melanoma cells in *in vitro* experiment. DSC and FTIR analysis confirmed the successful formation of phytosome loaded with Sinigrin, characterized by an average particle size of 153 ± 39 nm and with 10.09 ± 0.98 mV zeta potentials. Topical application of formulated complex at a higher concentration of 0.14 mg/ml for 42 h resulted in cent percent wound cure compared to 71% achievement by Sinigrin alone, with minimum cytotoxicity for HaCat cells but higher cytotoxicity for A-375 cells. This study opens a new vista of therapeutic application of phytosomes in wound healing, even for cancerous wounds also (Mazumder et al., 2016). Phytosome filled with an aqueous extract of *Moringa oleifera* (MO) leaves (MOPCT) has been developed to verify the optimized bioavailability of topically applied MO across the wound. TEM study revealed multilamellar vesicular appearance (avg. size of 198 ± 21 nm) of phytosome with zeta potential of −28.3 ± 1.31 mV. The filtered MOPCT exhibited 82.8%, 52.2%, 15.6%, and 8.44% encapsulation efficiency for quercetin, kaempferol, chlorogenic acid, and rosmarinic acid respectively along with maximized migration (closing gaps) and proliferation rate in *in vitro* investigation with normal human dermal fibroblast NHDF cell compared to the controls. Non-cytotoxic effect at and below 1.5mg/ml concentration has been recorded, suggesting the functional wound-repairing potentiality of MO phytosomes (Lim et al., 2019).

Phytosomes in Cancer Management:

The efficacy of phytosome-formulated drugs has been enormously studied in various types of cancer therapy. Inhibition of cell proliferation, invasion, metastasis, cell cycle arrest and induction of apoptosis are some of the strategies employed by phytosomal formulation to control cancer.

Nervous System Cancer:

Intraperitoneal administration of Curcumin Phytosome (CCP), into the GL261-implanted glioblastoma (GBM) mice showed tumor regression and positive alterations in phenotype of the tumor-associated microglial cells (TAMs). Augmentation of the Arginase1^{low}, iNOS^{high} M1-type tumoricidal microglia and inhibition of the tumor-promoting Arginase1^{high} , iNOS^{low} M2-type TAM population have been observed. Findings indicate role of CCP in GBM killing and repolarization of TAMs towards the tumoricidal M1 state (Mukherjee et al., 2016). Conversely negligible effect of CCP against medulloblastoma (CNS cancer in children) in D425MED (animal model) has been reported (Wright et al., 2017). Immune-competent syngeneic C57BL6 mouse model along with the GL261-implanted glioblastoma (GBM) mice have been used to find out the effect of CCP on immune modulation. Suppression of tumor-promoting proteins in M2 type (STAT3, ARG1, and IL10), induction of anti-tumor proteins in M1 type (STAT1) and nitric oxide synthase in the TAM, caspase 3 activation, GBM stem cells elimination along with activated NK cells and M1 type macrophage were observed in GBM tumor following CCP treatment. Thus, indicating the role of CCP in GBM as well as GBM stem cell destruction (Mukherjee et al., 2018). A recent investigation by Di Pierro et al. (2019) showed treatment with *Boswellia serrata* extract phytosome can attenuate side effects of radio-chemotherapy. Radiotherapy-induced cerebral edema in 10% GBM patients treated with formulation were found to decreased. Suggesting less dexamethasone uptake by brain edema followed by low side effects of steroid treatment.

Oral Cancer:

Celastrol (CST), a promising herbal drug with anticancer potency suffers limitations due to limited aqueous solubility, and poor gastrointestinal absorption that resulted in its low oral bioavailability. CST-phospholipid complex (CST-PHY) nanocarrier has been prepared by solvent evaporation technique with a particle size of 178.4±7.07 nm and zeta potential of -38.7±3.61mV. In-vitro release investigation suggested increased CST-PHY release compared to free CST which confirmed enhanced solubility of CST- phytosomes. *In-vivo* pharmacokinetic study was carried out in adult healthy male rabbits and assessment indicated higher oral absorption of CST-PHY compared to CST alone. Increased oral bioavailability suggested its therapeutic application in oral cancer treatment (Freag et al., 2018).

Skin Cancer:

A nanostructured lipid carriers (NLC) prepared with silymarin (silymarin-NLC) showed increased permeation, better drug release and stability compared to phytosomes available in market. *In vitro* study with melanoma cell line (SK- MEL-2) revealed it's anticancer efficacy in dose-dependent manner and apoptotic induction ability (Singh et al., 2016). The formulation of stable and nearly monodisperse lipid nanoparticle carriers depends upon the surfactants used in the structural design. Two different types of lipids nanocarriers, viz. solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) were prepared using 1,2-di(conjugated) linoleoyl-sn-glycero-3-phosphocholine ((CLA)PC) in relation to 1,2-distearoyl-sn-glycero-3-phosphocholine ((SA)PC) under high pressure homogenized condition and evaluated for the anticancer potentiality of both, in human cancer epidermoid carcinoma (A431) and malignant skin melanoma (MeWo) cell line. The higher efficiency of (CLA)PC phospholipid nanoparticles as effective drug delivery systems in the inhibition of cancer had been observed in both cell lines compared to nanosystems stabilized by (SA)PC. (CLA)PC phospholipid nanoparticles showed anticancer efficacy via increased necrosis, cell number reduction, and altered cellular morphology (Pucek et al., 2017).

Lung Cancer:

Mammary gland tumor cell line (ENU1564) inoculated into the mammary fat pad of athymic nude mice in a xenograft study, was treated orally with either curcumin or Curcumin formulated with phosphatidylcholine. Microscopic as well as histochemical results suggested the anticancer efficacy of fabricated phytosome over curcumin, along with reduced expression of MMP-9 hampered lung metastsis (Ibrahim et al., 2010). Diosgenin (3β- hydroxy-5-spirostene, Di), an herbal sterol was used to prepare phytosomes of different Di derivatives to evaluate its effect on human A549 and PC9 lung cancer cells. FZU-0021-194-P2 (P2), a derivative of DiP exhibited more cytotoxic and anti-proliferative effects compared to other DiPs after 72h of incubation. P2Ps were oval-shaped (53.6 ± 0.3 nm) with -4.0 ± 0.7 mV zeta potential. They were found to arrest the cell cycle at G0/G1 phase and induced apoptosis. The result suggested that P2P could be a potential anti-lung cancer formulation (Xu et al., 2019). A very recent study by Mao et al., 2021 showed, increased levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), omega-3 polyunsaturated fatty acids (n-3 PUFA) and unsaturated phosphatidylcholines (PC) after one month treatment with Grape seed procyanidin extract (GSE) complexed with soy phospholipids (leucoselect phytosome), could be correlated with anti-cancer properties. Again 3 months of treatment resulted in an increased serum level of prostaglandin (PG) E_3 (PGE_3) following a reduction in bronchial Ki-67 suggesting antineoplastic and anti-inflammatory responses. Further antiproliferation of human lung cancer cell lines A549 has been noticed.

Breast Cancer:

High expression of nuclear factor erythroid 2-related factor 2 (Nrf2) provide chemotherapeutic resistance to the cancer cell. *In vitro* investigation revealed co-treament of phytosomes loaded with luteolin and doxorubicin facilitated highest cell mortality in MDA-MB 231 human cancer cells through inhibiting Nrf2 and its downstream gene expressions (Sabzichi et al., 2014). In another study Mahmoodi et al., 2015 showed superior inhibitory effect of Silybin-phosphatidylcholine on cellular growth and HER2 down regulation in human breast cancer SKBR3 cell line compared to silybin. Metastatic breast cancer (4T1) bearing mice when treated with cryoablation (killing of tumor cells by cryotechnology) combined with phytosomal curcumin resulted into delayed development of lung metastases and survival on the long-term compared to control or only phytosomal curcumin (Chandra et al., 2015). Breast cancer cells MCF-7 when treated with doxorubicin combined to nano-quercetin phytosome showed significant increase in apoptosis from 40.11 ± 7.72 to 58 ± 7.13 ($p < 0.05$). Also exhibited sharp decrease in the expression of downstream genes, NQO1 and MRP1(Minaei et al., 2016). Serial investigations by Lazzeroni et al. (2016), (2017) showed quasi success in phytosome mediated drug delivery in breast cancer therapy. Where in first investigation insignificant changes in plasma IGF-1 and nitric oxide or Ki-67 in breast tumor tissue was observed for orally taken Silybin-phosphatidylcholine (milk thistle extract), in second study administration of oral Greenselect Phytosome (GSP) (a caffeine-free green tea catechin extract formulated with lecithin) were found to increase the bioavailability of epigallocatechin-3-O-gallate in breast tumor tissue with significant changes of Ki-67, suggesting antiproliferative efficacy of GSP in breast cancer. Phytosomal curcumin alone was found to inhibit cell growth, reduce invasiveness and migration and induce necrosis and inflammation in MCF-7 cells. Application of curcumin and 5-FU together showed, decreased lipid peroxidation but the enhanced level of MDA/SOD. In thrombin-treated breast cancer cell, curcumin downregulates cyclin D1 expression through the activation of AMP-kinase (Hashemzehi et al., 2018). In two consecutive studies researchers have formulated multi reservoir phytosomal nanocarriers for delivering the antineoplastic cocktail drug. Incorporating both, Monascus yellow pigments - Monascin and ankaflavin (MYPs) and herbal drug, resveratrol (RSV) within the hydrophobic core of casein micelles CAS MCs were found to be very much effective in controlling tumor size through eliciting cytotoxic effect in MCF-7 cells. In another study, similar combinations were incorporated within the core of folate-conjugated casein micelles (FA-CAS MCs, F1) and PEGylated RSV-phospholipid complex bilayer enveloping casein-loaded micelles (PEGPC-CAS MCs) were also prepared for targeting breast cancer cells. Both coloaded MCs exhibited superior cytotoxicity to MCF-7 breast cancer cells than free drugs. *In vivo* antitumor efficacy study revealed PEGylated MCs, compared to folate-conjugated MCs showed better tumor regression ability. CUR/IR780@SMEDDS, a hybrid self-microemulsifying drug delivery system has been manufactured with NIR dye IR780 and curcumin phospholipid complex by Liu et al. (2019) for deciphering combinatorial (chemotherapeutic and phototherapeutic) effect on breast cancer. *In vitro* as well as *in vivo* studies revealed prominent photodynamic and photothermal potency of hybrid formulation with increased bioavailability of both IR 780 and curcumin, enhanced cytotoxicity along with inhibited invasion and migration of 4T1 breast cancer cells compared to simple suspensions made of curcumin and IR780.

Liver Cancer:

The efficacy of phytosomal curcumin on hepatocellular carcinoma (HCC) related to hepatitis B virus (HBV) infection has been investigated in a transgenic mouse model. Treatment resulted into improved liver histopathology, decreased lipid accumulation and infiltration of leukocyte, reduction in tumor volume and inhibition of HCC formation in transgenic mice. Also found to activate anti-inflammatory response (Tang et al., 2019).

Pancreatic Cancer:

Patients with advanced or metastatic pancreatic cancer given curcumin complexed with phytosome as a complementary drug along with gemcitabine, have shown improved safety and efficacy of gemcitabine. On analyzing data, the total disease control rate was found 61.3% (27.3% of response rate + 34% of cases with stable disease). The recorded value for free survival and overall survivals were 8.4 and 10.2 months respectively with significant tolerability. But non-significant changes had been observed in the quality of life of patients during the period of treatment (Solda et al., 2015; Solda et al., 2016; Pastorelli et al., 2018).

Bowel Cancer:

Nude mice implanted with human colorectal carcinoma (CRC) HT29 xenograft were tested with 200 mg/kg dose of silibinin or 100 and 200 mg/kg doses of silybin-phytosome (5 days per week) for 32 days to search for anticancer efficacy. The result suggested antiproliferative and proapoptotic activity (suppression of ERK1/2 and Akt pathway) and antiangiogenic effect (down-regulation of NOS, COX, HIF-1 alpha, and VEGF expression) of both silibilin and silybin-phytosome on CRC (Singh et al., 2008). Howells et al., 2011 checked the efficiency of oxaliplatin, oxaliplatin combined with curcumin phytosome and curcumin phytosome separately *in vitro* in Oxaliplatin-resistant HCT116 p53wt and p53(-/-) cell lines as well as *in vivo* in mice bearing colorectal tumor. Treatment with combination showed more antiproliferative activity *in vitro* compared to oxaliplatin treatment. *In vivo* experimental result showed the efficacy of treatment in the following order combination > Meriva > oxaliplatin > control. Phytosomal curcumin in combination with 5-Flurouracil (5-FU) when investigated in mouse model bearing colitis-associated colon cancer, showed decreased number as well as the size of tumors in both distal and middle parts of the colon and also, found to suppress colonic inflammation through modulating malondialdehyde (MDA), thiol level and catalase (CAT) (Marjaneh et al., 2018). Another study by the same group with a similar formulation showed antitumor activity along with oxidative stress induction and antiangiogenic effect via VEGF signaling pathway modulation (Moradi-Marjaneh et al., 2018).

Prostate Cancer:

Silybin-phytosome fed to 20-week-old TRAMP (palpable prostate cancer) mice for 11 weeks showed suppressed angiogenesis and epithelial-mesenchymal transition followed by inhibited tumor growth, progression, local invasion, and metastasis to distal parts of the body compared to control (Singh et al., 2008). In a pilot study, patients with benign prostatic hyperplasia (BPH), were administered phytosomal curcumin in addition to the standard treatment (BSM). The result showed improved quality of life with a reduction of signs and symptoms of BPH evidenced by IPSS score, without creating any significant side effect compared to BSM alone (Ledda et al., 2012).

Endometrial Cancer:

Patients with endometrial carcinoma (EC) received 2 gm Curcumin Phytosome (CP) orally every day for 2 weeks showed decreased MHC expression levels on leukocytes, number of monocytes and ICOS expression on $CD8^+$ T cells but without any significant alterations in inflammatory biomarkers (Tuyaerts et al., 2019).

Overian Cancer:

Optimized phytosomal-Icariin (ICA) (a flavonol glycoside) formulation was found to induce cell cycle arrest at G2/M and pre-G1 stages in OVCAR-3 ovarian cancer cells. It also found to increase cytotoxicity along with apoptotic cell mortality and ROS generation (Alhakamy et al., 2020).

Phytosomes in Bowel Inflammation Management:

Symptoms of ulcerative colitis (UC) viz. intestinal pain, bowel movements and cramps, watery stools, blood in stools, anemia, malaise, rectal involvement, and white blood cells count were found to improve in UC patients following Lecithin-based delivery of *Boswellia serrata* extracts (BSE) (Pellegrini et al., 2016). In a similar experiment, abdominal pain, altered bowel movements, meteorism and cramps, the common symptoms of irritable bowel syndrome (IBS) have been found to improve without any side effects due to the administration of *Boswellia serrata* extract phytosome as a supplement with hyoscine butyl bromide, papaverine hydrochloride + *Atropa belladonna* extract (Belcaro et al., 2017). In another study with the same treatment regimen in healthy persons with mild IBS showed a lower mean score value for almost all the self-assessed IBS symptoms, compared to persons prescribed standard management. Altogether suggesting less need for medication or gastroenterologists' intervention (Rive et al., 2019).

Phytosomes in Integumentary Disease Management:

The effect of *Centella asiatica* phytosome (CA) has been examined through the application of CA dorsally to the skin of phthalic anhydride (PA) induced atopic dermatitis (AD) mouse model HR-1and RAW 264.7 murine macrophages. CA inhibited inflammatory cells infiltration, activity of NF-κB, release of TNF-α, IL-1β, IgE and expression of iNOS and COX-2 and also found to inhibit lipopolysaccharide-induced NO production as well as iNOS and COX-2 expression in murine macrophage (Ho et al., 2018).

Phytosomes in Cardio Vascular Disease Management:

Serial investigations by Panda and Naik, 2008, 2009 revealed cardioprotective effect of *Ginkgo biloba* phytosomes (GBP) alone or in combination with *Ocimum sanctum* extract (Os) in subcutaneously administered isoproterenol (ISO)-induced myocardial necrosis in rat models. Histoarchitectural analysis of heart along with reduced marker enzymes in serum viz. AST, LDH, and CPK served as pieces of evidence that orally administered GBP (200mg/kg b w) alone or in combination i.e., GBP (100 mg/kg b w) with Os at two doses (50 and 75 mg/kg b w) have significantly reduced ISO (85 mg/kg b w)-induced cardiac necrosis in the rat. Antioxidant parameters (GSH, SOD, CAT, GPx, and GR) get augmented and malondialdehyde (MDA) levels decreased, suggesting inhibited lipid peroxidation. Though the combination of Os 75 mg/kg b wand GBP 100 mg/kg b w elicited greater protection compared to a combination of Os 50 mg/kg b w and GBP 100 mg/ kg b w but none of the combined treatments showed greater cardioprotection and antioxidation activity compared to the treatment with either GBP or Os singly. Cytokines/chemokines released by vein endothelial cells (VEC) of chronic venous disease (CVD) patient in response to an inflammatory reaction, has been investigated in presence of α-lipolic acid and GBP. GBP-mediated reduction in the basal PDGF release and the TNF-α-induced PDGF, RANTES, and CXCL10 release has suggested the anti-inflammatory activity of GBP. Though data established α-Lipoic acid had a greater anti-inflammatory activity compared to GBP. While GBP downregulates TNF-α-induced p38/MAPK and Akt activation, α-Lipoic acid significantly inhibited TNF-α-induced NF-κB activation and also diminished p38/MAPK activation (Tisato et al., 2013). The effectiveness of a commercially fabricated phytosome loaded with *Vitis vinifera* seed extract, *Melilotus officinalis* extract and 100mg bromelain was tested in 648 CVD patients from 54 Italian centers. Significant reduction in the malleolus circumference of the right and left limb including calf, knee, and metatarsal was observed in all groups either received monotherapy or combinational therapy with standard compression stockings (Albrigo et al., 2019).

Phytosomes in CNS-Related Disease Management:

Prevention of Neuronal Damage and Cognitive Improvement:

Protection of rat fetal brain from maternally ingested ethanol (EtOH) by administration of silymarin phytosome compound had been investigated by La Grange et al. (1999). The activity of the antioxidant enzyme, Gamma glutamyl transpeptidase (GGTP) was found to be higher in the phytosome-treated batch. Cognitive improvement in old aged people with memory loss has clearly shown the role of EGb 761 (*Ginkgo biloba* leaf extract) on hippocampal plasticity through its direct interaction with the glutamatergic system (Williams et al., 2004). Phytosome with *Ginkgo biloba* was found to decrease pentobarbitone-induced sleeping time, bring changes in general behavioral patterns, enhance spontaneous motility, and suppress chlorpromazine-induced blockade of conditioned and unconditioned responses in Wistar rats. Though phytosome failed to exhibit anticonvulsant activity but still showed moderate antiamnestic as well as antidepressant activity. The same authors, in other work, showed antioxidant activity of the same formulated phytosome. Antioxidant enzymes get depleted in sodium nitrite-induced hypoxic conditions. In the brain tissue of treated rats, *Ginkgo biloba* phytosome was found to protect antioxidant enzymes against sodium nitrite (Naik et al., 2006a, 2006b). Husch et al. (2013) showed increased concentrations of KBA, AKBA, βBA in plasma as well as in Brain tissue following administration of BE (*Boswellia serrata* gum resin extract formulated with soy lecithin) in rodents compared to extract without phytosome. Mancini et al. (2018) searched for the efficacy of *Annona muricata* extract (antidepressant) loaded phytosome in amelioration of blood-brain barrier (BBB) permeability over the extract only. They found not only enhanced BBB permeability but also inhibited monoamine oxidase B (MAO-B) and scavenged H_2O_2. Thus, exhibited an enhanced antidepressant-like function of the extract. Chronic glial activation (increased number of activated microglia and astroglia) causes neuronal damage by secreting free radicals and cytotoxic cytokines. Soy-lecithin based phytosomal curcumin formulation has been tested for its ability to decrease glial activation in GFAPIL6 mice (mice with chronic glial activation). Reduction in the number of microglia in the Hippocampus and Cerebellum has been found following the treatment in GFAPIL6 mice brains. Also, the dose-dependent reduction in neuroinflammatory markers have suggested anti-inflammatory potentiality of phytosomal curcumin (Ullah et al., 2020). Brain-derived neurotrophic factor (Bdnf), a well-known neurotrophin of CNS play important role in brain development including neurite growth, survivability, and spine maturations mechanisms and maintenance. Cognitive performance increased in rats treated with phytosomes formulated with extracts of *Centella asiatica* paralleled with an increased level of Bdnf. In another study, phytosomes fabricated together with extracts of *Centella asiatica* and *Curcuma longa* was found to elicit Bdnf levels in the prefrontal cortex of adult rats. Increased Bdnf level upregulated expression of downstream genes and affected protein synthesis via mTOR-S6 pathway (Sbrini et al., 2020a, 2020b).

Neurodegenerative Diseases:

Formulated curcumin with phytosome showed increased bioavailability in the frontal lobe and hippocampus when given to adult male rat consecutively for 5 days compared to a single administration. Assessment of curcumin concentration in the brain, specifically in the frontal lobe revealed, the presence of 9 pg/mg after 30 mins, 20 pg/mg after 1 hr (highest) and 2 pg/mg after 3 hr (normalized) following administration (Dell'Agli et al., 2016). Formation and deposition of amyloid plaque in the intracellular and extracellular spaces of CNS is one of the main reasons for synaptic damage related to several neurodegenerative diseases. Curcumin (Cur) targeting amyloid protein has been found to rescue neuronal damage, restore normal cognitive and sensory-motor functions in different animal models with neurodegenerative diseases, suggesting its anti-amyloid, anti-inflammatory and neuroprotective activity (Maity & Dunbar, 2018). Application of GEN-TF2, a transfersome prepared by soybean phosphatidylcholine and isoflavone genistein showed decreased oxidative stress, and permeability efficiency with diminished apoptotic cell death in a neuronal cell line (PC12), suggesting a better drug delivery system compared to nonformatted genistin (Langasco et al., 2019). Improvisation of intranasal drug delivery using nanotechnology (nanoparticles, liposomes, exosomes, phytosomes, nanoemulsion, nanosphere) facilitating permeability across BBB as well as increased bioavailability, for the better management of Alzheimer's disease (AD) had been successfully investigated (Bahadur et al., 2020).

Cerebral Ischemia, Neuropathy and Migraine:

Rutin–phospholipid complexes (Ru–PLC's) showed improved functional outcomes in middle cerebral artery occlusion MCAO (rats with experimental ischemic brain) stroke model,compared to treatment with effective rutin only (Ahmad et al., 2016a). In another study the phytosomal complex (NIMPLC) prepared by extract of Ashwagandha (*Withania somnifera*) roots NMITLI118RT + loaded in phytosome. NIMPLC showed better beneficial effects over NMITLI118RT + tested in 1 h pre and 6 h post treatment validated by reduction in MDA levels, increment in GSH levels, reduction in neurological deficit (ND) scores and reduction in infarct size (Ahmad et al., 2016b).

Patients (n=141) with neuropathic pain either with lumbar sciatica, lumbar disk herniation, and/or lumbar canal stenosis or carpal tunnel syndrome (CTS) were given dexibuprofen (400 mg twice/day) along with lipicur (lipoic acid + curcumin phytosome and piperine) showed > 66% have reduced neuropathic pain of both conditions, indicating safety and efficacy of complementary treatment (Di Pierro & Settembre, 2013). In another study, patients (n=180) with CTS, awaiting surgery of median nerve have given a combination of oral supplements prepared with curcumin phytosome (500 mg), α-lipoic acid (300 mg), and vitamins of the B group. Patients who have received supplementation before and after surgery twice a day for 3 months, have shown diminished nocturenal symtoms and decreased number of positive Phalen's test at 3 months post-surgery compared to other treatment groups that either received no treatment or received treatment prior to surgery only. Thus, combinatorial supplementation proved to be a safe and effective against CTS patients (Pajardi et al., 2014).

Fifty women with MA (migraine with aura) has been treated with a combination of *Ginkgo biloba* phytosome (Ginkgolide B the key component), vitamin B2 and coenzyme Q 10 (twice daily) to find out its efficacy. Observed result showed complete disappearance of MA in 11.1% of patients during T1 and in 42.2% of patients during T2. Both frequency and duration of MA also get reduced. In other experiment same formulation of *G. biloba* extract tested on 25 subjects with MA showed a similar trend of result (D'Andrea et al., 2009; Allais et al., 2013). Phytosome formulated with the *Boswellia serrata* extract, magnesium, L-tryptophan, and vitamins (riboflavin, niacin, vitamin D) administered in patients with transient tension migraine and migraine without aura showed improvement in the monthly attack number, pain modulation without any side effects (Balzano & Ciccone, 2018).

Phytosomes in Hepatic Disease Management:

Serial investigations by Naik & Panda, 2007, 2008 established hepatoprotective effects of *Ginkgo biloba* phytosome (GBP) against chemically induced liver toxicity. In the first study, liver damage was induced in Wistar rats by administering carbon tetrachloride (CCl4) 1ml/kg daily for 7 days. GBP administered in two separate doses, 25 mg/kg and 50 mg/kg along with silymarin (200 mg/kg) as the standard reference drug. Treatment showed decreased lipid peroxidation, elevated level of SOD, CAT, GPx, GR, albumin, total proteins, but decreased levels of glutamic-pyruvic transaminase (GPT), alkaline phosphatase (ALP), glutamic oxaloacetic transaminase (GOT) but insignificant change in GSH level in serum. The second experiment was carried out in the same model but with rimpfacin-induced liver toxicity (500 mg/kg RMP administered daily for 30 days). Workers got similar results suggesting the hepatoprotective effect of GBP might be related to its antioxidant and free radical scavenging activity. Clinical trials of silybin phytosome complex in combination with Vitamin E for nonalcoholic fatty liver disease (NAFLD) patients showed improved hepatic histology with increased level of liver enzymes in plasma, and better insulin resistance with unchanged body weight.in body weight (Loguercio et al., 2012). Hepatoprotective efficacy of curcumin, silybin-phytosome and alpha-R-lipoic acid against thioacetamide induced liver cirrhosis in rat has been investigated. Result showed treatment reduced Glutathione (GSH) depletion, collagen deposition, matrix metalloproteinase-2 (MMP-2) activity, transforming growth factor-β1 (TGF-β1) level as well as α-smooth muscle actin (α-SMA) and heat shock protein-47 (HSP-47) gene expressions along with malondialdehyde (MDA) and protein carbonyls (Pr Co). Indicating antioxidant and antifibrotic potentials of supplements against chronic liver diseases (Ali et al., 2014). A comparative study has been made to understand superior hepatoprotective efficacy between silymarin phytosomes and milk thistle extract, administered in CCl4-induced hepatotoxicity in rats. Compared to milk thistle extract, Silymarin phytosome was found to increase SOD and decrease GPT levels (El-Gazayerly et al., 2014). Silymarin-phospholipid complex developed by solvent evaporation method using silymarin isolated from *Silybum marianum* and phospholipid showed improved bioavailability with stability and sufficient safety (Maryana et al., 2016). CCl4 induced liver damage in adult Charles foster rats was tested with a formulated phytosome prepared by extracts of *Abutilon indicum* leaves and *Piper longum* fruits in comparison to extracts from each plant separately with LIV 52 herbal medicine. Phytosomal formulation at a very low dose showed a greater hepatoprotective effect on liver toxicity CCl4 induced at a very low dose compared to a higher dose of the combined extract (Sharma & Sahu, 2016). Administration of phytosome curcumin formulation was found to be very much effective against paracetamol-induced liver injury. Efficacy was evidenced by decreased level of lipid peroxidation, the liver toxicity markers (ALT and AST) decreased, and enhanced antioxidant activities of superoxide dismutase, catalase, glutathione peroxidase enzymes in mice liver tissue receiving treatment (Tung et al., 2017). Hepatoprotection through increased anti-inflammatory cytokine (IL-10) and decreased pro-inflammatory cytokine (TNF-α and IL-6) levels following administration of *Boswellia serrata* extract phytosome in lipopolysaccharide- induced systemic inflammation in mice have been reported. Phytosomes also showed antioxidative efficacy (Loeser et al., 2018). Aluminum chloride ($AlCl_3$)-induced hepatotoxicity in rat characterized by increased concentrations of AST, ALT, ALP, LDH, total bilirubin, and LPO as well as decreased albumin, GSH, SOD, and GPx levels found to be attenuated by administration of Curcumin phytosome (CP) (Al-Kahtani et al., 2020).

Phytosomes in Renal Disease Management:

Patients with temporary kidney dysfunction (TKD) were given either standard management (SM) or SM and Curcumin Phytosome together to find out the ameliorative effect. Significant improvements in macro and microalbuminuria in combination therapy were noticed compared to control along with controlled blood pressure, reduced oxidative stress and fatigue.

Phytosomes in Osteo-Muscular Disease Management:

Curcumin phytosomes were found to attenuate oxidative stress and inflammatory response related to muscle damage in eccentric continuous exercise-induced delayed onset muscle soreness (DOMS) induced, evidenced by reduced pain intensity and recovery of muscle (Drobnic et al., 2014). Same complex showed anti-inflammatory response in osteoarthritis (OA) patients with decreased joint pain and improvement in joint function suggesting its application in the prolonged treatment of OA (Belcaro et al., 2010). A comparative study between lecithin formulation of curcumin, acetaminophen and nimesulide showed curcumin formulation at higher dose (2 gm) exhibit almost equal analgesic activity as well as gastric tolerability of acetaminophen (1gm) but lower pain killing effect than nimesulide (1 gm). Though the gastric tolerability is better compared to nimesulide therapy (Di Pierro et al., 2013). In another study 4-month consecutive administration of phytosomal curcumin combined to glucosamine exhibited faster recovery in OA patients compared to other patients group given chondroitin sulfate combined with glucosamine group (Belcaro et al., 2014). Phytosomal curcumin along with standard management had been evaluated either or not in combination with other nutritional supplements in aged healthy persons (>65 years) with sarcopenia, showed ameliorated muscle mass and strength as well as physical performance compared to persons only receiving SM (Franceschi et al., 2016). Curcumine phytosome mediated pain reduction in radiculopathy patients affected with spine arthritis or discopathy has also been reported (Maida. G, 2016). Male rugby players (n=50) with osteo-muscular pain due to either physical overload, traumatic injuries, or acute episode of chronic pain, half were treated with conventional pain killer drugs and other half treated with curcumin based phytosome (Algocur®) for next 10 days. Phytosome complex exhibited more analgesic effect than the other with more tolerability with increased physical activities (Di Pierro et al., 2017). In a pilot study Riva et al. (2017) demonstrated significant increment of bone density of upper jaw, heal and small finger in tested persons with osteopenia, following curcumin supplement in addition to standard management (SM) compared to the group only receiving SM. Recently, Miserocchi et al. (2020) reported curcumin phytosomal complex in addition with chronic systemic immunosuppressive therapy improves mild chronic anterior chamber flare with good safety profile in children with juvenile idiopathic arthritis-associated uveitis.

lecithin-encapsulated *Boswellia serrata* extract (BSE) was investigated for its efficacy in relieving osteo-muscular pain in rugby players. Observed parameters showed reduced local pain on effort, joint effusion, structural damage (joint, tendons, muscles), pain-free walking, and intramuscular hematomas suggesting its potential therapeutic role (Franceschi et al., 2016). Treatment group with grade II ankle sprain induced by sports activities were divided into two groups and advised to follow either SM or SM with BSE (1 tab of 250mg/day) for 7 days. The group that recieved combined therapy showed much-reduced signs and symptoms of ankle sprains on 3rd and 7th day of evaluation without any side effects (Feragalli et al., 2017).

In a recent study treatment with phytosome fabricated with *Zingiber officinale* and *Acmella oleracea* extracts ameliorated pain intensity, knee function, quality of life, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in 50 patients with moderate knee osteoarthritis (OA) (Rondanelli et al., 2020).

Phytosome in COVID-19 Management:

In the recent past SARS-CoV-2 the causative agent of COVID-19 pandemic was the major threat to human civilization. Serial investigations by Di Pierro et al. (2021a, 2021b, 2021c) had reported that quercetin can inhibit the 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), and spike (S) protein of SARS-CoV-2. In their first study, they treated 152 COVID-19 patients with early symptoms, with 1000mg Quercetin Phytosome® (QP) for 30 days. Observation suggested, a reduction in the number of deaths, ICU admission, duration of hospitalization, as well as severity in patients. In another investigation, supplementation of QP in addition to standard of care (SC), negative RT-PCR results suggested early recovery in patients (within 7 -14 days) along with decreased symptomatic severity compared to patients receiving only SC. Long COVID syndrome resulted in cognitive dysfunction and fatigue collectively known as Brain fog. Mitigation of such symptomatic conditions by using phytosomal formulation of luteolin has been documented by Theoharides et al. (2021). In a pilot study, Rondanelli et al. (2022) have proven that by receiving Quercetin phytosomes at a dose of 250mg twice/day for 3 months, prevented healthcare workers from symptomatic covid-19.

Conclusion

Phyto-phospholipid complexation strategy might increase the in vivo bioavailability of phytoactive components. Although the polyphenolic compounds found in plants, such as flavonoids, etc., have a high degree of therapeutic potential, their utility in the treatment and management of various illnesses like rheumatism, cancer, diabetes, and liver disease has remained unsolved as they cannot invade the lipid barrier. This issue has been successfully addressed by the encapsulation of plant-active ingredients with dietary phospholipids, which has allowed the production of herbal active pharmaceuticals with a high degree of lipid penetrability, persistent therapeutic action, and a slower elimination rate. Phytosomal technology has made a significant amount of phytoactive medication available at the site of action. The development of innovative drug delivery strategies creates a promising future for plant actives and extracts for their use as a successful medication. The phytosome technology connects cutting-edge medication delivery techniques with the traditional distribution method of phytoconstituents. In short, phytosomes are a blessing for naturally occurring herbal extracts that are not properly absorbed.

Conflict of Interest:

None

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Chapter- 9

Vegetables as traditional medicines cultivated in Purba-Medinipur District in West Bengal

Somnath Das

Keywords: vegetables, medicinal values, cultivated plants

Abstract:

In Purba Mednipur, various traditional vegetables are grown year-round in urban and rural settings. Despite the fact that some of these veggies have therapeutic properties. Healthy vitamins, minerals, and dietary fibres are present in every vegetable. Certain veggies may provide more health benefits to particular people depending on their diets, general health, and nutritional requirements. Enjoy the vegetables in this article to complement your daily diet. Vegetable consumption is crucial for good health. It delivers vital vitamins, minerals, and other nutrients, such as fibre and antioxidants. According to a growing body of evidence, persons who consume at least 5 servings of vegetables daily have the lowest chance of developing various diseases, such as cancer and heart disease.

Introduction:

Vegetables are significant in terms of nutrients. Almost all veggies naturally have few calories from fat. Numerous nutrients, such as potassium, dietary fibre, folate, vitamins A and C, vitamin B-complex, and others, are in significant amounts in nuts. Vegetables are a component of plants eaten as food by people and other animals. When applied to plants, the original definition is still frequently used to refer to all edible plant material, including flowers, fruits, stems, leaves, roots, and seeds. Traditional native veggies are abundant in vitamins and nutrients and may positively affect health. The Purba Mednipur district is home to many species of vegetables that are used medicinally to treat various disorders that can be cured. To benefit from as many health advantages as possible, consume a variety of veggies every day. One of the easiest methods to increase health and happiness may be to eat a lot of vegetables. Most nutrients, fibre, minerals, and natural vitamins may be crucial in treating numerous serious illnesses, including those of the heart, kidney, blood, lungs, and neurological system. This article discusses the many listed vegetables' ethnobotanical and medicinal benefits.

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Potato:

It serves primarily as a basic food but also offers various medicinal benefits. Compound leaves are placed spirally on potatoes. Each leaf has a terminal leaflet and two to four pairs of leaflets; it is 20 to 30 cm long (about 8 to 12 inches). Five joined petals, and yellow stamens are features of the white, lavender, or purple flowers. The fruit is a little highly toxic very. On the other hand, that has plenty of seeds.

Figure 1. Potato

Ingredients:

Potassium, starch, Vitamin C, carbohydrates, protein, fibre, Vitamin B6, iron, etc. are the main constituents.

Medicinal uses:

People use potatoes to treat indigestion, dyspepsia, high blood pressure, diabetes, and heart disease. Peptic ulcers can be treated with tuber juice, which relieves the pain and acidity.

Onion:

Despite being an annual plant, it is actually a biannual one. Nowadays, most cultivars reach a height of 15 to 45 cm (6 to 18 in). The flattened, fan-shaped swathe of leaves, which range in colour from yellow to blue-green, grows alternately. They have a flat side and are cylindrical, hollow, and made of flesh.

Figure 2. Onion

Ingredients:

Water, Protein, Carbohydrates.

Medicinal uses:

It is used to treat digestive issues like appetite loss, uncomfortable stomach, gallbladder disorders, heart and blood vessel issues like angina.

Zinger:

Although it is an annual plant, it is a herbaceous perennial. Size ranges from 30 to 90 cm. The underground stem, or rhizome, has thin, flattened branches and grows horizontally. It is coated in fibrous roots and small-scale leaves.

Figure 3. Zinger

Ingredients:

Among the phenolic substances are terpenes, polysaccharides, lipids, organic acids, and unprocessed fibres.

Medicinal uses:

Traditional medicine tackles cancer, indigestion, headaches, nausea, and vomiting. It is frequently used to treat bacterial infections, hypertension, hypercholesteremia, hyperuricemia, autoimmune illnesses, enhanced immunity, reduced pain, colds, and cough.

Garlic:

The average height of a garlic plant is 60 cm (2 feet). Depending on the cultivar, the long leaves typically emerge from a soft pseudostem of overlapping leaf sheaths or from a short, firm stem above the bulb. The clove-shaped bulb has a membrane skin covering and contains up to 20 edible bulblets.

Figure 4. Garlic

Ingredients:

Allicin, diallyl sulphide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), E/Z-ajoene, S-allyl-cysteine (SAC), and alliin are examples of organosulfur compounds.

Medicinal uses:

It is frequently prescribed for high blood pressure, high cholesterol or abnormal blood fat levels, hardening of the arteries, osteoarthritis, and the common cold.

Green chilli:

The shrub is made up of the main tap root and several lateral roots. The leaves have an uneven form with a pointed tip and can go up to 12 cm long and 7.5 cm wide.

Figure 5. Green chilli

Ingredients:

Proteins, fats, fibre, and carbohydrates. Minerals like calcium, iron, salt, magnesium, zinc, and copper are also present in green chillies. There are also vitamins, including vitamin B, vitamin C, and vitamin A.

Medicinal uses:

May reduce the risk of ulcers, moisture loss, pain, and cancer of the heart. It may also enhance heart health. Antimicrobial and antifungal characteristics of arthritis guard against skin infection. Digestion, weight loss, and blood sugar management.

Bottle gourd or Gourd:

Annuals with hairy stems, long forked tendrils, and a musky scent, bottle-gourd vines grow quickly. For various uses, bottle gourds have been cultivated in a variety of forms, with a wide range in the sizes of fruits, leaves, flowers, and vines. It is recognisable by its bottle-, dumbbell-, or oval-shaped shape.

Figure 6. Bottle gourd or Gourd

Ingredients:

Proteins, lipids, fibre, iron, calcium, potassium, sodium, magnesium, phosphorus, zinc, copper, manganese, selenium, vitamin c, riboflavin, thiamin, pantothenic acid, vitamin B6, niacin, and folate are all components of food.

Medicinal uses:

Traditional remedies for many different health issues, including fever, cough, discomfort, and asthma, include bottle gourd. Due to its advantages, it has been utilised for centuries. Additionally, it is regarded as a good

Cucumber:

Cucumbers are fragile annual plants with prickly, juicy stems that trail. The plant's stem includes branched tendrils that allow it to be trained to support the unisexual, five-petalled yellow flowers that give rise to a sort of fruit known as a pepo, and the hairy leaves have three to five pointed lobes.

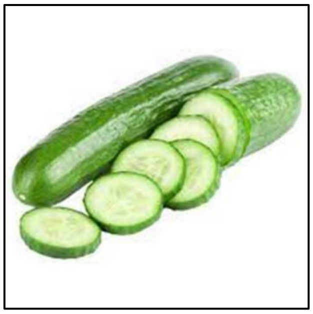

Figure 7. Cucumber

Ingredients:

Iron, calcium, fibre, protein, and fat are all food groups.

Medicinal uses:

Ingredient and therapeutic values preventing constipation, maintaining regularity, vitamin K's role in blood clotting and bone health. It supports healthy digestion, blood sugar regulation, the immune system, reproduction, and vision. It also has anti-inflammatory properties.

Bitter gourd:

The plant is a monoecious, annual climber with long-stalked leaves and single yellow blooms produced in the leaf axils by both males and females. The fruit is warty and oblong or elliptical in shape, and its botanical name is "pepo." The plant thrives in a variety of soils and starts to bloom approximately a month after planting.

Figure 8. Bitter gourd

Ingredients:

Calories, sodium, sugar, protein, fat, carbohydrates, and

Medicinal uses:

Asthma, constipation, colic, diabetes, cough, fever (malaria), gout, helminthiases, leprosy, inflammation, skin disease, ulcers, and wounds have all been treated with the fruit and pulp as traditional medicine since ancient times. In people, it also possesses anti-diabetic effec

Spinach:

The simple leaves might be flat or puckered, and they are roughly triangular or oval in shape. The blossoms are barely noticeable and give out little dry fruits. To develop quickly and produce the most amount of leaves, spinach needs chilly weather and deep, rich soil that has been limed.

Figure 9. Spinach

Ingredients:

Micrograms of vitamin A, folate, protein, calcium, iron, magnesium, and potassium.

Medicinal uses:

Due to its convenient iron and calcium content, spinach is one of the leafy green vegetables and an excellent source of calcium, vitamins, iron, and antioxidants. It is also a great complement to any meat- or dairy-free diet. Additionally, it offers folate, magnesium, vitamin C, vitamin A, and vitamin K. It provides a good amount of iron, which is necessary for energy and healthy blood, as well as magnesium for bones, vitamin B6, antioxidants for lower blood pressure (BP), and other health advantages.

Broccoli:

The cultivar group Italica of the species Brassica oleracea is where broccoli belongs. Large, typically dark-green flower heads on broccoli branch out from a sturdy, mostly light-green stalk in a tree-like arrangement. Leaves encircle the cluster of flower heads.

Figure 10. Broccoli

Ingredients:

Iron, potassium, vitamin K, vitamin C, and fibre.

Medicinal uses:

It belongs to the crucifer family of vegetables. It also contains calories from vegetables. In addition, it contains vitamins K and C. The National Cancer Institute's animan research identifies specific compounds as indoles and iso cyanalies. Cruciferous vegetables may prevent cancer growth in several organs, including the stomach, bladder, breasts, liver, and liver.

Peas:

Most frequently, the pea is the tiny, globular seed or seed pod of the flowering plant Pisum sativum. There are numerous green or yellow peas in each pod. Pea pods are considered to be fruit by botanists since they contain seeds and grow from the ovaries of a (pea) flower.

Figure 11. Peas

Ingredients:

Copper, niacin, manganese, vitamin E, thiamine, folate, and phosphorus.

Medicinal uses:

Vegetables peas are sweet. They are abundant in protein, fibre, vitamin A, C, and B. For vegetarians, it might be very helpful. It contains ingredients that support healthy gut flora and promote regular bowel motions and a strong digestive system. It is also abundant in saponins, plant substances that may offer protection.

Sweet Potato:

The plant is a herbaceous perennial vine with screw-shaped or palmately lobed alternating leaves and medium-sized sympetalous blooms. The stems of the plant typically creep along the ground and establish adventitious roots at the nodes. The length of the leaf stalk is 5 to 20 inches.

Figure 12. Sweet Potato

Ingredients:

Calcium, iron, magnesium, phosphorus, potassium, vitamin B, vitamin C,

Medicinal uses:

Most veggies are roasted in their peel. It contains vitamin A, C, B6, and potassium beta carotene, which is beneficial for diabetics and a high source of fibre and an antioxidant (alpha-lipoic acid).

Protect for:

Cancer, diabetes-related nerve issues, and blood sugar issues.

Beats:

It belongs to the group of Beta Vulgaris cultivars known as B. vulgaris subsp. Vulgaris Conditiva Group, which are planted for their culinary taproots and leaves (also known as beet greens). The sugar beet, the leaf vegetable known as chard or spinach beet, and the fodder crop mangelwurzel are further cultivars of the same species. Usually, three subspecies are identified.

Figure 13. Beats

Ingredients:

Taurine, caffeine, added sugar, fat, carbohydrates, proteins, and inositol.

Medicinal uses:

Beats are full with folate, a vitamin B9 that supports healthy cell growth and operation. Folate is essential for preventing blood vessel damage, which lowers the risk of heart disease and stroke. Beets also naturally contain a lot of nitrates, which the body converts to nitric oxide.

Carrots:

The edible taproot of the carrot (Daucus carota), a herbaceous, often biennial plant of the Apiaceae family, is produced. Among common kinds, roots might be spherical or lengthy, with blunt or pointy lower ends. There are also known white, pink, and purple-fleshed variations in addition to the orange-coloured roots.

Figure 14. Carrots

Ingredients:

Ash, Fat, Dietary Fiber, Protein, and Carbohydrates.

Medicinal uses:

Carrots' high fibre content can help regulate blood sugar levels. Additionally, they are abundant in beta-carotene and vitamin A, both of which have been linked to a decreased incidence of diabetes. They can also make your bones stronger. Both calcium and vitamin K, which are found in carrots, are crucial for healthy bones.

Cauliflower:

An annual plant, cauliflower grows to a height of about 0.5 metres (1.5 feet) and has broad, spherical leaves that resemble collards (Brassica oleracea, variety acephala). The terminal cluster develops as a solid, succulent "curd," or head, which is a juvenile inflorescence, as required for food (Cluster or flowers).

Figure 15. Cauliflower

Ingredient:

Carbohydrate, Protein, Fat.

Medicinal uses:

Vegetables include cauliflower. Cauliflower's head or curd is frequently used as food. In medical, it is also employed. Although cauliflower is used to treat obesity, diabetes, cancer, heart disease, and other ailments, there isn't any reliable scientific proof to back up these claims.

Cabbage:

All varieties of cabbage have spongy, hairless leaves that are coated in a waxy covering that frequently gives the leaf surface a gray-green or blue-green hue. The plants thrive in mild to chilly areas and can withstand frost.

Figure 16. Cabbage

Ingredient:

Protein, fat, vitamin K, vitamin C, and carbohydrates.

Medicinal uses:

The plant known as cabbage is frequently consumed as a vegetable. In addition, leaves are used medicinally. In addition to ulcers in the stomach and intestines, cabbage is also used to treat stomach pain, too much stomach acid, and Roemheld syndrome. Additionally, morning sickness and asthma are also treated with cabbage.

Ladies finger:

The lady's finger, often known as okra, is a flowering plant belonging to the genus Abelmoschus and family Malvaceae. This implies that it is a relative of the cotton, cocoa, and hibiscus plants.

Figure 17. Ladies finger

Ingredient:

Calcium, Zinc, Vitamin A, Vitamin B and Vitamin C, and Folic acid.

Medicinal uses:

Unexpected health benefits of Lady's finger: Supports heart health, blood sugar control, fights Cancer, boosts immunity, prevents anaemia aids in weight loss, prevents colon cancer beneficial in pregnancy.

Pointed gourd:

Trichosanthes dioica, also referred to as a pointed gourd, is a perennial vine plant in the Cucurbitaceae family, related to cucumber and squash.

Figure 18. Pointed gourd

Ingredient:

Calcium, phosphorus, iron, copper, potassium, vitamins A, B1, and C.

Medicinal uses:

The pointed gourd (Trichosanthes dioica Roxb.) is mostly grown as a vegetable and is also known by the popular name parwal. T. dioica leaf juice is used as a tonic, febrifuge in cases of edoema, alopecia, and subacute liver enlargement.

Papaya:

An umbrella-like canopy of palmately lobed leaves covers the trunk. Payas, which resemble large, juicy melon-like fruits, hang in groups from the top of the stem, just below the leaf cover. Papayas are well known for their edible melon-like fruit, which may reach heights of 6–20 feet (container plants can reach 10 feet).

Figure 19. Papaya

Ingredient:

Fiber, copper, magnesium, potassium, vitamin A, folate, and pantothenic acid.

Medicinal uses:

Consuming papaya may lower your risk of developing heart disease, diabetes, and cancer. It may also improve your digestion, help you manage your blood sugar levels if you have diabetes, lower your blood pressure, and speed up wound healing.

Arum (Arum Lilies, Araceae):

A spathe, a bract with a funnel form, typically surrounds the rod-like spadix in arum flower structures (on which the tiny flowers are borne). Usually unisexual, the tiny flowers on the spadix are. Usually shiny and somewhat arrow-shaped, the leaves.

Figure 20. Arum

Ingredient:

Vitamin A, Salicylic acid

Medicinal uses:

Root is used to create medication, which is intended to treat throat inflammation and colds. Additionally, it is utilised to encourage perspiration and ease chest contractions.

Tomato:

The tomato (Lycopersicon esculentum) is a short-lived perennial or annual herb with curled, uneven, greyish-green pinnate leaves. The fruits are red or yellow in colour and are produced by off-white blooms. It is a crop that pollinates

Figure 21. Tomato

Ingredient:

Vitamin C, potassium, and folate, Beta-carotene, Phytoene, Lycopene, and gamma-carotenoid.

Medicinal uses:

Some of tomatoes' health benefits include heart protection. Tomatoes are high in antioxidants, which support healthy blood vessels, prevent eye issues, control blood pressure, reduce inflammation, and lessen the risk of some cancers.

Radish:

The radish plant has a short, hairy stem and a rosette of oblong-shaped leaves that are 5–30 cm (2–12 in) in length and are horizontal and round at ground level. The plant's top leaves are smaller and lance-shaped. The plant's taproot is typically red or white in colour and cylindrical or tapered.

Figure 22. Radish

Ingredient:

Thamine, vitamin B6, vitamin B12, calcium, vitamin C, riboflavin, niacin, and potassium.

Medicinal uses:

Gallstones, bile duct issues, liver issues, and stomach and intestinal ailments are all treated with radish. Bronchitis-related appetite loss. Flu, fever and sneeze. High cholesterol is treated with it as well.

Brinjal:

Large, violet-coloured, solitary or found in groups of two or more, brinjal blossoms are in abundance. The parts of a flower are the calyx, which has five united, persistent sepals, the corolla, which has five united petals that are typically cup-shaped. The androecium has five stamens, and the gynoecium has one united carpel and a superior ovary.

Ingredient:

Fiber, Copper, Manganese, B6 and thiamine.

Medicinal uses:

Brinjal is beneficial for diabetics because it keeps blood sugar levels from skyrocketing. Brinjals are a good source of folate, which is needed to make red blood cells (RBCs) and prevents anaemia.

Figure 23. Brinjal

Beans:

The plant is virtually upright, growing to a height of 60 to 150 cm (2 to 5 ft) and has few branches. The stem and branches are covered in short-petioled leaves, the pods are arranged in axial clusters of leaves, and the seeds are large and unevenly flattened.

Ingredient:

Protein, Carbohydrates and Lipids.

Medicinal uses:

Antioxidants, heart health, reduced risk of cancer, diabetes and glucose metabolism, preventing fatty liver, managing hunger, etc. are a few of beans' medical benefits.

Figure 24. Beans

Drum stick:

Common names for this plant include moringa, horseradish tree (because of the flavour of the roots, which is akin to horseradish), drumstick tree (because of the tall, thin, triangular seed pods), and ben oil tree or benzolive tree.

Ingredient:

Sodium, Zinc, Copper, Manganese, Selenium, Thiamine Riboflavin, Vitamin B6, Folate, and Vitamin A are all essential minerals.

Medicinal uses:

Perhaps it's anti-diabetic (reduces blood glucose levels) It may have the potential to be anti-cancer (stops the development of cancer cells). It might have anti-seizure capabilities.

Figure 25. Drum stick

Table 1. List of vegetables grown primarily by residents of West Bengal's Purba-Medinipur District.

English Name/Bengali Name	Botanical Name	Parts or whole Uses
Potato	*Solanum tubersum*	Whole /part
Onion	*Allium cepa*	Fleshy Scale
Zinger	*Zinger officinals*	rezone
Garlic	*Allium sativum*	Fleshy root
Green Chilli	*Capsicum annuum*	Whole/part
Gourd/ Bottle Gourd	*Lagenaria siceraria*	Whole/Part
Cucumber	*Cucumis sativus*	Whole/Part
Bitter gourd	*Momordica charantia*	Whole/Part
Spinach	*Spinacia oleracea*	Except root
Broccoli	*Brassica oleracea* var. Italica	Whole/ Part
Peas	*Pisum sativum*	Seed
Sweet Potato	*Ipomoea batatas*	Root tuber
Beets	*Beta vulgaris* (subsp. vulgaris Altissima Group)	Whole
Carrot	*Daucus carota*	Whole
Calli flower	*Brassica oleracea* var. botrytis	Whole
Cabbage	*Brassica oleracea var. capitata*	Whole
Ladies Finger	*Abelmoschus esculentus*	whole
Pointed Gourd	*Trichosanthes dioica*	Whole
Papaya	*Carica papaya*	Fruit except for outer wall and seed
Arum	*Arum maculatum*	Whole, Except outer wall of root
Tomato	*Solanum lycopersicum*	Whole
Radish	*Raphanus sativus*	Whole
Brinjal	*Solanum melongena*	Whole
Beans	*Phaseolus vulgaris*	Whole
Drum Stick	*Moringa oleifera*	Whole, Except outer wall

Conclusion:

Daily vegetable consumption is crucial for good health. They deliver vital nutrients like fibre, antioxidants, and vitamins, minerals, and other foods. According to research, those who consume at least 5 to 6 servings of vegetables daily had the lowest risk of developing several ailments, such as cancer and heart disease. Enjoy a variety of vegetables every day to obtain the most health advantages. Numerous traditional vegetables in Purba Mednipur have therapeutic properties. These vegetables are frequently consumed and used medicinally by rural, urban, and town residents without regard to dosage. According to the paper, research is crucial for these vegetables.

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Chapter- 10

Amaranthus spinosus Linn. : A common culinary herb with potential medicinal value

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Keywords: Ethnomedicine, Amaranthaceae, Pharmacological, Herb

Abstract:

Amaranthus spinosus Linn., a well distributed common herb found in many tropical and subtropical countries. The plant is highly nutritious and rich in minerals, vitamins and amino acids. It is very popular as a vegetable due to its great health benefits, availability, and less high price on the market. Apart from the dietary values, these plants were used in traditional ethnomedicine to cure various types of health issues in many countries, including India. Phytochemicals present in plants are effective against a number of medical implications. This literature study represents information on traditional uses, therapeutic potential, ethnopharmacology, and nutritional aspects of *Amaranthus spinosus*.

Introduction:

Amaranthus spinosus Linn. (Family: Amaranthaceae), commonly known as spiny pigweed (in English), kantanote/ kantanotya (in Bengali), is a widespread plant in India. It is a straight, perennial, spiny, herbaceous plant with a green or purple stem (Holm et al. 1997). The plant can be found on roadsides, wastelands, gardens and fields. However, the plant is also cultivated in several tropical and subtropical nations. It is very popular as a vegetable among native people. The herb has a high amount of dietary fibre and essential amino acids (Baral et al., 2011; Das et al., 2014). In addition to its nutritional benefits, this plant has been used in traditional Indian Ayurveda. Phytochemical studies have confirmed its relevance as a beneficial therapeutic herb. It is a well-known resource of lipid, saponin, betalain, beta-sitosterol, stigmasterol, linoleic acid, and tannin in addition to alkaloid, flavonoid, carotenoids, glycosides, steroids, and carotenoids (Agbaire, 2011; Guria et al. 2014). A broad range of its pharmacological effects, including anti-diabetic, anti-tumour, analgesic, anti-microbial, anti-inflammatory, spasmolytic, bronchodilator, hepato-protective, antifertility, anti-malarial, antioxidant qualities, etc. has been investigated various by many researchers (Sarker & Oba, 2019).

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Traditional usage as ethnomedicine:

India has gained access to a valuable herbal heritage (Sarkar et al., 2016; Sarkar, 2017). Along with homoeopathy and folk medicine, the traditional medical system in India continues to be essential to the nation's total healthcare system (Sanyal et al., 2018; Kundu, 2022). Humans have employed medicinal plants as necessary components in diets, beverages, and remedies since the dawn of time. There are numerous industrial uses for medicinal plants' nutritional, pharmacological, biological, and toxicological traits (Erfani, 2021; Kar et al., 2022).

Natural products are routinely used in the discovery of novel therapeutic medicines. The most sensible and economical type of treatment has historically been traditional medicine. Plants have been utilised as a kind of therapy since the beginning of time (Maiti et al., 2013; Sanyal, 2016). New therapeutic compounds are frequently discovered thanks to the medicinal plant (Banerjee et al., 2014; Bhattacharjee and Manna, 2016). Alkaloids, flavonoids, tannins, and phenols are only a few of the phytochemicals that help medicinal plants function as medicines. Herbal medicine has a long history in Indian culture (Sarkar, 2016; Maiti et al., 2010). The country's overall healthcare system for the general public still heavily relies on traditional medical methods and homoeopathy and folklore medicine, both of which are practised in India (Bhattacharjee, 2021; Acharya et al., 2021; Acharya et al., 2022).

Amaranthus spinosus has been associated with various ethanopharmacological claims in many pieces of literature, and it has long been used to treat several diseases. Traditional preparations of the plant include boiling, steaming, or frying the leaves and tender stems before eating. Due to its bitter flavour, it is generally substituted for other vegetables and consumed in modest amounts. Some cultures also utilise the plant's ash as salt. *A. spinosus* is also used as feed for livestock animals (Kritikar & Basu, 2005). Since a very long time, this plant has been traditionally used for medicine in India and around the world. Some tribes in India and Nepal utilise this herb to cause abortions. Tribal communities of Kerala, India apply the juice of whole plants to cure stomach bloating and the leaves, when cooked without salt for a couple of days, can be used to treat jaundice. It is well-known in Africa for treating various illnesses and conditions associated with nutritional deficiencies. It is historically used to cure diabetes in China, however, in South-East Asian nations, the root extract is used to treat gonorrhoea by externally applying it. In Malaysia, it is used as a broncho-expectorant, easing the symptoms of acute bronchitis (Grubben & Denton, 2004). Topical and oral application of the root paste has many positive benefits. Root extract is given to kids to induce bowel movements and also has effective diuretic properties. To treat skin conditions such abscesses, burns, bruises, eczema, inflammation and wounds, a fine paste made of leaves and roots are applied as a bandage. In Sikkim, rural residents who practise ethnomedicine utilise this plant for stomach disorders, particularly indigestion and peptic ulcers, by infusing the leaves. Plant sap administered as an eye wash can treat ophthalmia in kids (Nawaz et al., 2009). The root paste also reduces vomiting when combined with an equal volume of honey. Administration of root paste combined with black pepper in a 1:3 (1 part of black pepper to 3 parts of root paste) in a daily manner can help treat rabies. The crushed leaves are used as an external emollient in several nations, especially those in Africa. They are said to be effective in conditions of earaches, haemorrhoids, burns, sores, boils, and ulcerated lips. To wash sores, a solution containing plant ash is utilised (Ganjare & Raut, 2019). In Ayurveda *Amaranthus spinosus* has a long history. Charaka, Sushruta, Vagbhata, and others have recommended it for the remedy of pradar, sarva visha, and raktapitta. It has also been recommended for the treatment of arsha and mushika visha (Chandrashekhar, 2018).

Phytoconstituents having pharmacological potential:

Amaranthus spinosus has a variety of active phytoconstituents that belongs to several groups of carotenoids, alkaloids, glycosides, phenolics, steroids, terpenoids, and saponins. These phytoconstituents, along with their potential pharmacological action and extract preparation, are demonstrated in Figure 1 (Kumar et al., 2010; Hussain et al., 2009; Olumayokun et al., 2004; Zeashan et al., 2009; Potllapalli et al., 2017; Chaudhary et al., 2012; Bulbul et al., 2011; Olumayokun et al., 2004; Panda et al., 2017; Olufemi et al., 2003; Lin et al., 2005; Sangameswaran et al., 2010; Hilou et al., 2006; Barku et al., 2013).

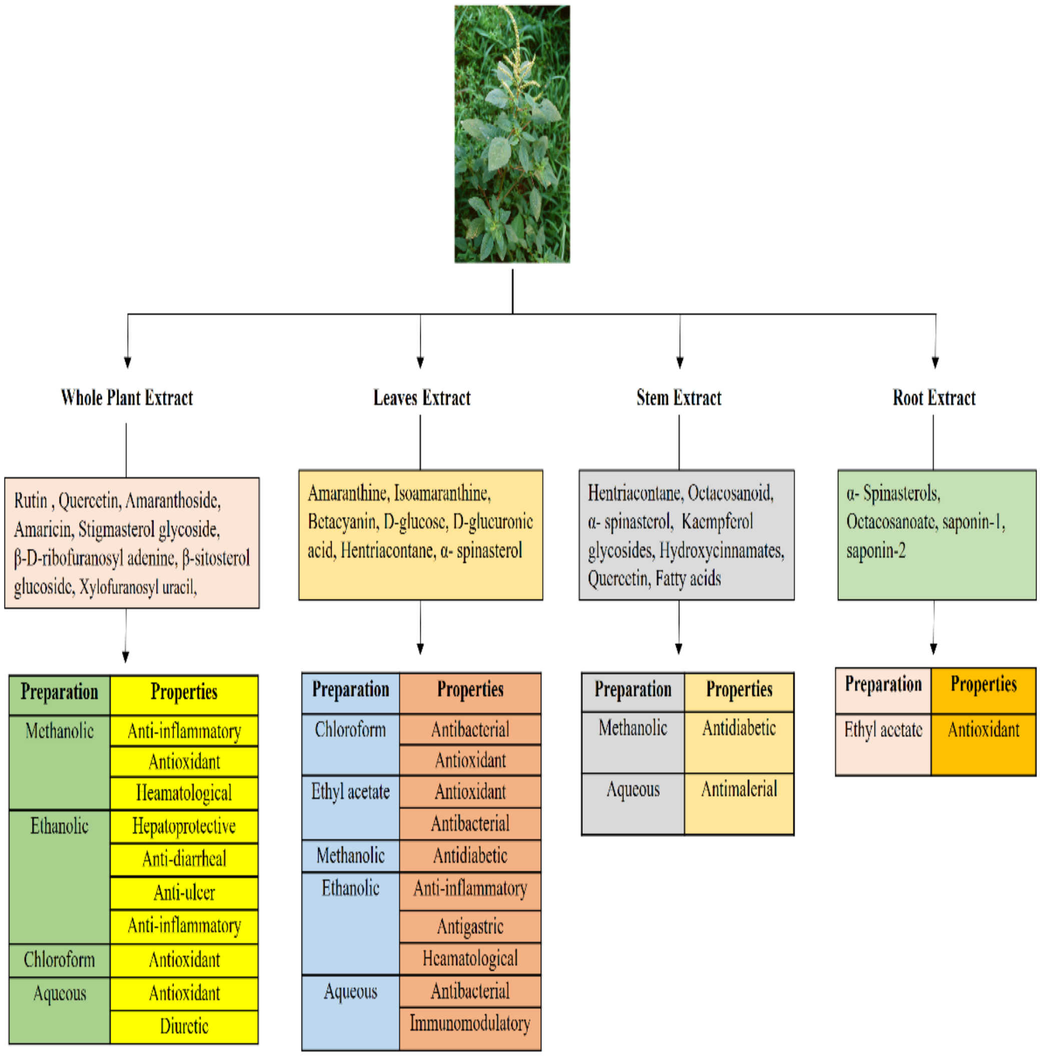

Figure 1. Pharmacological potential of the phytoconstituents present in plant extracts

Analgesic and Antipyretic Activity:

Numerous studies worldwide have scientifically supported traditional claims about the plant's ability to cure different sorts of pain. Methanol extracts of the plant were tested for antipyretic properties at dosages of 200 and 400 mg/kg in mice with yeast-induced pyrexia showed a significant reduction in body temperature (Kumar et al., 2011). Mice treated with an increased dosage of methanolic extract of *Amaranthus spinosus* had more pronounced central and peripheral analgesic action. Oral administration of 500 mg/kg of body weight methanol extract has been proven to have a considerable antinociceptive effect against the acetic acid exposed visceral discomfort and radiant heat tail-flick test model of mice (Taiab et al., 2011)

Antioxidant activity:

This plant has been found to have antioxidant activity against DPPH free radicals, superoxide radicals, ABTS-radicals, -NO radicals, and free -OH radicals (Kumar et al., 2010). 50% ethanolic extract of *Amaranthus spinosus* (whole plant) showed significant antioxidant activity in the in-vitro assay by DPPH, superoxide, hydroxyl radicals, hydrogen peroxide and nitric oxide scavenging methods. Complete plant material extract of the plant with petroleum ether, chloroform, methanol, and water exposed to an oxidation process (in vitro non-enzymatic hemo-glycosylation) revealed the antioxidant activity of methanol extract much higher than others (Kumar et al., 2010).

Hepatoprotective activity:

50% ethanolic extract of entire plants clearly suggest that *A. spinosus* possess high hepatoprotective action against CCl_3 induced liver damage in experimental rats. Dose-dependent recovery of increased blood enzymatic levels of serum glutamate oxaloacetate transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT) in considerable levels suggest the normality of liver function. The presence of flavonoids and phenolic compounds in the extract might be responsible for the hepatoprotective effect (Zeashan et al., 2008).

Antifertility activity:

Pregnant rats were treated with oral consumption of aqueous and ethanolic root extracts of the *Amaranthus spinosus* plant and showed significant antifertility effect. Female rats that were given alcoholic plant extracts at doses of 125, 150, and 175 mg/kg of body-weight between day one and day five of pregnancy had substantial pregnancy interception. On the contrary, from 11 days to 15, receiving 125mg/kg of aqueous and alcoholic plant extracts did not significantly lead to pregnancy interception. However, alcoholic extracts of plant medications at doses of 150 mg/kg and 175 mg/kg of body weight efficiently interfered with the pregnancy (Satyanarayana et al., 2008).

Haematological activity:

Aqueous extract from *Amaranthus spinosus* leaf revealed insignificant changes in haematological parameters. In contrast, ethanol extracts showed while the alcoholic extract was found to alter several haematological indicators such as PCV, RBC count, WBC count, and haemoglobin (HB) in pigs and rats. Alcoholic extract significantly decreases serum biochemical indicators like glucose and cholesterol when monitored in rats (Akinloye & Olorede, 2000; Olufemi et al., 2003). The entire plant extract was found to significantly reduce RBC, haemoglobin (Hb), PCV, and average concentration of haemoglobin (MCHC) while dramatically increasing WBC and the average volume of red corpuscles (MCV). All the toxic effect was proved dependent on the dose, but normal blood parameters were restored upon discontinuation of the treatment (Bhande & Wasu, 2016).

Antihyperglycemic effect:

Methanolic extracts of *Amaranthus spinosus* were shown to be effective in diabetic rats (caused by streptozotocin) and significant regulation of blood sugar balance was observed on a 15-day model

(Sangameswaran & Jayakar, 2008). Alloxan monohydrate induced Male Wister albino diabetic rats were used to test the antihyperglycemic effect revealed daily dose of methanolic extract of this plant stem restored the blood glucose level as much as was tested with the impact of a conventional anti-diabetic drug (Balakrishnan & Pandhare, 2010).

Antiulcer activity:

Several researchers utilising various animal models have found that *Amaranthus spinosus* has antiulcer activity. Whole plant extract demonstrated considerable dose-dependent protection against ulcers brought on by ethanol and aspirin. However, inhibition by the greatest dose (400 mg/kg) was less than that of the standard medication (Hussain et al., 2009). The level of gastric pepsin significantly increases during the development of gastric ulcers and is likely a factor in the process of gastric ulceration. This level decreased following the administration of a suspension of *A. spinosus* leaves. The crushed leaves of the plant in a water solution showed antiulcer efficacy against aspirin-induced stomach ulcers. Immersion of leaves is thought to have an antisecretory effect by reducing the acidic condition of the stomach (Mitra et al., 2014). A study showed that the plant's roots, stem, and leaves were as effective as omeprazole in protecting albino rats from hydrochloric acid, ethanol, and other substances that might cause ulcers (Mitra, 2013).

Diuretic activity:

It has been claimed that an aqueous extract of the entire *A. spinosus* plant has diuretic properties by elevating the urinary electrolyte concentration, including Na^+, K^+, and Cl^- in mice. 500 mg/kg of body-weight dose of the aqueous extract had diuretic effects. Treatment considerably increased urine volume, and an increase in electrolyte content in urine produced alkalinization of urine, which inhibited the action of saluretic and carbonic anhydrase (Potllapalli et al., 2017).

Antimalarial activity:

Aqueous extract of the bark collected from mature plant stems been tested for antimalarial properties in mice infected with RBCs parasitized by *Plasmodium berghei* showed positive response. The bark extract demonstrated dose-dependent antimalarial action in a 4-day suppressive antimalarial experiment with chloroquine as the standard antimalarial medication. The aqueous extract showed an ED_{50} value of 789.4 mg/kg for its antimalarial activity, while chloroquine was 14.6 mg/kg (Hilou et al., 2006).

Conclusion:

It is evident from the above discussion that *Amaranthus spinosus* has a wide range of nutritional and therapeutic benefits. The use of *Amaranthus spinosus* in traditional ethnomedicine has demonstrated its effective potential. Aqueous and alcoholic extracts of the different parts or whole plant are not only limited to jaundice, stomach problems or wound healing. Numerous pieces of literature support their anti-inflammatory, antioxidant, anti-malarial, analgesic, haematological, anti-diabetic and anti-fertility activity. Maintaining a balanced diet and including this plant as a functional food ingredient has both medical and nutritional benefits, which will undoubtedly keep people in good health.

Conflict of interest:

None

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