EDITED BOOK VOLUME

Emerging Trends In Therapeutic Agents From Medicinal Plants

Dr. K. Nirubama
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ACTA CLASSIC PUBLISHER

EDITED BOOK

"EMERGING TRENDS IN THERAPEUTIC AGENTS FROM MEDICINAL PLANTS"

(ISBN : 978-81-966183-7-7)

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Published by

ACTA Classic Publisher

A.C.T Academy, Office: Suleeswaranpatti, Pollachi, Coimbatore- 642002

Cell:+916369453300

Email: act.academy2021@gmail.com

Published in India.
International Standard Book Number (ISBN) **: ISBN : 978-81-966183-7-7**

Title of the Edited Book : EMERGING TRENDS IN THERAPEUTIC AGENTS FROM MEDICINAL PLANTS
Price: Rs. 725/-

PREFACE

We are glad to present the book entitled **EMERGING TRENDS IN THERAPEUTIC AGENTS FROM MEDICINAL PLANTS (ISBN: 978-81-966183-7-7**)to the students, faculty members and researchers of Biological Sciences and Pharmaceutical industry. We have observed that eminent professors and active researchers from various technical institutions across the Nation contributed to the book chapters which are focused on state-of-the-art areas related to Medicinal Chemistry, Plant Biology, Biochemistry, and Biotechnology.

We hope that the research issues covered in the book will be helpful to the professors, scientists and research scholars. We are grateful to the publisher and all the authors who contributed to the publication of **EMERGING TRENDS IN THERAPEUTIC AGENTS FROM MEDICINAL PLANTS**: First Edition.

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CHAPTER 1

Novel insights into the therapeutic effects and bioavailability of Flavonoids

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ABSTRACT

Flavonoids are group of natural substances with variable phenolic structures and are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine. These natural products are well known for their valuable effects on health and efforts are being made to isolate the constituents so called flavonoids. Flavonoids are now considered as an essential component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications. This is ascribed to their anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties coupled with their capacity to curb key cellular enzyme function. However, it has w been extensively known for centuries that derivatives of plant origin possess a broad spectrum of biological activity. Recent research and development activities on flavonoids relate to isolation, identification, characterisation and functions of flavonoids and finally their applications on health benefits. In the present review, attempts have been made to discuss the medicinal effects of flavonoids and their bioavailability. Flavonoids have low intestinal bioavailability and high urinary and biliary excretion. The bioavailability varies between different kinds of flavonoids. Flavonoids with complex structures and larger molecular weights, have lower bioavailability.

Keywords: *Flavonoids, Pharmaceutical, Bioavailability, Applications, Medicinal effects*

Introduction

Flavonoids are the antioxidants widely distributed in plants from roots to the aerial parts of the plants including flowers and fruits. Flavonoids are the group of polyphenolic compounds contributing to the plant's health, growth, reproduction, pigmentation and protection against microbial pathogens. Their concentrations in fruits and vegetables are influenced by various factors such as, light, environmental conditions, degree of ripening, germination, processing and storage. Most of the polyphenols are generally concentrated in the skin of the fruits. Total dietary intake of polyphenols is estimated as 1g/ day and that of flavonoids between 2 and 70mg/day. There are more than 10000 polyphenolic compounds identified and are grouped into 10 different classes, one of the major groups is flavonoids. Their structure includes at least one phenol which is a hexagonring with a hydroxyl group.

Flavonoids were discovered in 1930's when a factor was extracted from lemon juice that could attenuate blood vessel permeability and bleeding in scorbutic guinea pigs where vitamin C was ineffective. This factor was named as vitamin P and later renamed as flavonoid. More than 5000 flavonoids have been identified. Flavonoids are plant secondary metabolites, which together with other plant phenols share a common origin, the amino acid phenyl alanine. The basic structure of flavonoids consists of two benzene rings with a pyran ring in the middle. Flavonoids are classified into several sub classes including flavones, flavanols, flavanones, isoflavones and anthocyanins.

Flavones are one of the important subgroups of flavonoids. Flavones are widely distributed in leaves, flowers and fruits as glycosides. Parsley, red peppers, Celery, chamomile mint and ginkgo biloba are among the major sources of flavones. Luteolin, apigenin and tangeritin belong to this subclass of flavonoids.

Flavanols are flavonoids with a ketone group. They are building blocks of proanthocyanins. Flavanols occur plentifully in a variety of fruits and vegetables. The most important flavanols are kaempferol, quercetin, myricetin and fisetin. Onions, kale, lettuce, tomatoes, apples, grapes and berries are the rich sources of flavanols. Apart from fruits and vegetables, tea and red wine are also good sources of flavanols. Consumption of flavanols is found to be associated with a wide range of health benefits such as antioxidant potential and reduced risk of vascular disease.

Flavanones are another important class of flavonoids which is generally present in all citrus fruits such as oranges, lemons and grapes. Hesperidin, naringenin and eriodictyol are examples of this class of flavonoids. Flavanones are associated with several health benefits because they possess free radical-scavenging properties. Flavanone compounds are responsible for the bitter taste of the juice and peel of citrus fruits. Citrus flavonoids exert stimulating pharmacological effects as antioxidant, anti-inflammatory, blood lipid-lowering and cholesterol-lowering agents.

Bioflavonoids are a large and very distinguishing subgroup of flavonoids. Bioflavonoids enjoy only a limited distribution in the plant kingdom and are largely found in soyabeans and other leguminous plants. Some bioflavonoids have been reported to be present in microbes also. They are also found to play a significant role as precursors for the development of phytoalexins during plant microbe interactions. Isoflavonoids exhibit incredible potential to fight a few diseases. Isoflavones such as genistein and daidzein are commonly regarded to be phyto-oestrogens because of their oestrogenic activity in certain animal models.

Anthocyanins are colouring pigments present in plants, flowers and fruits. Cyanidin, delphinidin, malvidin, pelargonidin and peonidin are the most frequently studied anthocyanins. They occur chiefly in the outer cell layers of various fruits such as cranberries, black currants, red grapes, merlot grapes, raspberries, strawberries, blueberries, bilberries and blackberries. Stability coupled with health benefits of these compounds enable them to be used in the food industry in a variety of applications

Quercetin, Catechin, Kampferol, and myricetin are the well-known flavonoids spread widely in fruits and vegetables and may contribute to our daily flavonoid consumption. Quercetin is ingested largely from tea, onions, red wine and apples. Catechin are largely found in green tea. Other major sources of flavonoids are chocolate, pears, grapes etc. Anthocyanins such as cyanidin, malvidine and delphinidin, provide red and purple pigments for fruits. They are abundant in red and black cherries, berries, grapes, and legumes.

Therapeutic effects of flavonoids

Anticancer activity

Cancer is a major health issue caused by uncontrolled cell growth. There are numerous anticancer drugs available, and yet only a few exhibits inhibition against carcinogenesis, and most of them are toxic and have adverse side effects. Natural secondary

metabolites have phytochemicals and display biological activities over a wide range of spectrum, placing the basis for cancer prevention and treatment. Flavonoids are known to inhibit cell growth and act as an anticancer agent. Following are profuse examples of flavonoids and their use as anticancer agents.

Hesperedin is an important flavonoid which shows effective anticancer activity. Polylactic-co-glycolic acid (PLGA) nanoparticles were synthesized and loaded with Hsp to form hesperidin nanoparticles (HspNPs) and its anticancer activity was determined against C6 glioma cells. The encapsulated Hsp exhibited reduced in vitro cell viability against the C6 glioma cell line. Aurone, a benzo-furanone, is another flavonoid which has been widely used as an anticancer agent. Several analogues of aurone display different mechanisms against cancer cells because there are many possible targets. The targets of aurone are cyclin dependent kinases, histone deacetylase, adenosine receptors, telomerase, sirtuins, and microtubules. Quercetin, which is a natural flavonoid present in plants are commonly consumed foods such as berries, green tea, and grains. It has been used most efficiently for colorectal cancer. Cell cycle inhibition, increase in programmed cell death, modulation of oestrogen receptors, regulation of signalling pathways, inhibition of metastasis and angiogenesis are the various mechanisms underlying the chemo-preventive effects of quercetin in colorectal cancer. Luteolin is also a natural flavonoid with pro-apoptotic effect in hepatocellular carcinoma (HCC) cells and arrests the cancer cell cycle at the G2/M stage. Kaempferol, which is a natural flavanol, which can reduce the risk of cancer. Kaempferol stimulates the body's antioxidants against free radicals that cause cancer. Myricetin is an important flavonoid which has anti-inflammatory and anticancer activities, and in liver cancer it shows antimitotic effects, and it targets different metabolic pathways in mitochondria which result in cancer cell death.

Free radical scavenging activity

Reactive oxygen species (ROS) are produced in the human body primarily as byproducts of the electron transport chain. They are important for protein phosphorylation, initiation of numerous transcriptional factors, apoptosis, immunity, and differentiation processes. However, ROS causes oxidative stress upon reacting with molecules like lipids, proteins, or nucleic acids. Lipid peroxidation by ROS causes cellular membrane damage. This membrane has potential positive charges on the outside of the cell, and negative charges inside the cell. The damage to the membrane alters the cell membrane potential and the cell's osmotic pressure, ultimately causing cell death. The human defense system uses different mechanisms and enzymes to fight endogenous elevated ROS. Flavonoids act as exogenous antioxidants and are directly oxidized by radicals to form less reactive species via the four mechanisms, such as (1) inhibition of nitric-oxide synthase activity, (2) inhibition of xanthine oxidase enzyme activity, (3) modulation of channel pathways, or by (4) interacting with other enzyme systems.

Flavonoids can avoid injury caused by free radicals in different ways and one way is the direct scavenging of free radicals. Flavonoids are oxidized by radicals, resulting in a more stable but less-reactive radical. Flavonoids stabilize the ROS by reacting with the reactive compound of the radical. Due to the high reactivity of the hydroxyl group of the flavonoids, radicals are made inactive, as given in the following equation

$$\text{Flavonoid (OH)} + \text{r(O)} + \text{RH},$$

Where R is a free radical and O is an oxygen free radical. Hanasaki *et al*. found that some flavonoids can directly scavenge superoxides, whereas some other flavonoids can scavenge the highly reactive oxygen-derived radical called peroxynitrite. They found that flavonoids such as rutin and epicatechin are powerful radical scavengers and the scavenging ability of rutin may be due to its inhibitory activity on the enzyme Xanthine oxidase. Kerry & Abbeyreported that by scavenging radicals, flavonoids can inhibit LDL oxidation in *in vitro* studies. They further reported that this action protects the LDL particles and, theoretically, flavonoids have preventive action against atherosclerosis.

Xanthine oxidase inhibition

Sanhueza *et al*. worked on changes in the xanthine dehydrogenase: Xanthine Oxidase ratio in the rat kidney subjected to ischaemia–reperfusion stress and studied the preventive effect of some flavonoids. They mentioned that the XO pathway is an important route in the oxidative damage to tissues, especially after ischaemia–reperfusion. Xanthine dehydrogenase is the form of the enzyme present under physiological conditions, but its configuration is converted to XO during ischaemic conditions. XO is a source of oxygen free radicals. In the reperfusion phase, XO reacts with molecular oxygen, thereby releasing superoxide free radicals. Two flavonoids, silybin and quercetin were found to inhibit XO activity, thereby resulting in decreased oxidative injury. Cos *et al*. worked on structure–function relations in which the flavonoid luteolin (tetrahydroxy flavone) was reported to be the most potent inhibitor of XO.

Antioxidant activity

The antioxidant effect of flavonoids is associated with the molecular structure, and more accurately, with the location and total number of the –OH groups, the conjugation and resonance effects, the surrounding environment which alters the thermodynamically favoured antioxidant site, and the particular antioxidant mechanism for a compound. The most commonly used supplemented antioxidants are vitamins C (ascorbic acid) and E (tocopherol). The antioxidant potential of flavonoids is stronger than vitamin C and vitamin Therefore, it is important to regularly include those vegetables and fruits that are rich in flavonoids in daily food intake. For example, due to enhanced and established antioxidant and anti-inflammatory effects, flavonoids improve bone health. The utilization of flavonoids in biomaterials has great projections for bone tissue engineering. This exhibited that flavonoids should be supplemented in food of aged people. Quercetin, when present in the blood stream, improves vascular health and limits the risk of cardiovascular disease in its conjugated form. The quercetin and its derivatives prevent thrombosis or blood clotting and prevents chances of stroke. Hesperidin and hesperetin are the flavonoids present in citrus fruits and mushrooms that show antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Propolis is used as a folk medicine for several years and is now used in the pharmaceutical industry. It comprises many compounds, including flavonoids that are responsible for their pharmacological properties such as antioxidant, antimicrobial, anti-inflammatory, and anti-proliferative activities. Rutin, a flavonol, exhibited many biological activities that include anticancer, antioxidant, and cytoprotective, etc.

Almost every group of flavonoids can act as antioxidants. It has been reported that flavones and catechins seem to be the most influential flavonoids for protecting the body

against ROS. Body cells and tissues are continuously susceptible to the damage caused by free radicals and reactive oxygen species, which are produced during the normal metabolism of oxygen or are induced by exogenous damage. The mechanisms and the sequence of events by which free radicals interfere with cellular functions are not clearly understood, but one of the most important events seems to be lipid peroxidation, which results in cellular membrane damage. This membrane damage causes a shift in the net charge of the cell, changing the osmotic pressure, leading to cell swelling and ultimately cell death. Free radicals can attract several inflammatory mediators, causative to a general inflammatory response and tissue damage. To protect themselves from ROS, living organisms have established many effective mechanisms. In addition to the enzymatic antioxidant defense mechanisms like superoxide dismutase, catalase, and glutathione peroxidase, non-enzymic counterparts such as glutathione, ascorbic acid, and α-tocopherol are also used by our body. The enhanced production of ROS during injury results in the consumption and depletion of the endogenous scavenging compounds. Flavonoids may have an additive effect on the endogenous scavenging compounds. Codorniu-Hernández *et al*., carried out molecular docking studies to understand flavonoid–protein interactions. The results showed that hydrophilic amino acid residues demonstrate high-affinity interactions with flavonoid molecules, which was predicted by the theoretical affinity order. The docking modes among catechin molecules and four proteins (human serum albumin, transthyretin, elastase, and renin) also support this information. The theoretical affinity order among flavonoids and amino acid residues appears to have great applications in the theoretical predictions of flavonoid–protein interactions as a high-quality approach to understand the biological effects of flavonoids.

Cardioprotective activity

Dietary flavonoids show a favourable relationship between their consumption and reduction of cardiovascular diseases. Several studies demonstrated that those who consume a large number of flavonoids have 18% lower mortality risk of cardiovascular diseases. Various studies have shown that flavonoids have cardioprotective and neuroprotective actions and chemoprotective abilities. Tea is a major source of flavonoids, and its intake decreases the risk of cardiovascular diseases. Anthocyanidin and proanthocyanidin are the flavonoids, that have proven to be active against cardiac diseases. Isoflavone, anthocyanins, and cocoa flavan-3-ols progress vascular health. High consumption of these flavonoids decreases arterial stiffness which also reduces the risk of cardiovascular diseases. Chrysin is a flavone that has beneficial effects on epilepsy and depression, also suppresses neuroinflammation, and has neuro-protective effects. Morin, a bioflavonoid, has verified to be a cardio-protective agent through animal modeling. The mechanism for this cardio protection was reported due to modification of MAPK/NF-kappa B/TNF-alpha pathway.

Dihydro-quercetin (DHQ), a dihydroxyflavone used in animal models, demonstrated to be effective against cardiac dysfunction by decreasing the generation of ROS and lipid peroxidation and increasing the biological activity of antioxidant enzyme. The PI3K/Akt pathway activation is found to have defensive effects. Clinical trials on oxerutin showed that it is rather active in treatment of chronic venous hypertension. Remarkably, there a0re no detected toxicities or side effects of oxerutin clinical trial results. Different studies showed that a mixture of flavonoids like diosmin, troxerutin, Rutin,

hesperidin, quercetin, etc., enhance the vein function, pacify the capillary permeability, and increase the lymphatic and hemorrhoidal drainage. Thus, flavonoids are very much useful in control of piles and hemorrhoid diseases. Diosmin is the flavone glycoside of diosmetin effectively control different types of blood vessel disease like hemorrhoids, bleeding from gums and eyes, etc. It enhances blood flow inside the body.

Anti- neurodegenerative activity

Flavonoids prevent age related neurodegenerative diseases, and in particular, dementia, Parkinson'sand Alzheimer's disease. The ROS and nitrogen species (NOCs) are responsible for many neurodegenerative diseases. Tangeretin is a flavonoid present in citrus fruits and actas an antioxidant against ROS and NOCs species and confer protection in neurodegeneration disorders such as Parkinson's disease. Foods which are abundant in flavonoids lower the danger of neurodegenerative diseases and also counteract age related cognitive disorders. It is beneficial in two different ways; first, it regulates neuronal signal cascade produced by cell apoptosis, and second, shows significant effects on the peripheral and central nervous system. Hesperidin (Hsd) and hesperetin (Hst) are the two flavonoids responsible for their neuro-pharmacological effects, including neuroprotective, antidepressant, and effects on memory. Berries contain various natural flavonoids, such as polyphenolic compounds like stilbene, anthocyanins etc. These flavonoids are known to be effective as anti-neurodegenerative agents, anti-mutagenic and antimicrobial agents. Epicatechin, an antioxidant flavonoid profusely found in wood plants, has an analog 3-*O*-methyl epicatechinthat inhibits neurotoxicity in vitro. The polyphenolic compound luteolin has neuroprotective effects and also as protective effect against age related neuro-disorders

Excessive consumption of alcohol causes several health disorders and negatively affects the brain. The acetylpectolinarin (ACP) flavonoid gotten from the *Linaria vulgaris* Mill. has been described to treat hangover by increasing the spontaneous network function of the cultured hippocampal neurons when treated with low concentration of ethanol. This is due to the agonistic action on GABAergic synapses mediated by SK potassium channel. Hyperalgesia is a severe pain sensation due to peripheral nerve damage, and is associated with diabetic patients. Quercetin and sodium, when used together, can act as antinociceptives, reducing diabetes complications.

Prevention of Alzheimer's Disease (AD)

Acetylcholinesterase (AChE) is a major enzyme in the central nervous system and its inhibition leads to increases of neural acetylcholine levels which is one of the therapies for symptomatic relief of mild to moderate AD. Hence the inhibition of cholinesterases is one of the vitalfoci for drug development to fight AD. A number of flavonoids have been stated for their anti-cholinesterase activity. The *in vitro* inhibitory studies done on different flavonoids like quercetin, rutin, kaempferol 3-*O*-β-D-galactoside and macluraxanthone exhibited that quercetin and macluraxanthone possess a concentration-dependent inhibition capacity against AChE and butyryl cholinsterase (BChE).

Cyanidin-3-*O*-glucoside also known askuromanin is a flavonoid, a subgroup of anthocyanins that is found in many vegetables and fruits. The ROS are responsible for DNA damage, lipid peroxidation which resulted into different diseases including Alzheimer's disease (AD). This can be controlled by natural products, which may minimize its progression by acting as cholinesterase inhibitor, reducing oxidative stress, and avoiding

neuron damage. This neurodegenerative disorder may be identified by excess of amyloid beta (Aβ) fibrils, which accumulates, in the extracellular spaces of brain and tau protein. The neuro decline is found to be associated with these two proteins. Anthocyanins contain a pseudo aromatic ring C that increases their structural planarity and promotes amyloid fibril disruption due to effective incorporation of anthocyanins inside the amyloid beta fibril groove. They can also cross the membrane separating the blood from the cerebrospinal fluid and prevent neuron degeneration. The compounds of anthocyanin subcategory can hence be potentially employed as a therapeutic agent in those diseases that are caused by oxidative stress. Cyanidin-3-*O*-glucoside can therefore act as neuroprotective agent. Likewise, another flavonoid rich plant named gangobilobia may be used in the treatment of age-related dementia and Alzheimer's disease. Butyrylcholinesterase is an enzyme, found in the blood plasma of humans. Two types of neurotoxic inhibitors of cholinesterase are usually employed for AD that are active against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Increasing acetylcholine results in healthier neuron transport and in turn, better cognitive function. Flavonoids have been widely used as BChE inhibitors

Inhibition of Neuropathy

Nerve malfunction is called neuropathy. Peripheral neuropathy is one of the four types of neuropathies. Neuropathies refers to the conditions that arise when nerves that carry messages to and from the brain and spinal cord and to the rest of the body are damaged or diseased. High levels of glucose destroy the blood vessels that drives to the nerve, and thus, affects the nerves of hand and feet which progress with age. Natural compounds containing flavonoid have been used for to relieve neuropathic pain. *Cichorium intybus* is a medicinal plant that contains a variety of valuable biochemical constituents present, including flavonoid, saponin, and tannin. The presence of these compounds permits them to be used to suppress oxidative stress, and its possible interference of the two amino acid systems, namely GABAergic and glutamatergic systems in nerve injury and neuropathy.

Diabetes is associated with a number of complications which includes nephropathy, neuropathy, and cardiovascular disease. A number of studies exhibit that diabetes neuropathy (DN) and T2DM may be related to increased risk of Alzheimer's disease. Diabetic neuropathy is a complication that is most commonly faced by 50% diabetes patients, with development of burning sensation to complete loss of sensation of heat and cold in legs and feet, and the loss of peripheral nerve fibres.

Stroke Prevention

Chalcones are natural precursor compounds of flavonoids and iso-flavonoids. They are present in several plants and vegetables with a wide range of biological activities. Chalcone is an aromatic ketone and an enone with a capacity to activate nuclear factor erythroid 2-related factor (2NRF2) pathway. Numerous novel dihydroxy chalcones were synthesized and assessed for their ability to suppress ROS species and oxidative stress acting as an anti-ischemic stroke through KEAP1/NRF2/ARE pathway activation.

Various systems such as vascular and inflammatory system interact with each other to form a stable homeostasis of central nervous system and the semipermeable membrane that separates the circulating blood from the brain and extracellular fluid in the CNS known

as the blood brain barrier (BBB). The brain recovers itself from injury using CNS and BBB. The endothelium cells of BBB secrete molecules that adjust the after effect of ischemic stroke (stroke vasculome) when its genes are upregulated. Inflammation after stroke is linked with the upregulation of these inflammation genes. Stem cells can release anti-inflammatory agents. Endothelial progenitor cells (EPCs) directly modify the inflammation-associated stroke vasculome after ischemic stroke. Fisetin, a flavonoid inhibited LPS-induced TNFα production and suppressing nuclear factor jB activation there by acting as a neuroprotective and anti-inflammatory agent after post ischemia injury in vitro. The cortical development, where neurons in brain failed to migrate in the proper formation in utero, results in malfunctioning known as Focal cortical dysplasia (FCD). The naturally occurring flavonoid rutin has been used on animal models to treat FCD.This may act as a clinical drug in the future.

Recovery of Injured Nerves and Anti-inflammatory Properties

Paraplegia is a condition in which paralysis of the body occurs from the waist down. This is due to the injury to the spinal cord or central nervous system (CNS). Experimentation on animal model revealed that using isoflurane increased the number of motor neurons. The delayed preconditioning with a neuroprotective effect was observed, which may be related with the expression of protein complex NF-κB. The *Hypericum perforatum* L. is a medicinal plant with flavonoids as active phytoconstituents. It has a flavonoid content of 6%. It protects the neuron of adrenal phaeochromocytoma from oxidative stress caused by ROS species such as H_2O_2. A study was carried out using Wistar albino female rats. Sciatic nerve injury (SNI) was induced in order to determine the effect of plant extract on oxidative stress, cell signalling molecules, cytokine production, and caspase expression in brain muscle. The result recommended a delay in the progression of SNI caused by the plant extract. Flavonoid rich food derived from natural compounds such as mulberry, genistein, *Acanthus syriacus* etc., display protective effect against sciatic nerve injury.

Cyclooxygenase(COX) is an endogenous enzyme that catalyses the conversion of arachidonic acid into prostaglandins and thromboxanes. The enzyme exists in two isoforms, COX-1 and COX-2. COX-1 is a constituent enzyme that is responsible for the supply of prostaglandins which maintain the integrity of the gastric mucosa and deliver adequate vascular homeostasis whereas COX-2 is an inducible enzyme and is expressed only after an inflammatory stimulus. The function of COX-2 is to produce prostaglandins for the induction of inflammation and pain. The studies carried out by using *in silico* methods on the binding modes of flavonoids with COX-2 explored that some flavonols and flavones containing a 2, 3-double bond may act as preferential inhibitors of COX-2. The same observations were found for the flavonol, flavone, and flavanone or isoflavone classes. This discovery led to the progress of selective COX-2 inhibitors which are a class of compounds with good anti-inflammatory activity and minimized gastrointestinal side effects. COX-inhibitory activity was also exhibited by the commercially available flavonoids like silbinin, galangin, scopoletin, hesperitin, genistein, daidzein, esculatin, taxifolin, naringenin and celecoxib.

Angiogenesis is the formation of new blood vessels from existing vessels which is important for normal development. Uncontrolled angiogenesis causes serious diseases such as inflammatory disorders, obesity, multiple sclerosis, asthma, endometrioses, and

cirrhosis. Plant polyphenols such as flavonoids and chalcones control angiogenesis by regulating multiple signaling pathways. Viscosine is a flavonoid present in *Dodonea viscosa*, which has anti-inflammatory, antipyretic and antioxidant properties. Baicalin is a flavonoid present in medicinal plants named *Scutellaria baicalensis* Georgi and *Oroxylum indicum*. This flavonoid shows antioxidant and anti-inflammatory activity and is used in the treatment of certain diseases such as asthma, liver and kidney diseases, inflammatory bowel diseases, carcinogenesis, and cardiovascular diseases. Kaempferol is a flavonoid that possesses anti-inflammatory effects. Rutin, which is a common dietary flavonoid, having several pharmacological properties such as anti-inflammatory, antimicrobial, and anticancer properties. Chrysin is a flavonoid has anti-inflammatory and antioxidant effect. It has been proved that fruits which are rich in cyanidin and peonidin have high anti-inflammatory effects.

Antimalarial activity

Malaria is produced by the parasitic species of Plasmodium. *Plasmodium falciparum* and other species are now increasingly resistant to the common antimalarial drugs like chloroquine and this resistance is spreading toward artemisinin and its analogues. New drugs are essential to treat drug resistant strains of Plasmodium. In the current effort of producing antimalarial drug, it is reported that plant extracts that are rich in compounds, like flavonoids, chalcones, terpenes, quinones, and xanthones, are antimalarial in nature. *Prosopis* is plant genus which has been used for medicinal purposes since ancient times. Its components include flavonoids, tannins, alkaloids etc. These bioactive compounds are not only antimalarial but also antiulcer and antibiotic in nature. Species of the genus *Psiadia* extract comprise flavonoids, coumarins, phenylpropanoids, and terpenoids. These compounds exhibit pharmacological activities such as antimicrobial, antimalarial, antiviral, and anti-inflammatory etc. *Psiadiadentata* and *Psiadia arguta* plant extracts inhibit the growth of *Plasmodium falciparum*. *Waltheria indica* extract have flavonoids, (−) epicatechin, kaempferol, quercetin, sterols etc. These compounds are responsible for the treatment of malaria and other infectious diseases (e.gdiarrhea due to *Escherichia coli*, lungs infection due to *Klebsiella pneumoniae*), inflammation, and prevention of oxidative stress. Prenylated flavonoids found from the bark of *Artocarpus styracifolius* show antiplasmodial and antitrypanosomal effects. Silymarin isolated from *Silybum marianum* shows anti-plasmodial activity. Silymarin, a polyphenolic flavonoid, forms the silymarin-heme complex, and inhibits the conversion of toxic free heme into crystalline non-toxic heamozoid.

Antiviral Activities

Patients with poor immunity when infected with a transmittable viral infection can be deadly and the recent novel coronavirus pandemic showed that immunocompromised people are particularly vulnerable to the COVID-19. Serious efforts have been taken to synthesize antiviral agents with efficient activity. Natural bioactive flavonoids exist in medicinal plants and herbs have been extensively reported to have antiviral activity and are concentrated and modified for its better action. Both natural and synthetic flavonoids are probable medicines for many diseases, including HIV. Glabranine and 7-*O*-methyl-glabranine are the two flavonoids extracted from Mexican plant *Tephrosia madrensis*. The plaque assay established that these isolates exhibit antiviral activities, and inhibit dengue virus replication. Anthocyanins present in berry fruits have antiviral activity against

influenza virus. Baicalein, quercetin, and fisetin are potential inhibitors of chikungunya virus. The epicatechin 3-gallate, fisetin, quercetin inhibits murine norovirus and daidzein, and kaempferol inhibit feline calicivirus. Four flavonoids (5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-6,7-dimethoxyflavone, acacetin, apigenin) extracted from *Mosla scabra* show antiviral activity against influenza viruses. Burs (involucre) of *Castanea crenata*, have a extensive range of biological activities attributed to the bioactive phtyo-constituents present in it that includes flavonoids, tannins, phenolic acids, coumarins, phenylpropanoids, and steroids.

Antibacterial Action

The rise and spread of multi-drug resistance in pathogenic bacteria bring about into a number of antibiotics that have become ineffective for the treatment of a number of bacterial infections. Flavonoids have the ability to improve the protective immune systems of humans. Several flavonoids act both as bacteriostatic and bactericidal agents by damaging the plasma membrane, and inhibiting energy metabolism and nucleic acid synthesis of microbes. *Bridelia* is a plant of genus of Phyllanthaceae family, which is used as a pain-relieving medicine contains flavonoids like quercetin, gallocatechin-(4′-*O*-7)-epigallocatechin, myricetin-3-glycosides, and isoflavone. These flavonoids are accountable for its antimalarial, antibacterial, anti-inflammatory activities. Anthocyanidin plays a major role against tuberculosis and drug-resistant *Mycobacterium tuberculosis* strains. Studies have proven that hesperidin and hesperetin, two flavonoids, show very good antimicrobial activity. Flavonoids from *Cuscuta* are described for many biological activities, including antiproliferative, hepatoprotective, anxiolytic and antimicrobial activities. There has been extensive literature available on flavonoid rich plants showing antibacterial activities, such as flowers from *Acacia saligna* (Labill.), roots and aerial extract of *Lamium album*, *Tridax procumbens*, Tunisian Date Palm seeds, Aurone derivatives, Chrysoeriol, *Alanchoemortagei*, *K. fedtschenkoi*, Onion (*Allium cepa* L.), *Asplenium nidus* (fern), *Trianthema decandra*, pineapple (*Ananascomosus*), *Pseudarthriahookeri* (Fabaceae), Keigairengyoto, *Quercus brantii* L., *Acacia saligna* (Labill.), or the use of flavonoid rich marine algae such as marine algae *Sargassum swartzii* all of which show significant antimicrobial activities.

Bioavailability of Flavonoids

It is generally believed that an increased consumption of vegetables and fruits protect against various diseases. This is an attractive hypothesis that vegetables and fruits contain bioactive compounds that have a protective effect, in particular flavonoids contribute to this protective effect. To elucidate the role of dietary flavonoids in human health it is very much essential to know the concentrations and forms that are present in plasma and tissues after ingestion of these flavonoids with the diet. Hence it is important to study their absorption, metabolism and bioavailability.

Bioavailability refers to the proportion of a substance which reaches systemic circulation unchanged, after a particular route of administration. Dietary flavonoids are consumed through oral route, which involve transport across gastro-intestinal epithelium. Under normal conditions, the intestinal epithelium exists as a single layer of tightly connected cells, so that a continuous barrier is formed. Enterocytes are polarized cells, with

one pole facing the lumen and the other pole facing the blood capillaries. Hence there are two plasma membrane barriers for solutes to overcome. These barriers ensure selective uptake of materials through membrane proteins that control the transepithelial transport of dietary compounds.

Absorption

Before absorption from the gut, they must be released from plant foods by chewing and the actions of digestive juices ant finally the actions of microbial flora in the colon. It can be envisaged that the release from the plant tissue depends on the type of plant food, its processing conditions and the presence of other dietary components. The absorption of flavonoids liberated from the food will depend on its physico-chemical properties such as molecular size, configuration, lipophilicity, solubility and pKa.

Bioavailability and Metabolism

In nature, flavonoids are present as glycosides although their aglycone forms are also exist. The aglycones have stronger antioxidant activity than glycoside forms. The reduction in the antioxidant activity in the glycosidic forms may be due to the removal of hydroxyl groups by conjugation, and there by inhibiting them from scavenging reactive oxygen species or chelating transition metals. In addition, glycosylation enlarges the molecule, the passage through membrane may decrease upon glycosylation leading to less antioxidant activity. But glycosylation increases the solubility of the compound and subsequently increases the intestinal absorption. Flavonoid glycosides can be hydrolysed from sugar moieties by hydrolases at the intestinal brush border by colonic microorganisms. They are also transported via Na^+ dependent glucose transporter into enterocytes, where the sugar molecules are removed by beta glucosidases. The formed aglycones undergo conjugation reactions involving glucuronidation and sulfation with or without methylation. The conjugation occurs in enterocytes and liver. Conjugation facilitates their excretion and thereby shortens their plasma half- life. Most of the flavonoids in plasma and urine are in conjugated form. Therefore, cells in the body are usually exposed to flavonoid metabolites and conjugates rather than aglycones. The conjugates are physically and chemically different from aglycones and there by their biologic properties are also different. The conjugation blocks electron movement over the rings, the conjugated molecules exhibit less potential for redox reaction and therefore antioxidant activity, although this greatly depends on the position of the conjugation.

Conjugation is one of the defence mechanisms of the body against flavonoids as pro-oxidants. As flavonoids possess antioxidant activity, they may also accompany oxidative consequences. By conjugation the body reduces their antioxidant activity and potential pro-oxidant effects. Flavonoids vary in the magnitude and velocity of absorption and the rate of elimination and plasma half- life. Hence, they have low intestinal bioavailability and rapid urinary and biliary excretion, and therefore their plasma concentration rarely exceeds 1micro mole with regular diet.

According to the data provided by Manach *et al* by 97 bioavailability studies in humans suggested that the best rate of absorption among flavonoids is seen in gallic acid and isoflavones., followed by catechins, flavanones and quercetin glycosides. Gallic acid although has a good absorption its conjugation decreases the bioavailability. Proanthocyanidins and anthocyanidins have shown very low bioavailability. For instance,

the absorption rate of anthocyanins from concentrated black current juice was found to be less than 1%. Anthocyanins appear in plasma in unmodified form in contrast to other flavonoids which are separated from their glycosides during their absorption process. Polymerization markedly impairs the absorption of proanthocyanidins. They are not cleaved to their monomers by gastric secretions or by intestinal microflora.

Quercetin metabolites are excreted very slowly, having a half- life of 11- 28 hours in plasma which may be due to tight binding to serum albumin. Hence, considerable quantities of quercetin can be achieved by maintaining a regular diet with moderate amounts of quercetin. In contrast, anthocyanins and catechins are excreted as rapidly as they are absorbed. For instance, anthocyanins reach the highest levels in plasma within 1-4 hours and the maximum level in urine on an average of 2-5 hours after ingestion. Although catechins have shown short plasma half- life and rapid elimination, they may still may capable of accumulating in plasma over a period of consumption.

Conclusion

Flavonoids are groups of several compounds found naturally in many plants, fruits, vegetables, along with plant products such as coffee, chocolate, and tea. It had been continuously reported that flavonoids have a wide range of health benefits. For example, flavonoids are the rich sources of antioxidants, providing our body with natural immune shields from daily environmental and endogenous toxins. Different classes of flavonoids are isolated so far with several substantial biological activities such as anticancer, antibacterial, antifungal, anti-diabetic, antimalarial, neuroprotective, cardio-protective, and anti-inflammatory. Thus, consuming different types of flavonoids in daily diet is highly recommended to stay healthy and to reduce the risk of serval life threatening diseases such as diabetes mellitus, cancer as well as lowering the risk of stroke and heart attack. The therapeutic effects of flavonoids have been demonstrated in majority of pre-clinical studies in murine models. Different approaches should be used in clinical trials because the absorption and bioavailability of flavonoids are not compromised. Low bioavailability of flavonoids has been a concern as it can limit or even incumber their health effects. Therefore, attempts to improve their bioavailability in order to improve the effectiveness of flavonoids are being studied. Further investigations on bioavailability are important as it is a determining factor for flavonoid biological activity.

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***CHAPTER* 2**

Cosmeceutical Importance of Medicinal Plants

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ABSTRACT

Cosmeceuticals are cosmetic – containing herbal products that act as both cosmetics and medicines. They contain active ingredients with unique properties. They are designed specifically to improve skin health and repair damage such as fine lines, wrinkles, dryness, redness, sun damage, hyperpigmentation etc. Cosmeceuticals industries constantly evolving more potent and effective solutions than traditional cosmetics for consumers. Nanotechnology creates new formulas that will provide users with safer and more effective results by improving properties of cosmeceuticals at the nano scale, such as colour, solubility, and transparency. Nowadays, Nano cosmeceuticals used for skin, hair, nail, and lip care, for conditions like wrinkles, photoaging, hyperpigmentation, dandruff, and hair damage. Cosmeceuticals are recently playing an important role in medicine. Many dermatologists prescribe cosmeceuticals for cosmetic purpose as well as treating various diseases.

Keywords: *Cosmeceuticals, Phytocompounds, Chemical ingredients of Cosmeceuticals, Nano Cosmeceuticals, FDA guidelines*

Introduction

The beauty concept and usage of cosmetics is as ancient as humankind and civilization. One of the advantages of herbal cosmetics is, medicinal plants are commonly available, inexpensive, eco-friendly, and having less or no harmful effects as compared to synthetic drugs and even can be grown in household / kitchen gardens.

Herbal cosmetics are designed, using various cosmetic ingredients to form the base in which one or more herbal ingredients are used. These cosmetics are used to treat various skin disorders and for the beatification.

Nutraceuticals

In 1989, the term "nutraceutical" was coined by Stephen De Felice from "nutrition" and "pharmaceutical." Nutraceuticals are defined by Health Canada, which says that Nutraceuticals are products prepared from foods, but sold in the form of pills, or powder or other medicinal forms, not usually associated with foods."

Nutraceuticals are sourced from herbs, food industry, dietary supplements market, and the pharmaceutical industry, and now trending towards genetically engineered "designer" foods as well.

Therapeutic areas covered by Nutraceuticals are,

- Anti-arthritis
- Digestive problems
- Prophylaxis
- Treatment for cancers

- Lipid and sugar control
- Osteoporosis
- Blood pressure
- Depression among others
- Skin disorders

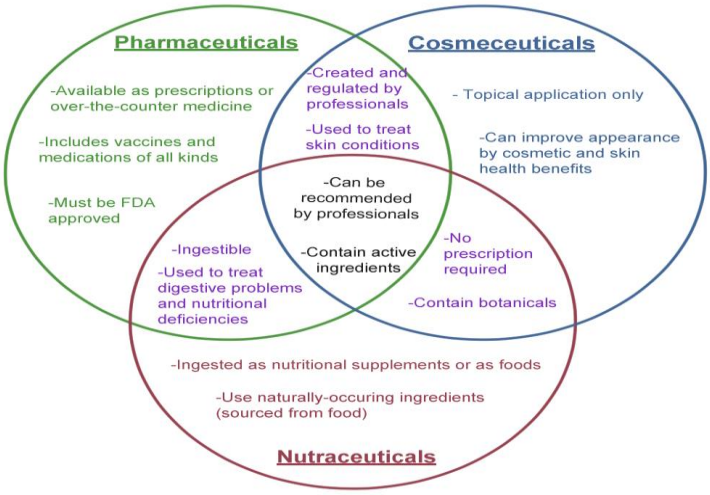
Cosmeceuticals

For decades, cultures worldwide have used ingredients like milk, honey, and essential vitamins to prevent aging, moisturize the skin, and avoid sun damage. Today, many cosmeceuticals use or build upon these methods to create new products that function as cosmetic beauty tools and tools to improve skin health and function.

In 1984, Dr. Albert Kligman from University of Pennsylvania coined the term cosmeceuticalsto describe a hybrid class of products on the spectrum of 'cosmetics and pharmaceutical.'

Cosmeceuticals are drugs, cosmetics, or a mixture of both. Cosmeceuticals are personal care products that not only beautify and have healing, therapeutic, and disease-fighting characteristics. Plant has become an eventual source for development of new drug entities for cosmeceuticals and pharmaceutical applications. Cosmeceuticals may be hybrid, natural or synthetic depending upon their compositions. Many medicinal plants and herbs offer effect like cosmeceuticals and used extensively for same purpose globally.

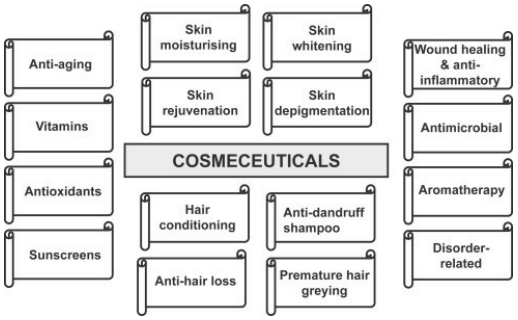
Herbal cosmeceuticals are gaining attention due to their wide range of availability and fewer side effects. There are many plants and natural ingredients available commercially as cosmeceuticals. Herbal cosmetics originated from plants, sea, rock salt and soil, etc. Herbal cosmetics are synthetic chemicals free and considered safe to use.



Role of Cosmeceuticals

- Anti-aging in general
- control acne
- anti-wrinkle effects
- Treatment of photo melanosis and photo tanning
- Treatment of pigmentation-related disorders like melasma or freckles
- Rhytide reduction
- Anti-inflammatory

- Fat loss
- Hair growth
- Hair fall prevention
- Improve physical appearance, health, beauty, and skin ailments.
- Maintenance of skin textures and clarity of complexion



Phytocompounds as cosmeceuticals

Phytocompounds have been employed in cosmeceuticals for decades, and have shown potential in applications such as moisturizing, sunscreen, antiaging, and hair-based therapy.

The major concerns in the usage of phytocompounds are their low solubility, low penetration and physio-chemical instability when applied on the skin. When compared to synthetic cosmetic ingredients, phytocompounds are milder, have a more favourable toxicity profile, biodegradable and used extensively for same purpose globally.

Some natural plants/herbs/ingredients used in cosmetic industry.

- Aloe vera
- Henna
- Neem
- Turmeric
- Shikakai
- Rose oil
- Coconut oil
- Sunflower oil
- Jojoba oil
- Hirda
- Behada
- Amalaki
- Bringaraj
- Rosary Pea and Mandor, etc.

CLASSIFICATION OF COSMECEUTICALS

There is no single/accepted classification of cosmeceuticals. Broadly, they fall into categories based on their chief etiological sign, i.e., the condition for which a person would use them, or based on their source or biochemical structure.

Cosmeceutical categories as per their chief sign based on etiology of the target condition:
1) Skin lightening or depigmenting
2) Sunscreens
3) Moisturizing agents
4) Anti-wrinkle/aging
5) Scar-reducing
6) Antioxidants
7) Hair strengthening
8) Specific disorder-related, e.g., acne, rosacea, melasma
9) Miscellaneous

A considerable number of commonly used and prescribed cosmeceuticals and nutraceuticals are as follows,

- Alpha-lipoic acid, oral
- Coenzyme Q10, oral
- Vitamin B-complex, oral
- Vitamin C, oral and topical
- Vitamin E, topical and oral
- Hydroquinone, topical
- Alpha and beta hydroxy acids, topical
- Polyunsaturated fatty acids, oral
- Peptides, topical
- Retinoids, oral
- Retinaldehyde, topical
- Retinal esters, topical
- Retinol, topical
- Comfrey, topical
- Feverfew, topical
- Jojoba oil, topical
- Licorice topical
- Pune bark extract and topical
- Rose, topical
- Turmeric, topical and oral
- Milk thistle, topical
- Lavender, topical
- Grapeseed, oral
- Green tea, oral
- Lycopene, oral
- Pomegranate: oral
- Arbutin: topical
- Kojic acid: topical
- Soya: oral and topical
- Aloe vera, topical and oral
- Chamomile: oral
- Caffeine: oral and topical
- Polypodium leucotomos, oral

- Glutathione, oral, parenteral, topical
- Phytosterols, oral and topical
- Proanthocyanidin, oral
- Panthenol, topical
- Ceramides, topical
- Zinc, topical and oral
- Licorice plant [glycyrrhiza] - glabridin
- Tyrowhite, topical
- Ellagic acid, topical
- Sunscreen ingredients
- Idebenone
- Resveratrol
- Hyaluronic acid
- Glucosamine
- Azelaic acid
- Niacinamide
- Allium cepa
- Allantoin
- Marine protein supplements (MPS)

POTENTIAL TOXICITY OF SOME COSMECEUTICALS

Cosmeceuticals has inappropriately eventuated into addition of many substances as additives in the commercially available preparations to enhance their properties, qualities, significance, performance, and viability.

Potential toxicity of some important chemical ingredients often used in cosmeceuticals:

- **1,4-dioxane ($C_4H_8O_2$, dioxane)** - It is an ether with emulsifying property, detergent, and solvent properties making it a preferred additive in shampoos, mouthwashes, and kinds of toothpaste. Accidental significant exposure to this chemical by ingestion/other modes of consumption at levels beyond standard lab animals' threshold can act as a potent carcinogen provoking cancer of breast, skin, and liver; potent inducer of irritation in the nasal cavity and tumours in the liver of animals, and endocrine disruption properties of 1,4-dioxane in animals. Providentially, there is no proof of genotoxicity effects on the human reproductive system to date.
- **Formaldehyde and paraformaldehyde** - Formaldehyde, commonly used as its 37% concentrated solution 'formalin' and paraformaldehyde, are popular preservatives in various cosmetic products, including liquid soaps and shampoos. Hence, inhalation makes up the most common route of exposure, this set of preservatives are considered one of the most common indoor contaminants. The toxic properties of formaldehyde and derivatives include - pro-allergenicity, carcinogenicity, mutagenicity, and high-level exposure correlates to an increased risk of developing myeloid leukaemia. More issues concerning these chemicals include - ophthalmic irritation and nose and throat irritations, amongst others.
- **Parabens** - Parabens are esters of p-hydroxybenzoic acid. They have extensive use as preservatives in cosmetics, cleansing products, and moisturizers. Methylparaben, ethyl paraben, benzyl paraben, butylparaben, and propylparaben are common

congeners used. Though they have a good safety profile, their continuous high-dose application may exert a potential menace to human health. Recently, research ash found ill-effects of parabens - on male reproductive health (damage to spermatozoa),detection of parabens in the mammary gland and breast cancer tissues, genotoxic effects of paraben on peripheral human lymphocytes. Since 2011, the Danish Environmental Protection Agency (EPA) banned the use of butyl and propylparaben in cosmetic products for children under three years owing to their harmful consequences for newborns and children.

- **Salicylic acid** - Salicylic acid in lesser concentrations is used in cosmetics, but 2% salicylic acid used in creams have a completely different effect.
- **Kojic acid –** Similar to Salicylic acid, kojic acid is used in many cosmetic creams in lower concentrations, while in concentrations of 2 to 5%, it conquers the status of a cosmeceutical.
- Toxicity profile is enormous which includes benzalkonium chloride, imidazolidinyl urea, and diazolidinyl urea, trace metals, phthalates, isothiazolinone derivatives, phenoxyethanol and many more.

Indian Market for cosmeceuticals

- The Indian beauty and cosmetic market have been showing a consistent growth between 15 to 20% per annum. Women are still the top consumers, although the use of cosmeceuticals by men is steadily increasing.
- Two major factors have contributed to the rising trend in this market.
    - - media exposure with attractive catchy advertising by manufacturing companies
    - -the corporate dressing cultures

Nanotechnology in Cosmeceuticals

The use of nanotechnology in cosmeceuticals is rising, to create new, unique products or to provide more coverage than the average skincare product. Nanotechnology includes the manipulation of molecules on a minuscule scale, including the creation, design, and application of ingredient structures. Already a significant part of modern medicine, cosmeceutical experts use nanotechnology to create new formulas that will provide users with safer, more effective results.

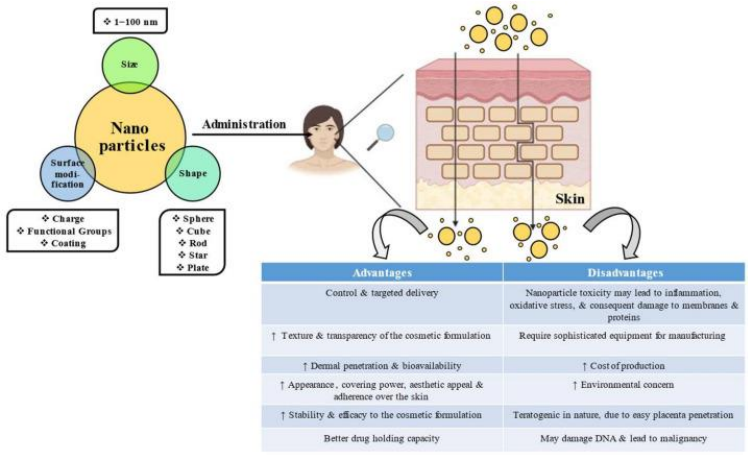
Concomitant with the growth, there has been a surge of development and employment of novel and innovative technologies for producing safer and more effective cosmeceuticals. Nanotechnology, penetration enhancers, stabilizers, and special excipients are hiking in use. Leading companies are developing formulations that can be conveniently assessed on 3D bio printed live human tissue, obviating the need for time- and cost-consuming elaborate animal and human trials.

The inability of phytocompounds to easily penetrate through the skin and their instability restrict their usage in cosmetic products. This can be corrected by incorporating nanotechnology into cosmetic products for a more stable and long-lasting release. Nanotechnologies can improve the solubility of poorly water-soluble compounds, ease skin permeation, and increase their stability against light and temperature, controlled and sustained drug release, higher stability, site specific targeting, and high entrapment efficiency.

Nanotechnology's substantial impact on the cosmetics industry is due to the improved properties reached by particles at the nano scale, such as color, solubility, and transparency.

The following are the examples of nanotechnology-based systems currently in use to improve the performances of phytocompounds in skin care.

- Liposomes
- Solid lipid nanoparticles
- Transferosomes
- Ethosomes
- Nanostructured lipid carriers
- cyclodextrins



Advantages	Disadvantages
Control & targeted delivery	Nanoparticle toxicity may lead to inflammation, oxidative stress, & consequent damage to membranes & proteins
↑ Texture & transparency of the cosmetic formulation	Require sophisticated equipment for manufacturing
↑ Dermal penetration & bioavailability	↑ Cost of production
↑ Appearance, covering power, aesthetic appeal & adherence over the skin	↑ Environmental concern
↑ Stability & efficacy to the cosmetic formulation	Teratogenic in nature, due to easy placenta penetration
Better drug holding capacity	May damage DNA & lead to malignancy

Cosmeceuticals are regarded as the growing segment of the personal care industry and the use has risen drastically over the years. Safety concerns for the usage of nanomaterials in cosmeceuticals have been raised lately, hence causing the limit on the use of nanomaterials by cosmetic companies and enforcing laws demanding thorough safety testing prior to market entry. Nano cosmeceuticals used for skin, hair, nail, and lip care, for conditions like wrinkles, photoaging, hyperpigmentation, dandruff, and hair damage, have come into widespread use.

COSMECEUTICALS IN MEDICINE

Although they are not classified as drugs, doctors and dermatologists often recommend cosmeceutical products to help their patients take care of their skin. Since cosmeceuticals have greater amounts of active ingredients, they tend to draw more attention in the clinical skincare market as over-the-counter products designed for the average consumer. However, dermatologists' involvement in the cosmeceutical industry is significant, even if some products are available without a prescription. Doctors and medical professionals play an essential role in regulating the industry, producing cosmeceuticals, helping patients find the right product, and even dispensing products as prescription or recommended items. For example, a dermatologist may recommend products high in retinoids like adapalene and tretinoin to treat cystic acne. While anyone can buy a cosmeceutical meant to treat acne, dermatologists and aestheticians can still recommend these products with their wide range of skincare knowledge.

HEALTH AND SAFETY OF COSMECEUTICALS

As a newly emerging form of dermatological medicine, cosmeceuticals must follow several regulations about their use, sale, and production, but the field still isself-regulated. While not fully recognized as separate from cosmetics in the United States and several other countries, the scientists and developers within the industry have set up their own tight regulations in place of the absent FDA standards.

FDA Guidelines

Although the FDA does notrecognize cosmeceuticals as a separate body from drugs or cosmetics, it acknowledges that a product can exist as both. In the Food, Drug, and Cosmetic Act, the FDA defines a drug as "products that cure, treat, mitigate or prevent disease or that affect the structure or function of the human body." Cosmetics, on the other hand, "are intended to beautify, promote attractiveness, alter appearance or cleanse [the skin]." Unlike drugs, cosmetics do not need FDA guidance or approval before reaching store shelves.

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***CHAPTER* 3**

An *in Vitro* and *in Silico* Study on the Anticoagulant Effects of Leaf Extracts of *Mukiamaderaspatana (L.) M. Roem*

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ABSTRACT

The study delves into the anticoagulant potential of *Mukiamaderaspatana*, a plant traditionally used in herbal medicine. The research combines *in vitro* and computer-simulated methods to thoroughly investigate this potential. In the *in vitro* segment, hexane, ethyl acetate, and aqueous extractof the leaves of *Mukiamaderaspatana*were tested for their effects on blood coagulation, particularly by measuring prothrombin time (PT) and activated partial thromboplastin time (aPTT). These tests indicate the efficiency of blood clotting, where prolonged time suggest anticoagulant activity. In the present study, the ethyl acetate leaf extract of *Mukiamaderaspatana*(L.) *M. Roem* displayed prolonged clotting time in the APTT test, however, no prolonged time in the PT test, suggesting that ethyl acetate extract inhibits preferentially intrinsic and/or common pathways of coagulation. Complementing this, the *in-silico* analysis was carried out that uses computational methods to predict interactions between the plant-derived compounds and key proteins in the coagulation pathway. The active compounds of *M. maderaspatana*namelyColumbin, Phloroglucinol, and 7,8-Dihydroxycoumarin along with the anticoagulant drug, Warfarin, were docked againstCEN(FXa), 4PXZ(P2Y12), 5QTT(FXIa), and 6WV3(VKORC1 gene) which are involved in the coagulation pathway. The results revealedcolumbin had the highest binding affinity with all the target proteins. This dual approach not only enhances the reliability of the findings but also underscores the therapeutic potential of *Mukiamaderaspatana* in preventing and treating thrombotic disorders. Ultimately, this study paves the way for further research and potential clinical applications of these natural anticoagulants, offering a promising alternative to synthetic anticoagulants with potentially fewer side effects.

Keywords: *Mukiamaderaspatana, anticoagulant, prothrombin time, activated partial thromboplastin time, Molecular docking, Columbin*

Introduction

1. Blood coagulation

Blood is a critical component of the human body, essential for transporting oxygen to tissues and cells, and losing it can be life-threatening. Blood is produced through a process called hematopoiesis and plays a crucial role in the body's defence against blood loss, primarily through the coagulation system. The clotting mechanism involves an array of components, including the vascular system, platelets, coagulation factors, prostaglandins, enzymes, and proteins. When the endothelial layer of blood vessels is disrupted, exposing blood to extravascular tissue, the coagulation system is activated. This activation leads to

the formation of a platelet plug, which initially occludes the vascular lesion through a series of well-coordinated reactions.

Mechanism

There are two stages of clotting mechanisms:

Primary hemostasis

Primary hemostasis, which results in the formation of a weak platelet plug, involves four critical steps: vasoconstriction, platelet adhesion, platelet activation, and platelet aggregation. This intricate process begins with vasoconstriction, the initial response following vascular injury. The damage to the blood vessel prompts a vasospasm, which in turn stimulates vasoconstriction. A primary mediator of this vasoconstriction is endothelin-1, a potent vasoconstrictor produced by the damaged endothelium. The injury exposes subendothelial collagen, von Willebrand factor (vWF), ATP, and inflammatory mediators. Von Willebrand factor is produced by megakaryocytes and stored in platel*et al*pha-granules, as well as being manufactured in the Weibel-Palade bodies of the endothelium. The interaction between vWF, subendothelial collagen, ATP, and inflammatory mediators facilitates the next step, platelet adhesion. Platelet adhesion occurs when platelets adhere to the exposed subendothelial vWF. Upon vascular injury, platelets roll along the vessel walls and bind to the exposed vWF and subendothelial collagen. The platelet membranes contain G protein-coupled (Gp) receptors distributed throughout their phospholipid bilayer. The GpIb-IX receptor on platelets binds to vWF in the endothelium, forming the initial connection.

Secondary hemostasis

During secondary hemostasis, the coagulation cascade works to stabilize the initially formed weak platelet plug by generating a solid fibrin clot. This process involves three critical steps: (1) the activation of clotting factors, (2) the conversion of prothrombin to thrombin, and (3) the transformation of fibrinogen into fibrin. The intrinsic and extrinsic pathways are the two initial routes that accomplish these steps, eventually converging at the activation of Factor X. It is important to note that calcium ions play a crucial role in the successful completion of secondary hemostasis. The extrinsic pathway involves tissue factor (TF) and Factor VII (FVII). Upon vascular injury, tissue factor binds to Factor VII, activating it to Factor VIIa (FVIIa), forming a TF-FVIIa complex. This complex is essential as it activates Factor X (FX) to Factor Xa (FXa), which then continues down the common coagulation pathway. Interestingly, the TF-FVIIa complex can also activate Factor IX of the intrinsic pathway, providing an alternative route for clotting. The intrinsic pathway consists of multiple factors, including Factor XII (Hageman factor), Factor XI, Factor IX, and Factor VIII. The process begins when subendothelial collagen is exposed due to vascular injury, which activates Factor XII to Factor XIIa (FXIIa). FXIIa then activates Factor XI to Factor XIa (FXIa). FXIa subsequently activates Factor IX to Factor IXa (FIXa). Factor VIII is activated to Factor VIIIa (FVIIIa), and together with FIXa, it forms a complex that activates Factor X to Factor Xa. Once Factor X is activated by the FIXa-FVIIIa complex, the cascade proceeds along the common pathway. In the common pathway, activated Factor X (FXa) converts prothrombin into thrombin.

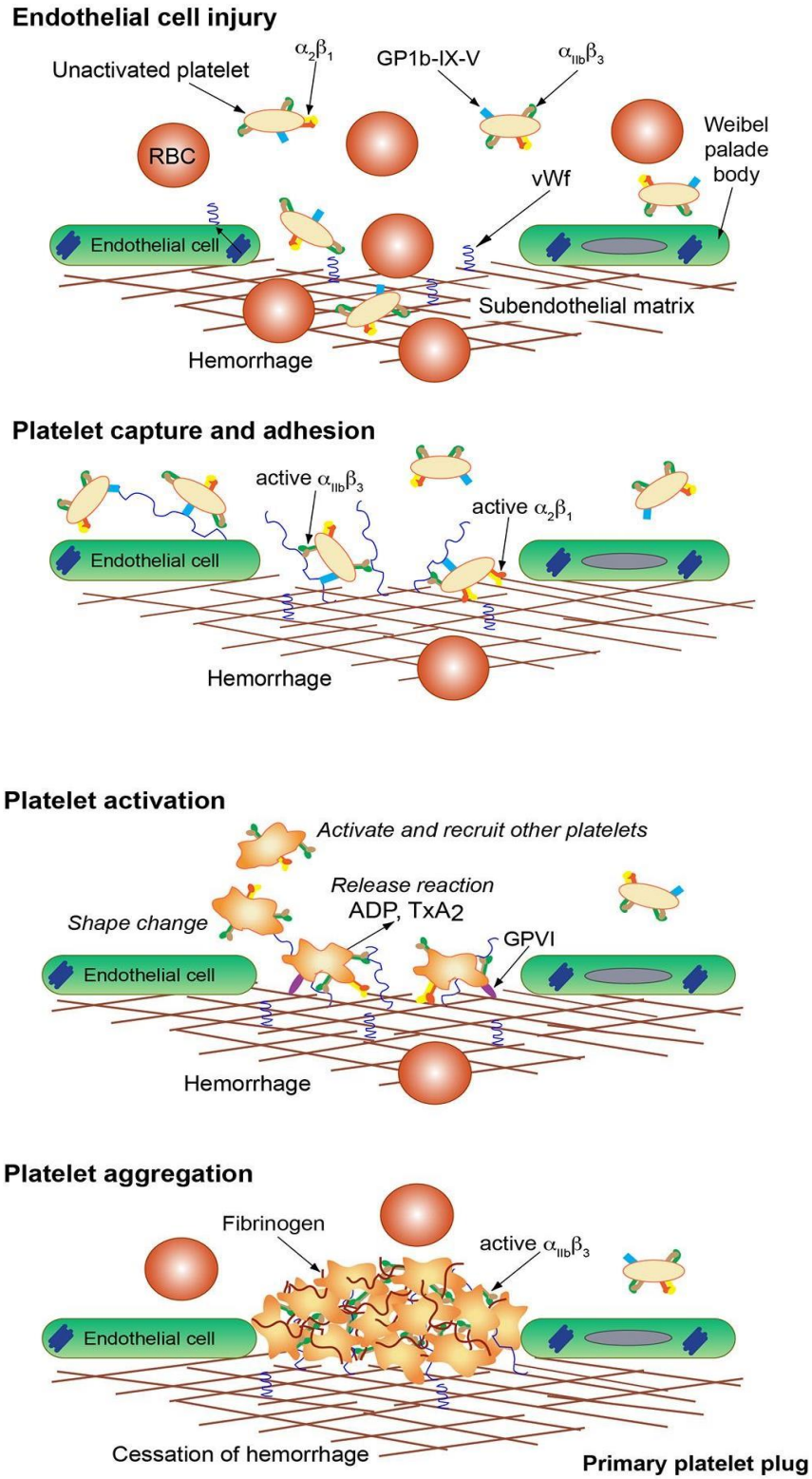


Figure 1. Primary hemostasis. The common pathway is initiated by the activation of factor Xa. Factor Xa forms a prothrombinase complex on phospholipid surfaces by joining forces with Factor Va and calcium. This complex then activates prothrombin, often referred to as Factor II, into thrombin. the method by which prothrombin is broken down by serine protease to release thrombin. Now, thrombin activates factor XIIIa (FXIIIa). A crosslink between fibrin and FXIIIa forms the stable clot.

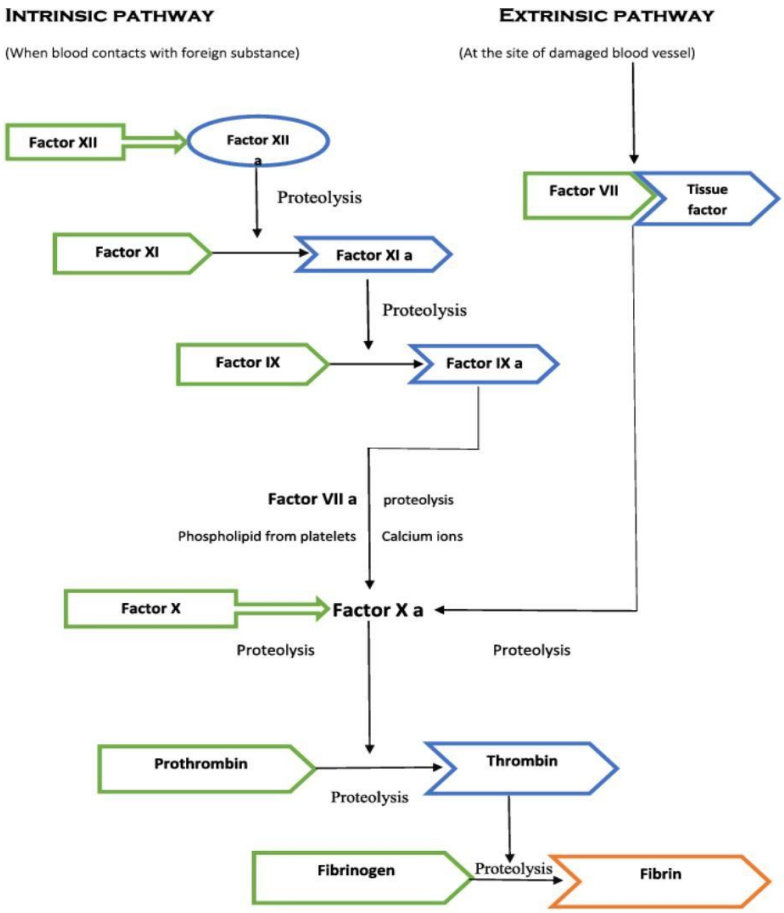


Figure2: Secondary hemostasis

2. Defects in the blood clotting mechanism

Such defects lead to either bleeding disorders or blood clotting disorders.

Bleeding disorders

Bleeding disorders are a group of medical conditions characterized by the blood's inability to clot properly, leading to excessive bleeding. Under normal circumstances, when a blood vessel is injured, platelets—specialized blood cells—rapidly respond by clumping together to form a plug at the injury site, initiating the clotting process. This initial platelet plug serves as a temporary barrier to control bleeding while a more stable fibrin clot forms through the coagulation cascade. However, in individuals with bleeding disorders, this intricate clotting mechanism is disrupted, resulting in prolonged or uncontrolled bleeding even from minor injuries.The causes of bleeding disorders can vary widely and may include genetic factors, such as hemophilia and von Willebrand disease, where specific clotting factors are deficient or dysfunctional. Acquired conditions, such as liver disease or vitamin K deficiency, can also impair clotting. Additionally, certain medications, like anticoagulants or antiplatelet drugs, can induce bleeding tendencies by interfering with the clotting process. In hemophilia, for instance, patients lack sufficient amounts of clotting factors VIII or IX, leading to severe bleeding episodes that can occur spontaneously or following injury. Von Willebrand disease, the most common inherited bleeding disorder, involves a deficiency or dysfunction of the von Willebrand factor, a protein crucial for platelet adhesion and aggregation.

a. Hemophilia is a hereditary disorder that impairs the blood's ability to clot properly, leading to excessive bleeding, bruising, and swelling. The condition is passed down through families and primarily affects males, although females can be carriers. The most common forms are Hemophilia A and Hemophilia B, both of which are caused by a deficiency in specific blood proteins necessary for clotting. In Hemophilia A, the body lacks sufficient levels of clotting factor VIII, while Hemophilia B involves a deficiency in clotting factor IX. These deficiencies prevent the formation of stable blood clots, leading to prolonged bleeding episodes, which can occur spontaneously or after injury. This condition often results in joint damage, muscle hematomas, and other complications if not managed effectively.

b. Liver Disease-Related Bleeding: The liver plays a critical role in producing clotting factors, so liver disease can significantly impact blood clotting. Conditions such as cirrhosis, hepatitis, and fatty liver disease can lead to scarring (fibrosis) and impaired liver function, which in turn increases the risk of bleeding disorders or thrombosis. Patients with liver disease may exhibit symptoms such as fatigue, weakness, and decreased appetite. Additionally, because the liver is responsible for metabolizing vitamin K, a key nutrient for clotting, liver disease can exacerbate bleeding tendencies by reducing the body's ability to utilize vitamin K effectively.

c. Vitamin K Deficiency Bleeding: Vitamin K is essential for the synthesis of several clotting factors. Deficiency in this vitamin can lead to severe bleeding, both internally and externally. Newborns are particularly susceptible to vitamin K deficiency due to low stores of the vitamin at birth, which is why vitamin K supplements are often administered to prevent bleeding complications. In adults, vitamin K deficiency can result from poor dietary intake, certain medications, or malabsorption disorders. Symptoms include easy bruising, excessive bleeding from wounds, and spontaneous bleeding in severe cases. Ensuring adequate vitamin K intake through diet or supplements is crucial for maintaining proper blood clotting function . Understanding these conditions highlights the importance of early diagnosis and tailored treatment strategies to manage and mitigate the risks associated with bleeding disorders. Each condition has specific therapeutic approaches, ranging from factor replacement therapy to dietary supplementation, aimed at restoring proper clotting function and preventing complications.

Blood clotting disorders

Blood clotting problems, also known as thrombophilias and coagulation disorders, can either be inherited or acquired. Inherited clotting disorders are present from birth due to genetic mutations affecting the blood's ability to clot properly. In contrast, acquired clotting disorders develop later in life as a result of other illnesses, injuries, or certain medications. Deep Vein Thrombosis (DVT) is a common consequence of blood clots forming in the deep veins of the lower limbs. These clots can cause significant pain, swelling, and redness in the affected leg. If a part of the clot breaks off, it can travel through the bloodstream to the lungs, leading to Pulmonary Embolism (PE). PE is a serious and potentially life-threatening condition where the clot blocks blood flow to the lungs, causing symptoms such as shortness of breath, chest pain, and rapid heart rate. Immediate medical attention is crucial for PE to prevent severe complications or death. Managing clotting disorders involves identifying and addressing the underlying cause, if possible. Treatment strategies may include anticoagulant medications to prevent new clots from forming and

to treat existing clots, lifestyle modifications to reduce risk factors, and in some cases, surgical interventions to remove or dissolve clots. Regular monitoring and follow-up care are essential to manage the condition effectively and prevent complications.

a. Thromboembolism

Thromboembolism is a significant condition that can lead to cardiovascular disease. It is characterized by the formation of blood clots that obstruct arteries, impeding normal blood flow and potentially causing serious health complications. Various factors contribute to the development of thromboembolism, including trauma, smoking, surgical procedures, and the use of estrogen-containing medications. Thromboembolism can result from both inherited and acquired causes. Inherited conditions, such as genetic mutations affecting blood clotting mechanisms, can predispose individuals to thromboembolism from birth. Examples include Factor V Leiden mutation and Prothrombin gene mutation, which increase the risk of abnormal clot formation. Acquired factors, on the other hand, develop later in life and can include conditions like cancer, prolonged immobility, autoimmune diseases, and liver disease. Lifestyle choices, such as smoking and obesity, also significantly elevate the risk of thromboembolism.

Symptoms of deep vein thromboembolism: Symptoms of deep vein thrombosis (DVT) can include:Leg edema Leg discomfort, cramping, or pain that frequently begins in the calf, Variation of skin tone on the leg, ranging from purple to red, based on the skin tone, A heated sensation on the afflicted leg

Causes: Deep vein thrombosis (DVT) is primarily caused by damage to the vein resulting from surgery, inflammation, injury, or infection.

Risk factors: Age, Lack of movement, Injury or surgery, Pregnancy, Birth control pills (oral contraceptives) or hormone replacement therapy, Overweight or Obese, Smoking, Cancer, Heart failure, Inflammatory bowel disease

Treatment:

Blood thinners These medications, often known as anticoagulants, aid in halting the growth of blood clots. The chance of getting additional clots is decreased by blood thinners.

Clot busters (thrombolytics) Clot busters are administered using a catheter, a tube inserted straight into the clot. They are often reserved for patients with very large blood clots since they can result in significant bleeding.

Filters Breakaway clots are kept out of the lungs via a vena cava filter.

Support stockings (compression stockings). These unique knee socks aid in preventing leg blood clots. They aid in lowering edema in the legs.

b. Pulmonary embolism

A blood clot in one of the blood veins of the lung is known as a pulmonary embolism (PE). This occurs when a blood clot travels from another area of your body—typically your arm or leg—through your veins and lodges in the lungs. A PE raises blood pressure in the pulmonary arteries, decreases oxygen levels in the lungs, and limits blood flow to the lungs. (Lee CH *et al* 2005). A pulmonary embolism may causeLung damage and heart failure.

Symptoms of Pulmonary embolism: Breathlessness that occurs suddenly, regardless of activity or rest; rapid respiration; gasping for air; sharp discomfort in your jaw, neck, shoulder, arm, back, or chest; Cough up bloody mucus or not; pale, blue, or clammy skin; Rapid heartbeat (pulse); Excessive sweating.

Causes: Vein damage, such as that caused by a fracture or surgery (particularly involving the hip, leg, pelvis, or knee); An additional illness, such as cardiovascular disease (which includes atrial fibrillation, congestive heart failure, heart attacks, or strokes).
Risk factors: family history of thrombosis, smoke, diabetes, cancer.
Treatment: Anticoagulant drugs; stockings with compression; thrombolytic medication

3. Anticoagulants

Blood coagulation inhibitors, commonly known as anticoagulants, play a crucial role in preventing the formation and growth of blood clots, or thrombi, within the bloodstream. These medications work by either inhibiting the synthesis of specific coagulation factors or interfering with their functional activity, which are essential components of the clotting cascade. Anticoagulants are widely used to reduce the risk of serious thrombotic events such as stroke, pulmonary embolism, and myocardial infarction, which can be life-threatening. They are administered through various routes, including injections, intravenous infusions, and oral tablets, making them versatile in clinical practice. Injectable heparin is one of the oldest and most commonly used anticoagulants. It functions by activating antithrombin III, which in turn inhibits the activity of thrombin and factor Xa—critical enzymes in the final stages of clot formation. Heparin is available in two forms: unfractionated heparin (UFH), which has a higher molecular weight, and low-molecular-weight heparins (LMWHs) like enoxaparin, which exhibit more predictable pharmacokinetics and can be administered subcutaneously at fixed doses without the need for frequent monitoring. Fondaparinux represents a newer class of anticoagulants known as selective factor Xa inhibitors. This synthetic molecule, derived structurally from heparins, specifically targets factor Xa, thereby inhibiting its role in the clotting cascade. Fondaparinux offers more predictable pharmacokinetics compared to heparins, contributing to its clinical utility in preventing thrombotic events . Factor Xa inhibitors, including direct oral anticoagulants like rivaroxaban and apixaban, specifically target factor Xa in the blood, inhibiting its ability to form new clots and preventing the extension of existing ones. Unlike traditional anticoagulants, factor Xa inhibitors do not affect platelet aggregation, which is crucial for maintaining hemostasis. Vitamin K antagonists (VKAs), such as warfarin and dicumarol, exert their anticoagulant effects by antagonizing vitamin K, a cofactor necessary for the activation of clotting factors. VKAs interfere with the conversion of inactive clotting factor precursors to active enzymes, thereby slowing down the clotting process.

Plant-derived anticoagulants

Plants have long been valued as a rich source of materials with diverse applications, including medicinal and pharmaceutical uses dating back to ancient times. In modern times, pharmaceutical medications are more commonly relied upon than herbal remedies in communities worldwide. However, pharmaceutical drugs often come with significant adverse effects, particularly those derived from synthetic chemicals. For instance, medications like warfarin, despite their efficacy in treating clotting disorders, can lead to complications such as bleeding issues (Ernst E *et al*., 2007). In contrast, medicinal plants are increasingly seen as a favorable alternative due to their perceived milder side effect profiles and potential holistic benefits.

4. Mukiamaderaspatana (L.) M.Roem

Mukiamaderaspatana (Linn.) M. Roem, a member of the Cucurbitaceae family, is a climbing plant native to tropical and subtropical regions, particularly prevalent in India and Sri Lanka. This plant species is rich in various phytochemicals including glycerides, alkaloids, flavonoids, tannins, steroids, and phenolic compounds with cardiac properties. It has been traditionally utilized in Ayurvedic and Siddha medicine for its wide array of therapeutic qualities attributed to its leaves, roots, and fruits. In agricultural applications, crude extracts of Mukiamaderaspatana have been investigated for their efficacy against cattle ticks, serving as an eco-friendly parasite control method. Additionally, herbal boluses made from Mukia leaves are used to enhance immune function in cattle and alleviate digestive disorders.

Figure 3: Mukiamaderaspatana (L.) M.Roem

Phytochemical analysis reveals that *Mukiamaderaspatana* extracts contain ether, acetate, acetone, and methanol fractions, each potentially contributing to its medicinal properties. The plant has been explored for treating conditions such as filariasis, highlighting its diverse pharmacological potentials. According to traditional medicinal practices, *Mukiamaderaspatana* exhibits a broad spectrum of therapeutic effects. It is recognized for its stomachic properties, anti-ulcer, anti-inflammatory, and antipyretic effects. Furthermore, it is valued as a diuretic, hepatoprotective agent, expectorant, carminative, and possesses anti-hyperglycemic, anti-hyperlipidemic, antibacterial, antioxidant, and antirheumatic properties.

Chemical constituents

Previous phytochemical studies utilizing GC-MS analysis have identified a diverse array of bioactive compounds in *Mukiamaderaspatana (L).* Phenolic compounds, cardiac glycerides, alkaloids, flavonoids, tannins, saponins, steroids, and terpenoids are among the notable constituents documented. These compounds are predominantly found in the leaves of the plant and include specific substances such as 2-MethylthioPhene, S, S-Dioxide, Diazeene, bis(1,1-dimethylethyl), 3-Buten-2-ol, 2-Butyn-1-ol, 4-methoxy, Dichloroacetic acid, 4-methylpentyl ester, and 2-(Chloromethyl)-2,3-dihydro-4(1H) quinolinone, which are associated with pantolactone derivatives.The presence of these phytochemicals' underscores *Mukiamaderaspatana's* pharmacological potential, particularly its antibacterial properties. For instance, eugenol, a constituent known for its antioxidant properties, has been identified in the plant extract and is implicated in preventing heart issues by inhibiting

lipid peroxidation (Gupta, S. K., *et al*., 2002). Saponins, another significant component present throughout the plant, are utilized by the body to help regulate cholesterol levels (Xu, R., 1996).

Medicinal uses

The infusion of *Mukiamaderaspatana (L)* roots and leaves is traditionally used to treat a variety of health conditions. It is employed for hypertension and nasobronchial disorders, and is also effective against fever, dyspnea, gastrointestinal issues, liver disorders, coughing, and vomiting. The leaves of *Mukiamaderaspatana* are particularly utilized in treating rhinorrhea, productive cough, chest discomfort, asthma, and respiratory mucus congestion. In cases of male infertility and conditions related to "pitha" imbalance, including gastritis, indigestion, vomiting, and foul-smelling sputum from the lungs, the root of *Mukiamaderaspatana* is recommended. Combining the root with the juice of *Mukiamaderaspatana* leaves is a common practice in traditional medicine to address these ailments. In Ayurvedic medicine, *Mukiamaderaspatana* is prescribed for a wide range of conditions including respiratory ailments, cough, burning sensation, dyspepsia, ulcers, colic, constipation, neuralgia, nostalgia, toothache, and vertigo. Both the leaves and roots are valued for their therapeutic properties and are incorporated into various formulations to alleviate these health issues.

Preparation of plant extract for the present study

The plant leaves were thoroughly washed with tap water, kept in shade, and dried for 14 days. The dried leaf material was crushed directly by the grinder without adding any solvent. 20g of powdered plant material were soaked separately in 200 ml of ethyl acetate, hexane, and distilled water for 48 Hrs. The extract was passed through a muslin cloth. The extracts were evaporated using a hot plate leaving a small yield of extracted plant material in the petri dish. The extracts were kept in sterile bottles and were put in the refrigerator at 2-4°C until further use. The crude extracts thus obtained were used for the PT and APTTassays.

Table1: Results of APTT Assay Ethyl acetate, Hexane and Aqueous leaf extract of *Mukiamaderaspatana(L)* M.Roem

concentration of plant extract	**ethyl acetate extract**	**hexane extract**	**aqueous extract**	**positive control (heparin)**	**negative control (dmso)**
50 µg/ml	No clot formation observed	6 min 53 secs± 30 secs	1 min 40 secs ±14 secs	No clot formation observed	1 min 17 secs±0 secs
500µg/ml	No clot formation observed	1 min 41 secs ± 11 secs	1 min 0 secs ±0 secs	No clot formation observed	1 min 17 secs±0 secs
1 mg/ml	No clot formation observed	1 min 32 secs ± 05 secs	0 min 13 secs ± 13 secs	No clot formation observed	1 min 17 secs±0 secs

Table 2: Results of PT Assay of Ethyl Acetate, Hexane, Aqueous leaf extract of*Mukiamaderaspatana (L)*M.Roem

concentration of plant extract	ethyl acetate extract	hexane extract	aqueous extract	positive control (heparin)	negative control (dmso)
50µg/ml	1 min 12 secs ± 12 secs	1 min 30 secs ± 32 secs	0 min 23 secs ± 0 secs	No clot formation observed	7 mins 45 secs± 0 secs
500µg/ml	2 mins 25 secs±25 mins	0 min 38 secs ± 01 secs	0 min 23 secs ± 0 secs	No clot formation observed	7 mins 45 secs± 0 secs
1 mg/ml	1 min 25 secs ± 07 secs	0 min 36 secs ± 08 secs	0 min 28 secs ± 3 secs	No clot formation observed	7 mins 45 secs± 0 secs

Values are expressed as Mean ± SD, (n= 3) for both PT and APTT Assay

5. Molecular docking

Molecular docking stands as an essential tool within the realms of computer-aided drug design and structural molecular biology. Its primary objective is to predict the optimal binding mode(s) of a ligand to a protein with a known three-dimensional structure. This predictive capability is crucial for understanding how molecules interact at the atomic level, guiding the development of new drugs and elucidating biological processes. In practical terms, molecular docking employs sophisticated algorithms and scoring functions to explore vast molecular landscapes efficiently (Figure 4 and Table 5). Its ability to simulate molecular interactions and predict binding affinities aids in lead optimization and rational drug design. Beyond drug discovery, docking plays a pivotal role in understanding signal transduction pathways involving proteins, peptides, nucleic acids, carbohydrates, and lipids. The orientations of interacting molecules influence the type and strength of cellular signals, impacting physiological responses such as agonism or antagonism. By elucidating these molecular interactions, docking contributes significantly to advancing our understanding of biological processes and designing therapeutics tailored to specific molecular targets.

Table 3: 2D and 3D structure of standard drug and bioactive compounds of *Mukiamaderaspatana(L)* leaf extract.

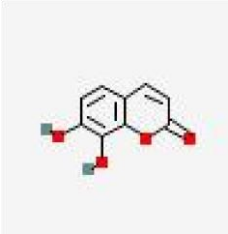
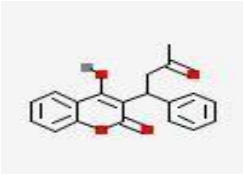
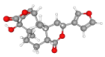
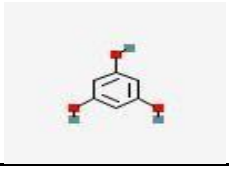
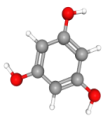
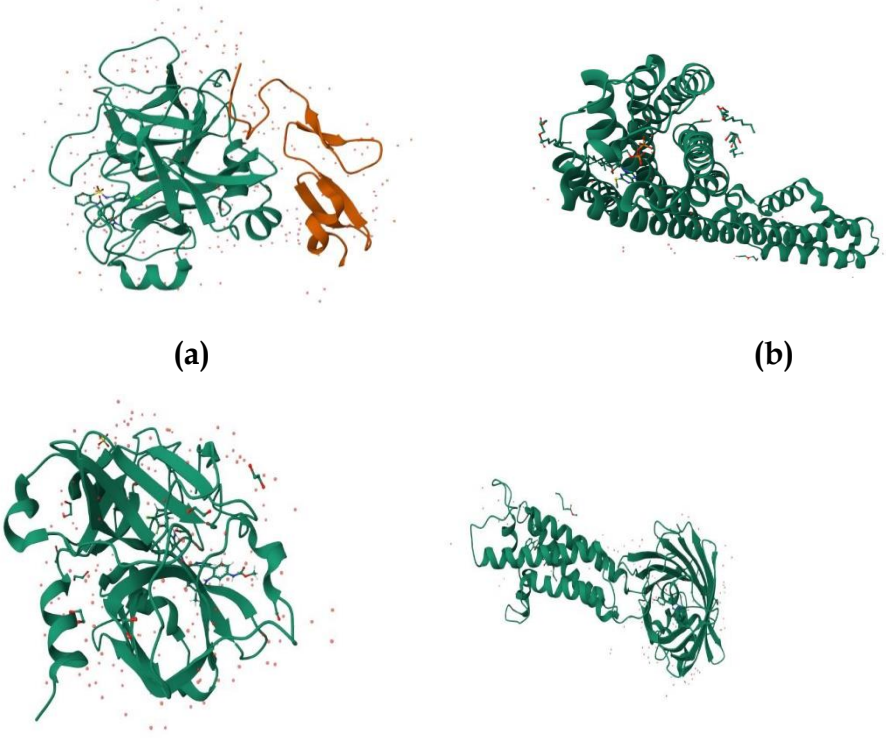
COMPOUND NAME	2D	3D	SMILES
7,8-DIHYDROXYCOUMARIN			CC(=O)C1=CC2=C(C(=C(C=C2)O)O)OC1=O
WARFARIN			CC(=O)CC(C1=CC=CC=C1)C2=C(C3=CC=CC=C3OC2=O)[O-].[K+]
COLUMBIN			CC12CCC3C(=O)OC(CC3(C1C4C=CC2(C(=O)O4)O)C)C5=COC=C5
PHLOROGLUCINO L			C1=C(C=C(C=C1O) O)O

Table 4. Molinspiration calculation of properties of standard drugs and Bioactive compound from *Mukiamaderaspatana(L)*M.Roem leaf extract

compounds	m.wt	mol. formula	Hydrogen bond donor	hydrogen bond acceptor	rotatable bonds	nviolations	tpsa	volume	N atoms
7,8-DIHYDROXYCOUMARIN	220.18 g/mol	C11H8O5	2	5	1	0	83.8		16

WARFARIN	346.4 g/mol	C19H15KO4	0	4	4		66.4		24
COLUMBIN	358.4 g/mol	C20H22O6	1	6	1		165		26
PHLOROGLUCINOL	126.11 g/mol	C6H6O3	5	5	6		62.7		9



(a) **(b)**

(c) **(d)**

Figure 4: 3D Structure of target proteins involved in coagulation pathway
(a) 3CEN(F Xa), (b) 4PXZ(P2Y12), (c) 5QTT(F XIa), (d) 6WV3(VKORC1)

Table 5: Binding energies of active compounds of *MukiaMaderaspatana (L)M.Roem* leaf extracts and Warfarin drug

Compound name	3CEN (F Xa)			4PXZ (P2Y12)			5QTT (F XIa)			6WV3 (VKORC1)		
	No. of	Binding energy	Key residue	No. of	Binding energy	Key residues	No. of	Binding energy	Key residues	No. of	Binding energy	Key residues
Columbin	6	-6.96	Thr136, Try130, Pro139, Pro131, Lys134, Pro136	6	-6.8	Phe51,Lys64, Ile68, Clr1202	6	-6.25	Asn153,Gln73,Ile151,Ser74,His40,Qey301,Edo310,Arg39	6	-7.53	Leu207,Val208,Gly258,Val254,Phe205, Phe225
phloroglucinol	5	-5.1	Ala233,Phe234,His91Asn179, Gln178	5	-4.43	Ile68, Clr1202	5	-4.91	Val131,Ile181,Leu162,Val232,Val210,Tyr133	5	-4.64	Lys26, Thy50
7,8-Dihydroxycouma	5	-4.26	Glu76, Arg67, Glu80, Gln75, Asp70	5	-4.24	Leu31 ,Phe28,Ser262,Olc1205	5	-4.32	Arg172,Arg224,Glu223,Arg170,Lys169		-	-

Warfarin	4	-5.73	Arg67, Glu76, Asp70	4	-5.73	Gly88, Leu87, asn171 ,Arg19 ,Thy18	4	-4.29	Val206 ,Trp207,Arg119,Cys112	4	-4.93	Trp289 ,Met288,Phe 292

Future aspects

The traditional medicinal uses of *Mukiama deraspatana (L)* suggest several promising future biomedical applications. Given its effectiveness in treating a wide array of conditions such as hypertension, nasobronchial disorders, fever, gastrointestinal issues, and respiratory ailments, there is potential for further exploration in modern biomedical research. The plant's ability to address conditions like dyspnea, liver disorders, and coughing, as well as its application in treating male infertility and "pitha" related ailments, highlights its multifaceted therapeutic properties. Future biomedical research could focus on isolating and studying the active compounds responsible for these effects. Understanding the mechanisms behind its efficacy could lead to the development of new pharmaceuticals or therapeutic agents. Moreover, *Mukiama deraspatana's* use in Ayurvedic medicine for conditions such as ulcers, neuralgia, and vertigo underscore its potential as a source of novel treatments. Research could explore its antioxidant, anti-inflammatory, and antimicrobial properties, which are crucial in combating various diseases and disorders prevalent in today's healthcare landscape. Additionally, exploring the safety profile, pharmacokinetics, and pharmacodynamics of *Mukiama deraspatana* extracts and isolated compounds would be essential for clinical applications. This could pave the way for integrating traditional herbal medicine with modern medical practices, offering alternative or complementary treatments for patients. In conclusion, *Mukiamaderaspatana* holds promise for future biomedical applications due to its rich phytochemical composition and diverse therapeutic uses. Continued research could unlock its full potential as a valuable source of natural remedies and pharmaceutical innovations.

Conclusion

The study presented here illustrates the significant anticoagulant activity of the ethyl acetate leaf extract derived from *Mukiamaderaspatana (L.) M. Roem*. Specifically, it was observed to prolong clotting time in the APTT test, indicating an inhibition of the intrinsic and/or common pathways of coagulation. Interestingly, no significant prolongation was noted in the PT test, suggesting a selective effect on specific pathways of clot formation. Moreover, molecular docking analysis highlighted columbin as a prominent bioactive compound within the extract. Columbin demonstrated strong interactions with key proteins involved in hemostasis, including FXa, FXIa, P2Y12, and VKORC1. These interactions underscore columbin's potential as a lead compound for developing anticoagulant therapies. Overall, this research provides compelling evidence for the anticoagulant effects of *Mukiamaderaspatana (L.) M. Roem's* ethyl acetate leaf extract, attributable to its diverse array of phytochemicals and bioactive substances. However, further investigation is warranted to elucidate the precise mechanisms through which the plant extract exerts its anticoagulant properties. This deeper understanding could pave the

way for leveraging *Mukiamaderaspatana (L.) M. Roem* as a potential source of novel anticoagulant agents in therapeutic applications.

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***CHAPTER* 4**

The Role of Medicinal Plants for Holistic Healing

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ABSTRACT

Medicinal Plants for Holistic healing is discussions on the use of medicinal plants to treat a range of conditions, such as acne, post-macular hypo melanosis, cancer, TB, and periodontal disorders. This article provides the scientific data supporting the pharmacological and therapeutic capabilities of medicinal plants, which were chosen for their historic uses in treating various diseases in a safe and effective manner. There is no denying the significant impact that medicinal plants have had and still have on people's lives all across the world. In the field of medicinal plants, these methods provide new and interesting viewpoints. Strategies for planning the future function and location of medicinal plants in illness prevention are put forth.

Keywords: *Medicinal plants, Pharmacological, Holistic, therapeutic Prevention, Strategies*

1. Introduction

Medicinal plants are thought to be abundant sources of chemicals that can be utilised to create synthetic, pharmacopoeial, or non-pharmacopoeial medications. Away from that, these plants are essential to the evolution of human cultures everywhere. Plants are a major source of medication and have a major impact on global health. It has long been recognised that medicinal plants and herbs offer a significant potential supply of treatments or healing agents. Throughout the world, the usage of medicinal herbs has come to dominate the healthcare system. This includes using medicinal plants as a possible resource for preserving health and conditions in addition to using them to treat illnesses. Two-thirds of the world's population, or many countries, rely on herbal medicine for their primary medical needs. They are less likely to induce negative side effects and are more culturally acceptable as well as more compatible and adaptable with the human body. Aspirin, atropine, artimesinin, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, taxol, tubocurarine, vincristine, and vinblastine are a few medications that are thought to be derived from plants.

The production of current medications and nutritional supplements for food and drink uses natural botanical ingredients. Because traditional medicines have been used for thousands of years, there is a considerable degree of confidence in their safety and efficacy. The utilisation of natural goods as dietary supplements, food and beverage ingredients, phytocosmetics, and other herbal products, as well as a source of novel chemical entities for the creation of modern medications, is becoming more and more popular.

1.1 **Pharmacology**

Pharmacology, which is further subdivided into two primary fields, pharmacodynamics and pharmacokinetics, is the therapy of the interaction of biologically active chemicals with living systems. The study of pharmacodynamics examines an agent's effects at the body's active areas. Pharmacokinetics, on the other hand, focuses on the medication's impact on the body. Examining the pharmacology of important chemical groups in plants as distinct herbs under phytochemistry is the goal for therapeutic research. The pharmacological effect of plants is mostly attributed to nutrients, including vitamins, minerals, and other elements.

2.0 Secondary metabolites

Plant secondary metabolites can be categorised into three main classes based on their metabolic origins: terpenoids, alkaloids, phenyl propanoid, and related phenolic chemicals. All terpenoids, including isopentenyl diphosphate, are produced from this five-carbon precursor. The primary biosynthesis pathways for alkaloids are the malonate/acetate process and the shikimic acid pathway, which both start with amino acids and phenolic chemicals.

Therefore, secondary metabolites, also known as natural products, are a diverse group of naturally occurring metabolic products that are not necessary for the producing organisms to grow vegetative. Instead, they are thought of as differentiation compounds that confer adaptive roles, such as serving as signalling molecules or defence compounds in symbiosis, competition, metal transport, ecological interactions, and so forth. Humanity uses the vast array of secondary metabolite secretions to boost agricultural productivity (pesticides, insecticides, effectors of ecological competition and symbiosis and pheromones), expand the pyramid of healthy nutrition (pigments and nutraceuticals), and improve human health (antibiotics, enzyme inhibitors, immune modulators, antitumor agents, and growth promoters of animals and plants). These uses also have a positive economic impact on our society. Antibiotics are sourced from them.

3.0 Herbal medicines and conventional drugs

Despite the fact that traditional medications or their precursors are produced from plants, administering a chemical in its pure form differs fundamentally from administering the same chemical in a plant matrix. A conventional physician prescribes a single agent, while a homoeopathic practitioner employs medications in complicated formulations. It makes sense that our medications should be chemically complex, just like our food is. However, there are a number of examples of phytotherapy; a few of these are covered below.

Synergy is the result of a mixture of substances working together in a way that is more effective than would have been predicted based on their individual contributions. Within the framework of the benefit of chemical complexity, this is a significant hypothesis in herbal pharmacology. It is possible to think of a cooperative or enabling impact between the components for a particular outcome if the action of a chemical combination is greater than the arithmetical sum of the actions of the mixture's constituent elements. Plant components that are not active in and of themselves can work to enhance the half-life, solubility, stability, and bioavailability of the active components. As a result, a given molecule may only have a small portion of its pharmacological activity in its plant matrix

when it is pure. Thus, there is a pharmacokinetic basis for this important synergistic mechanism.

4.0 Future Perspectives

Herbal medicines and plant extracts are widely used in the treatment of various infectious diseases due to their effectiveness, safety and affordability. Antimicrobial resistance being the major concern in today's modern medicine, the researchers are convinced to go for selecting and standardizing plant treatments since they heal or prevent infectious diseases. There is a need for precisely conducting in vitro and in vivo studies to target antimicrobial efficacy of plants. The quality of available plant species is limited to a particular geographical area. Because of environmental conditions and pollution, therefore scientific cultivation of medicinal plants is very necessary for the reproducibility of the composition of plant products. On the basis of increasing resistance of bacteria for the standard therapies, the current role of plants could be summarized as treating acute infections, skin or wound infections, and viral diseases including COVID 19.

Rather than using a single extracted alkaloid from the plant, if we use the plant as a whole, as available in nature, the naturally occurring group of alkaloids in the plants have better synergistic action without side effects. Average particle size of homeopathic herbal tinctures used, ranged between 2 to 34 microns which helped to deliver medicine to the patients very effectively. The above study shows the effectiveness of plant extracts of *Aegle folia* and *Holarrhenaantidysenterica* in the treatment of gastroenteritis, *Aspidosperma, Senega*, and Justicia in the treatment of viral bronchitis and cough. Also, for the treatment of viral diseases like dengue, *Eupatorium perfoliatum*, and *Bryonia alba* have shown excellent results. Skin and wound infections with pyogenic bacteria show excellent results (in vitro and in vivo) using herbal drugs like calendula and echinacea. Thus the knowledge of medicinal plants reveals the foundation to pharmacological research.

4.1 Utilizing the Healing power of Medicinal Plants

Plants are the source of a large number of modern medications. Originating from the bark of the willow tree, aspirin is one of the most widely used analgesics. The opium poppy is responsible for the development of drugs like codeine and morphine, which are extremely useful for treating pain. Even the commonly recommended diabetes medication metformin was originally derived from the French lilac shrub. These illustrations demonstrate the continuing importance of medicinal plants in the creation of contemporary medications. Indigenous groups all across the world have kept a wealth of information regarding therapeutic plants. Their extensive knowledge of regional plants and their medicinal use has been very helpful in ethnobotanical studies. Their deep understanding of local flora and their therapeutic uses has been invaluable in ethnobotanical research.

New medicinal substances and possible therapies for a variety of ailments have been discovered as a result of scientific and indigenous healers working together. These collaborations serve as a reminder of how crucial it is to protect and honour traditional knowledge. Numerous bioactive substances, such as terpenes, polyphenols, alkaloids, and flavonoids, are found in medicinal plants and each has specific therapeutic benefits. For example, an essential part of treating malaria is artemisinin, which is produced from the sweet wormwood plant. Red grapes and other plants contain resveratrol, which has drawn

interest due to possible cardiovascular advantages. The creation of tailored medications has been made possible by the identification and investigation of these substances.

The use of medicinal plants is still very important in contemporary medicine. Essential oils, plant extracts, and herbal supplements are easily accessible over-the-counter and have a range of applications, from lowering anxiety to enhancing digestion. Furthermore, a number of plant-based cancer medications that have saved many lives include vincristine, which is derived from the Madagascar periwinkle, and paclitaxel, which is produced from the Pacific yew tree. Phytotherapy, often known as herbal medicine, is a comprehensive method that uses medicinal plants to treat a variety of illnesses. Plant-based medications customised to each patient's needs are prescribed by herbalists, naturopaths, and traditional healers. Due to their immune-stimulating, energising, and mood-stabilizing qualities, herbs including echinacea, ginseng, and St. John's wort are frequently utilised. The practice of herbal medicine is regaining popularity as people seek natural alternatives to conventional drugs.

Despite their potential benefits, medicinal plants face several challenges. Overharvesting and habitat destruction threaten the survival of many plant species. The unsustainable exploitation of certain plants, such as the African yohimbe tree, has led to their inclusion on the endangered species list. Moreover, the quality and safety of herbal products can vary widely, leading to concerns about adulteration and contamination. Regulation and quality control are crucial to ensure the safety and efficacy of medicinal plant-based products. Scientific research into medicinal plants continues to yield results. Recent studies have identified compounds in plants like turmeric, ginger, and cannabis with anti-inflammatory and pain-relieving properties.

These discoveries have the potential to inform the development of novel treatments for chronic diseases like arthritis and neuropathic pain. Additionally, research on the gut microbiome has shed light on how certain plant compounds, such as prebiotics and polyphenols, can support digestive health.

The future of medicinal plants in healthcare is exciting and multifaceted. Integrative medicine, which combines conventional and complementary therapies, is gaining acceptance in mainstream healthcare. This approach recognizes the value of plant-based remedies in preventing and managing chronic diseases. Furthermore, biotechnology offers opportunities to enhance the production of medicinal compounds through plant cell cultures and genetic engineering, reducing the environmental impact of harvesting wild plants. To ensure the long-term availability of medicinal plants, efforts must be made to promote sustainable harvesting practices and protect their natural habitats. Ethical wildcrafting, cultivation, and organic farming of medicinal plants can help meet demand while conserving biodiversity. Initiatives like the FairWild certification program aim to promote responsible harvesting and trade of wild medicinal plants.

Medicinal plants represent a timeless source of healing, bridging the gap between ancient wisdom and modern science. Their rich history, diverse applications, and ongoing research make them a vital component of healthcare. While challenges like sustainability and quality control must be addressed, the potential for medicinal plants to contribute to safer, more effective treatments remains profound. As our understanding of these natural remedies deepens, medicinal plants will continue to play a pivotal role in nurturing health and well-being for generations to come.

4.2 Ethno medicinal use and phyto chemistry of medicinal plants

Natural products produced by aquatic and semiaquatic medicinal plants are known for their potential biological applications and diet supplements. Aquatic and semiaquatic plants are often used as medicines for many health disorders and diet supplements due to their nutritional values and medicinal uses, and in pharmaceutical industries for producing herbal-based cosmetic products. These plants diversified chemical and biological properties make them medicinally valuable and increase their demand globally. Some previous studies regarding the importance of aquatic and semiaquatic medicinal plants for biological, industrial, and other applications are discussed and presented in Figure 1.

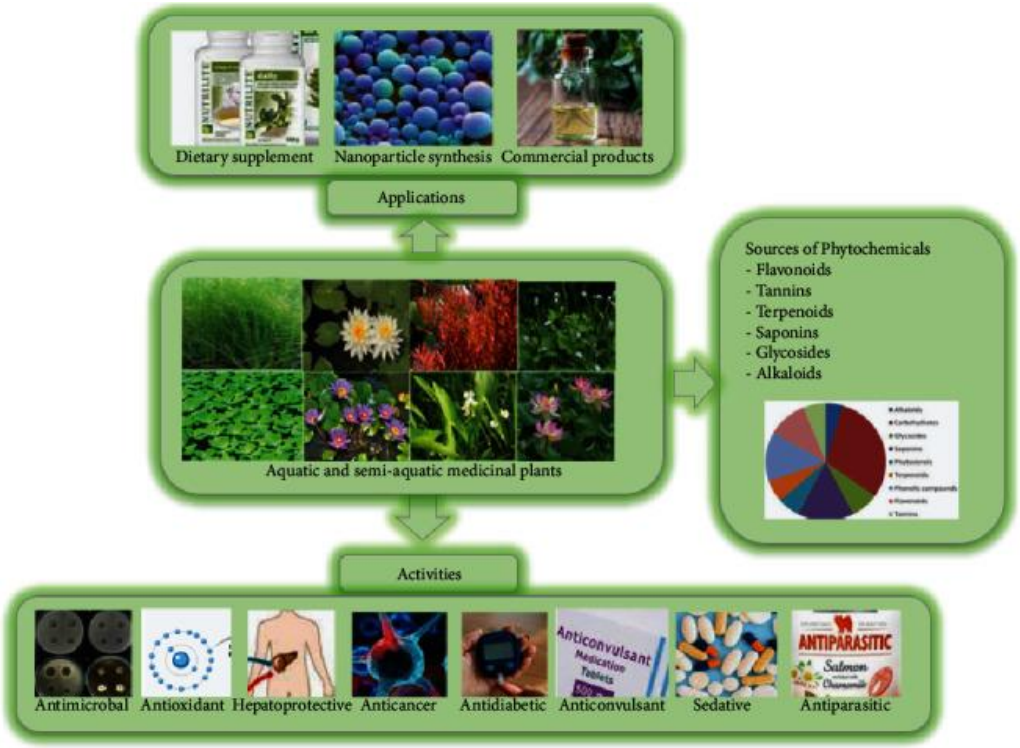

Fig 1: Phytochemical, biological and some other applications of aquatic semiaquatic medicinal plants

5.0 Bio accessibility studies of phytochemicals from medicinal plants used around the world

Plant-derived phytochemicals have emerged as novel agents for protecting against chronic disorders. As phytochemicals are so diverse, they cover a wide spectrum of therapeutic indications against various inflammation-related diseases, such as cancer, inflammation, cardiovascular, rheumatoid, autoimmune, and neurological disease, and have been a productive source of lead compounds for the development of novel medications. Harnessing the potential of phytochemical constituents from medicinal plants offers a promising new class of treatment for chronic inflammation.

These natural products provide a diverse range of anti-inflammatory mechanisms and demonstrate excellent safety profiles. Further research is needed to explore their efficacy, optimize dosage regimens, and identify potential drug interactions. Embracing the rich phytochemical repertoire of medicinal plants could pave the way for the development of novel and effective therapies for chronic inflammatory diseases, improving the quality of life for countless individuals worldwide.

5.1Bioactive properties of phytochemicals from medicinal plants against infectious diseases

Since earliest times, many plants have been known to exert healing properties against human infections due to their content of secondary metabolites, which in more recent times have been found to act as antimicrobial agents against human pathogens. Over the past decade, much attention has been placed on the study of phytochemicals for their antibacterial activity, especially against multidrug-resistant Gram-negative and Gram-positive bacteria.

Antibacterial resistance is defined as the resistance of bacteria to treatment with antibiotic drugs that was originally found to be effective for the treatment of infection caused by that microorganism. This means that antibiotics become ineffective against resistant bacteria allowing infections to persist in patients, putting them at increased risk of worse clinical outcomes and death. In fact, on average, the mortality rate for patients with infections caused by non-resistant bacteria is less than half of that of people with a resistant form of the same infection. Antibiotic resistance is present worldwide and new resistance mechanisms are continuing to emerge, strongly increasing the risk of spread of resistant strains.

Thus, antibiotic resistance represents a threat to global public health and represents an important economic issue, due to the higher health care costs of necessary therapies and the increased duration of illness, treatment, and potential hospitalisation when compared with non-resistant, common infections. It has been scientifically proven that the indiscriminate and inappropriate use of antibiotics has accelerated the emergence of drug-resistant strains.

In view of the potential of phytochemicals in providing effective antimicrobial drugs in the near future, the present paper is aimed at critically reviewing the scientific reports that demonstrate the *in vitro* antibacterial effects of different types of phytochemicals belonging to different chemical classes: alkaloids, sulfur-containing phytochemicals, terpenoids, and polyphenols. In addition, we discuss their chemical structure, traditional uses and sources.

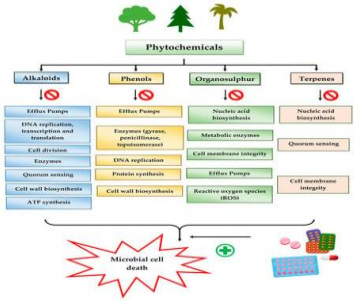

Figure 2: Flowchart of plant-derived phytochemicals and their mechanistic role as antimicrobials.

6.0 Medicinal Plant Resources of Himalayas and Alternate Systems of Medicine

The Indian subcontinent possesses one of the oldest and most well-structured medical systems, which originated more than 5000 years ago. The vast information on medicine is backed by different traditional medicinal practices such as Ayurveda and Unani and various literary manuscripts such as *Charak Samhita*, *Sushruta Samhita*, *Dhanvantri*, and *Nighatu*. These scriptures provide a solid foundation for traditional medicinal practices in India. Various communities in India, both tribal and urban, rely on traditional medicine, and it has long been an important element in the treatment of diseases and disorders.

Around 25000 phytocompounds are used as herbal formulations in rural Indian traditional medicine, particularly in tribal populations. Of these phytocompounds, only 5–10% have been confirmed scientifically. Due to the rising interest in adopting traditional medicine globally, government institutions in India have made attempts to validate the therapeutic efficiency of the drugs used in traditional medicine. The Himalayan region is home to many endemic human populations, and due to the remoteness of the area, the people have been relying on forest products for multiple needs, including the ethnomedicinal use of plants for disease treatment, as a result of which the people of the Himalayas have a strong belief in traditional herbal medicine.

The Indian Himalayas foster around 10,000 species of higher plants, of which 1748 species reportedly have medicinal properties. Medicinal plants of the region have played fundamental roles in the disease treatment of the people living in and around the Himalayan mountain range. The vegetation of the area is determined by the climate and weather conditions of the area. For instance, the North-Western Himalayas, including the areas of Ladakh and Gilgit, have weather conditions ranging from mild summers to severely cold winters, and the medicinal flora are represented by *Achillea millefolium* L., *Bunium persicum* (Boiss.) B. Fedtsch., *Picrorhiza kurroa* Royle ex Benth., *Juniperus communis* L., and *Ephedra gerardiana* Wall. ex Klotzsch & Garcke. The Western Himalayan region, including Jammu and Kashmir, Himachal Pradesh, Garhwal, and Kumaon Himalaya, experiences warm humid summers and cold humid winters, and the medicinal flora are primarily represented by *Saussurea costus* (Falc.) Lipsch., *Colchucum luteum* Baker, *Atropaacuminata* Royle ex Lindl., and *Physochlaina praealta* (Decne.) Miers. On the other hand, the Eastern Himalayas, comprising areas such as Darjeeling, parts of Assam, Sikkim, and Arunachal Pradesh, are characterized by warm summer and cool winter. Hence, the vegetation is represented predominantly by *Aquilariamalaccensis* Benth., *Coptisteeta* Wall., and *Panaxpseudo ginseng* Wall. In the adjoining Himalayan region of north-western Pakistan, medicinal plants such as *Berberis lyceum* Royle, *Achillea millefolium* L., *Bergeniaciliata* (Royle) A. Braun ex Engl., and *Aloe vera* L. have been reported to be used against urinary tract infections due to their antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*. Further, medicinal plants such as *Impatiens glandulifera* Royle, *Artemisia scoparia* Waldst. & Kit., *Ageratum conyzoides* L., and *Achillea millefolium* L. have been reported to be used as treatment options for various ailments such as urinary tract infections, cardiac diseases, baldness, abortion and miscarriage jaundice, hepatitis, typhoid, fever, and tuberculosis.

7.0 Conclusion

Humans have trusted on plants for many of their basic requirements, including the production of medicines that can save lives. The number of individuals suffering from illnesses including diabetes, diarrhoea, cancer, rheumatism, inflammation, jaundice, hepatic blockage, pain, cold, cough, etc. is on the rise in many nations these days. These conditions can be successfully treated using treatments derived from medicinal plants. India's Uttrakahand region boasts a wide variety of fragrant and therapeutic plants. These plants could provide the pharmaceutical industry with a significant number of raw materials to make medicines. Apart from the necessity of conservation ofmedicinal plants it has also become essential to protect and patent the traditional knowledge.

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***CHAPTER* 5**

Biomedical Application of Saponin From Medicinal Plants - Current Scenario And Future Prospects

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ABSTRACT

Saponins, a class of naturally occurring plant compounds, have gained significant attention for their diverse biological activities and potential therapeutic applications. This review delves into the current state of knowledge regarding the biomedical applications of saponins derived from medicinal plants, highlighting their pharmacological properties and future prospects. Saponins exhibit a wide range of biological activities, including anti-cancer, anti-inflammatory, antioxidant, antimicrobial, and immunomodulatory effects. These properties stem from their ability to interact with various cellular targets, such as cell membranes, enzymes, and receptors. The structural diversity of saponins, characterized by their aglycone core and sugar moieties, contributes to their broad spectrum of activities. Despite their promising potential, challenges remain in the development of saponin-based therapeutics. These challenges include the complex chemistry of saponins, their potential toxicity, and the need for efficient and sustainable extraction and purification methods

Keywords : *Phytochemical, saponins, industrial use, agricultural uses*

Saponin

One of the largest and most varied classes of naturally occurring plant compounds is saponins. A significant resource for upcoming drug development is probably the understudied biodiversity of plant saponins, as some saponins are also significant medicines. Though some saponins are known to have strong biological activities that depend on different aspects of their structure, the amphipathic qualities ofthese molecules which are composed of a hydrophobic triterpene or sterol backbone and a hydrophilic carbohydrate chain are typically attributed to the biological activity of saponins. Saponins are naturally occurring compounds that are widely distributed in all cells of legume plants. Saponins, which derive their name from their ability to form stable, soaplike foams in aqueous solutions, constitute a complex and chemically diverse group of compounds.

Fig:1 Diagrammatic illustration of potential surfactant applications of saponins as an alternative to synthetic surfactants in diverse fields.

Use of saponins in industrial and agricultural sector

Saponins are widely employed in the food and pharmaceutical industries because of their strong bioactive and pharmacological properties, which include hypolipidemic, antiulcer, expectorant, anti-inflammatory, and androgenic activity. Furthermore, plant saponins function as organic detergents. Numerous applications, including their beneficial physicochemical (such as as a surfactant) and biological (such as as a biocide and antibacterial) properties, have been studied for saponins. Because of these properties, steroid and triterpenoid saponins are intriguing molecules for industrial applications. Products with saponins are crucial to the food industry. Emulsifiers in processed foods, foaming agents in beverages, and the encapsulation and stability of bioactive compounds are some of its main uses. Using the saponin glycyrrhizin (found in the Glycyrhiza species) is one example.

Quillaja saponins are widely used to make saponin adjuvants; reports of similar production from gypsophila, Saponaria, soy, and quinoa saponins for a variety of purposes also exist. A Quil A derivative called QS-21, along with other derivatives, is being tested for use in human and animal vaccine formulations against bacterial infectious agents, viruses, HIV, cancer, and malaria. However, there are still few uses for plant saponins in the synthesis of human vaccines because of their toxicity, instability, hemolytic qualities, and structural complexity. Compared to QS-21, the lablabosides and soyasaponins had lesser hemolytic activity and increased adjuvant action. Currently, research is being done on innovative purification methods using cutting-edge processing technologies, and in tandem.

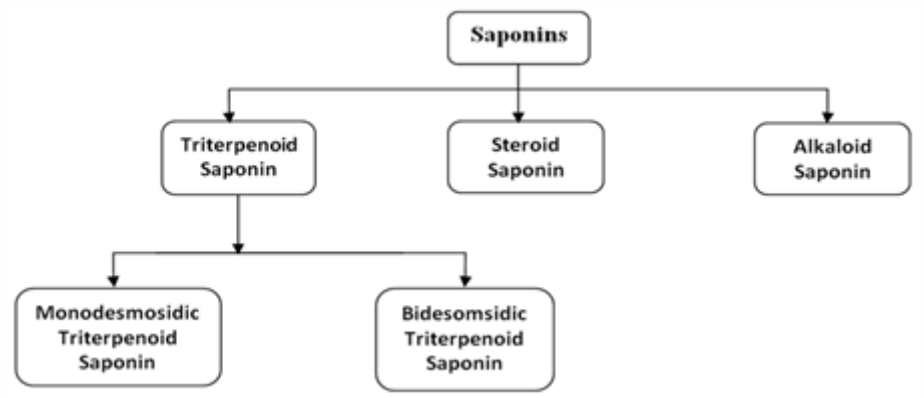

Fig:2 Categories of saponins

Saponins are used as natural biocontrol agents and as animal nutrition in the pet, livestock, and agriculture sectors. These terpenes have demonstrated several qualities that make them appealing natural adjuvants for improving animal feed and natural pesticide alternatives that don't damage the environment. Saponins are at the forefront of the biocontrol area, serving as molluscicidal agents, insecticides (both deterrent and antifeedant), and antimicrobials to treat and prevent a variety of plant diseases. Avenacins are essential for Avena species' resistance to the root-infectingfungus Gaeumannomyces graminis var. tritici. The 'take-all' disease that affects most crops is caused by this fungus.

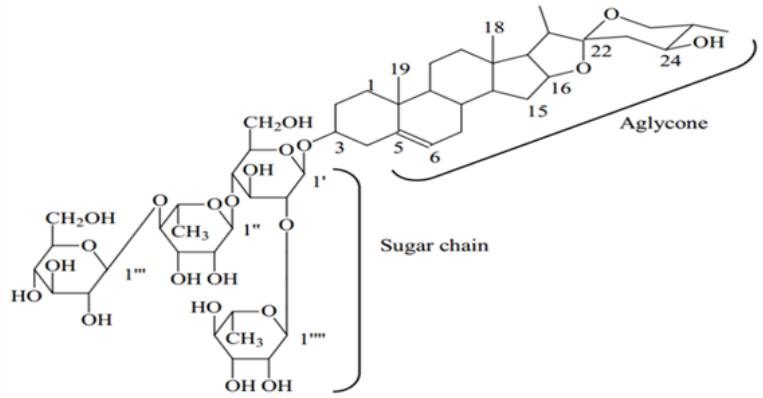

Fig: 3 The chemical Structure of saponin

Saponin extract (crude) of Saponaria, Sapindus sp. and Quillaja has the ability to enhance the growth of isolated pea and wheat embryos by two folds. Asiaticosides stimulate the growth as wellas biosynthesis of chlorophyll in pea (Linum, Lupinus sp.), and radish. Pea saponins have ability to regulate cellulose synthesis and gravitropism in various plant species. Chromosaponin Istimulates the elongation and division of cortical cells, resulting in increased root growth of Lolium multiforum, A. thaliana, Phleum pretense, Lactuca sativa, Cryptotaenia japonica, Chrysanthemum coronarium, Cryptotaenia japonica, Medicago sativa, Brassica compestris, Trifolium repens, Bras.sica juncea and Astragalus sinicus.

Saponins as Food Supplement and Medication

Saponins, a common component of many plants and plant-based products, are essential to the nourishment of both humans and animals. Additionally, a lot of foods high in saponins are recommended as dietary supplements for those with diabetes or other

conditions. Well renownedfor its intriguing bioactive components, saponin can improve both the nutritional and therapeutic value of food when added. For instance, Tribulus terretris, a well known herb is being used in folk medicine throughout the world. Furthermore, its saponin extract as food supplement with claims of a general stimulating activity is for sale in the USA and Europe. In the field of medicines, its extract is employed for the treatment of libido disorders in males and females, curing infertility and cardiac related diseases. However, the quantity and source of saponins that may be used in food items are specified by laws in several nations. Saponins are heavily marketed as dietary supplements and functional foods by the food industry. Quillaja bark saponin can boost the activity of α-galactosidase, one of the most significant and traditional biotechnological enzymes utilized in the food industry.

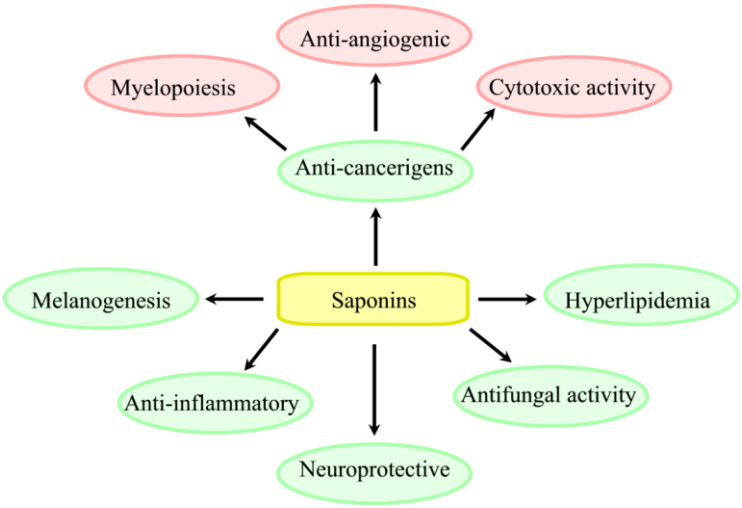

Fig: 4 Biological and Pharmacological effect of saponin in therapeutic application

The Distribution and Localization of Saponin in Plants

Saponin production has been found to vary in individual organs and tissues. Many plant species store saponins in the roots, where these molecules may act as antimicrobial phytoprotectants. For example, the major saponin from Avena spp., avenacin A-1, is localized in the epidermal cell layer of oat root tips and also in the lateral root initials, representing a chemical barrier to invadingsoil-borne microbes that attack plant tissues. Different distribution of saponins was found in the root of other species. The distribution of saikosaponins from Bupleurum falcatum root has been reported in the outer phloem layer which possesses many secretory canals, especially in the parenchyma cells located around pericycle but not in the mucilaginous exudates within the secretory canals. Ginsenosides were discovered in Panax ginseng outside the root cambium, specifically in the outer cortex and periderm beyond the phloem. According to research on the histochemical localization of saponins, the color of the solution containing glacial-perchloric acid and vanillinacetic acid changes from pale red to purplish red when saponins react with it. Using this method, histochemical analyses of the organs of Bupleurum chinense revealed that saponins were primarily found in the pericycle and primary phloem of the root's primary structures.

Saponins Have Various Medicinal Uses, Including:

Antimicrobial properties: Some saponins have demonstrated antimicrobial activity against bacteria, fungi, and viruses, making them potentially useful in treating infections.

Anti-inflammatory effects: Certain saponins exhibit anti-inflammatory properties, which can be beneficial in managing conditions like arthritis and other inflammatory disorders.

Antioxidant activity: Saponins can act as antioxidants, helping to neutralize harmful free radicals in the body and reduce oxidative stress.

Immune modulation: Some research suggests that saponins may modulate the immune system, potentially enhancing immune function and offering protection against certain diseases.

Cardiovascular health: Certain saponins have been studied for their potential benefits in improving cardiovascular health, including reducing cholesterol levels and supporting healthy blood pressure.

Cancer prevention: There is ongoing research into the potential anticancer effects of saponins, including their ability to inhibit tumor growth and induce apoptosis (programmed cell death) in cancer cells.

Digestive health: Saponins may have beneficial effects on digestive health, including promoting the growth of beneficial gut bacteria and reducing the risk of gastrointestinal disorders.

It's important to note that while saponins show promise in various medicinal applications, further research is needed to fully understand their mechanisms of action and potential therapeutic benefits. As with any herbal remedy, it's also crucial to use them under the guidance of a healthcare professional to ensure safe and effective use.

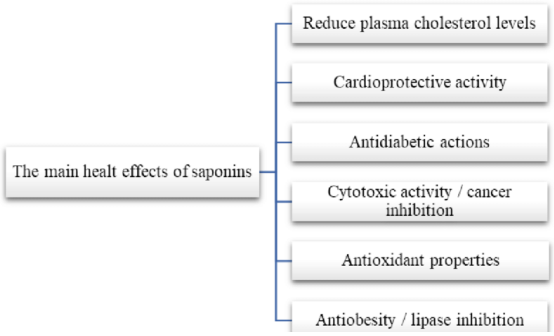

Fig:5 Role of saponin in human health

The Occurrence of Saponins in Plant

Around the world, plants that produce saponins can be found in a variety of climate zones and geographic locations. These consist of grasses, shrubs, trees, perennial evergreens, annual and biennial herbs, and both cultivated and wild species. Of the approximately 100 species listed, about half of these have been investigated for biological activities. Furthermore, a number of species listed were selected based on previous ethnobotanical studies on related species either from the same genus or family. One example is the genus Maesa from the family Primulaceae. They were investigated because they contain maesa saponins of which some were reported to have anti-cancer and lack haemolytic activity, which is commonly activity for most saponins. The substitution at position C-22 is an essential structural feature that influences haemolytic activity. These favourable biological properties prompted further research to investigate other species within the same genus.

Steroidal saponins are almost exclusively found in the class of Liliopsida or

monocotyledonous angiosperms. This is confirmed by the presence of steroidal saponin in Agavaceae, Asparagaceae,Dioscoreaceae, Liliaceae, Poaceae, Smilacaceae, and Taccaceae. The exception, however, found in Scrophulariaceae and Solanaceae, two plant families from class of Magnoliopsida or dicotyledoneus angiosperms in which all the species studied contained steroidal saponin. It's unclear how much the biosynthetic genes for triterpene and steroid sapogenins are conserved at this time, despite the possibility that the diversity of triterpenoid and steroidal saponins originated from species-specific separate evolution. After more biosynthesis genes from various species have been found, it will be crucial to address the diversity of both triterpenoid and steroidal saponin biosynthesis.

Table 1: New saponins molecules isolated from different plant species in the last ten years (2012-2022)

Family	Species	Saponin type	References
Class Magnoliopsida of Amaranthaceae	Achyranthes fauriei Alternanthera philoxeroides Celosia cristata	Triterpenoid	Ando *et al*. (2008) Fang *et al*. (2009) Wang *et al*. (2010)
Araliaceae	Aralia elata Cussonia arborea Hydrocotyle Bonariensis Hydrocotyle Sibthorpioides Meryta denhamii	Triterpenoid	Lee *et al*. (2009a) Kougan *et al*. (2009) Tabopda *et al*. (2012) Huang *et al*. (2008) Cioffi *et al*. (2008)
Balsaminaceae	Impatiens siculifer	Triterpenoid	Li *et al*. (2009)
Chenopodiaceae	Salicornia herbacea	Triterpenoid	Kim *et al*. (2012)
Fabaceae	Abrus precatorius	Triterpenoid	Xiao *et al*. (2012)
Liliaceae	Anemarrhena asphodeloides Trillium erectum	Steroidal	Lee *et al*. (2010) Hayes *et al*. (2009)
Poaceae	Panicum virgatum	Steroidal	Lee *et al*. (2009b)
Smilacaceae	Smilax excels	Steroidal	Ivanova *et al*. (2009)
Taccaceae	Tacca integrifolia	Steroidal	Shwe *et al*. (2010)

However, in mature roots, they were mainly distributed in vascular cambium and secondary phloem. In addition, they were also found to accumulate in mature fruit. The relationship between structural features of various organs and saponin accumulation was also studied in the important Chinese traditional medicinal plant Achyrantus bidentata.

Here, leaves are an active synthesis site rather than for storage. This is supported by the disappearance of saponins from leaves when they withered. A. bidentata saponins mainly accumulate in the primary root as well as in cambium cells and in the phloem cells of tertiary vascular bundles. In addition, the presence of saponin-related substances in stem vascular bundles indicated that the stems function as transport organ. Hence, saponins are commonly found in the outer cell layers and particularly in the epidermis to be effective as a first barrier against microbial attack. In addition, saponins accumulate in phloem as a transitory phase during transport from the shoot to the root or as an intrinsic component to combat insects or root-knot nematodes that feed on phloem sap. Furthermore, the phloem also represents a metabolically active site for biosynthesis of sterol and saponins as reported in Panax ginseng.

It has been documented that *Dioscorea caucasica* leaves accumulate oligofurostanosides, or steroidal saponins. This kind of saponin accumulates in the leaf epidermis receptacle cells, according to a histochemical analysis. These cells are typically used to store compounds. Conversely, oligofurostanosides have not been found in the leaf's mesophyll tissues, where they are generated. This suggests that there is active transport taking place between the mesophyll cellsand the receptacle cells in the epidermal layer.

Extraction and Isolation of Saponin

An extensive overview of the most recent developments in the extraction of a bioactive componentfrom medicinal plants has been published in reference to the growing public awareness ofpreventative health care. Numerous literary works elucidate three distinct methods for the extraction of saponins. While newer techniques like ultrasound-assisted extraction, microwave- assisted extraction, and accelerated solvent extraction methods are still in their infancy, conventional extraction and soxhlet extractor are well-known extraction procedures. According toChoon YC, maceration, reflux, and soxhlet extraction represent about ~60% of the employed techniques in the extraction of saponins from plant materials. Modern extraction processes represent about ~30 %, while subsequent extraction method represents about 10% of the employedtechniques.

Ordinary Extraction

The extraction of saponins by maceration is the famous method. using the ordinary solvent-like alcohols and n-butanol. It is a solid– liquid interface extraction where saponin's compounds insidethe plant material can easily extract by immersion or soaking the plant materials in a suitable specific solvent for a period of time with or without stirring or shaking.25 The polarity of the

solvent, temperature, maceration time, solubility of saponins and its effective diffusion in the liquid phase are the main operational variables affecting the efficiency of the ordinary extraction process. Generally speaking, nonpolar compounds dissolve in nonpolar solvents and polar saponins dissolve in polar solvents. The rate of mass transfer of a solute from the plant materialto the solvent determines how quickly saponins diffuse into the liquid phase. The saponins' diffusion into the solvent is propelled by the concentration gradient that exists between the liquid and solid phases. The standard maceration method is quite easy to use and doesn't require a complex experimental setup. The typical solvents used for the extraction of saponins from plant material are ethanol

(50–98%) and n-butanol CH3 (CH2), but ethanol C2 H5 OH, methanol CH3OH, acetone CH3 COCH3, ethyl acetate CH3 COOC2 H5, dichloro methane CH2 Cl2, and a mixture of solvents Maceration of plant materials by organic solvents may be accelerated or facilitated by heat, shaking and/or magnetic stirring. The temperature of extraction varies from ambient to the boiling point of the chosen solvent, and the amount of extracted materials also variesfrom a few grams to few kilograms. The amounts of isolated saponins are a function of time of extraction, temperature, shaking, and the amount of original material. The longer extraction time,the higher temperature, and the heavier extracted mass with shaking the more amount of isolated saponin will be, and vice versa. The amount of used solvent or extractant does not specify adequately and varied from few milliliters to few tens of liters. Ordinary column chromatographywith silica gel stationary phase and an organic solvent as a mobile phase consumes more and moresolvents than static maceration process.

Various saponins with different chemical structures can be extracted by maceration from the wild, desert, and cultivated plants with various species. Aftermaceration, the alcoholic crude extract of plant materials then evaporated to obtain a more concentrated saponin containing solution. This solution may dilute with water, and directly subjected to a solvent extraction process using n-butanol and separating funnel. Finally, n-butanol easily removed using rotatory evaporator under vacuum, and the remaining saponin residue staysin the round-bottomed flask. The dry residual saponin material can be fractionated and identified using one or more techniques e.g. column chromatography, Sephadex, thin layer chromatography (TLC), and/ or high-performance liquid chromatography (HPLC). The most commonly employed solvent system for TLC are chloroform - glacial acetic acid – methanol - water (60:32:12:8) and ethyl acetate - formic acid - glacial acetic acid - water (100:11:11:26). Methanol water system (MeOH - H2 O) is the common solvent system used with HPLC. The extraction and identification of saponin from the plant material are not easy and described as a tedious process.

Soxhlet Extraction

Distillation process of plant material by soxhlet is faster than the ordinary maceration process because it involves heating the organic solvent to its boiling point and then returning the condensed vapors to the original flask after passing through the plant tissue in the condenser, so the extraction process takes place via the direct contact between the plant tissue andthe hot fumes of the solvent. After a considerable extraction time, the colorless solvent becomes green dark solution due to the mass transfer into solvent. Then the solution was dried by rotaryevaporator to dryness to obtain the dry crude extract of the plant which suspended in water, extracted by n-butanol and fractionated as mentioned above. Still soxhlet extraction affected greatly by the polarity of the solvent, extraction time, and the extraction temperature. Ordinary maceration process is static extraction, but soxhlet is dynamic extraction due to the circulation ofsolvent during extraction. Before the final extraction, the plant powder might be first defatted statically or dynamically using 60–80˚C petroleum ether or n-hexane to remove the fatty components.

Qualitative Determination of Saponins

Saponin tests were carried out on the plant materials using standard procedures.

The occurrence of saponins can be determined and confirmed qualitatively in the laboratory by different saponin tests as follows in details:

1. Standard foam test:

3g of each dry plant powder were weighed and extracted with 300ml of hotdistilled water in a beaker. After filtration, the aqueous extracts were cooled, stirred and stored at 4°C in an automated refrigerator for 24h. About 5ml of the plant extract was transferred into a test tube and diluted with 5ml of distilled water. The mixture was shaken vigorously for 2 minutes. Persistent appearance of foam lasting for at least 15 minutes or the forming of an emulsion when olive oil was added confirmed the presence of saponins.

2. Wet foam test:

After dilution with water and a vigorous one to two minute shake, a stable foamy lather formed on top of the sample's test tube.

3. Dry foam test:

In a test tube, around 0.5 grams of the plant's crude powder was shaken with 5 milliliters of distilled water and heated in a water bath. The stable, persistent froth was then combined with 3 drops of olive oil and violently shaken again. Emulsion development is a sign that saponins are present.

4. Foam test for fresh samples:

About 2gram of fresh plant sample (leaves) was add to 20ml distilled water (w/w = 1:10), mixed together by electrical mixer, the mixture was filtered, the filtrate was concentrated by evaporation in a water bath to half of the original volume, then transferred into a test tube. The stable persistent froth was mixed with 3 drops of olive oil and shaken vigorously than observed for the formation of the emulsion, indicate the presence of saponins.

Quantitative Determination of Saponins

In this method, saponins are traditionally extracted into water/ ethanol mixtures, after which the alcohol is removed by evaporation and the saponins extracted from the water phase into n-butanol. Saponin can be determined quantitatively by taking the dry powder of the plant sample weighing about 5g and poured into 200ml of 20% ethanol solution. The suspension was heated over a hot water bath for 3-4h with continuous stirring at about 55- 60°C. The mixture was filtered and the solid residue of the plant powder was re-extracted with another 200ml of 20% ethanol solution. The two combined solutions were evaporated over a waterbath at about 80- 90°C to reduce the volume to about 40ml. The concentrated solution was transferred into a 250ml separating funnel and 20ml of diethyl ether was added and shaken vigorously to remove impurities from the original solution. The ether layer containing contaminants was disposed of, and the aqueous layer was recovered for further extraction. Following another round of purification, 60 milliliters of n-butanol were added, and the resulting 120 milliliters of n-butanol solutions were then twice washed with 20 milliliters of 5% aqueous sodium chloride. The leftover aqueous solution was moved to a porcelain crucible that had been dried and previously weighed. It was then dried at 60°C to a consistent weight in a drying oven. The saponin product, which is the residue that remains, may be computed using the following formula:

$$\text{Total saponin contents (\%)} = \frac{\text{weight of the saponin residue}}{\text{weight of the original plant material}} \times 100$$

To increase the isolated saponin contents, a large quantity of plant material will be used. The process seems to be efficient, but having many of technical and environmental disadvantages, like using three organic solvents (alcohol, ether, and n-butanol) with remarkable amounts, the need of heating, the need of drying, and time consuming. Another method for the determination of total saponin content was reported, in which the dry aerial parts of the plant (5.0g) were defatted twice with petroleum ether (60-80°C) (2x50ml), and alcoholic solution (75%, 150 ml) was addedto the defatted phase. Then, the mixture was refluxed at 70°C for four hours, the extract solution filtered and evaporated at 40-50°C in rotavapor. A sufficient volume of distilled water was used todissolve the dry residue, and n-butanol was used to extract it three times in triplicate (3x40ml). Using rotavapor, the mixed n-butanol solution was evaporated at 90°C until dry, and the saponin yield was computed using the given equation.

Safe Limits and Toxicity

The results of numerous studies have proven that they are almost nontoxic to the human body when ingested, because they usually stay in the digestive tract and are absorbed at very low levels. In addition, vegetarian human diet usually sums up to 200 mg of daily saponin intake. However,as discussed earlier, the safe limits for consumption and its toxicity depends on several factorssuch as source of saponin, type of saponins and many others. Recent study done on quinoa saponinsdepicts that the adverse effect of saponins are gender based as well, where the female rats weremore prone to have the adverse effect of saponins as compared to male rats. According to them,there was no adverse effect below 50 mg of quinoa saponins per kg of body weight per day. In

addition, for Quillaia saponins, the acceptable daily intake limits, as suggested by joint FAO and WHO committee, may vary between 0 mg to 1 mg/kg of body weight each day and there was no threat observed concerning genotoxicity, because it is hydrolyzed in the gastrointestinal tract andonly absorbs a small amount into the body. Despite increasing the dose to 1200 mg/kg body weight/day, the study found no negative effects. Similar findings pertaining to no toxicity have been documented even for lucerene consumption up to 2.6% saponin content; however, any amount beyond 3% proved harmful. FEMA states that quillaja saponins are safe to use as food additives in beverages up to a maximum of 95 parts per milliliter or seed growth in plants like Chinese blooming cabbage, maize, mung beans, and tea saponins, which are safe up to 0.1%.

The safety of saponins can be problematic, for example, in severe cases, gastrointestinal injury orirritation or lesions may occur, thereby allowing saponins to get into the blood stream. At this moment, the lethal dose of intravenous injection can reach 1/1000 of the lethal dose of oral injection. The result of saponins infiltration into the blood can be liver problematic, convulsions, coma, respiratory failure and hemolysis. They are therefore recommended for the people suffering from cirrhotic livers or inflamed intestines, who use several laxatives, should avoid the foods containing saponin in them. Also, saponins sometimes may alter the permeability of cells of intestinal mucosa and therefore may alter the process of absorption and excretion in small intestine,which result in enhanced absorption of allergens and absorption disorder of essential microelements.

This enhanced absorption by nerve cells may have direct effect on central nervoussystem, the initial symptoms of which may includes convulsions followed by paralysis and may ends up to death. . However the exact lethal dose for the saponins is still vague as it depends on various factors; still few researchers state the general lethal limits for saponins which range from 100 to 6000 mg/kg of body weight. This wide range is capable enough to demonstrate the lethal

effect of saponins from different sources. In addition, saponins are mostly toxic to cold blooded animals, whereas their oral toxicity is very low or almost negligible in case of mammals. Since they are toxic to various organisms, they are employed as fungicidal, insecticidal, antibiotic and inpharmacological sector. Thus further research still needs to be done to explore the toxicity of the compound, however till date no such drastic adverse effect has been observed by oral consumptionof saponins in any human.

Summary and Conclusions

Plants synthesis a greater number of bioactive chemicals, which are less harmful and biodegradable than synthetic ones. Among the bioactive chemical substances with surfactant qualities are plant-derived saponins. Because of their superior physicochemical and biological qualities, plants high in saponins are valuable sources of natural surfactants for both industrial and research use. Saponins are produced by more than 100 families of vascular plants, some of which are marine. Additionally, because natural source extraction and processing methods are underutilized and therefore costly, saponin has gained prominence in the food industry due to its biological properties that offer numerous health benefits,as well as its other properties, which include foaming, stabilizing, solublizing, emulsifying, cleaning agent, and many more. Saponins are made up of two main parts: the aglycone and the sugar fraction. They are classed as triterpenoid and steroid chemicals. In the last decade, many novel saponins derived from plants have been identified and characterised, in addition to those that were previously known. Some have shown promising biological and pharmacological capabilities, including antibacterial, antidiabetic, and anticancer activity. Given the previously stated findings, we can conclude that saponins represent a significant opportunity in the pharmaceutical, industrial, and extrapharmaceutical areas.

These properties have proven to be invaluable to the industrial sector. Though saponins possess both beneficial as well as adverse effects, the adverse effects of saponin have been ignored over the several health implications and have been employed potentially to be used in the drug delivery system. However, several studies reported the adverse effects of saponins on fish and other cold blooded animals. Thus it is important to determine the safe consumption limits of saponins suitable for human body as well in order to avoid any intoxication. The goodness of this magical component has not been exploited entirely.

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CHAPTER 6

Targeted Therapeutics from Medicinal Plants

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ABSTRACT

Medicinal plants have been explored as a source for targeted therapeutics, utilizing their broad range of phytochemicals to tackle a vast number of disease applications. This paper provided an overview of the mechanisms that bioactive molecules derived from medicinal plants can exhibit specificity in respect to targeting disease pathways, highlighting examples from cancer, certain autoimmune disorders and infectious diseases. Modern pharmacological and molecular biology technologies have enabled researchers to exploit these natural products by enhancing therapeutic potency with fewer side effects. Overview of Synergistic Effects, target modulation of biologically active components from some important medicinal plants and mechanistical basis for their functioning; Importance of traditional knowledge in natural products drug discovery therefore, a holistic review of traditional medicinal practices together with modern scientific modalities is critical for the development of biologically and molecularly targeted therapies that can be used in combination to combat cancers.

Keywords: *Medicinal plants, Ayurveda, Human health, illness*

Introduction

From the dawn of humanity, individuals have engaged with plants, utilizing them in various capacities throughout history. Early humans, in their quest for sustenance and relief from ailments, began to identify plants with medicinal properties, distinguishing them from those lacking therapeutic benefits. This evolving relationship between humans and plants has led to the incorporation of numerous species into medicinal practices. The accumulation of knowledge regarding disease treatment has accelerated, resulting in an increase in plant-based pharmaceuticals. India, endowed with a rich diversity of medicinal flora, is often referred to as the Medicinal Garden of the World. The therapeutic applications of plants are documented in ancient Indian texts, such as the Vedas, which outline their use for various ailments. Today, traditional medicine systems are widely embraced and practiced globally. India holds a distinctive position, being home to several recognized traditional medical systems, including Ayurveda, Siddha, Unani, Homeopathy, Yoga, and Naturopathy. Medicinal plants are increasingly acknowledged as promising candidates for drug development due to their pharmacological properties.

The use of plant sources for therapeutic remedies is as old as several thousand years and traditional medicine systems throughout the world are fully based on natural products to cure numerous ailments. These plants are now being considered with attention for their pharmacological potential in targeted drug application as we progress through modern science [3,4]. Targeted therapies differ from conventionally used chemotherapeutic drugs and other pharmacologic modes of intervention in that they involve targeting an underlying molecular genetic basis however they also have more limited range of effect

than those specific to symptom or generalized processes as well as less invasive altered varieties of a tumour and are often associated with fewer side effects.
Plants are the natural source of many medicinal compounds such as alkaloids, flavonoids, terpenoids, or glycosides and these bioactive molecules exert their effects through different mechanisms. Such compounds can modify cellular signalling pathways, immune responses and the course of specific diseases at distinct targets. Progress in phytochemistry and molecular biology has helped to identify and characterize these active components, which have gained promising application prospects.

The combination of traditional knowledge and modern scientific techniques offers a comprehensive framework for drug discovery. By examining the ways in which indigenous cultures have employed these plants, researchers can identify innovative compounds and therapeutic approaches that may have been neglected by contemporary medicine .

This introduction paves the way for an in-depth investigation into the role of medicinal plants in creating targeted therapeutics, emphasizing the significance of interdisciplinary research in realizing their complete therapeutic potential. As we explore the mechanisms of action, advantages, and obstacles associated with plant-derived compounds, our goal is to shed light on the development of new, effective treatments that could enhance or even substitute current therapies.

Introduction to Targeted Therapeutics:
Definition and relevant contemporary use in medicine

Targeted therapeutics mark a pivotal development in contemporary medicine, concentrating on specific biological pathways and molecules to improve treatment effectiveness while reducing side effects. Drawing from the historical application of medicinal plants in traditional healing practices, these therapies are designed to selectively engage with targets implicated in disease mechanisms, resulting in more personalized treatments that focus on the root causes rather than just symptom relief . Current examples include monoclonal antibodies and small molecule inhibitors that influence biological interactions, highlighting their importance in managing chronic illnesses and the growing need for personalized medicine. Advances in biotechnology and pharmacology are expediting the identification of new plant-based compounds, although challenges such as standardization and regulatory issues persist. As research continues, targeted therapeutics derived from medicinal plants have the potential to transform healthcare by providing safer and more effective treatment alternatives tailored to the specific needs of patients.

The significance of targeted therapeutics in modern medicine is highlighted by the increasing intricacy of diseases and the rising need for personalized treatment solutions. As chronic illnesses such as cancer, diabetes, and cardiovascular diseases become more widespread, conventional one-size-fits-all methods often fall short. Targeted therapeutics, which concentrate on specific biological pathways and molecular targets, provide a more accurate approach that can improve treatment effectiveness while reducing side effects. Moreover, the growing issue of antibiotic resistance and the emergence of new infectious diseases emphasize the critical need for innovative therapies sourced from natural origins, including medicinal plants. This strategy not only leverages the extensive pharmacological capabilities of plant-derived compounds but also resonates with the current movement towards holistic and integrative healthcare [12]. Additionally, progress in biotechnology, genomics, and pharmacogenomics is enabling the creation of targeted therapies that can be

customized for individual patients, ensuring that treatments are both effective and personalized. Consequently, targeted therapeutics are establishing themselves as a fundamental aspect of contemporary medicine, bridging traditional healing methods with modern scientific progress, ultimately enhancing patient outcomes and promoting a more sustainable healthcare system.

History and Conventional Medical Practices.

Ayurveda is a time-honoured healthcare system that originated in India approximately 5,000 years ago. Historical texts indicate that it was practiced during the Vedic period in India. The Charaka Samhita and Sushruta Samhita, dating back to the 1st millennium BC, document around 700 medicinal plants. Today, this medical system is recognized globally as a form of complementary medicine. The Ayurvedic approach focuses on maintaining, enhancing, and safeguarding health while preventing illness through healthy lifestyle choices. The term "Ayurveda" translates to "Science of Life."[15] It is estimated that approximately 7,500 plant species are utilized in local health practices across many rural and tribal communities in India. Herbal remedies are the most prevalent aspect of traditional medicine. Plant-based traditional medicine systems remain vital to healthcare. There is a growing global demand for herbal medicines, health products, pharmaceuticals, dietary supplements, nutraceuticals, and cosmetics. In the 21st century, natural products account for over 50% of all drugs currently in clinical use. Nearly half of the herbal drugs approved in the past 30 years have origins in natural products, including plants, microorganisms, fungi, and animals. According to the National Medicinal Plant Board (NMPB), the Indian herbal industry is projected to grow to approximately Rs. 80 to 90 billion by 2020. India is actively promoting the Traditional Medical System of AYUSH (Ayurveda, Yoga, Unani, Siddha, and Homeopathy) within the healthcare sector through international collaborations. Fig 1 and 2 show the different plant species use in Indian and global medicinal system.

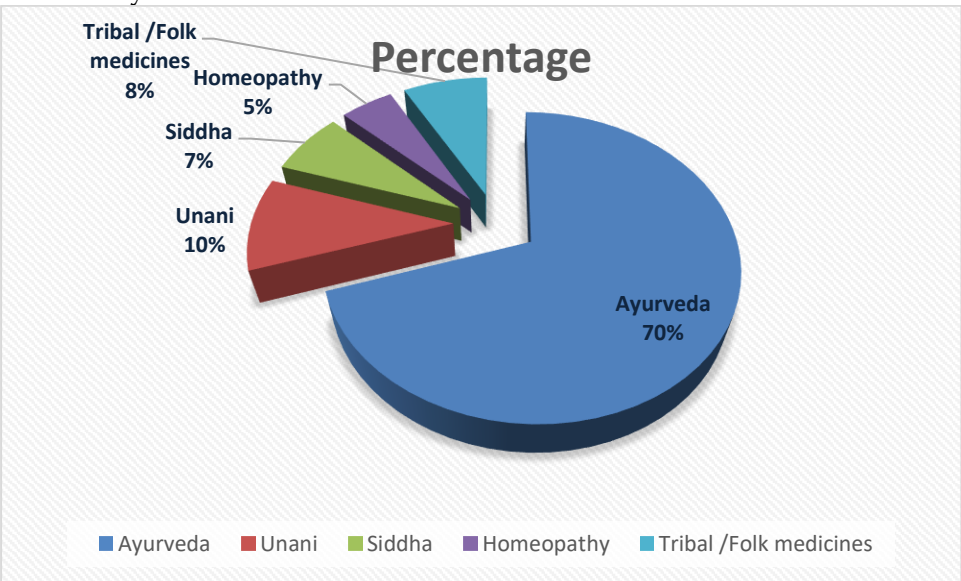

Fig.1 Distribution of Plant species use in different Indian medicinal system [18,19,20].

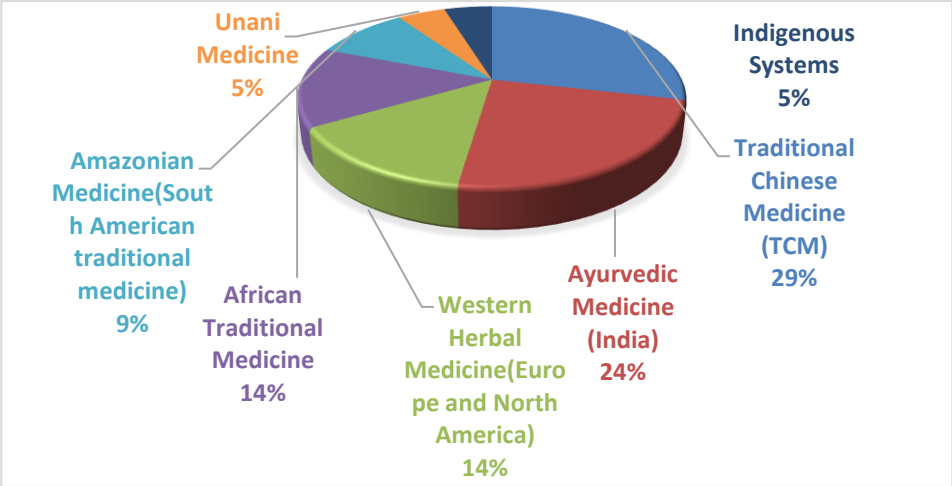

Fig.2 Distribution of Plant species use in different Global medicinal system [21,22,23,24,25,26].

Phytochemistry of Medicinal Plants:

2.1 Overview of Key Phytochemicals, properties and their therapeutic approaches

Phytochemicals are naturally occurring bioactive substances generated by plants, essential for their defense strategies and beneficial to human health. This section will outline several important phytochemicals, detailing their origins, characteristics, and possible health advantages.

Tab. 1 Overview of phytochemicals [27,28]

Name	Structure	Example	Therapeutic approaches
Alkaloids	Nitrogen containing compound	Morphine (from Opium poppy), Caffeine (from Coffee beans), and Quinine (from Cinchona bark).	Analgesic, stimulant, and antimalarial activities.
Flavonoids	Phenolic compound	Quercetin (found in Onions), Catechins (in green tea), and Anthocyanins (in Berries).	Antiinflammatory, cardiovascular protective, and neuroprotective effects.
Terpenoids (Isoprenoids)	Derived from five-carbon isoprene units.	Menthol (from mint), Limonene (from citrus), and Ginsenosides (from ginseng).	Antimicrobial, anti-inflammatory, and potential anticancer effects.

Saponins	Glycoside compounds with surfactant properties.	Found in beans, legumes, and ginseng.	Cholesterol-lowering, immune-boosting, and potential anticancer properties.
Phenolic Acids	Presence of one or more phenolic groups	Cinnamic acid (found in cinnamon) and gallic acid (in tea).	Antioxidant, anti-inflammatory, and antimicrobial effects.
Glycosides	Compounds that consist of a sugar and a non-sugar component (aglycone).	Digitalis glycosides (from foxglove), flavonoid glycosides (in fruits).	Heart-stimulating and antioxidant properties.
Essential Oils	Concentrated hydrophobic liquids containing volatile aroma compounds from plants.	Eucalyptus oil, lavender oil, and tea tree oil.	Antiseptic, antifungal, and relaxing properties.
Lignans	A group of polyphenolic compounds found in seeds, particularly flaxseeds.	Secoisolariciresinol and pinoresinol.	Antioxidant and potential hormone-regulating effects.
Carotenoids	Pigments responsible for the bright red, yellow, and orange colors in many fruits and vegetables.	Beta-carotene (in carrots), lutein (in spinach), and lycopene (in tomatoes).	Antioxidant, eye health benefits, and potential cancer-preventive effects.

Mechanisms of Action:

3.1 How Plant-Derived Compounds Interact with Cellular Targets

Plant-derived compounds demonstrate their therapeutic effects through a variety of mechanisms by interacting with specific cellular targets. They can act as agonists or antagonists by binding to receptors, modulate enzyme activity through either inhibition or activation, and affect critical signaling pathways like MAPK/ERK and NF-κB, which play vital roles in cancer proliferation and inflammation. Many of these compounds possess strong antioxidant properties, effectively scavenging free radicals and enhancing the activity of antioxidant enzymes. Additionally, some compounds promote apoptosis in abnormal cells via caspase activation and mitochondrial pathways. Certain compounds also inhibit angiogenesis, thereby impeding tumor growth, while others display antimicrobial properties by disrupting the integrity of microbial cell walls and membranes. Furthermore, plant-derived compounds can influence gene expression through epigenetic mechanisms, which may aid in the treatment of diseases such as cancer, cardiovascular disorders, and infections. Recognizing these varied mechanisms underscores the considerable therapeutic potential of plant-based compounds in contemporary medicine.

3.2 Pathways Modulated by Medicinal Plant Extracts:

Medicinal plant extracts play a significant role in modulating various biochemical pathways, which are essential for their therapeutic benefits in preventing and treating a range of diseases. These pathways encompass inflammatory, apoptotic, oxidative stress, and metabolic processes, all of which are vital for maintaining cellular health and influencing disease development.

1. NF-κB Pathway (Nuclear Factor Kappa B)

The NF-κB pathway serves as a key regulator of inflammatory and immune responses. Extracts from medicinal plants, such as curcumin derived from Curcuma longa (turmeric), have been found to inhibit NF-κB activation, thereby alleviating inflammation. This pathway is also implicated in cancer, where its suppression can hinder tumor growth and metastasis.

Therapeutic Example: Curcumin has demonstrated the ability to inhibit NF-κB, leading to a decrease in pro-inflammatory cytokine production and offering protection against inflammatory conditions like arthritis and inflammatory bowel disease [31].

2. MAPK Pathway (Mitogen-Activated Protein Kinase)

The MAPK pathway is crucial for regulating cell growth, differentiation, and survival. Certain plant extracts, such as epigallocatechin gallate (EGCG) from green tea, influence this pathway by blocking it signaling, which results in diminished tumor growth and reduced cell proliferation in cancer.

Therapeutic Example: EGCG has been shown to inhibit the MAPK/ERK pathway, leading to a decrease in cancer cell proliferation and the induction of apoptosis, positioning it as a promising therapeutic candidate for cancer treatment [32].

3. PI3K/Akt Pathway

This pathway is crucial for the regulation of cell growth, survival, and metabolic processes. Numerous compounds derived from plants have been shown to inhibit the PI3K/Akt pathway, which is frequently disrupted in cancer and metabolic disorders.

Therapeutic Example: Resveratrol, a compound present in grapes and berries, inhibits the PI3K/Akt pathway, leading to apoptosis in cancer cells and offering neuroprotective benefits in neurodegenerative conditions .

4. JAK/STAT Pathway (Janus Kinase/Signal Transducer and Activator of Transcription)

The JAK/STAT pathway plays a significant role in cytokine signaling and the regulation of immune functions. Flavonoids and various plant-based compounds influence this pathway to mitigate inflammation and prevent irregular immune responses.

Therapeutic Example: Quercetin, a type of flavonoid, inhibits the JAK/STAT pathway, thereby reducing inflammation in autoimmune conditions such as rheumatoid arthritis and multiple sclerosis.

5. AMPK Pathway (AMP-Activated Protein Kinase)

AMPK is essential for maintaining energy balance and is activated when cellular energy levels are low. Plant-derived substances, including berberine from Berberis vulgaris, stimulate AMPK, enhancing glucose metabolism and lipid management.

Therapeutic Example: Berberine activates the AMPK pathway, which improves insulin sensitivity and lipid metabolism in individuals with type 2 diabetes, positioning it as a potential anti-diabetic treatment.

6. Apoptosis Pathways (Intrinsic and Extrinsic)

Extracts from medicinal plants can initiate apoptosis, the process of programmed cell death, via both intrinsic (mitochondrial) and extrinsic pathways. This mechanism is especially significant in cancer treatment, where the goal is to promote apoptosis in malignant cells.

Therapeutic Example: Paclitaxel, which is sourced from the Pacific yew tree, promotes apoptosis through the mitochondrial pathway, resulting in the death of cancer cells. This agent is commonly utilized in chemotherapy .

7. Nrf2 Pathway (Nuclear Factor Erythroid 2–Related Factor 2)

The Nrf2 pathway plays a crucial role in managing the cellular response to oxidative stress by regulating the production of antioxidant proteins. Compounds found in plants, such as sulforaphane from cruciferous vegetables, stimulate the Nrf2 pathway, thereby bolstering the body's antioxidant defenses.

Therapeutic Example: Sulforaphane activates the Nrf2 pathway, leading to an increase in the production of detoxifying and antioxidant enzymes, which provides protection against diseases associated with oxidative stress, including cancer and neurodegenerative conditions.

Extraction and Isolation Techniques:

4.1 Methods for Extracting Bioactive Compounds

The extraction and isolation of bioactive compounds from medicinal plants are essential for exploring their therapeutic properties and for the formulation of plant-derived pharmaceuticals. The choice of extraction method varies based on the chemical characteristics of the compounds, the plant matrix, and the level of purity required.

1. Maceration

Maceration is a straightforward extraction technique where plant material is immersed in a solvent (such as water, ethanol, or methanol) at ambient temperature. The solvent extracts the bioactive compounds, which are subsequently filtered and concentrated. This method is particularly effective for compounds sensitive to heat, although it necessitates extended extraction periods.

Advantages: Easy to perform, cost-effective, ideal for heat-sensitive compounds.

Limitations: Prolonged extraction duration, lower efficiency compared to more advanced methods.

2. Percolation

Percolation entails the gradual movement of solvent through ground plant material within a percolator. As the solvent flows through the plant matrix, it continuously extracts bioactive compounds. This technique offers greater extraction efficiency than maceration and is applicable to a variety of plant materials.

Advantages: Enhanced efficiency, continuous extraction process.

Limitations: Requires specialized equipment, longer processing duration.

3. Soxhlet Extraction

Soxhlet extraction involves placing plant material in a thimble, where a solvent is continuously vaporized, condensed, and circulated over the material. This technique is particularly effective for extracting non-polar compounds; however, it may compromise thermally sensitive substances due to the elevated temperatures involved.

Advantages: Highly effective for non-polar compounds, allows for solvent recycling.

Limitations: Elevated temperatures can damage certain compounds, can be time-intensive.

4. Ultrasound-Assisted Extraction (UAE)

Ultrasound-assisted extraction employs ultrasonic waves to break down plant cell walls, facilitating the release of bioactive compounds. This approach is quicker and more effective than conventional methods and is compatible with a variety of solvents.

Advantages: Rapid, efficient, minimizes solvent usage, ideal for thermally sensitive compounds.

Limitations: High equipment costs, typically limited to small-scale extractions.

5. Supercritical Fluid Extraction (SFE)

Supercritical fluid extraction employs supercritical CO_2 as a solvent to isolate bioactive compounds. CO_2 is non-toxic and can effectively extract both polar and non-polar substances by varying pressure and temperature. This technique is both environmentally sustainable and efficient, although it necessitates costly equipment.

Advantages: Environmentally sustainable, high efficiency, minimal solvent residue.

Limitations: High cost of equipment, requires expertise in managing supercritical fluids.

6. Microwave-Assisted Extraction (MAE)

Microwave-assisted extraction utilizes microwave energy to heat both the plant material and the solvent, thereby enhancing the extraction rate. MAE is quicker than traditional methods and can effectively extract both polar and non-polar compounds.

Advantages: Rapid, efficient, low solvent usage.

Limitations: Potential degradation of sensitive compounds, requires specialized equipment.

7. Pressurized Liquid Extraction (PLE)

Pressurized liquid extraction, also referred to as accelerated solvent extraction, utilizes solvents under high pressure and temperature to extract bioactive compounds. This approach improves extraction efficiency and minimizes solvent consumption.

Advantages: Efficient, reduced solvent usage, faster than traditional methods.

Limitations: High equipment costs, not suitable for thermally sensitive compounds.

4.2 Advancement in phytochemical analysis:

Technological advancements have greatly improved phytochemical analysis by integrating a variety of techniques and tools that enhance both efficiency and precision. High-Performance Liquid Chromatography (HPLC) and Ultra-High Performance Liquid Chromatography (UHPLC) provide exceptional resolution for the separation and

quantification of compounds, while Gas Chromatography-Mass Spectrometry (GC-MS) is particularly effective for analyzing volatile substances. High-resolution mass spectrometers, such as Orbitrap and QTOF, enable comprehensive structural elucidation, and mass spectrometry imaging allows for the spatial mapping of phytochemicals within plant tissues. Moreover, Nuclear Magnetic Resonance (NMR) spectroscopy offers a non-destructive method for analyzing molecular structures. The fields of bioinformatics and chemoinformatics are essential for processing large datasets to identify bioactive compounds, further supported by high-throughput screening (HTS) that automates the rapid testing of samples. Molecular biology techniques, including PCR and RNA sequencing, reveal the genetic foundations of phytochemical production, while smart sensors and the Internet of Things (IoT) facilitate real-time monitoring in agricultural environments. Additionally, artificial intelligence and machine learning contribute to predictive modeling of phytochemical characteristics, and microfluidics technology minimizes sample volume and reduces analysis time. The emphasis on green analytical chemistry seeks to lessen environmental impact through sustainable practices. Together, these innovations are revolutionizing phytochemical research, which is vital for drug discovery, nutrition, and agricultural development.

These innovations are revolutionizing phytochemical analysis, allowing for more comprehensive and expedited investigations of plant compounds, which are crucial for drug development, nutrition, and agricultural practices.

Preclinical and clinical efficacy:

5.1 Evaluation of plant in animal models

Assessing plant-derived compounds in animal models is crucial for gaining insights into their pharmacological properties and therapeutic applications. This evaluation process starts with the careful selection of suitable animal models, such as mice, rats, or genetically engineered organisms, tailored to the specific research goals [43]. Subsequently, phytochemical isolation is carried out using extraction techniques like Soxhlet extraction, followed by characterization through methods such as HPLC and GC-MS. Preclinical investigations focus on safety through toxicity assessments and pharmacokinetic studies, which analyze how these compounds are absorbed, metabolized, and their modes of action. The therapeutic effectiveness is tested using disease models that replicate conditions such as cancer or diabetes, with both behavioral and physiological evaluations conducted to assess health outcomes. Mechanistic investigations typically involve biomarker analysis and histopathological studies to elucidate the biological pathways influenced by the compounds. Adherence to ethical standards in animal research is vital, ensuring the humane treatment of subjects throughout the investigation. Finally, thorough statistical analyses are performed to confirm the results, which are then interpreted for their potential application in human therapies. Together, these processes yield valuable information regarding the safety and efficacy of plant compounds, forming a foundation for subsequent clinical advancements.

Clinical trials: Successes and limitations:

Clinical trials play a crucial role in assessing the safety and effectiveness of new treatments, including those derived from botanical sources, presenting both significant achievements and notable challenges. On the positive side, these trials generate robust, evidence-based information that facilitates the approval of novel therapies and confirms

their safety for a wide range of patient demographics. Successful trials can pave the way for innovative treatments and enhanced safety profiles by uncovering potential side effects and determining optimal dosages. However, obstacles such as substantial costs, lengthy timelines, difficulties in participant recruitment, and ethical dilemmas can impede progress. Furthermore, high dropout rates and a narrow focus on specific outcomes may limit the applicability of findings, underscoring the necessity for a balanced strategy to optimize the advantages of clinical research while addressing its inherent challenges.

Case study of medicinal plants in targeted therapy:

Medicinal plants have increasingly been recognized in recent years as important sources of bioactive compounds for targeted therapies. Targeted therapy, which focuses on disrupting specific molecules that contribute to the growth, progression, and metastasis of diseases like cancer, has historically depended on synthetic drugs. However, natural products from medicinal plants present distinct advantages, such as greater structural variety and reduced toxicity. A prominent example is *Taxus brevifolia* (Pacific yew), the source of paclitaxel (Taxol), which specifically targets microtubules in cancer cells, thereby inhibiting their division and triggering apoptosis. Another significant example is *Camptotheca acuminata*, which yields the alkaloid camptothecin, known for its ability to inhibit DNA topoisomerase I, an essential enzyme in DNA replication. These compounds derived from plants have demonstrated efficacy in targeting specific cellular processes, highlighting their potential in the development of innovative targeted therapies. Ongoing research into medicinal plants is crucial for discovering new phytochemicals that can be utilized in targeted treatment strategies, providing hope for more effective and personalized approaches to complex diseases.

Future prospective in targeted therapeutics:

The landscape of targeted therapeutics is on the brink of significant evolution, fueled by advancements in personalized medicine, biologics, and innovative technologies such as gene therapy, nanotechnology, and artificial intelligence (AI). Personalized and precision medicine will utilize genomic and proteomic analyses to customize treatments according to individual molecular characteristics, thereby minimizing side effects and maximizing effectiveness. The emergence of next-generation biologics, including bispecific antibodies and antibody-drug conjugates (ADCs), will facilitate precise targeting of disease-specific antigens. Furthermore, the incorporation of AI and machine learning will accelerate the drug discovery process by uncovering new targets and forecasting drug interactions. Gene and RNA-based therapies, exemplified by CRISPR/Cas9 and small interfering RNA (siRNA), will enable direct alterations to genes responsible for diseases, paving the way for novel treatments for genetic disorders. Nanotechnology is set to transform drug delivery systems through the creation of nanocarriers that enhance drug stability, bioavailability, and targeting accuracy, ensuring that diseased cells are precisely addressed. Immunotherapy will advance with targeted strategies such as checkpoint inhibitors and cancer vaccines, bolstering the immune system's capacity to combat diseases. Additionally, the potential of natural product-derived compounds, including phytochemicals, will be investigated for their ability to influence disease pathways. Collectively, these innovations in targeted therapeutics promise to deliver more effective, safer, and personalized

treatment solutions, fundamentally transforming the healthcare landscape and providing new hope for managing complex and previously untreatable disease.

Conclusion

The investigation of targeted therapies derived from medicinal plants signifies an exciting advancement in contemporary medicine. As we enhance our comprehension of the intricate relationships between bioactive compounds and biological systems, the opportunity to create innovative treatments specifically designed for various diseases and conditions becomes increasingly apparent. The vast array of phytochemicals found in medicinal plants provides distinct benefits, such as multi-targeted effects, minimized side effects, and improved efficacy. Recent progress in technologies like genomics, metabolomics, and bioinformatics has expedited the discovery and analysis of these bioactive compounds, enabling their incorporation into modern therapeutic frameworks. Additionally, the renewed focus on traditional medicine and ethnopharmacology highlights the necessity of safeguarding indigenous knowledge and biodiversity.

Nevertheless, to fully exploit the therapeutic capabilities of medicinal plants, ongoing research must tackle issues related to standardization, quality assurance, and clinical validation. Collaborative initiatives among pharmacologists, botanists, and healthcare professionals are crucial to bridging the divide between traditional methodologies and contemporary scientific practices. In summary, the outlook for targeted therapies derived from medicinal plants is promising, offering the potential for groundbreaking treatments that can enhance and complement current therapeutic options. As we continue to explore the intricacies of these natural compounds, we advance toward a more comprehensive and personalized healthcare approach, ultimately benefiting both patients and society at large.

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CHAPTER 7

An overview on important traditional Indian medicinal herbs *Adathoda vasica* possessing promising activity against respiratory infection

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ABSTRACT

Adathoda vasica is a well-known plant drug in Ayurveda and Unani medicine. It has been used for the treatment of various diseases and disorders, particularly for the respiratory tract ailments. In the present study, *Adathoda vasica* was chosen to be tested against respiratory infections. Phytochemical analysis and antibacterial activity of the plant was studied. These reports are very encouraging and indicate that the herb should be studied more extensively for its therapeutic benefits. *Adathoda vasica* leaves contain rich content of alkaloids which contributes to its most of the pharmacological activity. The prominent alkaloid found in *Adathoda* leaves is the pyrralazoquinoline alkaloid known as vasicine. In addition to vasicine, the leaves and roots of *Adathoda* contain the alkaloids l-vasicinone, deoxyvasicine, maiontone, vasicinolone, 6-hydroxy vasicine, volatile oils, betain, vasakin, adhatodine, adhavasinone, anisotine, adhatodic acid, adhatonine, vasicolone, vasicolinone vasicinone, vasicol, vasicinol, vasicinine, kaempferol, luteolin, tritriacontane, phenols, tannins, anthraquinones, saponins, flavanoids, and common phytosterols sitosterol. The detail study reveals the use of *A. vasica* has a potential to cure both lower and upper respiratory infections and validates its use in Ayurveda.

Keywords : *respiratory diseases, Adathoda vasica, Haemophilus*

1.1 Background Introduction

As defined by WHO (World Health Organization), health is a state of complete physical, mental, and social well being, and not merely the absence of disease or infirmity. Various factors including climate change, natural and man-made activities influence the health state of human in a negative way followed by severe infectious diseases. These factors affect our organ systems in unique ways and lead to various diseases. Among the organ systems present in our body, respiratory system is more susceptible to different infections. Generally, respiratory system is broadly categorized into two tracts, namely upper respiratory tract consisting of nose, mouth, sinuses and throat, and lower respiratory tract includes trachea, bronchial tubes and lungs (Fig.1). The respiratory infections are usually classified as an upper respiratory tract infection (URI or URTI) or a lower respiratory tract infection (LRI or LRTI). URIs are chiefly caused by airborne respiratory droplets, saliva and contaminated saliva.

It can be usually resolved within two weeks. They spread easily and are self-diagnosable with the symptoms as scratchy sore throat, sneezing, cough and stuffy nose. The infections of upper respiratory tract include common cold, tonsillitis, sinusitis, laryngitis, epiglottitis and flu. Viruses (Rhinoviruses, coronavirus, para influenza viruses, adenovirus, respiratory syncytial virus, Epstein-Barr virus, cytomegalovirus, herpes

simplex virus and influenza viruses) are the important etiological agent for most of the upper respiratory infections.

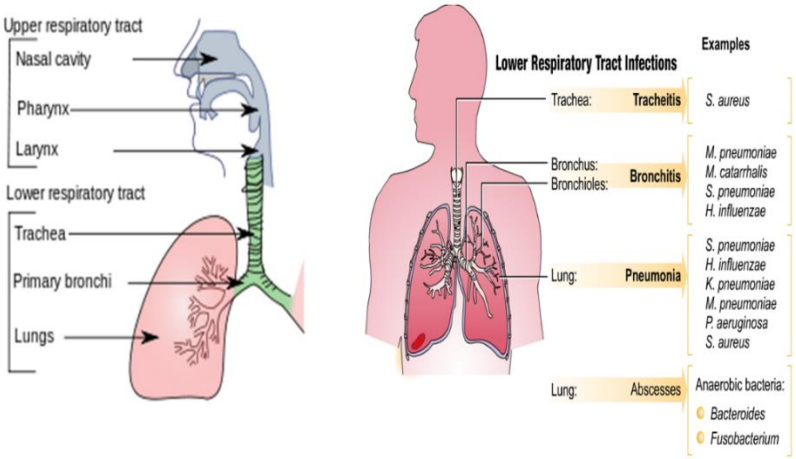
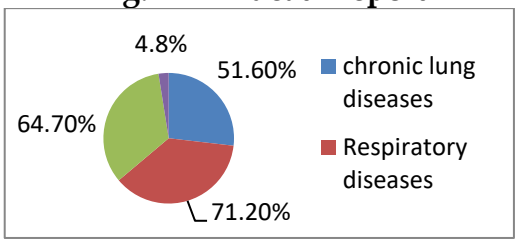


Fig. 1 Human respiratory tract and its infections
Source: https://en.wikipedia.org/wiki/Respiratory_tract_infection

Yet, certain infections such as epiglottitis, laryngotracheitis and pharyngitis are caused by bacterial species such as *Haemophilus influenza* and *Streptococcus pyrogenes* (Dasaraju and Liu 1996). In India, more than 10 million cases per year are recognized with upper respiratory infections predominantly common cold (Appllo Hospitals.com).

Diseases such as flu, bronchitis, pneumonia, bronchiolitis and tuberculosis are included as lower tract infections. Infections and clinical infestations are more severe in LRI when compared to URI. Bronchitis infections are caused by viruses. Among these LRI and URI, acute respiratory infections (ARI) of viral and bacterial foundation such as the common cold, pharyngitis, laryngitis, bronchitis, bronchiolitis, pneumonia, and bronchopneumonia pretence severe problems due to their great occurrence with related high death charge and financial expenses. Though several diseases of lower respiratory infection affects human, bronchial infection is the most common serious infection that can seriously block one's ability to breathe, and abruptly divest the individual of the most influential nutrient of all oxygen (Tattersfield *et al*., 2002).

Fig.2 ARI death report



The world pervasiveness related to respiratory infection is estimated about 20%. Current epidemic investigation reveals that there is an increasing motif in respiratory infection in the world. USA, reported about 35-49 cases in 1992 per 1000 population. In 1963,

WHO has been alarmed with the complicated trouble of contagious diseases acute respiratory infection. It's the most important cause of death in all age groups. Death rates related with ARI were tremendously high, chiefly in developing countries 1000 /100 000 reside births. The respiratory infections are world's third leading cause of death after heart disease and stroke. The risk factors causing lower respiratory infections in developing countries include large family size, lateness in the birth order, crowding, low birth weight, malnutrition, vitamin A deficiency, lack of breast feeding, pollution and young age.

Among acute respiratory infections, pneumonia is the single largest infectious cause of death in children worldwide. Pneumonia was the cause of death of 9,20,136 children under the age of 5 in 2015, accounting for 16% of all deaths of children under five years old (WHO 2016). Clinically, inflammation of the lung parenchyma and alveoli filled up with pus resulted in pneumonial infection. Many viruses and bacteria can cause both type of infections. They are bacterial pneumonia (*Streptococcus pneumoniae, Chlamydophila pneumonia* and *Legionella pneumophila*), viral pneumonia (respiratory viruses), *Mycoplasma pneumonia* (*M. pneumoniae*) and fungal pneumonia (*Histoplasma capsulatum, Candida albicans, Filobasidiella neoformans, Aspergillus fumigatus, Paracoccidiodes brasiliensis and Blastomyces dermatidis*). Among these pathogens, *Streptococcus pneumoniae* is the most common agent of community-acquired acute bacterial pneumonia. Infections due to *Haemophilus influenzae* and *Klebsiella pneumoniae* are more common among patients over 50 years old who suffer from chronic obstructive lung disease or alcoholism. Favorable conditions for acute respiratory infections would have more prevalence to acquire some other infections along with Pneumonia (Fig.2). For instance, measles, pertussis, bronchiolitis, group syndromes along with pneumonia causes 15%, 10% and 5% of death rate, respectively.

1.2 Problem statement

Elevated death rate due to pneumonia was equal in children and elderly people and are further common in chronically sick persons, such as those with chronic cardiovascular or chronic lung conditions, diabetes, etc. Primary acute bronchopulmonary infections due to *Pneumococci, Klebsiella pneumoniae, Streptococci, Staphylococci, Neisseria, Haemophilus influenzae, Pseudomonas aeruginosa.* Secondary bronchopulmonary infections emerge as bacterial infections through viral, *Chlamydial, rickettsial*, or fungal infections, or as a obstacle of preexisting chronic lung or cardiovascular diseases or immune-depressed patients. The side effects of the currently available anti-inflammatory drugs pose a major problem in their clinical use. Attention is being given to the investigation of the efficacy of traditionally used plants as they are affordable and have fewer adverse effects.

Amid the numerous bacteria that cause respiratory infections, several have become drug resistant. Fluoroquinolone resistant strains of *Pneumococcus* can be acquired from another person (as in cases of primary resistance), but resistance might also extend during treatment or as a result of previous fluoroquinolone exposure (as in cases of acquired resistance). The percentage of the peak attention to the minimal inhibitory concentration (MIC) for the infecting pathogen or the ratio of the area under the concentration time curve (AUC) to the MIC has been directly linked to the prospect of a thriving clinical or microbiologic conclusion in *S. pneumoniae* infections.

1.3 Justification

So far, pneumonial infections were treated with various antibiotics. Though there are several inconveniences associated with antibiotics, antimicrobial drug resistance is one

of the major drawbacks of antibiotic usage. Antimicrobial resistance (AMR) can be defined that the process of acquiring tolerance and overcoming ability of antibiotics by the microorganisms. It threatens the effective prevention and treatment of severe infections caused by bacteria, viruses, fungi and parasites. As depicted by WHO (2018), it is an increasingly serious threat to global public health. Microorganisms which develop such antimicrobial resistance are also called as superbugs. Due to their resistance power, regularly used drug would become ineffective and the uncured infections resulted in severe chronic condition along with increasing spread to other individuals. The alarming frequency of drug resistance has been attributed to combinations of microbial characteristics, selective pressures of antimicrobial use, and societal and technologic changes that enhance the transmission of drug-resistant organisms. Overuse and misuse of antibiotics also lead to drug resistance. Hence, the National Committee for Clinical Laboratory Standards does not propose that levofloxacin, moxifloxacin, or gatifloxacin be integrated in the regular sheet of agents used in susceptibility testing of *Pneumococci*.

The emergence of drug resistance has limited therapeutic options and has called for alternate forms of therapy. Higher plants have been described as living chemical factories that are capable of synthesizing unlimited numbers of highly complex and unusual chemical substances that have a great potential for producing new drugs of great benefit to mankind (Table 1). The number of higher plant species (angiosperms and gymnosperms) on our planet is estimated at 250,000, with a lower level at 215,000 and an upper level as high as 500,000. Of these, only about 6% have been screened for biologic activity, and a reported 15% have been evaluated phytochemically. With high throughput screening methods becoming more advanced and available, these numbers will change. More than 119 pure chemical substances extracted from higher plants are used in medicine throughout the world. For the most part, the discovery of the drugs stems from knowledge that their extracts are used to treat one or more diseases in folk medicine. The extracts are then subjected to pharmacological and chemical tests to determine the nature of the active components.

Table 1: Medicinal plants used by traditional healers in Tamil Nadu

Botanical Name	Tamil Name	Preparation and Medicinal uses
Adathoda vasica Nees	Adathodai	Leaves are ground with the flowers of *Hibiscus rosasinensis* and taken orally to treat asthma.
Andrographis paniculata	Nilavembu	Powdered leaf is mixed with hot water taken orally to cure URI
Trianthema portulacastrum	Saaranai	Decoction of roots is taken internally to treat asthma.
Aerva lanata	Siru peelai	Juice of whole plant is taken orally to treat cough, sore throat and wounds.
Wattakaka volubilis	Kurinjan	Leaf paste is applied topically to treat cough, fever and severe cold.
Mukia maderaspatana	Musumusukai	Leaf powder is mixed with boiled rice and taken orally to treat cold and cough.

Botanical Name	Tamil Name	Preparation and Medicinal uses
Phyllanthus emblica	Nelli	Fruit powder is mixed with cow's or goat's milk and taken orally to treat cold and cough.
Coleus aromaticus	Karpuravalli	Leaf juice is taken orally by children to treat Indigestion and cough.
Ocimum sanctum	Thulasi, Tulsi	Leaves are crushed with onion bulbs and the juice is taken orally to treat cough, cold and headache.
Cinnamomum verum	Lavangappattai, Karuvappatttai	Decoction of stem bark is taken internally to treat cough.
Citrus aurantifolia	Elumitchai	Decoction of leaves is inhaled to get relief from fever, headache and cold.
Murraya koenigii	Karuveppilai; Kari-vembu	Juice of tender leaves is taken orally to arrest vomiting.
Cardiospermum halicacabum	Mudakkathan	Root is boiled with oil and applied on head before bath to treat throat infection and headache.
Solanum nigrum	Manathakkali	Whole plant parts are taken as food to treat cough.
Solanum trilobatum	Thuthuvalai	The leaf juice is taken orally to treat cough.
Vitex negundo	Notchi	Leaves are boiled in water and the vapour is inhaled twice a day to get relief from headache, fever, cold, and cough.
Hybanthus enneaspermus	Orithal thamarai	Paste of whole plant is applied topically to treat cough.

1.4 The Experimental Crop

The present study utilizes *Adathoda vasica* Nees which is predicted to be a better alternative to treat bacterial pneumonia. It belongs to family Acanthaceae, usually called as Adosa and is a familiar plant drug in Ayurvedic and Unani medicine. It has been used for the treatment of different diseases and disorders, predominantly for the respiratory tract ailments. It is a small, evergreen shrub of 1-3 feet in height with many long opposite branches. Leaves are large and lance shaped. Stem is herbaceous above and woody below. Leaves are opposite and exstipulate, while flowers are spikes or panicles, small irregular zygomorphic, bisexual, and hypogynous. It has capsular four seeded fruits. The flowers are either white or purple in colour and found in many regions of India and throughout the world, with a multitude of uses in traditional Ayurveda.

1.5 Study area

India map depiciting Tamilnadu with Tiruchirappalli District map showing Ettarai where the plant available in abuntant

1.6 Scientific classification

Kingdom:	Plantae
Subkingdom:	Tracheobionta
Division:	Magnoliophyta
Class:	Magnoliopsida
Subclass:	Asteridae
Order:	Lamiales
Family:	Acanthaceae
Genus:	*Adathoda*
Species:	*vasica*

Photograph and Herbarium of plant *Adathoda Vasica*

1.7 Medicinal properties

A.vasica is most well known for its effectiveness in treating respiratory conditions. The leaves of *vasica* show stimulant effect on the respiratory system (Nair 2005). *Vasica* shows an antispasmodic and expectorant effect, and has been used for centuries with much success to treat asthma, chronic bronchitis, and other respiratory conditions. The powdered herb boiled with sesame oil, is used to heal ear infections and arrest bleeding. Boiled leaves are used to treat rheumatic pain, and to relieve the pain of urinary tract infections. The leaves, flowers, fruit and roots are extensively used for treating cold cough, whooping cough, chronic bronchitis and asthma, as sedative, expectorant and antiplasmodic.

Potent antimicrobial phytochemicals are present in extracted essential oil of *A. vasica* and the fragrant volatile oil rich in borneol is found to be responsible for its antimicrobial

effect against *E.coli, S.aureus, S.epidermidis, Pseudomonas vulgaris, Salmonella typhi* and *Candida albicans*. The plant has potent anti-periodic, astringent, diuretic and purgative action. It is a highly valued medicinal plant which is used in the treatment of respiratory diseases like asthma, cough, bronchitis, and tuberculosis. The flowers, leaves and root have antiplasmodic property. The activities against tuberculosis were reported by many researchers. It has been used extensively as an important herbal drug in treating wide variety of diseases and the leaves of the plant are the main source of drug formulation. 'Vasaka' is well known in the indigeous system of medicine for its beneficial health effects particularly in treating bronchitis.

1.8 Rationale of the study

A.vasica has been used to treat respiratory infections from time immoral by tribals. This required scientific validation. The active compounds in the leaves need to be analyzed and the mechanism of action has to be established to formulate a drug against respiratory infection. Hence research is needed to study the therapeutic values of *A.vasica* to be scientifically validated.

Acknowledgements

The authors gratefully acknowledge the encouragement of Dr W. C. Cockburn, formerly Director, Division of Communicable Diseases, World Health Organization, Geneva as well as the aid and technical advice of colleagues at WHO, namely Dr A. Zahra, Director, Division of Communicable Diseases, and Dr S. Plaza de Echeverria, Dr B. Cvjetanovid, Dr P. Bres, Dr F. Assaad, Dr B. Bytchenko, Dr 0. Sob8slavsk9, and Dr Y. Watanabe.

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***CHAPTER* 8**

Formulation of Poly herbals from few Indian medicinal herbs to treat Alcoholic Liver Cirrhosis and Hepatocellular Carcinoma in Siddha Indian System of Medicine (ISM)

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ABSTACT

Alcoholic liver cirrhosis is a severe liver condition that occurs when healthy liver tissue is replaced by scar tissue. This scarring prevents the liver from functioning properly. Excessive alcohol consumption is the primary cause of this condition. Hepatocellular carcinoma (HCC) is the most common type of liver cancer. It often develops in people with chronic liver diseases, including alcoholic liver cirrhosis. This chapter discusses about the formulation of herbal formulations which have been used for treating alcoholic liver cirrhosis and liver cancers.

Introduction to Alcoholic Liver Cirrhosis and Hepatocellular Carcinoma

Alcoholic Liver Cirrhosis (ALC) and Hepatocellular Carcinoma (HCC), both significantly associated with chronic alcohol abuse, represent a growing global health challenge, particularly in developing countries. HCC is the fifth most common cancer, accounting for approximately 75-90% of liver cancer cases, and is the third leading cause of cancer-related deaths worldwide. While both men and women are affected by this condition, the prevalence in men (16 per 100,000) is significantly higher than in women (6 per 100,000).

The treatment options for liver cirrhosis and HCC are dependent on the underlying cause and extent of liver damage. Currently, liver transplantation remains the most effective option, though it is often accompanied by a myriad of complications. Given this, alternative treatments, such as polyherbal formulations in Indian Siddha Medicine (ISM), are being explored as potentially curative options for both cirrhosis and HCC.

The Liver and Alcohol-Induced Damage

The liver plays a crucial role in a wide range of vital metabolic functions, which are essential for maintaining life. Some of these functions include filtering toxins from the blood, maintaining blood sugar levels, converting harmful ammonia into urea for excretion, producing immune factors, and removing bacteria from the bloodstream. Additionally, the liver detoxifies harmful substances such as alcohol, drugs, and chemicals.

Excessive alcohol consumption can severely damage the liver, leading to cirrhosis, a condition characterized by the replacement of healthy liver tissue with scar tissue. Cirrhosis develops in 15-25% of individuals with chronic alcohol abuse, typically after 10-20 years of heavy drinking. The most common form of alcoholic liver disease (ALD) is micronodular cirrhosis, which involves fibrosis and the transformation of the normal liver architecture into small, uniform nodules. This progressive damage can continue even after the cessation of alcohol consumption.

Liver cirrhosis is a serious condition with a high mortality rate. Studies have shown that patients with liver cirrhosis have a 1-year mortality rate ranging from 20% to 57%, depending on the degree of liver impairment. Furthermore, cirrhotic patients with hepatocellular carcinoma face even greater challenges, as they are more likely to succumb to tumor-related complications than to the cirrhosis itself.

ALD has been the leading cause of liver-related morbidity for decades. In its early stages, ALD manifests as hepatic steatosis, which may progress to fibrosis or cirrhosis, resulting in a loss of liver function. Another major concern is drug-induced liver injury (DILI), which is commonly caused by medications such as paracetamol, amiodarone, and methotrexate. Overdoses of these drugs can lead to liver damage, including cirrhosis and other severe liver conditions.

Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and is responsible for significant mortality worldwide. It is the third leading cause of cancer deaths, following cardiovascular diseases and accidents. Chronic alcohol consumption is a primary risk factor for cirrhosis, which often precedes the development of HCC.

The incidence of liver cancer increases with age, with the highest rates observed in individuals between 60 and 70 years old. The geographical distribution of liver cancer varies significantly, with higher rates in Africa and Asia compared to North America and Europe. More than 500,000 new cases of liver cancer are reported annually, with a 5-year mortality rate exceeding 95%, making it one of the deadliest forms of cancer.

In most cases, HCC arises in individuals with pre-existing chronic liver diseases, such as cirrhosis, which is present in 70-90% of cases. Other risk factors include exposure to aflatoxins, alcohol, tobacco, obesity, diabetes, and various metabolic conditions. The increasing incidence of liver cancer is also linked to socioeconomic factors, as evidenced by the correlation between the Human Development Index (HDI) and liver cancer rates.

Siddha System

Overview:

Siddha medicine, one of the oldest traditional medical systems, integrates herbal remedies, dietary practices, and unique health approaches to promote overall well-being.

Medicinal Plants

Global Use and Market:

There is a growing global interest in herbal remedies, particularly in developing countries where approximately 75-80% of the population relies on them for primary health care. The herbal drug market is estimated to be valued in the billions, reflecting their significant cultural acceptance and therapeutic potential.

Recent Findings:

Plants like *Phyllanthus amarus* have shown promising effects in treating liver conditions, such as jaundice, by inhibiting viral replication and providing hepatoprotection.

Polyherbal formulations, an integral component of traditional medical systems like Ayurveda, Siddha, and Unani, involves combining multiple medicinal herbs to create a synergistic therapeutic effect. These formulations are designed to treat complex conditions

by leveraging the diverse properties of various herbs, each targeting different aspects of a disease or condition. In the context of **Alcoholic Liver Cirrhosis (ALC)** and **Hepatocellular Carcinoma (HCC)**, polyherbal formulations can offer potential benefits through a multi-pronged approach, such as hepatoprotection, antioxidant effects, anti-inflammatory actions, and immune system support.

Polyherbal Formulation in the Treatment of ALC and HCC

The primary goal of polyherbal formulations in treating ALC and HCC is to **prevent liver damage**, enhance **detoxification**, **reduce inflammation**, and **promote liver regeneration**. Traditional formulations in Indian Siddha Medicine (ISM) and Ayurveda often include herbs that are known for their hepatoprotective properties. Here are some common herbs used in such formulations and their respective roles:

Common Key Herbs Used in Polyherbal Formulations

1. Phyllanthus niruri (Bhumyamalaki)

- **Hepatoprotective**: Protects the liver from toxins and prevents liver damage.
- **Antiviral**: Effective against hepatitis B virus, which is a major cause of liver damage.
- **Antioxidant**: Neutralizes free radicals, preventing oxidative stress-related liver damage.

2. Andrographis paniculata (Kalmegh)

- **Liver tonic**: Enhances liver function and supports detoxification processes.
- **Anti-inflammatory**: Reduces inflammation, which can prevent the progression of liver disease.
- **Antioxidant**: Protects liver cells from oxidative stress caused by toxins and alcohol.

3. Picrorhiza kurroa (Kutki)

a. **Hepatoprotective**: Supports liver cell regeneration and prevents fibrosis.
b. **Detoxifying**: Helps in detoxifying harmful chemicals and alcohol from the body.
c. **Anti-inflammatory**: Reduces liver inflammation associated with cirrhosis.

4. Glycyrrhiza glabra (Licorice)

a. **Antioxidant**: Protects liver cells from oxidative damage.
b. **Anti-fibrotic**: Prevents the progression of fibrosis in liver cirrhosis.
c. **Immunomodulatory**: Boosts the immune system to fight infections that exacerbate liver conditions.

5. Silybum marianum (Milk Thistle)

a. **Hepatoprotective**: Regenerates liver cells and reverses alcohol-induced liver damage.
b. **Antioxidant**: Neutralizes free radicals and oxidative stress, key factors in the progression of HCC.
c. **Anti-fibrotic**: Prevents the formation of scar tissue in cirrhosis.

6. Boerhaavia diffusa (Punarnava)

a. **Diuretic and anti-inflammatory**: Reduces fluid retention and liver inflammation.
b. **Hepatoprotective**: Supports liver detoxification and promotes the repair of damaged liver cells.

7. Terminalia arjuna

a. **Cardioprotective and hepatoprotective**: Protects both heart and liver health, often affected by chronic alcohol consumption.

b. **Antioxidant**: Protects the liver from oxidative stress and free radical damage.

8. **Tinospora cordifolia (Guduchi)**
   a. **Immunomodulatory**: Boosts the immune system, which is often weakened in patients with chronic liver disease.
   b. **Anti-inflammatory and hepatoprotective**: Helps in reducing liver inflammation and protecting liver cells.
9. **Curcuma longa (Turmeric)**
   a. **Anti-inflammatory**: Reduces liver inflammation associated with cirrhosis and HCC.
   b. **Antioxidant**: Curcumin, the active compound, protects liver cells from oxidative damage.
   c. **Anticancer properties**: Studies show curcumin may slow the progression of cancer, making it relevant in the treatment of HCC.

Mechanism of Action in Polyherbal Formulations

- **Synergistic Effects**: The herbs in polyherbal formulations work together to amplify the therapeutic effects. For example, combining hepatoprotective herbs like *Phyllanthus niruri* and *Picrorhiza kurroa* can provide both protective and regenerative benefits to the liver.
- **Hepatoprotective Actions**: These herbs protect the liver from alcohol-induced damage, reduce oxidative stress, and inhibit the progression of liver fibrosis, thereby preventing cirrhosis from worsening.
- **Detoxification**: Herbs like *Andrographis paniculata* and *Punarnava* aid in removing harmful toxins from the liver, helping restore normal liver function.
- **Antioxidant Defense**: Many herbs in these formulations, such as *Curcuma longa* and *Silybum marianum*, are rich in antioxidants, which combat the oxidative stress responsible for liver cell damage and cancer progression.
- **Anti-inflammatory Properties**: Chronic inflammation plays a critical role in the progression of liver cirrhosis and HCC. Herbs like *Tinospora cordifolia* and *Licorice* help control inflammation, reducing liver damage and improving overall liver health.
- **Immune Modulation**: Liver disease weakens the immune system, making the body more susceptible to infections. Herbs like *Guduchi* and *Licorice* help bolster immune defenses, crucial in the management of liver disease.

Benefits of Polyherbal Formulation for Liver Cirrhosis and HCC

1. **Comprehensive Liver Support**: Polyherbal formulations provide a holistic approach to liver care by addressing multiple aspects such as detoxification, regeneration, and protection from oxidative stress.
2. **Slows Disease Progression**: These formulations may slow the progression of cirrhosis to liver cancer by reducing liver inflammation and fibrosis.
3. **Minimal Side Effects**: Unlike conventional treatments like chemotherapy or radiation, polyherbal treatments are typically associated with fewer side effects, making them suitable for long-term use.

4. **Cost-Effective**: Herbal formulations are generally more affordable compared to liver transplantation or modern cancer therapies, making them accessible to a larger population, especially in developing countries.

Polyherbal formulations in Indian Siddha Medicine and Ayurveda offer a promising alternative or adjunct therapy for managing **Alcoholic Liver Cirrhosis** and **Hepatocellular Carcinoma**. By using a combination of hepatoprotective, anti-inflammatory, antioxidant, and immune-boosting herbs, these formulations provide comprehensive liver support. While further research is essential to validate their efficacy, the long-standing use of these formulations in traditional medicine indicates their potential to contribute meaningfully to liver health management, especially in contexts where modern medical treatments are limited or unaffordable.

ISM Formulation: Key Herbs Used in Polyherbal Formulations

- **Overview**:
  The ISM (Indian Siddha Medicine) formulation is an ancient polyherbal remedy specifically designed to protect against liver-related diseases such as hepatitis B, cirrhosis, and alcohol-induced liver damage.
- **Composition**:
  The ISM formulation consists of 15 herbs, each with hepatoprotective effects. The composition is as follows (per 5 ml):

Table 1.1. Composition of ISM

S.No	Plant Name	Quantity per 5 ml
1	*Phyllanthus amarus*	5 mg
2	*Fumaria vaillantii*	5 mg
3	*Ionidium suffruticosam*	5 mg
4	*Evolvulus alsinoides*	5 mg
5	*Hibiscus rosasinensis*	5 mg
6	*Wedelia calendulacea*	5 mg
7	*Murraya koengii*	5 mg
8	*Hydrocotyle asiatica*	5 mg
9	*Solanum nigrum*	1 mg
10	*Andrographis paniculata*	1 mg
11	*Cuminum cuminum*	1 mg
12	*Foeniculum vulgare*	1 mg
13	*Vitis vinifera*	1 mg
14	*Emblica officinalis*	1 mg
15	*Cyperus rotundus*	1 mg

Significance:

The ISM formulation seeks to harness the protective and regenerative properties of these herbs to support liver health and combat the adverse effects of modern medicinal treatments.

The integration of herbal remedies within the traditional Indian medical systems, especially the Siddha system, provides a promising avenue for liver disease management. With

ongoing research into their efficacy and safety, formulations like ISM present a natural alternative that may complement or provide alternatives to conventional treatments.

- Hindi: Kokam
- Sanskrit: Amlavetasa

- **Hepatoprotective Properties:**

Fig. 1: ***Fumaria vailantii***

- Exhibits protective effects against carbon tetrachloride-induced hepatotoxicity (Orhan *et al*., 2012).

1.6.1 Ionidium suffruticosam

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Malpighiales
  - Family: Violaceae
  - Genus: Ionidium
  - Species: suffruticosam
- **Vernacular Names:**
  - Tamil: Orilaiththamarai
  - Hindi: Ratanpurus
  - Sanskrit: Charati
- **Hepatoprotective Properties:**

Fig. 2: ***Ionidium suffruticosam***

- Studies show hepatoprotective activity against CCl4-induced liver injury (Chiang *et al*., 2013; Weigt *et al*., 2011).

1.6.2 Evolvulus alsinoides

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Solanales
  - Family: Convolvulaceae
  - Genus: Evolvulus
  - Species: alsinoides
- **Vernacular Names:**
  - Tamil: Vishnukranthi
  - Hindi: Phooli
  - Sanskrit: Visnukranta
- **Hepatoprotective Properties:**

Fig. 3: ***Evolvulus alsinoides***

  - Exhibits anticancer, antimicrobial, antioxidant, and antidiabetic activities.

1.6.3 Hibiscus rosasinensis

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Malvales
  - Family: Malvaceae
  - Genus: Hibiscus
  - Species: rosasinensis
- **Vernacular Names:**
  - Tamil: Chemparuthi
  - Hindi: Gudhal
  - Sanskrit: Aruna
- **Hepatoprotective Properties:**

Fig. 4: ***Hibiscus rosasinensis*****is**

- Demonstrates antioxidant effects and hepatoprotective activity against CCl4 and azathioprine-induced toxicity.

Wedelia calendulaceae

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Spermatopsida
  - Order: Asterales
  - Family: Compositae
  - Genus: Wedelia
  - Species: calendulaceae
- **Vernacular Names:**
  - Tamil: Acalomi
  - Hindi: Bhangra
  - Sanskrit: Bhringaraja
- **Hepatoprotective Properties:**

Fig. 5: ***Wedelia calendulacea***

  - Shows hepatoprotective effects in paracetamol-induced liver damage (Carmel and Rajasekaran, 2011).

Murraya koenigii

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Sapindales
  - Family: Rutaceae
  - Genus: Murraya
  - Species: koenigii
- **Vernacular Names:**
  - Tamil: Karivembu / Kariveppilai
  - Hindi: Bursunga
  - Sanskrit: Alakavhaya
- **Hepatoprotective Properties:**

Fig. 6: ***Murraya koenigii***

- Used in multiple ancient medicine systems, shows antioxidant properties and hepatoprotective activity against lead-induced hepatotoxicity.

Hydrocotyle asiatica

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Apiales
  - Family: Umbelliferae
  - Genus: Centella
  - Species: asiatica
- **Vernacular Names:**
  - Tamil: Vallarai
  - Hindi: Brahmamanduki
  - Sanskrit: Bheka-parni

- **Hepatoprotective Properties:**

Fig. 7: ***Centella asiatica***

- Demonstrates hepatoprotective activity against carbon-tetrachloride-induced liver injury.

Solanum nigrum

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Solanales
  - Family: Solanaceae
  - Genus: Solanum

- Species: nigrum

- **Vernacular Names:**
  - Tamil: Manathakkali
  - Hindi: Chirpoti
  - Sanskrit: Bahuphala

- **Hepatoprotective Properties:**

Fig. 8: ***Solanum nigrum***

  - Exhibits hepatoprotective effects against CCl4-induced oxidative damage and thioacetamide-induced liver fibrosis.

Andrographis paniculata

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Lamiales
  - Family: Acanthaceae
  - Genus: Andrographis
  - Species: paniculata
- **Vernacular Names:**
  - Tamil: Nila vembu
  - Hindi: Kalmegh
  - Sanskrit: Bhunimba
- **Hepatoprotective Properties:**

Fig. 9: ***Andrographis paniculata***

- Used extensively as a hepatoprotective agent, showing benefits against liver damage from various hepatotoxic agents.

Cuminum cyminum

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Apiales
  - Family: Apiaceae
  - Genus: Cuminum
  - Species: cyminum
- **Vernacular Names:**
  - Tamil: Cheerakam
  - Hindi: Jeera
  - Sanskrit: Ajaji

- **Hepatoprotective Properties:**

Fig. 10: ***Cuminum cyminum***

- Known for protective activity against liver toxicity, exhibiting antioxidant and antimicrobial effects.

Foeniculum vulgare

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Apiales
  - Family: Apiaceae
  - Genus: Foeniculum
  - Species: vulgare
- **Vernacular Names:**
  - Tamil: Sombu
  - Hindi: Saunf
  - Sanskrit: Madhura
- **Hepatoprotective Properties:**

Fig. 11: ***Foeniculum vulgare***

- Shows hepatoprotective effects on carbon-tetrachloride-induced fibrosis.

Vitis vinifera

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Vitales
  - Family: Vitaceae
  - Genus: Vitis
  - Species: vinifera
- **Vernacular Names:**
  - Tamil: Thiratchai
  - Hindi: Angoor
  - Sanskrit: Amrtaphala
- **Hepatoprotective Properties:**

Fig. 12: ***Vitis vinifera***

- Exhibits various biological activities including hepatoprotective effects against carbon tetrachloride-induced liver damage.

Emblica officinalis

- **Classification:**
  - Kingdom: Plantae
  - Division: Angiospermae
  - Class: Dicotyledonae
  - Order: Geraniales

- Family: Euphorbiaceae
- Genus: Emblica
- Species: officinalis

- **Vernacular Names:**
  - Tamil: Nellikai
  - Hindi: Amla
  - Sanskrit: Amla
- **Hepatoprotective Properties:**

Fig. 13: ***Emblica officinalis***

- Displays hepatoprotective activity against aflatoxin B1 and CCl4-induced hepatotoxicity.

Cyperus rotundus

- **Classification:**
  - Kingdom: Plantae
  - Division: Tracheophyta
  - Class: Magnoliopsida
  - Order: Poales
  - Family: Cyperaceae
  - Genus: Cyperas
  - Species: rotundus
- **Vernacular Names:**
  - Tamil: Koraipul
  - Hindi: Doongia
  - Sanskrit: Kachhola
- **Hepatoprotective Properties:**

Fig. 14: ***Cyperus rotundus***

Cyperus rotundus, commonly known as nutgrass, is a species rich in therapeutic properties. The rhizomes of *Cyperus rotundus* have long been used in Asian countries,

valued for their medicinal properties. Traditional folk medicine relies on the plant for various biological activities, with recent studies confirming its potential in modern therapeutic applications.Among the most notable properties of *Cyperus rotundus* is its **hepatoprotective activity**. The rhizome extracts demonstrate significant protection against liver damage, particularly in cases of carbon tetrachloride-induced hepatotoxicity. Its essential oils are rich in compounds with **anti-inflammatory properties**, contributing further to its role in liver health. Studies also show that *Cyperus rotundus* provides protection against **paracetamol-induced liver toxicity**, highlighting its potential as a natural remedy for drug-induced liver damage.

According to research, the role of natural products in **hepatoprotection** is crucial. Herbal medicine, particularly from the **Indian System of Medicine (ISM)**, offers valuable insight into treating ailments such as alcoholic liver injury. Phytochemicals—bioactive compounds found in plants—have become a cornerstone in identifying novel molecules that might serve as potential drug candidates. As noted by Starzl (1982), **phytochemical analysis** has paved the way for discovering new medicinal compounds, many of which hold untapped potential in modern medical research.

These 15 herbs continue to hold a revered place in traditional and modern medicine, thanks to their rich array of medicinal properties. Their hepatoprotective effects, along with their role in stabilizing harmful free radicals, make them essential for treating liver ailments. As science continues to explore the potential of natural products, the importance of plants like these 15 herbs in the world of herbal medicine remains undeniable.

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CHAPTER 9

Plant-Based Anti-Cancer Agents and Phytochemicals as Drug Candidates

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ABSTRACT

Cancer remains a leading cause of mortality worldwide, and there is an increasing need for treatments that are both effective and have fewer side effects than conventional therapies. As our understanding of cancer biology grows, plant-based compounds known as phytochemicals have gained attention for their potential in anti-cancer therapy. These bioactive compounds, long used in traditional medicine, are now being studied for their ability to inhibit cancer cell growth, induce apoptosis, and prevent metastasis. Phytochemicals such as curcumin, resveratrol, and EGCG have shown promising anti-cancer properties by targeting specific molecular pathways, promoting programmed cell death, and preventing tumour spread. One key advantage of phytochemicals is their relative safety compared to conventional therapies, as they are generally well-tolerated and exhibit fewer side effects. Additionally, their multi-targeted mechanisms make it harder for cancer cells to develop resistance, unlike many traditional drugs. As research continues, optimizing the bioavailability and delivery of these compounds will be crucial to harness their full therapeutic potential. Phytochemicals offer a promising future in cancer treatment, providing a natural and potentially less toxic alternative to conventional methods.

Keywords: *Phytochemicals, bioactive compounds, traditional medicine, anti-cancer therapy, inhibit cancer cell growth, induce apoptosis*

High-Throughput Screening (HTS) of Phytochemicals for Cancer Treatment

High-throughput screening (HTS) has become an indispensable tool in the realm of drug discovery, particularly for identifying new plant-based compounds with anti-cancer potential. This advanced technology enables the simultaneous testing of thousands of compounds, streamlining the search for bioactive molecules that can be developed into effective cancer treatments. The need for novel therapeutic agents is ever-growing, given the complexity of cancer and the limitations of current treatments. Through the systematic screening of natural compounds, HTS offers a rapid and efficient means of discovering lead compounds that exhibit significant anti-cancer activities, such as the ability to induce apoptosis, inhibit angiogenesis, or disrupt key molecular pathways associated with tumor progression.

Central to HTS is the automation and robotic handling of large compound libraries, allowing researchers to test a vast array of phytochemicals derived from diverse plant species. This technological approach has revolutionized the discovery process by dramatically increasing the throughput of chemical screening and reducing the time and labor required to identify potential drug candidates. In the context of cancer therapy, the goal of HTS is to isolate compounds that can selectively target cancer cells while minimizing harm to normal cells. Many of the plant-based compounds identified through HTS have

exhibited such selectivity, leading to the development of highly effective chemotherapeutic agents.

One of the most notable successes of HTS in identifying plant-based cancer treatments is the discovery of **taxanes**, a class of diterpenes derived from the bark of the Pacific yew tree (*Taxus brevifolia*). Paclitaxel, a taxane discovered in the 1960s through systematic screening, has since become one of the most used chemotherapy drugs, particularly in the treatment of breast, ovarian, and non-small cell lung cancers. Paclitaxel works by stabilizing microtubules and preventing their disassembly, which disrupts cell division and leads to cancer cell death. Its success in clinical settings has spurred further exploration of taxane derivatives, such as docetaxel, which has also been approved for various cancer types. The discovery of taxanes illustrates the power of HTS in identifying potent anti-cancer agents from plant sources.

Another significant breakthrough achieved through HTS is the discovery of **vinca alkaloids**, such as vinblastine and vincristine, from the Madagascar periwinkle (*Catharanthus roseus*). These alkaloids are now widely used in chemotherapy regimens for treating Hodgkin's lymphoma, leukemia, and other cancers. Like taxanes, vinca alkaloids interfere with microtubule dynamics, but instead of stabilizing them, they inhibit microtubule formation, preventing cancer cells from dividing. The identification of these alkaloids highlights the diverse mechanisms through which plant-based compounds can target cancer cells, making them invaluable in the development of multi-targeted cancer therapies.

Flavonoids, a group of polyphenolic compounds found in many fruits and vegetables, have also gained attention for their anti-cancer properties. Through HTS, researchers have identified flavonoids such as quercetin and kaempferol, which exhibit strong anti-cancer activities by modulating several signaling pathways involved in cell proliferation, apoptosis, and metastasis. These compounds not only act as antioxidants, neutralizing free radicals that can lead to DNA damage and cancer, but also inhibit key enzymes involved in cancer progression. Flavonoids are particularly attractive for cancer prevention and therapy because of their low toxicity and ability to target multiple cellular processes simultaneously.

As HTS continues to evolve, researchers are expanding their efforts to include underexplored and previously unstudied plant species. This is particularly important in the field of **ethnobotany**, where traditional knowledge about medicinal plants is being leveraged to identify new sources of bioactive compounds. Indigenous cultures have long used plants for healing, and their knowledge often points scientists toward species with untapped therapeutic potential. For example, many plants used in traditional Chinese, Ayurvedic, and African medicine have yielded promising anti-cancer compounds when subjected to HTS. By integrating ethnobotanical insights with modern screening technologies, researchers can uncover novel phytochemicals that may have been overlooked by conventional drug discovery approaches.

However, while HTS has been highly successful in identifying plant-based anti-cancer agents, there are challenges to overcome. One significant hurdle is ensuring the **bioavailability** of these compounds. Many phytochemicals, though potent in laboratory settings, have poor solubility or are rapidly metabolized in the human body, limiting their effectiveness as therapeutic agents. To address this, researchers are exploring strategies such as chemical modification of phytochemicals to improve their pharmacokinetic

properties, the use of **nanoparticle delivery systems**, and combination therapies that enhance the efficacy of plant-based compounds. Such advancements are critical for translating the success of HTS from the laboratory to clinical applications.

Through this technology, compounds such as taxanes, vinca alkaloids, and flavonoids have been identified and developed into some of the most effective cancer treatments available today. The integration of ethnobotanical knowledge with HTS holds great promise for discovering new anti-cancer compounds from underexplored plant species. As researchers continue to address challenges related to bioavailability and drug delivery, the future of plant-based cancer therapies looks increasingly bright, offering the potential for safer, more effective treatments that target cancer cells while minimizing harm to patients.

Nanotechnology-Enhanced Delivery Systems for Phytochemicals

One of the critical challenges in the development of plant-based drugs, particularly phytochemicals, for cancer treatment is their **bioavailability**. Bioavailability refers to the extent and rate at which a drug or compound is absorbed into the bloodstream and reaches its target tissues in effective concentrations. Many phytochemicals, despite showing significant anti-cancer potential in *in vitro* studies (laboratory tests on cells), face limitations when tested *in vivo* (in living organisms) due to their poor solubility, rapid metabolism, and degradation within the body. Compounds like **curcumin**, derived from turmeric, and **resveratrol**, found in grapes, are excellent examples of phytochemicals with demonstrated anti-cancer properties in preclinical studies. Curcumin, for instance, has shown the ability to induce apoptosis, inhibit angiogenesis, and modulate various cancer-related signaling pathways. However, its hydrophobic nature, poor absorption, and rapid clearance from the body severely limit its therapeutic potential. Similarly, resveratrol exhibits anti-inflammatory, antioxidant, and anti-cancer effects but suffers from poor bioavailability due to its rapid metabolism and elimination. These limitations underscore the need for innovative strategies to enhance the delivery and efficacy of such phytochemicals in cancer therapy.

Nanotechnology has emerged as a promising solution to overcome the bioavailability issues associated with phytochemicals. By employing nanoscale delivery systems, researchers can enhance the solubility, stability, and controlled release of phytochemicals, enabling them to remain in circulation for longer periods and reach their intended target tissues more effectively. One such strategy is **nano-encapsulation**, where phytochemicals are enclosed within nanocarriers such as **liposomes**, **polymeric nanoparticles**, and **dendrimers**. These nanocarriers protect sensitive compounds from degradation, improve their solubility in biological environments, and allow for controlled release, ensuring that the phytochemicals are delivered at therapeutic concentrations to the cancer cells. For example, studies have shown that curcumin encapsulated in liposomes or polymeric nanoparticles exhibits significantly improved bioavailability and anti-cancer efficacy in preclinical models compared to free curcumin. The use of nanocarriers not only enhances the stability and solubility of these compounds but also prolongs their circulation time in the bloodstream, giving them a greater chance to exert their therapeutic effects on tumor cells.

In addition to improving bioavailability, nanotechnology enables **targeted delivery systems**, a key advancement in cancer therapy. Targeted delivery involves using nanocarriers that are equipped with specific molecules, such as antibodies, ligands, or

peptides, that recognize and bind to cancer-specific markers. These markers, often overexpressed on the surface of cancer cells, allow nanocarriers to selectively deliver their therapeutic payloads directly to the tumor, minimizing damage to healthy tissues and reducing systemic side effects. For instance, **curcumin-loaded nanoparticles** that are modified with targeting ligands have shown enhanced accumulation in cancer cells and improved anti-tumor effects in animal models compared to non-targeted curcumin formulations. This targeted approach is particularly beneficial in cancer therapy, where the goal is to selectively kill cancer cells without harming normal cells, thus improving patient outcomes and quality of life.

Another exciting development in nanotechnology-based delivery systems is the use of **gold and silver nanoparticles** as carriers for anti-cancer phytochemicals. Gold and silver nanoparticles offer unique advantages, not only as drug delivery systems but also for their intrinsic anti-cancer properties. These metal nanoparticles can induce **localized hyperthermia**, a process where they absorb light or heat energy and convert it into thermal energy, raising the temperature of the surrounding cancer cells to induce cell death. When used in conjunction with phytochemicals, such as curcumin or resveratrol, gold and silver nanoparticles can enhance the overall therapeutic effect by combining the anti-cancer properties of the phytochemical with the tumor-killing capabilities of hyperthermia. For example, studies have shown that **curcumin-loaded gold nanoparticles** not only improve the bioavailability and stability of curcumin but also synergize with hyperthermia to effectively inhibit cancer cell growth. The dual action of these nanoparticles—improving phytochemical delivery and exerting direct anti-tumor effects—makes them a highly promising avenue for future cancer treatments.

By addressing the bioavailability challenges that limit the effectiveness of these compounds, nanocarriers such as liposomes, polymeric nanoparticles, and gold and silver nanoparticles provide a means of delivering phytochemicals at therapeutic concentrations to cancer cells. Moreover, the ability to design targeted delivery systems further improves the specificity and safety of these treatments. As research in this area continues to advance, nanotechnology-enhanced phytochemical delivery systems hold great promise for the development of safer, more effective cancer therapies that harness the therapeutic potential of natural compounds.

Phytochemicals in Combination Therapies with Conventional Cancer Treatments

The integration of **phytochemicals** into combination therapies alongside traditional cancer treatments has gained significant attention due to their potential to enhance therapeutic efficacy while minimizing adverse effects. **Combination therapies** capitalize on the synergistic interactions between phytochemicals and conventional drugs, leading to more potent anti-cancer responses. This strategy not only helps to improve the overall effectiveness of treatment but also reduces the required doses of toxic chemotherapeutic agents, thus lowering the risk of side effects typically associated with cancer treatments. The use of phytochemicals, derived from plants, has become an attractive adjunct therapy because of their ability to target multiple cancer-related pathways, modulate immune responses, and protect normal cells from the collateral damage caused by conventional therapies such as chemotherapy and radiation.

One of the most extensively studied phytochemicals in combination therapy is **curcumin**, a bioactive compound derived from turmeric. Curcumin has demonstrated

remarkable potential in sensitizing cancer cells to chemotherapy and radiation therapy. One of the primary mechanisms through which curcumin exerts its effects is by inhibiting key signaling pathways involved in cancer progression, including **NF-kB** (nuclear factor kappa B), **STAT3** (signal transducer and activator of transcription 3), and **COX-2** (cyclooxygenase-2). These pathways are associated with inflammation, cell survival, and cancer cell proliferation. By modulating these pathways, curcumin enhances the apoptotic response of cancer cells to chemotherapeutic agents like **cisplatin** and **paclitaxel**, leading to more effective tumor suppression. Studies have also shown that curcumin has a protective effect on normal cells, reducing the toxic impact of chemotherapy and radiation on healthy tissues. This dual function makes curcumin an ideal candidate for combination therapies aimed at improving the efficacy of existing treatments while minimizing side effects

Moreover, **resveratrol**, a polyphenolic compound found in grapes and other fruits, has been identified as another promising phytochemical for combination cancer therapies. Resveratrol has exhibited **synergistic effects** when combined with chemotherapy and radiotherapy, particularly in enhancing the sensitivity of cancer cells to these treatments. One of the challenges in cancer treatment is the development of drug resistance, which significantly hampers the effectiveness of chemotherapeutic agents. Resveratrol helps to overcome this by inhibiting various **drug resistance mechanisms** in cancer cells, including the expression of **drug efflux pumps** and the activation of survival pathways like **PI3K/Akt** and **MAPK** (mitogen-activated protein kinase). Additionally, resveratrol enhances **apoptosis** (programmed cell death) in cancer cells by modulating **p53**, a tumor suppressor protein, and downregulating **Bcl-2**, an anti-apoptotic protein. These actions make resveratrol a powerful adjunct to conventional therapies, as it can amplify the cytotoxic effects of drugs while also promoting the elimination of drug-resistant cancer cells.

Another exciting area of research is the combination of phytochemicals with **immunotherapy**, an emerging approach in cancer treatment that leverages the body's immune system to target and destroy cancer cells. Phytochemicals like **quercetin**, a flavonoid found in apples, onions, and berries, and **epigallocatechin gallate** (**EGCG**), a catechin derived from green tea, have demonstrated immunomodulatory properties that can enhance the efficacy of immunotherapeutic agents. Quercetin has been shown to modulate immune responses by inhibiting the release of pro-inflammatory cytokines and regulating **macrophage** and **T-cell** activity. These immune-modulating effects help to enhance the body's ability to recognize and attack cancer cells, thus boosting the effectiveness of immunotherapy. EGCG, on the other hand, has been found to improve the activity of **dendritic cells** and **natural killer (NK) cells**, both of which play crucial roles in the immune response to tumors. By augmenting the immune system's capacity to combat cancer, these phytochemicals offer a promising avenue for combining natural compounds with modern immunotherapy techniques.

The combination of phytochemicals with conventional cancer treatments also addresses a significant issue in cancer therapy: toxicity to normal cells. Chemotherapy and radiation, while effective at killing cancer cells, are notorious for their non-specific nature, often damaging healthy tissues in the process. Phytochemicals offer a protective role in this regard by selectively targeting cancer cells and sparing normal ones. For instance, curcumin has been shown to protect against **chemotherapy-induced nephrotoxicity** (kidney damage) and **cardiotoxicity** (heart damage), both of which are common side effects of drugs like cisplatin and doxorubicin . This protective effect not only reduces the severity of side effects

but also allows for higher doses of chemotherapy to be administered, potentially improving patient outcomes.

In conclusion, the use of phytochemicals in combination therapies with conventional cancer treatments represents a rapidly evolving field with immense therapeutic potential. By enhancing the effectiveness of chemotherapy, radiotherapy, and immunotherapy, and by reducing the associated toxicities, phytochemicals such as curcumin, resveratrol, quercetin, and EGCG offer new hope for more efficient and safer cancer treatments. As research continues to uncover the molecular mechanisms through which these compounds exert their effects, it is likely that their role in cancer therapy will become increasingly prominent. Combining the natural power of phytochemicals with the precision of modern cancer therapies could pave the way for more holistic, patient-centered approaches to cancer treatment.

Targeted Mechanistic Pathway Inhibition by Phytochemicals

Phytochemicals offer a distinct advantage over conventional chemotherapy by selectively targeting the molecular pathways that drive cancer progression, making them promising agents in cancer therapy. Unlike traditional treatments, which often lead to significant damage to healthy cells due to their non-specific action, **phytochemicals** exhibit precision in targeting dysregulated cancer pathways. This selective approach can significantly reduce the toxicity and side effects commonly seen with chemotherapy. Phytochemicals like **curcumin**, **resveratrol**, and **sulforaphane** have been widely studied for their ability to modulate key signaling pathways involved in cancer development, thus offering a targeted mechanism of action.

Curcumin, derived from turmeric, is a well-documented multi-targeted agent that has demonstrated its ability to modulate several critical pathways in cancer cells. One of the most important pathways curcumin affects is the **NF-kB** (nuclear factor kappa B) signaling pathway, which plays a pivotal role in inflammation and cancer cell survival. In cancer, the NF-kB pathway is often constitutively active, contributing to tumor growth, resistance to apoptosis, and metastasis. Curcumin inhibits this pathway, thereby reducing inflammation and promoting apoptosis in cancer cells. Furthermore, curcumin has been shown to affect the **PI3K/Akt/mTOR** pathway, a key regulator of cell growth, proliferation, and survival. This pathway is frequently dysregulated in cancers such as breast, prostate, and lung cancer. By inhibiting this pathway, curcumin helps to arrest the growth of cancer cells and induces programmed cell death, providing a mechanism for its anti-cancer effects.

Another phytochemical with targeted mechanistic action is **resveratrol**, a polyphenol found in grapes and red wine. Resveratrol's effects are largely mediated through the **sirtuin** pathway, particularly **SIRT1**, which is involved in cellular metabolism, DNA repair, and aging. By modulating sirtuin activity, resveratrol has been found to suppress cancer cell growth in types of cancers that are closely linked to metabolic dysregulation, such as breast and prostate cancers. In addition to its effects on sirtuin pathways, resveratrol also influences the **AMPK** (AMP-activated protein kinase) pathway, which regulates energy homeostasis and inhibits cancer cell metabolism. These targeted actions make resveratrol a promising candidate for cancer therapies aimed at metabolic pathways.

Sulforaphane, a compound found in cruciferous vegetables like broccoli, also exhibits potent anti-cancer properties through the modulation of specific molecular pathways. One of the primary mechanisms by which sulforaphane exerts its anti-cancer

effects is by inducing **phase II detoxification enzymes**, which help in neutralizing carcinogens and protecting cells from DNA damage (Zhang *et al*., 1994). Sulforaphane is also known to promote apoptosis in cancer cells by activating the **Nrf2** (nuclear factor erythroid 2–related factor 2) pathway. The activation of Nrf2 enhances the expression of antioxidant response elements, leading to an increase in cellular defense mechanisms against oxidative stress, a known contributor to cancer development. In addition to its effects on detoxification and oxidative stress, sulforaphane also influences **epigenetic modulation**, which involves changes in gene expression without altering the DNA sequence. By inhibiting histone deacetylases (HDACs), sulforaphane can prevent the silencing of tumor suppressor genes, thereby promoting the death of cancer cells and inhibiting their growth.

The ability of phytochemicals to target these critical cancer-related pathways highlights their potential in cancer prevention and treatment. As research continues, these compounds may become integral components of personalized medicine strategies, where therapies are tailored to target the specific molecular abnormalities of everyone's cancer. The use of **multi-targeted phytochemicals** not only offers a way to attack cancer from multiple angles but also holds the promise of developing therapies with fewer side effects and enhanced patient outcomes. The ongoing study of these natural compounds and their molecular targets provides hope for safer, more effective cancer therapies in the future.

Epigenetic Modulation by Phytochemicals

Epigenetic modulation offers a promising avenue in cancer therapy, and phytochemicals have emerged as powerful agents in influencing these mechanisms. Unlike genetic mutations, epigenetic changes such as **DNA methylation**, **histone modification**, and **non-coding RNA expression** are reversible, providing a unique opportunity for therapeutic intervention in cancer. Phytochemicals, which can modulate these epigenetic processes, represent a novel approach in both cancer treatment and prevention.

One of the most studied phytochemicals in this area is **sulforaphane**, found in cruciferous vegetables like broccoli. Sulforaphane has been shown to inhibit **histone deacetylase (HDAC)**, an enzyme that plays a key role in the repression of tumor suppressor genes. HDAC inhibitors work by allowing the reactivation of these suppressed genes, which can lead to the suppression of cancer cell growth and proliferation. This mechanism has been particularly noted in cancers such as prostate cancer, where sulforaphane-mediated HDAC inhibition has demonstrated a significant reduction in tumor growth. By influencing histone acetylation, sulforaphane helps restore normal gene expression patterns, highlighting its potential as an epigenetic therapy.

Another potent epigenetic modulator is **genistein**, an isoflavone found in soy. Genistein exerts its anti-cancer effects through its ability to modulate both **DNA methylation** and **histone modification**. In cancer cells, hypermethylation of DNA at the promoter regions of tumor suppressor genes leads to their silencing. Genistein has been shown to reverse this hypermethylation, effectively reactivating these suppressed genes. This dual action on both DNA methylation and histone acetylation makes genistein a promising candidate for targeting epigenetic abnormalities in cancer cells. It has been particularly effective in breast and prostate cancer models, where it enhances the expression of tumor suppressor genes and inhibits tumor growth.

Epigallocatechin gallate (EGCG), a polyphenol found in green tea, is another phytochemical that influences epigenetic changes, particularly through the inhibition of **DNA methyltransferases (DNMTs)**. DNMTs are responsible for adding methyl groups to DNA, a process that often leads to the silencing of tumor suppressor genes. By inhibiting DNMT activity, EGCG can demethylate these regions of DNA, thereby reactivating critical tumor suppressor genes and inhibiting cancer progression. In addition to its effects on DNA methylation, EGCG has been shown to modulate histone acetylation, further enhancing its epigenetic regulatory capabilities. The ability of EGCG to target multiple epigenetic pathways makes it a strong candidate for use in combination therapies aimed at reversing epigenetic silencing in cancer cells.

Personalized Phytotherapy: Tailoring Treatments Based on Individual Genetic Profiles

Personalized phytotherapy represents a cutting-edge approach to cancer treatment, aligning with the broader trend of **personalized medicine**, where therapies are tailored to the genetic, epigenetic, and molecular characteristics of an individual's cancer. By leveraging advances in **genomic sequencing**, scientists can now identify the specific mutations and dysregulated pathways that are unique to each patient's tumor. This precision allows for the development of customized treatments using phytochemicals, which are plant-derived compounds with therapeutic properties. This targeted approach has the potential to improve treatment outcomes while minimizing side effects, offering a more individualized strategy for cancer care.

Recent developments in **genomics** have significantly contributed to the personalization of cancer therapies. By identifying specific mutations and aberrations in gene expression, researchers can select phytochemicals that interact with these pathways, thereby improving their efficacy. For instance, **genistein**, a soy isoflavone, has shown promise in breast cancers that harbor mutations in the estrogen receptor pathway. These estrogen-dependent cancers can be more effectively targeted by genistein, which exerts its anti-cancer effects by modulating estrogen receptor activity and regulating the expression of estrogen-related genes. This makes genistein an ideal candidate for inclusion in personalized treatments for breast cancer patients with these specific genetic profiles.

Personalized phytotherapy represents a significant advancement in the treatment of cancer, merging the benefits of plant-based therapies with the precision of modern genomic and molecular technologies. As research continues to uncover the complex interactions between phytochemical and cancer-related pathways, it is becoming increasingly feasible to customize these treatments to the genetic and molecular makeup of each patient. This approach not only promises to enhance the effectiveness of cancer therapies but also to reduce the toxicity and improve the quality of life for patients undergoing treatment. The future of cancer care lies in this personalized, integrative approach, where **nature's compounds** are matched to the unique genetic profiles of individuals for optimal therapeutic outcomes.

Discussion

The ability of phytochemicals to target specific molecular pathways, modulate epigenetic changes, and act as immune boosters is driving new strategies in cancer prevention, treatment, and recurrence prevention. For instance, the immune-modulating properties of certain phytochemicals can enhance the efficacy of immunotherapeutic

agents, improving the body's natural defenses against cancer. As research continues to uncover the mechanisms behind these natural compounds, the integration of phytochemicals into mainstream oncology could lead to safer, more effective, and less toxic cancer therapies grounded in nature's pharmacopoeia. Additionally, addressing key challenges such as the bioavailability of phytochemicals is critical for their successful application in clinical settings. Innovative delivery systems, such as liposomes and micelles, are being developed to enhance the absorption and efficacy of these compounds. Sustainability is also a vital consideration; by exploring underutilized medicinal plants and employing sustainable harvesting practices, researchers can ensure the continued availability of these valuable resources while protecting biodiversity.

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Emerging Trends in Therapeutic Agents from Medicinal Plants (ISBN 9788196618377)

CHAPTER 10

Therapeutic Potential of Curcuminoids

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ABSTRACT

Curcuminoids, the bioactive compounds found in turmeric (Curcuma longa), have garnered significant attention in recent years due to their potential health benefits. These compounds, primarily curcumin, demethoxycurcumin, and bisdemethoxycurcumin, have been studied extensively for their antioxidant, anti-inflammatory, and anti-cancer properties. This chapter will delve into the diverse roles of curcuminoids in promoting health and combating various diseases.

Keywords: *Curcumin, Curcuminoids, human health, turmeric*

Curcuminoids: A Brief Overview

Curcuminoids are polyphenols derived from turmeric, a spice commonly used in Indian and Asian cuisine. Curcumin, the most abundant curcuminoid, is responsible for turmeric's distinctive yellow colour. The other two major curcuminoids, desmethoxycurcumin and bisdemethoxycurcumin, have similar structures but differ in the number of methoxy groups

Pharmacological Properties of Curcuminoids

Curcuminoids possess a wide range of pharmacological properties that contribute to their potential health benefits. These properties include:

- **Antioxidant activity:** Curcuminoids can neutralize free radicals, protecting cells from oxidative damage.
- **Anti-inflammatory effects:** They inhibit the production of inflammatory mediators, reducing inflammation and tissue damage.
- **Anti-cancer properties:** Curcuminoids have been shown to inhibit cancer cell growth, invasion, and metastasis.
- **Neuroprotective effects:** They may protect brain cells from damage and improve cognitive function.

- **Cardiovascular benefits:** Curcuminoids can help regulate blood pressure, cholesterol levels, and blood clotting.
- **Anti-diabetic effects:** They may improve insulin sensitivity and glucose metabolism.

Role of Curcuminoids in Disease Prevention and Treatment

Curcuminoids have been investigated for their potential to prevent and treat a variety of diseases. Some of the key areas of research include:

- **Cancer:** Curcuminoids have been studied for their potential to inhibit cancer cell growth, invasion, and metastasis in various types of cancer, including breast, colon, prostate, and pancreatic cancer.
- **Neurodegenerative diseases:** Curcuminoids have shown promise in reducing oxidative stress and inflammation in the brain, which may help prevent or delay the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's disease.
- **Cardiovascular disease:** Curcuminoids may help reduce the risk of cardiovascular disease by lowering cholesterol levels, improving blood flow, and preventing blood clots.
- **Diabetes:** Curcuminoids have been investigated for their potential to improve insulin sensitivity and glucose metabolism, which may help manage diabetes.
- **Inflammatory diseases:** Curcuminoids can help reduce inflammation, which is involved in many chronic diseases, including arthritis, asthma, and inflammatory bowel disease.

Challenges and Future Directions

Despite the promising potential of curcuminoids, there are several challenges that need to be addressed before they can be widely used as therapeutic agents. These challenges include:

- **Low bioavailability:** Curcuminoids are poorly absorbed from the gastrointestinal tract, limiting their effectiveness.
- **Lack of long-term safety data:** While curcuminoids are generally considered safe, more research is needed to assess their long-term safety.
- **Limited clinical evidence:** Although preclinical studies have been promising, more clinical trials are needed to establish the efficacy of curcuminoids in treating various diseases.

To overcome these challenges, researchers are exploring various strategies, such as formulating curcuminoids with bioavailability enhancers, developing curcuminoid derivatives with improved properties, and conducting larger clinical trials. Curcuminoids

are a group of bioactive compounds with significant potential for promoting health and preventing disease. Their antioxidant, anti-inflammatory, and anti-cancer properties have made them the subject of intense research. While there is still much to learn about the full extent of their benefits, the evidence to date suggests that curcuminoids could play a valuable role in maintaining health and combating various chronic diseases.

The Chemistry and Biochemistry of Curcuminoids

Curcuminoids, the bioactive compounds found in turmeric, are polyphenols with unique chemical structures that contribute to their diverse pharmacological properties. This chapter will delve into the chemistry and biochemistry of curcuminoids, including their structure, properties, and metabolism.

Chemical Structure of Curcuminoids

Curcuminoids are derived from ferulic acid and have a diarylheptanoid structure. The three major curcuminoids, curcumin, desmethoxycurcumin, and bisdemethoxycurcumin, differ in the number of methoxy groups attached to their aromatic rings.

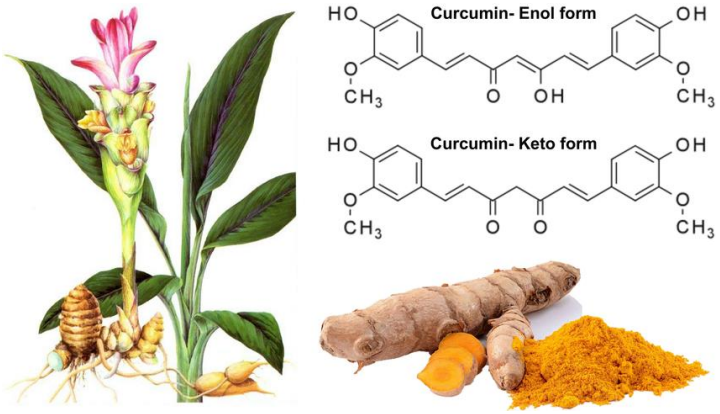

Figure 1 : Curcumin and Turmeric

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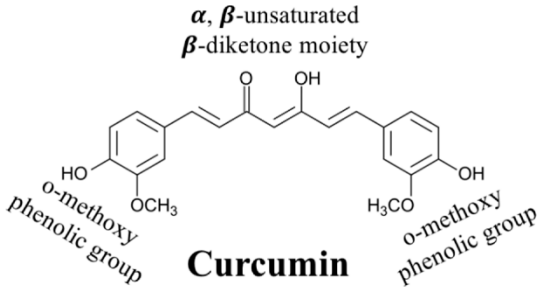

Figure 2 : Curcumin Structure

- **Curcumin:** Contains two methoxy groups.
- **Desmethoxycurcumin:** Contains one methoxy group.
- **Bisdemethoxycurcumin:** Contains no methoxy groups.

The chemical structure of curcuminoids is shown below:

Physical and Chemical Properties of Curcuminoids

Curcuminoids have several physical and chemical properties that influence their bioavailability, stability, and biological activity:

- **Color :** Curcuminoids are yellow pigments.
- **Solubility:** They are poorly soluble in water but readily soluble in organic solvents.
- **Stability:** Curcuminoids are relatively unstable, particularly under alkaline conditions and in the presence of light and heat.
- **Reactivity:** They can undergo various chemical reactions, such as oxidation, reduction, and conjugation.

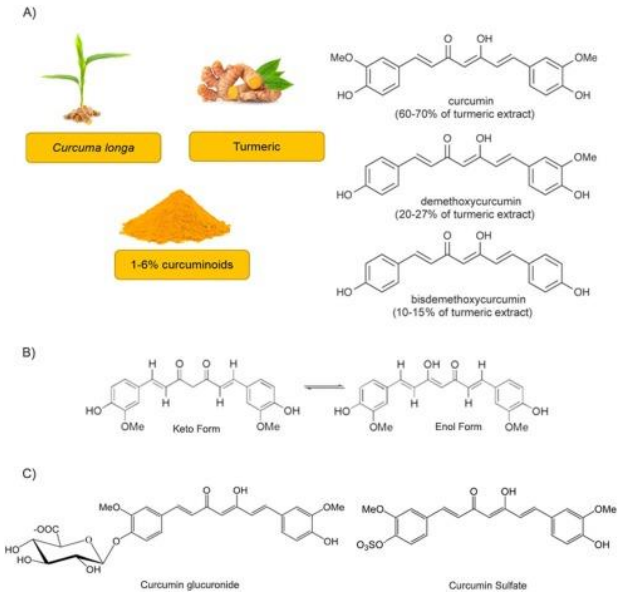

Figure 3 : Structures of Curcuminoids

Biochemistry of Curcuminoids

The bioavailability and bioactivity of curcuminoids are influenced by their metabolism and interactions with biological molecules.

- **Absorption:** Curcuminoids are poorly absorbed from the gastrointestinal tract due to their low solubility and rapid metabolism.

- **Metabolism:** Curcuminoids are extensively metabolized in the liver and intestines, primarily through conjugation with glucuronic acid and sulfate.
- **Distribution:** Once absorbed, curcuminoids are distributed throughout the body, including the brain, liver, and kidney.
- **Excretion:** The metabolites of curcuminoids are primarily excreted in the faces and urine.

Challenges in Studying Curcuminoids

The study of curcuminoids is challenging due to several factors:

- **Low bioavailability:** The low bioavailability of curcuminoids makes it difficult to achieve therapeutic concentrations in the body.
- **Chemical instability:** Curcuminoids are relatively unstable, which can affect their efficacy and safety.
- **Complex metabolism:** The complex metabolism of curcuminoids can make it difficult to understand their pharmacokinetics and pharmacodynamics.

Strategies to Improve Curcuminoid Bioavailability and Stability

To overcome the challenges associated with curcuminoids, researchers have explored various strategies to improve their bioavailability and stability:

- **Formulation:** Curcuminoids can be formulated with bioavailability enhancers, such as cyclodextrins or liposomes.
- **Derivatization:** Curcuminoid derivatives with improved properties, such as increased solubility or stability, can be synthesized.
- **Combination therapies:** Curcuminoids can be combined with other compounds that can enhance their absorption or biological activity.

The chemistry and biochemistry of curcuminoids play a crucial role in determining their bioavailability, stability, and biological activity. By understanding the unique properties of curcuminoids, researchers can develop strategies to improve their effectiveness as therapeutic agents.

Curcuminoids and Oxidative Stress

Oxidative stress, a condition characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defence mechanisms, is implicated in a wide range of diseases. Curcuminoids, with their potent antioxidant properties, have been extensively studied for their potential to mitigate oxidative stress and protect cells from damage.

Reactive Oxygen Species (ROS)

ROS are highly reactive molecules that can cause damage to cellular components, including DNA, proteins, and lipids. Common ROS include:

- **Superoxide anion (O2-)**
- **Hydrogen peroxide (H2O2)**
- **Hydroxyl radical (OH-)**

Excessive ROS production can lead to oxidative stress, which is associated with various diseases, such as cardiovascular disease, neurodegenerative disorders, and cancer.

Antioxidant Properties of Curcuminoids

Curcuminoids possess potent antioxidant properties that enable them to neutralize ROS and protect cells from oxidative damage. These properties are attributed to their ability to:

- **Scavenge free radicals:** Curcuminoids can directly interact with ROS, neutralizing them and preventing their harmful effects.
- **Chelate metal ions:** Curcuminoids can chelate metal ions, such as iron and copper, which can catalyse the production of ROS.
- **Induce antioxidant enzymes:** Curcuminoids can upregulate the expression of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, which help to neutralize ROS.

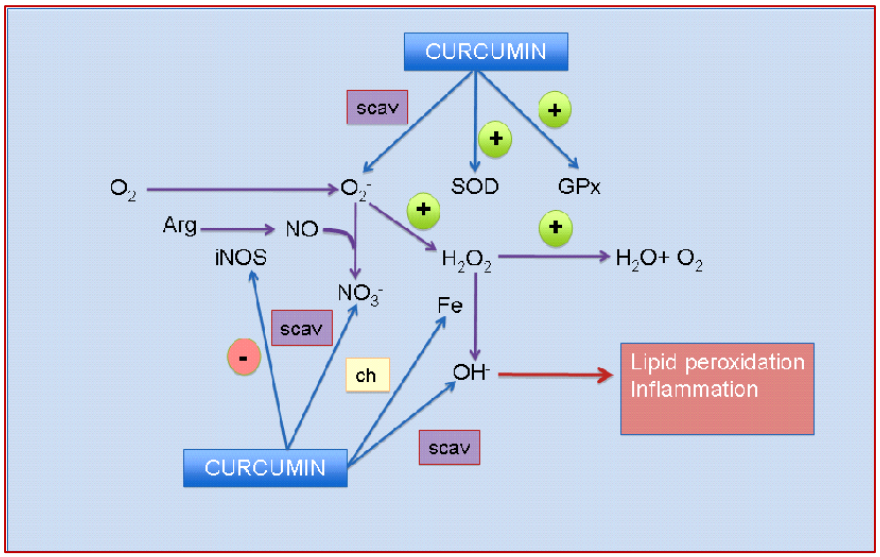

Figure 4 : Antioxidant properties of Curcumin

Role of Curcuminoids in Preventing Oxidative Stress-Related Diseases

Curcuminoids have been investigated for their potential to prevent or delay the progression of various oxidative stress-related diseases, including:

- **Cardiovascular disease:** Curcuminoids can help reduce oxidative stress in the cardiovascular system, protecting blood vessels from damage and reducing the risk of heart disease.
- **Neurodegenerative diseases:** Curcuminoids may help protect brain cells from oxidative damage, which is implicated in neurodegenerative disorders such as Alzheimer's and Parkinson's disease.
- **Cancer:** Oxidative stress can contribute to cancer development and progression. Curcuminoids may help prevent cancer by reducing oxidative damage and inhibiting cancer cell growth.
- **Aging:** Oxidative stress is thought to play a role in aging. Curcuminoids may help slow down the aging process by reducing oxidative damage to cells and tissues.

Mechanisms of Curcuminoids in Preventing Oxidative Stress

The mechanisms by which curcuminoids prevent oxidative stress are complex and involve multiple pathways. Some of the key mechanisms include:

- **Direct scavenging of ROS:** Curcuminoids can directly react with ROS, neutralizing them and preventing their harmful effects.
- **Chelation of metal ions:** Curcuminoids can chelate metal ions, such as iron and copper, which can catalyze the production of ROS.
- **Activation of antioxidant enzymes:** Curcuminoids can upregulate the expression of antioxidant enzymes, such as SOD, catalase, and glutathione peroxidase, which help to neutralize ROS.
- **Modulation of signaling pathways:** Curcuminoids can modulate various signaling pathways involved in oxidative stress, such as the Nrf2-ARE pathway and the NF-κB pathway.

Curcuminoids are potent antioxidants that can help protect cells from oxidative damage and prevent oxidative stress-related diseases. Their ability to scavenge free radicals, chelate metal ions, and induce antioxidant enzymes makes them promising agents for the prevention and treatment of a wide range of health conditions.

Curcuminoids and Inflammation

Inflammation is a complex biological response that plays a crucial role in host defense. However, chronic inflammation can contribute to a variety of diseases, including cardiovascular disease, autoimmune disorders, and cancer. Curcuminoids, with their anti-inflammatory properties, have been investigated for their potential to modulate inflammation and prevent disease.

Inflammation: A Brief Overview

Inflammation is a protective response that involves the activation of immune cells and the release of inflammatory mediators. While acute inflammation is essential for healing wounds and fighting infections, chronic inflammation can lead to tissue damage and disease.

Anti-inflammatory Properties of Curcuminoids

Curcuminoids possess potent anti-inflammatory properties that enable them to reduce inflammation and prevent tissue damage. These properties are attributed to their ability to:

- **Inhibit the production of inflammatory mediators:** Curcuminoids can inhibit the production of various inflammatory mediators, including cytokines, chemokines, and prostaglandins.
- **Modulate signaling pathways:** Curcuminoids can modulate signaling pathways involved in inflammation, such as the NF-κB pathway and the MAPK pathway.
- **Suppress the activation of immune cells:** Curcuminoids can suppress the activation of immune cells, such as macrophages and neutrophils, which contribute to inflammation.

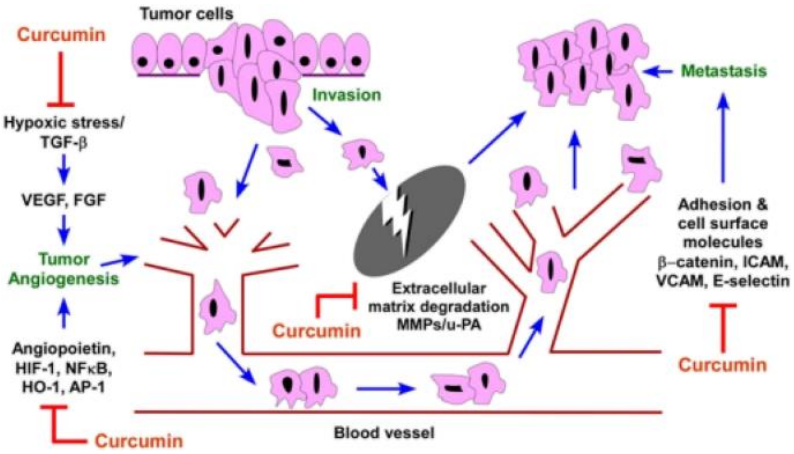

Figure 5 : Effect of Curcumin in enhancing cancer therapy

Role of Curcuminoids in Preventing Inflammatory Diseases

Curcuminoids have been investigated for their potential to prevent or treat various inflammatory diseases, including:

- **Arthritis:** Curcuminoids have been shown to reduce joint inflammation and pain in patients with rheumatoid arthritis and osteoarthritis.
- **Inflammatory bowel disease (IBD):** Curcuminoids may help reduce inflammation in the gut and improve symptoms of IBD, such as diarrhea and abdominal pain.

- **Asthma:** Curcuminoids may help reduce airway inflammation and improve lung function in patients with asthma.
- **Cardiovascular disease:** Chronic inflammation is a risk factor for cardiovascular disease. Curcuminoids may help reduce the risk of cardiovascular disease by modulating inflammation.

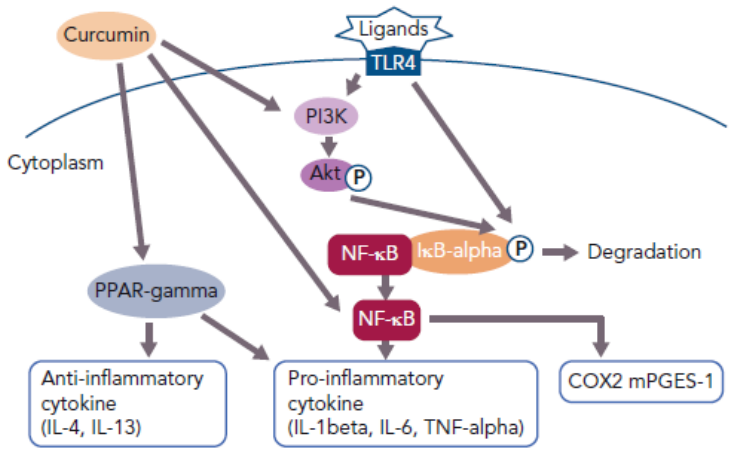

Figure 6 : Mechanism of curcumin mediated anti-inflammatory response

Mechanisms of Curcuminoids in Modulating Inflammation

The mechanisms by which curcuminoids modulate inflammation are complex and involve multiple pathways. Some of the key mechanisms include:

- **Inhibition of NF-κB:** NF-κB is a transcription factor that plays a key role in inflammation. Curcuminoids can inhibit NF-κB activation, reducing the production of inflammatory mediators.
- **Modulation of MAPK signalling:** MAPK signaling pathways are involved in inflammation. Curcuminoids can modulate MAPK signalling, leading to a reduction in inflammation.
- **Suppression of immune cell activation:** Curcuminoids can suppress the activation of immune cells, such as macrophages and neutrophils, which contribute to inflammation.
- **Induction of anti-inflammatory mediators:** Curcuminoids can induce the production of anti-inflammatory mediators, such as interleukin-10 (IL-10).

Conclusion

Curcuminoids are potent anti-inflammatory agents that can help reduce inflammation and prevent disease. Their ability to inhibit the production of inflammatory mediators, modulate signalling pathways, and suppress immune cell activation makes them

promising agents for the prevention and treatment of a wide range of inflammatory conditions.

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CHAPTER 11

Role of Phytomedicine in Cancer Prevention

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ABSTRACT

Cancer is still the world's biggest cause of death. Substantial side effects and disease recurrence provide substantial obstacles despite breakthroughs in treatment alternatives like as radiation, chemotherapy, and immunotherapy. The current research examines the epidemiology of cancer and how medicinal plants shows promising therapeutic properties of bioactive compounds obtained from plants that are employed in contemporary medicine. It also emphasis the role of Allium sativum, Curcumin, Apigenin, Green tea, Genistein, Carotenoids, Resveratrol an effective natural molecule having chemo preventive and chemotherapeutic activities. An increasing number of cancer cases are expected in India by 2035-over 1.7 million additional cases which is made worse by expensive treatment and limited access to care, according to the research. The possibility of phytomedicine as an affordable addition to traditional cancer treatments along with modern treatments could offer more holistic approach to cancer care.

Introduction

Cancer is a serious worldwide health concern, with India's cancer burden projected to quadruple by 2035. Cancer was the biggest cause of mortality in 2012, accounting for 8.2 million deaths and 14 million new cases. The country's epidemiology is complex, with a lack of a national cancer registry, high mortality rates among individuals under the age of 70. The local factors such as tobacco use, smoking, poor hygiene, infections, poverty and restricted treatment availability. Surgery, chemotherapy, radiation and palliative care are all viable treatment choices for cancer. The expense of treatment, including anticancer medications, is substantial and patients frequently endure adverse effects and treatment resistance. Several strategies have been proposed to minimize the expense of cancer treatment while increasing outcomes, including the incorporation of phytomedicine with conventional therapy. However, clinical investigations have yielded inconsistent results. The techniques are limited in terms of illness recurrence and undesirable side effects. Despite their exorbitant cost, synthetic chemotherapeutic drugs have failed clinical studies. Researchers are increasingly focusing on natural medications for cancer therapy and prevention. Natural products provide approximately 60% of the chemotherapeutic chemicals used in cancer treatment, with medicinal plants serving as the primary source The researchers are now concentrating on variables influencing cancer survival and

progression. Inflammation triggers genomic instability and mutations due to autoimmune disorders, infections, and lifestyle variables such as obesity, smoking, and alcohol consumption. Additionally, it controls the growth of cancer and may promote treatment resistance. Developing methods to take advantage of inflammatory pathways for therapeutic and diagnostic purposes will be made easier by better understanding of the function inflammation plays in tumour progression.

Epidemiology

Epidemiological research states with 9.4% of all cancer cases in men and 10.1% in women, colorectal cancer is a global concern. It is most common in industrialized nations affected by the West, with the largest occurrences seen in Australia, New Zealand, Canada, the United States, and portions of Europe. South America, Africa, China, and India are the nations with the lowest danger. According to the National Cancer Registry Programme - 2013, Thiruvananthapuram and Nagaland had the highest yearly incidence rates for males in India, while Aizwal had the highest rates for women. Although studies reveal a decreased incidence among Indian immigrants from nations with high cancer prevalence, India has a low age-standardized rate for colorectal cancer. The studies repeatedly suggest that a high consumption of fruits, vegetables, and whole grains is closely linked to a lower risk of acquiring chronic illnesses such as cancer and heart disease. It is predicted that one-third of all cancer deaths in the United States might be prevented with suitable dietary changes. The National Academy of Sciences of the United States issued guidelines in 1982 highlighting the significance of fruits and vegetables, namely citrus fruits, carotene-rich fruits, and cruciferous vegetables. In 1989, a report advocated eating 5 or more servings of fruits and vegetables per day to lower the risk of cancer and heart disease.

Cancer biomarkers

Biomarkers are biological substances present in the blood, organs, and lymph that indicate whether the body is working properly. Proteins, nucleic acids, antibodies, and peptides can all suggest illness owing to mutations, changes in gene expression, metabolic, and proteomic abnormalities. Biomarkers can be categorized according to disease status, biomolecules, imaging, pathological, or in-silico criteria. Cancer biomarkers can be classified as prognostic, predictive, pharmacodynamic, or diagnostic. Prognostic biomarkers assist predict cancer outcomes and therapy effectiveness, whereas predictive markers give information regarding treatment success or failure.

In recent research two theories, the hierarchical model sometimes called the Cancer stem cells Model (CSCs) and the stochastic model, explain tumorigenesis. CSCs are the principal driver of tumor creation and progression, according to the hierarchical model, whereas the stochastic model proposes that somatic cell transformation causes tumor production. Cancer progenitor cells (CPCs) or altered stem cells undergo repeated symmetric or asymmetric cell divisions to produce CSCs through clonal processes. They cause metastasizing tumor to become more aggressive or to relapse. CSCs serve as molecular biomarkers by expressing certain antigens that aid in their identification and confirmation. These overexpressed indicators are frequently employed in the characterization and isolation of distinct CSC subtypes from populations of drug-resistant cancer cells. The cancer progresses, the epithelial-mesenchymal transition (EMT) modifies the phenotype of tumor cells. Tumor cells must undergo EMT in order to invade and

extravasate, but they must also lose in order to multiply. The mesenchymal-epithelial transition (MET) contributes to the development and proliferation of tumors by increasing their invasiveness and resistance to radiation and chemotherapy.

Potential natural medicine source

Many ailments have been treated with traditional African, Indian, and Chinese methods. With 80,000 of 2,50,000 plant species having therapeutic qualities, animal observation has proven useful in differentiating between dangerous and edible plants. Ayurveda arranged around eight thousand herbal remedies and several writings have listed the pharmacological properties of diverse plant species that are used as medicines. 75–80% of people, according to the WHO, use medicinal herbs to prevent and treat illness. Approximately 11% of the 252 authorized drugs are made from medicinal plants. Medicinal plants include phytochemicals with promising therapeutic properties; bioactive compounds obtained from these plants are employed in contemporary medicine. Since ancient times, some ailments have been treated with antispasmodics, such as scopolamine, atropine, and tropane alkaloids.

The Importance of Phytochemicals

It has been demonstrated that medicinal plants may fight a variety of illnesses, including cancer, to enhance human health. It has also been demonstrated that plant-based chemotherapeutic drugs can support anticancer treatment plans with noticeably fewer side effects. It has become clear that we need to find phytopharmaceuticals as a more effective approach to treat cancer and need to screen plant extracts for bioactive components in order to find new therapies. *In vitro* cell culture experiments have demonstrated the anticancer activity of the majority of medicinal plants documented in the literature. Herbal medicines cytotoxic effects are mostly mediated through apoptosis induction. Where the whole-plant extracts have the ability to effectively kill human cancer cells and may include a variety of bioactive chemicals with anticancer effects. The advantage of employing whole-plant extracts in combination therapy techniques is suggested by the fact that, unlike isolated phytoconstituents, whole-plant extracts include a variety of chemicals that can target diverse intracellular pathways, hence enabling cancer cells to escape from death through several routes. However, significant limits may occur in the general use of herbal products, such as a lack of scientific proof regarding safety and efficacy. More study is needed to determine the therapeutic safety and usefulness of plant-derived extracts and chemicals.

Anticancer mechanism of phytoconstituents

Phytochemicals have been shown to target cancer cells in a variety of ways, including targeting abnormal cells and molecular factors, expressing antioxidant activity, inhibiting cancer cell growth, activating DNA repair genes and protein products, stimulating protective enzyme formation, and modifying cell growth factors. Polyphenols, brassinosteroids, flavonoids and antioxidants combat cancer by inducing apoptosis in cancer cells. Protective enzymes begin and inhibit malignant cell development. *Apigenin* promotes apoptosis in lung cancer cells via inhibiting the leptin receptor pathway. Curcuma inhibits or stimulates the development of human glioblastoma cells via a number of molecular pathways. Cyanidin glycosides inhibit colon cancer cells by inhibiting mitogen-triggered metabolic pathways and decreasing iNOS and COX-2 expression.

Isoflavone and genistein fight cancer by inhibiting the NF-kB and Protein Kinase B signalling pathways. A variety of mechanisms have been demonstrated by Chinese Herbal Medicines (CHMs) to have anti-tumour effects, such as triggering apoptosis, preventing cell division, controlling autophagy, reversing multidrug resistance, stifling angiogenesis, focusing on cancer stem cells, obstructing tumour invasion and metastasis, and controlling the immune system. Certain natural chemicals work on the glycolysis pathways of cancer cells to regulate their development, resistance to drugs, and ability to spread. In addition, CHMs inhibit angiogenic cells, break down the extracellular matrix (ECM), control T and B lymphocytes, natural killer cells, dendritic cells, TAMs, and MDSCs, as well as other immune cells.

Anticancer Phytochemicals

Allium sativum

The Medicinal Plant *Allium sativum* contains therapeutic qualities such as antidiabetic, hypolipidemic, antibacterial, antihypertensive, and anticancer activities. According to epidemiologic research, garlic consumption protects against gastrointestinal malignancies, slows the evolution of colorectal adenomas, and enhances natural-killer cell activity in advanced digestive system cancer patients, potentially reducing cancer-related mortality. Garlic's sulphydryl chemicals, which can prevent cancer-causing molecules, are recognized by the National Cancer Institute as potentially anticancer. Garlic intake has been linked in studies to a lower risk of stomach, colon, esophageal, pancreatic, breast, and prostate cancer. A daily consumption of 10g of garlic can lower the incidence of prostate cancer by 50%.Compounds found in *allium sativum* roots suppress the development of cancer cells and cause apoptosis by activating the phosphoinositide 3-kinase/Akt pathway. S-allylcysteine and S-allylmercaptocysteine found in garlic roots, have proven for anticancer qualities. Garlic extract has been shown to reduce the size and quantity of cancer cells in a clinical experiment including 51 individuals with colon cancer. Moreover, it releases cytokines, activates the spleen, and raises macrophages and natural killer cells.

Curcumin

Curcumin, a polyphenol produced from *Curcuma longa's rhizome*, has been demonstrated to have anticancer effects, including the ability to destroy tumor cells while sparing normal cells. It has been proven to cause apoptosis in numerous cancer cell lines as well as suppress tumor development in animal carcinogenesis models. *Curcumin's* antiproliferative action against multiple myeloma (MM) has been identified in several investigations. It can overcome chemoresistance and increase the action of thalidomide and bortezomib, which are used to treat MM patients. In mouse models, *curcumin* was also found to suppress colonic adenocarcinomas and adenomas.*Curcumin*, a fundamental component of turmeric, has been shown to have anticancer activities, notably in colon, breast, lung, and brain malignancies. It promotes apoptosis in cancer cells but has no deleterious effects on healthy cells, suggesting that it might be a novel mTOR inhibitor. Curcumin regulates tumor cell proliferation via several routes, however its effects can be paradoxical. *Curcumin* promotes cancer cell death by targeting cyclooxygenase-2, NF-kB, TNF-a, and cyclin D1. These targets possess anti-inflammatory and anti-tumorigenic effects. *Curcumin* also inhibits cyclin D1 and CDK-4 expression in breast and skin malignancies, downregulates angiogenic genes, and has therapeutic and chemo preventive applications. It is a cost-effective therapy due to its low toxicity, cheap cost, and ease of availability (George *et al.*,2021).

Apigenin

Apigenin, a flavonoid present in plants such as parsley, celery, and chamomile, exhibits cytotoxic properties against breast and colon cancer cells. It is thought to act as a mediator in the avoidance of chemotherapy and causes autophagia, which may lead to resistance. *Apigenin* also influences the leptin/leptin receptor pathway, causing cell death in lung cancer cell lines. It can also be used to treat hypopigmentation conditions(Wang.H,*et al*.,2012)Fruits and vegetables include a flavonoid called *apigenin*, which has chemopreventive qualities. It inhibits the transformation of cancer cells, triggers apoptosis, and controls signaling pathways. It has been demonstrated that *apigenin* inhibits HPV infections and malignancies linked to tobacco use, especially in human prostate cells. Research conducted in vivo has demonstrated that *apigenin* suppresses the production of the Her2/neu protein in mice with breast cancer, inhibits the PI3K/Akt/Forkhead box O-signaling pathways, and promotes cell cycle arrest and apoptosis. Additionally, *apigenin* decreases platelet aggregation, cell proliferation, plasma LDLs, and enhances biological antioxidant levels (George.B.P,*et al*.,2021).

Green tea

According to the study, EGCG and sulforaphane can work in concert to decrease LPS-induced IκB alpha phosphorylation and promote positive effects in human colon cancer cells. Additionally, the study discovered that in the liver and the gut, EGCG controls 671 Nrf2-dependent and 256 Nrf2-independent genes (Wang.H,*et al*.,2012).Polyphenols present in green tea, such as epigalloacatechin gallate (EGCG), have been shown to lower the amount of leukemia cells in individuals suffering from chronic lymphocytic leukemia (CLL). Additionally, drinking green tea lowers the incidence of prostate, pancreatic, and bladder cancer. It is unable to stop or lessen the recurrence of breast cancer, though. EGCG may improve or prevent the development of cancer by causing cancer cells to die in a manner similar to that of healthy ones.Polyphenols present in green tea, such as epigalloacatechin gallate (EGCG), have been shown to lower the amount of leukemia cells in individuals suffering from chronic lymphocytic leukemia (CLL). Additionally, drinking green tea lowers the incidence of prostate, pancreatic, and bladder cancer (Sarangi,M.K and Padhi,S.,2014).

Genistein

Isoflavones, a kind of flavonoid present in soy foods, are thought to help prevent and treat several types of cancer, including breast and prostate cancer. *Genistein*, the main *isoflavone* in the Leguminosae plant family, competes with 17-β-estradiol in Estrogen Receptor (ER) binding experiments, showing a stronger affinity for ER than ER. In vitro studies suggest that *genistein* suppresses the development of hormone-dependent and hormone-independent cancer cells, and its effects on cellular signaling vary with dosage. *Genistein* also reduces prostate-specific antigen production in androgen-dependent and independent prostate cancer cell lines, bolstering its function as a chemopreventive/therapeutic agent for prostate cancer. (Russo.M,*et al*.,2010).A kind of *isoflavone* that has antiangiogenic properties, *genistein* is an antioxidant and anthelmintic that may be found in plants such as kudzu, lupine, fava beans, soybeans, psoralea, and Flemingia vestita. By blocking the enzymes that control cell division and survival, it may prevent the unchecked cell growth linked to cancer from occurring. Since 70% of breast cancer cases involve overexpressed

estrogen receptors, *genistein* has been proven to be helpful in treating both diseases. Breast cancer and colon cancer growth rates can be accelerated by it since it can attach to estrogen receptors more quickly than 17β-estradiol (Wang.H,*et al*.,2012).

Carotenoids

Colorful terpenoid pigments called *carotenoids* can be found in eggs, meats, vegetables, milk, and some types of fish and crustacean shellfish. They consist of astaxanthin, capsanthine, β-carotene, and lycopene. In addition to being visually appealing, *carotenoids* are powerful antioxidants and essential for the synthesis of nutrients. Due to processes involved in cell development and death, they have been linked to cancer, and ingestion frequently alters their antioxidant capacity. *Carotenoids* also alter the processes involved in cell development and death (Rudzińska.A,*et al*.,2023).Due to their antioxidant qualities, *carotenoids* which are present in fruits, vegetables, and seafood—have potent anti-cancer effects. The DNA and cell membranes that free radicals attack are neutralized by these antioxidants. Non-all *carotenoids* may be converted to vitamin A, unlike what is often believed. The risk of endometrial, breast, prostate, lung, and skin cancer may be reduced by *carotenoids*. The liver cancer cell line HepG2 was shown to be considerably resistant to growth when exposed to astaxanthin, which also caused apoptosis. Genes such as p21CIP1/WAF1, GADD153, and c-myc were also expressed more strongly, indicating possible use in chemoprevention and cancer treatments (Sarangi,M.K and Padhi,S.,2014).

Resveratrol

It has been demonstrated that the *phytoalexin resveratrol*, which is present in berries, peanuts, grapes, and other fruits, inhibits the growth of cancer cells and possesses anti-inflammatory and antioxidant properties. It inhibits transcription factors, up-regulates caspases, Bax, and p53, and down-regulates survivalin, cyclins, and Bcl-2 to achieve its antiproliferative impact. It has been demonstrated that *resveratrol* protects against cancer at every step of the disease's development, including its beginning, promotion, and progression. Grape powder can decrease Wnt target gene expression in the normal colonic mucosa of colorectal cancer patients, despite the fact that it cannot block the Wnt pathway in colon cancer. *Resveratrol* decreases the growth of tumor cells in people with colorectal adenocarcinoma (Hosseini.A and Ghorbani.A.,2015). The *resveratrol* is a chemical that is present in red wine and grape skin. It works by blocking the activity of cyclooxygenase (COX), which stops tumor growth, spread, and initiation. It may also play a part in lowering oxidative stress and lipid peroxidation since it inhibits TNF-induced activation of NF-B, AP-1, and apoptosis (Sarangi and Padhi.,2014). *Resveratrol*, a polyphenolic chemical found in grapes, berries, and other plant products, has been linked to important advances in cancer research as well as age-related ailments such as diabetes, neurological disorders, arthritis, and cardiovascular and pulmonary diseases. *Resveratrol* affects all stages of carcinogenesis, modifying signaling processes to diminish cancer cell multiplication and development, triggering programmed cell death, lowering inflammatory responses, and inhibiting tumor metastatic dissemination. It also reduces hazardous side effects linked with medicines and improves cancer treatment outcomes. *Resveratrol* is a safe and effective natural molecule having chemopreventive and chemotherapeutic activities. It considerably lowers arsenic accumulation, arsenic-induced toxicities in renal cells, arsenic trioxide-induced oxidative stress, and arsenic accumulation in hepatic cells (George ,*et al*.,2021).

Role of phytochemicals in the prevention of cancer

Cells in humans and other creatures are continually exposed to oxidizing agents, which can be found in the air, food, and water or created by metabolic activity within cells. For optimal physiological circumstances, oxidants and antioxidants must be balanced. Oxidant overproduction can produce oxidative stress, which can damage big macromolecules and raise the risk of cancer and cardiovascular disease. To avoid or reduce the oxidative stress caused by free radicals, enough antioxidants must be eaten. Numerous antioxidant chemicals, including phenolics and carotenoids, are found in fruits, vegetables, and whole grains. These compounds may minimize the risk of chronic illnesses and shield cellular systems from oxidative damage. Owing to a 2-fold increased risk of cancer in those with a low intake, regular eating of fruits and vegetables might lower the risk of cancer (Liu 2004).

Plant polyphenols' role in cancer prevention:

Plant-based medications have been used for millennia to treat and manage a variety of conditions, including cancer. However, current study has concentrated on the active chemicals found in plants, which have gained popularity in recent decades. Herbal items have been utilized in conjunction with conventional anticancer medications to minimize chemotherapy resistance and increase healing efficiency. Dietetic phytochemicals are widely employed in cancer prevention owing to their numerous chemical components, complex structure, biological effects, cost-effectiveness, and minimized harmful side effects. Polyphenolic substances, such as flavonoids and phenolic acids, play an important role in cancer treatment and prevention by interfering with carcinogenesis at several stages. Environmental variables, such as diet, are substantially tied with cancer development, with one-third of cancer death rates associated with diet and nutrition. Many clinical investigations have demonstrated a beneficial relationship between the consumption of polyphenolic chemicals, also known as flavonoids, through the consumption of polyphenol-rich foods and beverages and a decreased risk of acquiring various cancer types, a decreased incidence of cancer, and a decreased risk of cancer recurrence. Nutritive and dietary polyphenols have a dual role as cytoprotective and cytotoxic agents, which underpins their anticancer and chemopreventive properties.

Conclusion

Phytomedicine plays the significant role in cancer prevention and treatment, highlighting its potential as an affordable, accessible addition to conventional therapies. With cancer rates on the rise globally, particularly in developing countries, treatment accessibility and cost continue to be barriers. The study points to the promising properties of plant-based compounds, such as antioxidants, flavonoids, and other bioactive phytochemicals, which have shown effectiveness in reducing inflammation, inhibiting cancer cell growth, and enhancing immunity. These natural compounds may work synergistically with standard treatments to lower recurrence rates and minimize side effects, though further research is needed to solidify clinical effectiveness and safety. The findings suggest that integrating phytomedicine with modern treatments could offer a more holistic approach to cancer care.

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