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Ethnobotanical Survey Of Leguminous Plants Used In Traditional Cancer Treatments

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Abstract: Medicinal plants have been used for therapeutic purposes since ancient times, playing a crucial role in healthcare. Approximately 70% of the population in developing countries relies on herbal medicines. Plant-derived compounds are considered safer and non-toxic compared to synthetic products. Traditional Indian Medicine (Ayurveda) and Traditional Chinese Medicine contribute significantly to the global knowledge of therapeutic plants. The World Health Organization identifies 21,000 medicinal plants globally used for medicinal purposes, with 2,500 species in India, 150 of which are used commercially. Herbal medicines are complex mixtures that require understanding of pharmacokinetics to identify bioactive compounds. Medicinal plants are crucial in developing anticancer drugs, with the National Cancer Institute screening about 35,000 plants, 3,000 of which show anticancer activity. Indigofera aspalathoides, widely used in India, possesses anticancer, antioxidant, anti-inflammatory, and antitumor activities. This plant's decoctions are traditionally used to treat cancer, leprosy, and other ailments, demonstrating its significant therapeutic potential.

Index Terms - Herbal Medicines, Indigofera Aspalathoides, Anticancer activity, Secondary Metabolites & Chemoprevention.

1. INTRODUCTION

Cancer involves the rapid creation of abnormal cells that invade other parts of the body, forming secondary tumors. It is the second leading cause of mortality worldwide, with most deaths due to metastasis, the main cause of morbidity and mortality. Metastasis, a multistep process involving detachment, migration, invasion, angiogenesis, and adhesion, is driven by stress response genes. Different cancers vary by metastatic origin and characteristics. Breast cancer, a common metastatic cancer in females, has a complex etiology influenced by genetic and environmental factors. In 2020, there were an estimated 2,261,419 new breast cancer cases are found and 684,996 deaths.[1]

Nearly 90% of breast cancer patients die due to metastasis, where cancer cells spread from the original tumor, travel through the bloodstream, and colonize distant sites. These metastatic lesions invade vital organs and develop resistance to systemic therapies.[3] Therefore, fighting cancer metastasis is crucial to winning the battle against breast cancer. Breast cancer is classified based on hormone receptor status into estrogen receptor alpha (ERα) and progesterone receptor (PR) positive, Human epidermal growth factor receptor 2 (HER2) positive, and triple-negative (ER/PR/HER2 negative). Understanding these molecular mechanisms helps predict prognostic factors and design targeted therapies for treatment.[2]

Prostate cancer, prevalent among men, often results from glandular cell changes. Both aggressive and non-aggressive forms are influenced by various risk factors. Metastatic prostate cancer (mPC) has a poor prognosis and with a 5-year survival rate around 30%. Since the 1940s, androgen deprivation therapy (ADT) has been pivotal in managing metastatic progression by reducing circulating androgens, thereby slowing disease advancement. (Powers et al 2020). ADT alone cannot always prevent disease progression, and hormone-sensitive prostate cancer (HSPC) can develop resistance, becoming castration-resistant prostate cancer (CRPC). mCRPC remains lethal, necessitating more effective therapies to improve clinical outcomes.[4,5]

The main challenge in treating cancer is evaluating various chemotherapy methods. Despite numerous established treatments, their effectiveness is often limited by low therapeutic index and cellular drug resistance. Notably, around 90% of cancer patient deaths are attributed to drug resistance. (Wang et al 2019). Multi-drug resistance in cancer cells is linked to several mechanisms, including increased xenobiotic metabolism, enhanced drug efflux, interstitial fluid pressure, and genetic changes (epigenetic alterations, gene mutations, and amplifications)[6] **Table-1.0.**

Identifying the active components in medicinal herbs is challenging due to their complexity. Directly adding herbal mixtures to in vitro cultures is not effective for evaluating their biological activity. Instead, "serum pharmacology" is a better strategy, where serum from animals administered with herbal extracts helps identify major active ingredients. Some plant-derived anti-cancer drugs in clinical use include vinca alkaloids, taxanes, podophyllotoxin derivatives, and camptothecin. These compounds often exhibit anti-metastatic potential and enhance apoptosis in tumor cells.[7]

Indigofera aspalathoides Vahl, a low undershrub in the Papilionaceae family, is found mainly in South India and Sri Lanka. Known as Shivanar vembu in Tamil, it contains an essential oil ingredient used to treat syphilis and skin disorders. The plant's aqueous extracts, rich in flavonoids, alkaloids, terpenoids, steroids, tannins, and reducing sugars, counteract carcinogens. Key compounds include mucronulatol, indigocarpan, erythroxydiol X, indigocarpan diacetate and erythroxydiol Y. hepatoprotective, chemopreventive, anti-inflammatory, anti-arthritic [8], anti-tumor The plant exhibits various pharmacological activities, including antiproliferative effects, and COX inhibitory activity [10].

The whole plant is used for edematous tumors, and the ashes treat dandruff. A decoction of the leaves and flowers treats leprosy and cancer, while the root is a remedy for toothache. Despite various phytochemical studies on I aspalathoides, its bioactive molecule triggering cancer metastasis is unknown. This study aims to evaluate the anti-metastatic properties of major bioactive compounds from I aspalathoides and their molecular mechanisms.

Disease / Condition	Characteristics	Reported Cases / Mortality
Breast Cancer	Most common metastatic cancer in women; classified as ER/PR+, HER2+, or triple-negative. Mortality is mainly due to metastasis and therapy resistance[2].	2.26 million new cases and 0.68 million deaths (2020). Nearly 90% of deaths from metastasis.
Prostate Cancer	Most prevalent cancer in men; progression from hormone-sensitive to castration-resistant forms. ADT is standard but limited by resistance[4-5].	Metastatic prostate cancer: ~30% 5-year survival; major cause of male cancer deaths.
Cancer (Overall)	Second leading global killer; metastasis and multi-drug resistance drive mortality. Resistance arises from genetic/epigenetic changes, drug efflux, and altered metabolism[6].	Accounts for ~1 in 6 deaths worldwide; ~90% of deaths linked to drug resistance.

Table 1.0 Overview of Major Cancers and Their Clinical Characteristics

2. Medicinal plants:

Medicinal plants, utilized for millennia, fulfill crucial therapeutic roles in human civilization. They serve as essential remedies, relied upon by 70% of the population in developing nations, leveraging plant extracts for medicine. Key to their efficacy are secondary metabolites, upon which their potency hinges. Natural products and their derivatives constitute over half of FDA-approved drugs, highlighting their profound impact. Unlike synthetic alternatives, plant-derived compounds are notably safer and less toxic to

human cells. Recent efforts have focused on harnessing these advantages to combat multi-drug resistance (MDR), emphasizing the potential of medicinal plants in therapeutic innovation.[11]

The two main traditional systems existing today are the Traditional Indian Medicine (TIM), i.e., Ayurveda & Traditional Chinese Medicine (TCM). Together, they contribute the knowledge of therapeutic to diverse. Both systems have significantly influenced global herbal medicine, providing a variety of plants and phytomedicines. Their contributions are integral to the regulation of herbal drug molecules in the pharmaceutical industry. In both TIM and TCM, medications are typically herbal products available in various formulations like tinctures, powders, poultices, and teas, tailored to specific diseases.[12]

The World Health Organization (WHO) has identified 21,000 medicinal plants globally used for medicinal purposes. In India, 2,500 species have been identified, with 150 used commercially by biopharmaceutical industries as mainstream medicines. Herbal mixtures contain complex combinations of bioactive constituents, complicating standardization and identification of lead bioactive compounds due to limited pharmacological data on all compounds. Understanding the pharmacokinetic properties like absorption, distribution, metabolism, and elimination (ADME) of phytoconstituents enables identification of lead bioactive compounds in these complex mixtures.[13].

2.1 Significance of herbal medicine in cancer:

Herbal medicine plays a crucial role in global healthcare by constituting the basis of alternative medicine and pioneering the development of novel drug molecules for treating cancer. In the nineteenth century, approximately 80% of medicines were derived from plants. Despite the scientific revolution, herbal medicine has continued to influence the pharmaceutical industry, leading to the development of bioactive molecules through sophisticated bioassays and bioassay-guided fractionation of medicinal plants. This method has successfully isolated numerous therapeutically valuable compounds[14]. Researchers' keen efforts have led to the development of potent drugs and numerous therapeutic leads from herbal sources, yielding novel pharmacologically active components. Medicinal plants' anticancer potential has been recognized for centuries[15].

The National Cancer Institute (NCI) has screened numbers of plants approximately 35,000 for anticancer activities, with around 3,000 showing consistent anticancer effects. Various compounds, such as polyphenols, taxols, and brassinosteroids, extracted from terrestrial plants are evaluated for their anticancer properties. Polyphenolic compounds, including flavonoids, tannins, resveratrol, curcumin, and gallocatechins, are known for their anticancer effects. Resveratrol, found in peanuts and grapes, acts as a natural antioxidant, improving health and reducing cancer risk. These polyphenolics induce apoptosis by modulating chromatin, leading to DNA fragmentation and degradation.

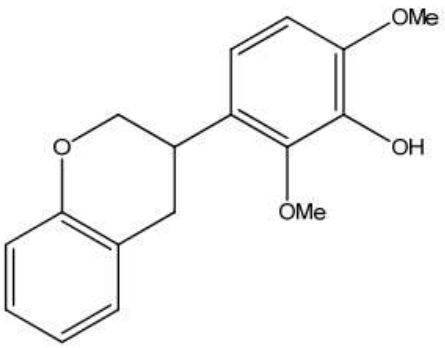
Flavonoids, a diverse group of polyphenolic compounds, are categorized into six sub-classes: flavonols, flavones, isoflavones, flavanones, anthocyanins, and flavan-3-ols. Genistein, found in leguminous plants, exhibits anticancer potential against human cancer cell lines. Similarly, delphinidin from blackberries demonstrates anticancer effects on ovarian cancer cells. Indigofera aspalathoides, a widely used medicinal plant in India, is known for its therapeutic efficacy and pharmacological mechanisms [16].

2.2 Indigofera aspalathoides:

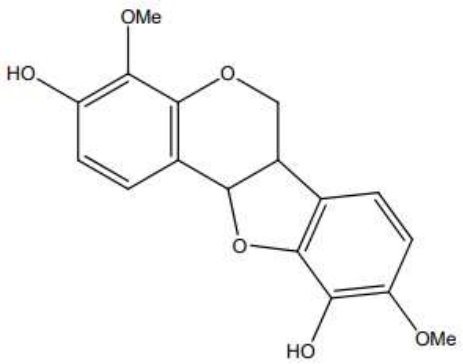
The medicinal plant *I. aspalathoides,* part of the Papilionaceae family, is found extensively in South India and Sri Lanka. Known as sivanar vembu in Tamil, its flowers, leaves, and tender shoots are traditionally regarded for their cooling and demulcent properties. (Fig 1.0).

Figure 1.0 *Indigofera aspalathoides* Plant

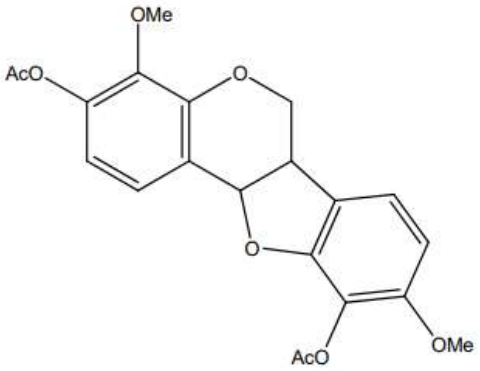
The plants are used in decoction for cancer and leprosy treatment. The whole plant treats edematous tumors, with its ashes combating dandruff. Leaves are applied for abscess treatment. The stem treats skin disorders and tumors traditionally. Numerous studies have explored its phytochemical and pharmacological properties, unveiling its anticancer and antioxidant qualities. The plant contains pterocarpan derivatives, flavonoids, alkaloids, terpenoids, steroids, tannins, carbs, and reducing sugars, countering carcinogenic effects. Its decoction treats secondary syphilis. The plant has different activity like COX inhibitory activity [10], anti-tumor activity [17], anti-arthritic, anti-mycobacterial, anti-inflammatory activity, anti-viral, and chemopreventive activity against N nitroso diethylamine induced phenobarbital-promoted liver tumors [18,19].



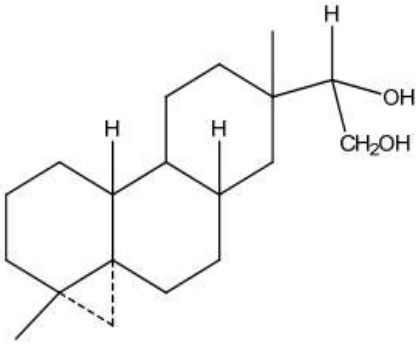
Mucronulatol



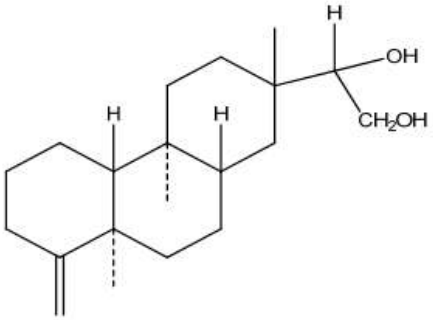
Indigocarpan



Indigocarpan diacetate



Erythroxydiol X



Erythroxydiol Y

Fig 2.0 Chemical structures of *I. aspalathoides* compounds

The major bioactive constituents in I. aspalathoides include indigocarpan, mucronulatol, indigocarpan diacetate, erythroxydiol X, and erythroxydiol Y (Fig 2.0). Indigocarpan, particularly, is the predominant bioactive compound in the plant.

2.3 Serum pharmacology:

Medicinal plants, utilized globally for millennia to treat diseases and enhance health, lack comprehensive clinical validation. Due to their complex constituents, identifying specific therapeutic metabolites is challenging. Typically administered orally, herbal medicines undergo absorption in the gastrointestinal tract, followed by biotransformation in the liver, before distribution through the bloodstream to target organs and tissues. Medicinal plants, utilized globally for millennia to treat diseases and enhance health, lack comprehensive clinical validation. Due to their complex constituents, identifying specific therapeutic metabolites is challenging. Typically administered orally, herbal medicines undergo absorption in the gastrointestinal tract, followed by biotransformation in the liver, before distribution through the bloodstream to target organs and tissues. Traditional Chinese Medicine (TCM) explains its mode of action through various components targeting multiple pathways. Identifying and analyzing bioactive compounds is crucial in drug discovery, especially for orally administered TCM where components must reach effective concentrations in target organs to exert therapeutic effects. Serum pharmacology, an experimental technique, tracks dosed serum to identify active constituents from herbal medicine that are absorbed into the bloodstream. This approach hypothesizes that only absorbed components can potentially become active constituents.[22].

The herbal drug, typically taken orally, undergoes metabolism reactions (Phase I and Phase II), which produce active or inactive metabolites. Consequently, these metabolites are less prevalent in circulation. In vivo, the active constituents differ significantly from those pharmacologically active in vitro due to oxido-reduction processes and biotransformation by metabolic enzymes. Some herbal drugs exhibit low bioavailability when orally administered, primarily due to challenges crossing the gastrointestinal epithelium, despite therapeutic benefits. Factors contributing to low membrane permeability include low lipophilicity, poor water solubility, or efflux by p-glycoprotein. Additionally, inadequate pharmacokinetic studies present

a major barrier to modernizing herbal products. Analysis of all components in rat serum following oral administration of TCM was conducted using UPLC-Q-TOF-MS/MS.[21] Via cytochrome P450, herbal compounds undergoes metabolism (phase-I & II). Additionally, some compounds serve as substrates for p-glycoprotein, which will predominantly seen in the brain, intestine, liver and kidney. Factors such as drug-metabolizing enzymes and other transporters primarily influence the in vivo bioavailability of these drugs.

2.4 Toxicity signatures of herbal medicine:

Herbal medicine, once the primary healthcare method globally before the advent of modern medicine, remains the predominant form of healthcare in many underserved populations. It continues to contribute novel ideas and treatments to modern medicine, benefiting individuals worldwide.[22]

The FDA insist on the need to screen the drug molecules for the toxicological and pharmacological activities on animals. Toxicity assessments of food substances, chemicals, and pharmaceuticals have gained importance in the 21st century. In 1493-1541, Paracelsus was researched and studied in toxicology and he identified some specific chemicals can be the reason for toxic to the animals and plants [23].

Vicine, an alkaloid glycoside from the bitter gourd plant Momordica charantia, induces neurological disorders due to its toxicity. With the rising use of herbal products, ensuring the safety and efficacy of medicinal herbs has become a critical public health concern [24].

Adverse health effects associated with herbal medicine, potentially exacerbated by adulterants/contaminants, highlight inherent toxic risks. Most countries introduce herbal products to market without prior toxicological evaluation, lacking effective regulatory oversight for quality standards. The World Health Organization (WHO) emphasizes preliminary assessment, safety monitoring, and identification of toxicity risks before herbal products gain conventional usage [25]. Our study aims to evaluate the toxicity of plant-derived drugs in animal models following OECD guidelines.

2.4.1 Acute toxicity studies

Acute toxicity assesses adverse effects occurring shortly after exposure to a drug molecule in a single dose to lab animals. It measures functional impairment or biochemical lesions affecting organ responses. Models include mice, rats, fish, and guinea pigs, evaluating dose-dependent effects to determine chemical substance toxicity profiles. Acute oral toxicity commonly determines lethality and LD50 values of drug molecules [26].

To determine the LD50 of drug molecules, some standardized protocols like FDP (Fixed Dose Procedure), ATC (Acute Toxicity Category), UDP (Up & down Procedures) could be used. Animals freely accessed food, followed by observation of drug-treated models over 24 hours initially and daily for two weeks, noting appearance and behavioral changes[27].

2.4.2 Different measurements in toxicity studies

Plant-based medicines have been utilized for preventing and treating various diseases. However, the dosages used in traditional medicine have not been scientifically studied. Therefore, toxicity testing must be conducted to ensure the safety of these herbal drugs [28].

To evaluate the stress responses of toxic compounds, some biomarkers together with enzymatic, physiological, bio-chemical & histological parameters were exceedingly recommended. Physiological parameters and bio-chemical parameters were mostly employed to assess the physiological exchanges occurred during stress and predicts associated risk levels effectively [29].

CONCLUSION:

The use of medicinal plants for the therapy of cancer which represents a rich source of bioactive compounds have been harnessed by long established medicinal systems like Ayurveda and TCM (Traditional Chinese Medines). These plants play a pivotal role in global healthcare, offering diverse therapeutic options with lower toxicity compared to synthetic drugs. The identification and isolation of bioactive compounds from medicinal plants, including flavonoids, polyphenols, and alkaloids, have paved the way for developing novel anticancer therapies. *Indigofera aspalathoides*, a widely utilized plant in traditional Indian medicine,

exemplifies this potential with its multifaceted pharmacological activities, including anticancer, antioxidant, and anti-inflammatory properties.

However, challenges such as standardizing herbal mixtures and understanding pharmacokinetic profiles remain significant hurdles in harnessing the full therapeutic potential of medicinal plants. Advances in analytical techniques, such as serum pharmacology and metabolomics, offer promising avenues for elucidating the mechanisms of action and optimizing the efficacy of herbal medicines in combating cancer metastasis. Further researches into the toxicity profiles & clinical studies are essential to conclude the safety and efficacy of the present

Natural compounds for broader therapeutic use in cancer treatment. By integrating traditional knowledge with modern scientific approaches, the exploration of plant secondary metabolites continues to hold immense promise in the ongoing quest for effective cancer therapies.

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