

SENNA (*CASSIA ANGUSTIFOLIA*) DERIVED PHYTOMOLECULES IN LUNG CANCER: A COMPREHENSIVE REVIEW OF PHYTOCHEMISTRY, PHARMACOLOGICAL ACTIVITIES, AND MOLECULAR TARGETS

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ABSTRACT

Senna (*Cassia angustifolia*) have been used extensively in traditional medicine and have become a valuable source of bioactive phytochemicals with a wide range of therapeutic properties. The genus contains a number of secondary metabolites such as anthraquinones (rhein, aloë-emodin, emodin and chrysophanol), flavonoids (quercetin, kaempferol, rutin and luteolin), phenolic compounds, tannins and glycosides which are important in terms of their pharmacological potential. Although the diagnosis and targeted therapy has advanced, lung cancer is still one of the most common and deadly cancers worldwide. Recent studies have focused on the role of phytomolecules from plant origin as modulators of important molecular targets involved in the development of lung cancer. A number of Senna compounds have shown to interact well with therapeutic targets including Epidermal Growth Factor Receptor (EGFR), Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS), Anaplastic Lymphoma Kinase

(ALK), Phosphoinositide 3-Kinase (PI3K), Protein Kinase B (AKT), Vascular Endothelial Growth Factor Receptor (VEGFR), B-cell Lymphoma-2 (BCL-2), Tumor Protein p53 (TP53) and Programmed Death-Ligand 1 (PD-L1). They have been claimed to have anticancer properties by a variety of mechanisms, such as induction of apoptosis, cell cycle arrest, inhibition of angiogenesis, metastasis inhibition, and regulation of oxidative stress and inflammatory pathways. This review aims to provide a comprehensive overview of the phytochemical profile of Senna species, the pharmacological activities of their main constituents and to critically analyze their potential application in targeting molecular pathways involved in lung cancer. Based on the evidence found, the phytomolecules obtained from Senna may be potential candidates for the development of anticancer drugs in the future, but in-depth preclinical and clinical trials are needed to prove their efficacy and safety.

KEYWORDS: Senna, Phytomolecules, Lung Cancer, Pharmacological Properties, Traditional Medicine.

1. INTRODUCTION

Lung cancer remains one of the most debilitating and widespread malignancies in the world since it is the number one cause of cancer mortality in both males and females. Lung cancer is one of the health problems that affect the whole world because it kills an estimated 1.8 million people every year, as cited by the World Health Organization (WHO) and the American Cancer Society.^[1] Histologically, there are two large categories of lung cancer: non-small cell lung cancer (NSCLC) representing the overwhelming majority of all cases (85 percent) and small cell lung cancer (SCLC) representing the minority (15%).^[2] The disease has a strong relation with tobacco smoking, environmental carcinogen, genetic mutations, and oxidative stress—all the factors involved in the malignant transformation of bronchial epithelial cells.^[3]

The existing treatment options like surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy have enhanced survival of the patients. Nevertheless, resistance, high rates of relapse, and adverse side effects are still the serious impediments to the control of the disease throughout the long-term period.^[4] Consequently, more focus has shifted towards the application of phytochemicals and medicinal plants as complementary/alternative anticancer agents because of their bioactivity, low-level toxicity and multi-target effects.

Senna (*Cassia angustifolia*), which is a medicinal plant, has been identified to have laxative

effects, has recently been of interest as a possible anticancer agent among natural compounds. Senna is a source of bioactive anthraquinones, including sennosides, emodin, aloe-emodin, and rhein, which exhibit antioxidant, anti-inflammatory and pro-apoptotic properties in different cancer models.^[5,6] There is an emerging evidence that these constituents have the potential to inhibit cell proliferation in lung cancer by inducing apoptosis, regulating reactive oxygen species (ROS) generation and preventing the activation of metastasis-related pathways, such as NF-KB, PI3K/Akt, and MAPK signaling.^[7,8]

2. PATHOPHYSIOLOGY

The pathophysiology of lung cancer is well-complicated interplay of genetic, molecular, and environmental factors that, together, cause normal lung epithelial cell to develop into malignant ones. The disease usually has a bronchial starting point and follows a multistage initiation, promotion, and progression path, with the development of genetic mutation, abnormal signaling pathways and cellular homeostasis.^[4]

2.1 Genetic and Molecular Alterations

Lung cancer progression is encouraged by the mutation in oncogenes and tumor suppressor's genes that control the proliferation, apoptosis, and differentiation of the cells. Such oncogenes are often activated, including KRAS, EGFR (epidermal growth factor receptor), ALK, ROS1, BRAF, and MET, which result in continual signaling via pathways including PI3K/AKT, RAS/RAF/MEK/ERK and JAK/STAT, which contribute to promoting tumor survival and growth.^[9,10]

On the other hand, tumor suppressor genes like, TP53, RB1, and PTEN are usually turned off leading to uncontrolled cell division and dysfunction of DNA repair. TP53 mutations are observed in more than half of non-small cell lung cancer (NSCLC), which indicates its central position in tumor genesis.^[11]

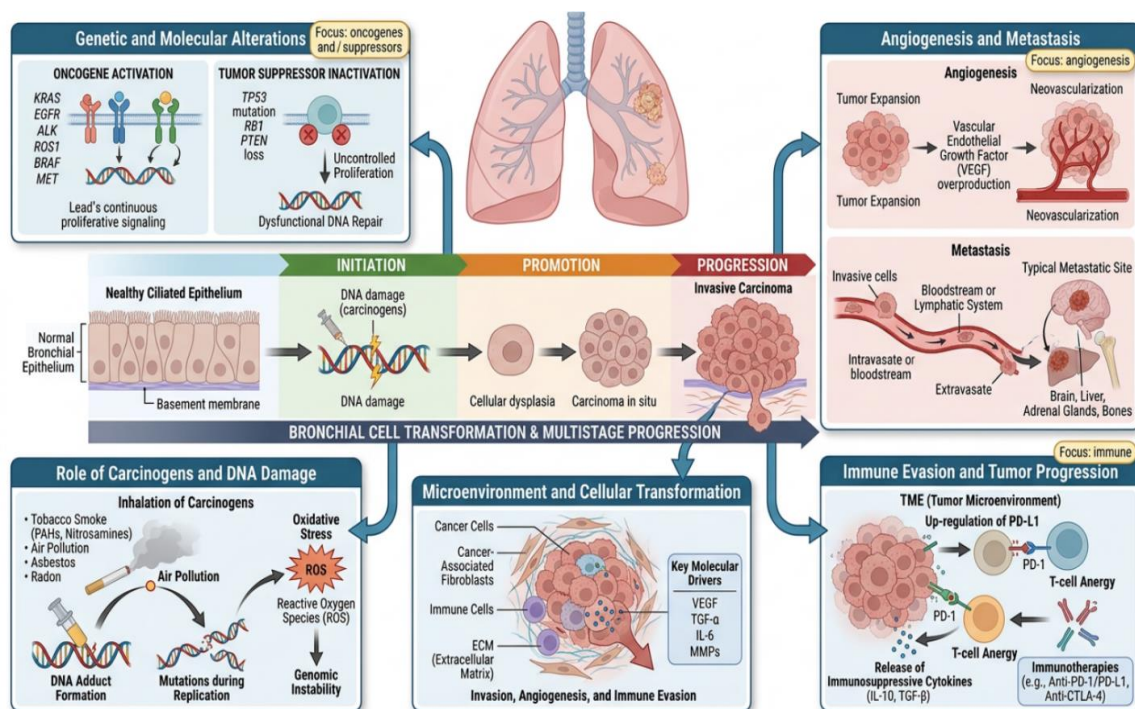


Figure 1: Schematic representation of the molecular mechanisms involved in lung cancer initiation, promotion, and progression, highlighting genetic mutations, tumor microenvironment interactions, angiogenesis, metastasis, and immune escape pathways. Generated using gpai.

2.2 Role of Carcinogens and DNA Damage

A role in carcinogenesis is played by carcinogens and DNA damage, much of the initiation of lung cancer is caused by the inhalation of carcinogens, especially tobacco smoking, air contamination and work with asbestos or radon. Tobacco smoke has over 60 carcinogenic organophosphates including polycyclic aromatic hydrocarbons (PAHs) and nitrosamines which creates DNA adducts leading to mutations during replication.^[12] Long-term exposure causes oxidative stress, which forms reactive oxygen species (ROS) that cause cellular DNA, protein, and lipid damage, leading to additional genomic instability.

2.3 Microenvironment and Cellular Transformation and Tumor

After genetic damage, bronchial epithelial cells go through a series of dysplasia to carcinoma in situ followed by invasive carcinoma. The tumor microenvironment (TME) is one of the critical factors in this transformation. These contacts form a microenvironment full of growth factors (VEGF, TGF- α), cytokines (IL-6, IL-8) and proteases (MMPs) and promote angiogenesis, invasion and immune evasion.^[13]

2.4 Angiogenesis and Metastasis

An angiogenesis is necessitated by tumor expansion over 12 mm, mostly by overexpressing vascular endothelial growth factor (VEGF), which is critical to adequate oxygen and nutrient delivery. Metastasis is a condition where the tumor cells gain invasive capabilities, destroy the extracellular matrix (ECM) and spread through the bloodstream or lymphatic. Typical metastatic areas of lung cancer are the brain, liver, adrenal glands, and bones.^[14]

2.5 Immune Evasion and Tumor Progression

There are various ways used by the lung cancer cells to avoid being detected by immunity. These involve an up-regulation of PD-L1 (programmed death-ligand 1) that inhibits the activation of T-cells and the release of immunosuppressive cytokines like IL-10 and TGF- β . These modes of immune evasion are the basis of contemporary immunotherapies against PD-1 /PD-L1 and CTLA-4 pathways that are now commonly applied to NSCLC management.^[15]

3. Plant Profile

Senna or Indian senna (*Cassia angustifolia* and *Cassia acutifolia*) is an important medicinal plant in the family Fabaceae. Small (0.5–1.5 m) perennial shrub with erect stems, paripinnate leaves with 4-8 pairs of lanceolate leaflets, bright yellow flowers in axillary racemes and flat oblong pods with many seeds. It is native to North Africa and the Arabian Peninsula and widely grown throughout India, especially in Tamil Nadu, Rajasthan and Gujarat. The dried leaves and pods are the official drug and are used in traditional and modern medicine.^[16,17]

Table 1: Taxonomical Classification.

Taxonomic Rank	Classification
Kingdom	Plantae
Subkingdom	Tracheobionta (Vascular plants)
Division	Magnoliophyta (Angiosperms)
Class	Magnoliopsida (Dicotyledons)
Subclass	Rosidae
Order	Fabales
Family	Fabaceae (Leguminosae)
Subfamily	Caesalpinioideae
Genus	Senna
Species	<i>Senna alexandrina</i> (syn. <i>Cassia angustifolia</i> Vahl and <i>Cassia acutifolia</i> Delile)

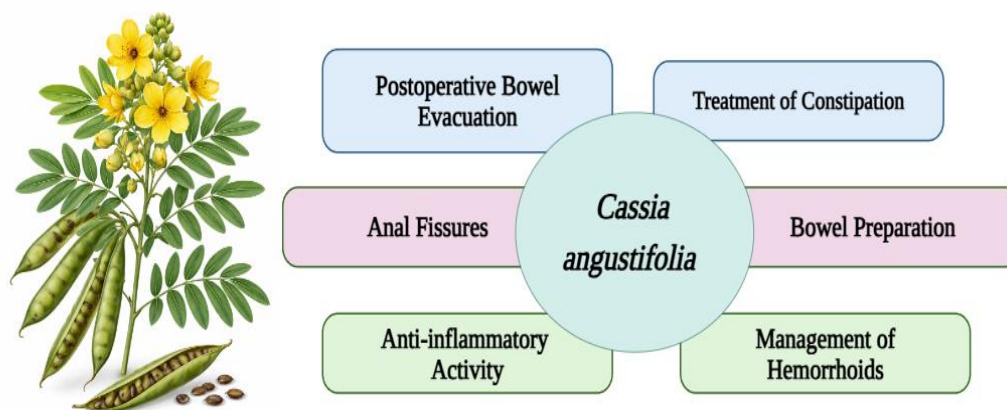


Figure 2: Plant profile of senna.

Table 2: Role of phytochemicals in Lung cancer.

Sr. No	Phytochemical	Category	Mechanism of Action (Lung Cancer)	Target Cell Line / Model	Reference
1.	Emodin	Anthraquinone	Induces apoptosis via ROS generation and mitochondrial pathway; inhibits NF- κ B signaling	A549 (human lung carcinoma)	[18]
2.	Chrysophanol	Anthraquinone	Suppresses PI3K/Akt pathway; promotes apoptotic cell death	NCI-H460, A549	[19]
3.	Aloe-emodin	Anthraquinone	Triggers cell cycle arrest and caspase-mediated apoptosis	A549, H1299	[20]
4.	Rhein	Anthraquinone	Modulates p53 signaling and oxidative stress in lung carcinoma	A549	[21]
5.	Kaempferol	Flavonoid	Downregulates Bcl-2 and upregulates Bax; antioxidant protection	A549	[22]
6.	Quercetin	Flavonoid	Inhibits STAT3 and MAPK pathways; anti-metastatic	A549	[23]
7.	β -Sitosterol	Phytosterol	Induces apoptosis and inhibits proliferation via caspase activation	A549	[24]
8.	Gallic acid	Phenolic acid	Inhibits EGFR phosphorylation; induces oxidative stress-mediated apoptosis	H1975	[25]
9.	Sennoside A	Anthraquinone glycoside	DNA fragmentation and apoptosis induction	A549	[26]
10.	Catechin	Flavan-3-ol	ROS-mediated apoptosis and inhibition of proliferation	A549	[27]

4. Pharmacological uses of *Cassia angustifolia*



Cassia angustifolia

Figure 3: Different pharmacological properties of senna.

4.1 Laxative and Digestive Aid

Senna is mostly used therapeutically as a means to treat constipation. The anthraquinone glycosides sennosides A and B, active constituents of it, are stimulant laxatives. On intake, the colonic bacteria hydrolyze these glycosides to active anthrones which increase intestinal peristalsis, prevent water reabsorption, and increase fluid secretion hence eased bowel evacuation.^[28,29] Pharmacopoeial forms of standardized Senna extract are extensively used in the treatment of acute and chronic constipation, in bowel preparation before colonoscopy or surgery.

4.2 Detox and Cleanse -Weight Loss

Due to the purgative effect, Senna is also commonly used in herbal hypodetoxication and weight reduction regiments. It helps to get rid of the toxins of the metabolism and gastrointestinal toxins, which gives a temporary sense of lightness and purification. Nevertheless, long-term usage, especially of the slimming teas, may cause electrolyte imbalance and dependency, which must be considered on such use.^[30]

4.2 Skin and Wound Healing

Traditional medicine uses the topical Senna preparations including leaf pastes or extracts in treating the skin disorders such as acne, eczema, ringworm and wounds. Antimicrobial and antifungal effects of bioactive compounds, especially rhein and chrysophanol, play a role in restoring the wound and preventing infection.^[31,32]

4.4 Animal trials with avian influenza

Preliminary results indicate an increase in body weight and decreased mortality rates in chickens treated with paroxetine. Experimental evidence in animals with avian influenza. It has been shown that chickens fed paroxetine gain weight and show reduced mortality rates. A number of experiments have revealed that Senna has an inhibitory effect on pathogenic microorganisms such as *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*.^[33, 34] It can also be used as an anthelmintic agent against intestinal parasites with the help of ethnobotanical evidence.^[33]

4.5 Anti-inflammatory and Anti-oxidant Effect

Senna has quercetin and kaempferol, flavonoids that help to enhance its antioxidant capacity of quercetin and kaempferol by neutralizing free radicals and preventing the damage of cells caused by oxidative stress. In addition, these substances regulate inflammatory mechanisms by inhibiting the action of pro-inflammatory cytokines (TNF- 6, IL-6).^[30-35]

4.6 Hepatoprotective and Anti Diabetic Effects

Experimental models show that ethanolic extracts of *Senna alexandrina* and *Senna tora* have hepatoprotective properties by lowering the serum transaminase levels (ALT, AST) and improving the antioxidant enzyme activity in hepatic tissue. Also, these extracts have demonstrated certain antidiabetic properties in enhancing insulin sensitivity and glucose metabolism of diabetic models.^[35]

5. CONCLUSION

Senna species are rich sources of bioactive phytochemicals, particularly anthraquinones such as rhein, aloe-emodin, emodin, chrysophanol along with flavonoids including quercetin, kaempferol, rutin, and luteolin, which exhibit diverse pharmacological activities and promising anticancer potential. Evidence suggests that Senna-derived compounds can modulate key molecular targets involved in lung cancer, including EGFR, KRAS, ALK, PI3K/AKT/mTOR, VEGFR, TP53, and PD-L1 pathways, thereby inhibiting tumor growth and progression. Although preclinical studies demonstrate encouraging therapeutic effects, further investigations are required to validate their efficacy, safety, and clinical applicability. Overall, Senna phytochemicals represent promising candidates for the development of novel natural-product-based strategies for lung cancer management.

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