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"Therapeutic Insights into Jamun (Syzygium cumini) Seed Extracts: Inhibition of Hep-2 Cancer Cell Growth and Beyond"

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Abstract-

The seeds of Syzygium cumini, also referred to as jamun or black plum, contain a complex phytochemical profile that include es alkaloids, tannins, phenolic compounds, and flavonoids, all of which have shown promise as medicines. The anticancer effects of jamun seed extracts on human laryngeal carcinoma (Hep-2) cells are examined in this work. The findings showed that the seed extracts successfully and dose-dependently suppressed the growth of Hep-2 cancer cells.

According to mechanistic study, the anticancer effect is mediated by stimulating apoptosis, interfering with the course of the cell cycle, and producing more reactive oxygen species (ROS), which causes oxidative stress in cancer cells. The extracts also shown anti-angiogenic qualities, which further slowed the growth of tumours. These results demonstrate the potential of extracts from jamun seeds as a natural, bioactive agent for supplementary cancer treatment, which calls for more research into their active ingredients and possible uses in medicine.

Keywords-Anti-carcinoma, Eugenia jambolana, Human laryngeal epithelioma type 2 (Hep-2) cells

Introduction-

A class of disorders known as cancer is defined by the unchecked development and dissemination of aberrant cells. Cancer cells proliferate because they disregard cues to cease division. Cancer cells are abnormal cells that have undergone genetic changes, leading to uncontrolled growth, invasion, and metastasis. They ignore signals to stop dividing, resulting in an overgrowth of cells.

Phases of the Growth of Cancer Cells

1. Initiation: A genetic mutation results in the development of cancer in a cell.

2. Promotion: A tumour is created when the cancer cell multiplies and divides.

3. Progression: As the tumour grows more aggressive, it invades nearby tissues and spreads (metastasises) to other areas of the body.

4. Metastasis: Cancer cells separate from the main tumour, move via the lymphatic or circulatory systems, and develop into secondary tumours in different body areas.[1]

Characteristic of cancer cell:

1. Unchecked growth: Cancer cells disregard cues to cease proliferating.
2. Invasion: Cancer cells spread to nearby organs and tissues.
3. Metastasis: The spread of cancer cells to different body parts.
4. Immortality: Cancer cells have the capacity to proliferate endlessly, which results in cell proliferation.
5. Genetic instability: The DNA of cancer cells is unstable, which promotes more mutations and the growth of tumours.[2,3]

Factors That Encourage the Growth of Cancer Cells

1. Genetic mutations: Cancer may result from inherited or acquired genetic alterations.
2. Environmental factors: Being around carcinogens, or things that cause cancer, like radiation, tobacco smoke, and certain chemicals.
3. Hormonal influences: Exposure to specific hormones or hormonal imbalances might encourage the growth of cancer cells.
4. Prolonged inflammation: Prolonged inflammation can promote the proliferation of cancer cells and the advancement of tumours.[4]

Cancer Types:

1. Carcinomas: Cancers originating from epithelial cells, such as cancers of the breast, lung, or colon.
2. Sarcomas: Cancers originating from cells of connective tissue, such as cancers of the bone, muscle, or fat.
3. Leukaemias: Blood cell-derived cancers, such as leukaemia.
4. Lymphomas: Cancers (like lymphoma) that develop from immune cells.[3]

Options for Cancer Treatment

1. Surgery: The tumour and surrounding tissue are removed.
2. Chemotherapy: The process of killing cancer cells with chemicals.
3. Radiation therapy: The process of killing cancer cells with radiation.
4. Immunotherapy: Fighting cancer by utilising the immune system.
5. Using drugs to target particular cancer cells is known as targeted therapy.

Early detection and prevention

1. Screening testing: Early cancer detection, when it is more curable, is possible with routine screening tests.
2. Healthy lifestyle: Eating a balanced diet, exercising frequently, and maintaining a healthy weight can all lower the risk of cancer.
3. Avoiding carcinogens: Cancer risk can be decreased by avoiding exposure to carcinogens like tobacco smoke and certain chemicals.[5]

Cancer Cell Growth Mechanism:

1) Enhance glycolysis :cancer cell exhibit increased glycolysis,when provides them with energy and building blocks for growth.[6]
2) Mitochondrial Metabolite Remodeling:Cancer cell undergo metabolic remodeling,which allows them to adapt to changing environment and sustain growth.[6]
3) Cell Signaling Pathways: Various cell signaling pathways such as the P13K/AKT and MAPK/ERK pathway, are involved in regulating cancer cell growth.[7]
4) Normal cellular functions are disrupted by a complex interaction of genetic and molecular alterations in cancer cell development pathways.[6,8]

a) Genetic mechanism: 1. Mutations: Cancer can result from genetic mutations in oncogenes (like KRAS) or tumour suppressor genes (like TP53). [9]

2. Epigenetic alterations: Epigenetic changes, including histone and DNA methylation, can modify how genes are expressed and cause cancer.[10]

3. Chromosomal instability: Cancer can result from chromosomal instability, which includes amplifications, deletions, and translocations.[11]

b) Molecular Mechanisms:1. Cell cycle dysregulation: Unchecked growth is frequently caused by cancer cells' distorted cell cycle regulation. [12]

2. Apoptosis evasion: By overexpressing anti-apoptotic proteins (like BCL-2), cancer cells can avoid apoptosis, or programmed cell death.[13]

3. Angiogenesis: To aid in their proliferation, cancer cells can stimulate the production of new blood vessels.[14]

4. Invasion and metastasis: Through processes like the epithelial-to-mesenchymal transition (EMT), cancer cells have the ability to infiltrate nearby tissues and spread to distant locations.[15]

c) Pathways of Signalling

1. PI3K/AKT pathway: This pathway promotes cell survival and proliferation and is frequently activated in cancer.

2. MAPK/ERK pathway: Often dysregulated in cancer, the MAPK/ERK pathway plays a role in cell differentiation and proliferation.

3. WNT/β-catenin pathway: Often dysregulated in cancer, the WNT/β-catenin pathway plays a role in cell differentiation and proliferation.[12]

d) Microenvironmental Elements:

1. Tumour microenvironment: The tumour microenvironment, which consists of blood vessels, fibroblasts, and immune cells, can either promote or prevent the progression of cancer.

2. Hypoxia: Low oxygen levels, or hypoxia, can encourage the growth and metastasis of cancer.

3. Inflammation: Prolonged inflammation can accelerate the development and spread of cancer.[16]

e) Mechanisms of Cancer Stem Cells

1. Self-renewal of cancer stem cells: These cells have the ability to differentiate and self-renew, which promotes the growth and recurrence of cancer.

2. Cancer stem cell niche: The tumour microenvironment is part of the cancer stem cell niche, which can promote the differentiation and self-renewal of cancer stem cells.[17]

Since cancer is still one of the world's top causes of death, research into new therapeutic agents—especially those sourced naturally—is imperative. The promise of plants in drug development

has long been acknowledged because of their abundance of bioactive chemicals with a wide range of pharmacological characteristics. Among these, the tropical fruit-bearing tree Syzygium cumini, often called Jamun or black plum, has drawn notice for the therapeutic properties of its seeds. Jamun seeds, which have long been used to treat oxidative stress, diabetes, and inflammation, are now being researched for possible anticancer effects.[18]

Recent studies have demonstrated that extracts from jamun seeds can stop the growth of Hep-2 (human laryngeal cancer) cells. Strong antioxidant and cytotoxic properties are due to the seeds' high concentration of flavonoids, phenolic acids, tannins, and other phytochemicals. It has been demonstrated that the bioactive substances in jamun seeds can cause apoptosis, interfere with the advancement of the cell cycle, and produce reactive oxygen species (ROS), which makes them a viable natural therapeutic option for the treatment of cancer.[19]

The goal of this review is to present a thorough analysis of the processes by which extracts from jamun seeds prevent the proliferation of Hep-2 cancer cells as well as their possible uses in the creation of complementary and alternative cancer treatments. The study also looks at the need for more investigation to confirm and utilize these qualities in therapeutic settings.[19]

Introduction to Syzygium cumini

About 150 genera and 3,600 species make up the vast plant family known as the Myrtaceae, which includes trees and shrubs that grow in tropical and subtropical regions. A significant member of this family that is extensively dispersed throughout the Indian subcontinent is Syzygium cumini L., often known as jamun. For many generations, South Asian traditional medicine has utilised the fruits and seeds of S. cumini to treat diabetes mellitus. According to Bhatia and Bajaj (2005), the seeds have diuretic and astringent properties. They have anti-inflammatory , antipyretic , psychopharmacological , hypolipidaemic ,hypoglycemic and antioxidant property [20]

Botanical description

Kingdom:Plantae

Division: Angiosperms

Sub Division:Eudicots

Order:Myrtales

Family:Myrtaceae

Genus:Syzygium

Species:cumini

Binomial name: Syzygium cumini (L.) Skeels

Synonyms :Eugenia cumini L,Eugenia jambolana Lam,Syzygium jambolanum DC.

Common names:Jamun (Hindi, Urdu, and Bengali),Indian blackberry (English), Java plum (English),Jambolan (English),Black plum (English).[21]

PHYTOCONSTITUENT OF *SYZYGIUM CUMINI*:

1) Polyphenols

1. Gallic acid: Has anti-angiogenic properties, causes apoptosis, and inhibits the growth of cancer cells.

2. Ellagic acid: Has anti-mutagenic properties, causes apoptosis, and inhibits the proliferation of cancer cells.

3. Quercetin: Has anti-inflammatory properties, causes apoptosis, and inhibits the growth of cancer cells.[22]

Flavonoids

1. Kaempferol: Has anti-inflammatory properties, causes apoptosis, and inhibits the proliferation of cancer cells.

2. Myricetin: Has anti-inflammatory properties, triggers apoptosis, and inhibits the growth of cancer cells.[23]

2) Anthocyanins

a) Delphinidin: Has anti-inflammatory properties, causes apoptosis, and inhibits the proliferation of cancer cells.

2. Cyanidin: Has anti-inflammatory properties, triggers apoptosis, and inhibits the growth of cancer cells.[24]

b) Terpenoids

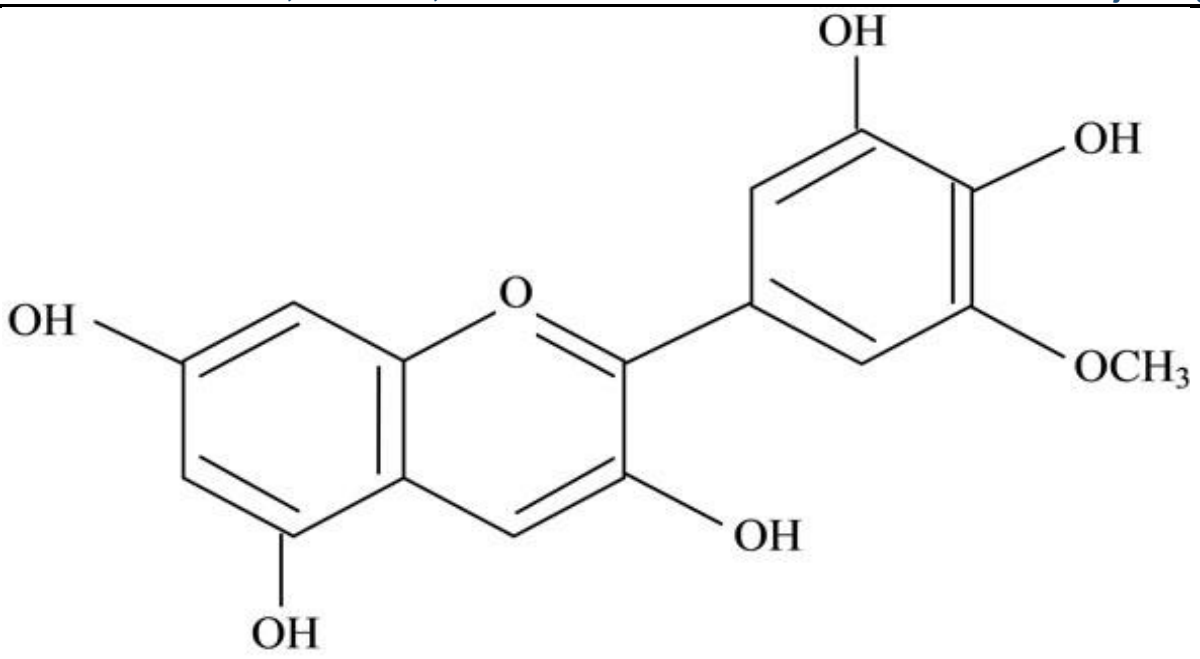
1. Ursolic acid: Has anti-inflammatory properties, causes apoptosis, and inhibits the proliferation of cancer cells.

2. Oleanolic acid: Has anti-inflammatory properties, causes apoptosis, and inhibits the growth of cancer cells.[25]

3)Additional phytochemicals

1. Jambosine: Has anti-inflammatory properties, causes apoptosis, and inhibits the proliferation of cancer cells.

2. Corosolic acid: Has anti-inflammatory properties, causes apoptosis, and inhibits the growth of cancer cells.[26]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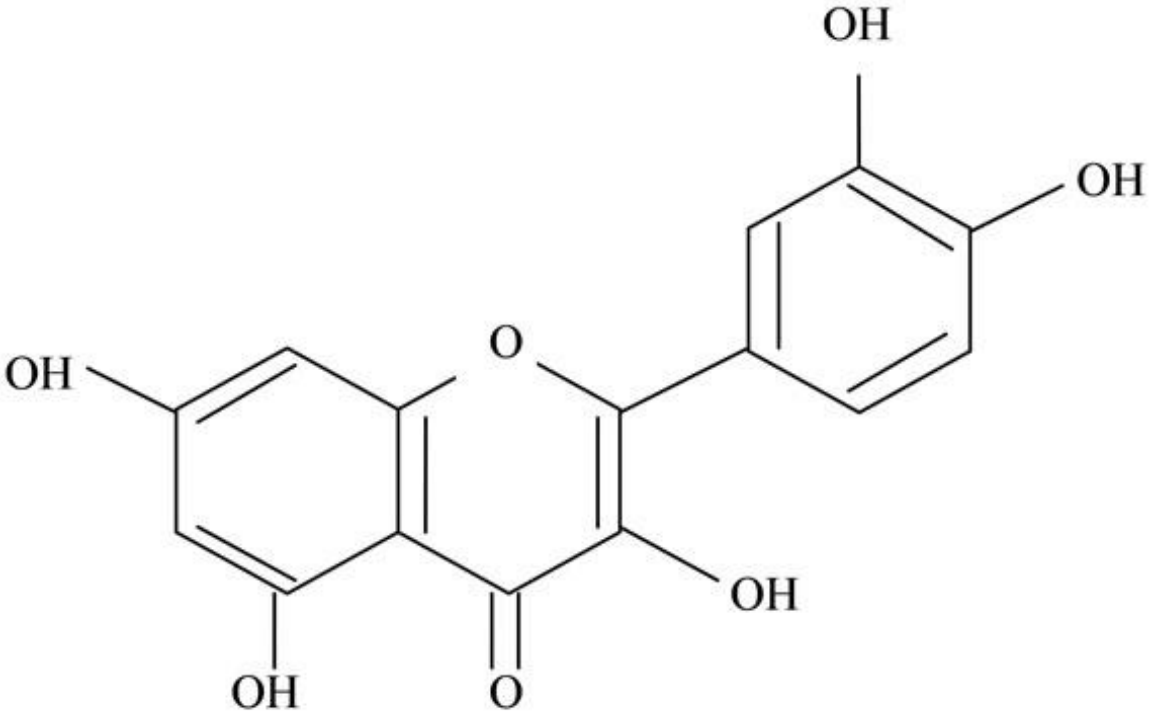
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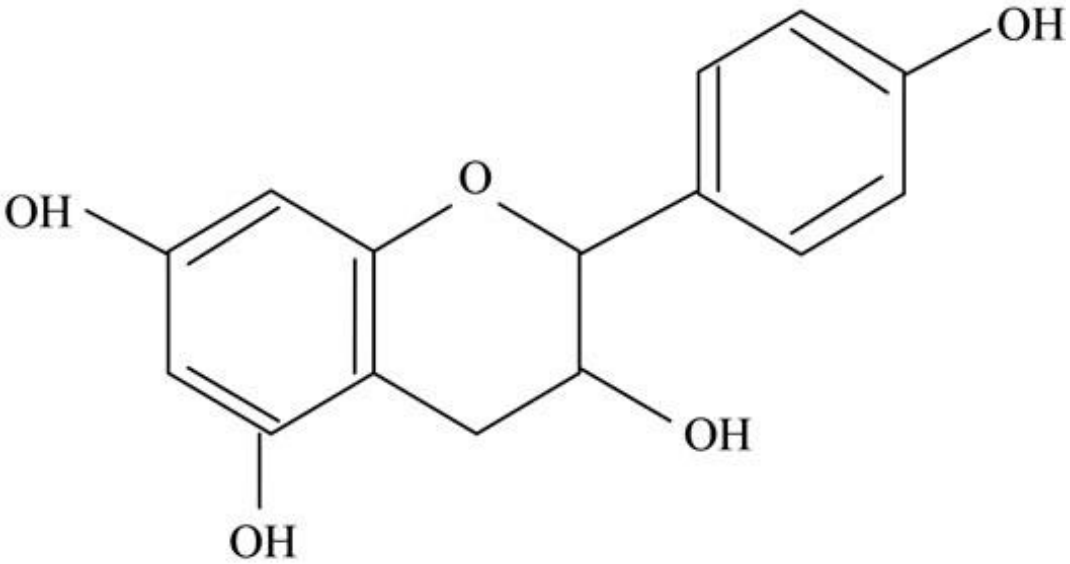
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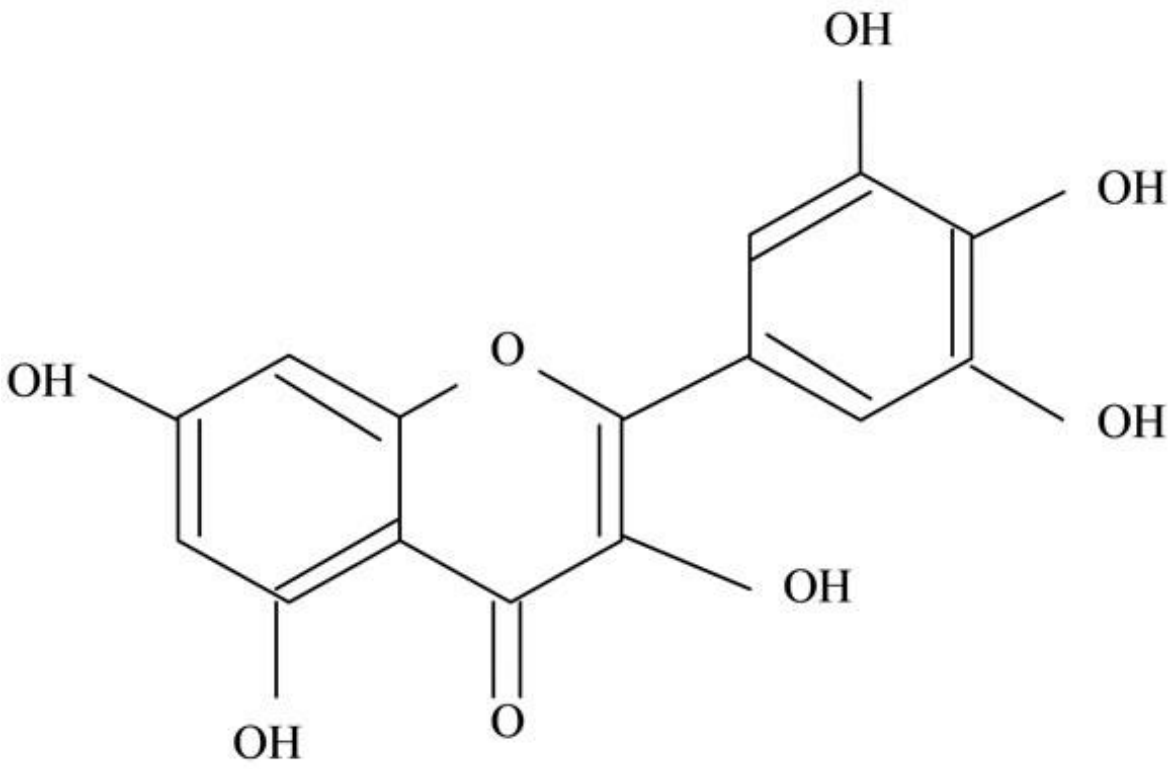

Mechanism of action of Syzygium cumini:

A. Antioxidant and Free Radical Scavenging :

1. Neutralisation of Free Radicals: Jamun's phytochemicals, including gallic acid, ellagic acid, and quercetin, neutralise free radicals, reducing oxidative stress and DNA damage.

2. Antioxidant enzyme activation: Jamun extracts activate antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, enhancing cellular antioxidant defences.[27]

B. Anti-Proliferative and Pro-Apoptotic Effects:

1. Inhibition of cancer cell proliferation: Jamun's phytochemicals, such as ursolic acid and oleanolic acid, inhibit cancer cell growth and proliferation.[28]

2. Induction of apoptosis: Jamun extracts induce programmed cell death (apoptosis) in cancer cells, reducing tumour growth and progression.[28]

C. Anti-Angiogenic and Anti-Metastatic Effects

1. Inhibition of angiogenesis: Jamun's phytochemicals, such as gallic acid and ellagic acid, inhibit the formation of new blood vessels, reducing tumour growth and metastasis.

2.Inhibition of metastasis: By preventing cancer cells from migrating and invading, jamun extracts lessen the likelihood of metastases.[29]

D. Signalling Pathway Modification

1. Inhibition of PI3K/Akt pathway: The phytochemicals in jamun reduce the survival and multiplication of cancer cells by inhibiting the PI3K/Akt signalling system.
2. MAPK pathway activation: By triggering apoptosis and inhibiting the development of cancer cells, jamun extracts stimulate the MAPK signalling system.[30]

E. Impact on Immunomodulation

1. Immune cell activation: The phytochemicals in jamun boost anti-tumor immunity by activating immune cells including macrophages and natural killer cells.
2. Immune suppressive cell inhibition: By preventing immune suppressive cells, such regulatory T cells, from activating, jamun extracts improve anti-tumor immunity.[31]

Uses of Syzygium cumini:

Ayurvedic medicine has long utilised jamun (Syzygium cumini) for its possible medicinal advantages, such as anticancer effects. Jamun has been investigated for its potential to treat a number of cancer forms, though further research is required to validate its efficacy.[32]

These cancer types include:

Cancer Types

1. Breast Cancer: It has been demonstrated that jamun extracts can cause apoptosis, or cell death, and limit the growth of breast cancer cells.[33]
2. Colon Cancer: The anti-inflammatory and antioxidant qualities of jamun may aid in halting the growth and multiplication of colon cancer cells.[33]
3. Liver Cancer: Research has shown that jamun extracts contain hepatoprotective properties that may help stop the growth and destruction of liver cancer cells.[34]
4. Prostate Cancer: The anti-inflammatory and antioxidant qualities of jamun may aid in halting the growth and multiplication of prostate cancer cells.[34]
5. Skin Cancer: It has been demonstrated that jamun extracts can cause apoptosis and stop the formation of skin cancer cells.[33]
6. Ovarian Cancer: The anti-inflammatory and antioxidant qualities of jamun may aid in halting the growth and multiplication of ovarian cancer cells.[34]

7. Cervical Cancer: It has been discovered that jamun extracts cause apoptosis and suppress the proliferation of cervical cancer cells.[35]

Materials and Methods-

1. Jamun Seeds

- Collected from mature Syzygium cumini fruits.
- Cleaned, dried, and powdered for extraction.[36]

2. Chemicals and Solvents

- Ethanol
- Methanol
- Hexane
- Dimethyl sulfoxide (DMSO)
- Phosphate-buffered saline (PBS)

3. Cell Culture Reagents

- Dulbecco's Modified Eagle Medium (DMEM)
- Fetal bovine serum (FBS)
- Penicillin-streptomycin solution
- Trypsin-EDTA

4. Cytotoxicity and Apoptosis Reagents

- MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) reagent
- Annexin V-FITC/Propidium iodide (PI) kit

5. Reactive Oxygen Species (ROS) Assay

- DCFH-DA (2',7'-Dichlorodihydrofluorescein diacetate)

6. Lab Equipment

- Soxhlet apparatus
- Rotary evaporator

- Microplate reader

- Fluorescence microscope

- Flow cytometer

- Incubator (37°C, 5% CO_2)

8. Analytical Instruments

- Spectrophotometer

- Centrifuge

Advantages of Using Jamun Seed Extracts for Cancer Therapy

1. Natural and Bioactive Compound Source:

Jamun seeds are rich in flavonoids, phenolic acids, and antioxidants, offering a natural alternative to synthetic drugs for cancer treatment with fewer side effects.[37]

2. Selective Cytotoxicity:

Studies have shown that Jamun seed extracts specifically inhibit the growth of cancer cells, such as Hep-2 cells, while sparing normal cells, reducing the likelihood of systemic toxicity.[38]

3.Multi-Targeted Mechanism:

The extract works through multiple pathways, including the induction of apoptosis, generation of reactive oxygen species (ROS), and inhibition of angiogenesis, enhancing its effectiveness against cancer.[39]

4. Anti-Inflammatory Properties:

The compounds in Jamun seeds help reduce inflammation, which is often associated with tumor progression and cancer development.[40]

5. Cost-Effective and Readily Available:

Jamun seeds are a by-product of the fruit and are abundantly available in many tropical regions, making them an affordable resource for therapeutic development.[41]

6. Antioxidant Power:

High levels of antioxidants in Jamun seeds protect against oxidative stress, which is a significant contributor to cancer cell survival and progression.[42]

7. Potential for Integration into Complementary Therapies:

The extract can be used alongside conventional cancer treatments, potentially enhancing their efficacy and mitigating side effects like oxidative damage.[43]

8. Environmentally Friendly Resource:

Using a plant-based approach promotes sustainability, utilizing natural waste (seeds) for therapeutic purposes, minimizing environmental impact. These advantages highlight the potential of Jamun seed extracts as a promising natural agent for developing safer and more effective anticancer therapies.[44]

Disadvantages of Using Jamun Seed Extracts for Cancer Therapy

1. Limited Clinical Evidence:

While in vitro and animal studies have shown promising results, there is a lack of robust clinical trials to confirm the safety and efficacy of Jamun seed extracts in humans.[45]

2. Variability in Composition:

The bioactive compound content in Jamun seeds can vary based on factors like geographical location, cultivation practices, and extraction methods, leading to inconsistent therapeutic outcomes.[46]

3. Potential Toxicity at High Doses:

Overuse or high concentrations of Jamun seed extracts may cause cytotoxic effects on normal cells, emphasizing the need for proper dosage standardization.[47]

4. Poor Bioavailability:

Some bioactive compounds in Jamun seeds may have limited solubility or stability in the human body, reducing their effectiveness when administered orally or topically.[48]

5. Unknown Long-Term Effects:

The long-term safety profile of Jamun seed extracts is not well-documented, which may pose risks when used as a prolonged treatment.[40]

6. Interaction with Conventional Therapies:

There is a possibility of interactions between Jamun seed extracts and conventional cancer treatments, such as chemotherapy or radiation therapy, which could reduce efficacy or cause adverse effects.[49]

7. Allergic Reactions:

Some individuals may experience allergic responses to plant-based products, including skin irritation or gastrointestinal discomfort.[50]

8. Challenges in Standardization:

The lack of standardized protocols for extraction, formulation, and quality control of Jamun seed products may hinder their development into reliable therapeutic agents.[50]

9.Resource Limitations:

Although Jamun seeds are widely available, large-scale production for therapeutic purposes might deplete local resources or compete with other uses of the plant.[49]

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