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Therapeutic Potential of Noni Fruit: A Review of its Anticancer and Immune-Modulating Properties

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ABSTRACT:

Morinda citrifolia L. (noni) is an evergreen shrub with a long history in Polynesian medicine, known for its medicinal uses spanning over 2,000 years. The fruit, characterized by its strong butyric acid odor, and the leaves are consumed for their various therapeutic properties, containing immune-modulating, antibacterial, antiviral, antifungal, and anti-inflammatory properties. The root is also used for dyeing. While laboratory studies have shown the fruit's antibiotic and antioxidant potential, human-based evidence supporting its health benefits is limited. Ongoing research is investigating its anticancer properties, and if proven, noni could significantly benefit the economies of producing nations.

KEYWORDS: Noni Fruit, Anticancer effect, Damnacanthal

INTRODUCTION:

Morinda citrifolia L. (Noni)

- **Synonyms:** Indian mulberry, Beach Mulberry, Great morbinda
- **Common name :** Noni fruit
- **Biological source :** Morinda citrifolia
- **Family:** Rubiaceae [1]

Fig.1: Noni fruit (morinda citrifolia)

Morinda citrifolia, commonly referred to as Noni in Southeast Asia, is an important medicinal plant that contains a wide range of phytochemical components, including alkaloids, flavonoids, and terpenoids, which are known to have antibacterial properties [2,3]. Different portions of M. citrifolia are traditionally used in some East Asian cultures to treat burns, headaches, arthritis, and even illnesses related to diabetes, hypertension, and TB [4]. Due to the identification and isolation of over 200 phytochemicals from different parts of the plant, it has also been proposed to possess antibacterial qualities [5].

Numerous bacterial species can be inhibited by the chemicals present in M. citrifolia's diverse plant structures. Photochemical investigations of the hexane and ethanol extracts of noni fruit revealed secondary metabolite chemicals, including flavonoids, terpenoids, alkaloids, and steroids [6]. Iridoids like acubin and pentacetyl-β-D-glucopyranose are bacterio-static substances [7]. These compounds were shown to have antibacterial properties against Shigella dysenteriae, Salmonella typhi, Escherichia coli, and Staphylococcus aureus in the pulp of M. citrifolia fruit. According to data, M. citrifolia casual root cultures may be an appropriate technique for the commercial production of biotechnology-based substances such as phenolics, flavonoids, rubiadin, and anthraquinones in order to lessen the effects of multi-drug resistance [2].

GEOGRAPHICAL DISTRIBUTION OF MORINDA CITRIFOLIA (NONI):

Morinda citrifolia, commonly known as Noni, is a small evergreen tree that thrives in coastal regions at sea level and up to 1300 feet above sea level. It often grows along lava flows and is characterized by:

- Straight trunk
- Large green elliptical leaves
- White tubular flowers
- Distinctive yellow, grenade-like fruit (up to 12 cm with a lumpy surface)
- Triangular and buoyant seeds

The plant's unique seeds facilitate its wide distribution across Polynesian islands. Despite its unpleasant taste and odor, Noni is not considered an endangered species in the wild (1).

MORPHOLOGY OF MORINDA CITRIFOLIA (NONI):

Size and Form:

Morinda citrifolia is a small evergreen tree or shrub, typically growing 3 to 10 meters in height. The plant exhibits variation in its form, fruit size, leaf morphology, fruit odor, and seed count (Figure-1)

Leaves:

- Opposite arrangement
- Pinnately veined
- Glossy
- Membranous, elliptic to elliptic-ovate shape
- 20–45 cm in length and 7–25 cm in width
- Glabrous blades with stout petioles (1.5–2 cm long)
- Stipules are connate or distinct, 1–1.2 cm long, with entire or lobed apices (Figure-2)

Flowers:

- Perfect flowers in ovoid to globose heads (75–90 flowers per head)
- White corolla with 5 lobes
- Greenish-white tube (7–9 mm long)
- Stamens (5) scarcely exserted
- Style approximately 15 mm long (Figure-3)

Fruit:

- Syncarp (compound fruit)
- Yellowish-white, fleshy, and 5–10 cm long
- 3–4 cm in diameter
- Soft and fetid when ripe (Figure-4)

Seeds:

- Contain air chambers
- Buoyant and viable after floating in water for months
- Chromosome count: 2n = 22, 44 (Figure-5) (8).

Figure – 2: Noni leaves

Figure - 3: Noni flower

Figure - 4: Noni fruit

Figure -5:Noni Seed

Biological Activity:

1. Antimicrobial activity
2. Antifungal activity
3. Antiviral activity
4. Anti-depressant activity
5. Antitumor activity
6. Hepatoprotective activity
7. Anti-diabetic activity
8. Anticancer activity
9. Anti- lipedemic activity
10. Immunostimulant activity

1. Antimicrobial Activity of Morinda citrifolia (Noni):

Powdered extracts of Noni leaves have been shown to inhibit the growth of various microorganisms, including:

- Escherichia coli (E. coli)
- Staphylococcus aureus (S. aureus)
- Candida albicans (C. albicans)
- Aspergillus niger (A. niger)

Dose Dependency: The growth inhibition of microorganisms increases with higher doses of Noni leaf extracts (9).

2. Antifungal Activity of Morinda citrifolia (Noni):

- Methanolic extract of dried Noni fruit demonstrated significant antifungal activity, with:
- 79.3% inhibition against Trichophyton mentagrophytes
- Approximately 50% inhibition against:
- Penicillium species
- Fusarium species
- Rhizopus species (10).

3. Antiviral Activity of Morinda citrifolia (Noni):

- The chemical 1-Methoxy-2-Formyl-3-hydroxyanthraquinone was extracted from Noni roots, has been identified as a potential antiviral agent.

- suppress HIV-infected MT-4 cells' cytotoxic actions
- Exhibit no cytotoxicity, as it does not inhibit cell growth or damage the endothelium (11).

4. Antidepressant Activity of Morinda citrifolia (Noni):

Noni, also known as Morinda citrifolia, possesses been investigated for its potential antidepressant properties.

Potential Use

- Noni has been studied alongside other plants, including:
- Hypericum perforatum, sometimes known as St. John's Wort
- Ginkgo biloba
- Valeriana officinalis (Valerian root) for treating depression and anxiety (12).

Mechanism:

According to recent research, Morinda citrifolia functions as an inhibitor of

- Monoamine Oxidase-A (MAO-A)
- Monoamine Oxidase-B (MAO-B) (13).

5. Antitumor Activity of Morinda citrifolia (Noni)

- Noni, also known as Morinda citrifolia, possesses been investigated for its potential antitumor properties.
- Synergistic Effects
- Noni-ppt, a compound derived from Noni juice, has been shown to:

Boost chemotherapy agents' effectiveness, including:

+ Cisplatin

+ Doxorubicin

+ 5-Fluorouracil

+ Vincristine

Improve survival time and show curative effects in cancer treatment (14).

Mechanism:

The antitumor effects of Noni juice are attributed to:

- Induction of vessel degeneration and apoptosis within days, at a concentration of 10% in growth media
- Inhibition of capillary initiation in human breast tumor explants (15).

6. Hepatoprotective Activity of Noni Juice:

- Noni juice has demonstrated significant hepatoprotective action against carbon tetrachloride (CCl_4)-induced acute liver damage in female Sprague-Dawley rats.
- Study Findings
- The placebo group, which received CCl_4 alone, showed significant liver damage.
- In contrast, the control group, which received Drinking water with 20% noni juice along with CCl_4, exhibited significantly reduced hepatotoxic lesions (16).

7. Anti-Diabetic Activity of Noni Juice

- The habitual consumption of Noni juice has been investigated as a potential adjunct therapy for managing type-2 diabetes.

Key Findings

- Combination therapy: Noni juice, when consumed in conjunction with oral hypoglycemic agents, has been reported to:
- Lower fasting glucose levelsReduce postprandial glucose levels

- Benefits for type-2 diabetes patients: The anti-diabetic activity of Noni juice may help improve glycemic control and mitigate the risk of diabetes-related complications.

Mechanism

- The benefits of noni juice for preventing diabetes are thought to be attributed to its:
- Antioxidant properties
- Anti-inflammatory effects
- Potential to enhance insulin sensitivity and glucose uptake in cells (17)

8. Anticancer Activity of TNJ (Tahitian Noni Juice):

Research has investigated the potential anticancer properties of TNJ, suggesting that it may help reduce cancer risk, particularly in heavy cigarette smokers (18).

Key Findings

Carcinogen DNA binding inhibition: Consuming 1-4 oz (30-120 ml) of TNJ daily may block the binding of carcinogens to DNA, potentially reducing cancer risk.

Clinical trial with smokers: A 30-day study involving 68 smokers found that taking 2 oz of TNJ twice daily provided protection against oxidative damage caused by cigarette smoke, which may lower cancer risk associated with smoking (19).

9. Antilipidemic Activity of Noni Seed Oil

Antilipidemic qualities of noni seed oil have been discovered to help control lipid profiles and lower the risk of cardiovascular disease.

Key Findings

- Studies on normal and hyperlipidemic mice demonstrated that Noni seed oil supplementation resulted in:
- Reduced total cholesterol levels
- Decreased triglyceride levels (20).

10. Immunostimulant Activity of Morinda citrifolia (Noni)

Noni, also known as Morinda citrifolia, possesses been found to possess immunostimulant properties, which can help enhance the body's immune response.

Key Findings

- The fruit of M. citrifolia has been shown to:
- Stimulate T and B lymphocytes, enhancing immune function
- Boost the immune system, providing potential protection against infections and diseases (21).

Fig.2: Morinda Citrifolia

CHEMICAL COMPOSITION OF NONI FRUIT (MORINDA CITRIFOLIA)

Noni fruit is rich in various bioactive compounds, contributing to its medicinal properties.

The key components include:

1. **Polysaccharides:**

Acemannan boosts immune function, while other polysaccharides exhibit antioxidant and anti-inflammatory effects.

2. **Iridoids:**

Scopoletin has anti-inflammatory, antimicrobial, and antihypertensive properties. Deacetylasperulosidic acid displays antioxidant effects.

3. **Phenolic Compounds:**

Quercetin and rutin provide antioxidant and anti-inflammatory benefits, supporting blood vessel health.

4. **Terpenoids:**

Limonene and β-sitosterol exhibit anti-inflammatory and anticancer effects.

5. **Xeronine Precursor:**

Involved in cell repair and function.

6. **Vitamins and Minerals:**

Rich in vitamin C (antioxidant), potassium (cardiovascular health), and trace amounts of vitamins A, iron, calcium, and magnesium.

7. **Alkaloids:**

Essential amino acids, such as lysine and methionine.

8. **Fatty Acids:**

Caproic and caprylic acids display antimicrobial properties, with small amounts of linoleic and oleic acids.

9. **Anthraquinones:**

Damnacanthal exhibits antimicrobial and anticancer potential (22).

CANCER:

- In 2020, cancer was responsible for around 10 million deaths, making it a major source of illness and mortality globally. Among the most prevalent forms of cancer are:
- Breast cancer: 2.26 million new cases
- Lung cancer: 1.8 million fatalities (highest number of deaths)
- Colon, rectum, and prostate cancers: significant incidence rates (23,24).
- In Malaysia, between 2012 and 2016, there were 115,238 new cancer cases, with breast cancer being the most common (19%) (25,26). Breast cancer is the most frequent malignancy and the second leading cause of cancer-related mortality in women (27).
- Despite advancements in surgical techniques and therapies, metastatic breast cancer remains a significant challenge without effective treatment options (28,29). The development of cancer is driven by uncontrolled cell growth, where proliferation exceeds cell death.Deregulation of apoptosis, a process frequently occurring in many cancer types, has become a critical target for anticancer treatments. Novel therapeutic approaches, including natural compounds, are being explored to combat cancer and improve patient outcomes **(30,31).**

PATHOGENESIS OF BREAST CANCER:

A malignant growth that starts in the breast's cells is called breast cancer. The development of breast cancer is a complex process, involving multiple factors that increase the risk.

Key Risk Factors:

1. **DNA damage and genetic mutations:**

Often linked to estrogen exposure, these mutations can disrupt normal cellular function.

2. **Inherited genetic defects:**

The risk can be considerably increased by mutations in genes including BRCA1, BRCA2, and P53, particularly in people with a family history of ovarian or breast cancer.

3. **Immune system failure:**

Normally, cancer cells and cells with damaged DNA are recognized and eliminated by the immune system. When this monitoring and immunological defense are compromised, breast cancer may occur.

4. **Disruptions in cell signaling:**

Abnormal communication between stromal and epithelial cells may have a role in breast cancer development (32).

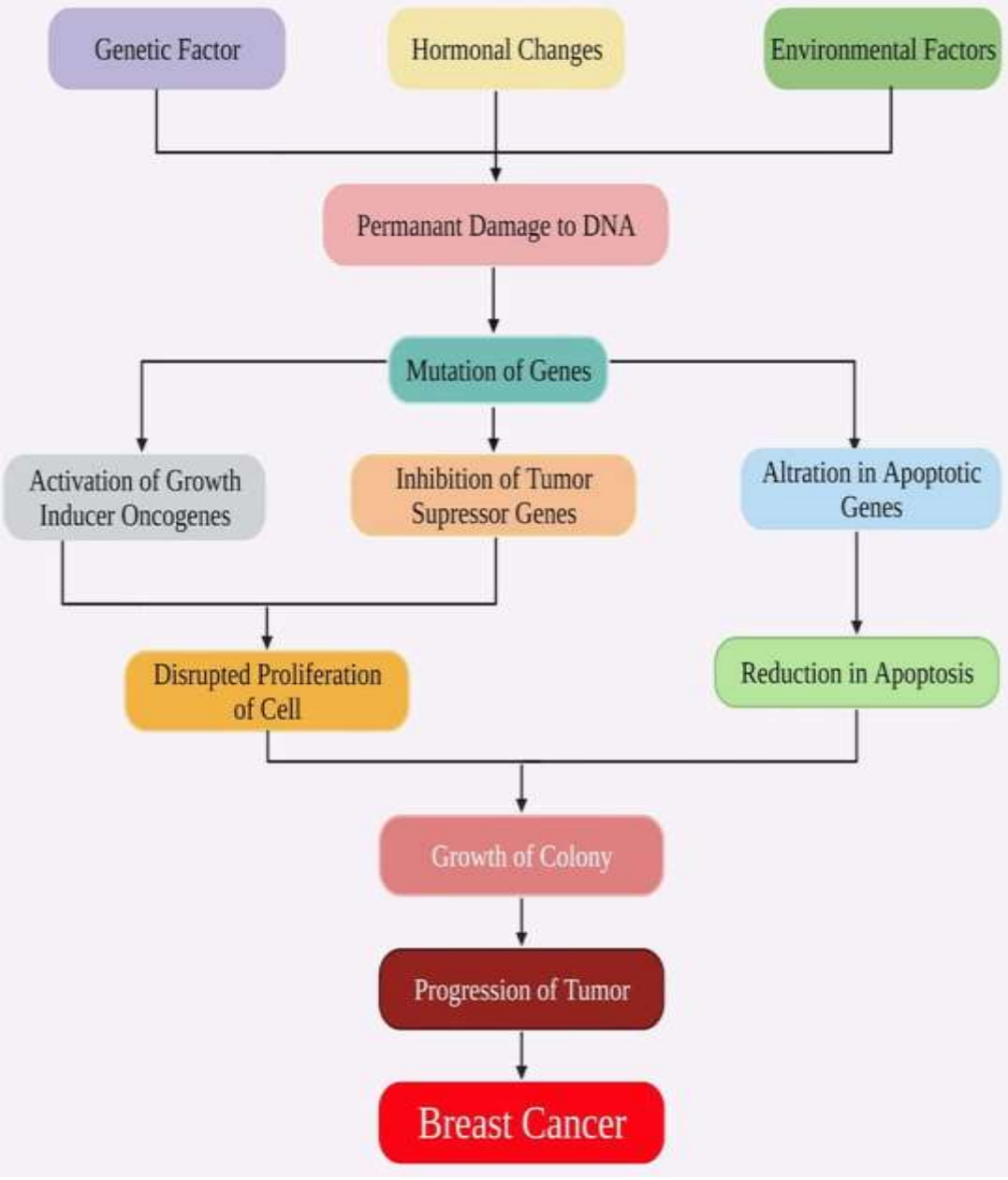

Fig.: Pathogenesis of cancer

ANTICANCER EFFECTS OF NONI FRUIT:

Despite the high expense of development, new synthetic chemotherapeutic drugs have not demonstrated therapeutic effectiveness in clinical settings during the past ten years. Therefore, creating new, efficient, and reasonably priced anticancer medications is crucial (33, 34). Because of their promise as innovative cancer prevention and treatment agents, plant products have grown in popularity over the past 30 years (35–37). Noni has also documented anti-mutagenic action, suppression of angiogenesis with capillary vessel degeneration, apoptosis, and prevention of the onset of carcinogenesis. It has been claimed that two components of Noni, an iridoid and a fatty acid glycoside, prevent the transformation of cancerous cells (38).

As a tyrosine kinase inhibitor, damnacanthal, a phytochemical anthroquinone component of Noni, inhibits the expansion of ras gene activation and inhibits the development of tumors (39). In human colorectal cancer cell lines, noni also induces apoptosis (40). By encouraging the thymus gland to release T lymphocytes that kill the carcinoma cells, limonene (an aromatic terpene) protects lung, liver, and breast cancers. Ursolic acid also stops the development of malignant cells by causing apoptosis (41). Noni's sulphated polysaccharides inhibit metastasis by destabilizing the connection between glycosaminoglycan and other proteins (42). Because of its antiangiogenic properties, alizarin (dihydroxy anthraquinone) is useful in the treatment of highly vascularized tumors (43).

According to clinical research, avoiding tobacco products, reducing alcohol intake, and leading a healthy lifestyle can all help reduce a large percentage of cancer-related mortality (44, 45). Remarkably, a number of Noni's components have shown promise in treating different kinds of cancer and tumors (46–50).

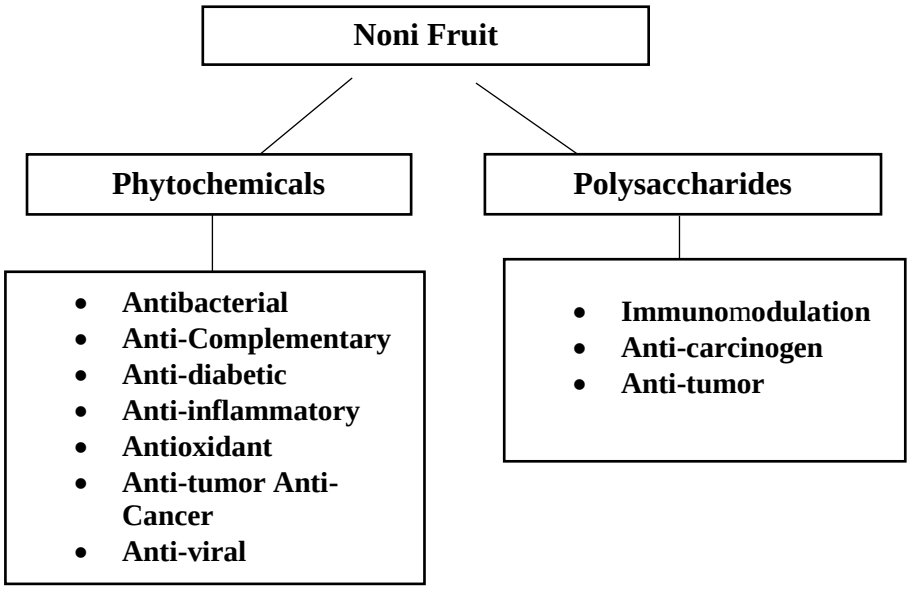

Fig.2. Biological activities of Noni fruit polysaccharides and phytochemicals.

ANTICANCER EFFECTS OF DAMNACANTHAL ANTHRAQUINONE:

Damnacanthal, an anthraquinone compound found in Morinda citrifolia (Noni), has demonstrated significant anticancer properties through multiple mechanisms:

Mechanisam Of Action:

1. Inhibition of Tyrosine Kinase Activity:

Damnacanthal inhibits c-Src, a tyrosine kinase involved in tumor growth, invasion, and metastasis, suppressing cancer cell proliferation and spread.

2. Induction of Apoptosis:

Damnacanthal triggers apoptosis by activating caspase-dependent pathways, increasing lowering anti-apoptotic proteins (like Bcl-2) and increasing pro-apoptotic proteins (like Bax).

3. Cell Cycle Arrest:

Damnacanthal causes cell cycle arrest at specific checkpoints (G0/G1 or G2/M phases), preventing cancer cell replication.

4. Anti-inflammatory Effects:

Damnacanthal reduces inflammation by suppressing inflammatory mediators like NF-κB and COX-2, associated with tumor growth.

5. Inhibition of Metastasis:

Damnacanthal affects the epithelial-to-mesenchymal transition (EMT) by downregulating matrix metalloproteinases (MMPs), which break down the extracellular matrix and promote metastasis.

6. Antioxidant Activity:

Damnacanthal reduces oxidative stress, protecting cells from DNA damage, a critical step in cancer development **(51).**

TREATMENT FOR BREAST CANCER:

Chemotherapy uses drugs to target and destroy rapidly dividing cancer cells, often in combination with surgery, radiation, or targeted therapies.

Types of Chemotherapy Drugs:

1. **Anthracyclines:** (e.g., Doxorubicin, Epirubicin)

Interfere with DNA replication, preventing cell division. Side effects include hair loss, low blood cell counts, and heart toxicity.

2. **Taxanes:** (e.g., Paclitaxel, Docetaxel)

Stabilize microtubules, inhibiting cell division. Side effects include nerve pain, fatigue, and nail changes.

3. **Antimetabolites:** (e.g., Capecitabine, 5-FU)

Disrupt DNA and RNA synthesis by mimicking normal cell components. Side effects include hand-foot syndrome, diarrhea, and mouth sores.

3. **Alkylating Agents:** (e.g., Cyclophosphamide)

Damage DNA, preventing cell reproduction. Side effects include infection risk, bladder irritation, and nausea.

4. **Platinum-based Compounds:** (e.g., Carboplatin, Cisplatin)

Form DNA crosslinks, disrupting cell division. Side effects include kidney damage, hearing loss, and nerve issues.

When Chemotherapy is Used:

1. **Neoadjuvant Chemotherapy:** administered before to surgery to reduce tumor size.
2. **Adjuvant Chemotherapy:** administered following surgery to eradicate any leftover cancer cells and lower the chance of recurrence.
3. **Metastatic Breast Cancer:** Controls cancer spread and relieves symptoms in advanced stages.

Administration Methods:

Chemotherapy can be administered:

1. Intravenously (IV)
2. Orally as pills
3. Via injection into a muscle or under the skin

Common Side Effects:

Chemotherapy can affect healthy cells, leading to:

1. Fatigue
2. Nausea and vomiting
3. Hair loss
4. Low blood cell counts (increased infection risk, anemia, bruising)
5. Long-term risks: heart damage, infertility, or secondary cancers (52).

CONCLUSION:

Noni is the popular name for the herbal treatment Morinda citrifolia. In Polynesian islands, different parts of the Noni plant have long been utilized as herbal remedies for a variety of illnesses. In addition to minerals, vitamins, and micro and macronutrients that are beneficial for a variety of illnesses,

several scientific publications indicate that it includes a wide range of chemical components, including amino acids, anthraquinones, fatty acids, flavonoids, iridoids, lignans, polysaccharides, sterols, and more. Because of its many modes of action and bioactive components, Morinda citrifolia has great promise as a supplemental anticancer drug. To determine its safety, effectiveness, and ideal application in the treatment of cancer, further thorough clinical research is required.

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