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Evaluation of Anticancer Potential of Some Herbal Formulations

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Abstract: India, sometimes referred to as the "Botanical Garden of the World," is the leading producer of medicinal plants worldwide. Medical plants provide basic materials for survival as well as natural treatments for a wide range of ailments. Two separate anticancer plant components, the fruit of Morinda citrifolia and the fruit of Opuntia elatior, were collected for the current investigation (bark and leaves of Simarouba glauca). The aforementioned plants' extracts were gathered. On the basis of DPPH and FRAP activity, the different approaches, such as bioactive compound analysis and antioxidant potential determination, were used. MTT analysis and Flow Cytometry Analysis were done to calculate anticancer activity. The study came to the conclusion that Opuntia elatior fruit extract mostly exhibits alkaloids, flavonoids, amino acids, and plant hormones among the various bioactive substances revealed by LC-MS/MS analysis. The Opuntia elatior fruit extract was subjected to a GC-MS/MS mass spectral analysis, which revealed a number of volatile bioactive compounds, including Neophytadiene, which has been reported to have anticancer and antioxidant potential, 9,12-Octadecadienoyl chloride, (Z, Z)-, Hexadecanoic acid, methyl ester. The number of cells in the G2/M phase of the cell cycle decreased and the number of cells in the G0/G1 phase increased in the cells treated with the Morinda citrifolia Leaf extract (MC1) as compared to the untreated reference. The plant alcohol extract of Opuntia elatior, Morinda citrifolia, and Simarouba glauca has potent anti-tumor activity, according to both the in vivo MTT assay and the flow cytometry research. Therefore, these plants have potent anti-cancer properties and can also stop cells in their tracks at specific cell cycle phases.

Keywords: Anti-cancer, Anti-oxidant, Anti-tumour, Flow Cytometry, MTT Analysis, Mass Spectral Analysis

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INTRODUCTION

Malnutrition, a shortage of food and medication, as well as an increase in industrialisation and environmental risks are all caused by the rising population pressure. Nutritional deficiencies and pesticide residues on fruits, vegetables, and food items cause the local populations to acquire cancerous consequences. The use of excessive amounts of non-prescription medications also contributes to the production of many carcinogenic metabolites. Changes in lifestyle, combined with drug and alcohol abuse, hormone therapy, and other factors, all contribute to the emergence of different malignancies. Radiation and chemotherapy are frequently used to eradicate the cancer-causing cells in order to treat these various types of cancers. The duration and dosage of these treatments cause a variety of side effects to emerge, which are then followed by a number of illnesses. So now is the perfect opportunity to research novel herbal combinations to test against various malignancies. Compared to radiation and chemotherapy, herbal formulations are safer, more environmentally friendly, and side effect free.

The vast majority of people worldwide rely on conventional medications. Due to the presence of different alkaloids, flavonoids, steroids, and polyphenols in medicinal herbs, the World Health Organization estimates that 80% of people living in rural areas rely on them as their major source of healthcare (Dhru

et.al., 2016 and Loc and Kiet, 2011). More than 60% of bioactive compounds that fight cancer come from natural sources. In India, 3000 traditional users employ the 45,000 different types of medicinal plants. India is therefore the world's greatest producer of medicinal plants and is referred to as the "botanical garden of the world" (Medical Plants India, 2010). Due to a rising awareness of the negative consequences of both designer drugs and medications, significant advancements are being made in the fields of pharmaceutical drug production and medicines. Plants also play a significant role in modern society and traditional medical systems (Kayastha, 2014). Products made from plants have gained major importance, not just in underdeveloped countries but also in Western Europe and the United States. Plant products are anticipated to play a significant part in healthcare programmes across all countries in the globe for a very long time (Nyeem et.al., 2017). There is little doubt that a thorough examination of native medicinal plants and their therapeutic potential would uncover a wide range of additional efficient remedies and broaden the scope of India's ancient methods (Umadevi et.al., 2013).

According to Motais et.al., 2020 most cancer treatments that have a multitude of side effects are treated using surgery, radiation, chemotherapy, immune, targeted hormone, and stem cell transplants. Both the percentage of deaths during recovery and those brought on by such therapy are rising daily. Thus, using a natural herbal composite product to treat patients is crucial. Thus, using a natural herbal composite product to treat patients is crucial. There has been a lot of interest in using conventional medicine to treat cancer. Therefore, scientific research into such composite herbal products is necessary to create natural cancer treatments.

The use of herbal medicine to treat people with harmful illnesses like cancer is universally acknowledged. Traditional Ayurvedic treatments have long included Triphala and other herbal concoctions as a healing tonic. In addition, it's possible that the number of active ingredients in the recipe, particularly tannins, are the primary causes reducing cell death via the production of free radicals in malignant cells. On the other hand, the three fruits of these plants are even rich in antioxidants that may effectively protect healthy cells from free radical damage (Wongnoppavich et.al., 2009).

About *Opuntia elatior*

Opuntia is a large genus of succulent plants native to the New World that are now widely grown in hotter climates due to their distinct personalities and alluring blossoms. Thorny pears were unintentionally brought into India and other eastern nations by early Western explorers who brought these crops to use as vegetables to prevent scurvy during their protracted voyages. They swiftly spread over neighbouring countries as well as India, becoming noxious weeds that dominated vast desert and developed areas (The Wealth of India, 2001).

Most of the 194 species that make up the *Opuntia* genus are found in dry and semi-arid regions. This shrub is native to many regions of the world, including the Mediterranean, Australia, Africa, and India. It is also native to the Caribbean, Central and South America, as well as the northern section of South America. West India is where one may find *Opuntia elatior* Mill. (The Wealth of India, 2001). Gujarat, Rajasthan, Madhya Pradesh, Maharashtra, Andhra Pradesh, Tamil Nadu, as well as a few other sparsely populated dry and semiarid areas around the nation.

Shrubby or subarborescent Subulate, recurved, reddish-tipped leaves with variable-sized joints that are obovate or elliptic in shape, rather thin, undulate-free, and dull bluish green in colour. Areoles with rust-brown, discrete glochidia that are nearly obscured by fuzzy hairs. 5 cm wide, yellow or orange flowers. The perianth rotates, with the inner spathulate segments being acutely spathulate, and the outer segments being short, oval, and crimson in the middle. A tiny bit shorter stamens than the perianth. Stigmas are six, and the style is larger than the stamens. When mature, the pyriform, angular, or rather warty berry becomes reddish purple and is covered in tufts of glochidia (Kirtikar and Basu, 1999).

Plate 1: *Opuntia elatior* Mill. A. Habit, **B.** Initiation of fruit, **C.** Green fruit, **D.** Fruit with flower, **E- F.** Red fruit

About *Mornida citrifolia*

Mornida L. belongs to the Rubaiceae family. Due to the fruit's resemblance to the *Mulberry indica*, the term *Morinda*, which is often referred to as the Indian Mulberry, is derived from the Latin word Morus, which means mulberry. In several nations, the genus *Morinda* is recognised by various local names.

It is abundantly produced in India's Andaman and Nicobar Islands and in the coastal regions of Kerala, Karanataka, and Tamil Nadu under natural conditions. It is discovered to be cultivated beside roads and fences in the coastal region, demonstrating its broad resilience to harsh environments (Rethinam and Sivaraman, 2007). Cooke (1903) noted the presence of noni in the coasts of Vengurla, Marmagoa and Malvan, Latur, Osmanabad, Nanded, and draught-prone Marathwada area districts in his Flora of Bombay Presidency (Naik, 1998). In Akola, Bombay, Jalgaon, Nagpur, Pune, Ratnagiri, the sea coast of Mumbai, and Thane, *Mornida citrifolia* is often farmed and also grows as an escape (Singh et.al. 2000). In Kolhapur district *Morinda* discovered in Panhala woodland, Kerala and Tamdalge (Yadav and Sardesai, 2002).

Small evergreen shrub or tree, ovate, wide elliptic, or oblong leaves, three long nodes per leaf, A terminal or axillary inflorescence Bisexual and protoandrous. The flower head that matured into a fruit, the calyx is

tubular, drastically reduced, and has few lobes. Corolla: Tube-shaped, actinomorphic, rather funnel-shaped. Stamens: Capitate, glabrous, and extended slightly beyond the corolla. Ovary: inferior, two or four locular, oblong, Fruit: globose syncarp that is densely clustered, initially green in colour, becoming white yellow when ripe; seed: vertical, ovoid to obovoid.

Plate 2: *Morinda citrifolia* L. A. Habit, **B.** Fruit with flowers, **C.** Healthy green fruit, **D.** Mature yellow fruit.

About *Simarouba glauca*

Simarouba glauca, a rainfed wasteland evergreen oil tree sometimes called "Laxmitaru" or "paradise tree," is a member of the Simaroubaceae family. The scientific name glauca, which alludes to the bluish-green leaves, literally means "covered with bloom" (Patil and Gaikwad, 2011).

The National Bureau of Plant Genetic Resources originally introduced it in 1966 at the research facility in Amravati, Maharashtra, then in 1986 at the University of Agricultural Sciences in Bangalore. It is grown in Orissa and Maharashtra in India, as well as at the beginning stages of planting in other states like Anand in Gujarat, Jodhpur in Rajasthan, Andhra Pradesh, Karnataka, Tamil Nadu, West Bengal, and Bhubaneswar (Orissa). The leaves are alternating, even, bluish oily green pinnately compound, with 3–21 oblong leaflets that are frequently notched or smooth at the apex. The terminal panicle's final branches produce a dichasial cyme in the inflorescence. Inconspicuous bisexual flowers have a green calyx that is formed like a dome and has a varied number of sepals. Single whorls of white, greenish or yellowish, creamy petals are present. The staminate blooms have a single ovule and gynophores but no carpel.

Plate 3: *Simarouba glauca* DC. A. Habit, **B.** Inflorescence, **C,D.** Single Flower

Plants Used Cancer

India, which is rightfully referred to as the "Botanical Garden of the World," is the world's leading producer of medicinal herbs. In addition to providing natural therapeutic benefits against many ailments, medicinal plants also offer high-quality food and raw materials for subsistence. On the basis of their traditional applications and scientific studies, significant research has been done on these plants to cure cancer, and certain plant components have been sold as anticancer medications. By restoring the body's homeostasis and training the bodily tissue, these plants may help the host develop resistance to infection (Umadevi 2013).

MATERIAL & METHODS

Materials

Fruit of *Morinda citrifolia* was taken from (------), whereas fruit of *Opuntia elatior* was gathered from (----------), two different anticancer plant parts (bark and leaves of *Simarouba glauca*). The plant material was verified utilising appropriate literature and prototypical consultation. The plant portion that was taken was

cleaned with running water before being extracted and having its anticancer activity studied.

Methods

Extract Preparation: *Opuntia elatior, Morinda citrifolia, and Simarouba galuca* plant material was extracted continuously in a Soxhlet device for 12 hours using ethanol as the solvent (boiling range: 40–45^{O}C) (Horwitz, 1980). Using a rotary evaporator, the solvent from the extraction was removed, and the resulting powder was dried over anhydrous sodium sulphate before being kept at 40°C for future investigation. For the further analysis, several ethanolic extract concentrations were generated.

Bioactive Compound Analysis (GC-MS/MS): To identify the various bioactive components, ethanolic extract from *Simarouba glauca, Opuntia elatior, Morinda citrifolia* leaves, and fruit were injected into GC-MS. The non-polar 60 M RTX 5MS column used in the Shimadzu manufacture QP-2010 GC-MS analysis of the ethanol extract was used. For these analyses, helium gas was employed as the carrier gas, with oven temperatures of 400°C for the first three minutes and 480°C with a rate of 100°C for the following three minutes

Bioactive Compound Analysis (LC-MS/MS): With the aid of a 6200 series TOF/6500 series Q-TOF B.05.01 (B5125.3) LC-MS apparatus, the alcoholic extracts of*Simarouba glauca's* bark, leaves, and fruits, as well as those of *Opuntia elatior and Morinda citrifolia*, were examined. A slope of collision energies between 5-45 eV was applied to the fragmentation of precursor ions in the collision cell after they had been chosen in Q1 with an isolation width of 2D.

Determination of Antioxidant Potential:

DPPH Activity: The DPPH technique (Koleva et.al., 2002) was used to determine the extract's DPPH radical scavenging activity. Methanol was added to the mixture of 2.5 ml of 0.1 mm DPPH and 0.1 ml of plant extract to make 3 ml in total. The reaction mixture's absorbance was measured at 517 nm at 0 and 30 minutes. The computation employed the common BHT. The percentage of inhibition used to express the scavenging action is indicated below: % discolouration = 1 - Abs sample / 100 - Abs control.

FRAP Activity: The total antioxidant strength of fruit extract was determined using the ferric reducing/antioxidant power (FRAP) test. The FRAP assay, which relies on the reduction of ferric tripyridyltriazine (fe(III)-TPTZ) complex to ferrous tripyridyltriazine (fe(II)-TPTZ) by a reductant at low pH, was used to determine the total antioxidant capacity of the fruit sample. Antioxidant activity assay were carried out in accordance with the method described by Benzie and Strain (1996).

Determination of Anticancer Activity:

Preparation of Plant Material: The sample was prepared using the following techniques: *Simarouba glauca* leaves and bark, *Morinda citrifolia* fruit, and *Opuntia elatior* fruit were all harvested from their native habitats. The plant material was extracted continuously for 12 hours in a Soxhlet system using ethanol as the solvent

MTT Analysis: This colorimetric test evaluates the degree to which mitochondrial succinate dehydrogenase reduces the yellow dye 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide

(MTT). The MTT penetrates the cells and travels to the mitochondria, where it is converted to a formazan product that is insoluble and coloured (dark purple). The released, solubilized formazan reagent is evaluated spectrophotometrically after the cells have been solubilized with an organic solvent (e.g., 0.5% DMSO, isopropanol). The amount of activity is a gauge of the viability of the cells since decrease of MTT can only happen in metabolically active cells.

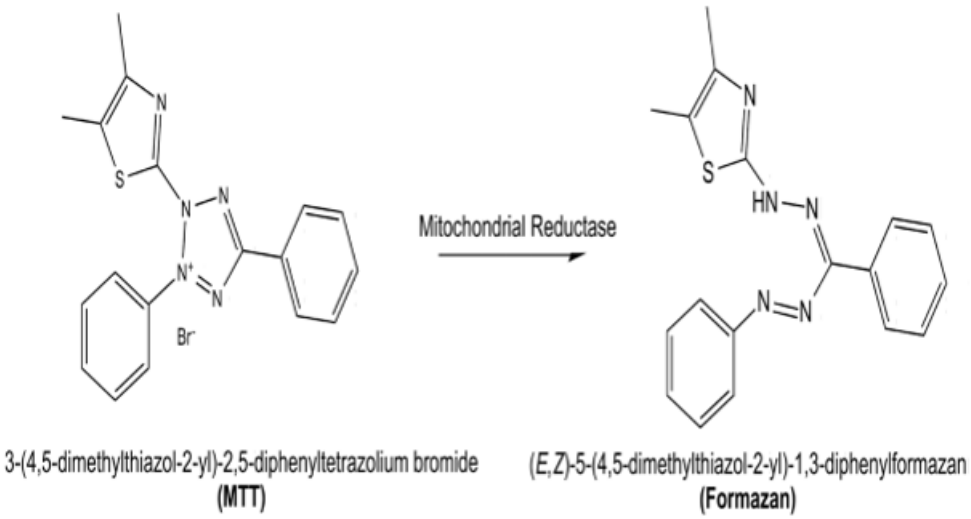

Figure 1: MTT Analysis

Flow Cytometry Analysis: Six-well plates with seeded cells underwent a 24-hour incubation period at 37°C. Cells were exposed to the test chemicals at their IC 50 concentration for 16 hours before being trypsinized and transferred to 15 ml tubes. After washing with 1X DPBS twice, cells were fixed in cold 70% ethanol (-20oC), resuspended in 400 l of PI-RNase solution per million cells, and transferred to 1.5 ml tubes. Samples were thoroughly combined before being examined by a Beckman Coulter, USA, Cytomics FC500 Flow Cytometer (Pozarowski and Darzynkiewicz, 2004).

RESULTS

The numerous bioactive chemicals discovered by LC-MS/MS analysis mostly display alkaloids, flavonoids, amino acids, and plant hormones in *Opuntia elatior* fruit extract. This can be depicted in Table 1.

Table 1: Analysis of major compounds in *Opuntia elatior* extract by LC-MS/MS

Name	Formula	Mass	RT	Anticancer Properties
Sulfabenzamide	C13 H12 N2 O3 S	276.0556	0.672	Breast cancer cell line T-47D
Arecoline	C8 H13 N O2	155.0957	0.962	Breast cell line p53.

				Human Leukemia Cell Line K 562.
				Human Oral Cancer Cell line T28.
Kinetin	C10 H9 N5 O	215.0788	1.051	Breast cancer cell line MCF-7
Leucine	C6 H13 N O2	131.094	1.089	Liver cancer cell line Hep G2 and Kidney cancer cell line A549.
				Human urinary bladder cell line T24.
				MARY-X human breast tumor xenograft.
				Chinese hamster cells line CHO (Ovary Cancer).
				Breast cancer cell line MDA-MB-231 and MCF-7
Chlorpromazine	C17 H19 Cl N2 S	318.0949	3.668	Colorectal cancer cell line HCT116 and Kidney cancer cell line A549.
				Human cervical cell line HeLa
Eseroline	C13 H18 N2 O	218.1414	5.524	Myeloma cell line RPMI 8226
Rhamentin	C16 H12 O7	316.0577	5.915	Ehrlich's ascites carcinoma cell line (EAC).
				Breast cancer cell line MCF-7
Bilirubin	C33 H36 N4 O6	584.2634	20.104	Colon cell lines HCT15, HCT116, SW480 and Lo Vo.
				Human gastric cancer cell line TMK-1 cell line

The *Simarouba glauca* leaves extract contains sixteen bioactive compounds with anticancer activity: Anisomycin, Dantrolene, Dihydromyricetin, Goyazensolide, HC Toxin, Hexahydrocurcumin, Lauric acid, Lycopodine, Minocycline, Mitomycin, Monensin, Nevirapine, Ouabain, Pristimerin, Procyanidin B1, Trolamine, Ursolic acid -Shogaol, Archangelicin, Carteolol, Coronatine, Digoxin, Ellagic acid, Entacapone, Eupacunin, Evocarpine, Harmalol, Lupulone, Lutein, Mitoxantrone, Nevirapine, Pyocyanine, Quercetagetin, Rotenone, Tamsulosin, Theophylline.

Breast cancer is caused by the chemical sulfabenzamide (Mohammadpour et.al., 2012.). Arecoline, derived from Areca catechu, was discovered to have anti-breast cancer, anti-blood cancer, and anti-oral cancer characteristics.

Table 2: Effect of leaves extract of *Simarouba glauca* on Breast cancer

Cell line	**Media**
MCF-7 (Breast cancer lines)	DMEM with low glucose (Cat No-11965-092)
IC 50 VALUE OF *Simarouba glauca* leaves	61.16 µl/ml
Concentration µl/ml	**SG**
400.0	30.18
200.0	32.37
100.0	38.13
50.0	41.24
25.0	71.20
12.5	78.23
Normal Cell	100

The *Opuntia elatior* fruit extract was subjected to a GC-MS/MS mass spectral analysis, which revealed a number of volatile bioactive compounds, including 9,12-Octadecadienoyl chloride, (Z, Z)-, Hexadecanoic acid, methyl ester, and Neophytadiene, which has been reported to have anticancer and antioxidant potential. Thus, following testing for toxicity and clinical research, the volatile chemical identified and extracted from the fruit of Opuntia elatior may be utilised to create a medication to treat leukaemia or blood cancer.

In comparison to the untreated control, the cells treated with the *Morinda citrifolia* Leaf extract (MC1) showed a decrease in the number of cells in the G2/M phase of the cell cycle and an increase in the G0/G1 phase. A reduction in the number of cells in the G2/M phase of the cell cycle was followed by an increase in the SubG1 (DNA damaged) population.

CONCLUSION

Medical plants offer both essential components for living and all-natural cures for a variety of diseases. The fruit of *Morinda citrifolia* and the fruit of *Opuntia elatior*, two distinct anticancer plant components, were gathered for the current experiment (bark and leaves of *Simarouba glauca*). Extracts from the aforementioned plants were obtained. The various methods, including bioactive compound analysis and antioxidant potential evaluation, were applied based on DPPH and FRAP activity. To determine anticancer activity, MTT assay and flow cytometry analysis were performed. The study came to the conclusion that, among the various bioactive substances identified by LC-MS/MS analysis, *Opuntia elatior* fruit extract primarily exhibits alkaloids, flavonoids, amino acids, and plant hormones. A GC-MS/MS mass spectrum investigation of the *Opuntia elatior* fruit extract identified many volatile bioactive chemicals, including Neophytadiene, which has been shown to have anticancer and antioxidant potential, 9,12-Octadecadienoyl chloride, (Z, Z)-, Hexadecanoic acid, and methyl ester. When compared to the untreated control, the number of cells in the G2/M phase of the cell cycle reduced and the number of cells in the G0/G1 phase rose in the cells treated with the *Morinda citrifolia* Leaf extract (MC1). Therefore, both the in vivo MTT-assay and the flow cytometry studies show that the plant alcohol extract of *Opuntia elatior, Morinda citrifolia, and Simarouba glauca* has powerful anti-tumor action. These plants therefore possess strong anti-cancer qualities and have the ability to halt cells in their tracks at particular cell cycle stages.

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