

UNCOVERING THE ANTI-CANCER POTENTIAL OF AEGLE MARMELLOS: A COMPREHENSIVE OVERVIEW

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Abstract: Aegle marmelos, commonly known as Bael, is a medicinal plant that has been extensively studied for its potential in inhibiting cancer growth. Several bioactive compounds present in the different parts of the plant, such as fruits, bark, leaves, seeds, and roots, have been identified to exhibit anti-cancer activity. This review presents an overview of the current research on the anti-cancer activity of Aegle marmelos. Various in vitro and in vivo studies have demonstrated the anti-cancer potential of this plant against different types of cancers such as breast cancer, colon cancer, and liver cancer. Aegle marmelos exhibits anti-tumor activity in cancer cell lines and has also been found to have antioxidant and immune-modulatory properties. The article emphasizes the need for further research to investigate the mechanisms behind the anti-cancer effects and identify the active compounds responsible for the anti-cancer activity of Aegle marmelos. Overall, Aegle marmelos holds great promise as a natural remedy for cancer treatment and has the potential to become a valuable addition to conventional cancer therapy.

Key words: Bael, cancer, antioxidant, cell lines, anti-tumor

Introduction:

Bael is a widely-cultivated indigenous fruit of India and the subcontinents that is a member of the Rutaceae family and has significant mythological importance. Many medicinal uses of bael are known from prehistoric time which is mentioned in ancient system of medicine.^[5,6] These medicinal uses are due to its active chemical constituents (phytoconstituents) that can produce a definite physiological action. Various parts of bael plant like leaves, bark, stem, fruit, seeds contain different active chemical constituents like alkaloids, terpenoids, flavonoids, cardiac glycosides, polysaccharides, saponins, steroids and tannins.^[3] This plant serves as climate purifier as it releases greater amount of oxygen.^[7] It can tolerate drought conditions as well as high rainfall.^[8] Bael is an ethnomedical plant native to India that is also found in a number of other nations, including Egypt, Malaysia, Myanmar, Pakistan, Bangladesh, and Sri Lanka.^[1]

This plant has been thoroughly examined using advanced scientific methods in recent years and has been reported for a variety of medicinal properties, including anti-cancer activity, anti-bacterial activity, anti-diarrhoeal activity, anti-fungal activity, anti-diabetic activity, antioxidant activity, hepato-protective activity, anti-ulcer activity, antimicrobial activity, and anti-inflammatory activity, among others. Every component of the Bael plant, including the leaves, roots, barks, seeds, and fruits, is used in numerous conventional medicines to treat a variety of ailments, and bioactive chemicals have been extracted from it.^[8] Several other names for this plant include bael, Bilva, Sriphal, Bengal quince, golden apple, wood apple, etc. It is grown as a garden plant, and Lord Shiva's prayers include the leaves of this plant.^[2] The bael fruit is a rich source of tonics, vitamins, carbohydrates, proteins, oils, and various medicinal compounds. It also has a high nutritional value. Fruits are therefore also used to produce a wide range of by-products including candy, toffee, jam, juice, etc. with the use of various post-harvest technologies. As a result of these innovations, the shelf life of Bael products is extended by

lowering post-harvest losses. Thus, it is a reliable source of revenue for a farmer in need.^[1,3,6] This review's goal is to provide an overview of the phytochemistry and findings from the tests conducted to determine *Aegle marmelos*'s anti-cancer potential

Taxonomical Classification^[10]

Table No. 1: Taxonomical Classification

Kingdom	Plantae
Species	<i>Marmelos</i>
Genus	<i>Aegle</i>
Family	Rutaceae
Order	Sapindales
Sub-class	Rosidae
Class	Magnoliopsida
Super-division	Spermatophyte
Division	Magnoliophyta
Sub-kingdom	Tracheobionta

Vernacular Names of *Aegle marmelos*^[2,16]

Table No. 2: Vernacular Names of *Aegle marmelos*

English	Indian quince, Golden Apple, bael fruit, elephant apple, Indian bael, Stone Apple, Holy Fruit
Hindi	Bel, Beli, Belgiri, Baelputri, sirphal, kooralam
Urdu	Bel, Bel kham
Sanskrit	Shivadruma, Bilva, Vilva, Shivaphal
Bengali	Bael
Telugu	Bilvapandu
Tamil	Vilvamarum
Kerala	Kuvalum
Oriya	Belo
Portuguese	Marmelo
Thai	Mapin, Matum
Indonesia	Mojo tree



Figure.1: Plant Leaves Figure.2: Plant Fruit

Topographical Allocation

Aegle marmelos is a subtropical plant that thrives at a about 1200 metre elevation above sea level. It is usually found in mountainous terrain and dry forests. It is currently growing across the majority of Indian states, including West Bengal, Punjab, Rajasthan, Uttar Pradesh, Tamilnadu, Kerala, Karnatka, Himachal Pradesh, Arunachal Pradesh Jammu and Kashmir, Bihar. In addition, it is grown in places like Vietnam, Tibet, Ceylon, Laos, Cambodia, Malayasia, Sri Lanka, Bangladesh, Nepal, Myanmar, Thailand, Java's dry parts, Fiji, Indonesia and some Philippine Islands.^[2,8,11]

Botanical Description^[1,2,7,17]

Aegle marmelos is a average-sized, slow-developing deciduous tree that can grow up to 12 to 15 metres tall and spread out with spiny branches. It has a short trunk, dense crown, and fuzzy, peeling bark. This tree is capable of adjusting to unfavourable soil and climate conditions. When completely grown, the branches' 3 cm-long, straight-shaped spines, which are derived from the leaf axis, are present. The compound trifoliolate leaves have leaflets that are oval or lance-shaped and measure 4–10 cm long and 2–5 cm wide. It has flowers that are greenish white in colour and grow in clusters of 4–7. Flowers feature four recurved petals and an odd scent. May and June are the months when flowers bloom. The exterior of a fruit is smooth and firm (i.e., pericarp). The bael fruit ranges in diameter from 5 to 20 cm and has a variety of shapes, including round, oval, oblong, and pyriform.^[11]

Morphological Characteristics of Plant Parts:

Table No. 3: Morphological Characteristics of Plant Parts

Plant Parts	Morphological Characteristics
Leaf	Bael leaves are trifoliolate, with rounded bases and pointed points. Leaflets range in size from 4 to 10 cm and are 2 to 5 cm wide. The petiole of the terminal leaflet is lengthy. An unpleasant stench is emitted when mature leaves are damaged.
Flower	A cluster of four to seven fragrant flowers with four fleshy, recurved petals that are green on the outside and yellowish on the inside, as well as 50 or more greenish-yellow stamens, are arranged along the immature branchlets.
Fruits	A rigid outer jacket and a diameter of roughly 5 to 12 centimetres characterise the bael fruit. When unripe, it is green; once ripe, it turns golden brown. Inside, there may be 20 orange pulp pieces.
Seeds	10-15 flattened-oblong seeds can be found in the pulp. Each seed is encased in a sack of sticky, transparent mucilage that solidifies when dried. The seeds are about 1 cm long, have fuzzy hairs, and are covered in this sack.
Bark	The bark has a brownish or grey colour and has several long, straight spines. It includes gum that frequently leaks from broken branches before solidifying. These gums are best described as a transparent, gooey sap. When first tasted, it is delicious but soon becomes throat-irritating.

Phytoconstituents:

The active chemical components from various Bael plant parts have been identified through a number of research projects. *A. marmelos* has undergone extensive research on various components, leading to the isolation of many types of compounds, including alkaloids, coumarins, terpenoids, fatty acids, and aminoacids. Notably, the majority of studies on compound and isolation characterizations have been submitted by numerous Indian workers.^[2]

Alkaloids, cardiac glycosides, terpenoids, saponins, tannins, flavonoids, and steroids have all been found to be present in the extracts made from *Aegle marmelos* leaves using various organic solvents. Steroids, terpenoids, flavonoids, phenolic compounds, lignin, fat and oil, inulin, proteins,

carbohydrates, alkaloids, cardiac glycosides, and flavonoids have all been found in the fruit pulp of *Aegle marmelos*.^[14] GC/MS profiling of *A. marmelos* extract detected a total of 51 compounds.^[10]

Phytoconstituents, isolated from various portions of the plant ^[14, 17]

Table No. 4: Phytoconstituents, isolated from various portions of the plant

Serial number	Plant Parts	Phytoconstituents
1.	Leaf	Eugenol, lupeol, Skimmianine, citral, Aegeline, Cineole, Citronellal, Cuminaldehyde, mermesinin, rutin, phenylethyl cinnamides, anhydromarmeline, and aegelinosides, sterols, and essential oils.
2.	Bark	Skimmamine, MarminFagarine, Aegelinol
3.	Fruits	Marmelosin, Luvangetin, Aurapten, Psoralen
4.	Seeds	d-Limonine, Cineole, Citral
5.	Roots	Psoralene, Xanthotoxin, Scopoletin, Tembamide

Chemical Composition of *Aegle marmelos*^[12,19,30]

Table no. 5: Chemical Composition of *Aegle marmelos*

Chemical Class	Phytoconstituents
Coumarins	The main component of bael fruit gum is called marmelosin. <i>A. marmelos</i> contains other compounds from the coumarins class, such as marmin, alloimperatorin, xanthotoxol, scoparone, gummarmesin, imperatorin, methyl ether, scopoletin, umbelliferone, psoralen, and marmelide. Marmenol, 7-geranyloxy coumarin has also been stated.
Alkaloids	Marmeline, dictamine, aegelin, aegelenine, fragrine are some alkaloids present in the bael tree.
Polysaccharides	Galactose, arabinose, uronic acid, and L-rhamnose are obtained on hydrolysis.
Seed Oil	Palmitic, stearic, oleic, linoleic and linolenic acid.
Tannins	There is as much as 9 % tannin in the pulp of wild fruits and less in cultivated form. Also, tannin is present in leaves in form of Skimmianine
Carotenoids	The pale color of the fruit is due to the presence of Carotenoids. Marmelosin, Skimmianine, and umbelliferone are the therapeutically main component of the bael plant.

Leaves: Coumarins (mermenol and praeltin), O-(3,3-dimthylally) halofordinol, N-4-methoxystyryl cinnamide, and N-2-methoxy-2-[4-(3',3'-dimethyl allyloxy)phenyl] ethyl cinnamide are among the chemical components recovered from the leaf section.

Fruits: In addition to tannins and alkaloids like aegeline and marmeline, bael fruits also contain xanthotoxol, imperatorin, alloimperatorin, and –sitosterol. Tannin levels were discovered to increase as fruits ripened, with fully ripe fruits having the greatest tannin levels. Only completely ripe fruits contain

riboflavin, a vital vitamin. The ascorbic acid level does, however, considerably decline as fruit ripens, suggesting a marked decline in antioxidant activity with maturation. Sesquiterpenes and monoterpenes make up the majority of the volatile substances in bael. ^[11]

Nutrient Profile of Bael Fruit^[11]

Table No. 6: Nutrient Profile of Bael Fruit

Components	Amount present in 100 g of bael fruit flesh
Vitamin C	8.0mg
Niacin	1.1mg
Riboflavin	1.2mg
Carotene	55.0mg
Thiamine	0.1mg
Carbohydrates	31.8g
Minerals	1.7g
Proteins	1.8g
Fat	0.4g

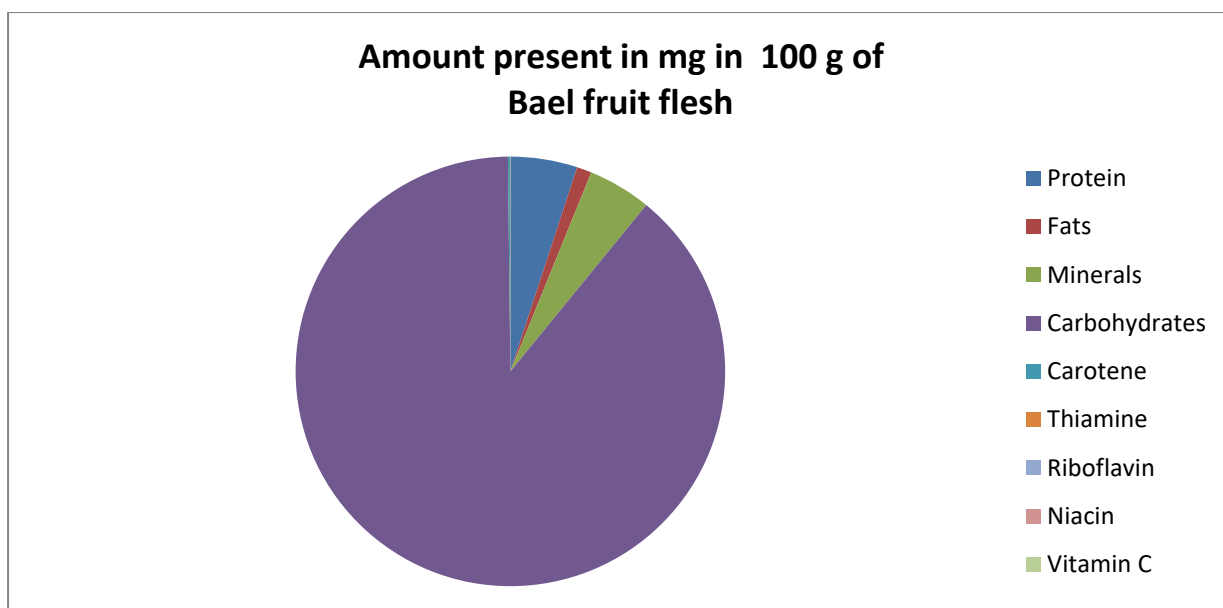


Figure 3: Pie Chart of Nutritional Profile of Bael Fruit

Traditional uses

Nearly whole parts of the bael tree are medicinally useful like flower, fruit pulp, leaves, root, stem bark, etc. We have talked about the conventional applications for *A. marmelos* in this part.

Fruit

Traditional medicine has employed both the ripe and unripe fruit to treat chronic diarrhoea and dysentery. Fresh fruit pulp juice is made and drunk twice in cases of persistent dysentery. Slices of the green fruit are dried in the sun, and the powder made from them is used to treat diarrhoea and dysentery. Consuming ripe fruit sharbat, made from pulp, milk, and sugar, can help ease constipation. For the treatment of intestinal parasites like *Entamoeba histolytica*, fine fruit powder is ingested with water. ^[18]

Leaves:

As well as treating asthma, leaves have a minor laxative effect. Jaundice, constipation, and dropsy are all treated with bael leaf juice, which is used in cases of abnormal liquid collection in cellular tissue (dropsy). Bael leaves are decocted and used as an expectorant as well as a means of lowering high body temperatures (fever). Hot poultices are applied for bronchitis and cases of inflammation of the conjunctiva or other regions. To treat an abscess, a bael leaf paste was applied to the diseased area and bandaged.^[18,19] By stimulating glucose uptake in a manner similar to that of insulin, bael leaf improves the body's capacity to use the external glucose load. Bael extract significantly lowers blood urea, lipid peroxidation, and cholesterol in experimental diabetic rats while raising superoxide dismutase, catalase, glutathione peroxidase, and glutathione levels in serum and liver.^[15]

Root:

The root contains alcohol, and the stem and bark can also be helpful for hypochondriasis and heart palpitations as well as intermittent fever. It is the source of the components used in Ayurvedic remedies.^[19] The polyherbal medicine made by mixing equal amounts of Ear aches and ear secretions can be treated using preparations from Bael root, *Allium cepa* Linn, and *Curcuma domestica*.^[16] The primary active component used in the formulation of Dasamula, Chyavanprash, etc. is derived from the bael plant.^[14]

Flower:

The medication made from flower distillation is used as an intestinal and stomach tonic. Additionally, it functions as an expectorant, local anaesthetic, antidiabetic, and anti-dysenteric. It can be applied to epilepsy cases.^[19]

Anticancer activity of *Aegle marmelos*:

The majority of powerful antineoplastic medications are pricy, mutagenic, and teratogenic which are obtained from natural sources (paclitaxel). Thus, focus is being placed on creating affordable, safe medications using alternative sources.^[31] Lupeol, an ingredient found in *A. marmelos*, has anti-cancer properties against several human cancer cell lines, including melanoma (451Lu) cells, hepatocellular carcinoma (SMMC7721) cells, human epidermoid carcinoma cells, pancreatic adeno-carcinoma cells (AsPC-120, A431), and prostate cancer cell lines (LNCaP, CWR22R1, and PC-3). Two other phytochemicals identified in *Aegle marmelos*, eugenol and citral, show anti-proliferative effects. Human melanoma cell lines WM1205Lu and B16, malignant hepatoma cells HepG2, salivary gland tumour cells HSG, malignant Caco-2 colon cells, non-malignant human VH10 fibroblasts, and healthy human gingival fibroblasts (HGF) have all been demonstrated to be cytotoxic to eugenol. Citral (3,7-dimethyl-2,6-octadien-1-al) has recently been demonstrated to induce apoptosis in a variety of haematological cancer cell lines.^[32] The hydroalcoholic extract of bael leaves proved effective in treating an animal model of Ehrlich ascites carcinoma, and it was hypothesised that the extract's skimmianine content induced apoptosis.^[29] Anthranilic acid, which is present in large amounts in bael, is the starting point for the production of the alkaloid skimmianine (C₁₄H₁₃NO₄), which is abundant in the plant. It has been demonstrated to be anticancer in human ovarian cancer cell line.^[13]

A. DMBA induced Breast cancer in Rats:

Lupeol, which was extracted from *Aegle marmelos*, is highly resistant to leukaemia, malignant ascites, malignant lymphoma, and malignant melanoma. *Aegle marmelos* has strong antioxidant activity and lessens chemo- and radiation side effects.^[20]

One of the most prevalent cancers in the world is breast cancer. Additionally, it is the main killer of cancer patients among women worldwide. Despite numerous clinical treatment options, Despite this, a significant fatality rate is linked to it. *Aegle marmelos* (L.) Correa is often used in the Indian Ayurvedic medical system because of its unique medicinal properties. Though few research have looked into its usefulness in the fight against cancer. The aim of this study was to investigate the potential protective effects of *Aegle marmelos* fruit extract against breast cancer in rats with breast cancer brought on by 7,12-dimethylbenz(a)anthracene (DMBA). The rats were female Charles Foster rats, weighing around 150 g, and they were between 55 and 60 days old. They received DMBA (20 mg/mL) orally after it had been dissolved in olive oil. *Aegle marmelos* ethanolic fruit pulp extract was administered orally to the

rats for 5 weeks after they developed breast tumours (approximately 0.5 cm in diameter), and the tumour volume was measured. Following therapy with *Aegle marmelos*, the amount of breast tumours was dramatically decreased (P 0.05), as were several blood indicators including TNF, glucose and malondialdehyde (MDA) levels in the serum (P 0.0001). Following ingestion of the ethanolic fruit pulp extract from *Aegle marmelos*, both kidney and liver serum biomarker levels significantly increased (P0.0001). Considering everything, it can be said that the ethanolic fruit pulp extract of *Aegle marmelos* has anti-proliferative efficacy in the rat model, which inhibits the growth of breast cancers. Another benefit of the plant extract is hepatoprotection. As a result, it may be used to treat breast cancer as a novel, potent anti-cancer drug. All things considered; it can be concluded that the *Aegle marmelos*' ethanolic fruit pulp extract has anti-proliferative activity since it inhibits the development of breast cancer in rats. Two phytochemicals present in the fruit pulp of *Aegle marmelos*, marmelin and marmelosin, have been identified to modulate the pharmacological effects of the plant extract. These phytochemicals work by preventing NF- κ B activation and subsequently lowering p-AKT levels, which reduces cell survival, proliferation, and invasiveness.^[21]

B. DMBA induced skin papillomagenesis with reference to oxidative stress:

Gupta N *et al* demonstrated the chemopreventive potential of *Aegle marmelos* bark extract and examined in relation to its effectiveness of antioxidants in mice carrying papillomas. For this experiment 30 swiss albino mice (6-7 weeks old, body weight 25±2) was taken and divided into 5 groups, containing 6 animals each, named Vehicle Control, DMBA alone, Croton oil alone, Drug treated Control, Carcinogen treated (Positive control), AMB Experimental. The skin initiator DMBA and croton oil (prepared in acetone at a concentration of 104µg/100µl) was given to produce the papilloma on the dorsal shaved surface. 2 weeks later, they received treatment with *A. marmelos* stem bark extract (900 mg/kg b.wt.) that was administered two times per week for up to 16 weeks, one hour before to the application of 1% croton oil. At the start and the end of the experiment, the body weights of the animals in each group were noted. After the treatment with *A. marmelos* stem bark extract the skin papilloma in the treatment group was found to be reduced by 50%. The extract may have either blocked the metabolism of DMBA to its active form, postponed the promotion of the carcinogenesis phase, or downregulated ROS (Reactive oxygen species) generation based on the significant effects that were seen. The hydromethanolic *Aegle marmelos* bark extract contains secondary metabolites like tannins, terpenoids, glycosides, and flavonoids, which may be the cause of the plant extract's chemopreventive effect. The existence of these secondary metabolite's anticancer effect has also been demonstrated by evidence.^[22]

C. Anticancer activity on MCF7 (Human breast cancer) cell line:

Vardhini *et al.* performed the experiment on the MCF7 cell line to assess the effectiveness of aqueous extract of fruit pulp against human breast cancer using MTT assay method. The MTT assay measures colorimetrically the metabolic activity of cells. One of the most used methods for assessing the preliminary anticancer efficacy of synthetic derivatives, natural compounds, and natural product extracts is the MTT in vitro cell proliferation assay. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, which is soluble in water, is converted to an insoluble formazan as part of the MTT experiment. Following the formazan's solubilization, optical density at 570 nm was used to calculate its concentration. Aqueous extract of *A. marmelos* fruit pulp had a maximal inhibitory concentration of 66.514.65% when diluted to 100 g/mL, while the IC₅₀ was 47.92 g/mL. The results of this study indicate that the aqueous extract of fruit pulp of *A. marmelos* has significant activity against cancer; ytrzxcvbnm, /?.,nbvz`12jhgg ser. Before the plant can be suggested for any practical, general application, more molecular research is needed to determine the mechanism of action of the bioactive chemicals present in *A. marmelos* against cancer cells.^[23]

Kumar *et al.* studied the anticancer activity of *Aegle marmelos* on MCF7 breast carcinoma cell by using methanolic extract of *A. marmelos* leaves and found 23.22% of decreased viability of tumor cell at 100th concentration. According to the results of its anticancer action, the methanolic extract of *A.*

marmelos greatly decreased the viability of cancer cells and changed their shape in a dose-dependent way.^[25]

D. Anticancer activity on human lung cancer

Sridevi *et al.* performed the experiment on Human Lung cancer cell line (A549), using the MTT assay method to estimate the anticancer activity of hydroethanolic extract of *Aegle marmelos*. The cell viability was found to decreased at 400 and 500 micrograms of AE leaf extract as the over proliferation of the cell is stopped by the plant extract. The plant's anticancer properties are mostly attributable to free radical scavengers found in its phytochemical components.^[24]

Table no. 7: Anticancer activity of *Aegle marmelos*

Sl.no.	Model used for the experiment	Plant part used	Cancer type	Reference
1.	Female Charles Foster strain rats	Ethanolic extract of fruit pulp	Breast cancer	Akhouriet.al ^[21]
2.	Swiss albino mice	Stem bark extract	Skin papillomagenesis	Gupta <i>et. al</i>
3.	MCF-7 cell line	Aqueous extract of fruit pulp	Human Breast Cancer	Vardhini <i>et.al</i>
4.	Human Lung cancer cell line (A549)	Hydro ethanolic leaf extract	Human Lung Cancer	Sridevi <i>et.al</i> ^[24]
5.	MCF-7 Breast carcinoma cell line	Methanolic extract of leaves	Breast cancer	Kumar <i>et.al</i> ^[25]
6.	HEP2 and Vero cell lines	Methanolic extract of leaves	Hepatocarcinoma	Rejiniemon <i>et.al</i> ^[26]
7.	Balb/c mice	Hydroalcoholic extract of leaf	Hepatocarcinogenesis	Verma <i>et.al</i> ^[27]

Anti-Proliferative Activity:

In the present study, we show that extracts from *Aegle marmelos* Correa can inhibit the in vitro growth of a number of different human tumour cell lines, including the leukemic K562, T lymphoid Jurkat, Blymphoid Raji, erythroleukemic HEL, melanoma Colo38, and breast cancer MCF7 and MDAMB-231 cell lines. Three derivatives of *Aegle marmelos* C. extracts, butyl p-tolyl sulphide, 6-methyl-4-chromanone, and butylated hydroxyanisole, were shown to exhibit strong anti-human K562 cell-growth capabilities by employing gas chromatography/mass spectrometry to identify the compounds in the extracts under study. It was shown that these compounds have antiproliferative properties similar to those of well-known anticancer medications as cisplatin, chromomycin, cytosine arabinoside, and 5-fluorouracil.^[8]

In order to determine the anti-proliferative activity of the leaf extract of *Aegle marmelos*, Rajbir Bhatti *et al.* conducted the experiment using a variety of human cancer cell lines, including lung (A-549), colon (CoLo-205), ovary (IGR-OV-1), prostate (PC-3), leukaemia (THP-1), and breast (MCF-7) cancer. Ethanol and chloroform extracts dramatically slowed the growth of several cancer cell lines, according to the effects of the different extracts on various cancer cell lines. The most efficient extract was found to be ethanol, which showed 69% inhibition in colon and breast cancer cell lines, equivalent to the conventional medication adriamycin. However, lung cancer cell lines showed significantly less inhibition (42%), indicating that this extract might not be as effective as it originally seemed. The chloroform extract showed an inhibition of 68% and 55%, respectively, in colon and breast cancer cell lines. The petroleum ether and hexane extracts demonstrated very little anticancer activity in any cancer cell lines.^[28]

Conclusion:

After reviewing multiple articles on the anti-cancer activity of *Aegle marmelos*, also known as Bael, it is clear that this medicinal plant has shown strong potential in inhibiting cancer growth. Various

bioactive compounds found in different parts of the plant, including the fruits, bark, leaves, seeds, and roots, have been reported to exhibit anti-cancer properties. The phytochemicals present in the plant possess a range of therapeutic properties that can help to curb cancer growth, prevent metastasis, and alleviate cancer-related symptoms. Studies have shown that *A. marmelos* has the potential to treat various types of cancers such as breast cancer, colon cancer, and liver cancer, among others. The plant has also exhibited anti-tumor activity in cancer cell lines. Therefore, *Aegle marmelos* holds great promise as a natural remedy for cancer treatment and however, further research is still needed to fully understand the mechanisms underlying the anti-cancer effects of *Aegle marmelos* and to optimize its use in cancer treatment and deserves further investigation to identify the potential molecular mechanisms behind its anti-cancer effects. Overall, *Aegle marmelos* presents itself as a valuable natural compound having potential as a chemopreventive agent and a complementary therapy for cancer patients.

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