

Potential of Curcuma amada in Cancer Therapy: A Phytochemical Perspective

Sonia Chhetry ^a, Ranjeet Kumar Sah^a, Shreyansh Maurya^a, Komal Hangloo^a, Tanisha Goyal^a, Madhuri Grover^b, Mohit Sanduja^{a*}

^aSchool of Pharmacy and Research, Dev Bhoomi Uttarakhand University, Dehradun, Uttarakhand, India-248001

^bSchool of Medical & Allied Sciences, K.R. Mangalam University, Gurugram, Haryana, India-122103

*Corresponding author

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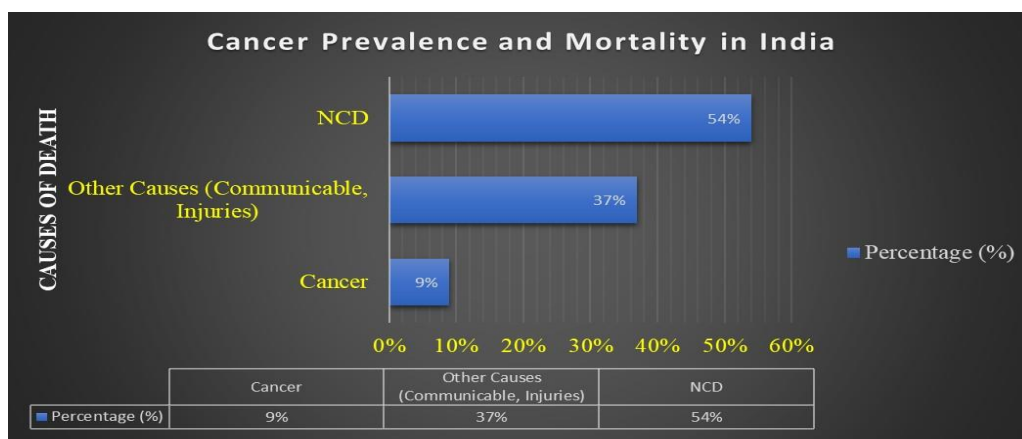
ABSTRACT

Medicinal plants are being used for therapeutic purposes since the human civilization. The efficacy of these medicinal plants is due to presence of broad range of phytochemical constituents present. Curcuma amada is very common herb belong to family Zingiberaceae and is used as spice in different regions of the world and also serves as a home remedy for treating different diseases. Curcuma amada is widely evaluated for its anticancer activity. The major constituents found in its rhizomes are Curcuminoids (Curcumin), Phenolic compounds, terpenoids and essential oils. The primary phytoconstituents Curcumin is responsible for its various therapeutic properties. Curcumin possesses broad remedial potential due to its multi targeting effect against many different carcinomas including Leukemia, breast cancer etc. Hence, Curcumin can treat several diseases because of its potential for the development of new medicine.

Key Words: Curcuma amada, Curcumin, Phytoconstituents, Curcuminoids, Anti-cancer

INTRODUCTION

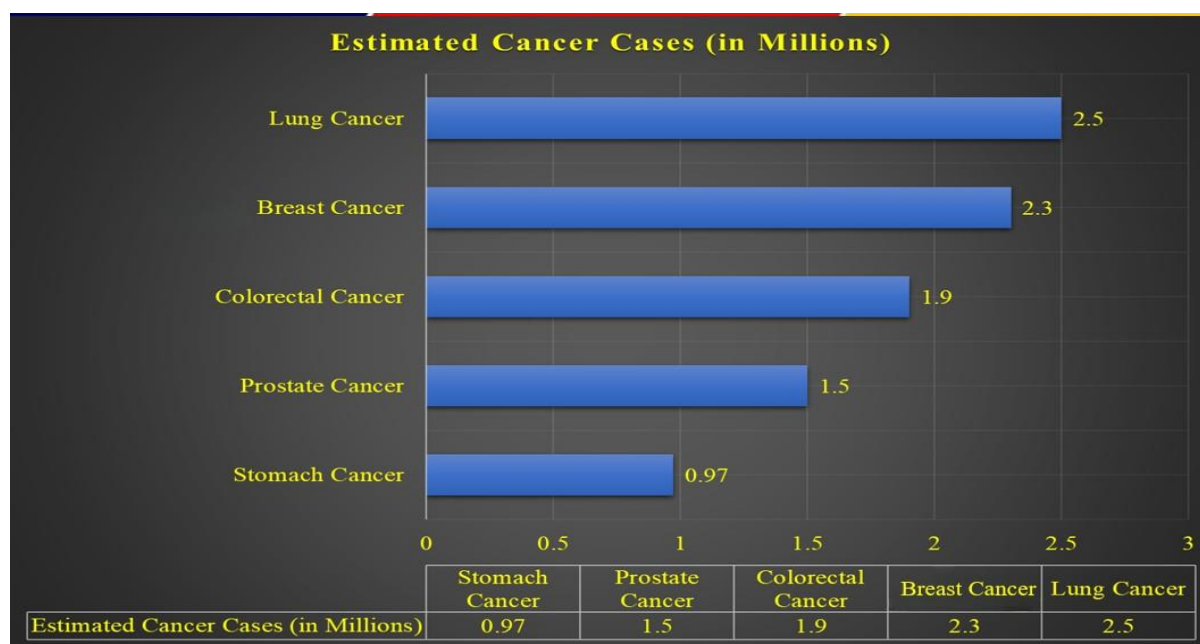
Cancer has been one of the main causes of sickness and death worldwide, which means it's a major health concern. Estimation of 70% increase in cancer cases is predicted for about next 20 years, even as continuous global efforts has been made to prevent cancer. ^[1,2] Estimation says about 63% of deaths in India was caused by NCDs and the cancer was in among top 9% mentioned in Figure_1.



Figure_1 Cancer prevalence and Mortality in India.

According to GLBOCAN 2018 database nearly half of the world's cancer cases and nearly half of the cancer deaths occurs in Asian nations.^[3] Evidences from the domestic and international sources has marked Indian

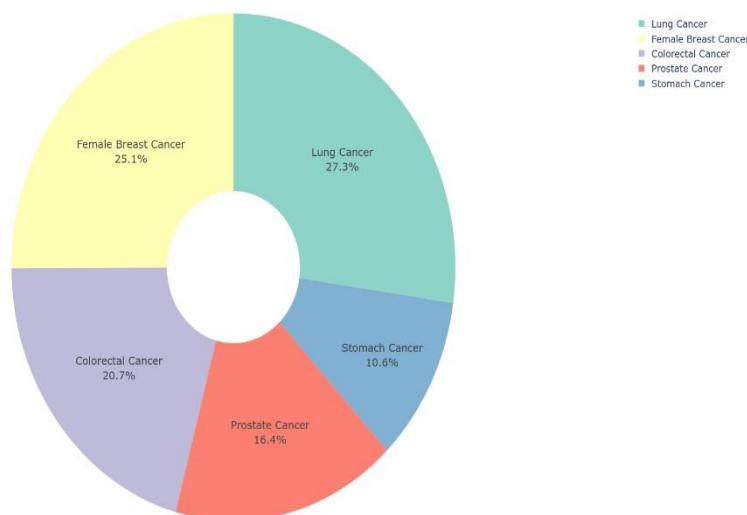
subcontinent as rise in the incidence, morbidity and death related to cancer. ^[4-8] Approximately 13.2 million cases have been expected by 2030 as shown in Figure_2 ^[9]



Figure_2 Estimated cases till year 2030

According to the data provided by Global Cancer Observatory report 2022, nearly 10 cancer types have been accounted for nearly two thirds of all new cases and deaths worldwide. Lung cancer led with 2.5 million new cases globally making this the most common cancer, next to this is Colorectal cancer with 1.9 million cases, Prostate cancer with 1.5 million cases, Stomach cancer with 970,000 cases, and female breast cancer with 2.3 million cases summarized in Figure_3 ^[10,11]

Top 5 Most Common Cancers Globally (2022)



Figure_3 Most common cancer statistics globally

The rising cases of cancer creates major burden on people financially as well as psychologically living in developed as well as in developing countries, driving the need for affordable, targeted and effective treatment strategies. While numerous approaches exist- surgery, immunotherapy, chemotherapy, Cancer vaccination stem cell therapy these often faces limitations such as toxic effects. ^[12] poor bioavailability, non-targeted or mono-targeted action and rapid clearance. ^[13-15] As a result researcher are more inclined on medicinal plants and their

phytochemicals has been promising alternatives. Notably such as Curcumin, Epigallocatechin, Isothiocyanates and garcinol are under clinical trials and can soon hit the market. ^[16]

Traditional herbal drugs have received notable acceptance as alternative and complementary therapy for the cancer patients. Previous studies have incorporated that herbal products alongside conventional treatments can improve quality of life. Therefore, there is growing interest on plant-based products in search for harnessing novel cancer treatments. ^[17-22]

Curcuma amada belongs to family Zingiberaceae and is characterized as perennial and aromatic herb which is commonly known as “Ama-haldi”, “Amba ada”, “Mango ginger” because of the flavor of the rhizome is similar to raw mango as shown in Figure_4. ^[23,24] *Curcuma* has 60-100 species of curcumin found in different countries of the world like in Northern Australia, Indian Subcontinent, America etc. ^[25] The rhizomes of this plant have been widely used in food industries and also as an alternative therapy to cure numerous illnesses such as bronchitis, colic, indigestion, cough, loss of appetite and constipation. ^[26] There are several reports available on anti-cancer activity of the leaves as well as in the rhizomes of *Curcuma amada*.

2. Taxonomic classification: ^[27]

S.no.	Taxonomy	Classification
1.	Kingdom	Plantae
2.	Subkingdom	Spermatophyta
3.	Division	Magnoliophyta
4.	Subdivision	Angiospermae
5.	Class	Monocotyledone
5.	Series	Epigynae
6.	Order	Scitaminales
7.	Family	Zingiberaceae
8.	Genus	<i>Curcuma</i>
9.	Species	<i>C. amada</i> Roxb

Table_1: Taxonomical classification of *Curcuma amada*



Figure_4 (a) whole plant (b) Rhizomes of *Curcuma amada*

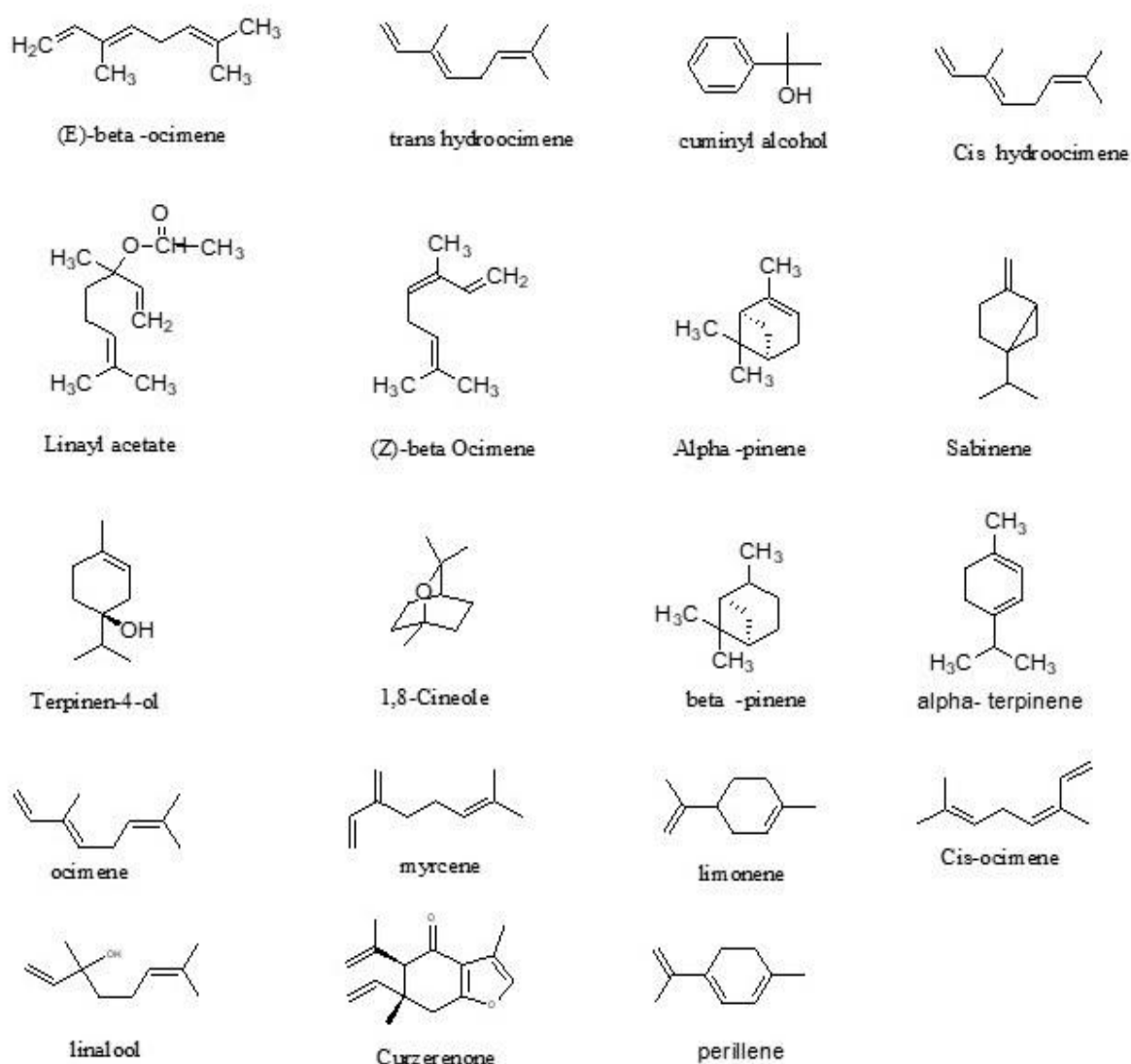
History and Origin:

The beginning of *Curcuma amada* (Mango ginger) is not well documented and is vague. It is said to have originated from India and is also found across tropical regions of Africa, Australia and Asia. The term *Curcuma* is believed to have been derived from the Arabic word *kurkum* which means yellow. ^[28,29]

Mango ginger grows in different climatic conditions but the favorable condition is hot climate as it is said that the maximum growth occurs. In India maximum growth is seen in Gujarat, Uttar Pradesh, West Bengal, Karnataka, Tamil Nadu and the hills of western coast. ^[29,30]

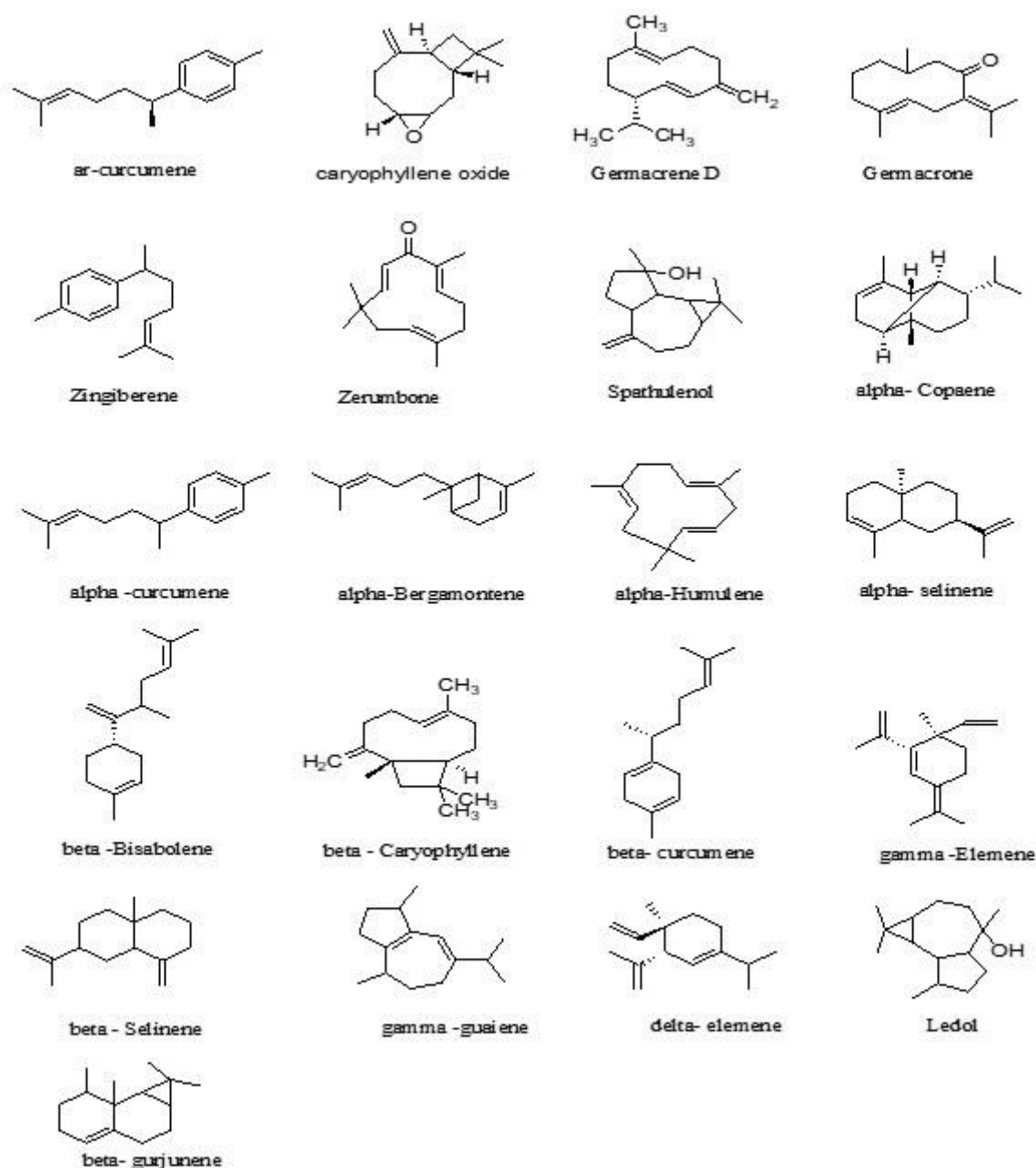
Chemical Constituents:

The Rhizomes of the plant was found to be rich in fibers and starch; the analysis of this edible rhizome plays a crucial role in order to assess its nutritional significance. ^[31] There are more than 130 chemical constituents which has been reported in the rhizomes part of which total of 121 has been identified ^[32-37] Most of studies is done on rhizome part of the plant while other part is rarely examined. The major constituents present in plant are mentioned in Figure_5 ^[38]



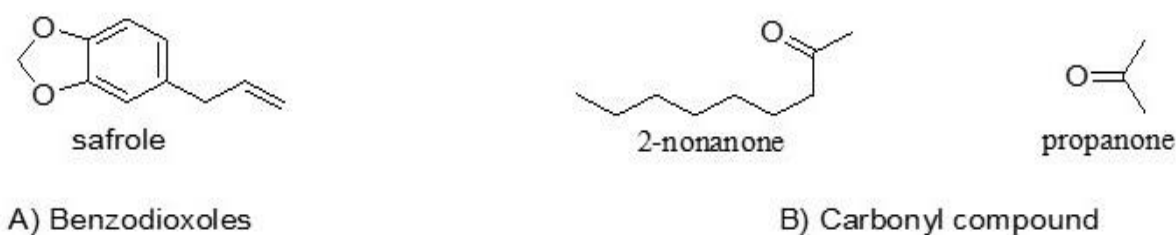
Figure_5 The chemical constituents present in *C. amada*

Monoterpenoids, are compounds containing a chain of two isoprene units. The known are beta-ocimene, trans-hydro ocimene, cuminyl alcohol, cis-hydro ocimene, Linalyl acetate, alpha-pinene, myrcene, 1,8 cineole etc are shown in Figure_6.



Figure_6 Monoterpenoids compounds of Curcuma amada plant

Sesquiterpenoids, are compounds with three consecutive isoprene units. The well-known compounds include beta-curcumene, ledol, ar-curcumene, caryophyllene oxide, alpha-curcumene, alpha-selinene, gamma-guaiene etc as shown in Figure_6.



Figure_7 Sesquiterpenoids compounds of Curcuma amada plant

Benzodioxols are the organic compounds containing a benzene ring fused to either isomer of dioxole, Dioxole is a five-membered unsaturated ring of two oxygen atom and three carbon atoms. Important compound includes safrole as shown in Figure_7.

Carbonyl compounds are organic compounds containing a carbonyl group with general structure $RC(=O)R'$ where R = organyl R' =H, N, O organyl group or halide group. It includes compounds like 2-nonanone and propanone as shown above.

Extraction Techniques:

Curcuma amada rhizomes are extracted using conventional solvent methods (methanol, ethanol, chloroform, acetone, ethyl acetate) and modern intensification techniques as mentioned in Table 2.

S. No	Method & Solvent used	Nature of the compounds	Name of the compound	Method of detection	Use /remark
1	Steam distillation, extraction and low temperature-high-vacuum distillation technique	Mono-terpenoids	Cis-ocimene Car-3-ene	GC-MS analysis	Cis ocimene contributes to the aroma of green α -pinene and car-3-ene is for floral and leafy mango aromas. ^[40]
2	Hexane	Monoterpenoids	Myrcene, Ocimene, Cis and Tran-di- hydrocimene	Hexane Extraction	It contributes on the aroma of both raw mango and turmeric.
3	Dichloromethane, ethyl acetate, methanol and double distilled water	Mono-terpenoids Phenol ethers	β -myrcene α -asarone	Spectrophotometric assay	It predominantly has myrcene (88.6%) and β -pinene (4.9%). Dietary phenolic acids (eg. caffeic, ferulic) exhibit antiulcer, antibacterial and antioxidant properties
Free compounds of phenol					
4	Gallic acid	Hydroxycinnamic acids and Derivative Benzoic acids and derivatives	Caffeic (26%, 195 mg/g) Gentisic (24%, 180 mg/g)	HPLC analysis	Serve as an effective indicator for determining the physiological age and quality of rhizome

		Hydroxycinnamic acids and derivatives	Gallic acid (10 %, 75 mg/g)		
Bounded phenolic compounds					
5	Methanol AR, ethyl acetate AR and dichloromethane	Hydroxycinnamic acids and derivatives Cinnamic acids and derivatives Hydroxycinnamic acids and derivatives	Ferulic acid (47%, 391.5 mg/g) Cinnamic acid (29%, 237 mg/g) P-coumaric acids(11%, 95 mg/g)	Uv- visible spectrophotometer analysis	It has many medicinal properties like anti-ageing, antibacterial, antioxidant, anti-inflammatory, antiallergic, antifungal, platelet aggregation inhibition activity and analgesic activity
Curcuminoids					
6	EPA-524.2 fortification solution	Linear diarylheptanoids /curcuminoids	Curcumin Demethoxycurcumin Bisdemethoxycurcumin	HS-SPME and GC-TOF-MS	Widely used in food industry and alternative medicines to treat a variety of internal diseases such as cough, bronchitis, indigestion, colic, loss of appetite, hiccups and constipation
7	n-hexane, chloroform, ethyl acetate, acetone and methanol	Terpenoids Fatty Acyls/terpenoids Terpenoids	Difluorocumenol Amadaldehyde Amadannulen	UV, IR, LC-MS, 2D-HMQUCT-NMR Spectral data UV, IR, LC-MS, 2D-HMQUCT-NMR Spectral data UV, IR, LC-MS, 2D-HMQUCT-NMR Spectral data	It is demonstrated as high and antibacterial activity against Gram negative and Gram-positive bacteria It is anti-cancerous and antibacterial properties method in them It has antibacterial antioxidant and antimicrobial activity

Table_2: Extraction techniques and bioactive compounds identified in Rhizome of Curcuma amada^[39]

Anti-cancer profile of *Curcuma amada*:

Recent Investigation had revealed that the curcumin has emerging potential application from *Curcuma amada* against cancer and its therapy which relates to its complications. It has been proven that *Curcuma amada* has potential against different types of cancer.

Mango ginger extracts prepared with solvents such as hexane, acetone, chloroform, methanol, and ethyl acetate have been observed to exert cytotoxic effects on both normal and cancerous cell lines. Importantly, their activity is consistently stronger against cancer cells, underscoring their potential as anticancer agents. In terms of relative toxicity, the extracts rank from most to least harmful as follows: hexane, chloroform, methanol, acetone, and finally ethyl acetate. Overall, cytotoxicity assessments indicate that these extracts are considerably less damaging to healthy cells compared to cancer cells.^[41]

Therapeutic role in Breast Cancer Treatment:

Across the world breast cancer is one of the common malignant cancers in females and thus is leading cause of deaths among females.^[39]

However, the *Curcuma amada* methanolic extract of leaves and the rhizomes was effective against breast cancer cell lines MCF-7 and MDA MB 231. The DNA damage was induced in yeast to assess using diphenylamine method and the DNA damage induced by the extract was assessed using single cell gel electrophoresis summarized in Table_3.

Type of cancer	Plant part used	Solvent used for Extraction	Animal/ Cell line used	Result
Breast Cancer	Leaves and rhizomes	Methanol	MCF7, MDA MB 231, HLB-100	The extract caused cell death in the MCF-7 and MDA MB 231 breast cancer cell with less DNA damage in yeast and HLB -100 cells. ^[42]
	Rhizomes	Hexane, chloroform and methanol	MCF-7	<i>Curcuma amada</i> shows anticancer activity against MCF-7 cell line With hexane showing IC ₅₀ of 75.9µg /ml ,while chloroform and methanol extract had IC ₅₀ >10µg /ml demonstrating higher anticancer activity then hexane . ^[43]
	Leaves and rhizomes	Methanol	MCF-7, MDA MB 231, HLB-100	<i>Curcuma amada</i> extract treatment enhanced pro- apoptotic P33 and Bax expression while decreasing the levels of anti-apoptotic Bcl-2 l. ^[44]

Table_3: Therapeutic role in breast cancer treatment

Therapeutic Role in Prostate Cancer Treatment

Prostate cancer is the fifth leading cause of cancer-related death in men and the second most common malignant tumour worldwide.^[42] Recent investigations indicate that *Curcuma amada* (mango ginger) rhizome extract (CARE) could play a beneficial role in prostate cancer therapy, although current findings are restricted to preclinical research. Phytochemical profiling has revealed sixteen active constituents in *C. amada*, many of which exhibit favorable drug-like characteristics, including flavonoids, terpenoids, and phenolic compounds recognized for their antioxidant and anti-inflammatory properties. CARE has demonstrated the ability to trigger

apoptosis, interfere with cell cycle progression, and suppress pro-inflammatory mediators that drive tumor development. Computational analyses further suggest that CARE interacts with multiple signaling pathways, notably PI3K/Akt and MAPK, which are central to cancer progression. Laboratory studies confirm that CARE reduces the viability of prostate cancer cells, while bioinformatics evidence supports its broad therapeutic potential as shown in Table_4^[45]

Plant part used	Extraction method	Solvent used for Extraction	Animal/Cell line used	Result
Rhizomes	Soxhlet apparatus	Methanol	PC-23	In vitro, CARE reduced PC-3 cell growth, induced apoptosis, caused G2/M cell-cycle arrest, and downregulated PI3K-AKT-related genes, indicating its potential as a therapeutic candidate.

Table_4: Therapeutic Role in Prostate Cancer Treatment

Therapeutic role in Rhabdomyosarcoma Cancer Treatment

Rhabdomyosarcoma (RMS) is a common type of cancer that mainly effects childhood and adolescent, accounting for half (50%) of soft tissue sarcomas. It has an incidence rate of 4.3 occurrences per million people under 20. It is uncommon in adults, accounting for less than 1% of solid tumours and 3% of soft tissue sarcomas.^[46] C. amada showed the highest cytotoxic activity against SJRH30 and RD cell lines as shown in Table_5.^[47]

Extraction	Animal/Cell line used	Result
Supercritical fluid extraction	aRMS (SJRH30), eRMS (RD) cell lines	Curcuma amada showed the highest cytotoxic activity against SJRH30 and RD cell lines, with IC ₅₀ values of 7.133 and 7.501 µg/ml, respectively, compared to other Curcuma species.

Table_5: Therapeutic role in Rhabdomyosarcoma Cancer Treatment

Therapeutic role in glioblastoma cancer treatment

Glioblastoma is considered as the most prevalent malignant brain tumour, accounting for almost 16% of all the primary brain and central nervous system neoplasms. It is commonly diagnosed around the age of 64, however it can develop at any age, including youth. Men have higher incident than women with a ratio of 1.6:1.^[48]

Supercritical fluid extract was used against U-87 MG, mHypoE -N1 and the results are shown in Table_6.

Solvent used for Extraction	Animal/ Cell line used	Result outcome
Supercritical CO2 Extract	U-87 MG, mHypoE -N1	Curcuma amada super critical CO2 extra exhibit strong cytotoxic activity against U-87MG glioblastoma cells with IC ₅₀ , IC ₇₅ , and IC ₉₀ values of 4.92 mg/mL, 12.87 mg/mL, and 21.30 mg/mL, respectively. In contrast high concentration were required to suppressed the growth of normal cell m Hypo E-N1 cells. ^[49]
Supercritical CO2 Extract	U-87MG	Curcuma amada extract show cytotoxic activity against U-87MG human glioblastoma cell line with IC ₅₀ , C ₇₅ and 1C ₉₀ values of 5.02 ± 0.10, 12.87 ± 0.25, 37.14 ± 0.19 mg / ml. The

		extract resulted in dose dependent apoptosis and downregulation of genes related to drugs resistant, proliferation, telomerase and metastatic ^[50]
Supercritical CO2 Extract	U-87MG	Supercritical CO2 of Curcuma amada demonstrate potent anti-cancer activity against U- 87 MG human glioblastoma nude mice xenografts. It shows high cytotoxic activity with IC 50, IC 75, IC90 values of 4.93 ± 0.81 , 13.47 ± 0.86 and 23.10 ± 1.13 mg/ml respectively. Oral administration of plant extract to xenografts mice reduced tumor volume by 40.2%, raised the therapeutic ratio to 40.3 and increase survival to 40%. ^[51]

Table_6: Therapeutic role in glioblastoma cancer treatment. ^[49-51]

Therapeutic role of Curcuma amada on lung cancer treatment

Lung cancer is the main cause of cancer-related death globally, accounting for the highest mortality rates in both men and women. Smoking is the leading cause of lung cancer, accounting for over 85% of cases. The International Agency for Research on Cancer (IARC)'s GLOBOCAN 2020 estimates of cancer incidence and mortality show that lung cancer is the top cause of cancer death, accounting for an anticipated 1.8 million deaths (18%) in 2020.^[52]

Curcuma amada rhizomes were evaluated against different cell lines as shown in Table_7.

Plant part used	Solvent used for extraction	Animal /cell line used	Result
Rhizome	n-hexane, chloroform, ethyl acetate, acetone, methanol and water	A-549 (human small cell lung carcinoma), Vero cell	Among all the ethyl acetate show maximum cytotoxic activity with lowest CTC-50 values (52-65µg). Hexane and chloroform extract showed moderate cytotoxic activity with CTC-50 values 90 to 100µg. Methanol and acetone extract show lower activity with CTC 50 value 132 to 407 µg. ^[53]
Rhizome	Acetone, hexane, isopropyl alcohol, phosphate buffer and distilled water for crude protein extraction	NCIH460	Curcuma amada shows anticancer potential through its antioxidant and cellular action. It neutralises free radicals with 58.6% DPPH activity (60 µg/ml), 68.42% superoxide scavenging and 66.6% hydroxyl scavenging (50 µg/ml) ^[54]

Table_7: Therapeutic role in lung cancer treatment. ^[53,54]

Therapeutic role of Curcuma amada on skin cancer treatment

Skin cancer is one of the most common malignancies in the world, and its incidence and fatality rates are steadily rising, particularly in places with a white population. Skin cancer accounts for one out of every three cancer diagnoses worldwide, with NMSCs being the most common. It is classified into two types: melanoma skin cancer (MSC) and non-melanoma skin cancers (NMSC). North America and Asia have the greatest incidence and fatality rates for non-melanoma skin cancer. The incidence of non- melanoma skin cancer is 18-20 times higher than melanoma skin cancer, resulting in more deaths.^[55]

The rhizome extract was prepared using maceration process and was tested against B16F10 melanoma cells and the result is mentioned in Table_8.

Plant part used	Extraction method	Solvent used for extraction	Animal /cell line used	Result
Rhizome	Maceration	The methanol extract of <i>C. amada</i> was fractionated using water, n-hexane, and ethyl acetate.	B16F10 melanoma cells	Curcuma amada showed higher tyrosinase inhibitory activity with IC ₅₀ of 53.4 µg/mL. The IC ₅₀ values of mushroom tyrosinase were 108.2, 89.2, 92.3, 21.7, and 41.3µM. All of the compounds decreased intracellular tyrosinase activity and melanin production in B16F10 melanoma cells. Compound 4 was the most potent, exceeding arbutin, and compound 5 had activity comparable to arbutin.

Table_8: Therapeutic role in skin cancer treatment ^[56]

Therapeutic role of Curcuma amada on cervical cancer treatment

Cervical cancer is the fourth most frequent cancer in women globally, with an estimated 660 000 new cases and 350 000 deaths in 2022. The continuous infection with human papillomavirus (HPV) causes cervical cancer. Women living with HIV are six times more likely to get cervical cancer than women who do not have HIV.^[57]

C. amada was tested against different cell lines of Cervical cancer and the results are mentioned in Table_9.

Plant part used	Extraction method	Solvent used for Extraction	Animal/ Cell line used	Result
Rhizome	Soxhlet apparatus	Ethanol	Adult female Sprague Dawley Rats (150-200g)	In female Sprague Dawley rats, BaP exposure significantly induced cervical tumor development (p>0.001), decrease the level of antioxidant, increase lipid peroxidation, elevated serum tumour makers (CEA, CA- 125, GTT) as well as membrane bound enzymes (Na ⁺ /K ⁺ -ATPase and Ca ²⁺ /Mg ²⁺ -ATPase).
Rhizome	Soxhlet apparatus	Methanol, chloroform, petroleum ether	HeLa	The cytotoxic effect of Curcuma amada was assessed using MTT test at doses ranging from 50 to 250 mg/ ml. Cell viability decrease in a dose - dependent way. The control group has a vitality of 97.25%, whole treatment with 50 mg / ml reduces it to 83.25%. At higher concentrations viability decrease: 100mg/ml (60.25%), 150mg/ml (55.26%), 200 mg/ml (44.25%) and 250 mg/ml (40.12%) respectively.
Rhizome	Maceration	Ethanol, aqueous	HeLa	Curcuma amada ethanolic rhizome extraction was investigated using the MTT test on heLa cells. The IC ₅₀ value of 51.1µg/ml suggest strong cytotoxicity in a dose -dependent manner. Trypan blue die exclusion experiment reveals maximum cell killing at increase doses.

Tablez9: Therapeutic role in cervical cancer treatment ^[58,59,60]

Therapeutic role of Curcuma amada on different cancer treatment on rhizome

Curcuma amada is potent to have therapeutic role against different types of cancer thus is written in a summarized manner in Table_10.

Type of cancer	Extraction method	Solvent used for extraction	Animal /cell line used	Results
Lung, cervical, pancreatic, breast	Sonication	Methanol	A549, HeLa, PANC-1 PSN-1 MCF7	Compounds 2-4,7,8,12 and 17 exhibit moderate activity (IC ₅₀ : 19.7-96.1μM). (E)-14-Hydroxy-15-norlabda-8(17), 12-dien-16-al (compound 11) show potent and selective antiproliferative action against HeLa, PANC-1 and PSN-1 cells, with IC ₅₀ values of 5.88, 1.00 and 3.98μM respectively comparable to 5- fluorouracil ^[61]
Cervical and Lymphoma (murine T- cell lymphoma)	maceration	Ethanol and water	DLA, HeLa cell line	Curcuma amada ethanolic rhizome extraction was investigated using the MTT test on heLa cells The IC ₅₀ value of 51.1μg/ml suggest strong cytotoxicity in a dose -dependent manner. Trypan blue die exclusion experiment reveals maximum cell killing at increase doses. ^[62]

Table_10: Therapeutic role in different cancer treatment

Local promotions and uses

Regarding Curcuma amada the accumulated knowledge is based on several years of experience, but its rapid disappearance is due to changes in priorities of local communities. Most common reason for the disappearance is knowledge sharing in different communities and generations. Solution is to promote local uses through knowledge sharing at different levels. International organisations and local non-government can participate with the local government in order to support the communities.^[63]

CONCLUSION

Medicinal plants serve as alternative therapeutic options having wide history of use for treating different types of cancer and it is well reported that herbs have potential source of chemotherapeutic compounds. On reviewing available data from different search engines, it was found that Curcuma amada is among less investigated species with genus Curcuma, specifically for its anticancer property. However, its complete description in provided in Ayurvedic system of medicine. ^[64] More than 130 chemical constituents have already been identified in rhizomes part. Most study of this plant have centred on its phytochemical properties. Therefore, special attention is needed to explore the pharmacological activities of the various constituents identified in Curcuma amada. Chemotaxonomy and allelopathy are yet to be explored for this plant.

Future prospects

Curcuma amada is known for its phytochemical constituents thus possesses various pharmacological actions and is prone for anti-cancer activity because of the presence of curcumin. Overall, Curcuma amada stands out to be a promising candidate for sustainable drug discovery and holistic healthcare innovation.

Ethics statement

Ethical approval is not applicable to this study as it does not contain any human/animal participants.

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None

Declaration of competing interest

There is no conflict of interest.

Declaration of generative AI in scientific writing

No generative AI tools were used in the writing or research of this manuscript.

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