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# A Review on Anticancer Properties of Chebulagic Acid from *Terminalia chebula*

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***Abstract***

*This review aims to explore the potential of Chebulagic acid, a hydrolysable tannin derived from Terminalia chebula, in the treatment of cancer. Chebulagic acid boasts a myriad of medicinal and pharmacological benefits, including but not limited to antibacterial, antiviral, antioxidant, antidiabetic, antifungal, antiulcer, anticancer, antimutagenic, and wound healing properties. The objective of this review is to compile existing scientific literature on the anticancer attributes of Chebulagic acid. Numerous studies have elucidated its ability to regulate apoptosis and inhibit proliferation in various cancer cell lines and pathways. Nonetheless, further in vivo investigations are imperative to thoroughly dissect the mechanism-based pharmacological profile of Chebulagic acid. Such studies will furnish robust scientific evidence elucidating its anticancer efficacy across different cancer types and appraise its suitability for clinical trials.*

***Keywords****: Anticancer Activity, Chebulagic Acid, Pharmacological Activities, Terminalia chebula.*

## Introduction

Cancer represents a substantial public health challenge with profound global ramifications, affecting populations in both developed and developing nations is considered to be second leading cause of death around the globe. Despite significant advancements in oncology research, cancer continues to be perceived as a formidable adversary, often deemed a 'hopeless case. In recent decades, extensive studies have been conducted to explore various approaches for cancer treatment. However, the quest for a definitive cure remains elusive, underscoring the complexity and heterogeneity of cancer as a disease [1]. Around the globe, there is a rapid increase in the rate of cancer and mortality. According to GLOBOCAN, it was estimated that over 19.3 million cases were registered to be cancerous [2]. The disease is a significant global health issue that remains a leading cause of mortality [3]. Nevertheless, there has been a notable enhancement in the prognosis of cancer as a result of advancements in various strategies. These strategies include radiotherapy, which employs radiation to eliminate malignant cells, chemotherapy utilising potent cytotoxic chemicals, immunotherapy or biological therapy, which involves the activation or suppression of the immune system to treat the disease, and targeted therapy involving antibodies targeting tumor-specific antigens. These techniques have the potential to induce cytotoxicity in healthy cells and give rise to significant adverse effects, including hair loss and skin damage [4, 5].

The demand for novel therapeutic interventions that exhibit reduced adverse effects while delivering enhanced therapeutic

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efficacy is on the rise. The need for new treatments with reduced side effects and improved therapeutic effectiveness is growing as patients develop resistance to antineoplastic medicines and radiation therapy. From this perspective, there is a growing interest in natural chemicals derived from plants and secondary metabolites due to their bioavailability, minimum adverse effects, and cost-effectiveness [6]. Nutraceuticals, particularly phytochemicals, have demonstrated distinctive mechanisms of action at various cellular levels. Flavonoids, polyphenols, phytosterols, terpenes, tannins, and catechins are among the phytochemicals that are currently under extensive study. Notably, tannins, including chebulinic acid as a polyphenolic compound, fall under the category of hydrolyzable tannins and have garnered significant attention in recent times [7].

### *Terminalia chebula*

*Terminalia chebula* is a tree, reaching heights of up to 30 meters and sporting a trunk diameter of approximately 1 meter. Part of the *Combretaceae* family, this plant is known by various common names such as chebulic myrobalan, black myrobalan, and ink tree. Additionally, various local names are used to refer to this tree. For instance, in Thailand, it is commonly referred to as Kot Phung Plea, while in India, it is known as Kadukkaai. There are approximately 250 species of *Terminalia* found worldwide, with this particular species being a medicinal plant native to the tropical countries such as India, China and Thailand. Tibetans have bestowed upon it the title of the "King of Medicines" due to its remarkable medicinal properties and diverse biological activities. Its fruits are widely utilized in ancient system of medicine such as Ayurveda, Unani and Homeopathic medicine, serving as important crude drugs with therapeutic applications [8].

The presence of biologically active compounds in *Terminalia chebula* contributes to its widespread use in traditional medicine, attributed to its diverse pharmacological activities. This versatile plant is utilized in the treatment of numerous ailments including gout, paralysis, cancer, arthritis, cardiovascular diseases, epilepsy and various other disorders. The compound possesses pharmacological properties such as antioxidant, anti-diabetic, anti-bacterial, anti-viral, anti-fungal, anti-cancerous, anti-ulcer, anti-mutagenic, and wound healing activity [9-12]. *Terminalia chebula* is extensively utilized in Ayurvedic formulations aimed at combating infectious and skin related diseases. Moreover, it is known to increase the frequency of stools and facilitate complete bowel evacuation. Its usage is associated with anti-aging properties, imparting longevity, enhancing immunity, and bolstering the body's resistance to disease. Additionally, *Terminalia chebula* exerts beneficial effects on all bodily tissues [13]. Research on *Terminalia chebula* plants has revealed the presence of diverse phytoconstituents, including tannins, flavonoids, phenolic acids, and various other compounds. The fruits and other parts of *Terminalia chebula* (Figure.1) have been extensively studied for their pharmacological activities, which encompass antibacterial, antiviral, antioxidant, antidiabetic, antifungal, antiulcer, anti-cancerous, antimutagenic, and wound healing properties.

### Taxonomy and Nomenclature of *Terminalia chebula:*

| | |
|---|---|
| **Kingdom** | **:** Plantae |
| **Subkingdom** | **:** Tracheobionta |
| **Super division** | **:** Spermatophyta |
| **Division** | : Magnoliophyta |
| **Class** | **:** Magnoliopsida |
| **Order** | **:** Myrtales |
| **Family** | **:** Combretaceae |
| **Genus** | **:** *Terminalia* |
| **Species** | **:** *chebula* |

**Figure 1:** *Terminalia chebula* flower and fruit.

## Chemical Composition of *Terminalia chebula*

*Terminalia chebula* is rich in various constituents, notably phenolic compounds, including a high concentration of tannins accounting for approximately 32%. These tannins belong to the pyrogallol (hydrolysable) type and consist of 14 different compounds such as gallic acid, corilagin, ellagic acid, chebulic acid, neochebulinic acid, punicalagin, chebulinic acid, terchebulin and casuarinin. These compounds collectively contribute to the therapeutic properties and medicinal efficacy of *Terminalia chebula* [14, 15]. The isolation process yielded various compounds from *Terminalia chebula*, including, coumarin conjugated with gallic acid called as chebulin, treterpenoids, flavonol and glycosides [16]. Furthermore, the fruit of *Terminalia chebula* has been found to contain ethyl gallate and luteolin. Additionally, it possesses essential nutrients, vitamins and minerals [17]. The fruit of *Terminalia chebula* is particularly rich in tannins, with prominent constituents including tannic acid, gallic acid, terflavin A, chebulinic acid, chebulic acid, punicalagin and corilagin. Additionally, flavonoids such as catechin, kaempferol and quercetin were found. Furthermore, the fruit contains saccharides like quinic acid, shikimic acid, fructose and glucose [18, 19] (**Table 1**).

**Table 1.** Various Pharmacological Properties of *Terminalia chebula* and its Bioactive Compounds

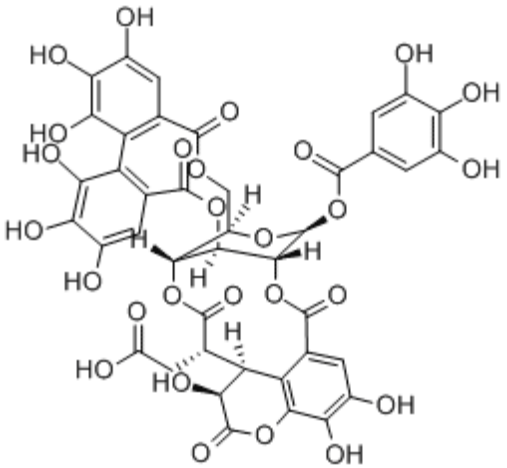
| **Bioactive compound** | **Class of secondary metabolite** | **Therapeutic potential** | **References** |
|---|---|---|---|
| Gallotannins | Hydrolysable tannin | Free radical scavenger and antimicrobial | [20, 21] |
| Ellagitannins | Hydrolysable tannin | Hepatoprotection, anti-inflammatory agent, antioxidant, cardio protectant, anti-apoptotic, anticancer | [22, 23] |
| Gallic acid | Phenolic compound | Immunosuppressive, anticancer, antioxidant, antimutagenic, improved cognition, cardioprotective, antimicrobial, neuroprotectant | [24-32] |
| Chebulic acid | Phenolic compound | Anti-HCV31, antidiabetic, hepatoprotective, Hepatoprotective, antiviral, immunosuppressive, antidiabetic, neuroprotective, antiangiogenesis, antiproliferative, anti-inflammatory | [33- 42] |

| | | | |
|---|---|---|---|
| Chebulagic acid | Hydrolysable tannin | Anti-HCV, antidiabetic, hepatoprotective, Hepatoprotective, antiviral, immunosuppressive, antidiabetic, neuroprotective, antiangiogenesis, antiproliferative, anti-inflammatory | [33- 42] |
| Chebulinic acid | Hydrolysable tannin | Cryoprotective, antitumor, antiangiogenics, antisecretory | [43-45] |
| Ellagic acid | Phenolic compound | Hepatoprotection, cognitive enhancer, anti-diabetic, antioxidant, antiarrhythmic, anti-inflammatory | [46-52] |
| Anthraquinone glycosides | Phenolic compound | Neuroprotective, and antidiabetic | [53, 54] |

## Chebulagic acid

Chebulagic acid, a bioactive compound found in *Terminalia chebula*, a plant widely utilized in traditional medicine, exhibits significant pharmacological effects including antioxidant, anti-tumor, antiviral, antibacterial, and anti-lipid peroxidation properties. It serves as a fundamental component in many traditional medicinal preparations. Chebulagic acid, categorized as a polyphenolic compound, falls under the classification of hydrolyzable tannins derived from plants. Hydrolyzable tannoids, particularly chebulagic acid and chebulinic acid, are identified as key bioactive constituents in *Terminalia chebula.* Extracts from *Terminalia chebula* typically contain approximately 8-15% by weight, around 20-25% by weight of chebulinic acid and low molecular weight hydrolysable tannoids [55] (**Table 2**).

## Molecular Structure of Chebulagic Acid



Nomenclature: 1-O-galloyl-2,4-O-chebuloyl-3,6-O-HHDP-β-D-glucose

**Table 2.** Various Anticancer Properties of Chebulagic Acid

| S.No. | Property | Type of Study | Source | Model used | Findings |
|---|---|---|---|---|---|
| 1 | Anti proliferative action | *In vitro* | Compound isolated from fruits of *T. chebula* | Y- 79 cells | Chebulagic acid exhibits a distinct potential that can trigger G1 cell cycle arrest, hinder NFκB activity, and initiate |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | programmed cell death in retinoblastoma cells [56] |
| 2 | Anti proliferative property | *In vitro* | | COLO-205 HCT-15, MDA-MB-231, DU-145 and K562 cells | Chebulagic acid functions as a compound that inhibits both COX-2 and 5-LOX enzymes and induces programmed cell death in COLO-205 cells. Furthermore, it demonstrates anti-proliferative properties in the HCT-15, MDA-MB-231, DU-145, K562 cell lines [57] |
| 3 | Apoptotic activity | *In vitro* | | PC-3 cells | Chebulagic acid has the capability to induce apoptosis by modulating intrinsic pathways, which holds great promise for treating prostate PC-3 cancer cells [58] |
| 4 | Apoptotic activity | *In vitro* | | HepG2 cells | Chebulagic acid can trigger apoptosis in human hepatocellular carcinoma via regulating reactive oxygen species and utilising its apoptotic pathways [59] |
| 5 | Cytotoxicity activity | *In vitro* | Chebulagic acid isolated from the fruits of *T. chebula* + Doxorubicin (Dox) | HepG2 cells | Chebulagic acid, which has dual inhibitory characteristics by inhibiting cyclooxygenases, has been shown to increase the sensitivity of DOX in the cell line of human hepatocellular carcinoma. It also affects the multidrug resistance protein-1 (MDR-1). MDR-1 mediated drug resistance in hepatic cells is caused by the COX-2 dependent regulation of MDR-1. [60] |
| 6 | Anti-angiogenic | *In vitro* | Compound | Human | Chebulagic acid impedes |

| | | | | | |
|---|---|---|---|---|---|
| | effects | | isolated from fruits of *T. chebula* | umbilical vein endothelial cells | angiogenesis by obstructing both the VEGF-VEGFR2 complex and downstream signaling pathways dependent on cell–cell contact [41] |
| 7 | Cytotoxicity activity<br>Efficacy study | *In vitro*<br>*In vivo* | Chebulagic acid of highest analytical grade was used. (Cat# TQ0180) | MKN1 and NUGC3 cells<br>Subcutaneous and orthotopic model MKN1 | Chebulagic acid inhibited Gastric cancer cell biological functions in vitro. This finding offers a hopeful avenue for addressing gastric cancer through treatment strategies.<br>Treatment with Chebulagic acid significantly reduced both the volume and weight of tumours, as well as metastasis, while also suppressing the levels of AURKA and the AURKA/β both in laboratory settings and in living organisms [61] |

## Molecular Mechanism Behind the Anticancer Property of the Chebulagic Acid

The research study showed that when Y79 retinal tumours cells were administered with Chebulagic acid, there was a decrease in the number of cells that was reliant on the dosage. Moreover, it was noted that the depolarization of the mitochondrial membrane caused the cytochrome C to be released into the cytoplasm, thereby initiating the intrinsic process of apoptosis. The cell cycle of cancer cells is a primary focus for many anti-cancer treatments, since the capacity to modify this cycle is seen as a vital characteristic in the development of anti-cancer medications. The formation of apoptotic complexes activates caspases, leading to membrane blebbing and DNA fragmentation, ultimately generating hypodiploid cells. These changes are mediated by an increase in p27 expression, a kinase inhibitor that regulates the cell cycle and induces cell arrest in the G1 phase, allowing for DNA repair in tumor cells and initiating apoptosis. The balance between Bcl2 and BAX proteins determines cell survival versus cell death, with apoptosis occurring when the expression of the anti-apoptotic protein Bcl2 is reduced, and the level of the pro-apoptotic protein BAX is increased. NFκB is a protein that promotes proliferation and is commonly activated in tumors, but Chebulagic acid was found to inhibit the translocation of NFκB to the nucleus. This suggests that Chebulagic acid may prevent tumor progression by modulating apoptosis and introducing checkpoints at critical stages (56). Another study demonstrated a dose-dependent inhibition of the growth of PC-3 cells by Chebulagic acid. This inhibition was associated with increased levels of proapoptotic protein Bax, along with a

decreased levels of Bcl-2 and Bcl-xL. The induction of apoptosis by Chebulagic acid was attributed to its regulation of intrinsic pathways, suggesting its potential therapeutic benefit in treating prostate cancer [58].

COX (cyclooxygenases) and 5-lipoxygenase (5-LOX) are pivotal enzyme markers associated with diseases characterized by impaired arachidonic acid metabolism. COX-1 and COX-2 represent two distinct isoforms of COX. COX-1 is constitutively expressed in nearly all mammalian tissues and serves as a source of prostaglandins. However, the COX-2 enzyme could be triggered, and it is most found during processes involving inflammation and the development of cancer. Both the cyclooxygenases are expressed and up regulated in inflammation and various human cancers.

Chebulagic acid has demonstrated potent inhibition against 5-LOX, COX-2 and COX-1. The compound was found to exhibits robust non-proliferative effects *invitro* and possesses potent antioxidant properties. Additionally, the same study revealed that the compound exerts broad-spectrum anti-malignant effects *invitro* using colon, breast, chronic leukaemia, and prostate cancer cell lines. Another study published on Chebulagic acid highlighted its 5-LOX/COX-2 inhibitory action. The study also explored the induction of multidrug resistance protein-1 (MDR-1) expression by PGE2, a metabolite of COX-2, and its subsequent downregulation by COX-2 knockdown or Chebulagic acid. Chebulagic acid was found to downregulate MDR1 expression by COX-2 depending on mechanism due to enhanced sensitivity of HepG2 cells to doxorubicin [60].

A recent study revealed that the administration of Chebulagic acid effectively inhibited the growth of hepatocellular carcinoma cells. This inhibition was observed in a manner that depended on the dosage and duration of therapy. The mechanism by which Chebulagic acid achieved this inhibition was through the regulation of reactive oxygen species (ROS) levels, which in turn triggered apoptotic processes. The impact of Chebulagic acid on ROS-mediated mitochondrial disruption during early apoptosis is evident in matrix cells, characterized by heightened intracellular ROS generation resulting in diminished mitochondrial membrane potential, oxidative DNA damage, and nuclear fragmentation [59].

Another study demonstrates that inhibiting angiogenesis is an effective approach to hinder the growth of cancer by specifically targeting the formation of new blood vessels that support the proliferation of actively growing tumour cells. Chebulagic acid hinders the process of phosphorylation of GSK-3β-dependent β-catenin, an essential component of VE-cadherin–β-catenin signals, as well as the activation of VEGFR2, a significant step in VEGF signal. Chebulagic acid hinders the process of angiogenesis by obstructing both the VEGF–VEGFR2 complex and subsequent pathways of signalling that rely on cell-cell interaction [41]. The current study unveiled the antitumor activities induced by Chebulagic acid and its impact on the beta-catechin signalling pathway. The AURKA/beta-catechin/Wnt pathway is essential for regulating activities such as cancer, apoptosis, invasion, and cell proliferation. Chebulagic acid exhibited substantial anti-gastric cancer (GC) properties in both laboratory experiments and live organisms, leading to decreased levels of AURKA and the suppression of beta-catechin, p-GSK3β and AXIN2. An increase in the incorporation of phosphate into beta-catechin protein levels was reported in xenograft tumour models.

## Conclusion

In conclusion, a comprehensive review of various articles highlights the multitude of anti-cancer properties associated with Chebulagic acid across different cancer cells. These properties encompass pathways

involved angiogenesis, metastasis, apoptosis, cell cycle proliferation, signalling and cell growth. Additionally, Chebulagic acid demonstrates free radical scavenging capabilities by enhancing antioxidant enzymes, further contributing to its anti-tumor effects. While many studies have primarily focused on in vitro assessments of its pharmacological properties, limited research has been conducted using anti-cancer models. Moreover, there is a notable lack of detailed investigations into the molecular mechanisms and mechanisms of action underlying Chebulagic acid's anti-cancer activity. Future studies should be designed to address these research gaps, thereby elucidating the potential significance of Chebulagic acid in cancer management in the foreseeable future.

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## Ethical Approval

This study does not involve experiments with animals or human subjects.

## Consent for Publication

Not applicable.

## Availability of Data and Materials

Data and materials used/analysed during the current study are available from the corresponding author on reasonable request.

## Competing Interests

The authors declare that there are no conflicts of interest.

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Not Applicable

## Author’s Contributions

R.S.K- Writing – Original Draft Preparation; P.A- Conceptualization, Supervision, writing-review and editing; R.V- Project administration; C.S.K-investigation; S.S- methodology and software. All authors have contributed equally to the article.

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