

A Review on Therapeutic Perspectives of Anticancer Properties of Chebulagic Acid

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Abstract

An attempt is made to write a review concerning the anticancer effect of hydrolysable tannin chebulagic acid obtained from *Terminalia chebula* Retz. Chebulagic acid has multitude of applications in medicine ranging from antidiabetic effect to antitumor effect. In this review, article we have analyzed the molecular mechanism behind the anticancer property of the compound. It has been observed from previous studies that regulation of apoptosis is one of the key factors in terminating cancer and chebulagic acid modulates apoptosis by altering the mitochondrial membrane potential which leads to a sequel of events. The dominant effect is the inhibition of expression of antiapoptotic factors and stimulation of expression of proapoptotic factors which paves the path for cell suicide. This in turn is due to the increase in life span of the factor I κ B α which is a stumbling block for the translocation of nuclear factor NF κ B to the nucleus of cells. Therapeutic efficacy of chebulagic acid, the potent tannin natural compound to combat cancer with updated review of literature and their mechanisms of action are discussed in detail. Further, more research needs to be done towards the utility of this compound for clinical utility.

Keywords: Chebulagic acid, Apoptosis, Proapoptotic factors, Antiapoptotic factors, NF κ B, I κ B α .

Introduction

Cancer is one of the leading causes of death and its incidence is growing every year. The etiology of cancer is multi factorial and like any other disease condition prevention is always better than cure. The world's oldest documented case of cancer was from Egypt in 1500 B.C¹. Hippocrates, a Greek physician used the word carcinos to describe tumours thus calling cancer 'karkinos'². These words were used to describe a 'crab' which Hippocrates thought a tumour resembled. The term seems to be apt for this disease as it is invasive and has the tendency to spread to far away sites from the site of origin.

There are several theories to explain the pathology of cancer like the Black bile theory, Lymph theory and only in the late 19th century Rudolph Virchow discovered that cancer spreads through undifferentiated malignant cells³. The greatest progression in cancer research was seen in the 20th century. The contribution by Nobel Laureate Madam Marie Curie in the field of radioactivity paved a big leap in the diagnosis and treatment of cancer.

Genetic selection, environmental factors like radiation exposure, inhalation of toxic fumes, industrial pollutants, occupational hazards, deleterious habits like tobacco chewing, smoking, alcohol and consumption of illicit drugs, food habits are some of the vital reasons for occurrence of cancer. The statistics given by WHO indicate that there were an estimated 18 million cancer cases globally and an estimated 9.6 million deaths in 2018⁴. The National Cancer statistics in India for the year 2020 has projected the incidence of cancer in 6, 79,421 males and 7, 12,758 females⁵. Thus there seems to be a huge responsibility for scientists and medical professionals to investigate and discover new treatment options and modalities to reduce the impact of cancer in humanity. Early diagnosis is fundamental in preserving the life of the patients. Negligence and indifferent approach in recognizing the early symptoms of cancer makes the consequences towards health costly.

The chemotherapeutic agents act through distinct mechanisms like certain drugs damage the DNA of cancer cells – alkylating agents, interfere with the normal metabolism of cells anti-metabolites, intercalates the DNA, others are either mitotic inhibitors and Topoisomerase inhibitors and certain others are hormonal drugs like steroids. Most of these drugs do not have the ability to distinguish between normal and malignant cells and destroy both the cells without any bias thus producing myriad of side effects. The cells which reproduce at a faster rate like the cells of bone marrow, GIT, hair follicles are affected to a larger extent than other cells and certain drugs have specific toxicities. Thus clinical trials and researches are being conducted to discover the alternative approaches in the treatment of cancer. Herbal nutraceuticals has been a supporting hand and newer studies are mushrooming to utilize the resources provided by nature. The major advantage in this field is that the quality of life of patients takes a big leap ahead as the side effects are not quite impairing.

Regarding nutraceuticals the phytochemicals have shown unique mechanism of action at various cellular levels. They have antioxidant activity by influencing the signaling pathway related to redox mediated transcription factors and also have an impact on immunological cascade and inflammation. They have the tendency to significantly raise natural killer cells function and tumor necrosis factor (TNF- α) in late stage cancer cells tells a 2002 study⁶. Flavanoids, polyphenols, phytosterols, terpenes, tannins, catechins are some of the phytochemicals which are being extensively studied. Among the tannins, chebulagic and chebulinic acid have attracted the limelight recently.

Chebulagic acid is benzopyran tannin which is one of the major bio active components present in the fruits of *Terminalia chebula*. It is an antioxidant and immunosuppressive agent found to be useful in eradication of prostate cancer and treatment of diabetes. It inhibits the enzyme alpha - glucosidase which is necessary for the absorption of glucose therefore its application in diabetes is evaluated. It regulates apoptosis in prostate cells thus useful in cancer research⁷. The compound has antiviral property against influenza virus A and human enterovirus 71. It exhibits antiviral property against

influenza virus by inhibiting viral enzyme neuraminidase that is responsible for the release of infected progeny virus. Previous studies reported that chebulagic acid and chebulinic acid exhibit broad spectrum antiviral activities by targeting viral glycoprotein glucose amino glycans. A recent study data has demonstrated that chebulagic acid and chebulinic acid do not interfere with influenza virus entry or RNA replication but act as neuraminidase inhibitors targeting virus release. Oseltamivir resistant cases seem to respond to this compound suggesting a different mechanism of action which has to be unwounded by research⁸.

Cancer

Cancer is the growth of abnormal cells in the body at an uncontrolled rate. Cells with the modified genes begin to multiply at an unprecedented pace producing a lack of resources for the normal cells to survive. The factors that regulate the cell cycle gets disrupted and the stumbling block which is required for arresting the uncontrolled proliferation of cells becomes insufficient. The process of apoptosis is not tuned to rhythm as the expression of anti-apoptotic factors is greater than the pro-apoptotic factors. Scientists also suggest that mutation of certain genes like the tumor suppressor genes and DNA repair genes also contribute to the disease development. According to Darwin's theory of evolution – Survival of the fittest occurs and normal cells lose their battle for existence. Thus the functioning of organs and organ systems get derailed deviating from the normal patterns.

Treatment Options

Depending on the stage of cancer these are the following options for treatment

- Chemotherapy
- Radiation Therapy
- Surgical approach

Role of Tannins in Cancer

Tannins are polyphenolic biomolecules that precipitate proteins and various other organic compounds. They seem to possess antioxidant, anticancer and cardio protective properties. They are present in certain plants. They possess anticancer activity by inducing apoptosis. In a study tannic acid was found to inhibit the JAK/STAT 3 pathway and induced G1 arrest which resulted in mitochondrial apoptosis in YD – 38 cells. They observed inhibition of antiapoptotic factor Bcl-2 and an increase in mitochondrial localization of apoptotic Bax leading to the loss of mitochondrial membrane potential. Caspases were also activated and there was release of cytochrome C which regulates intrinsic pathway of apoptosis⁹.

Punicalagin and ellagic acid mediated the cell cycle arrest at S phase & G0/G1 phase and lead to dose dependent action of programmed death of cells. In addition, the stimulation of apoptosis related proteins and elevation of intracellular H₂O₂ production were seen¹⁰. Cuphiin D1 exhibited chromatin condensation which resulted in apoptotic cells with low DNA content. A decrease in cell population at G2/M phase was also found. It also caused DNA fragmentation and inhibited Bcl-2 expression in HL – 60

cells¹¹. Corilagin has shown inhibitory activity against the growth of numerous cancer cells by prompting cell cycle arrest at the G2/M phase. It induced apoptosis and autophagic cell death which depends on production of intracellular reactive oxygen species in breast cancer cell line ¹². Chebulagic acid is benzopyran tannin whose antioxidant and antiproliferative property have been studied about recently. In this article we have made an attempt to write a review about the pharmacological effects of chebulagic acid giving significance to its antitumour effect.

Terminalia Chebula

Terminalia chebula Retzius (Family: Combretaceae), as a shade and ornamental tree with 250 species, is a medicinal plant that grows in the Middle East and tropical regions such as India, China, and Thailand. The color of the bark is dark brown and is usually cracked. Leaves are thin, elliptic-oblong, cordiform at the base, elliptical, and 7–12 cm long and 4–6.5 cm in width. The upper surface of the leaves is glabrous opposite of the surface beneath. The flowers are futile with a white to yellowish color and unsightly odor. Flowers have 5–7 cm long spikes, simple or branched, about 4 mm across. The ovary is inferior with 10 stamens. Fruits are yellow to orange-brown when ripe and 2.5–5 cm long and unruffled with an ovate-drupe shape¹³. Moreover, it is called by various names by the local people. For example, in the Thai language the plant's common name is "Kot Phung Pla," and in Indian it is called "Kadukkaai"; and its other names are Black Myrobalan, Ink Tree, or Chebulic Myrobalan¹⁴.

Chemical Composition of *Terminalia Chebula*

T. chebula contains 32% tannin. They pyrogallol (hydrolysable) type, they contain 14 components of hydrolysable tannins (gallic acid, chebulic acid, punicalagin, chebulanin, corilagin, neochebulinic, ellagic acid, chebulagic acid, chebulinic acid, 1,2,3,4,6-penta-Ogalloyl-β-D-glucose, 1,6-di-O-galloyl-D-glucose, casuarinin, 3,4,6-tri-O-galloyl-D-glucose and terchebulin). The tannin content varies with the geological variation. Flavonol glycosides, triterpenoids, coumarin conjugated with gallic acid called chebulin, as well as phenolic compounds were also isolated¹⁵. In addition, ethyl gallate and luteolin were isolated from the fruit of *T. chebula*¹⁶. It also consists of nutrients such as vitamin C, protein, amino acids and minerals¹⁷.

Table 1: Pharmacological Properties of *T. Chebula* Active Ingredients

Compound	Category	Pharmacological Properties
Gallotannins	Hydrolysable tannin	Antimicrobial ¹⁸ and antioxidant ¹⁹

Ellagitannins	Hydrolysable tannin	Anti-inflammatory, anticancer, cardiovascular protection ²⁰ , antioxidant, chemopreventive, antiapoptotic, anti-hepatocellular carcinoma (Anti-HCC) ²¹
Gallic acid	Phenolic compound	Anti-inflammatory ²² , antimutagenic ²³ , cardioprotective ²⁴ , antioxidant ²⁵ , anticancer ²⁶ , antimicrobial ²⁷ , neuroprotective ²⁸ , immunosuppressive ²⁹ , improved cognition ³⁰
Chebolic acid	Phenolic compound	Anti-HCV ³¹ , antidiabetic ³² , hepatoprotective ³³ , Hepatoprotective ³⁴ , antiviral ³⁵ , immunosuppressive ³⁶ , antidiabetic ^{37,38} , neuroprotective ³⁹ , antiangiogenesis ⁴⁰ ,
Chebulagic acid	Hydrolysable tannin	antiproliferative ⁴¹ , anti-inflammatory ⁴²
Chebulinic acid	Hydrolysable tannin	Antisecretory, cytoprotective ⁴³ , antiangiogenesis ⁴⁴ , antitumor ⁴⁵
Ellagic acid	Phenolic compound	Antioxidant ⁴⁶ , anti-inflammatory ⁴⁷ , anti-diabetes-induced sexual dysfunction ⁴⁸ , hepatoprotective ⁴⁹ , antiarrhythmic ⁵⁰ , cognitive enhancer ^{51,52}

Anthraquinone glycosides	Phenolic compound	Neuroprotective ⁵³ , and antidiabetic ⁵⁴
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Anticancer Effects of *Terminalia Chebula*

Terminalia chebula is rich in polyphenols and tannins which exhibit profound antitumour activity. The compounds extracted from the plant promote apoptosis in the tumour cells by modifying the expression of apoptotic regulatory proteins. In a study they have found that *T.chebula* triggers the release of cytochrome C from the mitochondria which in turn boosts up the levels of caspase 3 along with cleaved PARP thus initiating intrinsic apoptotic regulatory pathway. Enhanced expression of apoptotic proteins like Bax and decline in expression of anti-apoptotic proteins like Bcl-xL and Bcl-2 is observed in the cancer cell line whereas nil effect was seen on normal mouse lung cell by the aqueous extract of the plant⁵⁵. In another study, ETC affected the size of the lesion and found to decrease the tumor volume and extended the lifespan of animals by 88%⁵⁶. The cytotoxic effect of the ethanolic extract was evaluated by MTT assay in another study. The extract was potent and effective in inducing cytotoxic effects in buffalo rat liver 3A MCF – 7 (Human mammary gland adenocarcinoma) and A- 549 (Human lung cancer) cell lines with an IC50 value of $305.18 \pm 1.7 \mu\text{g/mL}$, $643.13 \pm 4.2 \mu\text{g/mL}$, and $208.16 \pm 3.7 \mu\text{g/mL}$, respectively. The extract was more effective against A549 cell lines when compared to others⁵⁷. It has also been discovered that the certain compounds extracted from the plant upregulates superoxide dismutase, glutathione S transferrase and glutathione peroxidase which scavenges the free radicals and forms a protective shield against tumor.

Table 2 Medicinal Properties of Chebulagic Acid

S.No.	Property	Type of Study	Source	Model used	Inference
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1.	Anti proliferative action	<i>In vitro</i>	Chebulagic acid isolated from fruits of <i>Terminalia chebula</i> 55	Y- 79 cells	50% of Y-79 cells was inhibited to proliferate and only 20 % of Human Corneal Epithelial Cell (HCE) was inhibited . This indicates CA is more inclined towards cancerous cells than the normal cells which can be explained due to the difference in constituent expression of cellular proteins signatures like the constitutive NFkB in the malignant cells58.
		<i>Invitro</i>	Chebulagic acid of highest analytical grade was used	COLO-205	Dose dependent broad spectrum intiproliferative property was observed in the cancer lines like COLO-205 with growth inhibitory GI -50 concentrations ranging from 18 – 30 µM 58.

2.		<i>Invitro</i>			<p>Inhibition of NO &PGE2 production &down regulation of iNOS, COX-2, 5- LOX, TNF- α &IL-6 was interpreted.</p> <p>Chebulagic acid exerts anti- inflammatory effect by inhibition of NFκB activation &MAP kinase phosphorylation⁵⁹</p> <p>LPS promoted the phosphorylation of p38, JNK &ERK in EA.hy 926 cells. This promotion was inhibited by Chebulagic Acid treatment at dose levels of 10 μM or greater than this value in a dose dependent manner⁶⁰.</p> <p>Chebulagic acid remarkably decreased the manifestations of experimental colitis in mice. It significantly increased expression of GFAP and GDNF by downregulation of TNF-α, IL-1β and phosphorylated p38 and thus reduced the infiltration of leukocytes ⁶¹.</p> <p>The result showed that the maltose hydrolysis activity was down regulated by chebulagic acid which proved to be a</p>
		<i>Invitro</i>	Chebulagic acid	LPS – stimulated RAW 264.7, mouse macrophage cell line	

Anticancer Activity Chebulagic Acid

Apoptosis, programmed cell death is vital for homeostasis of tissues. Deregulation of apoptosis can lead to development of malignancies. Induction of tumor cell death by apoptosis has been accepted as one of the fundamental objectives of cancer therapy 64. Bcl-2 family proteins are central regulators of caspase mediated cell death which acts on the mitochondria. They are divided into anti-apoptotic (Bcl-2, Bcl-xL, Mcl-1 and Bcl-w) and pro-apoptotic proteins (Bax, Bak, Box, Bid, Bim and Bad) based on the structural and functional characteristics⁶⁵. Disruption of balance between the expression of pro-apoptotic and anti-apoptotic proteins lead to genesis of cancer. A study was conducted to observe the effect of chebulagic acid on apoptotic regulators in prostate cancer cell line - PC-3. The anti-proliferative potential of chebulagic acid was determined by 3-2,5- diphenyltetrazolium bromide assay. The result was affirmative about the anti-tumor activity of chebulagic acid as the concentration of pro-apoptotic proteins Bax shot up whereas the anti-apoptotic protein concentration Bcl-2 and Bcl-xL declined. This may be due to the anti-angiogenic effect of chebulagic acid which is mediated by blocking both Vascular Endothelial Growth Factor (VEGF) and cell-cell contact dependent downstream signaling pathway⁶⁶.

In another study, Y79 cells when treated with chebulagic acid showed a dose dependent inhibition of cell proliferation. It was observed that Y79 cells were inhibited to a greater extent than normal HCE cells. This indicates chebulagic acid is more specific towards cancer cells⁶⁷. In the same study it was revealed that depolarization of mitochondrial membrane resulted in release of cytosol protein - cytochrome C into cytoplasm which initiates the intrinsic pathway of apoptosis. The apoptotic complexes formed activate caspases which causes membrane blebbing and fragmentation of DNA producing hypodiploid cells. Contributing to these changes the expression of p27 increases which is a cell cycle dependent kinase inhibitor and it causes arrest of cells in the G1 phase. This in turn gives time for DNA repair in the tumor cells and to instigate apoptosis in them. Caspase mediated changes suppresses nuclear factor NF- κ B thus affecting the expression ratio of anti-apoptotic (Bcl-1, Bcl-xL) to pro-apoptotic factors (Bax). These variations in the concentration of apoptotic factors leads to alteration in mitochondrial membrane potential and thus the process continues. The sequential drama of all these events in succession leads to repetitive vicious cycles of apoptosis. Thus chebulagic acid produces anti-tumor effect by modulating apoptosis and introducing check points at critical stages arresting the progression of tumor.

Antitumour Activity of Chebulagic Acid

Increased expression of apoptotic proteins (Bax) and suppression of antiapoptotic proteins (Bcl-2 & Bcl-xL) by inhibition of expression of NF κ B. Increased expression of p27 which arrests the cells in G1 phase. Inhibition of ROS generation by upregulation of SOD, Glutathione S transferrase & Glutathione peroxidase. DNA fragmentation resulting fall in cell count at S & G2 phase.

Antioxidant Activity of Chebulagic Acid

Polyphenols seem to exhibit free radical scavenging property and this property was substantiated in a study. The polyphenolic extract of *Terminalia chebula* Retz. exhibited H₂O₂ scavenging activity with IC-50 value close to the values of reference standard ascorbic acid. DPPH assay also exhibited convincing values indicating the polyphenols extracted from the fruits of *Terminalia chebula* has definite concentration dependent antioxidant property 68. In another study, the antioxidant activities of the phenolic compounds isolated from *Phyllanthus emblicus* were evaluated by *in vitro* models. The results revealed that all the tested phenolics showed strong radical scavenging activity, good potency to chelate Fe²⁺ and good inhibition ability of lipid peroxidation 69. From the above studies antioxidant activity of polyphenols can be understood and further evaluation is essential to demonstrate the antioxidant activity of Chebulagic acid.

Therapeutic Perspectives

Chebulagic acid, the tannins tannin that regulate apoptosis by magnifying the expression of pro-apoptotic factors to a greater extent than the anti-apoptotic factors and promoting cell cycle arrest by increasing the expression of CDK inhibitor p27. They possess free radical scavenging property by stimulating the antioxidant enzymes which contributes to the anti-tumor effect. The apoptosis regulating action of Chebulagic acid is clearly elucidated in the studies conducted previously and its very negligible side effects makes it one of the good choices in management of cancer in the upcoming days.

Conclusion

Chebulagic acid is reliable in treating cancer besides its forum of other applications in medicine. Human trials are a requisite in this era and bold but yet safe treatment protocols are to be implemented in the near future for the alternative medicine to fight the dreadful disease, the cancer.

Conflict of Interest

The authors declare they have no competing financial interests.

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