**TERMINALIA CHEBULA: SUCCESS FROM BOTANY TO ALLOPATHIC AND AYURVEDIC PHARMACY**

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**ABSTRACT**

*Terminalia chebula* (TC) is a unique herb having various therapeutic potentials as anti-inflammatory, antioxidant, anticancer, and digestant. It belongs to family Combretaceae. In the present review, an attempt has been made to decipher classification, chemical constituents, therapeutic uses, and patents that have been reported for TC. Various pharmacological activities of TC that make it as potential medicine and its Ayurvedic formulations are highlighted.

**Keywords:** *Terminalia chebula*, Anti-oxidant, Anti-cancer, Ayurvedic formulations, Anti-oxidant.

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**INTRODUCTION**

*Terminalia chebula* (TC) is a unique herb that is used from ancient time since Charak. It is used in many herbal formulations like Triphala. It is used as anti-inflammatory and digestant [1-3]. In recent years, an extract of TC has been reported for having anticancer and antioxidant properties [1-3]. TC belongs to Kingdom: Plantae, Division: Magnoliophyta, Class: Magnoliopsida, Order: Myrtales, Family: Combretaceae, Genus: *Terminalia*, Species: *Chebula* Retz [4,5].

It is known by different names in different languages such as Harad in English, *Haimavti* in Sanskrit, *Chebulic myrobalan* in English, *Karukkaya* in Telugu, and in Tamil known as *Kudukkai*. Some other synonyms of TC are Amrta, Abhya, Kayashta, Vayastha, Patthya, Vijaya, Siva Jaya, and Haimavti.

**CATEGORIZATION OF TC AS PER AYURVEDA**

TC has different varieties and the information of these varieties differ in Ayurvedic and modern text [6,7].

**Categorization as per Bhavamisra**

Acharya Bahvmishra mentioned about different varieties of *Haritaki* in his text. He explained about number of different varieties along with their uses are given below:

1. **Vijya** – used for *sarvarog* (all diseases)
2. **Rohini** – used as *varan* (bearing wound healing property)
3. **Putana** – used as *prulepe* (external applications)
4. **Amrta** – used for *shodhan* (purification procedures)
5. **Abhya** – used for *netrarog* (eye diseases)
6. **Jivani** – used for *sarvarog* (all diseases) [6].

**Categorization as per Indian Materia Medica**

Different varieties along their morphological charactes and uses according to Indian Materia Medica are given below.

**Survariharade**

Large, dense and heavy size about 2" long, yellowish to brownish in color, when cut it contains pulp of yellowish to brownish tinge. This variety is valuable purgative.

**Rangariharade**

These are smaller in size, less wrinkled, and less furrowed than *Survariharade* and its length is about one inch; when cut it presents a yellow dried pulp and stone. The pulp is also less astringent than above variety. These are alterative, stomachic, laxative, and tonic. It is generally used in fevers, cough, asthma, urinary diseases, piles, worms and rheumatism and scorpion-sting.

**Baliharade**

This variety is smaller than above two mentioned categories, its color is homogeneous, and the pulp is deep brown. There is no stone into it. This is mild and safe aperients and antibilious, though astringent. Ripe fruits are considered as purgative removing bile and phlegm and to adjust bile. It is used in is highly useful in chronic diarrhea and dysentery, flatulence, vomiting, hicups, colic and enlarged spleen and liver. Brayed with sugar and water it is used in ophthalmia.

**Java harade**

These are smallest than all of above varieties and rest characters are similar as that of *Baliharade*. The uses of this variety are similar as that of *Baliharade*. Along with that cold infusion of it is used as a gargle in sore mouth and stomatitis, spongy and ulcerated gums. Brayed in rose water it is a cooling application to swellings [8].

**Categorization as per Hooker’s flora of British India**

In Hooker’s flora of British India, apart from TC, six other varieties of TC are mentioned [9,10]:

**TC Retz. (variety chebula proper)**

Fruits, one-to one-and-a-half inches, ellipsoidal or obovoid, from a broad base, more or less glabrous, and five-ribbed are abundant in Northern India at 1000-3000 ft.

**TC (var. typica)**

They have a young ovary and are shaggy without calyx teeth. They are distributed in Deccan, Ceylon, and Burma.

**TC (var. citrina)**

They have a young ovary, are quite glabrous, with ovate fruit, and a broad base. It is common in Northern India, from Kumaon to Bengal and in Chhota Nagpur.

**TC (var.)**

The fruits of this variety are much smaller than the other varieties. Generally found in Bihar up to an altitude of 1000 ft.
**CHEMICAL CONSTITUENTS**

TC mainly contains hydrolysable tannins as active constituents. Chebulinic acid (CA) is the main active constituent present in TC. Other constituents are chebulagic acid and D-galloyl glucose, free tannic acid, gallic acid, ellagic acid, and resin myrobolanin. Anthraquinone glycosides, sennosides are also found in TC [1,3]. These tannins contain phenolic carboxylic acid like gallic acid, ellagic acid, chebulic acid, and gallo-tannins such as 1,6 di-O-galloyl-β-D-glucose, 3,4,6 tri-O-galloyl-β-D-glucose, 2,3,4,6 tetra-O-galloyl-β-D-glucose, and 1,2,3,4,6 penta-O-galloyl-β-D-glucose. Ellagittannin such as punicalagin, casurinagin, corilagin, and terchebulin and others such as chebulanin, neochebulanic acid, chebulagic acid, and CA are also present in TC [1,3].

**ISOLATION AND EXTRACTION OF ACTIVE CONSTITUENTS PRESENT IN TC**

CA and chebulagic acid was extracted from TC by high-speed counter current chromatography method [3]. The solvent system used for this was n-hexane-ethyl acetate-methanol-water (1:20:1:20 v/v). The partition coefficient at this solvent system for chebulagic acid was 0.65 and CA was 1.20 respectively. Using this process, Quanbin et al., in 2006, extracted 33.2 mg chebulagic acid and 15.8 mg CA with a purity of 95.3 and 96.1% recovery from 300 mg of TC crude extract [3].

Mahajan et al., in 2010, isolated CA from TC by reverse phase high performance liquid chromatography (HPLC). They isolate 8 compounds gallic acid, methyl gallate, ethyl gallate, chebulagic acid, tetra-O-galloyl-β-D-glucose, ellagic acid, CA, and penta-O-galloyl-β-D-glucose from TC. The purities were checked by spectroscopic methods. UV absorption maxima of the hydrolysable tannins obtained from TC is shown in Table 2 [4].

Pfundstein et al., in 2010, determined polyphenolic and other active constituents of TC and Terminalia harriadin. It was reported that TC contained 6.18 g/kg of chebulic ellagitannins. Out of this chebulagic acid was 24.2 g/kg. Methyl neochebulinate, chebulic acid, chebulin and methyl neochebulaglate were present in decreasing order, in the range 7.1-9.0 g/kg. The recovery of CA was 4.0% along with small amounts of the partial hydrolyzed product (0.11 g/kg). Methyl neochebulic acid was 2.2 g/kg. 32.2 g/kg gallic acid and gallate ester were present. The non-chebulic ellagitannins (25.0 g/kg) were represented by about equal amounts of corilagin and punicalagin. Ellagic acid was present at 4.1 g/kg [5]. In TC and its related plants, tannins are the main biologically active substances. They are present in different molecular forms such as dimers, tetramers and polymers, depending on the mode of extraction. In aqueous or ethanolic extracts the lower molecules are prevalent.

Kilka et al., in 2004 extracted and isolate 1.36-Tri-O-galloyl-2.4-chebuloyl-β-D-glucopyranoside (CA) and its novel thrice hydrolyzed derivative, 2.4-chebuloyl-β-D-glucopyranoside (galloyl-free CA), together with ellagic and gallic acids, ethyl gallate, and luteolin, from the dried fruit of TC. They also identified and confirmed structure by UV, MS, and NMR data [14].
it can used on the eyelids. Decoction of Haritaki is used for the washing of wounds. In combination with Phyllanthus emblica and Terminalia bellirica under the name Triphala, fruits of TC are extensively used as adjunct to other medicines in almost in almost all diseases [17]. Triphala had also been found to be anti-inflammatory activity in gouty arthritis [18].

**Anti-inflammatory activity**
Sabina *et al*, in 2008, in showed anti-inflammatory activity in monosodium urate crystal-induced inflammation in mice of Triphala. They showed its significance in gouty arthritis [18].

Reddy *et al*, in 2009, showed that chebulagic acid is the compound in TC responsible for anti-inflammatory activity. They showed that chebulagic acid inhibit COX and 5-LOX responsible for anti-inflammatory and anticancer activity. Chebulagic acid showed potent COX-LOX dual inhibition activity with IC50 values of 1.5±0.288, 0.92±0.011 and 2.1±0.057 µM for COX1, COX2, and 5-LOX, respectively. They also showed apoptosis by chebulagic acid in COLO 205 cells. While ethanolic extract of TC showed IC 50 for COX1 and COX2 and LOX is 90 µg/ml, 3.75 µ, 20 µg/m [19].

**Anti-viral activity**
Extract of TC has antiviral properties [20], Ma *et al*, in 2010, demonstrated the antiviral activity of aceton extract of TC. They used mixture of Tannic acid and TC, instead of a single compound in order to get synergistic action of mixture. They showed the activity of aceton extract against swine influenza A virus [21].

**Anti-cancer activity**
It is used traditionally as anticancer drug in Africa and Asia. Saleem *et al*, in 2002, showed in vitro anticancer activity of methanol extract of TC. Cytotoxicity of *Terminalia* phenolics in HOS-1 cells was determined by the level of adenosine triphosphate (ATP). IC50 of CA was reported to be 53.2 µM [22]. Anticancer activity of 70% methanolic extract of TC was shown on cell lines of human (MCF-7), mouse (S115) breast cancer cell line, human osteosarcoma cell line, human prostate cancer cell line (PC-3), non-tumorigenic, and immortalized human prostate cell line (PNT1A). The parameters used to prove anticancer activity were proliferation thymidine incorporation and coulter counting. Cell viability was determined by ATP determination. The results revealed that concentration of 100 µg/ml, inhibit cell growth. It took some time to start its effect due to initiation of cellular processes causing decrease in proliferation and cell death. But at concentration of 400 µg/ml, it showed direct cytotoxic effect. The main components responsible for this action are CA, tannic acid, and ellagic acid [22].

CA is reported to inhibit HeLa cancer cell of cervical carcinoma. Although action of CA was restoration of gap junctional intracellular communication, exact mechanism is unknown [23].

**Anti-ulcer activity**
Tannin extract of TC possess antimitogenic properties. Kaur *et al*, in 1998, showed that gallic acid derivative and other tannins have antimitogenic activity against S9-dependent mutagen and 2AF in *Salmonella* typhi [24].

Prasad *et al*, in 2006, showed the chemomodulatory effect of TC in Wister rat against nickel induced oxidative stress. Nickel chloride treatment caused an increase in tumor promoters. The treatment of rat with TC with 25 mg/kg body weight dose reduces effect of nickel chloride. Thus, its extract can also be used in the prevention of cancer [25].

Chebulagic acid also has anticancer properties. TC is used to cure and stomach cancers [26]. It has 5-LOX inhibitory action 2.1±0.057 µM. It had demonstrated anticancer properties against HCT-15 (colon), COLO-205 (colon), MDA-MB-231 (breast), DU-145 (prostate), and K562 (chronic myeloid leukemia) cancer cell lines. It also showed anti-proliferative activity against HCT-15, COLO-205, MDA-MB-231, DU-145, and K562 cell lines [19].

**Cardiac effect**
CA has anti-hypertensive properties. This effect may be decreased in cardiac output which causes decreased left ventricular contraction. Hydrolysable tannins potentiate activity of beta-adrenergic blocker by depressing muscle contraction [27-28]. Mitochondria play an important role at molecular level in ischemia. Pretreatment of alcoholic extract of TC at dose of 50 mg/100 g body weight had protective activity in isoproterenol (ISO) (at dose 20 mg/100 g body weight) induced toxicity in rats. It was reported that TC retains normal function of mitochondria in ISO induced toxicity [29].

**Antihyperlipidemic activity**
TC has hypocholesterolemic effect. Thakur *et al*, in 1988 showed hypcholesterolemic effect in rabbits. Authors reported that TC has more lipid lowering activity than Amla and Bahera and it could be used as antihyperlipidemic agent for the treatment of atherosclerosis [30].

**Antidiabetic activity**
Aqueous extract of TC has been reported to have antidiabetic activity. Chebulic acid has protective action in case of glycation induced end product that causes endothelial cell dysfunction. According to Lee *et al*, in 2011, chebulic acid had IC50 values of 1.71 mM for protein cross-linking and 1.32 mM for advanced glycation end products (AGE) formation. As a positive control, aminoguanidine had IC50 values of 21.3 mM and 2.37 mM, respectively. They treat human umbilical vein endothelial cell with chebulic acid in the presence of AGES. Due to chebulic acid dose-dependent reduction glycer-AGE induced formation to 108.2±1.9% for 25 µM versus 137.8±1.1% for glycer-AGEs treated alone. They showed chebulic acid may be an agent can be used in diabetic vascular complication [31].

Aqueous methanolic extract of TC has been reported to have alphaglucosidase inhibitory action. This extract has been reported to inhibit the inhibitory action of maltase that is present in rat's intestine. Chebulanin, chebulagic acid, and CA have maltase inhibitory action with IC50 of 690, 97 and 36 µM, respectively. It also has potent alpha-glucosidase inhibitory action. Thus, chebulin and CA can be used in treatment and control of diabetes specially in type 2 diabetes [32].

It is also reported that TC possesses dose-dependent anti-diabetic activity in lowering blood glucose of streptozotocin induced diabetic rats [33].

**Radioprotective action**
TC extract has been found to possess radioprotective action in mice. Damage to DNA due to radiation was reduced [33,34]. TC along with other herbs (Triphala) is shown to be radioprotective properties at a dose of 10 mg/kg when administered intraperitoneally in mice. It acts by scavenging free radicals that are produced by radiation [35].

**Anti-ulcer activity**
TC has antulcer properties. Sharma *et al*, in 2011, showed antulcer activity [26]. It acts by inhibiting action of *Helicobacter pylori* by inhibiting urease activity which is responsible for ulcers in stomach. It

| Serial number | Seasons (Ritu) | Vehicle used for administration of TC (Anupaan) |
|---------------|----------------|----------------------------------------------|
| 1             | Illaveni (mildly sunny) | Honey                                       |
| 2             | Muthuvaneni (intense sunny) | Jaggery                                     |
| 3             | Kar (cloudy rainy)       | Rock salt                                   |
| 4             | Kuthir (Cold)            | Sugar                                       |
| 5             | Munpani (Early misty)    | Dried ginger                                |
| 6             | Pinpani (Late misty)     | Long pepper                                 |

TC: Terminalia chebula
| Serial number | Year | Publication number | Single/Combination | Activity | References |
|---------------|------|-------------------|-------------------|----------|------------|
| 1             | Use of TC extract for treatment of osteoarthritis | US 20150174184 | Single | Osteoarthritis | [43] |
| 2             | Plants parts and extracts having anticoccidial activity | EP 2866794 | Combination | Control coccidiosis in poultry | [44] |
| 3             | TC and Terminalia belerica extracts for inhibition of xanthine oxidase | US 20150050369 | Combination | Uricemia, hyperuricemia, and gout in a human | [45] |
| 4             | Weight-reducing tea and preparation method thereof | CN 103976056 | Single | Weight-reducing | [46] |
| 5             | Traditional Chinese medicine preparation for effectively treating dry cough | CN 10393435 | Combination | Dry cough | [47] |
| 6             | Tea with function of smoking cessation | CN 103892005 | Combination | Clearing throat and smoking cessation | [48] |
| 7             | Traditional Chinese medicine preparation for effectively treating dry cough | CN 103933435 | Combination | Dry cough | [47] |
| 8             | Broad-spectrum anti-toxic and bacteriostatic traditional Chinese medicine preparation and preparation method thereof | CN 103877320 | Combination | Broad anti-virus range, strong bacteriostatic | [49] |
| 9             | Concentrated solution capable of clearing heat and removing toxicity | CN 103860859 | Combination | Treating sore tongue and mouth, and swelling and pains in throat caused by internal heat | [50] |
| 10            | Plant parts and extracts having anticoccidial activity | CN20140161919 | Combination | Coccidiosis in poultry and, more specifically, coccidiosis | [51] |
| 11            | Blood purifying mixture for treating skin diseases | CN103830379 | Combination | Skin diseases | [52] |
| 12            | Physalisalkekengi heat-clearing throat-wetting wine and production method thereof | CN103815400 | Combination | Hot cough, sound dumbness and other main syndromes | [53] |
| 13            | Compound tincture for treatment of porcine virus diarrhea, preparation method and application thereof | CN103800804 | Combination | Treatment of porcine virus diarrhea | [54] |
| 14            | Blueberry wine with functions of invigorating stomach and relieving diarrhea and production method thereof | CN 103805422 | Combination | Vomiting, nausea, abdominal pain and diarrhea | [55] |
| 15            | Traditional Chinese medicine effective part composition for treating chronic pharyngitis | CN103768138 | Combination | Chronic pharyngitis | [56] |
| 16            | Traditional Chinese medicinal decoction for treating bronchial asthma | CN103751674 | Combination | Bronchial asthma | [57] |
| 17            | Drug for treatment of rheumatoid arthritis and preparation method thereof | CN103751305 | Combination | Rheumatoid arthritis | [58] |
| 18            | Traditional Chinese medicine preparation for treating tonsillitis and pharyngolaryngitis and preparation method thereof | CN103690695 | Combination | Chronic pharyngolaryngitis and acute and chronic tonsillitis | [59] |
| 19            | Chinese herbal medicine feed for wide geese, wide ducks, African geese and wide chickens | CN103621837 | Combination | To reduce diseases of the wide geese, the wide ducks, the African geese and the wide chickens and eliminate sanguinary smell and smell of meton and improve the immunity | [60] |
| 20            | Chinese medicine (TCM) for treating allergic rhinitis | CN 103610788 | Combination | From relieving Vibrio vulnificus septicemia | [61] |
| 21            | Throat clearing and moistening healthcare tea | CN103493921 | Combination | Allergic rhinitis | [62] |
| 22            | Plant parts and extracts having anticoccidial activity | WO/2014/004761 | Combination | Anticoccidial activity | [63] |
| 23            | External powder for treating dental ulcer and preparation method thereof | CN103405578 | Combination | Dental ulcer | [64] |
| 24            | TC compositions and method of extracting same | WO/2013/155175 | TC | Antioxidant | [65] |

(Contd..)
is reported that aqueous extract has strong anti *H. pylori* activity. It also improves the activity of bruneers gland, thus helpful in the treatment of duodenal ulcers [33].

**Anti HIV activity**
CA present in TC has anti HIV properties. CA act by inhibiting binding of HIV gpg20 to CD4. CA was found to non-toxic at dose up to 10 times [36]. Several hydrolysable tannins inhibit the expression of HIV antigen present in human lymphotrophic virus type 1- positive MT-4 cells. These tannins inhibit HIV adsorption on cells [37].

**Antioxidant activity**
Aqueous extract of TC has antioxidant properties. Extract of TC is found to have more antioxidant properties than *Momordica charantia*, *Glycyrrhiza glabra*, and *Acacia catechu*. Aqueous extract of TC had antioxidant activity by IC50 by thiobarbituric acid reactive substances is 14.5 µg/ml, IC50 by DPPH is 11.5 µg/ml, and ascorbate equivalent is 60% [38].

Chebulagic acid has antioxidant properties. It has DPPH radical scavenging activity with IC50 of 1.4 µM and strong inhibition of ABTS radical with an IC50 value of 1.7±0.023 µM [19].
TC had antioxidant properties due to the presence of hydrolysable tannins [39]. Tannins were found to have more potent antioxidant activity than flavonoids [40]. Chebulinic and chebulagic acid, both were found to have antioxidant properties [14,19,41]. CA has been reported for better antioxidant activity than other tannins due to higher DPPH activity [5].

**Hepatoprotective action**

TC extract has hepatoprotective action against rifampicin, isoniazid, and pyrazinamide toxicity [33]. Hydrolysable tannins generally exhibit an intense enzyme inhibitory action on glutamic-pyruvic transaminase [42].

**Miscellaneous**

Adrenocorticotropin hormone-induced lipolysis could be enhanced by CA and tellimagrandin I at 5-100 g/ml [41]. TC and its extract are used in wound healing and as antisapmodic. It has antibacterial properties also. It is used as antacaries agent in mouth washes. It has been used to treat respiratory disorders in Ayurveda. It is also reported to be used in urticaea and skin allergies. It has also been found to have purgative and antiamoebic action [26,33].

**FORMULATIONS AND PREPARATIONS**

TC is a rejuvenating medicinal fruit and it is used with different vehicles for the rejuvenation of body. Different formulations and ayurvedic preparations of TC available are Abhayamodaka, Abhayasirshita, Pathyadivati, Pathyadivatsa, Vyaghritharitaki, Hartikaleha, Chitrakharitaki, Agastharitaki, DantiHaritaki, Haritakakhanda, Pathyadichurna, Abhayadiyoggu, AbhayadiKalka, Amritadharitaki, Abhyamalakayarasayana, and Kayakalpa. To act as Kayakalpa, it should be consumed with different vehicles according to the season as shown (Table 3) [6]. Various patents related to TC are depicted in Table 4.

From the medicinal point of view, most of tannins of TC bring good results. They are effective against bacteria, viruses, parasites, and cancer cells. They protect animals and organs with their antioxidant property. They are reported to be nearly not toxic. But because there are no dosages known for the use in humans, they cannot be recommended for the internal use in humans [26]. YL et al., in 2004, showed that ICGO of CA for erythroid differentiation was 40 μmol/L for hemin-induced cell and 4 μmol/L for BA induced cells, respectively. CA has an inhibitory effect on erythroid differentiation of K 56 cells [80].

**CONCLUSION**

TC is a unique herb having various therapeutic potential as anti-inflammatory, antioxidant, anticancer, and digestant. Classification, chemical constituents, therapeutic uses, and patents that have been reported for TC. Various pharmacological activities of TC that make it as potential medicine and its Ayurvedic formulations are highlighted.

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