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Review

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Terminalia chebula Retz.: A Comprehensive Review of Medicinal Plant, Their Immense Bioactive Phytochemical Constituents, Biodiversity, Pharmacological and Therapeutics Medicinal Values

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Abstract: *T. chebula* Retz. is widely known by names such as Harad, Haritaki, Halela Zard, or Black Myrobalan. Due to its remarkable medicinal properties, it has held great significance in the traditional Ayurvedic and Unani systems of medicine since ancient times. It is often referred to as “Amrita” or nectar due to its wide range of therapeutic benefits for their remarkable health care benefits and widely recognized as the "King of Medicine" in Ayurveda, Tibetan, Unani and Chinese therapeutics system of medicine. TCR has long held a historic global identity. It was initially introduced into practice and recommended for its highly reliable traditional and therapeutic properties in ancient Indian Ayurvedic texts (such as the Charaka Samhita), as well as in classical texts from Tibetan, Unani, and Chinese (Jin Dynasty) traditions. Consolidates existing information regarding the traditional medicinal uses, bioactive phytochemical constituents, and pharmacological properties of TCR, placing special emphasis on its clinical significance and the therapeutic potential of its marker compounds. Various scientific studies have identified numerous bioactive phytochemical marker compounds in this plant, including tannins, phenolic acids, lignans, triterpenes, various flavonoids etc. with their immense medicinal properties. These marker compounds have demonstrated various biologically active properties in *in-vitro* and *in-vivo* studies, such as anticancer and antitumor, antioxidant, antidiabetic, antiviral, antibacterial, anti-inflammatory, hepatoprotective, nephroprotective, and neuroprotective effects due to their highly potent therapeutic potential. Despite extensive research and development and considering the safety profiles of extracts obtained using various solvents and their marker compounds as the variations in the shape and size of the TCR plant’s fruits rind/pericarp parts indicate significant natural biodiversity resulting from their occurrence in diverse natural habitats. This comprehensive review emphasizes enhancing the clinical and therapeutic potential of TCR and facilitating the studies of its major marker’s flavonoids (6) as Luteolin, Quercetin, 3-methoxy quercetin and 3,4′-dimethoxy quercetin – (methylated quercetin derivatives), Isoquercetin, Rutin along with their detail’s structure descriptions along with their bioactive marker compounds and their pharmacological applications.

Keywords: *Terminalia chebula* Retz-TCR; bioactive phytochemical compounds-*BAPCC*; phytochemistry; pharmacology; traditional medicine

1. Introduction

T. chebula Retz., (TCR) commonly known as Haritaki, Harad or Black Myrobalan, TCR has been native to South and Southeast Asia, is highly regarded in both Tibetan and Ayurvedic medicine is primarily found in South Asia, particularly in the Indian subcontinent, but also extends to Southeast Asia and found of parts of China-Indo-China, and Southern China, Nepal, Sri Lanka, Myanmar, Thailand and has been reported in regions of Africa, Iran, Afghanistan, and Brazil [1–9]. *T. chebula* is a medium-to-large-sized tree belonging to the Combretaceae family. Its dried fruits is widely used from since ancient times due these remarkable medicinal therapeutics properties,

particularly in countries such as Northeast Iran, Iraq, Saudi Arabia, European countries, Asian countries China, Nepal, India, Myanmar, Sri Lanka, Thailand, and Bangladesh [1,2,10]. TCR is considered the "King of Tibetan Medicines", and it consistently tops the list in health and Ayurvedic medicinal classic texts from it's historical several ancient time. This status is attributed to its remarkable ability to regulate health, metabolism and its exceptional medicinal properties and benefits. Available in powder and capsule forms, it has gained immense global popularity as a nutraceutical food and dietary supplement [1,11,12]. In recent times, TCR has emerged as one of the most popular and widely used herbal medicines, extensively employed in the treatment of bronchitis, cough, and various complex disorders of the digestive system [2,10]. TCR is a traditional medicinal plant used globally; in recent years, it has garnered significant international attention due to its remarkable medicinal and nutritional properties and its ability to deliver effective health benefits, leading to extensive and significant research. It is a rich source of highly effective valuable flavonoids and phenolic acids BAPCC compounds (such as gallic acid, chebulic acid, chebulagic acid and corilagin) and alkaloids, which are demonstrated and extensively used to formulated herbal medicines that are not found toxic effects and adverse harmful effects in human body. [12] The great curative capacity and their remarkable traditional medicinal therapeutics potential of TCR earned the title "Mother of Medicine" and in Ayurveda called as a "Amrita" from since ancient time [2,10–14]. TCR has traditionally been used in India since ancient times. This tree is found across a vast region extending from the Ravi River in the west to the states of West Bengal and Assam in the east as well as the Leh-Ladakh and Tibetan areas and thrives in the biodiversity-rich sub-Himalayan zone. Evidence indicates that TCR species naturally occur in the Himalayan region at altitudes of up to 1500 m (4900 feet). In India, the presence of wild TCR populations has been confirmed, particularly in the mountainous forest regions of North India, as well as in the forests of the central provinces and Bengal. Additionally, it is found in the natural forests of southern India, particularly in the lowland forest regions of the former Madras, Mysore, and Bombay Presidencies [15,16]. Globally, the pharmaceutical industry produces a significant volume of goods derived from the extracts of TCR's fruits and seeds, and there is considerable consumer interest in purchasing these finished products [10,15,17,18]. The phenolic compounds present in the fruit and seeds of TCR are responsible for significant therapeutic efficacy, alongside their remarkable medicinal properties. Furthermore, its botanical, taxonomic, and structural characteristics—such as the hard seed coat, fleshy mesocarp, hard endocarp, and underdeveloped embryo- play an active role in this regard. TCR fruit seeds part has been reported that in various regions of distributed worldwide occurrence and their rich biodiversity in deep hills and forest region local hillers and wild mass consumed it as a various healthcare treatment and gained health wellness and well beingness for curing several diseases due there remarkable medicinal curing and healing properties from since ancient time. Isolated BAPCC marker compounds of TCR fruit seeds part various extracts have been demonstrated and perfumed immense pharmacological and therapeutics medicinal properties as an including antioxidant, anti-inflammatory, antiviral, anticancer, antibacterial, hepatoprotective, nephroprotective, neuroprotective, and anti-diabetic effects due to presence of yielded over more than 149 bioactive phytochemical compounds including monoterpenes, sesquiterpenes, diterpenes, flavonoids, phenols, phenylpropanoids, diarylheptanoids, aromatics, fatty acids, polysaccharides, steroids, organic acids, alkaloids, fatty alcohols. Particularly in their flavonoids such as Luteolin, Quercetin, 3-methoxy quercetin, 3,4′-dimethoxy quercetin, Isoquercetin, Rutin have been reported, attributed and performed Antioxidant Capacity, Anti-inflammatory Effects, anticancer & Antitumor Activity, Cardioprotective, Antiviral Properties, Neuroprotection pharmacological and therapeutics medicinal benefits. Furthermore, this review article outlines potential future research directions and R&D prospects regarding the vast biodiversity, botanical characteristics, and reported bioactive phytochemical marker constituents of this TCR-which serves as a rich source of effective flavonoids and anti-cancer/anti-tumor marker compounds—thereby providing a robust strategic framework for guiding future research and development efforts [1–3,5–7,9–11,19–22].

1.1. Traditional and Medicinal Uses

Since ancient times, the pericarp (P.)/fruit rind of TCR have been used as both food and medicinal supplements in Northeast India, Europe, and several countries across Asia [1,2]. According to the Unani Pharmacopoeia of India (Anonymous, 2007 Edition) [23], Ayurvedic Pharmacopoeia of India (Anonymous, 1986 Edition) [24] A Chinese Pharmacopoeia (Anonymous, 2020 Edition) [1,2]. *T. chebula* Retz. or *T. chebula* Retz. var. *tomentella* (Kurz) C.B. Clarke refers to the dried, fully mature fruits and seeds of this plant species. They are characterized by their distinctive bitter and sour taste, neutral nature, and specific therapeutic properties associated with the lung and large intestine meridians. Since ancient times, forest-dwelling tribal communities and traditional healers have utilized the dried fruits and seeds of this plant valued for their remarkable medicinal properties—to tone the lungs and intestines and to treat throat ailments. They are used to address conditions such as chronic diarrhea, persistent dysentery, chronic cough, sore throat, loss of voice, rectal prolapse, blood in the stool, and lung weakness (which causes wheezing and coughing). In both ASU (*Ayurveda*, *Siddha* and *Unani*) medical systems,

the fruits and seeds parts of TCR are employed in hemostatic agents treating a diverse spectrum of health conditions, including chronic diarrhea, gastroenteritis, constipation, malabsorption syndrome, asthma, ulcers, dyspnea, dyspepsia, hemorrhoids, cough, candidiasis, hepatomegaly, urinary discharge, skin diseases, memory loss, epilepsy, cardiovascular diseases, diabetes, anorexia, as a hemostatic agents, and also as a diuretic, antitussive, and wound healer, as reported in numerous studies [1,2,25,26]. Historically, the fruit and seeds of TCR have been used in India, Tibet, and China for millennia, as noted in Grasses and Trees in India and South China. The plant has long been integral to traditional Indian medical systems particularly in classical Ayurvedic and Unani formulations products preparations where its products are manufactured on a large scale due to their proven efficacy and a heritage dating back to ancient times. It's considered a key rejuvenating herb in Ayurveda and is a component of the well-known Triphala composition of formulation. The fruit and seeds of this plant are used to treat various intractable diseases, and in China and Tibet, it is even referred to as the "King of Medicines." Furthermore, references to its abundant medicinal properties rooted in a long-standing traditional history—can be found in ancient Indian texts, modern classical treatises, and historical literature. Ethnopharmacological and therapeutic medicinal values of TCR has shown in Figure 1. (Sharma et al., 2019; Bhavaprakasa Nighantuh, 2018, Edited by Dr. S.D. Kamat; Sushruta, Sushruta Samhita, 2015, Edited by Prof. G.D. Singhal; Dhanvantari Nighantu, 2011, Edited by Dr. S.D. Kamat; Agnivesha Charaka Samhita,2006, Edited by Dr. Brahmananad Tripathi) and Chinese ancient literature (Western Jin Dynasty, 266–317 AD) [1–3,10,11,25,27–65].

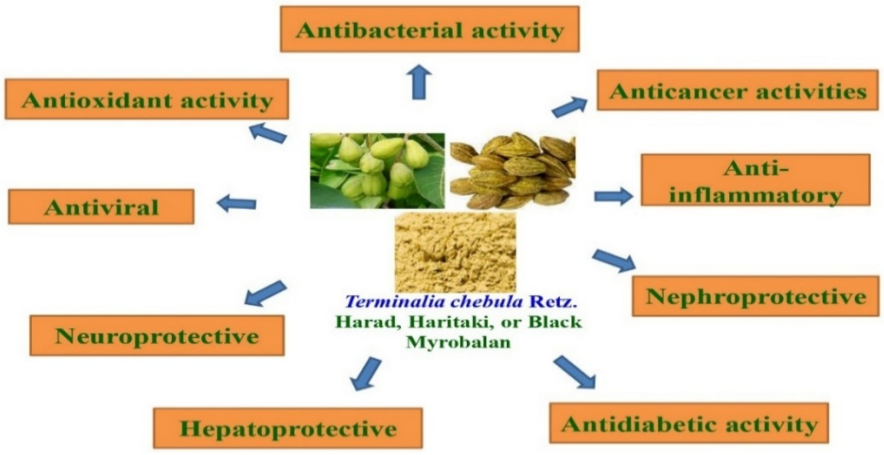


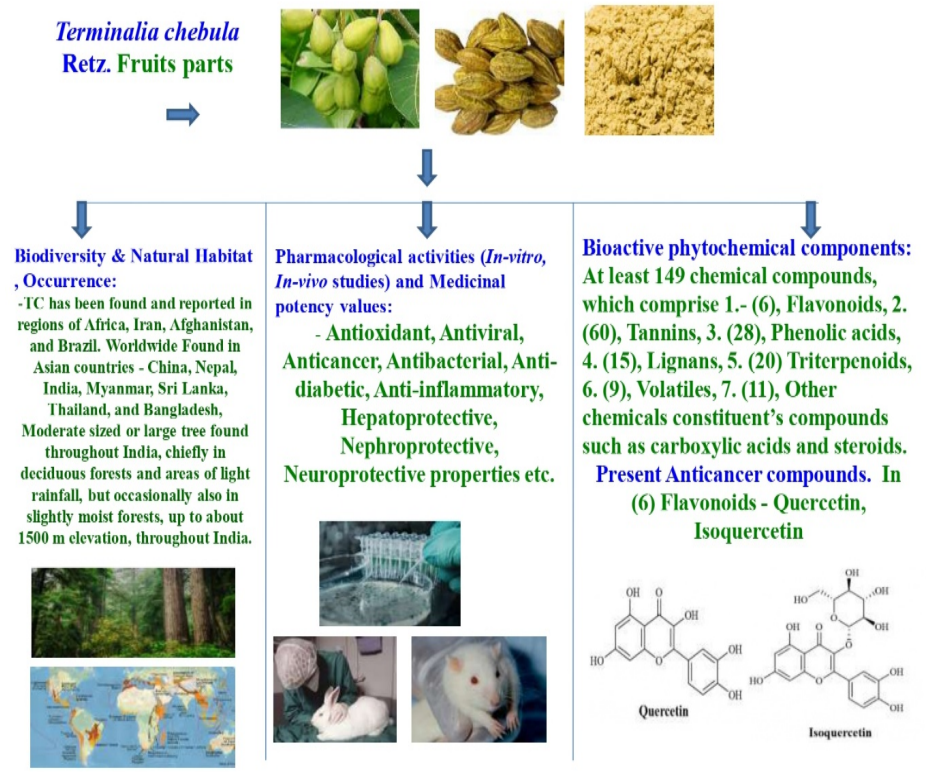
Figure 1. Ethnopharmacological and therapeutic medicinal values of TCR.

1.2. Phytochemistry and BAPCC Marker Compounds

Like other medicinal herbs, the remarkable medicinal properties of TCR are primarily attributed to the presence of a wide array of *BAPCC*-chemical compounds in abundance. To date, several pharmacologically active phytochemical compounds such as tannins, phenolic acids, lignans, triterpenoids, flavonoids and volatile polyphenolic compounds have been definitively identified through investigations using advanced laboratory techniques. specific part of the plant of TCR is rich in bioactive hydrolyzable tannins (such as chebulinic and chebulagic acids) and its major marker's flavonoids (6) as Luteolin, Quercetin, 3-methoxy quercetin and 3,4′-dimethoxy quercetin—(methylated quercetin derivatives), Isoquercetin, Rutin.

1.3. Phytochemistry

Like other herbs, the pharmacological activities of TCR have been primarily attributed to its various chemical compounds. To date, more and more pharmacologically bioactive phytochemical compounds, such as tannins, phenolic acids, lignans, triterpenoids, flavonoids, and volatiles, have been thoroughly understood and This has significantly boosted the use of products manufactured through TCR's large-scale global production. The sources of the *BAPCC*- markers compounds specified in TCR have been systematically identified via multiple databases, based on the unique medicinal properties associated with them, including Online Google searching engine, SciFinder., PubMed., Elsevier, Scopus, MDPI., and Web of Science [1,2,10–12,58–65]. It has been found that TC contains at least 149 chemical compounds. [2] which comprise 1—(6) Flavonoids, 2—(60) Tannins, 3—(28) Phenolic acids, 4—(15) Lignans, 5—(20) Triterpenoids, 6—(9) Volatiles, 7—(11) Other chemicals constituent's compounds such as carboxylic acids and steroids. details of (6) Flavonoids having Antioxidant, Anti-cancerous, Anti-tumorous compounds, TCR shown various shapes and sizes in Figure 2b, their molecular formula and structures respectively shown in Table 1 and Figure 3 [1,2,10,11,17,23,24,52,66].



(**a**)

(**b**)

Figure 2. (**a**) Graphical Illustration, Graphical Abstract of Biodiversity, pharmacological activities and Bioactive phytochemical compounds of TCR. (**b**) Graphical Illustration, Biodiversity and natural occurrence changes in/fruit rind/pericarp (P.) parts of TCR.

Table 1. flavonoids bioactive phytochemical compounds presents: [1,2,10,12,17,23,24].

Class	Bio Active Phytochemical Compounds	Molecular Formula	Belong to Functional Groups of Classes (Flavonoid Classes of Polyphenols)	Reported and Shown Therapeutics and Pharmacological Activities	References
Flavonoids	Luteolin	$C_{15}H_{10}O_6$	- hydroxyl (-OH)	- antioxidant aapacity,	[1,2,10]
	Quercetin	$C_{15}H_{10}O_7$	- hydroxy (-OH)	- anti-inflammatory effects,	[1,2,10]
	3-methoxy quercetin	$C_{16}H_{12}O_7$	- methoxy ($-OCH_3$)	- anticancer & antitumor activity,	[1,2,10]
	3,4′-dimethoxy quercetin	$C_{17}H_{14}O_7$	- methoxy ($-OCH_3$)	- cardioprotective,	[1,2,10]
	Isoquercetin	$C_{21}H_{20}O_{12}$		- antiviral Properties,	[1,2,10]
	Rutin	$C_{27}H_{30}O_{16}$	- flavanol glycoside - flavanol glycoside	- neuroprotection	[1,2,10]

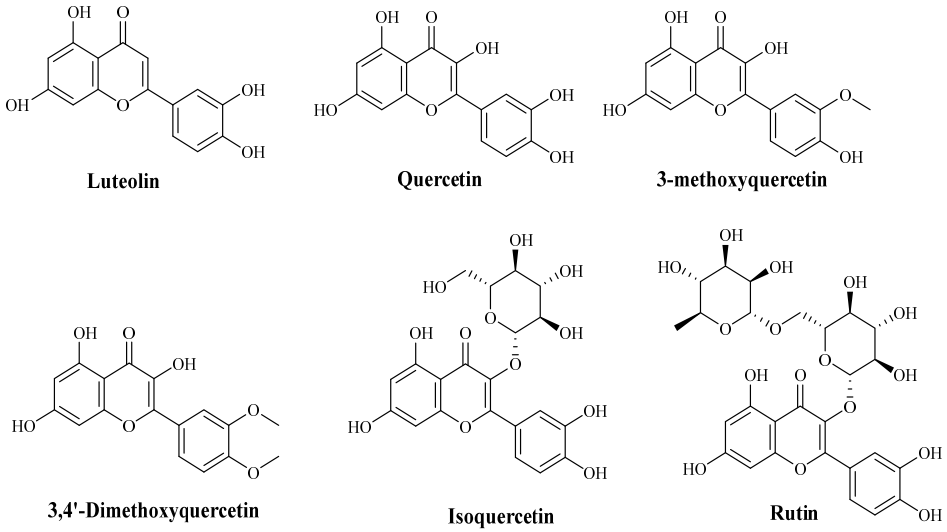


Figure 3. Structure of (6) Flavonoids of TCR.

2. Description

2.1. TCR Natural Habitat and Morphological Biodiversity Characteristics

The occurrence of TCR fruits rind/pericarp in various shapes and sizes is due to depends upon it varied, versed biodiversity, climatic zones, plant nature adaptations, and the genetical and zoographical sustainability of plant growths in their natural habitats occurrences. It is generally a medium-to-large tree found naturally having their rich biodiversity distributions in the dense forests across India. It primarily occurs in deciduous forests and areas with low rainfall, though it can also be found-sometimes up to an altitude of approximately 1500 m- in forests with moderate moisture, typically grows in mixed dry deciduous forests and tropical/subtropical zones, often in hilly areas, and can be found at altitudes up to 1500 m (4900 feet) in the Himalayas. It prefers free-draining clayey or sandy soils. Spared worldwide distribution in various countries regions of forest area as South Asia, particularly in the Indian subcontinent, but also extends to Southeast Asia and parts of China. It has been found and reported in regions of Africa, Iran, Afghanistan, and Brazil. Worldwide Found in Asian countries-China-Indo-China, and Southern China, Tibet, Nepal, India, Myanmar, Sri Lanka, Thailand, and Bangladesh. Refs. [1,2,10–18,23,24,67] TCR generally occurred and spread worldwide with their extreme biodiversity with their various shapes and sizes which have shown in Figure 2a,b and Box-1, *T. chebula* Retz. fruits parts—fruit rind/pericarp as e.g., TCF-1, TCF-2, TCF-3, TCF-4 & TCF-5.

2.2. TCR Fruits Parts—Fruit Rind/Pericarp Species Authentication and Confirmation

TCR species fruits parts—dried fruit rind/pericarp clearly authenticated, confirmed and verified by Repository, Pharmacognosy and Botany Department-PCIM&H, Kamla Nehru Nagar, District-Ghaziabad, Pin No.-201002, State-Uttar Pradesh, (under Ministry of AYUSH, Government of India) India, *T. chebula* Retz., Botany Repository Specimens (BRS) Nos.-dried fruit rind parts, specimen no.-BRS No./Field book no.-0513 and *T. chebula* Retz. pericarp parts, specimen no.-BRS No./Field book no.-0622.as well as *T. chebula* Retz. natural habitats and biodiversity occurrence, vernacular/Other's name and TCR used as traditional alternative medicine, in AU (*Ayurvedic and Unani*) important classic formulations briefly describe in Tables 2 and 3 and Box 1.

- TCR fruits and seeds parts of plant have been performed and shown BAPCC markers of Flavonoids e.g., Luteolin ($C_{15}H_{10}O_6$), Quercetin ($C_{15}H_{10}O_7$) which have belonged to hydroxy(-OH) groups, 3-methoxy quercetin ($C_{16}H_{12}O_7$) and 3,4′-dimethoxy quercetin ($C_{17}H_{14}O_7$)—(methylated quercetin derivatives) - belonged to methoxy(-OCH_3) groups, and Isoquercetin ($C_{21}H_{20}O_{12}$), Rutin ($C_{27}H_{30}O_{16}$) – belonged to glycoside groups including belong their functional groups—The flavonoid classes of polyphenols. their core structure (e.g., 2-phenylchromen-4-one skeleton) and specific functional groups (such as hydroxyl (-OH), methoxy(-OCH_3), and Flavanol glycoside groups. Isolated and various extracts of TCR Flavonoids markers compounds have been demonstrated and performed remarkable pharmacological and therapeutics medicinal potential values as antioxidant Capacity, anti-inflammatory effects, anticancer & antitumor activity, cardioprotective, antiviral Properties, neuroprotection which is shown along with their structure in Table 1, Figure 3.
- Isolated BAPCC and extracts of TCR plant have been shown, attributed and demonstrated to have immense pharmacological and therapeutic activities with their remarkable Flavonoids, tannins and phenolic bioactive

maker compounds and such as performed strong antioxidant activity, antiviral activity, anticancer activity, antibacterial activity, anti-diabetic activity (Shown in Table 4) and anti-inflammatory activity, hepatoprotective activity, nephroprotective activity, neuroprotective activity, anti-stress, immuno-modulator properties [1,26,66].

- In present scenario of research and development of TCR plant fruits extracts and isolated BAPCC of TCR plant, well known as an Amrita in traditional therapeutics and medicinal potent values of properties therefore due to global demand of TCR fruits extracts used as a food supplements and health care product due to these BAPCC immense medicinal potent values and product acceptability and traditionally their product effectiveness sustainable development.
- TCR dry fruit rind extracts based medicinal research can be utilized for advanced studies and investigations aimed at precise identification, the isolation of novel bioactive phytochemicals and secondary metabolites, and the validation of new drug discoveries. Advance studies can also be conducted on the traditional and classical fruits part components of the TCR plant to identify potential bioactive compounds that could be used to develop new medicines by investigated novel drug development marker compounds and provide health benefits to needful human being [1,2,10,13,59–65].
- There is an urgent need to conduct advanced research focused on isolation, characterization, and structural elucidation using modern instrumental techniques such as GC-MS, LC-MS, XRD, and SEM-EDX. Simultaneously, advanced research including cell line studies and *in-vivo* (animal-based) experiments must be undertaken to investigate pharmacological and biological activities, such as anti-cancer, anti-tumor, anti-diabetic, antiviral, antioxidant, and anti-stress properties [1,2,10,13,59–65].

Box 1. Natural Habitats and biodiversity occurrence: [1,2,10–18,23,24,67].

TCR typically grows in mixed dry deciduous forests and tropical/subtropical zones, often in hilly areas, and can be found at altitudes up to 1500 m (4900 feet) in the Himalayas. It prefers free-draining clayey or sandy soils. South Asia, particularly in the Indian subcontinent, but also extends to Southeast Asia and parts of China. It has been found and reported in regions of Africa, Iran, Afghanistan, and Brazil. Worldwide Found in Asian countries-China-Indo-China, and Southern China, Tibet, Nepal, India, Myanmar, Sri Lanka, Thailand, and Bangladesh. It is generally a medium-to-large tree found naturally having their rich biodiversity distributions in the dense forests across India. It primarily occurs in deciduous forests and areas with low rainfall, though it can also be found─sometimes up to an altitude of approximately 1500 m in forests with moderate moisture [1,2,10–18,23,24,67].

Table 2. Vernacular/Other's Name: [11,13–15,23,24,68,69].

Sanskrit	Abhaya, Kayastha, Siva, Pathya, Vijaya, (Not Bhanga)	**Arabic**	Halelaj
English	Chebulic Myrobalan, Black Myrobalan	**Hindi**	Harra, Harad, Harar, Harre, Pile Har, Bal Har
Urdu	Halela, Halela Kabuli, Halela Zard.	**Persian**	Halela Kabuli
Assamese	Helikha, Silikha, Hokikha	**Bengali**	Haritaki, Hora
Gujarati	Hirdo, Himaja, Pilo-Harde, Kabuli-harda, Hardo	**Kannada**	Alalikai, Kale Har, Zangli Har, Har, Harara
Kashmiri	Halela	**Malayalam**	Katukka, Kayastha, Kadukhai, Divya
Marathi	Harda, Hirda, Harba	**Oriya**	Haridra, Hirdar, Hirada, Horida
Punjabi	Halela, Haser, Harrar, Har Hush, Harar	**Tamil**	Kadukkai, Amagola, Arabi, Aridadi
Telugu	Karaka, Karakkaya, Haritaki Karaka, Sringitiga, Karakai		

Table 3. TCR used as traditional alternative medicine, in AU (*Ayurvedic* and *Unani*) important classic formulation's: [13–17,23,24].

Unani Formulation's	Itrifal Kishneezi, Itrifal Zamani, Itrifal-e-Ustukhuddus, Itrifal-e-Shahtra, Itrifal-e-Sagheer, Itrifal Mulaiyin, Itrifale-Kabir,Majoon-e-Kundur, Majoon-e-Khabs-ul-Hadeed,Kohal-ul-Jawahir.	**Ayurvedic Formulation's**	Triphala Churna, Triphaladi Taila, Abhayarishta, Agastya Haritaki Ras¡yana, Citraka Haritaki, Danti Haritaki, Dasamula Haritaki, Brahma Rasayana, Abhaya Lavana, Pathyadi Lepa

Table 4. Pharmacological and Therapeutic medicinal activities.

Sr. No	Pharmacological and Therapeutic Activities Reported and Investigated	TCR Extracts	"*In Vitro*" and "*In Vivo*" Effects	References
01	antioxidant Activity	70% methanol extract of TCR, Methanol, Water, Hydro-alcoholic extracts of TCR, Polyphenolic extract of TCR TCR contained and attributed—phenolic carboxylic acids and tannins such as chebulagic acid, chebulinic acid, gallic acid, and ellagic acid. Ellagic acid of TCR	- Shown and demonstrated scavenging of free radicals like DPPH, nitric oxide, and hydrogen peroxide. - Shown high phenolic content and strong antioxidant activities. - Protects against ROS-induced oxidative stress due to its phenolic composition. - Prevent oxidative stress, inhibited oxygen-induced reactions, and offer anti-aging benefits. - Antioxidant effects shown and protected against cyclophosphamide-induced renal toxicity in rats. - Shown and performed scavenging free radicals as well as modulating antioxidant enzyme activities and shown potential therapeutic benefits in oxidative stress-related conditions.	[1,2,4,10, 11,70–79]
02	antiviral Activity	Applied and used TCR Extracts in various *in-vitro* and *in-vivo* cell lines studies. Applied and used TCR Extracts in various *in-vitro* and *in-vivo* cell lines studies. Applied and used TCR Extracts in various *in-vitro* and *in-vivo* cell lines studies. Applied and used TCR Extracts in various *in-vitro* and *in-vivo* cell lines studies. Applied and used TCR Extracts in various *in-vitro* and *in-vivo* cell lines studies.	- Shown, performed and Inhibited of 3-chymotrypsin-like cysteine protease (3CLpro), a crucial enzyme for the virus's replication. - The activities demonstrated by 1,2,3,4,6-penta-O-galloyl-β-D-glucose against SARS-CoV-2, 3CLpro highlight its potent and exceptional capacity to inhibited viral protease activities. - TCR possesses tremendous potential to inhibited RNA-dependent RNA polymerase (RdRp). Both are crucial targets for antiviral therapy, particularly because they play a vital role in the replication of the RNA virus. - Compounds chebulagic acid and chebulinic acid of TCR extracts shown tremendous potential as a novel inhibitors capable and promising NA inhibitors, with the potential for development into effective antiviral agents targeting IAV and managing H1N1 virus infections. - TCR isolated extracts shown and inhibited antiviral potential effects against several viruses as HSV-1, HSV-2, and HIV-1 and 2 hydrolysable tannins- punicalagin and chebulagic acid isolated compound of TCR extracts—effectively inhibited and controlled the entry of study used A549 cells for VSV and adenovirus-5a and HEp-2 cells for RSV by targeting and neutralizing of main viral components. - Several tannins compounds of TCR isolated extracts Investigated and attributed, significantly mitigate lung lesions and reduced viral burdens and inflammatory markers, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE2) *in-vivo* studies of BALB/c mouse infected with respiratory syncytial virus. - Demonstrated and attributed that isolated TCR extracts contained four inhibitors of HIV-1 integrase, specifically gallic acid and three derivatives of galloyl glucose and these derivatives were controlled and crucial in inhibited the 3′-processing activity of HIV-1 integrase. - Attributed and performed that chebulinic acid and chebulagic acid, isolated extracts from TCR, exhibit potent antiviral effects against HSV-2 virus.	[1,2,11,51, 80–88]

Table 4. *Cont.*

Sr. No	Pharmacological and Therapeutic Activities Reported and Investigated	TCR Extracts	"*In Vitro*" and "*In Vivo*" Effects	References
03	anticancer and antitumor Activity	Applied ethanolic TCR plant extracts Applied methanolic TCR plant extracts. Applied ethanolic and hydro-alcoholic TCR plant extracts. Applied ethanolic and hydro-alcoholic TCR plant extracts. Applied ethanolic TCR plant extracts. Applied ethanolic TCR plant extracts. Applied ethanolic TCR plant extracts. Applied TCR plant extracts. Applied TCR plant extracts.	- Isolated corilagin, gallic acid and ellagic acid compounds of TCR plant extracts were attributed and demonstrated anticancer activities against breast cancer cells line. - In several in various studies, a cytotoxic effect was inhibited and observed on four human cancer cell lines derived from colon, melanoma, prostate, and lung cancers. - Shown and performed that corilagin, gallic acid and ellagic acid isolated from TCR extract possess immense potential anti-breast cancer activities in several studies. - Indicated, controlled, and demonstrated of isolated corilagin from TCR plant extracts again MDA-MB-231 and MCF-7 breast cancer cells lines growths in various studies. - Demonstrated, performed and shown significantly inhibited MCF7 cell line studies, controlled breast cancer growth in both in-various studies. - Demonstrated and inhibited isolated Gallic acid and the exosomal secretory pathway of TCR extracts, CDK6-targeted human breast cancer cell lines, anticancer in several studies. - Demonstrated and controlled of 1,2,3,4,6-penta-O-galloyl -β-D-glucose isolated from TCR plant extracts effectively β-PGG inhibited HepG2 cells survival and induced apoptosis in *in-vitro* several studies. - RT-PCR and western blot techniques were performed, and demonstrated anti-cervical cancer properties by applied both the PI3K/AKT and MAPK signalling pathways. - TCR extract isolated Chebulagic acid, effectively shown and inhibited the expressed of AURKA as well as the AURKA/β-catenin/Wnt signalling pathway including MKN1 and NUGC3 cells and a tumor-bearing mouse model prevented and controlled in several gastric cancer cell line studies.	[1,2,10,11, 14,52, 89–100]
04	antibacterial Activity	Applied ethanolic TCR plant extracts. Applied ethanolic TCR plant extracts. Applied Ethyl acetate, methanol, and aqueous TCR plant extracts. Isolated TCR plant extracts Isolated TCR plant extracts	- Plant extract has been found to possess growth-inhibiting and controlling capabilities and exhibits an 'anti-*Staphylococcus aureus*' effect. Furthermore, due to its excellent antibacterial properties. - TCR plants extracts have been demonstrated and investigated antibacterial effects on several bacterial strains. It effectively inhibited *Helicobacter pylori*, *Xanthomonas*, *Salmonella typhi*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus mutans* bacterial growths. - TCR plants extract of ethyl acetate shown and exhibited superior anti- Porphyromonas gingivalis activities related to the methanol and aqueous extracts in several studies. - Plant extracts both isolated phenolic acid, corilagin compounds shown and inhibited immense antibacterial properties against *Staphylococcus aureus* bacterial growths. - Plant extracts Isolated compounds ellagic acid demonstrated, and inhibited growth, resistant pathogenic bacteria, including Methicillin-resistant, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* bacterial growths in several antibacterial activities studies.	[1,2,10,11, 74,101–104]
05	anti-diabetic Activity:	Aqueous/ethanolic fruits TCR plant extracts. TCR plant extracts. Isolated TCR plant extracts	- Plant extracts shown and demonstrated of managing type 2 diabetes, reduced oxidative stress and enhanced the expression of SIRT1 (Sirtuin 1) in diabetic rats in various studies. - Plant extracts attributed and demonstrated that higher doses of TCR ethanolic extracts exhibited immense therapeutic medicinal potential, particularly shown and enhanced anti-diabetic and antilipidemic effects. - Plant extracts isolated compound chebulinic acid demonstrated, performed and identified as a promising strong anti-diabetic agent for the treatment of type 2 diabetes that simultaneously targets PTPN9 and PTPN11 as well as demonstrated, exhibited strong inhibitory potential with IC50 values of 34 nM for PTPN9 and 37nM for PTPN11these several studies.	[1,2,10,11, 68,89,105–108]

3. Conclusions and Future Perspectives

T. chebula Retz. (TCR) has long been used by tribal communities and local traditional healers. It has been extensively utilized in various traditional and folk medical systems such as *Ayurveda*, *Unani*, and *Tibetan* traditions as well as in specific medicinal formulations since ancient times. In addition to its medicinal applications and their immense medicinal potent values, TCR is also valued for its nutritional, health care and wellness benefits. Researchers have been identified several marker compounds in TCR plant extracts, notably flavonoids, tannins, and phenolic acids (*BAPCC*). Numerous studies have revealed that TCR extracts and their distinct marker compounds exhibited and performed remarkable pharmacological and biological activities in several *in-vitro* and *in-vivo* studies such as antioxidant, antiviral, anticancer, antitumor, antibacterial, anti-diabetic, anti-inflammatory, hepatoprotective, nephroprotective, and neuroprotective effects. The presence of *BAPCC* as hydrolyzable tannins (such as chebulinic and chebulagic acids) and important six flavonoids marker compounds such as Luteolin, Quercetin, 3-methoxy quercetin and 3,4′-dimethoxy quercetin (methylated quercetin derivatives), Iso-quercetin, Rutin, along with tannins and phenolic acids, confirms and clearly demonstrates that these are the key bioactive constituents primarily responsible for exhibiting antioxidant, anti-cancer, anti-tumor, and other immense medicinal activities. There is an urgent need for further advanced and reconfirmation of required research regarding of the marker compounds, phytochemistry, and pharmacological aspects as changing of their markers compounds metabolic behaviors and medicinal potent activities of TCR fruits and seeds several extracts. While evidence confirming their effects is currently available through various *in-vitro* and *in-vivo* studies, more advanced, detailed research and sustained, high-impact development efforts are essential to bridge existing gaps in our understanding. The objective of this comprehensive review is to provide a detailed discussion and reference-worthy information regarding the therapeutic benefits, uses, *BAPCC* markers, phytochemistry, and pharmacological properties of this medicinal plant, which is rich in the traditional medicinal qualities associated with TCR. It is hoped that this review will provide researchers with valuable information, referential supports such as details on several flavonoids marker compounds that exhibit remarkable antioxidant potential as well as anticancer and antitumor activities, facilitate the further development, advanced research, and application of TCR in various *in-vivo* biological, pharmacological and therapeutic contexts.

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Abbreviations

TCR	*Terminalia chebula* Retz.
BAPCC	Bioactive phytochemical constituents
DPPH	2,2-diphenyl-1-picryl-hydrazyl-hydrate
FRAP	Fe3+-reducing antioxidant power
LDH	lactate dehydrogenase, neuraminidase
LPS	Lipopolysaccharide
NF-Kb	nuclear factor kappa B
TNF-α	tumor necrosis factor-α
IL	interleukin(IL)
NLRP3	NOD-like receptor protein 3
iNOS	inducible nitric oxide synthase
COX-2	cyclooxygenase-2
PGE2	prostaglandin E2
IC50	half maximal inhibitory concentration
ROS	reactive oxygen species
3CLpro	3-chymotrypsin-like cysteine protease
RNA	ribonucleic Acid
RdRp	RNA-dependent RNA polymerase
H1N1	novel pandemic influenza virus
IAV	influenza A virus

HSV-1	herpes simplex virus 1
HSV-2	*h*erpes simplex virus 2
HIV-1	human immunodeficiency virus 1
A549 cells	human alveolar basal epithelial cells derived from a lung carcinoma
BALB/c	bagg albino with the lowercase **c** denoting the albino coat color genotype
MDA-MB-231	M.D.-anderson-metastasis breast-231
MCF-7	michigan cancer foundation-7
CDK6	cyclin-dependent kinase 6
RT-PCR	reverse transcription polymerase chain reaction
PI3K/AKT	phosphoinositide 3-kinase/ protein kinase
MAPK	mitogen-activated protein kinase
AURKA	aurora kinase A
β-catenin	beta-catenin
SIRT-1	silent information regulator 2 homolog 1
PTPN9	protein tyrosine phosphatase non-receptor Type 9
PTPN11	protein tyrosine phosphatase non-receptor Type 11

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