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Traditional, Current and Prospective Therapeutic Uses of *Muntingia calabura*: A Comprehensive Literature Review

[1]Bhanita Saud, [1]K.M. Geetha, [1]Sonal Dubey, [2]Pankaj Kumar Singh, [3]Shweta Shrivastava, [4]Dilpreet Singh and [1]Prashant Tiwari

[1]Department of Pharmacology and Toxicology, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru 560078, India

[2]Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Hyderabad 500037, India

[3]Department of Pharmacology, School of Pharmacy, Arka Jain University, Jhmshedpur, 832108, India

[4]Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab 142001, India

ABSTRACT

Muntingia calabura is a blooming evergreen plant. This plant has a unique traditional significance in different parts of the world. Based on traditional value pre-clinical research being conducted around the world, including identified phytochemicals responsible for various pharmacological activities. This review focuses on the taxonomical classification, worldwide geographical distribution, isolated constituents, traditional importance, therapeutic activity as well as the toxicity of the plant extract on animals. All the data included in this article was gathered from different online search engines. As a result of the survey signified that this plant has several traditional utilization-like headaches, tranquilizer, antispasmodic, including colds, gastric ulcers, antibacterial, insomnia and so on. Modern scientific studies have revealed that *M. calabura* has significant pharmacological properties, such as gastroprotective, anti-cancer, hepatoprotective, anti-bacterial and anti-diabetic, which are attributed to various phytochemicals found in various parts of the plant which are identified by using various techniques. This review focuses on ethnomedicinal applications, phytochemicals, toxicity and pharmacological properties, as well as continuing pre-clinical trials. Moreover, the review's findings will be valuable in building a full plant profile, which will support the investigator in subsequent research and fill in the gaps in clinical investigations.

KEYWORDS

Muntingia calabura, traditional system, ethnobotany, pharmacological action, phytochemistry, medicinal value, therapeutic aid

INTRODUCTION

Plants have played an important part in supplying nutrition as well as sustaining health. Nature has been an immense source of medicine as well[1]. Medicinal plants have been for a long time to cure various human ailments for their pharmacological and therapeutic qualities, which are attributed to the active

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chemical constituents which have been isolated from their crude extracts[2]. Plants from all over the world are being studied for their therapeutic values like *Vitex negundo* (from China)[3], *Martynia annua* (from Mexico and South Africa)[4] etc., including Indian species[5] have been shown to possess a wide array of activities and their exhaustive phytochemical studies is the subject of interest.

Mutengia calabura has its traditional medicinal values since long time. Around the globe *Mutengia calabura* known as Jamaican cherry. It is the only species belonging to genus *Muntingia*. This plant is widely available in Philippines, India, South as well as Central America, Indonesia, Malaysia etc[3].

Mutengia calabura have been in use for a long time as a folk medicinal herb because a different part of the plant possess different medicinal value such as anti-diabetic, anti-gout, antihypertensive, laxative, antiseptic, anti-seizure, gastroprotective, antioxidant and anti-inflammatory effects, as well as it shows efficacy against productive cough, flu, headache and fever[4]. Along with medicinal value, this species has been identified as a good bio-indicator of air pollution in various studies[5]. The presence of phenolic or polyphenols, flavonoids, tocopherols, cinnamic acid derivatives, flavonoids, polifungsional acids and coumarin in *Muntingia calabura* leaves contributes to their antioxidant action. Flavonoids with antioxidant properties include flavonol, flavanon, flavones, isoflavones, catechins and kalkon. Other extraction processes can be used to detect phenolic antioxidant compounds[6]. The various part of the *M. calabura* plant were extracted using various solvents and extraction procedures before being subjected to *in vitro* and *in vivo* research in order to demonstrate their scientific activity[7]. The phytochemical chapter of *M. calabura* has been well standardized through the use of advanced technology, which contributes to the plant's therapeutic efficacy. There have already been numerous studies published that focus on the validation of both conventional and current pharmacological properties. This study intends at collecting the most recent information on *M. calabura*, including isolated chemicals, appearance, therapeutic effects, distribution and so on. This review will also focus on mending the gap in further research of *M. calabura* toward its clinical utility. The geographical presence of *M. calabura* across the globe has been tabulated in Table 1.

Table 1: Vernacular names

Name	Place/country	References
Bolaina or capulı'n blanc	Spain	Sufian *et al.*[8]
Pau de seda and Calabura	Brazil	Bandeira *et al* [9]
Pu'an and capulin rojo	Mexico	Zakaria *et al* [10]
Bois ramier	France	Suganthi and Dubey[11]
Gasagase hanninamara	India	Kumar *et al.*[12]
Kerukup siam	Malaysia	Pungot[13]
Buah cheri	Malaysia	Ragasa *et al.*[7]
Cay trung ca	Vietnam	Rajamma *et al.*[14]
Takhop farang	Thailand	Selvanathan *et al.*[15]
Kersen and talok	Indonesia	Sarimanah *et al.*[16]
Krakhob barang	Cambodia	Carter *et al.*[17]

MATERIALS AND METHODS

PubMed, Scopus, Springer, Science Direct, Google Scholar Web of Science, Elsevier, National Centre for Biotechnology Information (NCBI) and other search engines were used to conduct the complete literature search. Some standard ethenopharmacogonosy books are also used to congregate more information on *Muntingia calabura*. Until November, 2021, an advanced literature search was conducted using various keywords such as "*Muntingia calabura*", *Muntingia,* therapeutic use, traditional use, phytochemistry and botany.

Taxonomy: *Muntingia calabura* is a pioneer species[18]. *Muntingia calabura* was previously classified as a member of the *Elaeocarpaceae* or *Tiliaceae* family. However, the given genus exhibits characteristics that would be atypical in either family, this is why this placement is not widely accepted by specialists. Similarly, *Muntingia* might be found in the Flacourtiaceae family or in the Tiliaceae family, which is a large and heterogeneous notion. Based on DNA sequence evidence, these families are far segregated in the "eudicots. *Muntingia* has numerous characters with other two monotypic genera such as Neotessmannia Burret and *Dicraspidia* Standl. Previous researchers, on the other hand, came to different conclusions based on such commonalities. Hutchinson classified *Muntingia* as a member of the Tilieae Bartl. Tribe, whereas the other two genera were assigned to the Neotessmannieae Burret tribe. Tilieaea, including *Muntingia* at the subfamilial level (as Neotessmannioideae Burret), although Benn and Lemke considered the three genera to comprise a distinct tribe, Neotessmannieae inside Tiliaceae any of the above-mentioned families should exclude *Muntingia*, *Dicraspidia* and most likely, Neotessmannia. They represent a distinct family with no ties to other families[19,20].

Botanical profile: *Muntingia calabura* is a neotropical[21], small tree that grows quickly[22] with nearly horizontally spreading branches, it reaches a height of 7.5-12 m[23].

Leaf: *Muntingia calabura* has evergreen oblong-ovate or lanceolate in shape leaves that are around 5-12.5 cm long[24]. The leaf, its singular stipule, the extra-axillary bud and the supra-axillary peduncles all have vascular supply in *Muntingia calabura* L. The median and two lateral bundles make up each leaf trace and the node is trilacunar. After detaching from the axial stele, the two laterals diverge through the cortex toward the median, where they eventually join to form the petiolar trace at its base. One of the laterals lets out a branch that produces the trace of a single stipule as it passes through the cortex, whereas the other lateral does not branch and stipule production on this side of the axis is repressed. As a result, the creation of stipules appears to be inextricably linked to the branching of the lateral trace bundle[25].

Flower: The flowers of *Muntingia calabura* have five green sepals and five white petals as well as several noticeable stamens that are yellow and only endure a single day. In the afternoon, petals fall. The flowers resemble strawberry blooms so commonly known as a strawberry tree. They exude a mildly sweet aroma because of this small to medium-sized bees, diurnal moths, butterflies, hoverflies, hummingbirds and ants are attracted to the flower[26]. Flowers are bisexual, however, the size of the pistil and the number of stamens vary greatly[27].

Fruit: Fruits are rounded or spherical in shape, about 1-1.5 cm in diameter. It is green in colour and becomes crimson when fully mature. The fruit has a smooth, slender, succulent peel and a lightish-brown, velvety, tender pulp with a sweet, musky, fig-like flavor and visible extremely little yellowish seed.

Geographical distribution: *Muntinga calabura* is extensively grown in tropical Asian countries like India, Malaysia, the Philippines, Indonesia, Thailand, Vietnam and Singapore. Previously, the Portuguese were said to be the principal distributors of Jamaican cherry fruit, which was originally shipped to Thailand or Vietnam before spreading to Malaya.

Phytoconstituents found in leaves: From the article reported that the upper part of the leaf that is adjacent to the cuticle was smaller in size and phenolic compounds were mostly present in that area. The inner portion extended to the mesophyll was filled with mucilaginous content[28].

Two important bioactive catechin elements Epigallocatechin Gallate (EGCG) and genistein are discovered in *Muntingia calabura* leaves[29]. By using QR induction assay fractionating an ethyl acetate soluble extract of *M. calabura* leaves leads to purification of the new flavanone [3,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one] is a metabolite of [3,5,8-trihydroxy-7-methoxy-2-phenyl-2,3-dihydrochromen-4-one], along with this 24 other flavonoid was also reported that include [(2S)-7-hydroxy-2-phenyl-2,3-dihydrochromen-4-one], [5,7-dihydroxy-2-phenyl-2,3-dihydrochromen-4-one], [5,7-dihydroxy-2-(3-hydroxyphenyl)-2,3-dihydrochromen-4-one], [5-hydroxy-7-methoxy-2-phenyl-2,3-dihydrochromen-4-one], [7-hydroxy-2-phenylchromen-4-one], [chyrsin], 3-methoxy-5,7,4 -trihydroxyflavone,3,3 -dimethoxy-5,7,4 -trihydroxyflavone, [5,7-dihydroxy-2-(4-hydroxyphenyl)-3,8-dimethoxychromen-4-one], [5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-methoxychromen-4-one], [3,5-dihydroxy-7,8-dimethoxy-2-phenylchromen-4-one], [5-hydroxy-7,8-dimethoxy-2-(4-methoxyphenyl)chromen-4-one],5,4 -dihydroxy-3,7,8-dimethoxyflavone, [2-(3,4-dimethoxyphenyl)-5-hydroxy-7,8-dimethoxychromen-4-one], [(E)-1-(2,4-dihydroxyphenyl)-3-phenylprop-2-en-1-one], [(E)-1-(2,4-dihydroxyphenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one], [7-hydroxy-3-phenylchromen-4-one], [3-(3,4-dimethoxyphenyl)-7-methoxychromen-4-one], [1-(2,4-dihydroxyphenyl)-3-phenylpropan-1-one], gallic acid, lupenone and (2α,3β)-2,3-dihydroxyolean-12-en-28-oic acid reported by Su *et al*.[30].

Sufian *et al*.[8] reported four new novel compounds from chloroform and butanol soluble leaves fractions, they were two new dihydroxychalcone, flavanol and flavanone. For example 2,4-dihydroxy-3-methoxydihydrochalcone, (-)-3-methoxy-2,4,β-trihydroxydihydrochalcone, muntingone, [2-(3,4-dimethoxyphenyl)-5-hydroxy-7-methoxychromen-4-one].

Fruit: The volatile constituent present in ripe *Muntingia calabura* fruit collected from campus of University Sains Malaysia, for example-ethyl propionate, ethyl 2-methyl propionate, 2,3-butanedione, 2-methylpropyl acetate, 2-methyl-3-buten-2-01, 2,3-pentanedione, hexanal, 2-methyl propanol, (E)-3-penten-P-one, 3-methylbutyl acetate, 4-methyl-3-penten-2-one, 2-methyl-4-pentenal, 1-penten-3-ol, pyridine2,3-dihydro-4-methylfuran, llimonene, 3-methyl butanol, (E)-2-hexenal, ethyl hexanoate, thiazole, 2-methyltetrahydrofuran-3-one, 3-hydroxybutanone, 1-hydroxyQ-propanone,(Z)-2-pentenol, 3-methyl-2butenol, 2-acetyl-1-pyrroline, [ethyl (2*R*)-2-hydroxypropanoate], hexanol, (E)-3-hexenol, (Z)-3-hexenol, (E)-2-hexenol, 3-(methylthio)propanal, furfural, 2-ethyl hexanol, 2-acetylfuran, camphor, benzaldehyde, (*E*)-non-2-enal],linalool,5-methylfurfural bomyl acetate, (E,Z)-P,bnonadienal,terpinen-4-ol, beta-santalene, y-butyrolactone[oxolan-2-one], phenylacetaldehyde,(E)-p-farnesene,ethyl benzoate, furfuryl alcohol[furan-2-ylmethanol], (Z)-3-nonenol, a-terpineol, B-bisabolene,(Z,Z)-3,6-nonadienol, (E,Z)-2,6-nonadienol, methyl salicylate, ethyl salicylate, hexanoic acid, guaiacol, 2-buten-1, 4-diol diacetate, benzyl alcohol, 2-phenylethanol, dendrolasin [3-[(3*E*)-4,8-dimethylnona-3,7-dienyl]furan],p-methylguaiacol,0-cresol[2-methylphenol], carotol, nerolidol 2,4-dimethylphenol[2,4-dimethylphenol], cedrol [(1*S*,2*R*,5*S*,7*R*,8*R*)-2,6,6,8-tetramethyltricyclo[5.3.1.0^{1,5}] undecan-8-ol], eugenol, p-vinylguaiacol, [6-methyl-2-(4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol], (E,E)-famesal, cinnamyl alcohol[(*E*)-3-phenylprop-2-en-1-ol], tricosane, (E,E)-farnesol, p-vinyl phenol, indole, vanillin[4-hydroxy-3-methoxybenzaldehyde],heptacosane, consolacion[31].

The dichloromethane extract of *M. calabura* freeze-dried fruit collected from San Pedro, Laguna in June, 2014 isolated four squalene compound for example-triglycerides, fatty acids and a mixture of β-sitosterol and stigmasterol[32].

The polyphenolic fruit extract contained considerable amounts of vitamin C (33.6 mg AAE g^{-1} extract) and E (14.7 mg tannic acid equivalent/g extract), total phenolics (121.1 mg gallic acid equivalent/g extract), flavonoids (173.2 mg rutin equivalents/g extract) and anthocyanins (82.4 mg cyanidine-3-glucoside extract/g extract) estimated using standard spectrophotometric techniques. Further standard analysis identified rich phytochemicals like phytol (26.26%), n-hexadecanoic acid (11.97%), 8-cyclopropyloctanoic acid (10.26%), isoprenoids including γ-sitosterol (11.15%), stigmasterol (7.20%) and campesterol (4.48%).

This study too discovered minor components namely ethyl linolenate (4.48%), ethyl (9*Z*,12*Z*)-octadeca-9,12-dienoate (3.14%), ethyl hexadecanoate (3.65%), 7,11,15-trimethyl-3-methylidenehexadec-1-ene](3.03%), isoamyl acetate(2.32%). As 1-Deoxy-d-mannitol (1.86%), α-tocopherol (1.27%), β-cholest-5-en-3-ol (0.97%), ethyl stearate[ethyl octadecanoate] (0.88%), γ-tocopherol (0.82%), (2E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol (1.81%), 3-cyclopentylpropionic acid (0.75%), 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran (0.78%), 2-dimethylaminoethyl ester (0.66%), 1,3,5-triazine-2,4,6- tri-amine (0.56%), octanoic acid (0.54%), 2,3-dihydrobenzofuran (0.41%), 1,2,3-propanetriol, monoacetate (0.40%) and n-nonanoic acid (0.33%)[33].

The calabura fruits were rich in glucose, fructose and sucrose content and show fewer l-kestose, maltopentaose, maltohexaose and maltoheptaose contents. The sesquiterpene Farnesene (28.7%) and the aromatic monoterpene dendrolasin (15.4%) were the most abundant volatile constituents in calabura, followed by -himachalene (3.9%), -curcumene (3.7%), limonene (3.1%), 3-hexen-1-ol (2.8%) and methyl salicylate (MeSA, 2.7%), among others with an area less than 2.5%. The peel of the fruit is rich in anthocyanins, the total anthocyanin concentration of calabura fruits was equivalent to that of nectarine, peach and apple (4.4 mg/100 g), but lower than that of blackberry, blueberry, black and red currant, raspberry and strawberry[34].

Stem: The ethanolic extract of air dried *Mutengia calabura* stem leads to the isolation of two cytotoxic flavonoids chrysin, 2′,4′-dihydroxychalcone and galangin 3,7-dimethyl ether[35]. Further research into the cytotoxic components found in the stem bark of Formosan species of *Muntingia calabura* resulted in the isolation and characterization of thirteen novel components together with two novel flavones, 3'-Hydroxy-7,8,4',5'-tetramethoxyflavone[2-(3-hydroxy-4,5-dimethoxyphenyl)-7,8-dimethoxychromen-4-one] and 5,6-dihydroxy-7,8-dimethoxy-2-(4-methoxyphenyl)chromen-4-one. Among the thirteen compound the isolates 8-hydroxy-7,3,4,5-tetramethoxyflavone (2-(3-hydroxy-4,5-dimethoxyphenyl)-7,8-dimethoxychromen-4-one), 8,4-dihydroxy-7,3,5-trimethoxyflavone(5,6-dihydroxy-7,8-dimethoxy-2-(4 methoxyphenyl)chromen-4-one) and 3-hydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)propan-1-one have effective cytotoxicities against the P-388 cell line *in vitro* (ED50 values = 3.56, 3.71 and 3.27 g mL^{-1}, respectively[36]. In the ethanolic stem extract triterpenes were detected along with relative amounts of flavonoids, saponins, glycosides and tannins. Alkaloids and sterols were absent in the stem extract[38]. From the methanolic exract of stem wood of *Muntingia calabura* 15 compound was reported, among which of a new bioflavan that was (M),(2S),(2"S)-,(P),(2S),(2"S)-7,8,3',4',5',7",8",3'",4"',5"'-decamethoxy-5,5'' biflavan, a new flavone, 4'-hydroxy-7,8,3',5'-tetramethoxyflavone(2-(3-hydroxy-4,5-dimethoxyphenyl)-7,8-dimethoxychromen-4-one), a new dihydrochalcone, (R)-2',β-dihydroxy-3',4'-dimethoxydihydrochalcone and 12 known compound. Among the known compounds with IC50 values of 1.77, 0.70, 3.82 0.46 and 4.92 1.71 M, respectively, 5-hydroxy-7-methoxyflavone, quercetin and (2S)-7-hydroxyflavanone[(2S)-7-hydroxy-2-phenyl-2,3-dihydrochromen-4-one)] showed effective suppression of fMLP-induced superoxide anion produced by human neutrophils reported by Prashant and Kumar[37].

Acute toxicity: Acute toxicity of the methanolic extract of *Muntingia calabura* was reported by Kuo[38]. This acute toxicity test was done on rats, where the animals were treated with leaf extract orally at doses of 300, 500 mg kg^{-1} and a maximum dose of 2000 mg kg^{-1}. After dosing animals were observed for 2-3 hrs. Neither toxicity nor mortality was recorded up to 14 days[39].

Acute toxicity of ethanolic extract of *M. calabura* reported in Sprague Dawley male rats. The animals were treated with extract at doses of 2000 and 5000 mg kg^{-1}. No sign of abnormal changes, behavioural changes, macroscopic findings, body weight and mortality was reported for up to 14 days[40].

Traditional use: The *M. calabura* flower infusion is traditionally used as a treatment for incipient colds and headaches in East Asia. This flower infusion is also used for anti-hysteric, antidyspeptic, diaphoretic and antispasmodic in both South America and East Asia. In Colombia, the same type of infusion is also utilized

as a tonic or tranquillizer[41]. In Vietnam, the roots were used as an emmenagogue and in Malaysia, they were used as an abortifacient. Along with antidyspeptic, diaphoretic and antispasmodic activity headache was also treated by the flower of *M. calabura* in the Philippines[41]. Its leaves, bark and flowers are thought to have medicinal value, according to Peruvian folklore medicinal usage. The leaf part also have a role in mitigating stomach ulcers and to minimise prostate gland enlargement. Along with this the bark strips, were used to reduce swelling in the lower extremities as wash and believed that the flowering part had anti-septic effects[42]. The detailed pharmacological activity of different parts of *Muntingia calabura* have been tabulated in Table 2.

Table 2: Pharmacological activity of different parts of *Muntingia calabura*

Muntingia calabura (Parts)	Activity	Solvent	Results	References
Leaf	Anti-cancer (Colon cancer)	Methanol	Decrease in the creation of aberrant crypts indicates anti-cancer action, while an increase in colon antioxidant markers indicated antioxidant activity	Zakaria *et al.*[43]
	Anti-cancer (colon cancer)	Methanol	Methanolic extract reduces the severity of colon cancer	Nasir *et al.*[44]
	Hepatoprotective effect	Methanol	Established two major pathways involved in hepatoprotective activity	Rofiee *et al.*[46]
	Hepatoprotective effect	Methanol	Protection of hepatic structure after paracetamol induced liver toxicity	Mahmood *et al.*[47]
	Gastroprotective effect	Methanol	Gastric acid content decrease, mucus content increase	Niwele *et al.*[48]
	Gastroprotective effect	Ethyle acetate fraction of methanolic extract	Prevent formation of gastric lesion	Kuchekar *et al.*[49]
	Anti-inflammatory effect	Methanol	It reduces hind paw edema	Zakaria *et al.*[50]
	Anti-inflammatory effect	Methanol	It reduces edema	Tiwari *et al.*[51]
	Anti-bacterial effect	Methanol	Showed inhibition of total growth	Mogollon *et al.*[52]
	Anti-bacterial effect	Ethyle acetate extract	Anti-microbial compound identified	Zakaria *et al.*[53]
	Anti-nociceptive activity	Methanol	Showed anti-nociception on thermally and chemically induced animal model	Sani *et al.*[54]
	Anti-nociception activity	Aqueous	Showed anti-nociception activity	Yusof *et al.*[55]
	Anti-diabetic activity	Ethanol	Showed glucose level reduction in blood at 7th and 14th days	Solikhah and Solikhah[56]
	Anti-diabetic activity	Ethanol:Water	Identification of six compounds for future diabetic therapy	Zolkeflee *et al.*[57]
	Myocardial infraction	Aqueous	Showed reduction in transaminase (aspartate and alanine), lactate dehydrogenase (LDH) and creatine phosphokinase (CK) compared to control group	Zakaria *et al.*[58]
	Anti-hypertensive effect	n-butanol soluble fraction	Showed dose related bradycardia and anti-hypertensive effect	Shih[59]
	Anti-platelate aggregation	Methanol	Isolated compound showed 85-90% aggregation	Chen *et al.*[60]
Fruit	Anti-cancer activity (Laryngeal cancer)	Aqeuos extract	Gold nanoparticle of *M. calabura* show cytotoxicity in laryngeal carcinoma cell line by cell proliferation inhibition via apoptosis	Jisha *et al.*[45]
Fruit, leaf	Anti-anxiety	Ethanolic extract, fruit juice	Showed anxiolytic activity	Sharma *et al.*[61]
Leaf	Anti-aging	Water	Increase in fibroblast number and collagen density, Malondealhyde level was also seen to be decreased	Sulistyoningrum *et al.*[62]
Stem, bark	Anti-hyperuricemic effect	Ethanol	Groups treated with bark extract showed reduce in uric acid concentration and no damage noticed in renal histology	Aligita *et al.*[63]

Anticancer activity: *Muntingia calabura* has been discovered to have good anticancer efficacy in numerous preclinical studies.

Nasir *et al.*[44] published a study on the anticancer potential of *Muntingia calabura* leaf by using methanolic extract against colon cancer generated by azoxymethane in Sprague Dawley rats implicated in the transformation of the antioxidant system of the colon mediated by flavonoids. The rats were categorized into five groups and in each group, seven animals were there, except the normal groups other four groups were receiving 15 mg kg^{-1} of azoxymethane intraperitoneally once a week for 15 days. After the last dose, the control group was receiving 80% of tween 80 and the test groups were receiving 50, 250, or 500 mg kg^{-1} of extract in the volume of 10 mL kg^{-1} of body weight for 8 weeks. Colonic samples were obtained when treatment was finished for histological evaluation, measurement of aberrant crypt foci (ACF) produced and detection of the antioxidant level of the colon. The result obtained from the study was that the less formation of aberrant crypt shows anticancerous activity along with that increase in colon antioxidant marker gave a measurement of antioxidant activity. The study's findings revealed that a decrease in the creation of aberrant crypts indicates anti-cancer action, while an increase in colon antioxidant markers indicated antioxidant activity[43].

Another study of colorectal cancer using a leaf of *Muntingia calabura methanol* extract in a 1,2-Dimethyl Hydrazine (DMH)-induced Wister rat model discovered that antioxidant enzyme levels were normal, as well that the rise in oxidative stress markers after DMH administration was lowered after treatment with the 100 and 200 mg kg^{-1} of extract dose and histopathological evaluation revealed that colorectal cancer was also reduced[44].

The 2nd most common cancer in the growing world is laryngeal cancer. The anticancer effect of gold nanoparticles prepared by using aqueous fruit extract of *Muntingia calabura* was investigated. For this study cell line of laryngeal carcinoma cells and green monkey kidney cells were found in Africa. The MTT reduction assay was used to evaluate the anti-cancer activity. Antiproliferative assay, cytomorphology study, Hoechst 33258 staining, tunnel assay, cell cycle distribution and determination of cell apoptosis were the other parameters for anticancer activity. As a result, the gold nanoparticle of *M. calabura* shows cytotoxicity in the laryngeal carcinoma cell line by cell proliferation inhibition via apoptosis. The apoptosis in the cell line was associated with cell membrane disruption, alteration in nuclear morphology and cell cycle arrest in the G2 phase[45].

Hepatoprotective activity: *Muntingia calabura* isolates a novel metabolic route for hepatoprotective action in CCL4-induced liver damage. Six groups of animals were employed in this investigation, where the test groups were given treatment with methanolic extract of *Muntingia calabura* were given at doses of 100, 200 and 400 mg kg^{-1} of body weight, with 1st group serving as a normal control group, the second as a negative control group and the third as a positive control group receiving silymarin. The animals were slaughtered for serum collection after 10 days of treatment. The body weight, as well as the amount of food and drink consumed, were all reduced. Based on histopathological analysis steatosis was identified in CCL4 induced animals, while no pathological alterations were present. The animals were slaughtered for serum collection after 10 days of medication. The body weight, as well as the amount of food and drink consumed, were all reduced. in the animals treated with plant extract. In rats given silymarin, normal liver histology was seen. The metabolite profiles of the norm *Muntingia calabura* isolate a novel metabolic route for hepatoprotective action in CCL4-induced liver damage. Six groups of animals were employed in this investigation, with the test groups getting methanolic extract at doses of 100, 200 and 400 mg kg^{-1} of body weight, with one serving as a normal control group, the second as a negative control group and the third as a positive control group receiving silymarin, CCl4-treated and extract of *M. calabura* (MCME) pre-treated groups exhibit considerable separation in PCA score plots. Primary bile acid production and arachidonic acid metabolism were the two separate pathways from the biomarkers network that was responsible for the protective mechanism[46].

Mahmood *et al*.[47] reported a study in which the hepatoprotective effect of methanolic extract of *Muntingia calabura* in paracetamol induced liver toxicity in rats were done. For the investigation of this study, 6 groups are selected. In between the six groups, three groups were pre-treated with 50, 250 and 500 mg kg^{-1} of body weight of MEMC. The negative control group was pre- treated with 10% DMSO and the positive control group was pre-treated with 50 mg kg^{-1} of N-Acetyl Cysteine (NAC). The average body weight of the DMSO treated group was not increased but it caused a significant increase in liver weight compared to the normal control group. The decrease in average body weight was seen in 50 mg kg^{-1} NAC and 250 and 500 mg kg^{-1} of MEMC treated groups. The 50 mg kg^{-1} NAC treated groups was not able to decrease the extra liver weight as compared to the control group. The only 500 mg kg^{-1} MEMC treated groups showed significant decrease in both mean liver weight and average liver weight (LW/BW)[47].

Gastro protective activity: Numerous pre-clinical study has revealed that *Muntingia calabura* possessed gastroprotective activity. A study reported on the mechanism of action of gastroprotective effect *Muntingia calabura* in 2014 by using methanolic extract. The MEMC show its activity by decreasing the volume of gastric acid content and total acidity was also decreased on the doses of 100 and 500 mg kg^{-1} and mucus content were also seen to be increased[48].

The gastroprotective effect of the ethyl acetate fraction of crude methanolic leaf extract of *Muntingia calabura was* reported in 2016. In this study, HPLC was done to confirm the presence of quercetin and gallic acid in ethyl acetate fraction. The pylorus ligation method was used to evaluate the gastroprotective effect after the animals were administered 100, 250 and 500 mg kg^{-1} of leaf extract. The results were found to be an increase in gastric acid volume and protein content along with that total free acidity was reduced at the doses 250 and 500 mg kg^{-1}. Moreover, all gastric lesion formation were prevented[49].

Anti-inflammatory activity: Preethi *et al*.[21] reported anti-inflammatory activity of the fruit part of this particular plant at the dose of 100, 200 and 300 mg kg^{-1} and found that methanolic extract of the fruit part reduced the hind paw edema within 3 hrs[50].

Another carrageenan-induced anti-inflammatory effect of *Muntingia calabura* was reported 14 days and reported that both doses of the methanolic extract showed inhibition at 71.42 and 76.18% and the standard drug showed the percentage of inhibition was 75.36%[51].

Anti-bacterial activity: The methanolic extract of *Muntingia calabura* leaf was studied against different micro-organisms for example *Staphylococcus aureus* FNCC 0047, *Staphylococcus epidermidis* FNCC 0048 and *Escherichia coli* FNCC 0091. Using the broth microdilution method, the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of extracts that inhibited total growth were measured. The MIC values found were for *Staphylococcus aureus* FNCC 0047 was 0.5 mg mL^{-1}, *Staphylococcus epidermidis* FNCC 0048 was 1 mg mL^{-1} and *Escherichia coli* FNCC 0091 was 2 mg mL^{-1}. While the MBC levels are 1, 2 and 4 mg mL^{-1} [52].

Muntingia calabura contains three flavone and chalcones compounds. Sufian *et al*.[8] isolated three flavone and bchalcones compounds. Two compounds in between them possessed antibacterial activity which was determined by the micro-broth dilution method. The chalcones compound shows minimal inhibitory concentration 50 and 100 mg mL^{-1} against MSSA and MRSA and at identical MIC values (200 mg mL^{-1}), flavones inhibited the development of MSSA and MRSA[53].

Anti-nociceptive activity: Sani *et al*.[54] published a study on the anti-nociception activity of *Muntingia calabura* extract at dosages of 100, 250 and 500 mg kg^{-1} and observed that the extract has anti-nociception activity in chemical induced and thermal induced nociception models. In this study methanol used as a solvent to prepare the extract[54].

The study of antinociceptive action of *Muntingia calabura* in mice and the participation of the L-arginine/nitric oxide/cyclic guanosine monophosphate pathway was carried out in 2005. In this study water was used as a solvent for the preparation of the plant extract. The animals were pre-treated with distilled water, L-arginine (20 mg kg^{-1}), N G-monomethyl-L-arginine acetate, NG-nitro-L-arginine methyl esters and methylene blue before being treated with doses 27, 135 and 270 mg kg^{-1} concentration dependent antinociceptive activity was seen in the group pre-treated with distilled water. The L-arginine pre-treated group shows antinociception activity at high concentrations only. Pre-treatment with L-NAME was found to considerably improve low-concentration AEMC antinociception while inhibiting high concentration AEMC antinociception. Methylene blue significantly improves the aqueous extract of *M. calabura* antinociception at all concentrations. Excluding the greater concentration of aqueous extract of *M. calabura* employed, co-treatment with L-NAME was observed to insignificantly and significantly counteract the L-arginine effect when administered alone or in combination with a low concentration of aqueous extract of *M. calabura*. Furthermore, co-treatment with MB substantially ($p = 0.05$) reversed the L-arginine effect when administered alone or at a 10% concentration[55].

Anti-diabetic activity: The antidiabetic activity of *Muntingia calabura* leaf extract was studied in 2021. In this study, alloxan induced diabetic mice model was used. The parameters of the study were blood glucose and body weight of the animals. The animals were given 100, 300 and 600 mg kg^{-1} of extract. The extract shows a significant decrease in blood glucose levels at the 7th and 14th days when compared modern control group. Along with that increase in body weight was seen in the 7th and 14th days compared to the modern control group[56].

Another study was reported in 2022 regarding anti-diabetic activity of *Muntingia calabura* decoction. The study comprises of evaluation of three drying methods that were freeze drying, air-drying and oven-drying and for *in vitro* anti-diabetic activity the ethanol-water ratios were 0, 50 and 100%. The freeze drying leaves extracted with 50% of ethanol possessed high alpha glucosidase and alpha-amylase inhibitor activity and act as most active extract with 0.46, 0.05 g mL^{-1} and 26.39, 3.93 g mL^{-1} IC50 values, respectively. From this active extract yielded 61 chemicals, which were tentatively identified using an ultrahigh-performance-liquid chromatography-electrospray hydroxyflavanone, geniposide, quercitrin, daidzein, formononetin and kaempferol. The findings have set the groundwork for the development of *Muntingia calabura* leaves extract as a possible source of bioactive chemicals for diabetic therapy[57].

Myocardial infarction: In 2009 cardioprotective effect of *Muntingia calabura* evaluated in isoproterenol-induced myocardial infarction in rats. One group of animals was treated with 300 mg kg^{-1} of leaf extract dose and the other three groups were treated with 100, 200 and 300 mg kg^{-1}, respectively and isoproterenol 20 mg kg^{-1} before myocardial infraction induction. Reduction in aspartate transaminase was seen in the group which was pre-treated with 300 mg kg^{-1} of body weight, along with that reduction in alanine transaminase, lactate dehydrogenase and creatine phosphokinase was also seen when compared to the control group[58].

Antihypertensive effect: The antihypertensive effect of *Muntingia calabura* is yet unknown. In 2009 a study reported on antihypertensive effect of *M. calabura*, in this study activity of n-butanol soluble fraction of methanol leaf extract was reported in mice. The mice model was spontaneously hypertensive, this model was greater than normotensive Wistar-Kyoto rats. The n-butanol soluble fraction show dose related bradycardia and anti-hypertensive effect in spontaneous model. At a dosage of 25 mg kg^{-1} of n-butanol soluble fraction, i.e., pre-treatment with a nonselective nitric oxide (NO) synthase (NOS) inhibitor substantially inhibited both the immediate and delayed antihypertensive and bradycardic effects. Additionally, activation of the sGC (Soluble guanylyl cyclase)/cGMP (cyclic guanosine 3', 5'-monophosphate)/PKG(cGMP-dependent protein kinase or protein kinase G) signalling pathway may also play a role in the biphasic cardiovascular effects generated by *M. calabura*[59].

Anti-platelet aggregation: Chen *et al.*[60] investigated the anti-platelet aggregation efficacy of *Muntingia calabura* leaf extract prepared by using methanol as solvent. The research included the discovery of two novel dihydrochalcones, one new flavone and nineteen previously unknown chemicals. Some of them have an anti-platelet aggregation activity of 85-90% *in vitro*. The test was carried out in washed rabbit platelate generated by, arachidonic acid, thrombin, collagen and platelate-activating factor (PAF) using a turbidimetric technique[60].

Anti-anxiety activity: Sharma *et al.*[61] reported anti-anxiety activity of *M. calabura* leaf in mice. In this study ethanolic extract of leaf and fresh fruit juice of *M. calabura* was used. The animals were treated with 200 and 400 mg kg^{-1} of leaf extract and 0.2 mL of fruit juice and anxiolytic activity was evaluated by using light and dark test, rota-rod test, elevated plus maze etc.[61].

Anti-aging effect: The anti-aging effect of this particular plant is reported by using water extract from the leaf. The D-galactose was used to induce skin aging in the animals for 42 days by using the oral gavage route. Along with this, free radicals and glycation also played an important role in skin aging. There were five groups of animals for this research, in which two groups acted as the control group that was healthy control and two groups were treated with a low and high dose of extract that was 35 and 70 mg kg^{-1} along with inducing drug, the fifth group was treated with inducing drug and vitamin C at 28 mg kg^{-1} body weight. For analysing the aging parameters including fibroblast cell, dermal collagen density and epidermal thickness, Routine and Gieson's stained method were used. Malondealhyde level was analysed before and after the treatment with the drug. As a result, the groups that received plant extract and vitamin C show an increase in fibroblast number and collagen density as compared to the control group and plasma Malondealhyde level was also seen to be decreased. The epidermal thickness remained the same in all the groups[62].

Antihyperuricemic effect: In 2019 the effect of *Muntingia calabura* in themaintenance of uric acid concentration in diabetic rats and its comparison with allopurinol reported. In this experiment six groups of animals were there, one group acted as a normal group, second group was act as the negative control group, the 3rd groups the diabetic mice were treated with 1 mg kg^{-1} of allopurinol, other three groups were treated with 150, 300 and 450 mg kg^{-1} of bark extract, respectively. As a result, the groups treated with bark extract show reduce in uric acid concentration and no damage noticed in renal histology[63].

Future prospective: Future researchers will be aided by the information provided in this article in exploring the undiscovered pharmacological property and its active phytoconstituents. Through traditional use to modern pharmacological application, this plant has a lot of potentials. This article includes many assays for evaluation of anti-cancer, gastroprotective, hepatoprotective antibacterial etc. There has been relatively little pre-clinical research on the central nervous system reported so far. *Muntingia calabura* is high in flavonoid, phenol and alkaloid and some of the plant's constituents have blood brain permeability. Perhaps in the future, this plant will aid in the study of the central nervous system. But some studies also lack the proper essential pharmacological parameters like negative or positive control, maximum and minimum dose-response and time response in many investigations, which leads to difficulty in the sustainability and reproducibility of data. Still very few pre-clinical studies such as neuroprotective, cardioprotective and antihypertensive have been on *Muntingia calabura*. Furthermore, any research on the plant extracts requires proper chemical standardization in terms of possible active phytochemicals to comprehend and evaluate the therapeutic potential based on the active phytochemicals.

CONCLUSION

The current study reviewed *M. calabura's* progression from traditional use to modern medicines, botanical description, active phytonutrients and modern pharmacological activities. Furthermore, it also includes the future prospect of *M. calabura* in different unexplored pharmacological area. Based on the

ethnomedicinal value different pre-clinical study is going on around the world However, no clinical studies have been published too far. The *M. calabura* extract shows different pharmacological activities like anticancer, gastroprotective, hepatoprotective, antidiabetic, anti-bacterial, etc. But the journey is still incomplete because of limited pharmacological activity. Along with this now that so many active phytochemicals are being identified but still proper standardization of extract is still needed so that in near future many newer bioactive phytochemicals should be isolated. Thus we can finally conclude that the *Muntingia calabura* needs to be further investigated in terms of phytochemicals, pharmacological properties, dose, mechanistic study, evaluation of clinical activity, etc. Pharmacology needs to be explored on the molecular level. If these things are evaluated properly than may be in the future *M. calabura* can be used as an alternative medicine.

SIGNIFICANCE STATEMENT

Medicinal plants are well-known sources of important therapeutic aid for alleviating human disorders. *Muntingia calabura* possesses remarkable medicinal value, which warrants further and in-depth studies. *Muntingia calabura* showed several pharmacological actions including cytotoxic, antinociceptive, antiulcer, anti-inflammatory, anti-anxiety activity, anti-aging effect, antihypertensive effect, myocardial infraction, anti-diabetic activity etc.

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