A Review on Ethnomedicinal, Phytochemical and Pharmacological Aspects of *Myrica esculenta*

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Sood and Shri: A Review on Phyto-pharmacological Aspects of *Myrica esculenta*

***Myrica esculenta* (Myricaceae) commonly known as box berry or *kaphal* is an important Indian medicinal plant. It is found in foothill tracks of Eastern Himalayas, Meghalaya, Nepal, China and Pakistan. Local tribes mainly use its fruits to prepare pickle and refreshing drinks. Traditionally, the bark has been used for the treatment of cough, asthma, fever, chronic bronchitis, diarrhoea, rheumatism and inflammation; roots have been used in bronchitis, asthma, cholera and flowers claimed to treat earache, diarrhoea, paralysis. Phytochemical studies of the different parts of plant revealed the presence of various bioactive phytoconstituents such as phenolic compounds, alkaloids, glycosides, triterpenoids and volatile oils. The plant is also reported to have innumerable significant pharmacological activities like analgesic, anxiolytic, antiallergic, antidiabetic, antimicrobial, antihypertensive, antiulcer, antioxidant and antiinflammatory evaluated by using various animal models. The objective of the present review article is to compile all the relevant published information regarding traditional uses, phytochemistry and therapeutic potential of *M. esculenta*. For this purpose various databases and books were examined. The review clearly demonstrates the importance of this plant in ethnomedicine and its immense potential in modern medicine.**

Key words: *Myrica esculenta, kaphal,* box berry, phytoconstituents, pharmacology

The genus *Myrica* consists about 97 species of small tree and aromatic shrubs belonging to family Myricaceae. These are reported to be globally distributed in both temperate and sub-tropical regions of the world[1]. There is only one species *Myrica australiasica* F. Muell, which has been reported in Australia[2] while *M. cerifera* L. (Wax myrtle/Southern wax myrtle) and *M. persylvanica* Mirb. (Northern bayberry)[3] are reported as official drugs of North America[4] and claimed to have same medicinal properties there, as *M. esculenta* in the Indian systems of medicine[5]. The another species of genus *Myrica*, such as *M. rubra* known as Chinese bayberry are commonly found in China and Japan only[6-8]. Some other species, which belong to genus *Myrica* are *M. adenophora* hance, *M. caroliniesis* (evergreen bayberry), *M. cordifolia* (waxberry/candle berry), *M. californica* (Californian bayberry), *M. dentulata* Baill., *M. heterophylla* Raf. (swamp bayberry), *M. inodora* W. Bartram (odourless bayberry), *M. integra* (A. chev.) Killick, *M. nana* A. Chev., *M. quercifolia* L.[6,9], *M. faya* Ait., *M. gale* L. (bog-myrtle/sweet gale)[6,8,10], *M. hartwegi* S. Watson (Sierra babyberry/mountain wax myrtle)[6,10].

M. esculenta commonly known as Boxberry, *Kaiphal* and *Kathphala* has been reported to be the only species found in India[11]. Its synonyms are *M. nagi* Hook. F. non Thunb[12], *M. sapida* Wall.[13] *M. farqhariana* Wall. and *M. integrifolia* Roxb.[10,14]. It is an economical medicinal plant with multipurpose uses[15]. Being actinorhizal, it is also useful in regeneration of nitrogen depleted soils[1]. The plant is primarily sourced for the fruits, which are one of the tastiest wild fruits of the sub-Himalayan region[16] and have recognized for its nutritional and therapeutic potential[17]. Fruits of the plant are also used to prepare jams, syrups, refreshing drinks and pickles[18]. It is the rich source of vitamin C and polyphenolic compounds such as tannins, phenols, flavonoids and flavonols[19]. Local tribes utilize tree as timber, fuel, fodder, wood[20] as well as used for tanning and obtaining yellow colored dye[21,22].

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In spite of being a multipurpose tree, the cultivation of the plant is very limited and most of the traditional and commercial uses of *M. esculenta* plant depend exclusively on the collections from the wild sources by indigenous people[23]. Thus, the species is under imminent danger of extinction from wild sources due to increase in urbanization, over harvesting, negligence of sustainable utilization and over exploitation of forests and waste lands for commercial uses[18,24]. Poor regeneration in natural habitat due to high anthropogenic activity is another important factor, which affect the natural population of this plant species[25]. The present review article is an attempt to summarize the ethnomedical uses, phytochemistry and therapeutic potential of *M. esculenta* for its future prospects such as conservation, cultivation and sustainable utilization as well as to recognise the medicinal properties of this plant in the modern system of medicine.

TAXONOMY

Botanical classification and vernacular names:

Kingdom: Plantae, Division: Magnoliophyta, Class: Magnoliopsida, Order: Fagales, Family: Myricaceae, Genus: Myrica, Species: *M. esculenta*[12]. Assami: *Ajooree*, *Nagatenga*, *Vdulbark*, Bengali: *Kayachhal*, *Kaiphal*, *Satsarila*, English: Box myrtle, Bayberry, Gujrati: *Kariphal*, Hindi: *Kapha*, *Kaiphal*, Kannada: *Kandujai kai*, *Kirishivani*, *Kirishivane*, Malayalam: *Maruta*, Marathi: *Kayaphala*, Nepali: *Kobuli*, *Katphala*, Punjabi: *Kaiphal*, *Kahela*, *Kahi*, Sanskrit: *Kathphala*, *Aranya*, *Krishnagarba*, *Mahavalkala*, Tamil: *Marudam*, *Marudampatai*, Telugu: *Kainaryamu*[13,16,26].

Habitat:

M. esculenta is a subtemperate evergreen dioecious small tree[26]. It is native to India and found to be widely distributed in the foothills track of mid Himachal Pradesh starting from Ravi eastwards to Assam including Arunachal Pradesh, Sikkim, Manipur, Uttranchal and Khasi, Jaintia, Naga and Lushai Hills of Meghalaya in between 900-2100 m above the sea level[27-29]. Apart from India, it is also found in Nepal[30], China, Japan[9], Pakistan, Singapore, and Malaya Islands[6].

BOTANICAL DESCRIPTION

Morphological evaluation of the plant *M. esculenta* (fig. 1A) reveals that it is medium to large woody tree about 12-15 m in height with trunk diameter about 92.5 cm[28]. The outer bark is greyish dark in colour, rough, vertically wrinkled while inner bark is dark brown in colour with smooth surface (fig. 1B); fracture hard; bitter in taste and nauseating odour[5,26]. Leaves (fig. 1C) are lanceolate with entire or serrate margin, having pale green at lower surface and dark green at upper surface, about 9-12 cm in length and 3-3.5 cm in width and are mostly crowded toward the ends of branches[16,28]. Pistillate flowers are small, sessile, solitary and bracteates; sepals and petals are either absent or not visible; inflorescence (catkin), 4.2 cm long, axillary, bearing about 25 flowers in a thread-like style[28,31] while inflorescence of staminate flowers is compound raceme[25]. The flowering season starts from February and continues till second week of April but peak season for flowering was observed during first week of March while the fruiting season was observed during the first week of May, which continues till the end of May[22]. The tree yields a drupe fruit, red to dark brown in colour, ellipsoidal or oval in shape and about 2-7 mm in diameter (fig. 1D) having sweet and sour taste containing ovoid shaped, smooth surface light brown coloured seed of about 1-6 mm in diameter with oily taste[17,26].

Microscopical evaluation:

Transverse section through midrib shows upper and lower epidermis, few epidermal cells on upper surface elongated to form non glandular/covering unicellular trichomes. Below the epidermis, single layer of palisade cells present followed by spongy parenchyma and vascular strands. Midrib region of leaf shows vascular bundle containing xylem and phloem surrounded by collenchyma cells. Prism shaped calcium oxalate crystals, unicellular thin walled covering trichomes, starch grains, anisocytic stomata and non-lignified fibres were observed as microscopical diagnostic features of powder microscopy of leaves[32].

The transverse section of matured *M. esculenta* bark shows multi-layered rectangular shaped thick lignified cork cells followed by 5-8 layers of phelloderm cells consisting of narrow and tangentially flattened parenchyma cells with single or small groups of round to slightly oval shaped thick walled lignified stone cells, spheroidal shaped starch grains and prismatic calcium oxalate crystals. The phloem tissue was composed of thick walled sieve tubes, companion cells, thick lignified phloem parenchyma phloem fibres, stone-cells and some of the crystal fibres and was traversed by medullary rays. Prisms of calcium oxalate were present in crystal fibres and in phloem parenchyma.

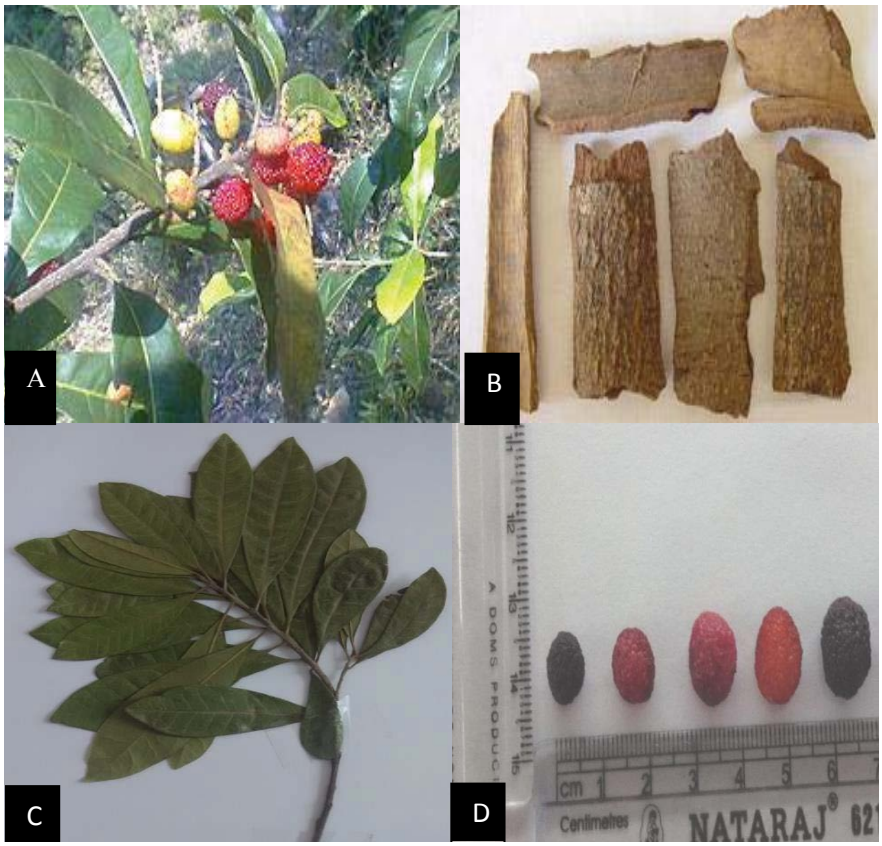

Fig. 1: Morphological evaluation of the plant *M. esculenta*
(A) Tree (B) bark (C) leaves (D) fruits

The reported diagnostic microscopical characters of *M. esculenta* powder are numerous calcium oxalate crystals up to 24.8 µm in size, spheroidal shaped starch grains up to 15.5 µm in diameter, rounded or rectangular shaped thick lignified stone cells up to 370 µm in length, thick walled sclerenchyma fibres usually accompanied by crystal fibres and fragments of the parenchyma, some of them rich in starch grains[5,26].

Epicarp shows single layer, unlignified, thin walled, reddish brown parenchymatous cells with numerous unicellular trichomes, a few elongated tubercled cell with smooth walls; endocarp hard and stony consisting of sclerenchymatous cells[6,26,31]. Seed coat shows single layered, thick, brown coloured cell; cotyledons composed of single layered, thin walled epidermal cells containing oil globules and aleurone grains; mesophyll cell thin-walled, isodiametric densely packed with oil globules and aleurone grains[6,26,31].

ETHNOBOTANY

A large part of population living in rural areas of Uttrakhand use stem bark to cure chronic cough, asthma and ulcers[33] and bark powder is inhaled to cure headache[34]. Local people of Sub-Himalayan region use decoction of bark as mouth freshener and to cure toothache[35] while paste of bark is applied on wounds, joints pains and paralysis as well as used to cure cold and headache[36]. Bark is also used in the treatment of mental illness by different ethnic groups of the rural region of Orissa[37]. Fruit are eaten raw or used to prepare refreshing drinks while its juice is used against bacterial dysentery by tribal communities of Meghalaya[38-40] and bark is chewed to relieve toothache and for washing putrid sores[22,41]. The paste of leaves is applied externally by local tribe of Uttranchal to cure headache[42].

Traditional uses:

M. esculenta is well recognized medicinal plant since from ancient Ayurveda and Unani system of medicine[43]. The detailed report on traditional uses of *M. esculenta* plant are summarised in Table 1[44-48].

Ayurvedic formulations:

Fruits and roots are used to prepare Ayurvedic formulations such as *Chwayanprash* and *Brahmarasayan* to enhance digestion, memory, intelligence, concentration and physical strength[49]. The bark of *M. esculenta* is used as one of the common

ingredient of Ayurvedic formulation *Visweshwara rasa* to treat fever of *kapha* and *pitta* origin[50]. Other Ayurvedic formulations, which contain fruits or bark of *M. esculenta* as an important ingredient include *Katphaladi churna*, *Kaas-har churna*, *Katphala taila*, *Katphala kvatha*, *Khadiradi gutika*, *Maha vatagajankush rasa*, *Brihatphala ghrita*, *Pusyanuga churna*, *Arimedadi taila*, *Bala taila*, *Mahavisagarbha taila* used for the treatment of various ailments such as rheumatoid arthritis, diarrhoea, dysentery, headache, menorrhagia and other menstrual disorders[26,51].

NUTRITIONAL VALUE

The proximate analysis of nutrients such as crude fibre, crude protein, crude fat, crude carbohydrates, ash value, moisture content and mineral contents such as Na, K, Ca, Mg, Fe, Zn, Mn, Cu of *M. esculenta* fruits were evaluated[52,53]. The results reported in Table 2 supported the use of fruit for nutritional purpose and adequate protection may be obtained against diseases arising from malnutrition if consumed in sufficient amount.

PHYTOCHEMISTRY

Various preliminary phytochemical studies carried out on the fruits[53], leaves[54] and bark[5,24,53] of *M. esculenta* showed the presence of various active phyto-constituents that exhibit a variety of biological effects. This plant is found to be a rich source of phenolic compounds, flavonoids and flavonols[25]. Other bioactive compounds reported in the plant belong to the class of alkaloids, glycosides, diarylheptanoids, ionones, steroids, saponins, triterpenoids, volatile compounds, which are listed in the Table 3[55-73]. The structure of some important bioactive phyto-constituents reported in *M. esculenta* plant is presented in fig. 2.

PHARMACOLOGY

The traditional uses of *M. esculenta* have inspired researchers to verify its utility through scientific pharmacological screening. Several crude extracts from various parts of the plant and isolated bioactive compounds have been evaluated for different biological activities such as analgesic, antiasthmatic, anticancer, antioxidant, antiinflammatory, antidiabetic, antiulcer, anxiolytic, hepatoprotective, chemopreventive, hypotensive and wound healing activity by using a number of *in vitro* and *in vivo* animal models, which prove the traditional utilization of this plant scientifically.

Analgesic activity:

Oral administration of methanol extract of the fruits of *M. esculenta* manifested a significant ($p<0.05$) analgesic activity in dose-dependent manner by increasing the paw licking and jumping time on hot

TABLE 1: TRADITIONAL USES OF *M. ESCULENTA* PLANT

Part	Traditional uses	References
Fruits	Claimed to act as sedative, stomachic, carminative, antiulcer	28, 44
	Used in abdominal tumours, asthma, fever, piles, irregular bowel function, anaemia, nausea, oral disorders, cough, dyspnoea	26
	Useful to retain placenta and bone fracture	13
	Juice of the unripe fruit is used as an antihelmintic	45
	Fruit wax or oil is used to cure bleeding piles, toothache, menorrhagia and other menstrual disorders	6,13
	Reported to be used as astringent, stimulant, antiseptic, carminative, antirheumatic	13, 46, 47
	Claimed to be useful in the treatment of abdominal tumours, asthma, chronic bronchitis, fever, piles, ulcer, anaemia, diarrhoea, dysentery, nausea, oral disorders, cough, dyspnoea, indigestion, anorexia, ear, nose and throat disorders	13, 26, 28, 46
Bark	Bark oil is used in earache	28
	Act as fish poison	12,48
	Decoction of bark in combination with *Quercus lanata* bark used in the treatment of dysentery and in form a gelatinous mass it is applied as a poultice on sprains	45
	Bark powder mixed with ginger is used as a rubefacient in the treatment of cholera Externally bark juice is applied to heal cuts and wounds while internally it is used to cure catarrh and headache	45
Flowers	Oil from flower has been found to be useful in earache, diarrhoea, paralysis and inflammation	16, 28, 34
Roots	Used in bronchitis, asthma, cholera and cough	12

TABLE 2: NUTITIONAL VALUE OF *M. ESCULENTA* FRUIT

Parameters	Value
Ash (%)	2.18±0.02
Moisture content (%)	72.33±0.23
Crude fat (%)	4.93±0.06
Crude fibre (%)	5.22±0.08
Crude protein (%)	9.62±0.03
Carbohydrates (%)	78.03±0.14
Energy (Kcal/g)	395.04±0.54
Minerals (mg/g):	
Calcium	4.63±0.06
Magnesium	8.4±0.20
Potassium	7.75±0.11
Phosphorus	0.24±0.25
Sodium	0.81±0.013
Manganese	0.032±0.0001
Zinc	0.216±0.0016
Iron	0.404±0.0021
Copper	0.004±0.0002

plate until 50 min as compare to control by using Eddy's plate method whereas hot plate reaction time in indomethacin treated mice was maximum at 60 min[74]. The ethyl acetate fraction of methanol extract (ME-EtAC) of leaves was found to possess significant analgesic effect in acetic acid-induced writhing assay and tail immersion assay[32] while methanol extract of leaves showed 54.56 % inhibition of writhing in acetic acid-induced writhing model at the dose of 200 mg/kg[75].

Antiasthmatic activity:

Following ethnomedicinal approach, screening of *M. esculenta* bark was done for the treatment of asthma. The ethanol extract of bark at dose of 75 mg/kg given by oral route was found to exhibit remarkable antiasthmatic activity through several mechanisms which include: antianaphylactic activity in guinea pigs induced by egg albumin, spasmolytic activity

TABLE 3: VARIOUS PHYTOCONSTITUENTS ISOLATED FROM DIFFERENT PARTS OF *M. ESCULENTA*

Phyto-constituent	Plant source and reference
Tannins and phenolic acids:	
Tannin, ascorbic acid	Fruits[13,21,55]
Gallic acid	Bark[56,57], fruits[58], leaves[59]
Catechin, cholorogenic acid, *p*-coumaric acid, caffeic acid, trans-cinnamic acid, ellagic acid	Fruit[58]
Ethyl-ß-D-glucopyranoside; 3-hydroxybenzaldehyde, isovanillin, 4-(hydroxymethyl) phenol, 4-methoxybenzoic acid	Leaves[59]
Castalagin, epigallocatechin-3-*O*-gallate; epigallocatechin-(4ß→8)-epigallocatechin-3-*O*-gallate; 3-*O*-galloylepigallocatechin-(4ß→8)-epigallocatechin-3-*O*-gallate	Bark[56]
Flavonoids:	
Myricetin	Bark[60,61], fruits[19], leaves[62]
Quercetin	Leaves[63]
Flavonoid Glycosides:	
Myricitrin (myricetin 3-*O*-rhamnoside)	Bark[61], leaves[59,62]
Flavone 4'-hydroxy-3',5,5'-trimethoxy-7-O-ß-D-glucopyranosy) (1→4)-α-L-rhamnopyranoside; flavone 3',4'-dihydroxy-6-methoxy-7-O-α-L-rhamnopyranoside	Leaves[63]
myricetin-3-*O*-(3"-*O*galloyl)-α-L-rhamnoside; myricetin-3-*O*-(2"-*O*galloyl)-α-L galactopyranosideside; myrecetin 3-*O*-(2"-*O*-galloyl)-α-L-rhamnopyranoside	Bark[61]
Steroids:	
ß-sitosterol	Bark[12,64], leaves[59,63]
Taraxerol	Bark[12,64]
Stigmasterol	Bark[57]
ß-rosasterol, daucosterol	Leaves[59]
ß-sitosterol-ß-D-glucopyranoside	Leaves[63]
Ionones:	
Corchoionoside C; (6*S*,9*R*)-roseoside	Leaves[62]
Diarylhetanoids:	
Myricanol	Bark[65,56,66], leaves[59,62]
Myricanone	Bark[56,66], leaves[59,62]
16 bromomyricanol	Bark[66]
5-*O*-*ß*-D-glucopyranosyl myricanol	Leaves[62]
13-Oxomyricanol	Root[67]

Terpenes:	
3-*epi*-ursolic acid; 3-*O*-(*E*)-caffeoylursonic acid	Leaves[62]
Lupeol; oleanolic acid;	Bark[57]
Triterpene diol (3β,28-dihydroxytaraxerane)	Bark[12,68]
3β,30-dihydroxy-taraxerane-23-oic acid; 3β,28,30-trihydroxy- taraxara-23-oic acid; 3β,12α,28,30-tetrahydroxytaraxeran-23-oic acid	Bark[68]
Monoterpinoidal glycosides: myresculoside (4-hydroxy-1,8-cineole 4-*O*-*β*-dapiofuranosyl (1→6)-*β*-D-glucopyranosie); (1*S*,2*S*,4*R*)-2-hydroxy-1,8-cineole *β*-D-glucopyranoside	Leaves[62]
Triterpinoidal glycosides: arjunglucoside	Leaves[62]
Proanthocyanidin:	
Proanthocyanidin acetate, proanthocyanidin methyl-ether	Bark[69]
prodelhinidin	Bark[70]
Volatile compounds:	
Nerolidol, α-pinene, α-selinene, ß-caryophyllene, ß-selinen, α-caryophyllene, α-cadinol, linalool	Leaves[71]
n-Hexadecanol; eudesmol acetate; palmitic acid; cis-ß-caryophyllene; n-pentadecanol; n-octadecanol	Bark[72]
Saponin:	
Arjunolic Acid	Leaves[62]
Others:	
Amino acids: L-Hydroxyproline, iso-leucine, valine, 2-aminobutyric acid, L-cystein hydroxyl, L-cystein hydroxychloride, alanine, leucine, tryptophan, glutamic acid, tyrosine, threonine, lysine monochloride	Fruit[53]
2-Furancarboxyaldehyde, 2,5-furandionedihydro-3-methylene, furfural, oxirane, myo-inositol, 1-ethyl-4-methylcyclohexane, methyl-d-lyxofuranoside	Fruits[73]

by relaxation of guinea pig smooth muscle (tracheal muscle) in histamine and acetylcholine (Ach)-induced contraction[76], bronchodilatory activity by protecting against Ach- and histamine aerosol-induced bronchospasm in guinea pigs[76,77], inhibition of total and differential leucocytes in bronchoalveolar lavage fluid as well as inhibition of histamine release from chopped lung tissues of egg albumin sensitized guinea pigs[77]. The antiasthmatic potential of ethanol extract of the bark (75 mg/kg and 150 mg/kg, p.o.) was further supported by exhibiting antiallergic activity due to marked inhibition of eosinophil accumulation ($p<0.05$) in allergic pleurisy test as well as significant inhibition in the rise in plasma exudation ($p<0.05$) in acetic acid-induced vascular permeability[78]. However, water extract of the bark even at lower doses (27 and 54 mg/kg, p.o) was found to possess more potent antiasthmatic activity than ethanol extract by showing significant protection against histamine aerosol-induced bronchospasm in guinea pigs and by relaxing histamine-induced guinea pig tracheal chain contraction[79]. Additionally, polar extracts (200 mg/kg)[80] as well as ethyl acetate and water extracts (100 and 200 mg/kg)[81] of *M. nagi* bark showed significant dose-dependent better mast cell protection in treated animals as compared to control group in compound 48/80 and egg albumin-induced allergy test[80,81]. Thus, all these results scientifically support the use of *M. esculenta* bark in traditional medicine for the treatment of allergic reactions including asthma and bronchitis.

Anticancer activity:

Preclinical studies have shown that acetone and acid-methanol extracts of *M. esculenta* fruits showed potent anticancer proliferative activities resulted in 70-92 % reduction in the viability of $C_{33}A$, SiHa, and HeLa cancer cells while exhibiting no cytotoxicity towards normal transformed cell lines[82]. The methanol extract of fruit showed moderate anticancer activity leading to 50, 48.29 and 46.19 % inhibition of Hep G2, Hela and MDA-MB-231 cancer cell lines at concentration 5 mg/ml in methylthiazolyltetrazolium (MTT) assay. It was observed that effect of extract on percent inhibition of cancer cells was found to be increased with increase in dose which may be attributed due to presence of bioactive compounds such as ferulic acid and gallic acid determined by LC/MS analysis[73].

Antidepressant activity:

Screening of ethanol extract of *M. nagi* bark at doses 300 and 500 mg/kg for neuro-pharmacological

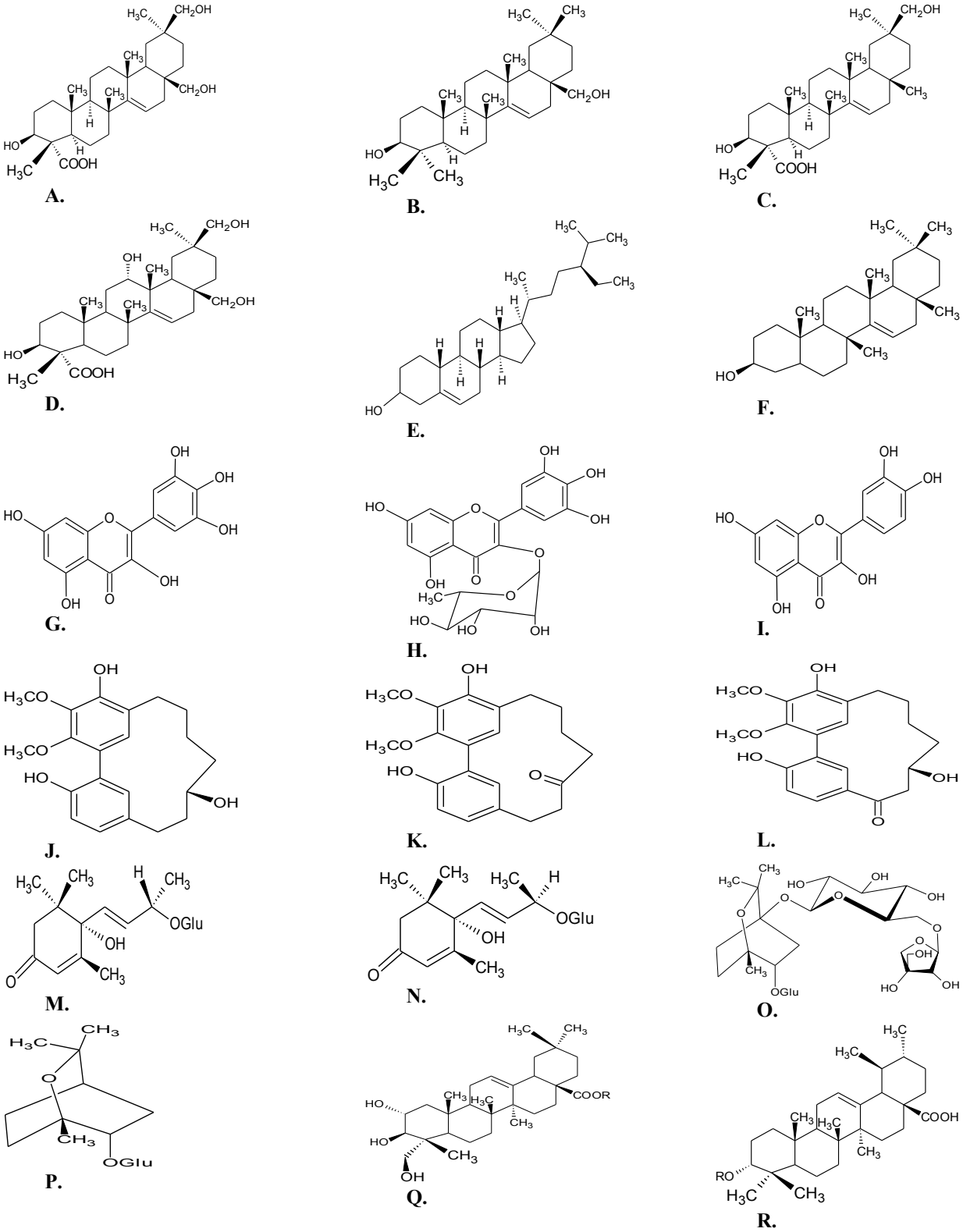

Fig. 2: Structure of some important isolated phytoconstituents of *M. esculenta*
A. Trihydroxytaraxaranoic acid; B. dihydroxytaraxerane; C. dihydroxytaraxaranoic acid; D. tetrahydroxytaraxaranoic acid; E. β-sitosterol; F. taraxerol; G. myricetin; H. myricitrin; I. quercetin; J. myricanol; K. myricanone; L. 13-oxomyricanol; M. corchoionoside C; N. (6*S*,9*R*)-roseoside; O. myreculoside; P. R=H arjunolic acid; Q. R=H 3-*epi*-ursonic acid R=Glu arjunglucoside; R. R=caffeoyl 3-*O*-(*E*) caffeoylursonic acid

activities showed that bark extract exhibited significant dose-dependent antidepressant activity with respect to control group in open-field test, cage-crossing test, head-dip test, rearing test, traction test and forced

swimming test[83], which contradicts the previous report that ethanol extract of *M. nagi* bark exhibited significantly and dose-dependent CNS-depressant effect as evident by increased duration of immobility in animals of extract treated groups as compare to control evaluated by tail immersion test and forced swimming test[37].

Antidiabetic activity:

A significant hypoglycaemic effect was observed in dose-dependent manner by methanol extracts of *M. esculenta* leaves in streptozotocin-induced diabetic rats as the results showed that oral administration of extract produced significant reduction ($p<0.05$) in the blood glucose, blood cholesterol and body weight as well as showed beneficial effect ($p<0.05$) on lipid profile of extract treated group as compared to positive vehicle treated group[84].

Antihelmintic activity:

In a study, 50 % ethanol extract of *M. esculenta* bark was evaluated for antihelmintic activity against Indian earthworm *Pheretima posthuma* at different doses (50, 25 and 12.5 mg/ml) compared with piperazine citrate as standard. The result of such activity revealed that the crude extract at low dose (12.5 mg/ml) showed both paralysis and death in 20.11 and 41.25 min, respectively. The effect of extract was increased in a dose-dependent manner[85].

Antihypertensive activity:

The effect of active phyto-constituents isolated from *M. esculenta* leaves for the management of hypertension was investigated by angiotensin I-converting enzyme inhibition. The results revealed that the compounds corchoionoside C and (6*S*,9*R*)-roseoside were found to be most potent ACE inhibitors with rates 29.97 and 25.63 % at the concentration of 100 µM, while myricanol, 5-*O*-*β*-D-glucopyranosyl myricanol and myricetin showed weak hypotensive activity with inhibition rate 0.07-1.41 % at same concentration[62].

Antiinflammatory activity:

The methanol extract of *M. esculenta* leaves (200 mg/kg) has proven its potential for amelioration of acute inflammation as it showed a significant reduction (21.71 %) in inflammation in treated animals after 4th h of treatment, which was comparable to diclofenac (10 mg/kg; 32.75 %) treated group[75]. The essential oil isolated from *M. esculenta* bark exhibited significant topical antiinflammatory activity compared to standard drug in Swiss albino mice ear[72]. ME-EtAC of leaves was found to have significant ($p<0.05$) antiinflammatory effect against carrageenan-induced paw edema and the results were compared with diclofenac 10 mg/kg[32]. The ethyl acetate extract of *M. nagi* bark (200 mg/kg/p.o) showed significantly greater antiinflammatory activity than the aqueous extract with 27.51 and 26.82 % inhibition of edema in the carrageenan- and the histamine-induced rat paw edema models, respectively, which was almost as effective as the standard aspirin (100 mg/kg/p.o; 28 %)[86].

Antimicrobial activity:

Volatile oil isolated from *M. esculenta* bark was reported to exhibit potent antibacterial activity against Gram-positive and Gram-negative bacteria[72]. The comparative *in vitro* antibacterial screening using disc diffusion assay on *M. nagi* bark and fruit extracts showed that methanol and chloroform extracts of the bark possessed greater antibacterial activity than fruit extracts when compared to the standard drug[87]. Gram-positive bacteria (*S. aureus*) was found to be most sensitive to methanol extract of bark while Gram-negative bacteria (*E. coli*) was found to be less sensitive[88]. Methanol extract of *M. esculenta* fruits showed antibacterial activity against *S. epidermis* and *S. aureus* comparable to that of the standard tetracycline with maximum zone of inhibition 18±0.5 and 16±0.5 mm, respectively. The antimicrobial activity of the extract could be attributed to the presence of dodecanol, phytol, furfurals and 4-H-pyran-4-one, which were reported to possess antimicrobial activity[73]. However, the ethanol extract of *M. nagi* fruit pulp (10 and 50 mg/ml), in disc diffusion assay inhibited food poisoning bacteria such as *E. coli* (MTCC 729), *Streptococcus* pyogenes (MTCC 1925) and *E. coli* (MTCC 443) in a dose-dependent manner[53]. It was also reported that methanol extract[74], ethanol and aqueous extract[53] of fruits showed significant antifungal activity.

Antioxidant activity:

Three different *in vitro* radical scavenging assay *viz*. 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, 2,2-azinobis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS) assay and ferric reducing antioxidant power (FRAP) assay were used to access the antioxidant potential of methanol extract of *M. esculenta* fruit[73] and fruit pulp[58]. The results had showed significant antioxidant activity by both extracts in all tested assays

which is probably due to the presence of phenols, flavonoids and flavonols[58,73]. Seal compared free radical scavenging activity of acetone and 20 % v/v methanol extracts of four wild edible fruits including *M. esculenta* by DPPH assay. The acetone extract of *M. esculenta* fruit, which contained highest amount of phenolic compounds showed highest DPPH radical scavenging activity[89]. On the other side, the acid acetone extract of fruit had proved much higher DPPH radical scavenging activity and ferric reducing ability than acetone extract of fruit[82]. In another comparative study on methanol extracts of wild edible fruits of same species collected from three different regions of Uttrakhand (India) showed variation in DPPH antioxidant activity and Fe^{2+} chelating activity maximum up to 96.98±0.1847 and 72.17±0.2367 %, repectively due to variation in phenolic and flavonoids content affected by various biological factors of natural climates[74]. Additionally, fresh fruit juice of *M. esculenta* showed much higher DPPH scavenging activity (89.62 %) and nitric oxide scavenging activity (75.11 %) at the concentration of 2 mg/ml as compared to standard drug ascorbic acid[90]. The ME-EtAC fraction of leaves exhibited weaker activity than ascorbic acid used as standard[32] and methanol extract[75] in DPPH assay. Preliminary study on antioxidant and radical scavenging activity of the aqueous extract of *M. esculenta* bark showed marked inhibition in lipid peroxidation, complex metal ions (Fe^{2+}) and significant DPPH scavenging activity[91]. The polar extract of *M. nagi* bark also showed remarkable DPPH free radical scavenging activity than non-polar and methanol extracts which might be owing to the presence of higher phenolic and flavonoid compounds like myricetin, myricanol, myricanone[92]. These results strongly supported the use of *M. esculenta* plant as a source of natural antioxidants.

Antipyretic effect:

Screening of methanol extract of *M. esculenta* fruits for antipyretic activity in the Brewer's yeast-induced pyrexia model in the mouse demonstrated that oral administration of the extract produced significant antipyretic activity comparable to that produced by paracetamol[74].

Antiulcer effect:

Oral administration of ethanol extract of *M. esculenta* bark at the dose of 100 and 200 mg/kg showed protection against pylorus ligated ulcer in rats by significant reduction in gastric secretions, acidity, lipid peroxidation and myeloperoxidase enzyme as compared to control. The antiulcerogenic potential of the bark could be related to antioxidant mechanism as evident from significant increase in the catalase activity, nitrite and glutathione level[93]. Thus, the study provided scientific evidence for the traditional use of *M. esculenta* in ulcer treatment.

Anxiolytic activity:

The ethanol extract of *M. nagi* bark tested at three different doses (100, 200 and 400 mg/kg, p.o.) has been reported to exhibit a dose-dependent significant anxiolytic activity as compare to standard drug diazepam evaluated by using two *in vitro* animal models such as elevated plus-maze and light/dark exploration test[37].

Chemopreventive activity:

Pretreatment of mice with ethanol extract of *M. nagi* (2.0 and 4.0 mg/kg) showed significantly ameliorating the cumene hydroperoxide-mediated inhibition of cutaneous glutathione and the activities of antioxidant enzymes such as catalase, glucose-6-phosphate dehydrogenase, glutathione peroxidase, glutathione reductase and phase II metabolizing enzymes in a dose-dependent manner due to the presence of flavonoids, terpenoids and alkaloids in crude extract. Thus, suggested that it might be used as an effective chemopreventive agent[94].

Hepatoprotective activity:

A polyherbal Ayurvedic formulation, Herbitars (50 and 100 mg/kg) containing 5 mg/g of *M. esculenta* as one of the ingredient exhibited hepatoprotective effect against carbon tetrachloride (CCl_4)-induced hepatotoxicity in Wistar rats by significantly decreasing the levels of thiobarbituric acid reactive substance and hydroperoxides along with significantly increasing the antioxidant enzyme activities of superoxide dismutase, catalase, glutathione peroxidase and the levels of reduced glutathione in tissues (liver and kidney) of CCl_4-induced rats[95].

Wound healing activity:

Ethnotherapeutic claim of *M. esculenta* bark for wound healing was scientifically proven by using wound excision and incision model. Application of ointment prepared from the aqueous extract of bark facilitated wound healing process in the treated animals as evident by significant increase in the tensile strength, hydroxyproline content, faster wound contraction and decrease in the epithelization period found comparable

with standard drug 0.2 % w/w nitrofurazon[45]. Thus, the ethanol extract of bark might be used as wound healing agent.

TOXICOLOGICAL STUDIES

Generally, *M. esculenta* is considered safe and only a few toxicity studies have been carried out. Rawat *et al*. studied toxic effects of the methanol extract of *M. esculenta* leaf. They did not find any sign of toxicity up to the dose of 300 mg/kg on oral administration of extract for two weeks. But, at 2000 mg/kg dose of the methanol extract toxic effects were observed in Wistar rats[84]. In addition, acute toxicity studies performed with ethyl-acetate and water extracts of *M. nagi* bark at three different i.v. doses, 100, 200 and 1000 mg/kg, showed that the LD_{50} of the ethyl-acetate and water extracts in mice was 1000 mg/kg[81].

M. esculenta has been used for its therapeutic and nutritional potential since from the ancient Ayurveda and Unani system of medicine. It is evident from this review that *M. esculenta* contains a number of phytoconstituents, which are responsible for medicinal value of this plant. Now, the road ahead is to establish the active therapeutic compound with specific mode of actions, which might be responsible for the medicinal properties of the plant. *M. esculenta* has been reported to have numerous pharmacological effects to treat various disorders including asthma, diabetes, cancer, ulcer, anxiety but being a rich source of vitamin C and polyphenolic compounds there is the need to explore the potential of this plant for immunomodulatory, cardioprotective, nephroprotective, and neuroprotective activity. As the population of this medicinal and economical plant species is in the verse to extinction due to overexploitation of forests and wastelands, negligence of sustainable resources, poor cultivation as well as poor regeneration of the species in natural habitat. Hence, it is high time to take preliminary necessary action to increase its population size, productivity, conservation and utilization.

Conflict of interest:

The authors report no declarations of interest.

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