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Therapeutic potential of Habb-ul-Aas (*Myrtus communis* Linn.) with Unani Perspective and Modern Pharmacology: A review

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Abstract
Myrtus communis Linn. (MC) is an important medicinal shrub being used in Unani Medicine for the treatment of diarrhoea, peptic ulcers, leucorrhoea, urethritis, haemorrhoids, conjunctivitis, palpitation, pulmonary and skin disease. This review provides data on the botany, phytochemical, Preclinical & Clinical Studies and Unani traditional uses of MC, with an aim to make update of the current information and obtain opportunities for further therapeutic potential. The information was obtained from scientific literature databases including PubMed, Research Gate, Google Scholar, Web of Science and Science Direct. Additional information was gathered from classical Unani text books, and published materials. MC are used traditionally for the treatment so many diseases. The Anti-inflammatory, Antimicrobial, Antioxidant, Hypoglycaemic, Anticancer, Analgesic, Antidiarrheal properties have been widely investigated. More than 50 active ingredients have been isolated from this plant including monoterpene, sesquiterpene, oxygenated sesquiterpenes, tannins and flavonoids. The present review verifies the real identity of Myrtle, summarizes its valuable description in Unani literature, and its medicinal efficacy in haemorrhoid, aphthous stomatitis, chronic rhinosinusitis, bacterial vaginosis (BV) and other disorders. Phytochemical and pharmacological studies and clinical investigations on the crude drug and isolated principles proved the multipotent action of Myrtle.

Keywords: *Myrtus communis*, Habb-ul-Aas, unani medicine, traditional uses, antidiarrheal

Abbreviations
MC, *Myrtus communis* Linn.; DPPH, 2,2-diphenyl-1-picrylhydrazyl; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; FRAP, Ferric Reducing Antioxidant Power Assay; ORAC, Oxygen Radical Absorbance Capacity; AHH, aryl hydroxylase; E, Escherichia; bw, body weight; i.p., Intraperitoneal injection; TNF-α, Tumor necrosis factor alpha ; IL-6, Interleukin 6 ; MBJ, myrtle berries juice; ER, oesophageal reflux; P; Plasmodium; HSV-1, Herpes simplex virus-1; Ery^S, Erythromycin sensible; Ery^R, Erythromycin resistant; CQ, Chloroquine

1. Introduction
Traditional medicine is an evolutionary process as communities and individuals continue to discover new techniques that can transform practices. Ethnopharmacology and drug discovery using natural resources remain important issues in the current target-rich, lead poor scenario [1, 2]. MC (Family: Myrtaceae) commonly referred to as "myrtle" in English and "Habb-ul-Aas" in Arabic is an aromatic evergreen perennial shrub or small tree, 180-240 cm tall with small foliage and profound fissured bark [3]. This plant is found mainly in the Mediterranean regions, Asia, Southern Europe, New Zealand, America and Southern Russia [4]. *Myrtus*, the Greek name for *Myrtle* and communis means the growing of common plants in clusters. The first reference of Myrtle occurs in the Bible. It was introduced into Britain around 1597 and described by Linnaeus in 1753. Myrtle is notable in the writings of *Hippocrates* (460 – c. 370 BC), Pliny the Elder (23/24 – 79 AD), *Dioscorides* (40–90 AD), Galen (129-210 AD) and the Arab writers [3]. Different parts of this plant such as berries, branches, leaves, fruits and seeds have been extensively used in traditional medicine in various doses form to treat diarrhoea, peptic ulcers, haemorrhoids, palpitations, leucorrhoea, conjunctivitis, pulmonary and skin disorders [4-6]. In India, myrtle oral products are used to treat neurological disorders such as epilepsy, and the topical products are used mostly for haemorrhoid and infectious diseases. In Unani medicine, fruit and seeds are used in the form of powder and decoction to treat *Ishaal* (Diarrhoea), *Jiryan-ud-Dam* (Haemorrhage), *warm litha* (Gingivitis), *litha damiya* (Bleeding gums), Bawl al-Dam (Haematuria) *Kathrat-i-Tamth* (menorrhagia), *Salisul Bawl* (incontinence of urine) [7]. It contains many important biologically active chemical constituents such as myricetin, coumarins, myrtucommulone A and B, Myrtenol, myrtenol acetate, limonene,

pinene, p-cymene, geraniol, phenylpropanoid, methyl eugenol phospholipids, phenolic compounds and essential oil. The essential oil are used for rheumatoid pain and pyorrhoea treatment [7, 8]. The composition of oil from various locations has substantial variability [7]. It possesses analgesic, anti-bacterial, antispasmodic, anti-carminative, antidepressants, anti-diabetic, fungicidal, anti-parasitic and anti-viral activity [4, 7, 9, 10].

2. Vernaculars

Arabic: Habb-ul-Aas, Hadass (South Arabia); China: Xiang tao mu; English: Myrtle; Greek: Mirtia; Italy: Mirto; Persian: Barg-e-murad (leaves); Russia: Mirt; Turky: Mersin; Urdu: Aass, Moorad; Hindi: Sata Sova, Vilayati mehndi; Sanskrit: Gandhamalati [11–14].

3. Materials and methods

The literature of Myrtle was obtained from online databases including PubMed, Google Scholar, Web of Science, Science Direct, ResearchGate and a library search was conducted from classical Unani books, and published Books. The keywords used for the search were *Myrtus communis* Linn., Myrtus, *Aas*, common myrtle. For Arabic writings, the term *Habb-ul-Aas* (حب الآس), *Murad* (مورد) was used. The synonyms and scientific names have been validated by 'The Plant List' (www.theplantlist.org).

4. Botanical description

Myrtus is a small genus of the Myrtaceae family that includes around 150 genera and 3300 species that grow in tropical and temperate regions of the world [15, 16]. It is an evergreen shrub that grows to a height of about 1-5 m and whose longevity could exceed 300 years. It is distributed in India, South America, Europe, north-west of Himalayas, Australia and in the Mediterranean region. It is cultivated in gardens for its fragrant flowers [8]. It can be found in altitudes as high as 1000 m above sea level. Wild Myrtle is abundant in the coastal lands of most north and south Mediterranean regions and islands [17]. Leaves are opposite, simple, ovate or oblong-lanceolate, 0.5-2 cm long, entire, acute, glossy, dark green, pinnately veined, short petiole and glabrous. When crushed, they have a delicate aromatic [16, 18, 19]. Flowering will start from May to June and last until August [8]. Flowers are white, star-like, with five petals, five sepals and a tufted mass of stamens. After the summer, bluish-black (or sometimes yellowish-white) sub-globose to ellipsoid berries (7–10 mm) appears on maturation around November [8, 16]. The fruit is internally divided into three sections which contain various irregular shapes and sizes of seeds. Seeds are reniform, bright, off-white coloured, and resinous. In the centre of seeds there is an elaiosome, which develops through cell divisions from the outer tegument cells nearby the micropylar and funicular zone. At the termination of the growth, some internal integument cells contribute to its development so that myrtle elaiosomes can be categorized as epidermal and internal tissues [20].

Source: https://commons.wikimedia.org/wiki/File:Myrtus_communis_10.jpg

Fig 1: A. Myrtle Berries

Source: https://commons.wikimedia.org/wiki/File:Starr_080304-3229_Myrtus_communis.jpg

Fig 2: B. Myrtle flower

Source: https://www.kalliergeia.com/en/common-myrtle-or-true-myrtle-myrtus-communis-l/

Fig 3: C. Myrtle Seeds

5. Ethinomedicinal uses

Al-Antaki characterized 57 plants in his *book "Tadhkirat Uli l-al-Bab wa l-Jami li-L-'Ajab al-'Ujab"* that were used as sources for simple and complex drugs. In this, he also includes common myrtle [21]. In the literatures of *Hippocrates*, *Dioscorides*, *Galen* and the Arab physicians, myrtle enjoyed a

prominent place. *Galen* said that it's all part are equally astringent. According to Pliny, fruits were used in diarrhoea, dysentery, ulcers and inflamed eyes and in wine they are antidote to mushroom poisoning [11]. For an anal protrusion it was advised to sit in a decoction of myrtle leaves. It is believed that the latex extracted from the crushed leaves prevents the anal protrusion associated with haemorrhoids [22]. The decoction of fruit has been used to bathe new-borns with reddish skin, and the decoctions of both leaves and fruit are used in many countries for vaginal lavage, enemas and respiratory diseases. Leaves decoctions is also effective in sore washing [5]. Avicenna listed it as one of the medicines to treat excessive uterine bleeding in his famous book "The Canon of Medicine" [22]. In Unani medicine, due to its expectorant qualities, has been indicated against respiratory disorders such as emphysema and bronchitis. In different types of doses form such as infusion, decoctions, *majoon*, myrtle has been used to treat gastric ulcers, stomach pain, diarrhoea and haemorrhoid. Diarrhoea was also treated by the use of decoctions of myrtle flower and seeds [8]. 2 cups of fruit infusion have been given orally between meals to treat haemorrhoids, oral aphthous and diarrhoea [22]. It also indicated as a urinary antiseptic [8].

6. Properties of *Myrtus communis* in Unani medicine

6.1 Temperament (*Mizaj*)

The definition of *Mizaj-e-advia* (drug temperament) in Unani medicine is not only unique in defining the properties of drug substances in its own way, but it also stands the test of time by proving extremely useful in predicting drug actions on administration or topical application to humans [23-25]. The *Mizaj* of myrtle are mentioned in Unani literature are cold in first degree and dry in second degree [12-14, 26, 27].

6.2 Pharmacological actions

It possesses *Qabiz* (astringent), *Habis-i-Dam* (Hemostyptic), *Mani'-i-'Araq* (antiperspirant), *Muqawwi-ī-Dimagh* (stomachic), *Muqawwi-ī-Qalb* (cardiac tonic), *Mufarreh qalb* (exhilarant), *Mujaffif* (desiccant), *Musaddid* (obstruent), *Mudirr-ī-bawl* (diuretic), *Mufattit-ī-haṣāt* (lithotryptic), *Muqawwi-ī-chasm*, *Muqawwi-ī-Sha'r* (hair tonic) properties [12-14, 26].

6.3 Therapeutic uses

It is used for management of *Khafaqān* (palpitation) and for the treatment of *Ishāl* (Diarrhoea), *Ṣudā'* (headache), *Sayalan al-khoon* (to stop bleeding), *Ramad (*Conjunctivitis), *Ru'āf* (epistaxis), *Qay* (antiemetic), *Bawāsīr* (piles), *Zaḥīr* (dysentery) *Taqṭīr al-Bawl* (Dribbling of urine), *'Usr al-Bawl* (Dysuria), *Qurūḥ al-Mathāna* (Ulcers of bladder). Its decoction strengthens the roots of the hair and prevents their loss and to make hair blackish. Its decoction is used as *Nutool* (irrigation) in bone fracture. Decoction of its fruit mixed with olive oil are used to prevent perspiration, relief in hot inflammations, to treat erysipelas, herpes, pimples, urticaria, wounds of the palms and burns. It also acts as a corrective in intestinal abrasions [12, 13, 26].

6.4 Adverse effect and Corrective

Most of the natural drugs used in Unani system are safe for human use, but some crude toxic drugs are first processed and purified in many ways before use to make them safer [24,28]. Some time it is used with other drugs to optimize the adverse effect. In crude form myrtle cause headache and insomnia [12, 26, 27]. So, to minimize the adverse effect of myrtle it is used with *Rasaut* (*Berberis aristata* DC) and *barg-e-toot* (leaves of *Morus alba*) [12, 26].

6.5 Substitute

Unani drugs are substituted when they are threatened, costly, scarce, prohibited or difficult to procure. A medicine is prescribed only as a replacement for a particular action, because the replacement may vary from the main drug in certain actions [29]. So, for some specific actions *Bekh Anjbar* (roots of *Polygonum bistorta*) and *Gul-e-hina* (*Lawsonia inermis*) are used as a substitute for myrtle seeds [12, 26, 27].

6.6 Therapeutic Dose

It is given in the dose of 3-5 g [12, 26]

6.7 Compound formulation

Compound formulation, therapeutic dose and its uses are mentioned in Table 1.

Table 1: Compound formulation which contains MC [12, 26, 30-32]

Formulation name	Therapeutic uses	Doses
Sharbat-e-Habbul aas	To treat weakness of the Digestive System, Diarrhoea and Colic pain	25 to 50 ml with water
Jawartish Jalinoos	Gastric diseases, Gastralgia, Dyspepsia, Sexual Weakness and Liver Disorder	5-10g
Jawarish Muqawwi-e-Meda	To strength stomach and intestine and increase appetite, improve digestion, relieves flatulence and regulates intestinal functions	5–10 g with water at bedtime
Majoon masik-ul-bawl	Effective in incontinence of urine, bladder problems, enuresis, diabetes insipidus and weakness of the liver.	5 g with water in the morning or at night
Itrifal-e-muqil mumsik	To treat haemorrhoids (bleeding piles) and constipation	10 to 15 g with Luke warm water at bedtime
Majoon-e-bawaseer	To treat haemorrhoids (bleeding piles)	7-12 g with Luke warm water at bedtime
Majoon muqawwi-e-rahem	To treat uterine disorders	5 grams with water or milk
Majoon-e-sangdana Murgh	Strengthens the stomach and intestine.	5 g with water in the morning and evening.
Majoon-e-Alkula	To strength kidney and bladder, and also used in Sexual Weakness	10 g
Maaski	For the treatment of increased frequency of micturition and Urinary incontinence	4 tablets with water twice a day
Raughan-e-Benazeer	It is used in the weakness of brain and Asthenopia, it helps in growth and nourishing of hair roots,	External use only

7. Chemical constituent

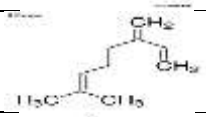
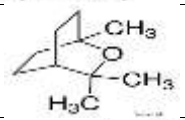
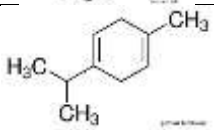
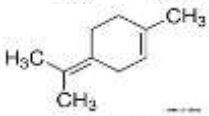
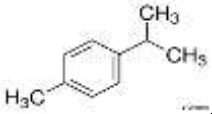
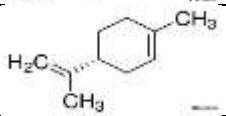
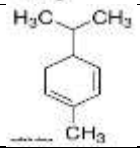
The plant contains various active biological compounds. The leaves include tannins, flavonoids, coumarin, galloyl-glucosides, ellagitannins, caffeic acid, gallic acid and ellagic acids [3, 33]. Both leaves and berries produce large amounts of phenolic content that are responsible for their antioxidant properties. Berries contains tannin, citric acid, caffeic acids, anthocyanin glucosides, kaempferol, quercetin, myricetin 3,

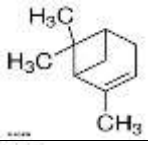
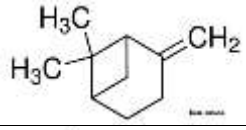
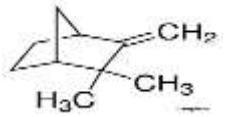
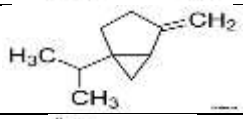
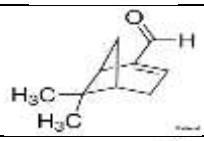
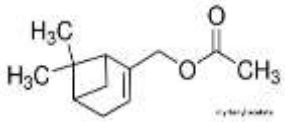
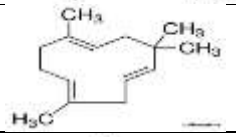
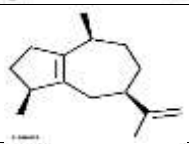
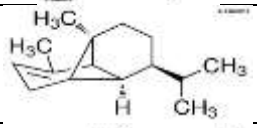
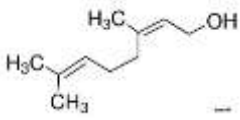
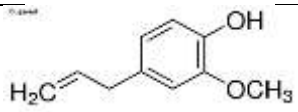
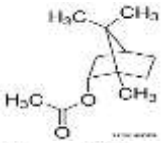
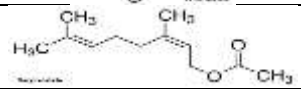
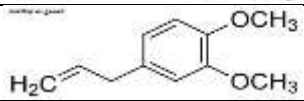
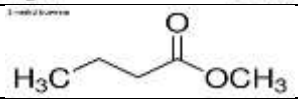
3-di-ogalactoside, and myricetin-3-(600-O-galloyl galactoside). Berries also have a rich mineral source [3, 11, 34]. Ethanolic extract of berries are abundant in anthocyanins, especially malvidin-3-O-glucoside, and flavanols, but only a few gallic acid derivatives have been reported at high levels. Phenolic composition of myrtle berries extracts contains Gallic acid and its derivatives, Ellagic acid, Anthocyanins, Delphinidin-3-O-glucoside, Petunidin-3-O-glucoside, Malvidin-3-O-glucoside, other anthocyanins, flavanols, myricetin-3-O-galactoside, myricetin-3-O-ramnoside, myricetin, quercetin [34]. The volatile oil berries comprise large amounts of monoterpene hydrocarbons and oxygenated monoterpenes with α-pinene, 1,8-cineole, as the main components [35].

7.1 Essential oil

The essential oil of Myrtle is yellow or greenish yellow with a refreshing odour. The oil has been extensively examined and its composition varies greatly depending on the area of origin, harvest season and distillation period [5]. The components of essential oil of leaves were characterised by a highly oxygenated monoterpene fraction (70.1–73.2%) [36] followed by monoterpene hydrocarbons (39.61%), sesquiterpene hydrocarbons (1.39%) and oxygenated sesquiterpenes (0.60%) [37] and the highest accumulation was observed during the flowering stage [36]. The active components of Essential oil are α-pinene (56.73%) in Corsica variety; 1,8-cineole (46.98%) and limonene (19%) in Lebanon variety [38,39]; myrtenyl acetate, 1,8-cineole and *α*-pinene in Morocco variety [40]. Beside these the essential oil of myrtle different part are also contains α-pinene; Camphene; Sabinene; 1,8-cineole; Cis-β-ocimene; Trans-β-ocimene; γ-terpinene; α-terpinolene; 2-methylbuterate; Terpinen-4-ol; α-terpineol; Linalylacetate; Hydroxycineole acetate; α-terpinyl acetate; Cis-geraniol; Methyleugenol; 10-nonadecanone; [39] Isobutyl isobutyrate; α-Thujene; β-Pinene; δ-3-Carene; β-Myrcene; α-Terpinene; Limonene; (E)-2-Hexenal; (Z)-β-Ocimene; c-Terpinene; cis-Linalool oxide; trans-Linalool oxide; Linalool; α-Campholenic acid methyl ester; trans-Pinocarveol; Borneol; Terpinen-4-ol; 3-Hexenyl butanoate; Myrtenal; Myrtenol; trans-Geraniol; Linalyl acetate; trans-Pinocarveyl acetate; Myrtenyl acetate; p-Menth-1-en-8-ol acetate; Neryl acetate; Geranyl acetate; trans-Caryophyllene; α-Humulene; Estragole (isoanethole); Caryophyllene oxide; Eugenol methyl ether; Humulene epoxide II; [36] 2-propanol; ethyl isobutyrate; isobutyl isobutyrate; P-pinene; 6-3-carene; α-phellandrene; myrcene; (Z)-p-ocimene; y-terpinene; (E)-p-ocirnene; Terpinolene; perillene; cis-linalool oxide (furanoid); nerol oxide; trans-linalool oxide (furanoid); α-copaene; linalool; linalyl acetate; bornyl acetate; limonene; p-cymene; P-caryophyllene + terpinen-44; y-patchoulene; sabinol; methyl chavicol; citronellyl acetate; myrtenyl acetate; a-terpenyl acetate; a-guaiene; P-guaiene'; neryl acetate; cis-carveol; geranyl acetate; myrtenol; nerol; myrtenyl 2-methyl butyrate; p-cymen-8-01; caryophyllene oxide; geraniol; methyl eugenol. Structure and classification of chemical are described in Table 2 [36-38, 41-44].

Table 2: Classification and structure of main compounds of MC

Classification	Component	Structure	PubChem CID
acyclic monoterpenoids	Cis-β-ocimene		5320250
acyclic monoterpenoids	β-Myrcene		31253
monocyclic monoterpene	1,8-cineole		2758
monocyclic monoterpene	γ-terpinene		7461
monocyclic monoterpene	α-terpinolene		11463
monocyclic monoterpene	p-Cymene		7463
monocyclic monoterpene	Limonene		22311
monocyclic monoterpene	α-phellandrene		7460

bicyclic monoterpene	α-pinene		6654
bicyclic monoterpene	β-Pinene		14896
bicyclic monoterpene	Camphene		6616
bicyclic monoterpene	Sabinene		18818
bicyclic monoterpene	α-Thujene		17868
bicyclic monoterpene	Myrtenal		61130
bicyclic monoterpene	myrtenyl acetate		61262
monocyclic sesquiterpene	α-Humulene/ α-caryophyllene		5281520
Bicyclic sesquiterpene	α-guaiene		5317844
sesquiterpene	α-copaene		70678558
monoterpenoid alcohol	nerol		643779
phenolic monoterpenoids	Eugenol		3314
monoterpene ester	bornyl acetate		6448
acetate ester, a monoterpenoid)	Neryl acetate		1549025
phenylpropanoid	methyl eugenol		7127
fatty acid	2-methyl butyrate		22253297

8. Pharmacological activity

The plant is reported for antioxidant, Cardiovascular, Anticancer, Antidiabetic, Anti-inflammatory, Antinociceptive, Antidiarrheal Antiviral, antimicrobial, Anthelmintic, Gastroprotective and other beneficial activities which are mentioned in Table 3.

8.1 Antioxidant Activity

In general, various chemical methods are used to evaluate the antioxidant potential of natural products, including DPPH, ABTS, FRAP and ORAC. By using DPPH, ABTS, Hydroxyl radical, Ferrous ion chelating, β-carotene bleaching assay, Bouaziz *et al.*, evaluates the antioxidant activity of methanol, chloroform, ethyl acetate and aqueous leaf extracts of MC. The result showed that extract of ethyl acetate exhibited the highest antioxidant activity in DPPH, while methanol extract exhibited higher chelating activity. In β-carotene bleaching assay, ferric thiocyanate, and thio-barbituric acid, chloroform was found to be a good inhibitor of lipid peroxidation relative to butylated hydroxytoluene. The antioxidant activity are may be due to presence high amount of polyphenols and flavonoids [45]. Another study shows that myrtle berry seeds aqueous extract has rich in total polyphenols and anthocyanins and revealed an important antioxidant activity [46]. The essential oils of MC showed high scavenging activity against DPPH radicals due to the high content in hydrocarbon monoterpenes and oxygenated monoterpenes [37]. According to Gardeli *et al*., the strongest antioxidant activity and the highest phenolic content for MC were obtained during full flowering stage (August) [36].

8.2 Cardiovascular effect

Traditionally Myrtle is used for treatment of heart diseases. To investigate the hypotensive effects of myrtus extracts Bouaziz *et al*., used the invasive blood pressure recording method to assess the hypotensive effects of methanolic and ethyl acetate extracts of berries in anaesthetized rats. Intravenous administration of both extracts (0.04 to 12 mg/kg bw) decreased the maximum mean arterial blood pressure at 12 mg/kg by 20.6% and 32.49% respectively and indicated that both extracts have dose-dependent blood pressure lowering effect in rats [45]. Another research found that in isolated rabbit aorta preparations, MC crude methanol extract relaxed phenylephrine (1 μM) and K^+ (80 mM)-induced contractions, and the results were identical to verapamil, a standard calcium channel blocker [47].

8.3 Anticancer Activity

According to Alwan *et al*., [48] the ethanol extracts of MC have significant inhibitory effect on both aryl hydroxylase (AHH) and 3 H-benzo(a) pyrene binding to rat liver microsomal protein. In the same study, no inhibitory effect was shown with aqueous extracts. In another study the essential oils of MC exhibited anticancer effects in two human cell lines HL-60 and NB4 and also showed that essential oil is more effective on Ehrlish Ascites Carcinoma Cells in both *in vitro* and *in vivo* studies [37]. Another study evaluates the antiproliferative properties of ethanolic extract of myrtle *in vitro* on HaCat keratinocytes by using the BrdU incorporation assay. The result showed that extract inhibit keratinocyte proliferation by 27% (1 μg/mL) and 76% (3 μg/mL) [49]. According to Mimica-Dukic *et al*., myrtle oil expressed higher reduction of mutagenesis, in a dose dependent manner on spontaneous and t-BOOH-induced mutagenesis in E coli [44].

8.4 Antidiabetic Activity

Several studies have examined antidiabetic activity of MC, mainly with *in vivo* models. Elfellah *et al*., used hydroalcoholic extract of MC (2000 mg/kg intragastrical), 30 min before streptozotocin induced hyperglycaemia in mice to evaluates antidiabetic Activity. After 48 hour, the extract significantly reduced the hyperglycaemia and no effect observed on the blood glucose level of normal mice [50]. Another study [51] evaluated *in vivo* antidiabetic activity of aqueous and methanolic extracts of MC (500, 750 and 1000 mg/kg bw orally) in alloxan induced diabetic mice. The result showed that aqueous extract of MC significantly lowered blood glucose level in mice at dose of 500 mg/kg by 61.8% and methanolic extract significantly lowered blood glucose level by 48% at 1000 mg/kg [51].

8.5 Anti-inflammatory Activity

MC have been widely investigated for their anti-inflammatory activity. To investigate the Anti-inflammatory Activity of Myrtucommulone (isolated from myrtle leave), paw oedema and pleurisy were induced by injecting carrageenan in mice. The result revealed that Myrtucommulone reduced the growth of carrageenan-induced paw oedema, and at dose 4.5 mg/ kg i.p. also exerted anti-inflammatory effects in the pleurisy model [52]. Another study showed that aqueous and ethanolic extracts of aerial part of MC demonstrated anti-inflammatory effects against chronic inflammation and the aqueous extract exhibited dose dependent acute inflammatory activity in xylene-induced ear oedema and a cotton pellet test in mice. These effects of the extracts may be due to presence of flavonoids and/or tannins contents [53]. Fiorini-Puybaret *et al*., evaluates *in vitro* anti-inflammatory activity of an ethanolic extract of myrtle by measuring 6-keto-prostaglandin F1α and [3H]-arachidonic acid metabolite production in keratinocytes. The result showed that at concentration of 3 and 10 μg/mL, the extract significantly decreased all metabolite production from cyclooxygenase and lipoxygenase pathways [49]. In another study on topical application, myrtus oil showed a significant reduction in ear oedema and MPO activity in mice and also inhibited cotton pellet-induced granuloma and serum TNF-α and IL-6 [54].

8.6 Antinociceptive Activity

Hosseinzadeh *et al.* [53] investigates the antinociceptive effect of aqueous and ethanolic extracts of aerial part of MC in mice by using hot plate and writhing tests. The result shows that both extracts have significant central and peripheral antinociceptive activity and the effects of the extracts may be due to presence of flavonoids and tannins contents. Another study evaluated the analgesic effect of essential oil of MC Leaves in mice by using acetic acid induced writhing test. The result showed that essential oils exhibited analgesic effect dose dependently in comparison with standard drug and significantly inhibited the writhing at 100 and 150 mg/kg [55].

8.7 Antidiarrheal Activity

Myrtle seeds aqueous extract have a strong protective effect against acute diarrhoea caused by castor oil because of its antioxidant and antimicrobial properties [46]. A study investigates the antidiarrheal effect of methanol extract and solvent fractions of the leaves of MC in mice against charcoal meal, entero-pooling tests and castor oil induced diarrhoeal model. The result possesses that all extracts significantly delayed the onset of diarrhoea and in the entero-pooling test, all extracts produced a significant decline in the weight and

volume of intestinal contents [56]. Another study evaluates the effect of myrtle berries juice (MBJ) on normal gastro-intestinal transit, castor oil-induced diarrhoea and enteropooling tests in Adult male wistar rats. The MBJ was given orally and result compared with standard drugs loperamide and clonidine. Result shows that MBJ significantly inhibited the intestinal motility and gastric emptying [57].

8.8 Miscellaneous

A study evaluates the protective effect of aqueous extract of myrtle seeds against oesophageal reflux (ER)-induced damage in oesophageal mucosa of adult male Wistar rats. The result possesses that aqueous extract exerted a potential protective effect against ER-induced damage in rat oesophagus due to its antioxidant properties [58]. Moussouni *et al*., evaluate the *in vitro* anthelmintic activity of leaves of MC ethanolic and water extracts against digestive strongyles in naturally infected cattle using the egg hatch and larval mortality assay. Result showed that, both extracts have a potential anthelmintic activity on eggs and larvae of bovine strongly parasites [59]. Dellagli *et al*., evaluates *in vitro* anti-plasmodial activity of essential oils of MC on D10 and W2 strains of Plasmodium (P) falciparum. The result showed that essential oils inhibited the growth of both strain in a dose-dependent manner [43].

9. Toxicity

The oral dose of aq. extract of MC is almost non-toxic and safe for use, because its LD50 is greater than 5 g/kg [51]. According to Hosseinzadeh *et al*., [53] the LD50 of the aqueous and ethanolic extracts were 473 and 790 mg/kg, respectively. An acute toxicity profile of the leaf extract was determined Sisay *et al*. The LD50 was found on this test to be > 2000 mg / kg for 80ME [60].

Table 3: The activities of MC extract, essential oil and isolated compounds

Pharmacological activities		Extract	Target/model	Control	Dose/ IC 50	Result/remark	Ref.
Anti-inflammatory	*In vitro*	Ethanolic extract of MC leaves	6-keto-prostaglandin F1α and [3H]-arachidonic acid metabolite production in keratinocytes	----------	0.3-10 µg/ml	Significant anti-inflammatory activity at the maximum concentration	[49]
Anti-inflammatory activity	*In vivo*	essential oil	Croton oil induced ear oedema and cotton pellet induced granuloma in mice	Indomethacin	1 and 2 mL/kg	1. Significant ↓ ear oedema 2. Inhibit cotton pellet-induced granuloma and serum TNF-α and IL-6	[54]
Anti-inflammatory activity	*In vivo*	Myrtucommulone (isolated from leaves of MC)	Carrageenan-induced paw oedema and Pleurisy in mice	Indomethacin	0.5 to 4.5 mg/kg i.p.	1. ↓ the growth of paw oedema in a dose-dependent manner 2. At 4.5 mg/kg i.p. myrtucommulone exerted potent anti-inflammatory effects in the pleurisy model	[52]
Anti-inflammatory activity	*In vivo*	Aqueous and Ethanolic Extracts of MC aerial Parts	Xylene-induced ear oedema and cotton pellet test in mice	Diclofenac and morphine	Aqueous extract: 5 to 200 mg/kg i.p., Ethanolic extract: 50 to 350 mg/kg i.p.	Aqueous extract showed significant activity against acute inflammation in dose dependent manner	[53]
Antinociceptive activity	*In vivo*	Aqueous and Ethanolic Extracts of MC aerial Parts	Hot plate and writhing tests in mice	Diclofenac and morphine	Aqueous extract: 5 to 200 mg/kg i.p., Ethanolic extract: 150 to 350 mg/kg i.p.	Both extracts showed significant antinociceptive activity against acetic acid induced writhing and in Hot plate test	[53]
Antinociceptive activity	*In vivo*	Essential oil	Acetic acid induced writhing test in mice	Diclofenac sodium	50 to 150 mg/kg i.p.	The oil showed dose dependent analgesic effect in comparison with diclofenac sodium	[55]
Antiviral (anti-herpetic)	*in vitro*	Hydroalcoholic extract	Herpes simplex virus-1 (HSV-1)	----------	IC50 before cellular attachment 3.1 mg/ml, and after entering the cells 1.11 mg/ml	By increasing the extract concentration, percentage of inhibition of cytopathic effect was increased	[61]
Hypotensive effects	*In vivo*	Methanol, ethyl acetate extracts	Invasive blood pressure recording in anaesthetized rats	----------	0.04 to 12 mg/kg bw	I/v administration of methanol and ethyl acetate extract ↓ the maximum mean arterial blood pressure	[45]
Antioxidant properties	*in vitro*	Methanol, chloroform, ethyl acetate and aqueous extracts	DPPH, ABTS, Hydroxyl radical scavenging activity, Metal chelating activity, Reducing power, β-carotene/linoleic acid bleaching assay, Ferric thiocyanate test, TBA test	BHT, Trolox, Vitamin C	DPPH: 4±0.3 g/mL to (21±0.1 g/mL), ABTS: 0.001 50±0.000 09 to 0.004 80±0.000 08 mg/mL,	Ethyl acetate extract exhibited the highest activity in scavenging DPPH, ABTS, hydroxyl radical and reducing power	[45]
Antioxidant activity	*In vitro*	myricetin-3-o-galactoside and -rhamnoside, isolated from the leaves of MC	Xanthine oxidase, lipid peroxidation and DPPH	----------	In lipid peroxidation IC50: 160 µg/ml and 220 µg/ml respectively, DPPH IC50: 1.4 µg/ml	Both compounds showed the most potent inhibitory effect in xanthine oxidase	[62]
Anti-diabetic activity	*In vivo*	Aqueous and methanolic extracts	Alloxan induced diabetic mice	----------	500 to 1000 mg/kg bw orally	Aqueous extract significantly lowered mean blood glucose level at dose of 500 mg/kg by 61.8%	[51]
Anti-diabetic activity	*In vivo*	ethanol-water extract	Streptozotocin-induced diabetes in mice	----------	2 g/kg orally	Significantly reduced the hyperglycaemia	[50]
Anthelmintic activity	*In vitro*	Ethanolic and water extracts	Egg hatch assay and larval mortality assay	Albendazole	0.78 to 50 mg/ml	Both extracts have a potential anthelmintic activity on eggs	[59]

						and larvae of bovine parasites	
Antidiarrheal activity	*In vivo*	Methanol extract	Castor oil induced diarrhoea in mice	---------	100, 200 and 400 mg/kg	At dose 200 & 400 mg/kg, the extract significantly delayed the onset of diarrhoea	[60]
Antidiarrheal activity	*In vivo*	MBJ	Castor oil-induced diarrhoea in rat	Loperamide	5 and 10 ml/kg bw orally	Acute pre-treatment with MBJ delayed the onset of diarrhoea and also decrease the frequency and severity of defecation	[57]
Antidiarrheal activity	*In vivo*	Aqueous extract of berries	Castor oil-induced diarrhoea in rat	Loperamide	25 to 100 mg/kg bw orally	The extract induced a significant dose-dependent protection against diarrhoea and intestinal fluid accumulation	[46]
Antimicrobial activity	*In vitro*	Leaves methanolic extract	Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Micrococcus luteus, Listeria monocytogenes, E coli, Proteus vulgaris, Pseudomonas aeruginosa and Campylobacter jejuni	----------	MIC: 0.1-2mg/ml	Inhibition zone diameter: 8-18mm	[63]
Antimicrobial activity	*In vitro*	Aqueous extract of berries	Strains of E coli; Salmonella typhimurium; Staphylococcus aureus; Pseudomonas aeruginosa; Aeromonas hydrophila; Bacillus cereus / Disc diffusion assay	Gentamicin	MIC: 03.12 to 06.25 mg/ml	Inhibition zone diameter 14 ± 0.8 to 18 ± 0.8 mm	[57]
Antimicrobial activity	*in vitro* and in situ	Hydro-alcoholic extract of MC leaves	Pseudomonas fragi and Brochothrix thermosphacta	----------	MIC: 12.5–50 and MLC values: 25–100 mg DM/ml.	**1. *In vitro*:** extract was significantly more effective against Brochothrix thermosphacta. **2. In situ:** the microbial population ↓ significantly in ground meat with added 5% of freeze-dried MC extract	[64]
Bactericidal activities	*In vitro*	Myrtacine® (Ethanolic extract of MC leaves)	Erythromycin sensible (Ery^S) and resistant (Ery^R) P. acnes strains	Erythromycin	1 and 3mg/mL	Compared with erythromycin, Myrtacine® activity was much higher on the Ery^R strain	[49]
Gastroprotective effect	*In vivo*	Aqueous extract of berries	ER-induced damage of mucosa/ rats	Famotidine	25 to 100 mg/kg, bw orally	The extract significantly protect oesophagus due to antioxidant properties	[46]
Gastroprotective effect	*In vivo*	aqueous and methanolic extracts	Ethanol-, indomethacin- and pyloric ligation-induced models in Wistar rats	Omeprazole	93 to 175 mg/kg orally	1. In ethanol-induced ulcer mode, low dose of aq. and high dose of methanolic extract showed more significant effect in comparison with standard drug. 2. All dose of both extracts also ↓ the gastric juice volume, total acidity and ↑ the gastric pH and gastric mucus content in all the models of ulcers	[65]
Anti-plasmodial	*In vitro*	essential oils	Chloroquine (CQ) -sensitive and resistant strains of P. falciparum	Chloroquine	1–100 µg/ml	Significant activity present against CQ-sensitive and the resistant strains of P. falciparum	[43]
Antimutagenic activity	*In vitro*	Myricetin-3-o-galactoside and -rhamnoside, (isolated from the leaves of MC)	SOS chromotest and the Comet assay	----------	150 and 220 µg/ml	Both compounds showed significant inhibitory activity against nifuroxazide, aflatoxin B1 and H2O2 induced mutagenicity	[62]
Antiproliferative activity	*In vitro*	Myrtacine® (ethanolic extract of MC leaves)	BrdU incorporation assay in HaCat keratinocytes	---------	0.1-3 µg/ml	Inhibited HaCat keratinocyte proliferation in a concentration-dependent manner	[49]
Spasmolytic, bronchodilator and vasodilator activities	*In vitro*	methanol extract	K+ (80 mM)-induced contractions in isolated rabbit jejunum	Verapamil	0.1–5.0 mg/ml	The extract exhibited inhibition of the spontaneous contractions in a dose dependent manner, also caused a dose dependent relaxation of K+ (80 mM)-induced contractions	[47]

Clinical pharmacology

Many clinical trials were performed to evaluate the efficacy of *M. communis* L. in skin disorders, haemorrhoid, aphthous stomatitis, chronic rhinosinusitis, BV, abnormal uterine bleeding and HSV-1 infection. Detailed study is mentioned in Table 4.

Table 4: Clinical trial with MC

S. No.	Clinical study	Doses form	Subject	Trial type	Standard drug	Observation	Ref.
1.	Therapeutic effect of MC in recurrent aphthous stomatitis (RAS)	Mouthwash with MC five times a day, preferably after oral hygiene for seven days	150 patients with history of RAS (occurring at least 3 times a year)	Randomized, single-blind, placebo-controlled clinical trial	Adcortyl ointment	No significant difference in the meantime of ulcer healing compare with standard drug	[66]
2.	Compare the effect of MC and anti-haemorrhoid ointments in haemorrhoid	60 gm MC ointment	134 women in the postpartum period with grade I and II haemorrhoid. (aged 18–40 years)	Triple-blind randomized controlled trial	Anti-haemorrhoid ointment (contain hydrocortisone acetate, aluminium sub-acetate, lidocaine and bicarbonate oxide)	1. ↓ severity of all symptoms of haemorrhoid in both groups, 2. Mean of anal itching significantly lower in the MC group	[67]
3.	To verify the effects of MC essential oil in acne and skin irritation	MC essential oil every morning and evening for 6 weeks	20 Korean women those who have not used any acne treatment	Two group simple randomize trial	----------	MC essential oil is a safe effective substance for treating acne with skin-soothing effects from the results of reduced erythema	[68]
4.	To assess the effects of MC aqueous extract in the treatment of chronic rhinosinusitis.	Aqueous extract of fruit of the plant MC for one month	38 patients (18 – 68) age	Double-blinded randomized placebo-controlled trial	---------	According to the SNOT- 22 parameters, symptoms improved in the treatment group after treatment in most parameters	[69]
5.	To evaluate the efficacy of MC solution in dandruff	MC solution for 30 days	90 individuals aged 18-60 years	Double-blind randomised clinical trial	Ketoconazole shampoo	1. Both groups showed significant improvement in all outcome 2. No significant differences in terms of efficacy, satisfaction rate and side effects	[70]
6.	To evaluate the therapeutic effects of the vaginal gel of MC in BV	MC 2% (in metronidazole base) for five consecutive nights	80 Married women of 18-40 years	Double blind randomized clinical trial	Metronidazole vaginal gel	The combination of metronidazole and MC showed higher efficiency and the patients receiving MC in metronidazole gel base did not experience any recurrent BV	[71,72]
7.	To evaluates the effect of MC syrup in menometrorrhagia	15 ml MC syrup daily orally for 7 days starting from the onset of bleeding for 3 consecutive menstrual periods	30 women 20 to 55 years old, married women	Randomized, double-blind, placebo-controlled pilot study	----------	Significant reductions of bleeding duration and intensity of bleeding	[73]
8.	To investigate the impact of MC syrup on the recurrence of symptoms in reflux patients	MC syrup 5 mL after meal were prescribed for 6 weeks	89 patients 20 to 60 years old	Double-blind, randomized clinical study	Omeprazole 20 mg	Significantly delayed the onset of symptoms in test group	[74]
9.	To assess a relevant pharmaceutical dosage form of MC in reflux disease	MC berries freeze-dried aqueous extract, 1000 mg/d for 4 weeks.	Forty-five 18 to 60 years	Double-blind randomized controlled clinical trial	Omeprazole 20 mg/day	Significant changes were found in FSSG, dysmotility-like symptoms and acid reflux related scores.	[75]
10.	To investigate the efficacy of MC in warts	One-part leaves of MC and two parts of water	A 10 and 12-year-old girl who presented with history of a common wart on her neck and face	Case study	----------	The facial warts of both cases have completely cured by using MC	[76]
11.	To evaluate the efficacy of a paste containing MC in RAS	MC leaves oral paste four times a day for 6 days	45 patients with RAS (18–58 years)	Randomized, double-blind, controlled before–after clinical trial.	----------	Significant reduction in size of ulcer, severity of pain, erythema and exudation level, and no side effects were reported	[77]
12.	To compare the effect of MC fruits with tranexamic acid in the treatment of menorrhagia	Powdered MC fruits for first five days of menstrual cycle consecutively for two cycles	40 patients	Single blinded randomized standard control study	Tranexamic acid	1. Significant improvement in haemoglobin percentage 2. Marked improvement in overall quality of life in both groups	[78]
13.	To assess the efficacy of a novel herbal suppository, containing MC and oak gall (MOGS) in treatment of vaginitis	Freeze-dried powder of 10% aq. extract of MC and oak gall powder	120 women (18 to 55 years old)	Parallel randomized clinical trial	Metronidazole	MOGS effectively improved vaginal discharge and pH	[79]
14.	To evaluate the efficacy of a topical lotion prepared from MC essential oil of in the alleviation of haemorrhoids symptoms	MC lotion (30 mg 1, 8 cineole in each mL of product) for a period of two weeks	106 patients	randomized double-blind double-dummy trial	Anti-haemorrhoid ointment (containing hydrocortisone, lidocaine, aluminium subacetate and zinc oxide)	All evaluated symptoms (bleeding, permanent pain, pain during defecation, anal itching and irritation, heaviness and tenesmus) were significantly decreased in either of the study groups ($p<0.001$).	[80]
15.	To investigate the effect of an herbal suppository based on MC in cervicovaginal HPV infections	Vaginal suppositories (contained 10% of MC aqueous extract and 0.5% of MC essential oil) 20 suppositories at each menstrual cycle for 3	Sixty women, (18 to 50 years old)	Double-blinded randomized placebo-controlled trial	----------	MC vaginal suppository increases virus clearance and improve lesions of the cervix and the vagina with no serious side effects.	[81]

		months					
16.	To evaluates therapeutic Efficacy of different concentrations of MC in the treatment of RAS	MC extract 5% and 2.5% (10 drops on lesion for 20 seconds 5 times per day).	60 patients	Randomized, double-blind clinical trial	----------	The therapeutic efficacy of both concentrations of MC extract was similar and effective in decreasing RAS diameter, pain, and burning sensation	[82]
17.	HSV-1 infection	MC oil 3 to 5 times a day for up to 5 days	80 patients with HSV-1 infection	double-blind randomized placebo	----------	Duration and severity of clinical signs and symptoms in all patients [time of healing, complete crusting of lesions, pain and itching] were significantly reduced in test group by day 2, [p<0.01] compared with placebo-treated group	[83]
18.	To evaluate the efficacy of MC in reduction of the number and size of warts	Apply the paste topically on each wart twice a day for 40 days	100 patients 6-45 years old	Quantitative randomized controlled clinical trial	salicylic acid	MC showed more rapid response than salicylic acid and also fewer side effects.	[84]

10. Mechanism of actions

Fig 4: Shows in Mechanism of actions

11. Discussion and Conclusion

The present review verifies the real identity of Myrtle, summarizes its valuable description in Unani literature, and its medicinal efficacy in haemorrhoid, aphthous stomatitis, chronic rhinosinusitis, BV and other disorders. Phytochemical and pharmacological studies and clinical investigations on the crude drug and isolated principles proved the multipotent action of Myrtle. It is a long-used medicinal plant in various ethno-medical systems. Traditionally it is used to treat wide range of disorders and most of the traditional uses have been verified by scientific researches. A number of phytochemicals isolated from various part of the plants like terpenoids, alkaloids, glycosides, flavonoids, coumarins, tannins, essential oil etc. have shown a variety of pharmacological activities like antioxidant, antimutagenic, antidiabetic, Cardiovascular, anti-diarrhoeal, antiulcer, antimicrobial activities, etc. in various pharmacological trials. Among them, anti-haemorrhoid activity is the main activity that has been studied. These studies validate the pharmacological actions claimed by Unani physicians. In total, the extensive use and application of MC in the past, it has been studied inadequately. So, more clinical studies are needed to be specified this drug.

Conflict of interest

There is no conflict of interest to declare.

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