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Review

A Complete Review of Ethnopharmacology, Pharmacology and Phytochemistry of *Anacyclus pyrethrum* DC

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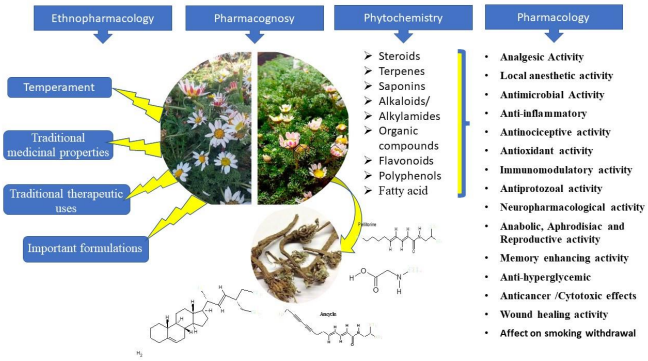
Abstract

Anacyclus pyrethrum DC is an important medicinal plant belonging to the family Asteraceae, indigenous to North Africa and found in the Arabian peninsula, the Mediterranean, and north India. It is a perennial herb known as Aqarqarha, Pellitory, Akarkara, or Spanish Chamomile. This herb is widely used in traditional medical systems such as Unani, Siddha, and Ayurveda systems of medicine. Its root has been traditionally employed to address ailments like toothache, gingivitis, dental caries, periodontitis, Ludwig's angina, migraine, epilepsy, hemiplegia, facial palsy, headache, hysteria, atony/flaccidity, tremor, nasal congestion, anaphrodisia, premature ejaculation, amenorrhea, coccydynia, sciatica, backache, polyarthritis, general weakness, rheumatism, cholera and edema. This review summarises studies gathered up to January 2022 from databases including PubMed, Scopus, ScienceDirect, Google Scholar, Wiley Online Library, ResearchGate, and Web of Science, using keywords such as *Anacyclus pyrethrum* DC, Aqarqarha, and Akarkara. *A. pyrethrum* is rich in bioactive compounds including saturated fatty acids (isovaleric acid, decanoic acid, lauric acid, myristic acid, octadecanoic acid, palmitic acid), unsaturated carboxylic acid (cinnamic acid), fructans (inulin), phenols, polyphenols, tannins, flavonoids, pellitorine, pyrethrin, anacycline, herculin, sesamin, polysaccharides, volatile oils, essential oils, propanedioic acid, levulinic acid, squalene, steroids, terpenes, saponins, and stigmasterol. Medicinal studies show that the plant exhibits a wide range of pharmacological properties, including antioxidant, antimicrobial, anti-inflammatory, antinociceptive, immunomodulatory, analgesic, antiprotozoal, neuroprotective, anti-hyperglycemic, wound healing, anticancer (cytotoxicity), anabolic, aphrodisiac, and reproductive activities, as evidenced by *in vivo, in vitro*, and clinical studies. This manuscript provides a comprehensive overview of the traditional uses, phytochemistry, and pharmacological activities of *A. pyrethrum*, identifying significant gaps and research objectives, especially regarding the active compounds and their mechanisms of action.



Keywords: Anacyclus pyrethrum DC; Aqarqarha; Traditional medicine; Unani medicine; Natural products

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Introduction

Anacyclus pyrethrum, DC, commonly known as Aqarqarha, Pellitory, Akarkara, or Spanish Chamomile, is an important medicinal plant belonging to the Asteraceae family. Indigenous to North Africa [1], this plant also grows in the Arabian Peninsula, the Mediterranean, and north India (Figure 1). *A. pyrethrum* is one of several species in the *Anacyclus* genus. This herb is widely used in several traditional medical systems, such as Unani, Siddha, and Ayurveda.

A. pyrethrum is a perennial herb whose root is used as medicine. The root has a characteristic fragrance; its outer surface is brown and wrinkled from where it breaks down. When chewed, it has a pungent taste, stimulating saliva production and creating a tingling sensation in the throat accompanied by a sharp, prickling feeling [2]. The root is traditionally used to treat sexual dysfunction, dental and gum issues, epilepsy, aches and pains, colds, headaches, nerve weakness, numbness, oral and throat ailments, sciatica, and arthritis. In addition, it acts as a body tonic or stimulant, aphrodisiac, and muscle relaxant.

A. pyrethrum is a valuable medicinal plant with a diverse range of applications. Various dosage forms are prepared from this plant, such as powders, decoctions, oils, ointments, pills, toothpowders, pastes and more. It also plays an essential role in treating ailments in different regions. For example, in Turkey, it is traditionally applied as a stimulant, insecticide, rubefacient, and mouthwash. At the same time, it is also recognised for its effectiveness in managing conditions like toothaches and various aches in other regions, including Europe and the UK [3].

This review explores the ethnopharmacology, phytochemistry, and pharmacology of *A. pyrethrum* to provide a comprehensive understanding of its traditional uses, active compounds, and medicinal properties. It highlights recent scientific insights and identifies gaps in existing research to further explore the active compounds and their mechanisms; thus, contributing to the scientific validation and therapeutic potential of *A. pyrethrum* in modern medicine.

Here is the Scientific /Taxonomical Classification [4,5] of *A. pyrethrum,* and table 1 [6] shows synonyms and vernacular names of the plant.

Kingdom: Plantae
Division: Spermatophyta
Sub Division: Angiosperms
Class: Dicotyledons
Sub Class: Metachlamydae
Order: Companulatae
Family: Compositae or Asteraceae
Genus: *Anacyclus*
Species: *pyrethrum*
Botanical Name: *Anacyclus pyrethrum* DC.

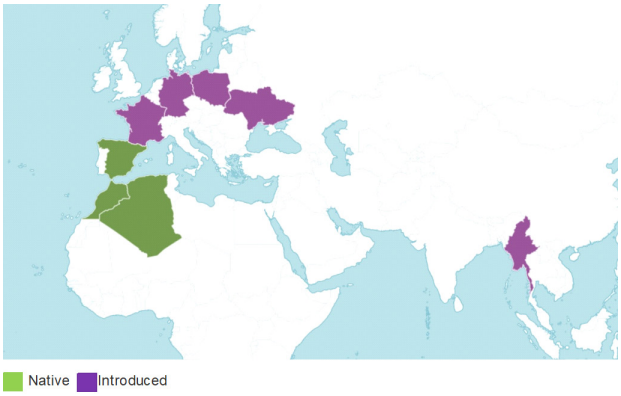


Figure 1. Distribution of Anacyclus pyrethrum DC [6] http://www.plantsoftheworldonline.org/taxon/urn:lsid:ipni.org:names:941366-1

Materials and Methods

A. pyrethrum was explored in classical Unani literature for its temperament (*Mizaj*), medicinal properties, and therapeutic uses. Urdu translations of the classical books such as Al Jami ul Mufradat Al Advia Wal Aghzia of Ibn al Baithar (1197-1248 AD), Muheet Azam of Hakeem Mohammad Azam Khan (1806–1902 AD), Khazainul Advia of Najmul Ghani, (19th century), Al Mukhtarat fit Tib of Ibn Hubl Baghdadi (1122 -1213 AD), Bastanul Mufradath of Hakeem-Muhammad Abdul Hakeem, Mufradath e Azeezi of Hakeem Mohammad Abdul Haleem, Kitabul Umda fi Jarahath of Ameenudawla Abuwal Faraj Ibn Al-Qaffa Al-Masihi, Kanzul Advia Mufrada of Muhammad Rafiquddin, Kitab Ul Kulliyath (Urdu Translation) of Abu Al Walid Ibn Rushd (1153 -1169 AD), Kitab al-Fath fi al-Tadawi (Urdu Translation) of Abu Saeed Bin Ibrahim Ahrabi, Makhzan-ul-Mufredath (Kitabul Adviya) by Allama Hakeem Mohd. Kabeeruddin (1894-1976AD) and Al Qanoon fil Tibb by Ali Ibn Sina (980-1037AD) were conferred. Published works available on PubMed, Science Direct, and Google Scholar were referred to collect all the information regarding its phytochemicals and pharmacological studies. Standard Unani Medical Terminology, published by the Central Council for Research in Unani Medicine in collaboration with the World Health Organization, was used to describe the appropriate Unani terminologies. National Formulary of Unani Medicine, Standardisation of Single Drugs of Unani Medicine, and the Unani Pharmacopoeia of India published by the Central Council for Research in Unani Medicine in collaboration with the World Health Organization were also used to describe Unani terminology and botanical name of Unani single drugs. The name of the plant was checked on the www.theplantlist.org website. Chemsketch was used to draw the Chemical Structures of the phytochemicals, and Pubchem was used to find the PubChem CID

Table 1. Synonyms and Vernacular names of *A. pyrethrum*

Synonyms	*Anthemis pyrethrum* L. *Anacyclus officinarum* Hayane [6–8]
Vernacular names	
Unani name / (Greek)	Forthun, Qaws Dara and Qubrun, Aaqarqarhaa [9,10]
Ayurvedic	Aakallaka, Aakulakrit, Agragraahi [11]
Arabic	Aqarqarha, Oodul-qarah [9,12–14] Damascus dialect - Od al-Qarhin [10] Barbarian dictionary – Tafand, Shirazi – Akluana [10]
Sanskrit	Akarakarabha, Akarkara, Akalka [13], Akarakarava [15]
Persian name	Kakarah, Kaloo, Kalooh, Kazdam, Akova [9], Beekh Tarkhoon [16], Beekh Tarfoon [13], KartarKhon [10], Beikh-e-Tarkhun Kohi, Kakrah [12], root - Beq Tarkhun Kohi
Hindi	Akarkarah [10,12,14,16], Aarkarah [15,16], Akalkara [13]
Urdu	Aqarqarha [4,12]
Bengali	KuraKura [16], Akarkara [12,13,15]
Marathi	Akalkara [13], Akkalkadha [4]
Gujarathi	Akorkaro [12,13]
Kannada	Akkal-kare [12]
Tamil / Siddha	Akkalkadha [12], Akkirakaram [4,15]
Telungu	Akarkaram [13,15], Akkirakaram [4]
Malayalam	Akkilakaram, Akkikaruka [4,17]
French	Racine de pyrethre d " Afrique [4]
English	Pyrethrum Root [11,12] Spanish Pellitory [12], Pellitory [11,15]

of those chemicals.

Botany and Ethnopharmacology

Botany

The plant is native to North Africa and is commonly found in Algeria. It was later introduced into southern Europe and cultivated in the Arabian peninsula and North India. This plant has two varieties: *Anacyclus pyrethrum* var. *pyrethrum* (L) and *Anacyclus pyrethrum* var. *depressus* (Ball) Maire. These two varieties differ morphologically in flower head size, root length, and petal back colour (Figure 2). However, they share the same chemical components with few exceptions [18-20].

A. pyrethrum is a perennial and procumbent plant with numerous stems and downy branches. It grows erect towards the ends, with the upper portions being more or less hairy and the lower portions nearly smooth. The leaves are radical, stalked, smooth, and pinnatisect into linear, subulate segments. Cauline leaves are sessile. The branches are one-headed, with lanceolate and acuminate involucral scales that are brown at the edge. The receptacle is convex [7,12,21]. The root is cylindrical, slightly twisted, vertical, and branched, measuring 8 to 12 cm long and 0.5 to 1 cm thick. Externally, the roots appear brown with bright black spots and are rough, shrivelled longitudinally, often topped with a cluster of grey hairs. The root is brittle and breaks with a close, compact, resinous fracture. Internally, radiating secondary wood occupies about two-thirds of the total thickness, particularly in older roots; while the pith is nearly obliterated.

(**a**) (**b**)

(**a**): *Anacyclus pyrethrum* var. pyrethrum (L.); (**b**)*: Anacyclus pyrethrum* var. depressus (Ball) Maire.

Figure 2. Two varieties of *A. pyrethrum* [19]. Reproducted with permission from Jawhari et al., Plants, 2021, 10, 149 https://www.mdpi.com/2223-7747/10/1/149/htm#fig_body_display_plants-10-00149-f003

The root is characterized by an aromatic odor and a persistent pungent taste, inducing excessive salivation and a pricking sensation in the mouth and throat [1,12,21,22]. Leaves are long-stalked, alternate, and arise singly from the root crown. They are ovate or oblong in outline, more or less hairy or nearly glabrous, deeply bipinnatisect, with linear and acute segments. The terminal heads are large, measuring 1-1 ½ inches or broader, ovate-lanceolate, varying in width, and blunt or subacute. They are smooth, pale green, and bordered with a brown edge. The receptacle is slightly convex, with large obovate, rounded transparent scales beneath the flowers [21]. The flowers of *A. pyrethrum* exhibit distinct characteristics: the disk flowers are bisexual, possessing a tubular corolla contracted below with five equal triangular spreading teeth, coloured yellow. Their anthers are apiculate, not tailed at the base, and are included within the corolla; while the style is exserted and bears a bifid stigma with two linear branches.

In contrast, the ray flowers are female, with a ligulate corolla arranged in a single row. Their limb is broadly oval, trifid at the apex, predominantly white above, and tinged with bright pink below. Fruit dorsally compressed, obovoid, smooth, the outer ones drawn out once at least drawn at each edge into a narrow wing, more or less deeply denticulate above forming a short scarious pappus, and prolonged ones at the sides into two short auricles. It is propagated by seeds. The flowering and fruiting take place during the winter season (April-June). The stem bears one large flower at the end of each branch, with a yellow disk and white colored rays, and it is tinged with purple beneath [12,21].

Cultivation

A. pyrethrum is cultivated in tropical regions at altitudes of 1500 to 3500 meters, requiring dry to soft sandy soil, an average of 800-1300 mm of rainfall, temperatures between 15-25°C, and sunny intervals between rainfalls for optimal growth [23]. Propagation methods include seeds, root division, and slicing (cutting). When cultivated from seeds, they were sown in February or March, thinned to 2-3 inches between plants, and transplanted to permanent locations by early June with about one foot between plants and two feet between rows, preferably on rainy days for optimal establishment. Hand weeding was used, as hoeing could damage young plants.

For division-based propagation, plants were lifted in March or when roots were rough and compact, somewhat fusiform, approximately finger-sized, and often topped with leaf remnants. These roots, outwardly brown and deeply fissured, were cut into strips. Cuttings were taken from the plant base, with a portion of the old plant attached to encourage rooting. Cuttings were planted in light, sandy soil beds from October through May, with leaves trimmed to about 3 inches before planting. Beds were then covered with sand, regularly watered, and shaded while cuttings were rooted [5,24].

Properties of Anacyclus pyrethrum DC in Unani system of medicine

Temperament (Mizaj)

Temperament (Mizaj) is a fundamental principle in the Unani system of medicine that helps understand drug action and disease processes. A person's temperament and substance provide a conceptual foundation for effectively utilizing the drug, forecasting its effect on the body, and determining drug potency. A drug's temperament is defined by the type and amount of bodily deviation caused by pharmacological activity after it has been administered. Physicians have divided the medications into four qualities *(Kaifiyat)* based on their impact on a moderate human body: hot (*Har*), cold (*Barid*), dry (*Yabis*), and moist *(Ratab)*. The drugs were then divided into four categories (degrees) based on how strong their effects were. Most medications function by counteracting a disease condition with the opposing temperament.

According to Unani medicine, *A. pyrethrum* is considered as Hot 3^0 and Dry 3^0 (*Har Yabis* 3^0) [15-17,25-29], and some books mention it as Hot and Dry 4^0 [9] or between third grade to the fourth grade [10,30].

Parts Used and Dosage Forms

The roots of *A. pyrethrum* are primarily used for medicinal purposes and prepared in various dosage forms for internal and external applications. Traditional forms as single ingredient as powder (Safoof) in a dose of 0.5-3.5 grams and as an ingredient in many formulas shown in Table 2 like decoctions (*Joshanda*), oil (*Roghan* for external application), oral semi-solid forms (*Khameera* and *Majoon*), pills (*Habb*), liniments (*Tila*), tooth powders and dentifrices (*Manjan*), smoke, compound powders (*Safoof*), and pastes, as well as linctus (*La'uq*) [1,9,10,14,15,27]. Some sources also mention the medicinal use of flowers and leaves, although these are less commonly utilised [1].

Traditional medicinal properties

A. pyrethrum is traditionally valued in Unani medicine for its diverse therapeutic properties, primarily derived from its roots, which have been described with the following actions:

Nervous System Benefits- The root acts as an aphrodisiac, sexual stimulant/tonic (*Muqawwi-e-Bah, Muharrik-e-Bah*), retentive of semen (*Mumsik-e-Mani*) [12,14,16,25,29,31], mild anaesthesia (*Khafeef-i-Mukhaddir*) [2,14,30–32], functions as an analgesic in tetanus (*Musakkin-e-Alam fil Kuzaz*) and local

anaesthetic (*Mukhaddir Kharji*) [4]. It is also a nerve tonic [7,15] and nervine stimulant (*Muharrik-e-A'sab*) [2,29], helping with nervous debilities and addressing anti-stammering properties (*Naaf-e-Luknath*). Additionally, it removes matter from the brain/brain purifier, specifically phlegm *(Munaqqi-i-Fuzlat-i-Dimagh, Mushil-e-Balgham*) [2,10,14,16,26,30].

Respiratory and Digestive Support- The root is very effective for phlegmatic disorders and removes phlegm (*Munaqqi-e-Balgham*) [14,16] from various parts of the body. It is a sialogogue (*Mudirr-e-Lu'ab/ Lu'ab-e-Dehan*) ([4,16])[1,2,7,11,14,15,30,32], and an expectorant. As an expectorant, it eases phlegm expulsion (*Munaffith-i-Balgham*) from the respiratory system and acts as a detergent (*Jali*) in the respiratory system [26]; while its emetic properties help clear phlegm from the brain and regularly support respiratory health [26,33]. It is a deobstruent (*Mufattih-e-sudad*) [10,14,16,25,26,29,32]. It supports digestion and purges phlegm (*Munaqqi-e-Balgham*) from the stomach and intestines [26,33]. It serves as an antispasmodic, stomachic, and anti-helminthic [25,33].

Skin and Muscular Health- The plant root is a pungent, rubefacient [1,11,17], and irritant [7,9,15], enhancing blood flow to treat skin and muscle stiffness (externally). As an anti-flaccidity (*Naaf-i-Istirha*) [25], it is useful in toning nerves and muscles. Its diaphoretic action induces sweating (*Mudirr-e-Arak*) [10,14,32].

Reproductive and Urinary Health- *A. pyrethrum* promotes menstrual health as an emmenagogue (*Mudirr-e-Hayd*) [10,14,16,32,33] and supports urinary health through its diuretic (*Mudirr-e-bole*) [2,10,25] effects.

Anti-inflammatory and Analgesic Properties- The plant root is an effective anti-inflammatory agent [7,32,34], relieving conditions like arthritis. It has analgesic [32] and sedative (*Musakkin*) [1] properties, alleviating dental pain (*Musakkin-e-Dard-e-Dandan*) [26,29] and reducing general pain. Its resolvent action (*Muhallil*) helps dissolve thick humors, and it acts as an absorbent (*Jadhib*) [10,26].

Additionally, *A. pyrethrum* is recognized as a galactagogue (*Mudirr-e-laban*) [2,10,25], a cardiac tonic (*Muqawwi-e-Qalb*) [35], and a warming agent for humors (*Musakhkhin-e-Akhlath*) [16]. It also functions as a general tonic (*Muqawwi-e-Aam*) [36] and stimulant (*Muharrik*) [1,9–12,17,35], promoting overall vitality.

Principal action/specific action (Nafae Khas)

Although a drug has several functions, some predominantly occur, called *Nafae Khas* or Principal action. The main actions/functions of *A. pyrethrum* are sex stimulant and tonic and brain purifier [29].

Traditional therapeutic uses

Traditionally, the root of *A. pyrethrum* was used in various dosage forms in medicine [15]. This plant is used in conditions in the mouth and throat like toothache [2,9,14,32,35,36], gingivitis (*Warm al-Litha*), paralysis of the uvula (*Istirkha'-i-Lahat*) [2], dental carries, instability of teeth, pyorrhea (periodontitis) [32], hoarseness (*Buhha al-Sawt*) [2], hanging of the epiglottis and atony/flaccidity of the tongue, glossoptosis [10], Ludwig's angina (*Khunaq*). The *A. pyrethrum* is also indicated in various neurological conditions like migraine (*Shaqiqa*) [17], relaxing limbs and numbness, chronic atony and sensory loss in nerves, paralysis, epilepsy, hemiplegia, facial palsy, tremor (*Ra'sha*), tetanus (*Kuzaz*), headache [16], and hysteria [30].

The decoction of *A. pyrethrum* is used alone or with other medicines for various oral conditions. For example, Ibn Baithar mentioned that decoction with vinegar relieved toothache [9]. It is also beneficial in hanging epiglottis and atony/flaccidity of the tongue caused by the temporary dominance of phlegm (*Balgham*) - (by Ishaq bin Imran) [9]. According to Ibn Sina, keeping the decoction made in vinegar in the mouth for a few minutes will strengthen the shaking or unstable teeth (*Tarkah-ul-Asnan*) [9,10,27]. Rinsing the mouth with decoction in water or vinegar relieves toothache caused by cold (*Barid Waj al Asnan*) [10,27,30], pharyngitis, sore throat, tonsilitis [7,15], Ludwig's angina, uvuloptosis and mucous glossoptosis [10]. Toothpaste made from *A. pyrethrum* and honey relieves toothache [13,30].

Because of its sialogogue (*Mudir-e-Luab*) and mild anaesthetic (*Mukhaddir*) action, its fine powder (*Butur* and *Sanoon*) can be used in toothache, atony of uvula (*Istirha-e-Lihath*) and Ludwig's angina [37]. According to Allama Hakeem Mohd. Kabeeruddin, a piece of *A. pyrethrum* pressed against the carried tooth, also relieves toothache [16].

Applying fine powder of *A. pyrethrum* soaked and cooked in vinegar (fermented) inhibits dental caries. It has been used as a masticatory or massage on the tongue for its reflex action on the salivary gland.

When used *A. pyrethrum* with *Pistacia lentiscus* Linn/ Mustagi *(P. lentiscus*) or Mineral Pitch-Asphaltum/Bitumen (Zift*)*, it removes phlegm from the mouth and throat, thus improving hoarseness of voice and Ludwig's angina, and also it is useful in chronic cough and chronic colds [9,10]. Chewing *A. pyrethrum* root or applying its tincture and iodine tincture in the ratio of 1:1 with the help of a cotton wool ball relieves toothache. A mix of *A. pyrethrum*, *Chlorophytum borivilianum* Santapau & R.R.Fern. (Moosli) and milk is applied to relieve toothache. *A. pyrethrum* powder mixed with Camphor (1:1) rubbed on the teeth is beneficial for all kinds of toothache [30].

Due to its action of brain purifier and nervine stim-

ulant action, it removes the morbid matter from the brain and is used in facial palsy, hemiplegia, atony/flaccidity (*Istirha*), tremor, tetanus, headaches [2,10,14,16,26,30,31] and migraine [17]. Due to its nerve stimulant action, massage with its decoction/oil/ mixed with rose oil treats chronic atony and sensory loss in nerves [10,27], epilepsy, migraine and paralysis in Unani medicine. Galen recommended its use to relax limbs and cure numbness [9]. Some physicians mentioned that *A. pyrethrum* with olive oil benefits tetanus, numbness, chronic flaccidity, especially paralysis and epilepsy [9,10,14].

Oral use of *A. pyrethrum* root in honey and the local application of powdered root under the tongue benefit facial paralysis [7]. For epilepsy, it is given in honey. Sitz bath (*Abzan*) in its decoction also benefits these disorders. In paralysis patients, 2 g of *A. pyrethrum* is given to evacuate/purge unripe phlegm (*Balghum Kham*). Massage with the decoction of *A. pyrethrum* on the head provides warmth to the head and prevents cold. Application of a paste of almond in the decoction of *A. pyrethrum* on the forehead relieves frontal headaches [9,10,14].

It is highly deobstruent for nasal obstructions. Powdered root used as snuff clears the nasal obstruction/ sinuses and relieves headaches, chronic/cold migraines (*Shaqiqa Barida*), nasal congestion, and epilepsy. Massage with *A. pyrethrum* oil alone or combined with olive oil causes excessive perspiration. So it is useful in numbness (*Khadar*), tetanus, hemiplegia, atony/flaccidity, facial palsy [10,27,30,36], tremor, coldness, tingling, trembling and shivering [9,10,26-28]. The amount of 24-36 g of *A. pyrethrum* powder mixed in honey and licked 2 or 3 fingers at bedtime improve general weakness [30]. *A. pyrethrum* is also used in pediatric conditions; a gentle tongue massage with *A. pyrethrum* root powder improves delayed speech, stammering and glossoptosis in children [9,13,28,30]. Massage with *A. pyrethrum* oil on limbs is beneficial for paresis and plegic limbs [9,16,30].

Licking of *A. pyrethrum* mixed with honey relieves chronic cough and atony of tongue and stammering [2,10,16,31,32]; Abu al Salath mentioned that oral use of 9 g *A. pyrethrum* expels phlegm; it is also useful in the recurrent cold. *A. pyrethrum is* also beneficial in Cough (*Surfa-i-Bulgami*) [2], and insufflation (*Nafukh*) of it in the nose clears nasal obstruction [10]. The ointment from *A. pyrethrum* root is good for pneumatic phlegmatic inflammation [28].

A. pyrethrum root is a well-known and popular aphrodisiac medicine among traditional physicians; oral use of *A. pyrethrum* root stimulates libido and strengthens the organ [9,14]. Being an anaesthetic also causes a delay in ejaculation; It is also included in compound formulations for aphrodisiac activity. Its oil may be used locally for its aphrodisiac activity [14,16,26]. In females, its decoction regulates mensuration. In addition, a decoction of the *A. pyrethrum* is beneficial for treating edema and ascites [10,30].

Massage with *A. pyrethrum* mixed with *Juglans regia* L. oil (walnut oil) relieves pain and arthritis; For example, coccydynia, sciatica, backache, knee pain and polyarthritis (*Waj Al Mufasil*) [10,14,30]. A Decoction of *A. pyrethrum*, *Bacopa monnieri* L. (Brahmi), and *Evolvulus alsinoides* Linn (Sankhaholi) or a powder of *A. pyrethrum* and cloves relieves laziness and fatigue [30,36].

Ancient physicians used *A. pyrethrum* to treat indigestion induced by cold intemperament. The amount of 7 g of *A. pyrethrum* root powder mixed with honey expels unripe phlegm (*Balgham Kham*) from the stomach [9]. *A. pyrethrum* root powder and ginger cure indigestion and bloating and strengthen the stomach [30]. Its decoction is beneficial for dry cough and cardiac disorders/heart diseases. It is an important ingredient of some Unani compound formulations used for colds, flu, chronic cough, and rhinorrhea [13]. A pinch of *A. pyrethrum* with *Swertia chirayita* Roxb. (Chiraitah*)* relieves the continuous fever. A pinch of *A. pyrethrum* with *Itrifal* (*Phyllanthus emblica, Terminalia chebula* and *Terminalia bellirica*) and sugar relieves urinary obstruction [30]. Local application of *A. pyrethrum* mixed in vinegar is useful in vitiligo/ leukoderma [26].

The ancient Ayurvedic physician Charaka mentioned it as a '***Vajikaran Rasayana***' (a particular category of immunomodulators). According to Ayurveda, *A. pyrethrum* reduces vitiated *Kapha* and *Vata dosha*s (*Kapavatha Shamaka* and *Nadi Uttejana*). The flower head is cooked with milk and given for erectile dysfunction to promote sexual power, delay ejaculation time, and act as a sexual stimulant. A gargle of the flower head or root powder infusion is used for tonsilitis and sore throat; a gargle prepared from the root is used for gingivitis, aphthous ulcers, toothaches and dental caries. In case of urine retention, it is used with ghee. Moreover, the root is used in conditions like bradycardia and general debility [38,39].

In Ayurveda, the root of *A. pyrethrum* is indicated in sciatica, hemiplegia, paralysis, and amenorrhoea and is also used for toothache neuralgic affection on rhinitis. For epilepsy, the root of *A. pyrethrum* is used with the root of *Withania somnifera* (Asgand) and *Vitis vinifera* (Maweez Munakka) [11,38]. An Ayurvedic formulation, ***Aqrqarha Vati*** contains *A. pyrethrum, Myristica fragrans* Houtt. (Jawtri / nutmeg mace), *Cinnamon zeylanicum*/ *Cinnamomum verum*, *Argyreia nervosa* (Beeh-e-Samandashokh) and *Opium pure*. Another Ayurvedic formulation, ***Aqarqarha Adi Choran***, contains *A. pyrethrum*, dry *Zingiber officinale* Roscoe rhizome, cold sugar, *Crocus sativus* L., *Rhododendron ferrugineum* L., *Myristica fragrans*

Houtt seeds, *Syzygium aromaticum* L. (Qaqila / clove) dry flower buds, and *Santalum album* L. wood. Both drugs are used for sexual weaknesses [13]. Six grains of ***Akara Karabbadi Churna*** were used for impotence and chronic bowel complaints [15]. In facial paralysis, hemiplegia and epilepsy, it is used as a nerve tonic, and it is also used for rheumatism, cholera, edema and sciatica. Ayurvedic physicians used *A .pyrethrum* as a local application for headaches [40]. *Akarakarabadi yoga, Akarakarabadi Avaleha, Choipachinyadi Choorna* and *Kumaryasava* are some other important Ayurvedic formulations of this drug [38].

Dose

According to traditional Unani practice, the dose should be adjusted to suit the patient's age, temperament (*mizaj*), and severity of the condition [14]. The Maximum dose is 3.5 g, and the minimum is 1g [14]. The therapeutic doses of *A. pyrethrum* vary in classical texts based on the intended therapeutic effect. For general tonic and aphrodisiac purposes, the root powder dosage ranges from 1-3 g [29], with a typical effective dose of 2–3 g [12]. For use as an anti-inflammatory or analgesic, 0.5–1 g [11,13] may be prescribed. Higher doses, such as 2.75–3.5 g [10,30], are recommended for conditions requiring stronger effects, like deobstruent and phlegm-clearing actions.

Adverse effect (Muzir)

Because some medications have intriguing pharmacological action but may also have unfavourable side effects due to their inherent nature, they are subjected to appropriate correction measures (*Islah-e-Advia*) as prescribed in Unani literature to improve their therapeutic efficacy. In addition, the drugs are exposed to particular rectification techniques to lessen toxicity (*Amal- e-tadbeer*). If corrective steps on the drug are not practicable, a corrective agent (*Musleh*) is admixed or administered concurrently with the initial treatment to reduce the drug's expected adverse effects [30]. According to texts, the root powder of *A. pyrethrum* irritates the stomach and intestine in larger doses, causing bloody stools, tetanus-like spasms, and profound stupor [41], and prolonged use in lung diseases is harmful to the Lungs [10,14,16,25,26,30]. Seeds may Cause abortion in 15% of albino rats [34].

Corrective (Muslih)

To counteract the adverse effect of *A. pyrethrum*, *Sterculia urens* Roxb (Kateera) [1,10,14,16,25,30], *Vitis vinifera* [14,25] and dry extract of *Glycyrrhiza glabra* L. (Rubbusoos) [1,10,26,30], *Acacia arabica* (Samaghe Arabi) [29] are used as correctives.

Substitute (Badal)

Unani Medicine's primordial concept of *Abdale-e-Advia* (drug substitution/ therapeutic interchange) determines drug substitution principles. It is a critical concept in Unani pharmacotherapy and has been thoroughly described in single medications [42]. "The objectivity and utility of this medical system would be lost if the medicines required for the treatment of a particular condition were not available, and the physician was unaware of another possibility that may be used in place of the required drugs," Al Razi (865-925 AD) stated [42,43] as all crude drugs cannot be procured at all times at every clinical unit. As a result, when conventional pharmaceuticals are unavailable because they are endangered, expensive, rare, outlawed, or difficult to obtain, Unani drugs are used in their place. If the targeted substance is unavailable, a drug with a similar effect, temperament, physical qualities, or two or all of these is considered a feasible substitute [44–46]. Therefore, the Unani texts are mentioned substitute as follows;

In some books, *Piper longum* L./ Dar Fil Fil [1,29], *Plumbago zeylanica* L. (Seetraj /Seetraj Hindi) [10,26], *Alpinia galanga* (L.) Willd. / Khulanjan / Rasan, dried *Zingiber officinale*, *Mentha spicata* (Pudinah booti), and honey are mentioned as [14] substitutes for *A. pyrethrum*.

Some physicians mentioned substitutes of *A. pyrethrum* according to diseases or conditions, for example- *P. longum* with honey in liver diseases [10], *A. galanga* in stomach diseases, *P. longum* and honey are used as substitutes for liver disease; if *A. galanga* and *P. longum* are not available, the half dose of *Z. officinale* or *P. nigrum* can be used as a substitute of *A. pyrethrum* [10,30].

In gargle, one and a half part *Mentha sylvestris* [47]), *Piper cubeba* L.f. (Kababa) and *Syzygium aromaticum* for pharyngeal pain [10,30].

Important formulations (Table 2)

Anqaruya-e-Kabir, Barshasha, Jawarish- Zarooni Sada, Luboob Sagheer, Majoon-e- Baladur, Majoon-e-Salab, Raughan-e-Seer, Raughan-e-Sudab, Tila-e-Mulazziz, Sunoon- e-Mukrij-e-Rutubat, Habb-e-Falij Mulayin, Habb-e-Mumsik Qawi, Majoon-e-Zabeeb, Raughan-e-Qust, Sunoon-e-Mujalli, Sunoon-e-Muluk, Qairooti-e-Aarad-e- Karsana [12]. *Sanoon-Muhrij Rutoobath, Sanoon Majli Dandan* (tooth cleaning powder) [16].

Phytochemical constituents

It contains an acrid brown resin containing alkaloid pyrethrin, the active principle of the drug and tannic acid, gum, inulin, various salts, and lignin are also present. In addition, the cortical portion of the root contains five percent of pyrethrin and volatile oil. Furthermore, many researchers have found a crystalline sialagogue named pellitorine, which causes an intense

Table 2. Important compound formulations containing *A. pyrethrum*, their actions, dose and indications

Formulation	Dose	Actions	Indications	References
Semisolid preparations (example - Confection)				
Barshasha	1-3 g	Hypnotic, analgesic	Chronic cough, chronic catarrh, acute pain, coryza	[48]
Jawarish-Zarooni Sada	5-10 g	Renal tonic, liver tonic, brain tonic, stomachic	Excess urination, frequency of urination, renal problems, weakness of the liver, stomach, brain	[48,49]
Jawarish Zarooni Ambari	5-10 g	Renal tonic, liver tonic, stomachic, brain tonic, cardiac tonic, nerve tonic, spermatogenic, strengthen the spine	Weakness of the liver, stomach, and brain, excessive urination, frequency of urination, backache, and gout	[49,50]
Jawarish-e-Buqrath	5-10 g	Stomachic, aphrodisiac, digestive, carminative	Sexual weakness, indigestion, flatulence, sialagogue, hiccough	[51]
Labub Sagheer	5-7 g, 10 g with milk in the morning	Aphrodisiac, brain tonic, nerve tonic, cardiac tonic, renal tonic, spermatogenic	Weight loss, underweight impotence, premature ejaculation, loss of libido, anaphrodisia, spermatorrhoea and oligospermia	[49,50]
Jawarish e Qaiser	5-10 g	Laxative, carminative	Colic, chronic constipation	[51]
Majoon-e-Baladur	3-7 g [49] 5-10 g [48]	Aphrodisiac, nervine tonic, memory enhancer	Nerve and phlegmatic diseases, *neurasthenia,* amnesia	[48,49]
Majoon Muravvahul Arvah	1 g	Cardiac tonic, brain tonic, liver tonic, stomachic, memory enhancer, procurator of the latent energy of the body	Premature ejaculation, erectile dysfunction, general weakness, weakness of nerves, heart, brain, liver, stomach and memory	[49]
Majun Nishat Angaiz	6 g with milk or water	Aphrodisiac, nervine tonic, tonic for vital organs	Anaphrodisia, loss of libido, weakness of sexual power, sexual disorders, and weakness of vital organs	[52]
Majoon-e-Salab	5-10 g	Aphrodisiac, inspissant to semen	Anaphrodisia, attenuated semen	[48]
Majoon-e-Zabeeb	5-10 g	Deobstruent	Epilepsy	[48]
Anqaruya-e-Kabir	5-10 g	Nervine tonic, nerve stimulant, deobstruent	Facial palsy, hemiplegia, epilepsy, dyspepsia	[48]
Imsakeen	6 g before breakfast with water or milk	Retentive	Premature ejaculation	[52]
Qairooti-e-Aarad-e- Karsana	Local application (chest)	Anti-inflammatory	Pleurisy, mediastinal pleuritis, posterior mesodinitis, pneumonia	[48]
Oil				
Raughan-e-Seer	External Use	Nerve stimulant, anti-inflammatory	Hemiplegia, polyarthritis	[48]
Raughan-e-Sudab	External Use	Analgesic	Otalgia, coccydynia, shoulder pain, lumbago	[48]
Roghan-e-Naf-e-Falij	Local Application	Nerve stimulant, nervine tonic	Hemiplegia, facial palsy, nerve weakness, tremor, polyarthritis	[53]
Roghan-e-Qust	External Use	Nervine tonic	Hemiplegia	[48]
Liniment				
Tila-e-Mulazziz	External Use	Nerve stimulant	Lack of sexual pleasure	[48]
Tila e Musk-Wala	3 or 4 drops	Stimulate sexual organs	Massage three or four drops on the organic root and mouth, and tie the betel leaf on top	[13]

Tila Benazeer	Q.S* applied locally at bedtime	Stimulate sexual organs	Erectile disfunction	[52]
Tila-e-Khaas	Q.S* applied locally at bedtime	Stimulate sexual organs	Erectile disfunction	[52]
Tila Nishat Angez	Q.S* applied locally at bedtime	Stimulate sexual organs	Erectile disfunction, weakness of the Penis, atony of the penis.	[52]
Powder				
Sunoon Muqawwi Dandan	Toothpowder	Tonic for teeth, breath freshener	Yellow teeth, shaking of teeth, pyorrhea	[52]
Sunoon pyorrhea	Toot powder	Anti-pyorrheic, hemostatic, strengthen teeth and gums	Pyorrhea, bleeding gums, shaking teeth	[52]
Sunoon Wajaul Asnan	Toot powder	Sedative, analgesic, anti-inflammatory	Odontalgia	[52]
Sunoon-e-Mukrije Rutubat	Toothpowder Q.S*	*Habis* (styptic)	Bleeding gums	[48]
Sunoon-e-Mujalli	Q.S* Toothpowder	Detergent	Yellow teeth	[48]
Sunoon-e-Muluk	Q.S* Tooth powder	Analgesic	Odontalgia, ozostomia / halitosis	[48]
Sunoon-Mukhrij Rutoobat	Q.S* Toothpowder	Styptic	Bleeding gums	[48]
Sanoon Majlli Dandan	Toothpowder	Teeth Cleaning	To promote oral hygiene	[16]
Aqrqarha Manjan	Toothpowder	Analgesic	Toothache	[13]
Ali tooth powder	Toothpowder	Strengthening action	Weakness of teeth and gums.	[13]
Antidote				
Tiryaq Farooq	1 gm with 5 g Dawaulmisk and 5 g Khameera Gaozaban Ambari	Nerve tonic, concoction of phlegm, desiccant,	Hemiplegia, facial palsy, tremor, epilepsy, phlegmatic and nervine diseases	[49]
Tiryaq ul Asnan	Apply on painful teeth	Analgesic, galactopoietic, anti-inflammatory	Odontalgia, gingivitis, suppressed lactation	[51]
Tiryaq-e-Aqrab	3-5 g	*A*ntidote for scorpion bite, carminative, stomachic, tonic for viscera	Scorpion bite, colic, gastralgia, visceral pain	[51]
Linctus				
Laooq-e- Falij	Dose 5-10 g	Brain tonic, nerve tonic	Hemiplegia, facial palsy	[53]
Pills/tablets				
Habb-e-Falij Mulayin	5-10 g	Purgative, nerve tonic	Hemiplegia, facial palsy, constipation, neurasthenia	[48]
Habb-e-Mulazziz	250 mg-External	Retentive, sedative	Premature ejaculation	[51]
Habb-e-Mumsik Jadeed	Two pills with milk at bedtime	Retentive	Premature ejaculation	[52]
Habb-e-Nishat Jadeed	One pill with milk twice a day	Retentive	Anaphrodisia	[52]
Habb-e-Mumsik Ambari	420 mg	Retentive	Premature ejaculation	[50]
Hab-e-Mumsik Qawi	125-250 g	Retentive	Anaphrodisia, premature ejaculation	[48]
Habb-e Magziyath	250-500 mg	Expectorant, antispasmodic	Dry cough, sore throat	[51]
Habb-e-Beesh	150 g	Nervine tonic, analgesic	Neurasthenia, hysteria	[54]
Habb-e-Luknat	550 mg-1g	Nerve tonic, nerve stimulant	Stammering	[54]
Habb-e-Rasha	3 g	Nerve tonic, sedative	Tremor	[54]

*Q.S – Quantity sufficient

burning taste and copious salivation when chewed. Anacyclin has low insecticidal effects on grain insect *Tenebrio molitor* Linn. It also contains decanoic acid, dodecanoic acid and tetradecanoic acids. Total of 13 compounds of N-alkyl amides were identified in the ethanolic extract of *A. pyrethrum* using high-performance liquid chromatography (HPLC)/UV/ electrospray ionisation mass spectrometry (ESI-MS), which act as an aphrodisiac [5,18,23,41]. Among these thirteen, six were identified as new compounds, named undeca-2E,4E-diene-8,10-diynoic acid N-methyl isobutylamide, undeca-2E,4E-diene-8,10-diynoic acid isobutylamide, tetradeca-2E,4E-diene-8,10-diynoic acid tyramide, tetradeca-2E,4E,XE/Z-trienoic acid tyramide, tetradeca-2E,4E,XE/Z,YE/Z-tetraenoic isobutylamide and deca-2E,4E-dienoic acid N-methyl isobutylamide [23,55]. In addition, palmitic acid, naphthalene, 9,12-octadecadienoic acid (Z, Z)-, benzofuran 2-carboxaldehyde, decahedron-1,1-dimethyl-, 7- tetradecenal, (Z)-, N-isobutyl-tetradeca-2,4-dienamide and gamma.-sitosterol in ethanol extract of the root were revealed by gas chromatography-mass spectroscopy analysis [23,56]. (Table 3 shows Phytochemical constituents and their therapeutic action of *A. pyrethrum* DC.)

The antioxidant capacity of hydromethanol crude extracts of *A. pyrethrum* (root, leave and flowers) was determined through the 1,1 – diphenyl-2-picrylhydrazyl (DPPH) test. It exhibits effective antioxidative activity depending on polyphenol concentration, inhibiting the formation of free radicals and opposing macromolecule oxidation [23,57].

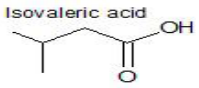
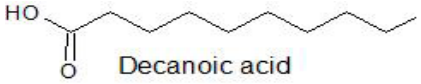
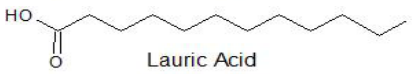
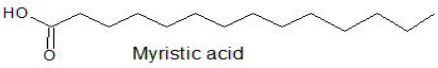
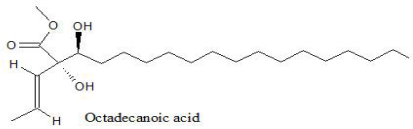
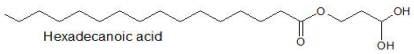
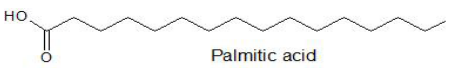
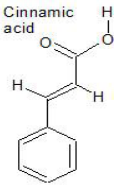
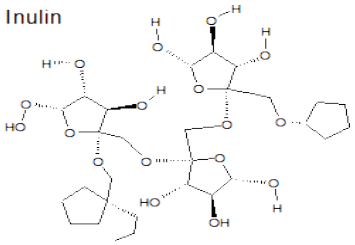
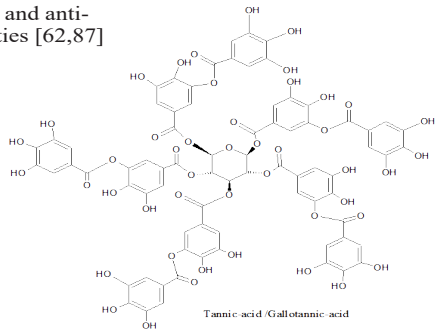
A study by Althaus et al. identified seven pure alkaloids on the root of *A. pyrethrum* by NMR- spectroscopic methods as deca-2E,4E-dienoic acid isobutylamide (pellitorine), deca-2E,4E,9-trienoic acid isobutylamide, tetradeca-2E,4E-dien-8,10-diynoic acid isobutylamide (anacycline), deca-2E,4E-dienoic acid 2-phenylethylamide, undeca-2E,4E-dien-8,10-diynoic acid isopentylamide, tetradeca-2E,4E,12Z-trien-8,10-diynoic acid isobutylamide and dodeca-2E,4E-dien acid 4-hydroxy-2-phenylethylamide. The column chromatography followed by the preparative HPLC method detected undeca-2E,4E-dien-8,10-diynoic acid 2-phenylethylamide and deca-2E, 4 E-dienoic acid 4-hydroxy-2-phenylethylamide [23,58]. The reversed-phase partition chromatography method separates decanoic, dodecanoic, and tetradecanoic acids from hydrogenation and acidic hydrolysis of the roots [23,59]. Furthermore, chromatographic HPTLC of the alcoholic extract of root expresses the picric acid, nitric acid, acetic acid, sulphuric acid, hydrochloric acid, ferric chloride, aqueous KOH, alcoholic KOH, ammonia solution and iodine solution [60,61].

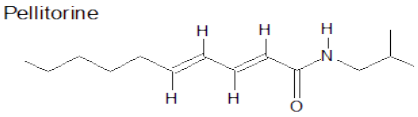
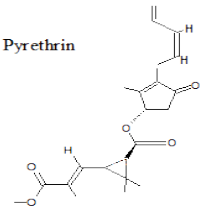
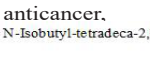
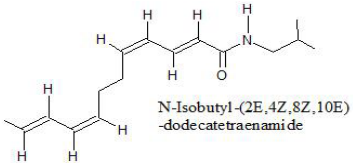
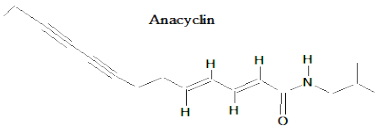
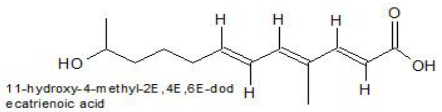
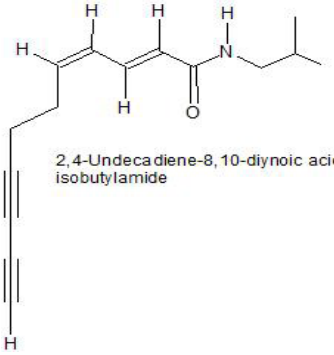
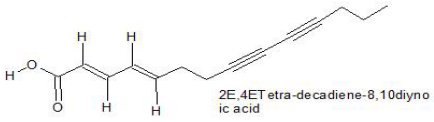
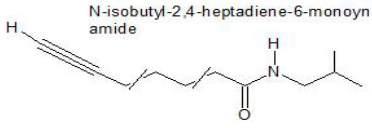
Pyrethrins obtained from the roots are a naturally occurring set of six chemically related esters, each insecticidally active. Pyrethrins-I, cinerin-I, and jasmolin-I are chrysanthemic acid esters; while pyrethrins-II, cinerin-II, and jasmolin-II are pyrethric acid esters. pyrethrelone, cinerolone, and jasmolone are the alcohol moieties found in pyrethrin 1 and 2, cinerin 1 and 2, and jasmolin 1 and 2, respectively [23].

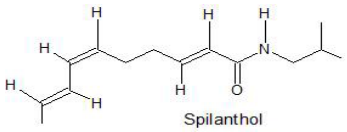
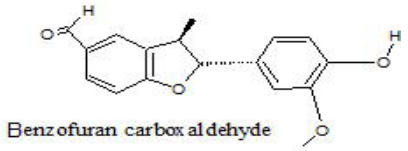
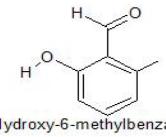
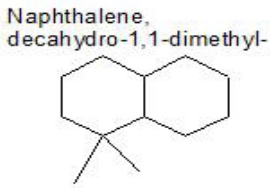
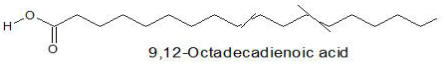
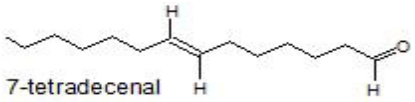
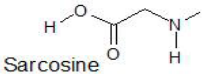
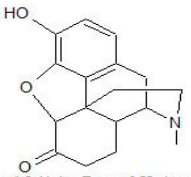
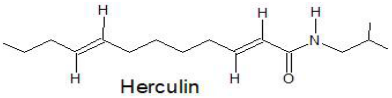
Chromatographic analysis of the studied extracts confirmed the presence of several components in the leaves, capitula, and seeds of *A. pyrethrum* var. *pyrethrum* (L.) and *A. pyrethrum* var. *depressus* (Ball) that might be involved in antioxidant and antibacterial activities [19]. The flowers contain more flavonoids, total phenol, and polyphenols than leaves and roots. On the other hand, the roots are rich in alkaloids, phenylethylamine, inulin, pellitorin, anacyclin, sesamin, and polyacetylenic amides I-IV. Tannins and flavonoids are rich in aerial parts. Ethanolic root, leaf, and stem extracts contain steroids, triterpenes, reducing sugar, sugar, alkaloids, flavonoids, saponin, tannins, anthraquinones and amino acids [23]. It also contains inorganic compounds like aluminium, iron, magnesium, and potassium in the root; leaves are rich in calcium, bismuth (Bi), Cu, Fe, K, Mg, Mn, Na, P, Se, Zn, and seeds contain more iron and copper [1,12,20,62].

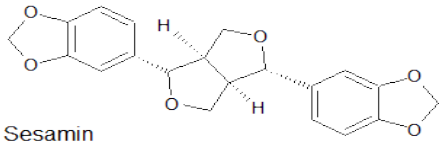
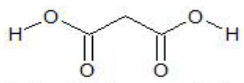
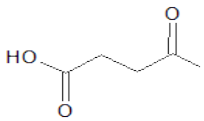
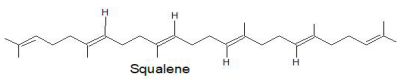
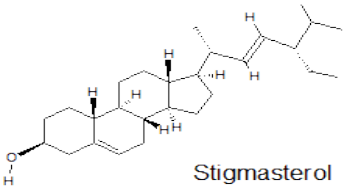
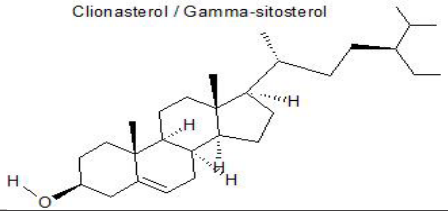
A study by Jawhari et al., 2021, studied twenty-two compounds of hydroethanol extracts of *Anacyclus pyrethrum* var. *pyrethrum* (L) Maire and *Anacyclus pyrethrum* var. *depressus* (Ball) Maire (roots, seeds, leaves, and capitula) by GC-MS after silylation. This study showed that both varieties share the same chemical constituent except for a few differences. N-isobutyl-2,4-heptadiene-6-monoynamide and cinnamic acid compounds reported in *Anacyclus pyrethrum* var. *pyrethrum* only and N-isobutyl-2,4-undecadiene-8,10-diynamide and thiadiazole [5,4-d] pyrimidin-7-amine compounds were limited to *A. pyrethrum var. depressus* (Ball) only. Moreover, in this study, among twenty-two compounds, levulinic acid, propanedioic acid; sarcosine, N-(trifluoroacetyl)-butylester; isovaleric acid, morphinan- 6-one; 2,4-undecadiene-8,10-diyne-N-tyramide and 4,5α-epoxy-3-hydroxy-17-methyl were detected newly [19]. In studies [41,63–65] several activities of pellitorine were identified (Table 3). Previously confirmed activities of Alkylamides (N-isobutyl-2,4-octadiene-6-monoynamide; N-isobutyl-2,4-heptadiene-6-monoynamide; (2,4)-N-isobutyl-2,4-undecadiene-8,10-diynamide; N-isobutyl-2,6,8 datrienamide) and N-isobutyl-dodeca-2,4,8,10-tetraenamide; showed on table 3 [19,55,66–68]. According to Hafizur et al. (2015), cinnamic acid significantly enhanced glucose-stimulated insulin secretion in isolated islets and exerted antidiabetic activity by improving glucose tolerance in diabetic rats in a dose and time-dependent manner and stimulating insulin secretion *in vitro* [19,69].

Table 3. Phytochemical constituents and their therapeutic action of *A. pyrethrum* DC

Main category	Chemical constituents present in *A. pyrethrum*	Parts of the plant	Therapeutic actions	Chemical structure
Saturated fatty acid	• Isovaleric acid	Seed, Leaves [20]	Antidyslipidemic, anticonvulsant [20,70]	
	• Decanoic acid (capric acid)	Root [23]	antibacterial, anti-inflammatory agent [71]	
	• Dodecanoic acid (Lauric acid)	Root [23]	Bactericidal [72], anti-inflammatory [71], antifungal and antiviral [73]	
	• Tetradecanoic acid (Myristic acid)	Root [23]	Antibacterial, anti-virulence properties [74]	
	• Octadecanoic acid, 2,3-dihydroxy propylester	Root [56]	Antibacterial cancer, antim	
	• Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl) ethyl ester	Root [56]	Antibacterial [75,77] anti-inflammatory [78]	
	• Palmitic Acid	Capitula [20,56]	anti-inflammatory [78,79]	
Unsaturated carboxylic acid	• Cinnamic acid	Leaves [41]	Antioxidant, antimicrobial, antitumor, antimycobacterial, antidiabetic activity [20,69,80–82]	
Fructans	• Inulin	Root [5,7,11,18,41]	Prebiotic, fat replacer, sugar replacer, texture modifier [83,84], antibacterial, immunomodulatory [85]	
Polyphenols	• Phenol and polyphenols	Flowers [23]	Antioxidant, antimicrobial [86]	
	• Tannins	Arial part (Leaves, Stem) [23]	Antimicrobial and antioxidant activities [62,87]	
Flavonoids	• Flavonoids	Flowers, arial part (leaves, stem) [23]	Antioxidant, antimicrobial [86]	-----

Alkaloids/ Alkyl-amides and N-Alkyl-amides	• Pellitorine (N-isobutyl-2E,4E-decadienylamide/ deca trans-2- trans-4-dienamide)	Root, seeds [7,11,15,17,18,20,40]	Insecticidal [63], antimycobacterial, antiplasmodial, and antifungal activities [64], sialagogue [41], cytotoxic activities [65]	
	• Pyrethrin	Root [7,11,15,17,18,20,40]	Insecticidal [41]	
	• N-Isobutyl-(2E,4Z,8Z,10E)-dodecatetraenamide	Root [5,7,11,18,41]	Anthelmintic [88]	
	• Dodeca-, and tetradeca trans-2-trans-4-dienamide, (N-Isobutyl-tetradeca-2,4-dienamide)	Root [5,7,11,18,41]	Antioxidant, antimicrobial, antiviral, anticancer, antithrombot flammatory, i modulatory, a antiprotozoal ic [20], hepatoprotective [89].	 
	• Anacycline	Root, seed, leaves and capitula [5,7,11,18,20,41]	Immune modulation [90,91]	
	• Dodeca-2E ,4E, nE-trienoic acid 4-hydroxyphenyl-ethylamide	Root, seed, leaves and capitula [20]	Insecticides [92]	
	• Undeca- 2E,4E-diene-8,10-diynoic acid N-methyl isobutylamide (undeca-2E,4E-diene-8,10-diynoic acid isobutylamide) / (2,4)-N-isobutyl-2,4-undecadiene-8,10-diynamide • Tetradeca-2E,4E-diene-8,10-diynoic acid tyramide, • Tetradeca-2E,4E,XE/Z,YE/Z-tetraenoic isobutylamide	Root, leaves, stem [23,55]	Antitumor [67] antimicrobial, insecticidal, antifungal, anti-inflammatory, immune-modulating, analgesic effects [66,93], antithrombotic, antiviral, antioxidant, antidiabetic, antiprotozoal activities [66]	 
	• N-isobutyl-2,4-heptadiene-6- monoynamide	Leaves [41]	Insecticide [93]	

	• N-isobutyl-2,6,8-decatrienamide/Affinin/ Spilanthol	Leaves [41]	Antimicrobial activity [94], antifungal [95], antinociceptive effects [96]	 Spilanthol
	• Benzofuran-2-carboxaldehyde	Root [56]	Antifungal [97], antibacterial [98]	 Benzofuran carboxaldehyde
	• Benzaldehyde, 2-hydroxy-6-methyl-	Root [56]	Antibacterial activity [99], aphrodisiac [100]	 2-Hydroxy-6-methylbenzaldehyde
	• Naphthalene, ' :ahydro-1,1-di- :thyl-	Root [56]	Cytotoxic, antioxidant, antitumor antiangiogenic, cholesterol-lowering activity, bacteriostatic and bactericidal effects [101]	 Naphthalene, decahydro-1,1-dimethyl-
	• 9,12-Octadecadienoic acid (Z,Z)-/ alpha-linoleic acid	Root [56]	improves learning and memory, prevents oxidative stress, neuroinflammation, and neuronal death caused by Aβ1− 42 in the hippocampus [102], antibacterial, antifungal [103]	 9,12-Octadecadienoic acid
	• 7-Tetradecenal, (Z)-	Root [56]	Sex pheromone [4,104]	 7-tetradecenal
	• Sarcosine, N-(trifluoroacetyl)-, butyl ester	Root, leaves [20]	Antidepressants [105,106]	 Sarcosine
Phenanthrenes and derivatives	• Morphinan-6-One, 4,5.Alpha.-Epoxy-3-Hydroxy-17-Methyl	Root, leaves, capitula [20]	Analgesic [107]	 Morphinan-6-One, 4,5.Alpha.-Epoxy-3-Hydroxy-17-Methyl
	• 2,8-N-isobutyl-2,8-dodecadienamide / Herculin	Leaves, capitula [20]	Myotonic electrical activity [108]	 Herculin

Other Organic compound	• Sesamin	Root [1,7,12,15,40]	Antioxidant, anti-inflammatory, antihypertensive, anti-atherogenic, anti-thrombotic, antidiabetic, anti-obesity, lipolytic properties [109,110]	 Sesamin
	• Polysaccharides	Root [111]	Antioxidant and anti-inflammatory activity [111], immunostimulating activity [112]	--------
	• Volatile oils	Root [1,7,12,15,40]	Antioxidant [113]	--------
	• Essential oils	Root [1,7,12,15,40,114], Aerial [115]	Antimicrobial and Anticandidal activity [114,115].	--------
	• Propanedioic acid	Leaves [20,41]	Antimicrobial, antiviral, anticancer, antiparasitic, anticonvulsant, antidiabetic, antihypertensive, antihyperlipidemic activities [20,116]	 malonic acid / propanedioic acid
	• Levulinic acid	Root Seeds [20]	Antioxidant, anticonvulsant, anti-inflammatory activities [20]	 Levulinic acid
	• Squalene	Root [56]	Anticancer properties [117], antioxidative activities [118], Antimicrobial [119], immune enhancing activity [120]	 Squalene
Steroids, terpenes, saponins	• Stigmasterol	Root [56]	anticancer, antipyretic, anti-inflammatory and immune-modulating effects [117,119,121,122]	 Stigmasterol
	• Gamma-sitosterol/ Clionasterol	Root [56]	Cholesterol-lowering action [123,124], anti-inflammatory effect [125], Thyroid inhibitory, antiperoxidative and hypoglycemic effects [126]	Clionasterol / Gamma-sitosterol 

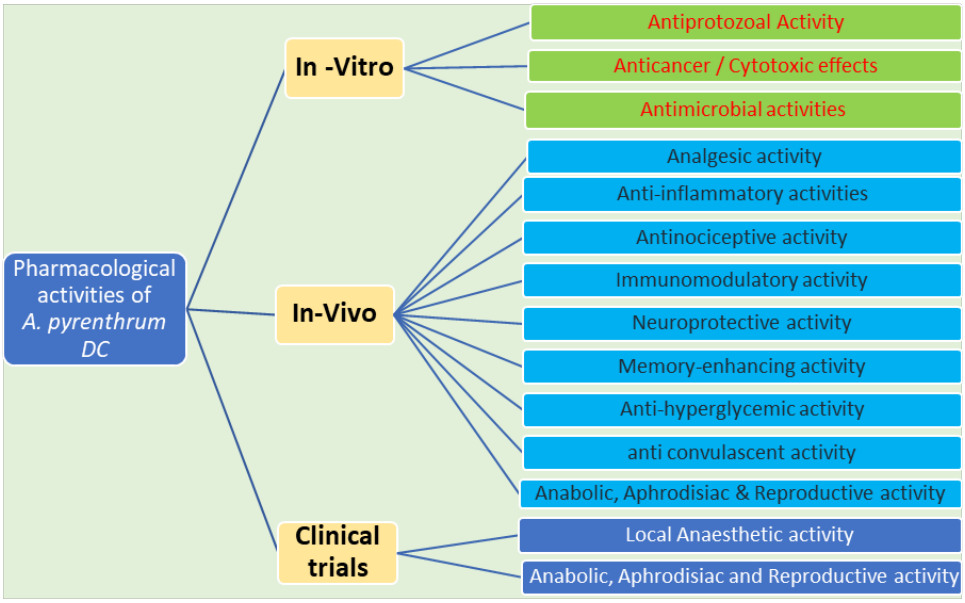


Figure 3. Pharmacological activities of *A. pyrethrum*

Pharmacological activities

This plant possesses several pharmacological activities by *in vitro*, *in vivo* and clinical trials (Figure 3).

Analgesic activity

The analgesic activity of different parts (root, seed, leaves and capitula) of the *A. pyrethrum* was tested in mice by acetic acid injection-induced abdominal contractions. Diclofenac was used as the reference product, which showed 43 percent pain inhibition. The results show that the fraction of *A. pyrethrum* roots was the most active, at a 300 mg/kg dose, with an inhibition percentage of 94.10 ± 4.35%. Next, 300 mg/kg of seeds fraction shows an inhibition percentage of 78.84 ± 11.79%, followed by the capitula sample with an inhibition percentage of 70.29 ± 4.27% at 500 mg/kg and 500 mg/kg of leaves fraction shows the least inhibition percentage of 12.00 ± 5.27%. This study also proves that *A. pyrethrum* (all parts) showed a dose-dependent effect except for the root, where the effect decreases with increasing doses. According to Jawhari, reducing the number of contractions at 300 and 500 mg/kg of leave and capitula fraction had the best effect. However, these results differed significantly from the control group [20]. In the same study, the analgesic activity of different parts (root, seed, leaves and capitula) of the *A. pyrethrum* and diclofenac (100 mg/kg) was also observed in the Formaldehyde Method. The pain intensity was recorded during the first (0–5 min) and second phases (15–30 min) after the formaldehyde injection in the paws of mice. The inhibition ranged from 67% to 94% In the first phase (0–5 min). The first and second phases' inhibition ranged from 67% to 94% and 76 to 91%, respectively (Table 4). These results were significant compared to the control group. Therefore, according to this study, the plant extract and Diclofenac were similarly effective in pain inhibition [20].

Local anaesthetic activity

A study was conducted by Muralikrishnan et al. (2017) on guinea pigs to evaluate the local anaesthetic activity of root extracts of the *A. pyrethrum* and check its effect of interaction at the injection site. Thirty-nine animals were used. Injection of 1% and 2% concentrations were prepared from root extracts using three types of solvent. All animals were divided into groups (five groups, six per each) injected with 0.5 mL of 1% concentration injection in the left and 2% in the right dorsal flank intradermally based on the type of extract used, control and a standard drug; the local anaesthetic activity tested by pinprick test. A biopsy was done after 72 hours from the injected site to check for drug interaction. The result showed a significant effect on the 2% ethanol compound [127] (Table 4).

Antimicrobial activities

The various solvent extracts of the aerial part of the *A. pyrethrum* were qualitatively and quantitatively assessed for *in vitro* antimicrobial activities against employed bacteria. The best antimicrobial activity resulted from the methanolic extract against Gram-positive bacterium (*Listeria monocytogenes*-100%, *Bacillus cereus* - 69% and *Staphylococcus aureus* -66%), and also against the fungus *Candida albicans* (81%) [86].
Another study was conducted in Iran by Jalayer Naderi et al. to determine the antibacterial activity of *A. pyrethrum* (methanolic extract) against some oral bacteria. The extract of the *A. pyrethrum* root was tested *in vitro* against *Streptococcus mutants, Pseudomonas aeruginosa, Streptococcus sanguis* and *Staphylococcus aureus*. At first, the root extract's serial concentrations (1.10 to 1.100 mg/mL) were tested against bacteria using the well diffusion assay method. Then, the agar dilution method was used to test 150-1000 mg/mL concentrations of extracts; this test was used to determine the extract's lowest concentrations, which inhibited the visible growth of organisms on the media plate. Jalayer Naderi et al. concluded that *A. pyrethrum* extract had a mild antibacterial effect against *Staphylococcus aureus* and *Streptococcus sanguis* and no antibacterial effect against *Streptococcus mutans* and *Pseudomonas aeruginosa* [128]. In another study by Noushin Jalayer-Naderi et al., methanolic extracts of *P. lentiscus* and *A. pyrethrum* were examined in disk diffusion and skipped wells methods. This study proves the antibacterial activity of methanolic extracts of *A. pyrethrum* (from 300 to 1000 mg/mL) on *Escherichia coli* [129] (Table 4).

Anti-inflammatory activities

The anti-inflammatory effect of methanol and aqueous extracts of *A. pyrethrum* was determined in xylene-induced ear edema and complete Freund's Adjuvant (CFA)- induced paw edema in the mouse. Both extracts significantly reduced CFA-induced paw edema and xylene-induced ear edema; a single oral dose (250 mg/kg and 500 mg/kg) significantly reduced mechanical hypersensitivity induced by CFA. The effect was begun 90 minutes after treatment and maintained for up to seven hours. In addition, when treated long-term, both extracts significantly reduced mechanical hypersensitivity in persistent pain conditions induced by CFA [130].
Another study was performed by Jawhari et al. in rats to ensure the anti-inflammatory activity of hydroalcoholic extracts from different parts (roots, seeds, leaves, and capitula) of *A. pyrethrum*. Carrageenan (1%; NaCl 0.9%) was injected to induce inflammation. Paw volumes were measured one hour before the induction and the first, third and fifth hours after. The extracts (roots, seeds, leaves, and capitula) prevent-

ed the evolution of the rat paw volume in all phases (1, 3, and 5) compared to the control group. Here, the inhibitory method of edema induced in rats was used to measure anti-inflammatory activity [20] (Table 4).

Antinociceptive activity

In mice, the antinociceptive activity of methanol extract and aqueous extract of *A. pyrethrum* were assessed in CFA-induced paw edema by the acetic acid-induced writhing, hot plate, formalin tests, and mechanical allodynia. The doses of 125 mg/kg, 250 mg/kg, and 500 mg/kg of both extracts were administered by gavage to mice. There was a significant decrease in acetic acid injection-induced abdominal writhes in acute pretreatment with methanol extract or aqueous extract of *A. pyrethrum* at a high dose and a noticeable increase in the paw withdrawal latency in the hot plate test. In addition, the formalin test showed significant inhibition of both phases [130] (Table 4).

Immunomodulatory activity

Petroleum ether extract (PEE) of *A. pyrethrum* roots was tested on albino rats at 50 mg/kg and 100 mg/kg doses. The effect of both doses on leukocyte count (total and differential), cyclophosphamide-induced immunosuppression, the survival rate from *Candida albicans* infection, percentage neutrophil adhesion, delayed-type hypersensitivity reaction, and phagocytic activity were tested. Blood parameters were normalized in PEE-treated albino rats, and they overcame cyclophosphamide-induced myelosuppression. Furthermore, by treating with PEE *A. pyrethrum* extract, the survival rate of *Candida albicans*-infected animals was improved. Similarly, extract administration increased the HA titer value and IgG antibodies, delayed-type hypersensitivity response, *in vivo* phagocytosis by carbon clearance method, and percentage neutrophil adhesion observed after treatment. Thus, this study concluded that *A. pyrethrum* roots contain immunomodulatory activity and significant improvements were observed in both humoral and cellular immunity components [39] (Table 4).

Antiprotozoal Activity

Alkamides contain wide structural diversity and a broad spectrum of bioactivities. Dichloromethane extract of the *A. pyrethrum* root was used for the study. Nine alkamides were isolated by column chromatography followed by preparative HPLC. Mass and NMR-spectroscopic methods were used to identify the alkamides. The antiprotozoal activity of isolated alkamides was tested *in vitro* against protozoans (*Trypanosoma brucei rhodesiense*, *Leishmania donovani, Plasmodium falciparum* and *Trypanosoma cruzi*) and cytotoxicity against L6 rat skeletal myoblasts. A moderate activity against the NF54 strain of *Plasmodium falciparum* and *Leishmania donovani* (amastigotes, MHOM/ET/67/L82 strain) resulted [58] (Table 4).

Neuroprotective activity

The central nervous system activity of *A. pyrethrum* was studied in albino Wistar rats by Sujith et al.; the study includes general behavioral studies, muscle relaxant, sedative, anxiolytic, nootropic activity and antidepressant studies in rats. This study proves the potential neuroprotective activity and nootropic and antidepressant properties of the *A. pyrethrum* [131].

The antidepressant activity of root extract of *A. pyrethrum* was revealed in another study by *Badhe* et al. The forced swim test, tail suspension test, locomotor activity, haloperidol-induced catalepsy, reserpine-induced hypothermia, and clonidine-induced hypothermia were tested on Swiss male albino mice. Root extract reduced immobility and significantly affected the forced swim test and tail suspension test. Also, root extract increased ambulatory behavior and inhibited haloperidol-induced catalepsy. It was also found effective in reversing clonidine and reserpine-induced hypothermia. Therefore, this study suggested the significant antidepressant activity of the root extract of *A. pyrethrum* [132].

Anticonvulsant activity and myorelaxation activity of ethanolic extract of *A. pyrethrum* were studied in albino mice by Gautam et al. Doses of 200, 400 and 600 mg/kg., i.p. of the extract were given orally, and anticonvulsant and myorelaxation activity was assessed on albino mice against maximum electroshock (MES) seizure test and rotarod test, respectively. Dose-dependent hind limb tonic extension duration reduced by ethanolic extract of *A. pyrethrum* against the MES model. This study concluded that the ethanolic extract of *A. pyrethrum* inhibits MES-induced convulsions [133] (Table 4).

Anabolic, Aphrodisiac and Reproductive activity

Aqueous extract of the *A. pyrethrum* roots was studied for anabolic, aphrodisiac and reproductive activities in albino rats. This study investigated the effects on sexual behavior, spermatogenesis, and sperm count in albino rats. Doses of 50 and 100 mg/kg of extract were administered to rats and showed marked anabolic and spermatogenic effects. Sperm count and fructose levels in seminal vesicles were noticeably increased; sexual behavioral improvement of male rats was characterized by high mount and intromission frequency and reduced mount and intromission latency. The significant dose-dependent influence and increase in sperm count and seminal fructose concentration resulted [134].

Another study was done by Sharma et al. on male Wistar rats to evaluate the ethanolic extract's androgenic and spermatogenic potential of *A. pyrethrum* roots.

Rats were randomized and divided into five groups. *A. pyrethrum* at three doses of 50, 100, and 150 mg/kg were administered to test group rats for 28 days and compared with testosterone-treated and control group rats. HPLC/UV/electrospray ionization mass spectrometry method was used to detect the alkylamides (thirteen N-alkylamides) in the extract. In the final evaluation, all three test groups showed a significant increase in body weight, motility, viability and sperm count, serum testosterone, luteinising hormone (LH), and follicle-stimulating hormone (FSH) concentrations. Increased spermatogenic activities were discovered in histological studies of the testis. A significant increase in seminal fructose contents was shown after 28 days of treatment. This study proved androgenic activity, enhanced spermatogenesis, and improved male fertility activity [135]. Shahraki et al. (2014) have conducted a study investigating the effects of *A. pyrethrum* aqueous root extracts on serum LH, FSH (gonadotropins) and testosterone in adult male rats. A total of 60 rats was randomly divided into five groups, each containing 12 rats. Groups are named group A (control group), B (sham control), C, D and E (three test groups). The test groups intraperitoneally received 50, 100, and 150 mg/kg doses of aqueous root extracts of *A. pyrethrum* for 28 days. LH, FSH (gonadotropins) and serum testosterone levels were determined at the end of the study, and the result reveals a significant difference between the treatments and control groups ($p<0.05$). Therefore, the aqueous root extracts of *A. pyrethrum* increased gonadotropins (LH, FSH) and serum testosterone levels [136] (Table 4).

Memory-enhancing activity

A study was carried out in albino Wistar rats to explore the potential effect of ethanolic extract of *A. pyrethrum* root in memory dysfunction. To induce memory impairment, 1 mg/kg scopolamine i.p were administered to rats. Social learning tasks, passive avoidance paradigms, and elevated plus mazes were used to access learning and memory. Studies were done on six groups, respectively, treated with 50, 100, and 200 mg/kg (treatment groups), control vehicle (2%v/v tween 80), scopolamine and with standard drug piracetam (200 mg/kg, p.o) for 14 days. Transfer latency decreased in the elevated plus-maze model paradigm, the indicator of cognition improvement in the *A. pyrethrum* extract-treated group. Also, the extract shows memory-enhancing activity in social learning tasks. This study also finds that the drug increases cholinergic neurotransmission and improves cognitive deficits. The present study suggests that ethanolic extract of *A. pyrethrum* increased brain cholinesterase level, and hence, it possesses memory-enhancing activity in the scopolamine-induced amnesia model by enhancing central cholinergic neurotransmission [137] (Table 4).

Anti-hyperglycemic activity

Tyagi et al. found the antidiabetic activity of aqueous root extract of *A. pyrethrum* in alloxan-induced diabetic rats. The rats were orally administered 150 and 300 mg/kg body weight of the extract. The blood glucose level was lower in experimental animals, suggesting the antihyperglycemic effect of the root extract (aqueous) of *A. pyrethrum* [138]. Another study was conducted by Selles et al. (2012) on an aqueous extract of *A. pyrethrum* root in normal and streptozotocin (STZ)-induced diabetic rats. The four groups (each per five rats) were included in this study. Two non-diabetic groups were orally given only saline (9 g/L) (normal control group) and 250 mg/kg of aqueous extract (control treated with aqueous extract), respectively, daily for 21 days. The STZ-induced diabetic rats were orally given only saline (9 g/L) (diabetic control group) and aqueous extract of 250 mg/kg dose (diabetic rats treated with aqueous extract group), respectively, daily for 21 days. Glucose oxidase (GOD) - peroxidase (POD) methods were used to measure blood glucose levels. Aqueous extract of *A. pyrethrum* root showed significant antihyperglycemic activity in diabetic rats [139] (Table 4).

Cytotoxic effects

5-diphenyltetrazolium bromide (MTT) assay, 3-(4, 5-dimethylthiazol-2-yl)-2, and trypan blue viability dye methods were used to assess the cytotoxic effects of *A. pyrethrum* root extract. Cell death and apoptosis stages were measured by flow cytometry assay. The effect of *A. pyrethrum* on the cancer cell migration was assessed by scratch test. The real-time polymerase chain reaction (PCR) quantified the expression levels of caspase 3, Bcl-2, MMP1, and Vimentin genes. A significant inhibition of cell growth by *A. pyrethrum* extract was found in the MTT assay. Also, this study has confirmed the ability of the extract to induce apoptosis in colorectal cancer cells. The study also proved that extract increases the caspase 3 mRNA expression and decreases Bcl-2, MMP1, and vimentin. In the G1 stage, cell cycle arrest was also observed. This study concluded that *A. pyrethrum* extract could effectively induce apoptosis in HCT cells and be a new therapeutic option for colorectal cancer [140] (Table 4).

Wound healing activity

Wound healing activity was studied using excision and incision wound models in rats. The six groups containing five rats were treated with madecassol (control group), diclofenac, and pomade prepared from hydroalcoholic extracts of *A. pyrethrum* root, seed, leave, and capitulum for 20 days. The test groups showed a significant difference in the mean

wound area compared to the control group. It took 12 and 14 days to heal 10% and 5% of capitula extract pomade, respectively. The root extract pomade at 5% and 10% concentrations took 14 and 16 days to treat wounds, respectively. On the 20th day, complete healing and a reappearance of hair in the scars were recorded for all extracts [20] (Table 4).

Effect on smoking withdrawal

A study was conducted by Kenza et al. on rats to evaluate the behavioral effects of *A. pyrethrum* ethanolic extract on smoking withdrawal. Twelve groups of rats (each group of five animals) were included in the study. Six control groups received distilled water, 200 mg/kg; 400 mg/kg; 800 mg/kg of *A. pyrethrum* ethanolic extract (orally), clomipramine 15 mg/kg and diazepam 1 mg/kg (intraperitoneally), respectively. After three months of cigarette exposure in a special apparatus, smoking withdrawal groups were prepared by 24-hour smoking cessation. The smoking withdrawal untreated group received distilled water, and five treated groups received 200 mg/kg, 400 mg/kg; 800 mg/kg of *A. pyrethrum* ethanolic extract (orally), clomipramine 15 mg/kg and diazepam 1 mg/kg (intraperitoneally), respectively. The level of depression and anxiety were measured by the forced swim test, open-field, marble-burying, and plus-maze tests were used. The novel object recognition test tested memory impairment. Animals treated with extract showed decreased immobility time in forced swimming tests, and they buried fewer marbles. Recognition of memory of the rats increased in the novel object recognition test. This study concluded that the *A. pyrethrum* ethanolic extract has potential antidepressant-like and anxiolytic-like effects [141] (Table 4).

Toxicological evaluation

Acute toxicity

Methanol and aqueous extracts of *A. pyrethrum* were administered orally to the mice. The dose up to 5000 mg/kg did not produce any visible signs or symptoms of toxicity. After 14 days of the administration, No mortality and significant changes in organ weights ($p>0.05$) or body weights ($p>0.05$) were reported [130].

Subchronic/chronic toxicity

Subchronic toxicity studies of ethanolic extract of *A. pyrethrum* (prepared in 2%v/v tween 80) were done in albino Wistar rats at the dose of 1000 mg/kg per day for 90 days by oral gavage. Simultaneously, only 2%v/v tween 80 were given to the control group. The rats were observed weekly for changes in body weight and daily for signs of toxicity and mortality throughout the study. In addition, hematological, biochemical and histopathological examinations were done in both groups at the end of the study. Relative organ weight of the liver, kidney, brain, lungs and spleen in rats in two groups were examined at the end of the dosing period. The study revealed no effect on body weight, growth, and survival in the test group.

There was no significant difference between the test and control groups in the relative weight of organs. Furthermore, no evidence of pathological lesions in vital organs was found. These results specify that the ethanolic extract of *A. pyrethrum* had no treatment-related toxicological abnormalities and can be considered safe for long-term treatment [147].

Conclusion

A. pyrethrum is an important medicinal herb in Unani and other traditional systems of medicine, known for its wide-ranging therapeutic applications. There are two recognized varieties: *A. pyrethrum var. pyrethrum* (L.) and *A. pyrethrum var. depressus* (Ball) Maire, which share similar chemical compositions and medicinal properties. The plant contains numerous bioactive compounds, with the roots being particularly rich in alkaloids, tannins, and N-alkyl amides, alongside tannic acid, gum, inulin, various salts, and lignin. Alkaloid pyrethrin is the principal active component, contributing to the plant's diverse pharmacological properties. Research has highlighted a range of therapeutic activities, including antioxidant, antimicrobial, anti-inflammatory, analgesic, neuroprotective, immunomodulatory, antiprotozoal, memory-enhancing, and antihyperglycemic effects. However, despite these promising findings, clinical research studies on *A. pyrethrum* remain limited. More extensive investigations are essential to uncover additional therapeutic potentials, identify novel chemical constituents, and elucidate the molecular mechanisms underlying its actions. Such studies would also help clarify interactions with other medicines and establish evidence-based applications for modern healthcare practices.

Conflict of Interests

None.

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Table 4. Pharmacological activities of *A. pyrethrum*

Preparation/constituents/dose/ administration route	*In vitro* or *in vivo* model	Parameters/Tests	Outcome	Reference
1. Analgesic Activity				
- Hydroalcoholic extracts (roots, seeds, leaves, and capitula) 300 and 500 mg/kg doses	*In vivo* study (albino rats)	Acetic acid method	Most active, at a 300 mg/kg dose -Root ⟶ inhibition 94.10% ± 4.35%. - Seed ⟶ inhibition 78.84% ± 11.79 - Capitula ⟶ 66.42% ± 6.50 - Leaves ⟶ 40.79% ± 8.91. dose-dependent effect, root extract decreases the inhibitory effect with increasing doses	[20]
- Hydroalcoholic extracts (roots, seeds, leaves, and capitula). - 300 and 500 mg/kg doses	*In vivo* study (albino rats)	Formaldehyde Method. (injection in the paws of mice)	Pain inhibition during 1st (0–5 min) & 2nd phases (15–30 min), respectively, (300 mg/kg) - Root ⟶ 88.31 ± 1.28%, 88.87 ± 0.96% . - Seed ⟶ 83.69 ± 5.89%, 76.45 ± 6.09% - Capitula ⟶ 67.96 ± 2.50%, 91.29 ± 2.51% Pain inhibition during 1st(0–5 min) and 2nd phases (15–30 min), respectively, (500mg/kg) - Leave ⟶ 94.08 ± 2.26%, 87.74 ± 2.22%	[20]
2. Local anaesthetic activity				
2% Alcoholic extract. (freshly dissolved in sterile distilled water) (root)	- Double-blinded controlled clinical trial - 200 dental patients	Anaesthesia induced by 0.3 mL at the time of focal surgery.	Low concentration less than 2% useful and safe	[142]
3. Antimicrobial Activity				
Methanolic extract (310.78 mg	*In vitro*,	Antimicrobial activity	Antimicrobial	[86]

GAE/g*) aqueous extract (183.82 mg GAE/g)	laboratory and microbiological study		activity - against Gram-positive bacterium (*Listeria monocytogenes*- 100%, *Bacillus cereus* - 69% and *Staphylococcus aureus* -66%), - against *Candida albicans* (81%)	
Root extract serial concentrations - For Well assay method (1.10 to 1.100 mg/ml) - Agar dilution method (150-1000 mg/mL)	*In vitro* microbiological study	1. Well assay method 2. Agar dilution method	- Mild antibacterial effect against *Staphylococcus aureus* and *Streptococcus sanguis* - No antibacterial effect against *Streptococcus mutans* and *Pseudomonas aeruginosa*	[128]
Methanolic extract (root) doses from 30 to 1000 mg/mL concentration	*In vitro* microbiological study	1. Disk diffusion 2. Skipped wells methods	- Affective against *Escherichia coli* - Minimum inhibitory concentrations (MIC) – 800 mg/mL - Minimum Bactericidal Concentration (MBC) – 800 mg/mL	[129]
Ethanolic extract (root) 30µL, 60µL and 120µL,	*In vitro* microbiological study	Disk diffusion method against 17 bacteria and fungi (*Candida albicans*)	- Showed antimicrobial activity (except *E. faecalis* and *S. typhimurium)* - potent activity (IZ** > 30 mm) (volume of 120 µL) & - Strong activity (21-30 mm) (30 µL, 60 µL) against *Staphylococcus epidermidis* and	[56]

			Enterococcus faecium - Strong activity (120 µL) against *Staphylococcus aureus*	
Essential oils obtained from hydrodistillation of *A .pyrethrum*.	*In vitro* microbiological study	1. Solid - medium Disc-diffusion method 2. Liquid medium - macro dilution method	Inhibition diameters 9 [+ or -] 0.81 mm and 9.66 [+ or -] 0.47 mm against susceptible *Escherichia coli* and *Staphylococcus aureus.*	[143]
Ethanolic extract of (root) 28.5%.	*In vitro* study (Saliva samples)	Bauer & Kirby method for *Enterococcus faecalis, Staphylococcus aureus,* and *Bacillus species*	56%, 62% and 60% sensitivity against *E. faecalis, S. aureus* and *Bacillus* sp., respectively, with the MIC >100 µg/mL	[144]
Methanolic, petroleum ether, acetone, and aqueous extracts of *A. pyrethrum* root	*In vitro* study	Agar well diffusion method against *Staphylococcus aureus, S. mutans, S. sanguis, S. sobrinus, S. salivarius* and *Lactobacillus acidophilus*	Effective - with maximum antibacterial activity against *L. acidophilus* and *S. aureus*.	[145]
4. Anti-inflammatory				
Methanol and aqueous extracts of *A .pyrethrum.* single oral dose (250 mg/kg and 500 mg/kg)	*In vivo* study, (adult Swiss male mice)	1. Xylene-induced ear edema	- Both extracts 1. Xylene-induced ↓ ear edema. ↑ anti-inflammatory effects (acute and chronic)	[130]
		2. Complete Freund's Adjuvant (CFA)-induced paw edema	2. ↓ in paw thickness dose and time-dependent anti-inflammatory effects	
Hydroalcoholic extracts (roots, seeds, leaves, and capitula)	*In vivo* study (Male adult Wistar rats)	Inhibitory method of edema induced in rats	- The extracts prevented the evolution of the rat paw volume in 1st, 3rd, and 5th hours after induction (anti-inflammatory effect)	[20]

5. Antinociceptive activity				
Methanol and aqueous extract (root) 125 mg/kg, 250 mg/kg, and 500 mg/kg.	*In vivo* study, (adult Swiss male mice)	1. Acetic acid-induced writhing, hot plate, formalin tests 2. Mechanical allodynia assessed CFA-induced paw edema test	↓ number of writhes ↑ paw withdrawal latency Formalin test - showed analgesic action at central and peripheral levels	[130]
6. Immunomodulatory activity				
Petroleum ether extract (PEE) of *A .pyrethrum.* roots 50 mg/kg, 100 mg/kg doses	*In vivo* study (albino rats)	Effects on cyclophosphamide-induced immunosuppression, survival rate against *Candida albicans* infection, percentage neutrophil adhesion, delayed-type hypersensitivity reaction, DLC*** and TLC**** phagocytic activity	Cyclophosphamide-induced myelosuppression (Blood parameters were normalized). ↑Survival rate of *Candida albicans*-infected animals ↑ HA titer value and IgG antibodies, delayed-type hypersensitivity response, phagocytosis (by carbon clearance method), ↑ % of neutrophil adhesion	[39]
7. Antiprotozoal activity				
Dichloromethane extract of the *A .pyrethrum.* root	*In vitro* study	tested 1. For antiprotozoal activity against *Plasmodium falciparum, Trypanosoma brucei rhodesiense, Trypanosoma cruzi,* and *Leishmania donovani* 2. For cytotoxicity against L6 rat skeletal myoblasts	- Moderate activity against the NF54 strain of *Plasmodium falciparum* and *Leishmania donovani* (amastigotes, MHOM/ET/67/L82 strain) was observed.	[58]
8. Neuroprotective activity				
Ethanolic extract of *A .pyrethrum.* root, 50, 100 and 200mg/kg doses Orally	*In vivo*, study (Albino Wistar Rats)	- General behavioral studies - Sedative, muscle	- Study proves the potential neuroprotective activity nootropic	[131]

		relaxant, anxiolytic, nootropic activity - Antidepressant studies in rats	and antidepressant properties of the *A. pyrethrum*	
Aqueous and alcoholic extract (root)	*In vivo* study (Swiss male albino mice)	Antidepressant activity assessed by Locomotor activity, Haloperidol-induced catalepsy, FST[#], Clonidine-induced hypothermia, TST[##], and Reserpine-induced hypothermia	- ↓immobility - significantly affects the FST, TST - ↑ ambulatory behavior - Inhibits haloperidol-induced catalepsy. - Effective in reversing clonidine and reserpine induce hypothermia.	[132]
Ethanolic extract 200, 400 & 600 mg/kg Orally	*In vivo* study (albino mice)	Anticonvulsant and myorelaxation activity - assessed by maximum electroshock seizure test (MES) and rotarod test.	- Hind limb tonic extension duration ↓ (dose-dependent) against the MES model - Dose-dependent muscle relaxant effect ($p<0.001$)	[133]
1% and 2% concentration injections prepared from *A .pyrethrum.* root extracts using three types of solvent	*In vivo* study (guinea pigs)	0.5 mL of - 1% injection in the left & - 2% in the right dorsal flank intradermally to test the myorelaxation activity	- Biopsy ⟶ after 72 hours from the injected site to check for drug interaction. Showed a significant effect on the 2% ethanol compound	[127]
9. Anabolic, Aphrodisiac and Reproductive activity				
Aqueous extract (roots) 50 and 100 mg/kg, orally	*In vivo* study (albino rats)	Anabolic, Aphrodisiac and Reproductive Activity assessed by sperm count and fructose levels in seminal vesicle	↑Sperm count and Fructose levels in seminal vesicles (dose-dependent)	[134]
Ethanolic extract (roots) 50, 100, and 150 mg/kg for 28 days	*In vivo* study (male Wistar strain rats)	Thirteen alkylamides Isolated by using HPLC/UV/electrospray ionisation mass spectrometry method. Androgenic and	- Showed positive effect on androgenic activity, Enhanced spermatogenesis, increased body weight, sperm count, motility, and	[135]

		Spermatogenic Activity is assessed by weight, sperm count, motility, viability serum testosterone, LH, and FSH concentrations. Histoarchitecture of testis	viability with serum testosterone, LH, and FSH concentrations	
Root powder 1 g twice orally before meals with honey X 4 weeks	RandomiZed, controlled, parallel, single-blind clinical trial	Specific questionnaires were prepared to assess drug efficacy and sexual function (IIEF18 -International Index of Erectile Function)	- Effective in erectile dysfunction and premature ejaculation	[146]
Aqueous root extracts intraperitoneally 50, 100, and 150 mg/kg X 28 days.	*In vivo* study (adult male rats)	Determined levels of gonadotropins (LH, FSH) and testosterone in the serum of rats were	- Gonadotropins (LH, FSH) and serum testosterone levels increased.	[136]
10. Memory-enhancing activity				
Ethanolic extract (root) 50, 100, and 200 mg/kg X 14 days.	*In vivo* study (albino Wistar rats)	1. Assessed memory-enhancing activity in scopolamine i.p induced impaired memory. 2. Access Learning & memory by Social learning tasks, passive avoidance paradigms and elevated plus maze	- Reversed the amnesia induced by scopolamine - Transfer latency ↓ in the elevated plus-maze model paradigm ###, memory in social learning tasks, the drug increased cholinesterase levels in the brain	[137]
11. Antihyperglycemic				
Aqueous extract (root, oral) 150 and 300 mg/kg body weight	*In vivo* study (alloxan-induced diabetic rats)	Oral Glucose Tolerance Test (OGTT)	- Significantly improves OGTT in experimental animals,	[138]
Aqueous extract (root) 250 mg/kg daily for 21 days oral	*In vivo* study STZ-induced diabetic rats	Measured blood glucose levels Glucose oxidase-peroxidase (GOD-POD) (Kit spin react)	- Significantly reduced Fasting blood glucose level and OGTT values	[139]
12. Anticancer activity/Cytotoxic effects				
Ethanolic extract (root) (250 g/2 L)	*In vitro* cell line study	Anticancer activity assessed by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium	- Cell growth inhibited significantly, - Induced cell death substantially	[140]

		bromide (MTT) assay, and trypan blue viability dye. Cell death and apoptosis stage were measured by flow cytometry assay, expression of Caspase 3, Bcl-2, MMP1, and Vimentin genes quantified by real-time PCR	- ↑ caspase 3 mRNA expression, - ↓ Bcl-2, MMP1 & Vimentin, - Cell cycle arrest.	
13. Wound healing activity				
Hydroalcoholic extracts (root, seed, leave, capitulum)	*In vivo* study, (Male adult Wistar rats)	Excision and incision wound models in rats	- On the 20th day, complete healing and reappearance of hair in the scars	[20]
14. Affect on smoking withdrawal				
Ethanolic extract (root) 200, 400 & 800 mg/kg Oral	*In vivo* study, (adult male, Sprague Dawley rats)	Measured -Level of depression and anxiety by FST, open-field, marble-burying, and plus-maze tests in cigarette smoke exposure in a special apparatus-induced depression.	- ↓ immobility time in FST - Novel object recognition test ⟶ Recognition of the rats' memory increased. - Concluded antidepressant-like and anxiolytic-like effects	[141].

GAE/g* - milligrams of gallic acid equivalents per gram, IZ** – inhibitory zone, DLC*** Differential leucocyte count, TLC**** - Total leucocyte count phagocytic activity, FST# - the Forced swim test, TST## - Tail suspension test, LH - Luteinising Hormone, FSH - Follicle-Stimulating Hormone, paradigm ### - an indicator of cognition improvement, STZ- streptozotocin

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