Chamomile (*Matricaria chamomilla* L.): An overview

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ABSTRACT

Chamomile (*Matricaria chamomilla* L.) is a well-known medicinal plant species from the Asteraceae family often referred to as the "star among medicinal species." Nowadays it is a highly favored and much used medicinal plant in folk and traditional medicine. Its multitherapeutic, cosmetic, and nutritional values have been established through years of traditional and scientific use and research. Chamomile has an established domestic (Indian) and international market, which is increasing day by day. The plant available in the market many a times is adulterated and substituted by close relatives of chamomile. This article briefly reviews the medicinal uses along with botany and cultivation techniques. Since chamomile is a rich source of natural products, details on chemical constituents of essential oil and plant parts as well as their pharmacological properties are included. Furthermore, particular emphasis is given to the biochemistry, biotechnology, market demand, and trade of the plant. This is an attempt to compile and document information on different aspects of chamomile and highlight the need for research and development.

Key words: Amino acid, cadmium, co-cultivation, copper, cultivation, medicinal plant, salicylic acid, secondary metabolites, tissue culture

INTRODUCTION

Chamomile (*Matricaria chamomilla* L.) is one of the important medicinal herb native to southern and eastern Europe. It is also grown in Germany, Hungary, France, Russia, Yugoslavia, and Brazil. It was introduced to India during the Mughal period, now it is grown in Punjab, Uttar Pradesh, Maharashtra, and Jammu and Kashmir. The plants can be found in North Africa, Asia, North and South America, Australia, and New Zealand.[1] Hungary is the main producer of the plant biomass. In Hungary, it also grows abundantly in poor soils and it is a source of income to poor inhabitants of these areas. Flowers are exported to Germany in bulk for distillation of the oil.[2]

In India, the plant had been cultivated in Lucknow for about 200 years, and the plant was introduced in Punjab about 300 years ago during the Mughal period. It was introduced in Jammu in 1957 by Handa *et al.*[3] The plant was first introduced in alkaline soils of Lucknow in 1964–1965 by Chandra *et al.*[4,5] There is no demand for blue oil as such at present in India. However, flowers of chamomile are in great demand. Presently, 2 firms, namely, M/s Ranbaxy Labs Limited, New Delhi and M/s German Remedies are the main growers of chamomile for its flowers.

Chamomile has been used in herbal remedies for thousands of years, known in ancient Egypt, Greece, and Rome.[6] This herb has been believed by Anglo-Saxons as 1 of 9 sacred herbs given to humans by the lord.[7] The chamomile drug is included in the pharmacopoeia of 26 countries.[8] It is an ingredient of several traditional, unani, and homeopathy medicinal preparations.[9-12] As a drug, it finds use in flatulence, colic, hysteria, and intermittent fever.[13] The flowers of *M. chamomilla* contain the blue essential oil from 0.2 to 1.9%,[14,15] which finds a variety of uses. Chamomile is used mainly as an antiinflammatory and antiseptic, also antispasmodic and mildly sudorific.[16] It is used internally mainly as a tisane (infuse 1 table-spoonful of the drug in 1 L of cold water and do not heat) for disturbance of the stomach associated with pain, for sluggish digestion, for diarrhea and nausea; more rarely and very effectively for inflammation of the urinary tract and for painful menstruation. Externally, the drug in powder form may be applied to wounds slow to heal, for skin eruptions, and infections, such as shingles and boils, also for hemorrhoids and for inflammation of the mouth, throat, and the eyes.[17] Tabulated products from chamomile flower

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extracts are marketed in Europe and used for various ailments. Chamomile tea eye washing can induce allergic conjunctivitis. Pollen of *M. chamomilla* contained in these infusions are the allergens responsible for these reactions.[18]

Antonelli had quoted from writings of several doctors of ancient time of the 16th and 17th century that chamomile was used in those times in intermittent fevers.[19] Gould *et al.* have evaluated the hemodynamic effects of chamomile tea in patients with cardiac disease.[20] It was found in general that the patients fell into deep sleep after taking the beverage. Pasechnik reported that infusion prepared from *M. chamomilla* exercised a marked stimulatory action on the secretary function of the liver.[21] Gayar *et al.* reported toxicity of acetone-extract of *M. chamomilla* against larvae of *Gulex pipens* L.[22] The other pharmacological properties include antiinflammatory, antiseptic, carminative, healing, sedative, and spasmolytic activity.[23] However, *M. chamomilla* has exhibited both positive and negative bactericidal activity with *Mycobacterium tuberculosis*, *Salmonella typhimurium*, and *Staphylococcus aureus*.

The international demand for chamomile oil has been steadily growing. As a result, the plant is widely cultivated in Europe and has been introduced in some Asian countries for the production of its essential oil. *M. chamomilla* L., *Anthemis nobilis* L., and *Ormenis multicaulis* Braun Blanquet and Maire belonging to the family Asteraceae is a natural and major source of "blue oil" and flavonoids. The oil used as a mild sedative and for digestion[20,24-29] besides being antibacterial and fungicidal in action.[20]

In addition to pharmaceutical uses, the oil is extensively used in perfumery, cosmetics, and aromatherapy, and in food industry.[27,30-33] Gowda *et al.* studied that the essential oil present in the flower heads contains azulene and is used in perfumery, cosmetic creams, hair preparations, skin lotions, tooth pastes, and also in fine liquors.[34] The dry flowers of chamomile are also in great demand for use in herbal tea, baby massage oil, for promoting the gastric flow of secretion, and for the treatment of cough and cold.[35] The use of herbal tea preparations eliminated colic in 57% infants.[36] Because of its extensive pharmacological and pharmaceutical properties, the plant thus possesses great economic value and is in great demand in the European countries.

BOTANY

True chamomile is an annual plant with thin spindle-shaped roots only penetrating flatly into the soil. The branched stem is erect, heavily ramified, and grows to a height of 10–80 cm. The long and narrow leaves are bi- to tripinnate. The flower heads are placed separately, they have a diameter of 10–30 mm, and they are pedunculate and heterogamous. The golden yellow tubular florets with 5 teeth are 1.5–2.5 mm long, ending always in a glandulous tube. The 11–27 white plant flowers are 6–11 mm long, 3.5 mm wide, and arranged concentrically. The receptacle is 6–8 mm wide, flat in the beginning and conical, cone-shaped later, hollow—the latter being a very important distinctive characteristic of *Matricaria*—and without paleae. The fruit is a yellowish brown achene.

The true chamomile is very often confused with plants of the genera *Anthemis*. Special attention has to be paid to avoid confusion with *Anthemis cotula* L., a poisonous plant with a revolting smell. In contrast to true chamomile, *A. cotula* similar to as *A. arvensis* L. and *A. austriaca* Jacq., has setiform, prickly pointed paleae, and a filled receptacle. The latter species are nearly odorless.[37] Although the systematic status is quite clear nowadays, there are a number of inaccuracies concerning the names. Apart from misdeterminations and confusion, the synonymous use of the names *Anthemis*, *Chamomilla*, and *Matricaria* leads to uncertainty with regard to the botanical identification. Moreover, the nomenclature is complicated by the fact that Linnaeus made mistakes in the first edition of his "Species Plantarum" that he corrected later on. The best-known botanical name for true chamomile is *Matricaria recutita* (syn. *Matricaria chamomilla*, *Chamomilla recutita* (L.) Rauschert, belonging to the genus *Chamomilla* and family Asteraceae.[37] *M. chamomilla* is a diploid species (2n=18), allogamous in nature, exhibiting wide segregation as a commercial crop.

Chamomile, a well-known old time drug, is known by an array of names, such as Baboonig, Babuna, Babuna camornile, Babunj, German chamomile, Hungarian chamomile, Roman chamomile, English chamomile, Camomilla, Flos chamomile, Single chamomile, sweet false chamomile, pinheads, and scented mayweed, suggesting its widespread use.[38,39]

The three plants, namely, *A. nobilis* Linn, *Corchorus depressus* Linn, and *M. chamomilla* Linn. are reported under one unani name Babuna at different places in the literature. This created a lot of confusion and misuse of the drug as an adulterant, etc. Ghauri *et al.* conducted a detailed taxonomic and anatomical study and concluded that Babuna belongs to the family Compositae (Asteraceae) and that the correct scientific name of Babuna is *M. chamomilla* L.[40]

CULTIVATION AND CO-CULTIVATON

Soil and climatic requirements

German chamomile can be grown on any type of soil, but growing the crop on rich, heavy, and damp soils should be avoided. It can also withstand cold weather with temperature ranging from 2°C to 20°C. The crop has been grown very successfully on the poor soils (loamy sand) at the farm of the Regional Research Laboratory, Jammu. At Banthra farm of the National Botanical Research Institute, Lucknow, the crop has been grown successfully on soil with a pH of 9.[41] Soils with pH 9–9.2 are reported to support its growth. In Hungary, it grows extensively on clayey lime soils, which are barren lands and considered to be too poor for any other crop. Temperature and light conditions (sunshine hours) have greater effect on essential oils and azulene content, than soil type.[42] Chamomile possesses a high degree of tolerance to soil alkalinity. The plants accumulate fairly large quantity of sodium (66 mg/100 gm of dry material), which helps in reducing the salt concentration in the top soil.[43] No substantial differences were found in the characteristics of the plants grown 1500 km apart (Hungary–Finland). Under cooler conditions in Finland, the quantity of the oxide type in the essential oil was lower than in Hungary.[29,44]

Propagation

The plant is propagated by seeds. The seeds of the crop are very minute in size; a thousand seeds weigh 0.088–0.153 gm. About 0.3–0.5 kg of clean seed with a high germination percentage sown in an area of 200–250 m^2 gives enough seedlings for stocking a hectare of land. The crop can be grown by two methods i.e. direct sowing of the seed and transplanting. Moisture conditions in the field for direct sowing of seeds must be very good otherwise a patchy and poor germination is obtained. As direct sowing of seeds usually results in poor germination, the transplanting method is generally followed. The mortality of the seedlings is almost negligible in transplanting.

The optimum temperature for good seed germination lies between 10°C and 20°C. Nursery beds were prepared by applying good quality of farmyard manure (FYM) and compost and kept moist. The most appropriate time for raising seedlings in the nursery is soon after the cessation of monsoons in North India, that is, during the month of September. Seed germination starts within 4–5 days of sowing, and the seedlings area ready for transplanting within 4–5 weeks. Seedlings older than 5 weeks should not be transplanted; it results in a poor and indifferent crop. Based on the thermal model, appropriate time and method of sowing was studied. The study revealed that transplanting the crop was better than direct sowing, and the best time to transplant the crop was found to be from October 10 to 18 for getting higher yields. Transplanting should not be delayed beyond the end of October.

Zalecki reports that different sowing times affect the shifting of the harvesting time but do not affect the oil and chamazulene content significantly.[45] The work on crop geometry shows that transplanting the crop at narrow spacing of 15, 20, and 30 cm, gave the highest yields of flowers.[46-49] Dutta and Singh reported that the highest yields of fresh flowers and oil content was obtained under 30 cm^2 spacing. In case of varieties with a spreading habit of growth, a wider spacing of 40 cm^2 is desirable.[46]

Crop growth

The crop growth is slow till mid-January and picks up gradually till early February. As the season warms up, there is high activity in crop growth (increase in height, branching, bud formation) and stray flowers may be seen in the crop. Bud formation is profuse in March, there is all round growth in the plants, the early formed buds open into flowers, hence the plucking of flowers has to be also selective all through the crop cycle. With sudden rise in the temperature from 33°C to 39°C within a few days, heavy seed-setting and plant maturity will be observed in the crop. There is seed shedding and in the next year a self-germinated crop is observed.

Irrigation

As the roots of the plant are shallow, the plant is unable to draw moisture from the lower moist horizon of the soil and therefore needs frequent irrigation to maintain an optimum moisture level. Irrigation during the bloom period is helpful in increasing the flower yield, one additional flush of flowers is obtained and seed formation is delayed. Krèches observed that irrigation at the rosette stage increased the yield substantially.[42] On alkaline soils, the crop is irrigated more frequently and about 6–8 irrigations are required during the crop cycle.[43] Good performance is obtained if the soil is kept moist, but flooding should be avoided.

Manures and fertilizers

The effect of nitrogen (N) is very marked on the fresh flowers and oil yield, whereas that of phosphorus (P) and potassium (K) is negligible. Dutta and Singh observed that application of N in the form of ammonium sulfate at 40 kg/ha significantly increased fresh flower and oil yield, while the oil content decreased from 0.64 to 0.59%.[50] Addition of organic matter increases the humus content of such soil and thereby improves the crop performance. Application of 15–25 t/ha of FYM is proved beneficial before transplanting.[48] El-Hamidi *et al*.[51] advocates the ratio of 2:2 for N2 and P for obtaining the highest yield. Application of N at a higher level caused a notable decrease in the chamazuler percentage. Paun and Mihalopa[47] found that the application of P and K at 50 kg/ha each in autumn before sowing and application of N at 50 kg/ha in early spring was responsible for satisfactory crop growth. However, neither volatile oil nor chamazulene content was affected. On saline alkaline soils, Singh found plants showing good response to N and P fertilizers.[48] Application of 20–25 t/ha of FYM was useful before transplanting the crop. Misra and Kapoor[33] found the optimum dose of N and P to be between 50–60 kg N/ha and 50 kg P_2O_5/ha. It is reported that N significantly increased the contents of α-bisabolol and chamazulene, but significantly decreased the contents of bisabolol oxides A and B in the essential oil.[52] N significantly increased essential oil yield per unit dry flower weight in both Bohemia and Tisane varieties. The quantity of essential oil in chamomile was inversely related to its quality in terms of α-bisabolol and chamazulenes.[51]

No deficiency symptoms of trace elements have been observed on the crop in the country so far. Peskova[53] has reported the good effect of the sulfates of manganese and cobalt; and borax on lime soils, whereas Koeurik and Dovjak[54] indicated that combined application of boron and molybdenum increased dry matter significantly.

Weed control

There are many herbicides for the control of weeds in *M.*

chamomilla. Generally 3–4 weedings are required for a good crop. The application of 1–1.5 kg/ha of sodium salt of 2,4-dichlorophenoxyacetic acid (2,4-D); four weeks after transplanting gave good control of weeds for four weeks. The experimental results of researchers in other countries suggests that herbicides, such as atrazine, prometryene, propyzamide, chloropropham, mecoprop, trifluralin, linurones, give satisfactory control of weeds, but these should be used with caution. It was found that afalone was the best selective weedicide.[55] Herbicide-treated crop had lower chamazulene content, and bisabolol content was lower in the second harvest as herbicides interfere with the metabolism of secondary products. Certain herbicides have little influence on the total essential oil content, but greater differences were found in the quantitative composition of useful substances.[55-58]

On saline–alkali soils only one thorough weeding and hoeing one month after transplanting, may be enough, as the plant once established, smothers the weed and no further weeding is required.[48] It was reported that weed removal during 5–11 weeks after planting the crop was necessary to obtain a higher yield of the flower and oil.[52] The uncontrolled weed growth caused 34.4% reduction in the dry flower yield as compared with the weed-free condition. The application of oxyfluorfen (0.6 kg/ha) gave higher returns.[59]

Harvesting

Harvesting is the most labor-intensive operation in chamomile cultivation, accounting for a major portion of the cost of production. The success of *M. chamomilla* cultivation as a commercial venture lies in how efficiently and effectively one can collect the flowers at the right stage during the peak flowering season extending over a period of 3–6 weeks during March–April. Flowering is so profuse that practically every alternate day at least 30–40 units of labor will be required to be employed to pluck the flowers from an area of 0.25–0.3 ha. Flower plucking is a selective process as flowers in all stages, namely, buds, semi-opened buds, flowers in all stages of bloom appear on the plants. Flowers at the near full bloom stage give the best quality of the product, hence care has to be exercised to see that as little as possible buds, stems, leaves, and extraneous material is plucked. Flowering will be observed on plants here and there all over the field from the later half of February and these flowers are plucked at the appropriate stage. Flowers are produced in flushes and 4–5 flushes are obtained. The 2nd, 3rd, and 4th flushes are the major contributors to flower yield. The peak period of plucking is between the 2nd week of March and the 3rd week of April in North India. In normal soils, Singh obtained a maximum yield of 7637 kg of fresh flowers, the average being 3500–4000 kg/ha.[60] In saline–alkaline soils, Singh obtained a yield of 3750 kg fresh flowers/ha.[48] Temperature affects the number of flowers per kg. The weight of 1000 flowers is reduced from 130 to 80 gm by the 2nd week of April.

Diseases and pests

The various insects, fungi, and viruses have been reported, which attack the chamomile crop. The following fungi are known to attack this plant: *Albugo tragopogonis* (white rust), *Cylindrosporium matricariae*, *Erysiphe cichoracearum* (powdery mildew), *E. polyphage*, *Halicobasidium purpureum*, *Peronospora leptosperma*, *Peronospora radii*, *Phytophthora cactorum*, *Puccinia anthemedis*, *Puccinia matricaiae*, *Septoria chamomillae*, and *Sphaerotheca macularis* (powdery mildew). Also, yellow virus (*Chlorogenus callistephi* var. *californicus* Holmes, *Callistephus* virus 1A) causes severe damage to this plant. In the years 1960–1964 when the crop was cultivated in the Regional Research Laboratory, Jammu, no incidence of disease was reported. However, after 20 years in the month of February about two dozen plants were observed to produce symptoms resembling those of plant viruses. These plants were burnt to prevent further spread of the disease. In early March, the incidence of leaf blight caused by *Alternaria* spp. was observed in the crop. A spray of Benlate (0.1%) controlled the disease. Fluister reported that black bean aphids (*Aphis fabae*) were feeding on *M. chamomilla*.[61] The insect *Nysius minor* caused shedding of *M. chamomilla* flowers,[62] whereas *Autographa chryson* causes defoliation of the plant. The one spray with fosfothion 0.2%, controlled successfully aphid infestation (*Doralis fabae* Scop.) on chamomile. Methyl bromide (3 kg/100 m^3) proved satisfactory as a fumigant against pest infestation of *Ephestia elutella* Hb in the desiccated herb of chamomile. *Metalydacolus longistriatus* in the Giza region of Egypt, was found to be associated with the roots of chamomile.[52]

Besides damaging the cultivated crop of chamomile, fungi and insects also cause extensive damage to the dry flowers during storage and reduce the quality of the dried raw product. This is because dried chamomile, the flowers in particular, contain a large amount of hydrophilic constituents (sugars, flavonoids, mucilages, phenyl carbonic acids, amino acids, choline, salts), and also chamomile herbs are hygroscopic. Microbiological deterioration caused by fungal agents occurs in a very short time. Thus, at the marginal condition of the dry product, the most xerophilic species, molds of the species *Aspergillus* and *Penicillium* form first. The metabolism of bacteria and fungi releases more and more moisture for the more demanding organisms, such as *Fusarium* and *Rhizopus*, so the attack continues to develop in a kind of cascade effect.[63] The metabolic excretions from the microbiological agents also make the stored product smell musty or damp, which is rated very negatively in terms of quality. In addition there is a risk that the stored product will be contaminated with mycotoxins, which are a health hazard.

The dried product is also a favorite habitat for certain insects. Larvae and beetles generally damage the stored product by eating away and polluting it with excreta and webs. This considerably reduces the quality and leads to total deterioration in a short time. The main stock pests that affect the drug are *Plodia interpunctella* Hb. (copper red-Indian meal moth), *Ptinus latro* F. (dark brown thief beetle), *P. testaceus* Oliv. (yellow brown thief beetle), *Gibbium psylloides* Gzemp. (smooth spider beetle), *Lasioderma servicorne*, and *Stegobium paniceum*.[64]

Co-cultivation

Patra *et al.*[65] reported that chamomile is grown as a winter (Rabi) season crop and, therefore, fits well in rotation with major summer (Kharif) season crops, such as paddy, maize, and others. It may follow pulses, such as green gram, pigeon pea, and other summer vegetables, such as "Okra," cucumber, and others. It can be grown even after early maturing *Brassica*s; chamomile can be grown on the residual soil fertility preceding green manuring and crops that are heavily fertilized. It can be grown as an intercrop with many arable crops.

In 1999 Mishra *et al.*[66] reported intercropping of celery + chamomile, ajwain + chamomile, fennel + chamomile, and sowa + chamomile, all in 1:1 ratio. Sowing of the main crop was done on 2nd November, and 8-week-old seedlings of chamomile were transplanted in the 1st week of January. Spacing of 45 × 20 cm was maintained for all the crops, dried biogas slurry was supplied at the time of land preparation, and three irrigations were given to the crops. Chamomile started blooming from the second week of March and three flower pickings (between March 25 and April 19) were done manually at an interval of 7–10 days. Also, chamomile has been found to be a suitable intercrop with aromatic grasses, such as lemon grass and palmarosa, which remain dormant in winter.

Table 1: Biological activity attributed to *Matricaria chamomilla*

Activity	References
Analgesic	[98]
Antiallergic	[99]
Anticancer	[100]
Antihyperglycemic	[101]
Antiinflammatory	[102]
Antimicrobial	[103]
Antipruritic	[104]
Antisolar	[105]
Antispasmodic	[89,106]
Antistress	[107
Antiulcer	[108]
Anxiolytic	[109]
Arcaricadal property	[110]
Gastrointestinal disorders	[111]
Hepatoprotective	[112]
Immunomodulatory	[113]
Inhibition of poliovirus replication	[114]
Intracanal irrigant	[115]
Lousicidal, ovicidal, repellent	[116]
Prevent osteoporosis	[117]
Sedative	[118]
Treatment of infant botulism	[119]
Treatment of oral mucositis	[120]
Uterotonic	[121]
Virucidal agent	[122]
Wound healing property	[123]

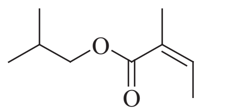
CHAMOMILE (*M. CHAMOMILLA*) AS A SOURCE OF NATURAL PRODUCTS

M. chamomilla belongs to a major group of cultivated medicinal plants. It contains a large group of therapeutically interesting and active compound classes. Sesquiterpenes, flavonoids, coumarins, and polyacetylenes are considered the most important constituents [Figure 1] of the chamomile drug.[64] The coumarins are represented in *M. chamomilla* by herniarin, umbelliferone, and other minor ones.[67,68] (Z)- and (E)-2-β-D-glucopyranosyloxy-4-methoxycinnamic acid (GMCA), the glucoside precursor of herniarin, were described as native compounds in chamomile.[69,70] Eleven bioactive phenolic compounds,[71] such as herniarin and umbelliferone (coumarin), chlorogenic acid and caffeic acid (phenylpropanoids), apigenin, apigenin-7-O-glucoside, luteolin and luteolin-7-O-glucoside (flavones), quercetin and rutin (flavonols), and naringenin (flavanone) are found in chamomile extract.

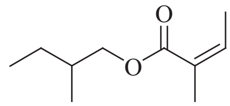
More than 120 chemical constituents have been identified in chamomile flower as secondary metabolites,[72,73] including 28 terpenoids, 36 flavonoids,[13,74,75] and 52 additional compounds with potential pharmacological activity [Table 1].[15] Components, such as α-bisabolol and cyclic ethers are antimicrobial,[76,77] umbelliferone is fungistatic, whereas chamazulene and α-bisabolol are antiseptic.[78] The chamomile was found to have the most effective antileishmanial activity.[79]

German chamomile is a natural source of blue oil (essential oil). The flowers and flower heads are the main organs of the production of essential oil. It is remarkable that chamomile flower oil mainly consists of sesquiterpene derivatives (75–90%) but only traces of monoterpenes. The oil contains up to 20% polyynes. The principal components of the essential oil extracted from the flowers are (E)-β-farnesene (4.9–8.1%), terpene alcohol (farnesol), chamazulene (2.3–10.9%), α-bisabolol (4.8–11.3%), and α-bisabolol oxides A (25.5–28.7%) and α-bisabolol oxides B (12.2–30.9%),[33,80-84] which are known for their antiinflammatory,[27,85,86] antiseptic,[87] antiplogistic,[81,88] and spasmolytic[89] properties. Among the various major constituents, α-bisabolol and chamazulene have been reported to be more useful than others. Chamazulene is an artifact formed from matricine, which is naturally present in the flowers during hydrodistillation or steam distillation. The color of the oil determines its quality. Blue color of the oil is due to sesquiterpene. The chamazulene content of the various chamomiles depends on the origin and age of the material. It decreases during the storage of the flowers.[90]

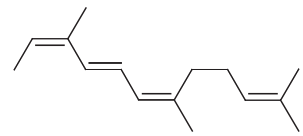
Bisabolol has been found to reduce the amount of proteolytic enzyme pepsin secreted by the stomach without any change occurring in the amount of stomach acid, due to which it has been recommended for the treatment of gastric and upper intestinal diseases.[91] It has also been reported to promote epithelization and granulation, and to produce a pronounced and antiphlogistic effect on paw carrageenin edema and cotton pellet granuloma of the rat.[81] Similarly, it is recommended that, if chamomile extracts were to be used for their antiphlogistic effects then plants rich in bisabolol and chamazulene should be chosen.[88,92] Also, because of the antiinflammatory properties of bisabolol, it is recommended in cosmetic preparations.[85] The



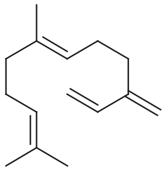
1. Isobutyl angelate



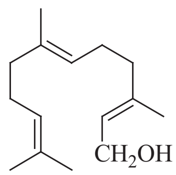
2. 2-Methylbutyl angelate



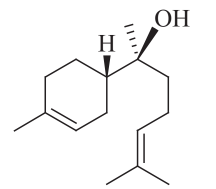
3. Farnesene



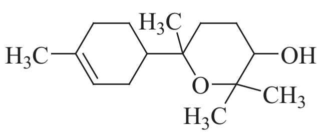
4. β-Farnesene



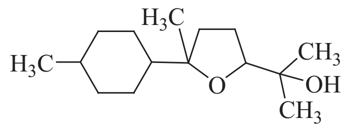
5. Farnesol



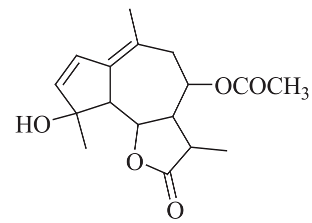
6. (-)-α-bisabolol



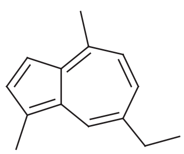
7. Bisabolol oxide A



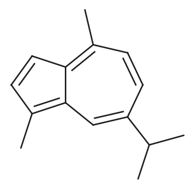
8. Bisabolol oxide B



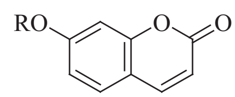
9. Matricin



10. Chamazulene

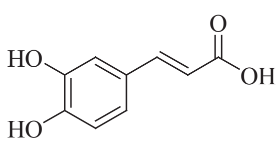


11. Guaiazulene

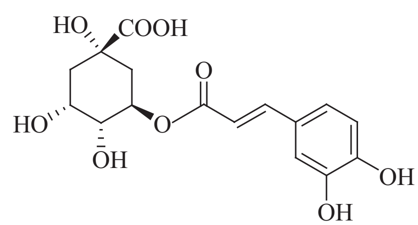


12. Umbelliferone (R=H)

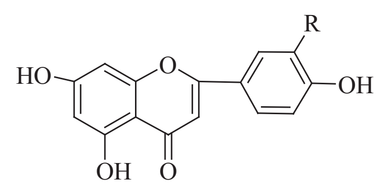
13. Herniarin (R=CH_3)



14. Caffeic acid

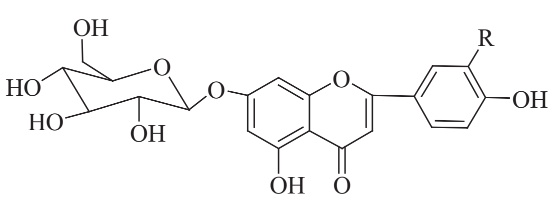


15. Chlorogenic acid



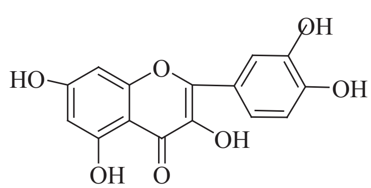
16. Apigenin (R=H)

17. Luteolin (R=OH)

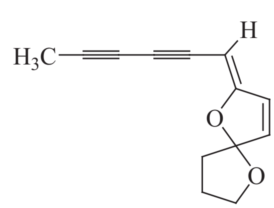


18. Apigenin-7-O-glucoside (R=H)

19. Luteolin-7-O-glucoside (R=OH)



20. Quercetin



21. Z-Enyne dicycloether

Figure 1: Secondary metabolites from *M. chamomilla*

presence of *cis*-en-yne-dicyclo ethers, perillyl alcohol, triacontane, cadeleric hydrocarbon, and cadeleric tertiary alcohol was reported in chamomile.[93,94] The other compounds, such as thujone and borneol were present in very low amounts. The main constituents of the flowers also include several phenolic compounds, primarily the flavonoid apigenin, quercetin, patuletin, luteolin, and their glucosides.

Besides the capitula, the shoot (leaves and stem) and root of the plant also contain essential oil. Earlier investigations on the oil of this herb reported[55,83] the presence of (Z)-3-hexenol, (E)-β-farnesene, α-farnesene, germacrene D, (E)-nerolidol, spathulenol, hexadec-11-yn-11,13-diene, and (Z)- and (E)-en-yn-dicycloethers, whereas the root oil was reported to contain linalool, nerol, geraniol, β-elemene, (E)-β-farnesene, α-farnesene, spathulenol, τ-cadinol, τ-muurolol, β-caryophyllene, *cis*-caryophyllene, caryophyllene oxide, chamomillol, hexadec-11-yn-11,13-diene, *cis*- and *trans*-en-yn-dicycloethers, and chamomile esters I and II.[55,95] These oils were devoid of chamazulene and α-bisabolol and its oxides were present as minor constituents. α-Humulene, hexadec-11-yn-13,15-diene, phytol, isophytol, and methyl palmitate were detected for the first time from *M. chamomilla*.[10]

All these and other compounds were found in different amounts and ratios in various parts of the inflorescence depending on the growth stage and the time of picking during the day. The quantity of α-bisabolol and α-bisabolol oxides A and B in the flowers reached a maximum at full bloom and then declined.[96] Farnesene content of the flowers decreased gradually with their growth and development. The accumulation of essential oils in the flowers continued during drying. Harvesting at the early flowering phase and drying in shaded places is recommended. Franz,[97] in pot trials, showed that the oil content was the lowest in decaying heads and highest in one week of flower initiation. Farnesene and bisabolol were highest in the flower buds and lowest in the decaying flowers. Chamazulene and bisabolol oxide content increased from buds to fully developed flower buds.

BIOCHEMISTRY AND BIOTECHNOLOGY

Effect of nitrogen on *M. chamomilla*

Environmental stress, irrespective of its nature, enhances reactive oxygen species (ROS) formation,[124] thereby activating both protective mechanism and cellular damages. Tissue damage occurs when the capacity of antioxidative systems becomes lower than the amount of ROS generated.[125] To protect cells under stress conditions and maintain the level of ROS, plants possess several enzymes to scavenge ROS. Important in regulating intracellular hydrogen peroxide (H_2O_2) are catalase (CAT) and peroxidases (guaiacol peroxidase [GPX]).[124] A previous study has shown that both CAT and GPX increase their activity under conditions of N starvation in rice leaves.[126] Moreover, both CAT and GPX showed the highest activities, while H_2O_2 accumulation and superoxide dismutase activity was the lowest in the leaves of bean plants cultivated with the lowest N dosage compared with the highest N dosage.[127] Since growth of the leaves and roots was the highest in the lowest N dosage, this could be an indication that removal of H_2O_2 occurs also under optimal nutrient conditions. Additionally, this indicates that the highest N dose is toxic and drastically depresses the growth of the plants.[127] Phenolic compounds are potent inhibitors of oxidative damage due to availability of their phenolic hydrogen.[128] Their involvement in H_2O_2 detoxification through peroxidases is well established.[127] Enhancement of phenylalanine ammonia-lyase (PAL) activity and higher accumulation of leaf phenolics and root exudation of phenolics under phosphate and N deficiency were recorded.[129]

In a previous study, Kovacik *et al*. reported that with prolonged N deficiency the majority of detected phenolic acids and coumarin-related compounds increased in chamomile leaf rosettes.[130] Recently Kovacik and Backor[131] showed that N deficiency enhanced root growth and inhibited shoot growth in *M. chamomilla* plants. Chlorophyll composition was not affected by N stress, but N and soluble proteins decreased in both the rosettes and the roots. PAL activity was enhanced in N-deficient rosettes and tended to decrease by the end of the experiment, while in the roots PAL activity was maintained. The total phenolic contents increased in both rosettes and roots under N deficiency. N-deficiency also affects peroxidase and CAT activities as it decreased them in the rosettes, while it increased them in the roots. Furthermore, lipid per oxidation status increased in N-deficient roots, indicating that antioxidative protection was insufficient to scavenge ROS being generated. Surprisingly, H_2O_2 content was lower in N-deficient roots, while in the leaves it increased.

Effect of Cd and Cu on *M. chamomilla*

Heavy metals have become one of the main biotic stress agents for living organisms because of their increasing use in the developing field of industry causing high bioaccumulation and toxicity.[132] Heavy metal toxicity usually depends on the metal amounts accumulated by plants. Cadmium (Cd) has no known physiologic function in plants, whereas Copper (Cu) is an essential plant micronutrient. Being a redox active metal, Cu generates ROS, whereas Cd is a redox inactive metal unable to catalyze the generation of ROS via Fenton–Haber-Weiss reactions.[133,134] Nevertheless, Cd may induce the expression of lipoxygenases in plant tissues, and thus indirectly causes oxidation of polyunsaturated fatty acids.[135] Cu has a greater ability to cause lipid peroxidation than redox inactive metals, such as Cd; this fact was previously demonstrated also in Cd- and Cu-treated chamomile.[136,137] Hydrogen peroxide is the main ROS being formed from superoxide radical and scavenged by specific enzymes. Therefore, regulated production of ROS and maintenance of "redox homeostasis" are essential for the physiologic health of organisms.[138]

Plants develop different mechanisms enabling them to cope with metal accumulation in the tissues and ROS formation induced by the presence of metals. Kovacik and Backor[139] studied the

Cd and Cu uptake by 4-week-old chamomile plants and their effect on selected antioxidative enzyme activities, such as CAT, GPX, and glutathione reductase (GR) up to 7 days of exposure to 3, 60, and 120 μM Cd or Cu. Cd content in the rosettes was 10-fold higher in comparison with Cu, whereas Cu was preferentially accumulated in the roots. The increase of CAT and GPX activity was similar in the rosettes of Cd- and Cu-treated plants, indicating the nonredox active properties of Cd and low Cu accumulation. In the roots, Cu showed strong pro-oxidant effect, as judged from extreme stimulation of CAT and GPX, followed by an increase in H_2O_2 and malondialdehyde (MDA). However, alleviation of oxidative stress (ca. 93- to 250-fold higher activity in 120 μM Cu-treated roots) seemed to be more important. Cd had substantially lower influences and stimulated GR activity more than that by Cu.

Kovacik *et al*.[136] reported that Cu decreased dry mass production, water, chlorophyll, and N content in both the leaf rosettes and roots at 120 μM. Most of the 11 phenolic acids detected increased in 60 μM Cu but in the 120 μM treatment their contents were lower or not significantly different from the control. Among the coumarin-related compounds, (Z)- and (E)-GCMAs increased in 60 and 120 μM Cu, whereas herniarin rose in the 3 and 60 μM Cu. The amounts of umbelliferone were not affected by any of the doses tested. The MDA content of the leaf rosette was not affected by the exposure of plants to 120 μM Cu, but a sharp increase was observed in the roots. At 120 μM Cu stimulated a 9-fold higher K^+ loss than the 60 μM treatment, whereas at the lowest concentration it stimulated K^+ uptake. Cu accumulation in the roots was 3-, 49-, and 71-fold higher than the leaf rosettes in the 3, 60, and 120 μM Cu treatments, respectively. The 120 μM Cu dose is limiting for chamomile growth.

Chamomile is reported to accumulate high amounts of Cd preferentially in the roots and also in anthodia,[140-142] indicating that it belongs to the group of facultative metallophytes or metal excluders. Grejtovsky *et al*. studied the effects of Cd on secondary metabolites of chamomile, and did not observe any changes in apigenin-7-O-glucoside and other derivatives in anthodia.[143] On the other hand, the quantities of two coumarins in the leaves, herniarin and umbelliferone, as well as herniarin glucosidic precursors (Z)- and (E)-GMCAs, were affected by foliar application of Cu^{2+} ions and biotic stress.[144,145] These two stress factors resulted in a decrease in the GMCAs, but an increase in herniarin as well as umbelliferone compared with the control. However, nutritional starvation, such as N deficiency, did not cause this pattern of coumarins dynamics, indicating the presence of other mechanisms governing their accumulation.[146]

Kovacik *et al*.[137] reported that the dry mass accumulation and N content were not significantly altered under low (3 μM) and high (60 and 120 μM) levels of Cd. However, there was a significant decline in the chlorophyll and water content in the leaves. Among coumarin-related compounds, herniarin was not affected by Cd, whereas its precursors (Z)- and (E)-GCMAs increased significantly at all the levels of Cd tested. Cd did not have any effect on umbelliferone, a stress metabolite of chamomile. Lipid peroxidation was also not affected by even 120 μM Cd. Cd accumulation was approximately 7- (60 μM) to 11-fold (120 μM) higher in the roots than that in the leaves. At high concentrations, it stimulated K^+ leakage from the roots, whereas at the lowest concentration it could stimulate K^+ uptake. This supported the hypothesis that metabolism was altered only slightly under high Cd stress, indicating that chamomile is tolerant to this metal. Preferential Cd accumulation in the roots indicated that chamomile could not be classified as a hyperaccumulator and, therefore, it is unsuitable for phytoremediation.

Effect of amino acids on *M. chamomilla*

Amino acids can act as growth factors of higher plants because they are the building blocks of protein synthesis, which could be enzymes important for metabolic activities. There is evidence that ornithine is a precursor of polyamines that are essential in the regulation of plant growth and development.[147,148] Proline has been shown to accumulate in the plant tissue under various conditions.[149,150] The suggested functions of the accumulated proline are osmoregulation, maintenance of membrane and protein stability, growth, seed germination, and provision of storage of carbon, nitrogen, and energy.[149,151,152]

Gamal el-Din and Abd-el-Wahed[153] investigated the effect of different concentrations of ornithine, proline, and phenylalanine on vegetative growth, essential oil, and some biochemical constituents of chamomile. They observed that all the amino acids significantly increased the plant height, number of branches, number of flower head, fresh and dry weights of the aerial parts, and flower head per plant. Foliar application of 50 mg/L ornithine and 100 mg/L proline or phenylalanine resulted in greater effect as compared with other treatments. This regulatory effect of amino acids on growth could be explained by the notion that some amino acids (eg, phenylalanine and ornithine) can effect plant growth and development through their influence on the gibberellin biosynthesis.[154] The total phenol and total indole contents in the vegetative aerial parts were significantly increased by all the amino acids. The maximum effect showed ornithine, proline, and phenylalanine at a concentration of 150 mg/L. Proline or phenylalanine at 50 or 150 mg/L decreased the total carbohydrates, whereas 150 mg/L of ornithine had such effect. The greatest increase in the oil percentage and yield were obtained at 150 mg/L of ornithine and 100 mg/L of proline or phenylalanine.

Effect of salicylic acid on *M. chamomilla*

Salicylic acid (SA) is a well-known endogenous plant signal molecule involved in many growth responses and in disease resistance.[155,156] Stimulation of growth after exposure to SA has been recorded in some plant species, such as wheat,[157] soybean,[158] and maize.[159] It can also contribute to stress tolerance by stimulating highly branched metabolic responses.[160] The effect of exogenous SA depends on numerous factors, including the species and developmental stage, the mode of application, and the concentration of SA.[160,161] A range of plant physiologic reactions to SA application are known. Pastirova *et al.* have shown that accumulation of coumarin-related compounds in chamomile was affected by exogenous SA application at a dose of 2 mM.[162] Kovacik *et al.*[163] reported that SA exhibited both growth-promoting and growth-inhibiting properties at doses of 50 and 250 μM, respectively. The latter being correlated with the decrease of chlorophylls, water content, and soluble proteins. In terms of phenolic metabolism, it seems that the higher SA dose has a toxic effect, based on the sharp increase in PAL activity, which is followed by an increase in total soluble phenolics and lignin accumulation. GPX activity was elevated at a dose of 250 μM SA. However, PAL activity decreased with prolonged exposure to SA, indicating its inhibition. Accumulation of coumarin-related compounds (umbelliferone and herniarin) was not affected by SA; whereas (Z)- and (E)-GCMAs increased in the rosettes at 250 μM SA.

Tissue culture studies

Tissue culture is the culture and maintenance *in vitro* of plant cells or organs in sterile, nutritionally and environmentally supportive conditions. It has applications in research and commerce. In commercial settings, tissue culture is often referred to as micropropagation, which is really only one form of a set of techniques. Micropropagation refers to the production of whole plants from cell cultures derived from explants, the initial piece of tissue put into culture of meristem cells. Two types of tissue culture of *M. chamomilla* were isolated, namely, E40 and BK_2 derived from leaf and stem, respectively.[164] These cultures were also maintained in modified Murashige and Skoog medium and essential oil was present in both types of tissue culture and chromatograms of both essential oils showed similarity. Szoke *et al.*[165,167] obtained callus tissues from root, stem, and flower clusters of wild chamomile. They studied the dynamics of growth of callus tissues on the basic growth medium containing 2,4-D and kinetin in light and in dark. It was observed that the growth of inflorescence callus, either cultured in light or dark, was sensitive to added growth regulators. It grew better with kinetin + 2,4-D. Use of 10% coconut milk instead of kinetin + 2,4-D was effective in improving the growth. Differences in the composition of essential oil in the three parts studied were attributed to the level of tissue organization. Cellarova *et al.*[168] has dealt with the possibility of morphogenesis induction in callus tissue cultures of some representatives of *M. chamomilla*. Shoot in calli has been induced by 0.1 mg/L kinetin or by combination of 0.5 mg/L kinetin and 0.5 mg/L alpha naphthyl acetic acid (NAA) added to Murashige and Skoog medium. Rhizogenesis took place without any other addition of auxin.

IMPROVED VARIETIES OF CHAMOMILE AS A SOURCE OF DRUG

The world market currently has chamomile drug of various origins and therapeutical values. The medicinal value of the plant material was evaluated by the content of essential oil and the content of chamazulene, etc.[6] The quality of blue oil (essential oil) is determined by its color. As the name indicates, bluer the oil better is the quality, because blue color serves as the chemical marker for the presence of terpenoids and flavonoids, chiefly chamazulene and α-bisabolol. For manufacturing chamomile extracts of antiphlogistic effectiveness, only such types of chamomile should be used, which exhibit a high content of (-)-α-bisabolol and the synthetic racemic bisabolol.[88] Thus, chamomile of a particular chemical composition is used as drug as it shows specific pharmacological activity.

As efficient methods for determining the drug constituents and effectiveness have been developed, the content of (-)-α-bisabolol and its oxides in the flowers has become an important indicator of drug quality and value. As a result, four basic types of chamomile A, B, C, and D are recognized, according to the qualitative and quantitative composition of the essential oil.[80,169]

-Chemical type A (dominant component of essential oil is bisabolol oxide A).
-Chemical type B (dominant component of essential oil is bisabolol oxide B).
-Chemical type C (dominant component of essential oil is (-)-α-bisabolol).
-Chemical type D ((-)-α-bisabolol and bisabolol oxide A and B present in 1:1 ratio approx.).

The major suppliers of chamomile for the world market, which are Poland, Hungary, Germany, Argentina, and Czecho-Slovakia, have recently initiated intensive plant improvement programs to produce plants with high levels of essential oils with a defined chemical composition. The varieties "Bona," "Kosice-II," and the cultivar "koice-1" have been developed through selection and breeding efforts. Normally, these new types have over twice the essential oil content of the older "Bohemia" variety, and "Bona" and "Kosice-II" have chemical profiles much higher in (-)-α-bisabolol and chamazulene [Table 2].[23,170]

German chamomile was introduced in India during the 17th century. But its commercial cultivation remained marginalized mainly due to poor yield of flowers coupled with low oil content and poor oil quality. No attempt was ever made to scientifically organize the cultivation of such valuable cash crop. As a result of germplasm enhancement and exploitation program, an improved variety, Vallary, was developed and finally released for commercial cultivation in India.[171] It is the first ever genetically improved variety of German chamomile, bred specially for agroclimatic conditions of North Indian plains. Its oil is highly viscous and dark blue in color, indicative of high concentration of terpenoids and flavonoids.[26]

Trade

German chamomile enjoys good domestic and international market. It is the fifth top selling herb in the world and is a major food cosmetic and pharmaceutical additive. It sold either as flower head or as blue oil. "Blue oil" is the commercial trade name of chamomile oil in the international market, which fetches

Table 2: Characteristics of varieties and breeding material in chamomile[170]

Characteristics	Variety/line/origin
High matricin/chamazulene	Olanda Sregez Turkey
Low matricin/chamazulene	Egypt Turkey
High matricin/chamazulene and bisabolol	Adzet Bona Camextrakt Degumill Goral (Kosice-II) Lutea Mabamille Manzana Novbona Robumille
High matricin/chamazulene and bisabolol oxide	Bodegold Bohemia Budakalaszi 2 (BK-2) Camoflora Flora Tetra Tonia Zloty Lan Argentina Mexico
High matricin/chamazulene and bisabolone	Lazur rkey Bulgaria

about Rs. 40,000 for a kilogram.[171] The world production of chamomile blue essential oil was estimated by the USDA to be 5.4 t, in the year 1989.[172]

The medicinal plant sector in India is unorganized and it is difficult to get regular update of statistics *vis-à-vis* the demand and supply, collection, and economics of chamomile. Also, worldwide production figures are difficult to isolate due to small-scale farming and the fact that statistics generally do not quote chamomile separately from herbs. In 1995, the worldwide production was estimated to be approximately 500 t of dried flower per annum from large-scale farming. In 1998, this figure raised to 1000 t of dried flower per annum from large-scale farming.[172]

Price is largely regulated by supply and demand in the world. In 1991, the world price for dried chamomile flower ranged from US $ 1,000/t for low grade to approximately US $ 16,000/t for high oil content flower.[172] Bulk botanical herbs, in 1997, was advertising organically grown chamomile on the Internet at US $ 28 per pound (US $ 61.73 per kg).[172] Recently, it is selling at the rate of US $ 700 per kg.[173] With the current trends, these prices should increase within the next two years.

CONCLUSIONS

There is a great demand for chamomile in the world market because of its extensive medicinal values and impeccable pharmacological properties. Also, there has been an increase in the use of natural substances instead of synthetic chemicals because many herbal medicines are free from side effects, easy to obtain, considered healthy, and create income. It is a well-established fact that chamomile plant diversity is being threatened by unregulated harvesting of natural populations and expansion of urban centers. So it is advisable to cultivate chamomile for better quality control of the target bioactive components. This approach also allows for the production of uniform plant material at predetermined intervals in the required quantities. A strong need is felt to screen the different chemotypes of chamomile growing at different phytogeographical locations. Similarly, biodiversity studies at morphologic, biochemical, and genetic levels will enable the research community to realize the extent of variability within the existing germplasm of chamomile, and hence help in the conservation of the plant. However, there is still a wide scope for exploring different aspects of chamomile.

In India, it appears that there is a good potential for chamomile cultivation as a commercial medicinal and industrial crop. Because of the high international market price of chamomile, it is necessary to promote this valuable crop as a commercial crop mainly for export of chamomile oil from India.

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