THESIS

Eden Fima
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University of Veterinary Medicine Budapest
Department of Botany

Special medicinal plants of dogs and cats in Israel

By
Eden Fima
Supervisor:
Dr. Péli Evelin Ramóna, Ph.D.

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Abstract

The use of medicinal plants as alternative or complementary therapies in veterinary medicine has gained considerable attention in recent years. A systematic literature review was performed to investigate the therapeutic potential of selected medicinal plants in the management of health conditions in dogs and cats, which especially grow in Israel.
Due to its unique geography, Israel has many indigenous plants, connecting three continents with different climatic zones.
The research encompasses a multidisciplinary approach, incorporating botanical, pharmacological, phytochemical, and clinical perspectives.
By providing scientific evidence supporting the safety and efficacy of selected plant-based treatments, this research seeks to expand the therapeutic options available for veterinarians, enhance animal well-being, and promote sustainable and holistic approaches to veterinary healthcare.

Összefoglaló

A gyógynövények alternatív vagy kiegészítő terápiaként történő alkalmazása az állatgyógyászatban az elmúlt években jelentős figyelmet kapott. A szakirodalmi áttekintés szisztematikus áttekintését végezték el, hogy megvizsgálják a kiválasztott gyógynövények terápiás potenciálját a kutyák és macskák egészségi állapotának kezelésében, amelyek különösen Izraelben nőnek.
Izraelben az őshonos növények nagy választéka található egyedi földrajzi adottságai miatt, amelyek három kontinenst kötnek össze különböző éghajlati övezetekkel.
A kutatás multidiszciplináris megközelítést ölel fel, amely botanikai, farmakológiai és klinikai szempontokat is magában foglal.
A kiválasztott növényi alapú kezelések biztonságosságát és hatékonyságát alátámasztó tudományos bizonyítékokkal ez a kutatás az állatorvosok számára elérhető terápiás lehetőségek bővítését, az állatok jólétének javítását, valamint az állategészségügyi ellátás fenntartható és holisztikus megközelítésének előmozdítását célozza.

Content

Introduction

In my review, I discuss the relevant medicinal plants found in Israel and their ethnoveterinary aspects.
Medicinal plants encompass a vast and varied domain, yet certain countries, including Israel, need more research. There is a growing global acknowledgment of the efficacy of natural remedies over time. Present-day societal norms regard pets as integral family members, warranting healthcare standards akin to those for humans. Consequently, pet owners have a burgeoning interest in utilizing herbal remedies for their animals. Conducting studies to accurately identify and use these plants to benefit pet owners and educate and raise awareness within the veterinary community is imperative.

Literature review

Classification of the phytochemical compound

Since ancient times, there has been a belief in the therapeutic properties of biologically active compounds present in plants, which are utilized for treating various ailments such as asthma, gastrointestinal issues, skin disorders, respiratory and urinary complications, and hepatic and cardiovascular diseases, among others, in pet medicine. The medicinal value attributed to these plants underscores their potential for discovering and developing new pharmaceuticals, owing to the presence of chemical substances that elicit positive physiological actions in the human and animal bodies. Phytochemicals are derived from a diversity of plant organs, encompassing roots, stems, leaves, flowers, fruits, and seeds [97]. are often observed as pigmented molecules in the outer layer of plant tissue. Plants accumulate bioactive phytochemicals, both primary and secondary metabolites, contributing to their pharmacological benefits.

Primary metabolites, including glucose, starch, polysaccharides, proteins, lipids, and nucleic acids, are essential for the growth and development of animals' bodies. In contrast, plants biosynthesize secondary metabolites, comprising alkaloids, flavonoids, saponins, terpenoids, steroids, glycosides, tannins, and volatile oils [98]which possess therapeutic properties. Secondary metabolites, particularly phytochemicals, play a significant role in treating various animal diseases.

Phytochemicals display a broad spectrum of pharmacological activities. Alkaloids, for instance, manifest antispasmodic, antimalarial, analgesic, and diuretic effects, whereas terpenoids showcase antiviral, anthelmintic, antibacterial, anticancer, antimalarial, and anti-inflammatory properties.

Glycosides are known for their antifungal and antibacterial properties, while phenols and flavonoids possess, antiallergic, and antibacterial properties.

Saponins exhibit anti-inflammatory, antiviral, and plant-defense activities.
In India, numerous studies have been conducted to validate the traditional use of medicinal plants by investigating their phytochemical ingredients. Efforts have been made to consolidate and manage the collected records and information from various sources, including published literature and books, towards summarizing the phytochemical activity of medicinal plants widely used in India.[1]

In contemporary usage, many phytochemicals are widely recognized for their associated health benefits, with their historical significance extending into modern medicine. While not all, many of these compounds are categorized as secondary metabolites. However, this term may inaccurately imply that they are not vital for a plant's expected growth, development, or reproduction. Exploring phytochemicals has been extensive, with numerous dedicated resources, including journals, books, dictionaries, and databases.

Many journals in natural products chemistry, acknowledged by the American Society of Pharmacognosy, serve as platforms for research in this field. These include Chemistry of Natural Compounds, Economic Botany, Fitoterapia, Journal of Antibiotics, Journal of Asian Natural Products Research, and many others. Additionally, professional societies such as the

American Society of Pharmacognosy, the Phytochemical Society of Europe, AFERP (Association Francaise pour l'Enseignement et al. Recherche en Pharmacognosy), the Phytochemical Society of North America, and the Society of Medicinal Plant Research, among others, are dedicated to advancing research in phytochemistry.
In conclusion, phytochemicals have gained significant recognition for their medicinal value and continue to be a subject of extensive research and exploration, underscoring their importance in traditional and modern medicine.[2]

In the following paragraph, I will explain the phytochemical compounds of the later detailed medicinal plants of my review.

1. Triterpenes: C_{30}

Triterpenes, particularly C30 terpenes, are compounds derived from squalene and comprise six isoprene units. They are typically solid at high melting points and are colorless. Widely distributed among plant resins, cork, and cutin, triterpenes encompass various groups, such as Prominent triterpenes, steroids, saponins, sterolins, and cardiac glycosides are among the common phytochemicals found in plants. Azadirachtin, derived from the seeds of the neem tree (Azadirachta indica), represents a noteworthy triterpene renowned for its potent insect antifeedant properties [99].
Azadirachtin was first isolated 1985 from neem oil and has notable medical applications.
Common triterpenes, such as amyrins, ursolic acid, and oleanolic acid, are found in waxy coatings on leaves and as protective coatings on fruits.
Other triterpenes, such as limonins and cucurbitacins, act as potent insect steroid hormone antagonists.[3]

2. Saponins

Saponins are high-molecular-weight triterpene glycosides found widely across the plant kingdom. They consist of a sugar group attached to a sterol or triterpene. Comprising two parts, namely the glycone (sugar) and the aglycone or genin (triterpene), saponins typically exhibit detergent properties, can foam readily in water, have a bitter taste, and are toxic to fish (piscicidal).

Historically, many plants containing saponins, including soaproot, soapbark, soapberry, and soapnut, were utilized as natural soaps
Saponins' aglycones can be categorized into the triterpene, steroid, or steroid alkaloid classes. Depending on the quantity of attached sugar moieties, saponins may exist as mono- or polydesmodic compounds.

Saponins are derived from squalene and composed of six isoprene units. Biosynthetically, they are derived from squalene. Recent studies have elucidated many details, including the cyclase enzymes involved in their synthesis.

Commercially significant preparations containing saponins include extracts from sarsaparilla root, licorice, ivy leaves, primula root, and ginseng. Glycyrrhizic acid, derived from licorice root, comprises the ammonium and calcium salts of glycyrrhizins, possessing a sweetness level 50 to 100 times greater than sucrose [100]. These active compounds showcase expectorant,

bacteriostatic, and antiviral properties; however, excessive consumption may result in elevated sodium secretion.
Ginsenosides, another triterpene saponins found in ginseng, are believed to be responsible for its immunostimulant and pain-relieving properties. [4]

In the *Calendula officinalis* (field marigold), the major constituents of the analyzed substance include triterpene saponins.

3. Flavonoids

Flavonoids stem from flavone and are identified by a unique chemical arrangement consisting of two benzene rings divided by a propane unit.
Flavonoids are predominantly water-soluble compounds, and some exhibit bright colors due to their conjugated structures. They are commonly found in plants as glycosides, which can make determining their exact structures challenging [41].

Different subclasses of flavonoids exist, including chalcones, flavones, flavonols, flavanones, anthocyanins, and isoflavones, each distinguished by unique structural features such as additional heterocyclic rings and hydroxyl groups. Some notable examples include quercetin, silybin, and neohesperidin, which possess antioxidant properties and potential health benefits [41]
(Figure 1.)

Isoflavones, a subgroup of flavonoids with a rearranged skeleton, are prevalent in the legume family Fabaceae. Compounds like genistein and daidzein, found in kudzu and soybeans (Figure 2.), demonstrate anticancer activity, while others like biochanin A, genistein, and coumestrol act as phytoestrogens with antifungal activity [42]
Flavonoids play diverse roles in plants and offer potential therapeutic applications in human and animal health and medicine.
Ongoing research aims to further elucidate their structural diversity and biological activities, with implications for drug discovery and development.[5]

Sylimarin is a flavonoid complex in *Sylibum marianum* (milk thistle), which I will discuss later in my review.

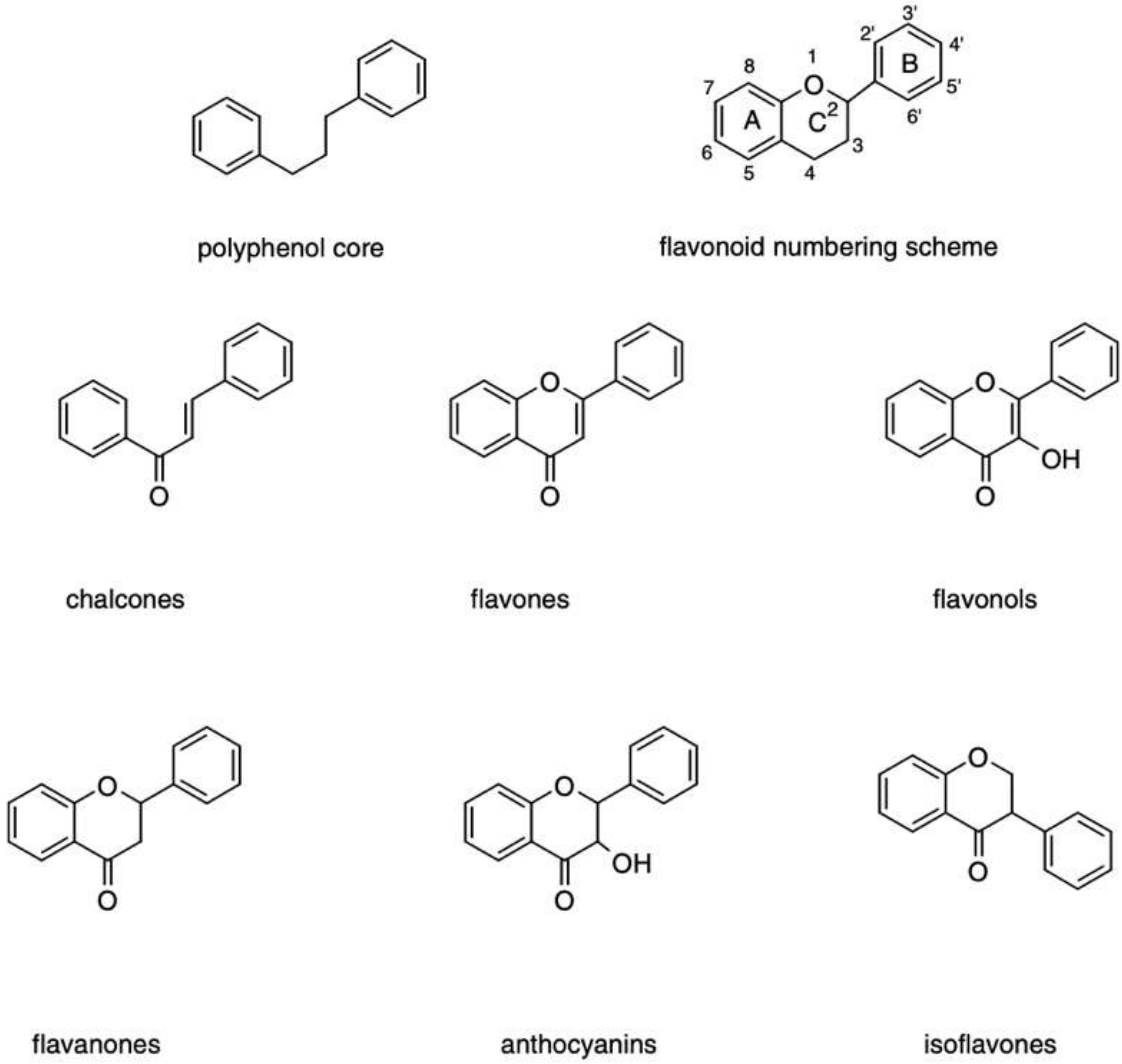


Figure 1. Flavonoid classes: Natural Products from Plants, Second Edition, Phytochemicals: The Chemical Components of Plants. p. 23

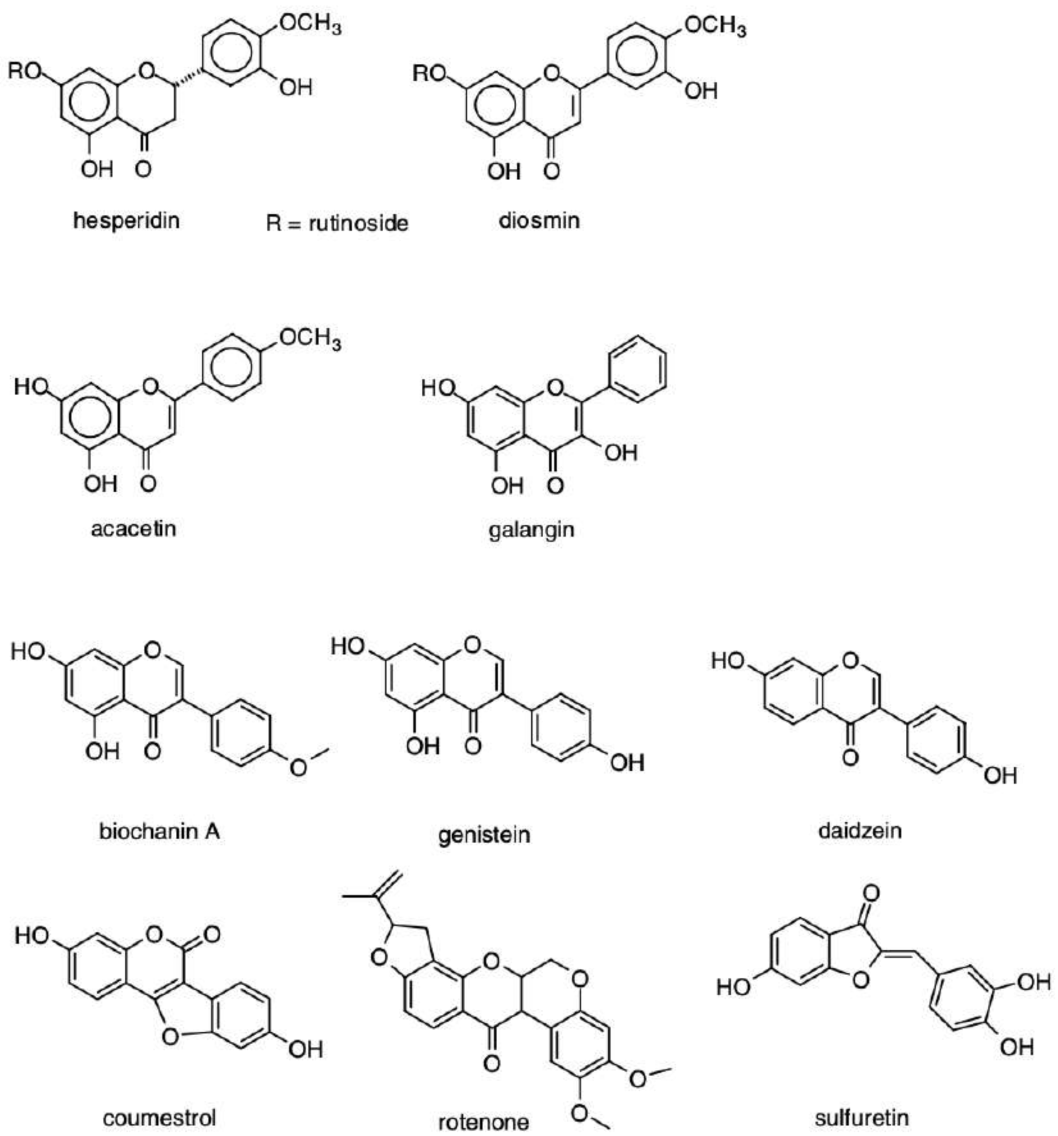


Figure 2. Flavonoids. Natural Products from Plants, Second Edition, Phytochemicals: The Chemical Components of Plants, p. 24

4. Alkaloids

Alkaloids, plant-derived nitrogen-containing compounds, are widely distributed among various plant groups. They are pharmacologically active, basic compounds with one or more heterocyclic nitrogen atoms, often derived from aromatic amino acids (Figure 3.). Alkaloids are classified based on their ring systems and exhibit diverse physiological effects, including narcotic, antihypertensive, and smooth muscle relaxant properties. Some notable alkaloids include reserpine, vinblastine, morphine, atropine, cocaine, and strychnine.

In addition to their pharmacological roles, plant alkaloids serve as chemoprotective agents against herbivory or growth regulators. Historical use of alkaloids in plant extracts for poisons,

narcotics, stimulants, and medicines dates back several thousand years. Common alkaloid-based drugs include caffeine, quinine, nicotine, cocaine, morphine, and strychnine.
Alkaloids may originate from amino acids, terpenes, or aromatics biosynthetically. Their chemical complexity often necessitates their extraction from plants rather than synthetic production. Examples of alkaloids with therapeutic applications include berberine, papaverine, codeine, psilocybine, ajmaline, and ellipticine.
While some alkaloids offer promising medical benefits, others, like scopolamine, have a history of abuse and are associated with adverse effects. Camptothecin, for instance, is a quinoline alkaloid with potential in cancer treatment, as demonstrated by the FDA approval of its topotecan derivative for advanced ovarian cancers.
Overall, alkaloids represent a diverse group of compounds with significant pharmacological and therapeutic potential, underscoring the importance of ongoing research in this field. [6] [43] [104-119]

As discussed later, *Marrubium vulgare*, commonly known as white horehound, is an example of a plant containing alkaloids.

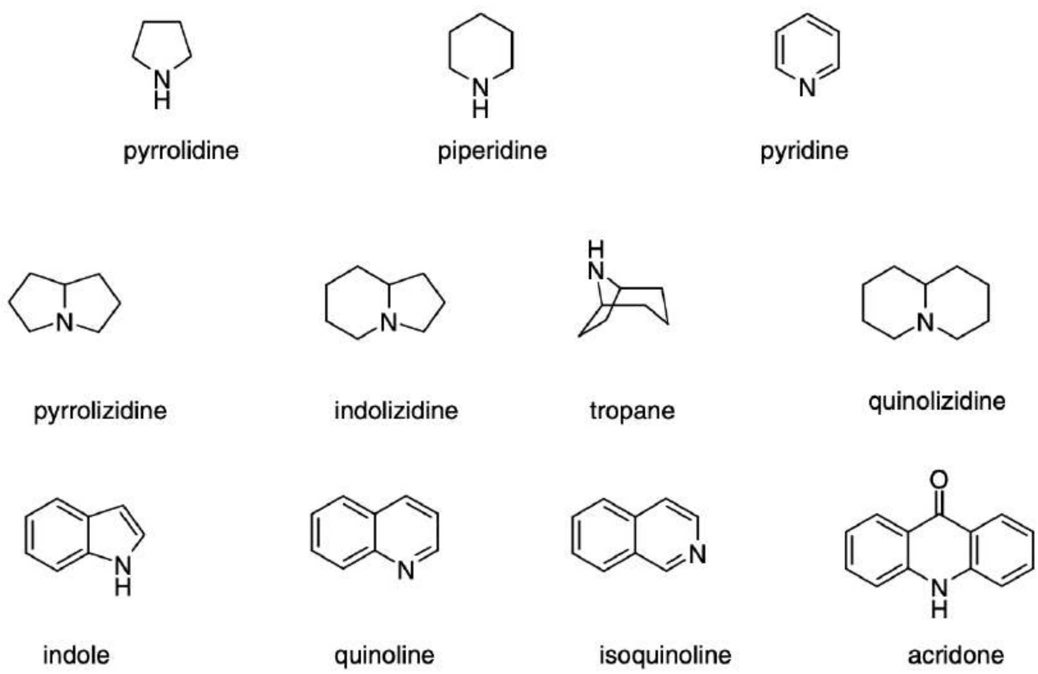


Figure 3. Alkaloid classes. Natural Products from Plants, Second Edition, Phytochemicals: The Chemical Components of Plants, p. 31.

5. Tannins

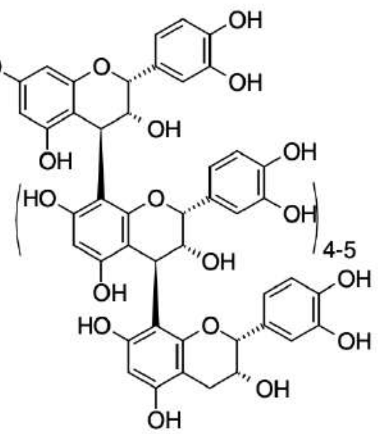
Tannins are water-soluble oligomers rich in phenolic groups that can bind or precipitate water-soluble proteins.

These compounds, frequently encountered in vascular flora, are predominantly distributed within lignified tissues but can also be detected in foliage, blossoms, or seeds.

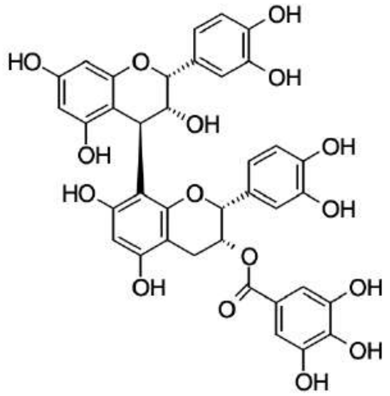
Plant organs exhibiting elevated tannin levels generally exhibit a pronounced bitterness, serving as a deterrent against consumption by the majority of herbivores.

Tannins are broadly categorized into two categories: condensed tannins and hydrolyzable tannins [101]. Condensed tannins undergo biosynthesis via the condensation of flavanols, leading to the formation of polymeric networks. Examples of condensed tannins, known as proanthocyanidins. On the other hand, hydrolyzable tannins are esters formed between a sugar, usually glucose, and one or more trihydroxybenzenecarboxylic acids, such as gallic acid. When reacted with albumin, starch, or gelatin, these compounds yield insoluble precipitates. This protein-reactive property is employed industrially in tanning to convert animal skins into leather. Examples of hydrolyzable tannins encompass corilagin, sourced from the leaves of sumac (*Rhus* spp.) and eucalyptus (*Eucalyptus* spp.) [44], together with geraniin, obtained from geranium (*Geranium* spp.) and *Phyllanthus* spp. [44] (Figure 4.). Both corilagin and geraniin have demonstrated anti-human-immunodeficiency-virus (HIV) activity by inhibiting reverse transcriptase [45]. [7]

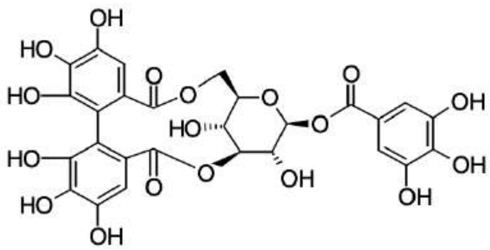
An example of the later described medicinal plants in Israel is the *Quercus ithaburensis* (Mount Tabor oak), which is known for its Antiseptic, astringent, anti-inflammatory, bleeding-stopping, pain-relieving, diuretic, and fungicide properties.



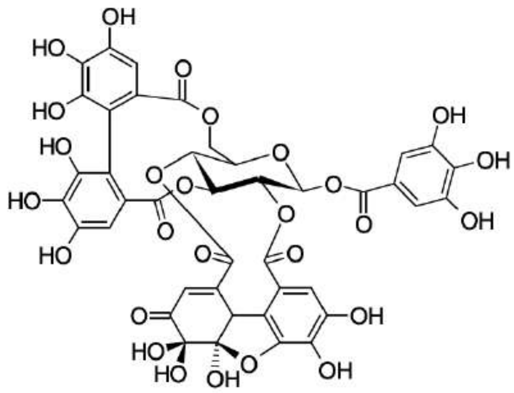
proanthocyanidin from ***Sorghum***



proanthocyanidin from ***Eucalyptus***



corilagin



geraniin

Figure 4. Structures of condensed and hydrolyzable tannins. Natural Products from Plants, Second Edition, Phytochemicals: The Chemical Components of Plants, p. 26.

6. Sesquiterpenes: C_{15}

The C15 sesquiterpenes, constituted of three isoprene units, manifest a wide array of structural arrangements, encompassing aliphatic, bicyclic, or tricyclic frameworks. Like monoterpenes, the majority of sesquiterpenes are present as components of the essential oil within the plant from which they are derived. Among this group, farnesol holds significance, containing a pyrophosphate moiety that acts as a pivotal intermediate in terpenoid biosynthesis. [8]

An example of a special medicinal plant in Israel that contains sesquiterpene lactones, including artemisinin and arteannuin B, is *Artemisia judaica* (Judean wormwood).

7. Phenylpropanoids

As indicated by their name, Phenylpropanoids consist of a three-carbon side chain linked to a phenol (refer to Figure 5). This group includes hydroxycoumarins, phenylpropenes, and lignans. Additionally, various hydroxycinnamic acids like caffeic and coumaric acids are common within this category. Coumarin, found in many plants, is the fragrant compound released from freshly cut grass. Phenylpropenes, such as eugenol found in clove oil (*Eugenia caryophyllata* or *Syzygium aromaticum*), or myristicin in nutmeg (*Myristica fragrans*), are significant constituents of essential oils.

Hydroxycinnamic acids such as caffeic and p-coumaric acids are detected in both green and roasted coffee beans. Umbelliferone and scopoletin, belonging to the coumarin class of phenylpropanoids, were first discovered in 1884 and are extracted from the roots of Scopolia japonica. Eugenol, classified as a phenylpropene, is derived from various plant sources, and is employed as a dental analgesic.

An example is *Melissa officinalis L.*, (lemon balm), where the main components of the plant comprise hydroxycinnamic acids, with rosmarinic acid being the most abundant (<6%), alongside p-coumaric, caffeic, and chlorogenic acids. [9]

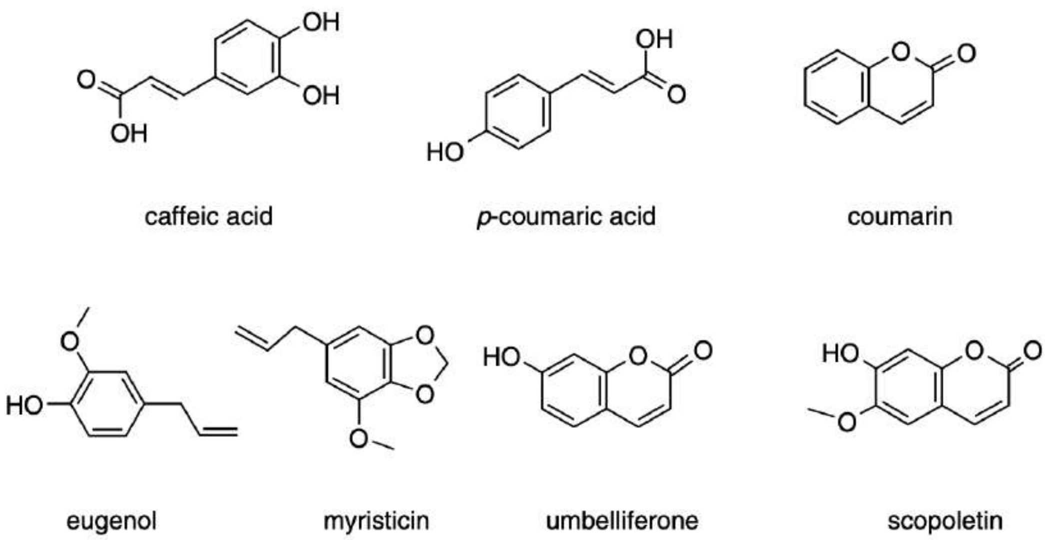


Figure 5. Phenylpropanoids. Natural Products from Plants, Second Edition, Phytochemicals: The Chemical Components of Plants, p. 22.

8. Diterpenes: C_{20}

The diterpenes constitute a diverse group of compounds formed from four isoprene units. due to their relatively higher boiling points, they are not classified as essential oils but are traditionally regarded as resins, remaining after the steam distillation of plant extracts. [46]

Several notable examples of plant bioactive compounds showcase their diverse pharmacological properties.

Zoapatanol, a cyclic ether obtained from the Mexican zoapatle plant (Montanoa tomentosa), has traditionally been employed as an abortifacient.

Another compound, marrubiin, a diterpene lactone found in white horehound (*Marrubium vulgare*), which will be discussed in more detail later in my review, demonstrates vasorelaxant properties.

Additionally, Taxol® or paclitaxol, derived from the needles and bark of Taxus spp. (yews), emerges as a distinctive antimitotic agent employed in breast cancer treatment.

Taxol®, characterized by a diterpenoid core with an alkaloid side group, functions by stabilizing microtubules, differentiating its mechanism from other tubulin-binding antimitotics such as vincristine, podophyllotoxins, and colchicine. These examples underscore the potential of plant-derived compounds in pharmaceutical applications. [10] [47]

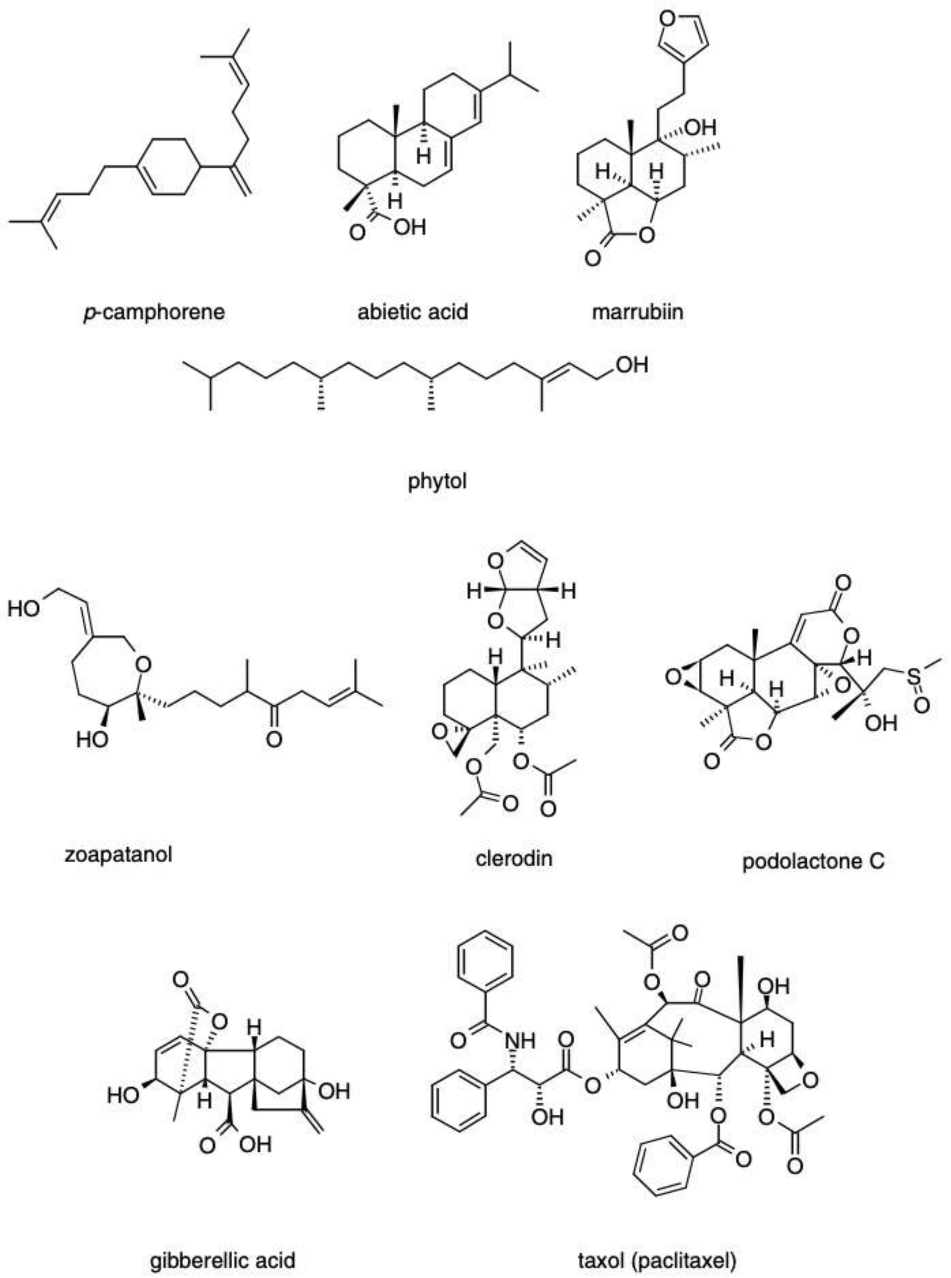


Figure 6. assorted diterpenes. Natural Products from Plants, Second Edition, Phytochemicals: The Chemical Components of Plants, p. 16.

Background to ethnoveterinary Medicine [11]

Ethnoveterinary medicine (EVM), or veterinary anthropology, encompasses a holistic and interdisciplinary approach to studying local knowledge, practices, beliefs, and social structures related to animal healthcare and husbandry. The ultimate goal is to enhance human well-being by improving livestock production and livelihood systems (McCorkle, 1998a). EVM draws upon various scientific disciplines to explore diagnostic, preventive, and therapeutic aspects of animal healthcare, management techniques and traditional medicinal practices.

The scope of EVM includes the utilization of local materia medica, encompassing minerals, animal products, plants, and other natural materials, along with diverse treatment modalities and management strategies. This encompasses various practices, from basic surgery to immunization, environmental controls, and socio-organizational structures involved in transmitting and implementing knowledge [48].

Driven by livestock development projects, EVM has expanded to encompass zoo pharmacognosy, participatory epidemiology, gendered knowledge, food safety, agri-business skills, biodiversity conservation, and ecosystem health. Additionally, it includes the integration of EVM into primary education curricula and veterinary training programs, as well as policy and economic analyses [49].

While various aspects of EVM have been studied, veterinary ethnopharmacopoeia, particularly the use of botanicals, remains a focal point of research within this field [50].

Ethnoveterinary medicine (EVM) has its roots in diverse cultural traditions worldwide, spanning centuries of livestock-keeping practices. Ancient civilizations such as India and China developed sophisticated systems like Ayurveda and acupuncture, encompassing healthcare for humans and animals. Written records from various cultures, including scrolls, manuscripts, and hieroglyphic papyri, provide insights into early EVM practices, such as pastoralism and care of warhorses and sacred animals.

In preliterate societies, EVM knowledge was transmitted orally through generations. The European Renaissance and colonialism facilitated the documentation of indigenous veterinary practices through expanded literacy and publishing opportunities. European colonialism, spanning between the 16th and the 20th century, spurred the generation of governmental reports and memoirs. detailing native veterinary knowledge, albeit often from a biased perspective. Even today, much EVM knowledge continues to be passed down orally, as seen in rural areas of the United States.

The formal recognition of EVM in academic literature began in the 1970s, marked by an increasing number of peer-reviewed articles, book chapters, and reports dedicated to traditional animal healthcare and husbandry. Graduate theses and dissertations in anthropology and veterinary medicine began addressing EVM, initially in universities in Africa, India, West Germany, and France, later expanding to include institutions in the Netherlands, the United Kingdom, and the United States.

The interest in ethnoveterinary medicine (EVM) stems from several compelling reasons, applicable across both developing and developed nations:

- **Cost-Effectiveness:** EVM provides realistic healthcare options for poor or remote livestock keepers who cannot afford or access conventional veterinary services.

- **Tailored Solutions:** Conventional services may not adequately address the specific needs of certain stockraisers, making validated EVM techniques more suitable.

- **Economic Viability:** In certain production systems and market conditions, the cost of professional veterinary care and inputs may outweigh the value of the animals.

- **Availability and Quality of Commercial Drugs:** Commercial drugs may be unavailable, expired, insufficient, or adulterated, posing challenges to effective treatment.

- **Trust and Cultural Comfort:** People prefer healthcare services from trusted local practitioners who share their language, culture, and community.

- **Emergency Response:** Local practitioners and treatments may be the only feasible option during emergencies or epidemics, offering quicker and potentially more sustainable solutions.

- **Joint Extension Services:** Collaborative efforts between human and veterinary traditional and modern medicine can provide cost-effective and sustainable services to rural populations.

- **Environmental Concerns:** Ethnomedical alternatives may be considered safer and less environmentally harmful than powerful modern drugs and biocides.

- **Preventive Potential:** EVM interventions rooted in local ecological knowledge may be more effective in disease prevention, thus reducing the need for therapy and associated costs.

- **Cultural Insights:** Studies of EVM treatments and practices across different cultures and social groups may uncover valuable Materia medica or techniques beneficial for animal and human health and well-being.

These factors collectively contribute to EVM's growing interest and recognition as a practical, culturally sensitive, and potentially more sustainable approach to animal healthcare and husbandry.

Survey of medicinal herbs in Israel, the Golan Heights, and the West Bank: An Ethnopharmacological perspective [12]

The study conducted an extensive ethnopharmacological survey among indigenous Arabic herbal practitioners in Israel, the Golan Heights, and the West Bank to assess the potential of local plants in treating various diseases.

Thirty-one practitioners were interviewed, and they revealed the use of 129 plant species to treat conditions such as skin diseases, kidney and urinary system disorders, diabetes, digestive issues, liver diseases, respiratory ailments, cancer, and weight loss.

The survey highlights the importance of preserving indigenous medicinal plant knowledge amid a decline in traditional practices and the potential for drug discovery from natural sources [51].

The elevated terrain of Israel, Palestine, and the Golan Heights boasts a rich botanical diversity. Over 2600 plant forms exist, over 700 of which are recognized for their medicinal or pesticidal properties [51].

Previous ethnopharmacological surveys have highlighted the therapeutic potential of these plants.

For instance, a study involving 27 Bedouin informants in the Negev region identified 81 plant species for treating 115 ailments [93]. Similarly, a recent survey of 102 individuals in the West Bank documented 63 plant species employed for treating various conditions, including skin, urinary, gastric, and prostate diseases, as well as cancer [52].

The decline In the utilization of medicinal plants In the Middle Eastern region, despite a global surge in interest in herbal medicines, poses a paradoxical challenge. While herbal medicine gains popularity, the indigenous medicinal knowledge of the area is diminishing, raising concerns about its potential disappearance. This decline is particularly concerning given the substantial contribution of natural products to drug discovery. Natural sources have yielded a significant proportion of newly approved drugs, highlighting the importance of ethnobotanical and ethnopharmacological research in drug development. Knowledge about the identification, preparation, clinical use, gathering, and preservation of medicinal plants significantly accelerates drug discovery processes.

Consequently, the diminishing regional knowledge base concerning medicinal plants significantly constrains the capacity of ethnobotany and ethnopharmacology for drug discovery [101]

The urgency in preserving the medicinal plant diversity in the region is further underscored by the fact that approximately 30% of the flora in Israel, the Golan Heights, and the West Bank are classified as rare, with lots of species facing endangerment [102] To address these concerns, this study aimed to conduct an extensive survey among reputable Arabic traditional medicine practitioners in Israel, the Golan Heights, and the West Bank. The information gathered from this survey is integral to ongoing projects exploring the pharmaceutical significance of potential bioactive compounds derived from medicinal plants in the region.

Primary Metabolic Pathways in Plants [13]

The comprehensive scheme illustrated in Figure 7 outlines the interconnectedness of major metabolic pathways within plants, serving as a pivotal reference for understanding plant metabolism. Unique pathways exclusive to plants, such as the carbon reduction cycle in photosynthesis and the shikimic acid pathway, yield essential amino acids vital for both plant and animal life. While microbes and mammals possess distinct metabolic routes, shared pathways like the pentose phosphate pathway, glycolysis, and the tricarboxylic acid (TCA) cycle underscore the universal mechanisms of aerobic respiration and ATP biosynthesis across organisms.

This scheme delineates the major metabolites produced by plants, highlighting their interrelations and emphasizing carbon dioxide fixation in photosynthesis as the foundation for synthesizing diverse molecules.

Most plant products stem from sugars, acetyl CoA, or amino acids, pivotal components shaping biochemical pathways. Notably, terpenoids, nitrogen-containing compounds, and phenolic compounds constitute crucial categories essential for plant growth and development and higher organisms' sustenance.

A significant revision in Figure 7 pertains to the synthesis of terpenoids, reflecting recent insights into the diverse pathways contributing to their biosynthesis. While past understanding favored the cytosolic acetate/mevalonate pathway for IPP synthesis, recent evidence highlights the plastid DOXP/MEP pathway's role, shedding light on the complexity of terpenoid biosynthesis.

The study of natural plant products underscores the ongoing exploration of the Intricate pathways governing their synthesis. Despite considerable advancements, the full complexity of these pathways still needs to be discovered. Innovations in genomics, proteomics, and metabolomics offer promising avenues for unraveling the intricate mechanisms underlying plant product biosynthesis, shaping our evolving understanding of plant metabolism [53] [13]

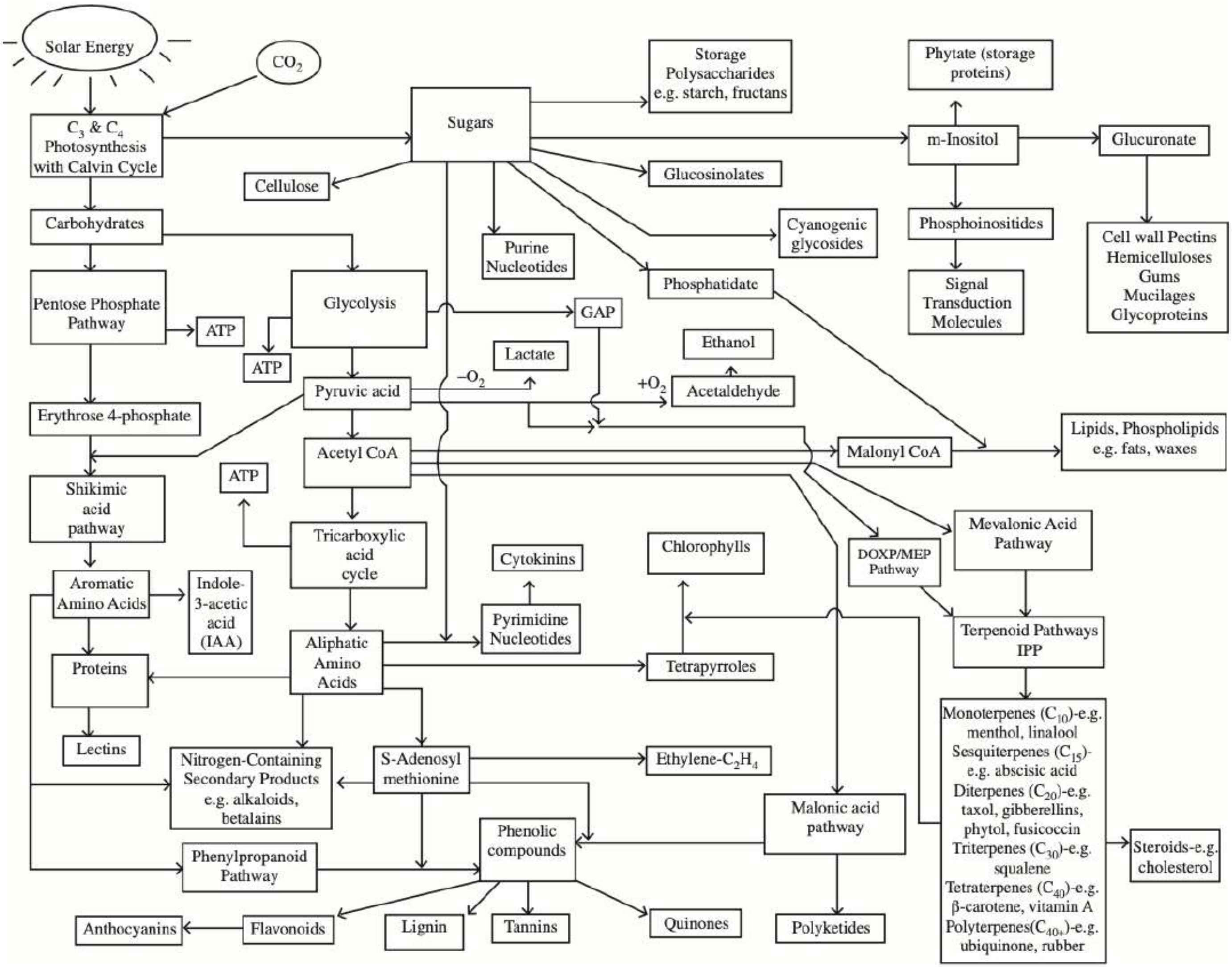


Figure 7. primary metabolic pathways in plants. Natural Products from Plants, Second Edition, chapter 2, Page 53.

Special medicinal plants in Israel and their uses in veterinary medicine

1. Calendula arvensis

Other names: Calendula officinalis, field marigold.

Family: Asteraceae.

Parts Used: Flowers.

Background mechanism and clinical actions: Antiseptic, lymphatic; reduces blood lipids; anti-inflammatory, astringent, spasmolytic, vulnery, cholagogue.[14]

Distribution in Israel: Golan, Hermon, Gallilee, Mediterranean coast, Upper Jordan valley, Northern valleys, Gilboa, Carmel, Samarian mountains, Samarian desert, Judean mountains, Judean desert and Dead Sea valley, Ein Gedi, Sharon, Shefela, Northern Negev, Negev hills and Eilat, Aravah.[15]

Flowering months in Israel: December – April.[15]

Chemistry: The major constituents of the analyzed substance include triterpene saponins (2%-10%) primarily based on oleanolic acid (calendulosides) and flavonoids (3-O-glycosides of isorhamnetin and quercetin), such as astragalin, hyperoside, isoquercitrin, and rutin. Additional components include essential oil, sesquiterpenes (e.g., caryophyllene), and triterpenes (e.g., a- and b-amyrins, lupeol, and lupenone). Immunostimulant polysaccharides have also been identified [54].[14]

Veterinary medicine indications and its usage in Israel:

Calendula officinalis is indicated for use as a mouthwash for gums, mucous membranes, and throat, as well as in cases of stomach infection and ulcers. It is also used as an eyewash and for gastrointestinal, skin, and genitourinary tract infections.

The herb is recommended for Skin inflammation, eczema, itching, swollen glands, high cholesterol and triglyceride levels, and its application for treating wounds.

In veterinary applications, Calendula officinalis is utilized in bioorganic farming as a mastitis salve, especially for gingivitis, ulcers, erosions, eyewash, dermatitis, and as a wound-cleansing agent (often administered as tea) [55] [15]

Traditional usage: Calendula, believed to be native to Egypt, has a rich history of 5000 years. Ancient Egyptians mentioned it in records, and hieroglyphics depict stylized calendula flowers. The Romans named it after the "calends" of each month due to its continuous blooming. Calendula petals were historically used in salads or dried for manufacturing and medicine. The plant produces a yellow dye, once used to color cheese in the 1700s and 1800s, and is now employed in various products such as beverages, cosmetics, food, and pharmaceuticals. Traditional medicinal uses include treating cuts, skin inflammations, wounds, varicosis, phlebitis, eczema, and acne. Internally, it is used for inflammatory conditions, gastrointestinal ulcers, toothache, and eye inflammation. Folk medicine attributes calendula to treating amenorrhea, angina, fever, gastritis, hypotension, jaundice, rheumatism, and vomiting. Goats and sheep are drawn to calendula, which is considered a tonic and heart medicine. It is used raw for warts and tumors, and as an infusion, it may be applied for alopecia in dogs. [56] [120-123] [15]

Figure 8 (left): Calendula arvensis (wild flowers of Israel: medicinal plants)[16]
Figure 9 (right): Calendula arvensis (wild flowers of Israel: medicinal plants)[15]

Figure 10: Common marigold (Calendula officinalis L.).[17]

2. **Matricaria recutita**

Other names: Wild chamomile, matricaire, matricaria flowers, pin heads, sweet false chamomille, feverfew. *Anthemis nobilis* (Roman chamomile)- which is also a widely used and accepted form of chamomile.

Family: Asteraceae.

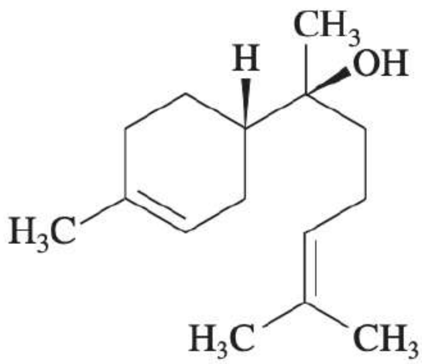
Parts Used: Dried flowering heads.

Background mechanism and clinical actions: Carminative, spasmolytic, mild sedative, cholagogue, antiallergic, anti-inflammatory, healing, bitter tonic (treating atonic digestion). [18]

Distribution in Israel: Golan, Gallilee, Upper Jordan valley, Carmel, Judean mountains, Sharon, Shefela[19]

Flowering months in Israel: April – May [19]

Chemistry: Chamomile is characterized by an essential oil content ranging from 0.4% to 1.5%, known for its intense blue color attributed to chamazulene (1%-15%). The oil's other major components include a -bisabolol and related sesquiterpenes, which can make up to 50% of the oil (figure 11) . Additionally, apigenin and related flavonoid glycosides constitute up to 8% of the herb's dry weight [57] [124] [18]



(−)-α-Bisabolol

Figure 11: α-bisabolol, a major constituent in the chamomile plant.[18]

Veterinary medicine indications and its usage in Israel[18]:

1. **Mouth and throat lesions**

Chamomile preparations have shown potential benefits in treating mucositis resulting from radiation therapy and chemotherapy in the head and neck region. However, conflicting results were observed in studies investigating chamomile mouthwash for relieving stomatitis in individuals undergoing 5-fluorouracil treatment. Similarly, trials using chamomile spray or gel as lubricants for endotracheal tubes did not demonstrate a significant difference compared to placebo lubricants.

2. **Skin inflammation**

Chamomile extract exhibited therapeutic efficacy In a double-blind trial conducted after tattoo dermabrasion, there was a statistically significant decrease in the area of weeping wounds and an improvement in the tendency for drying. In a comparative study with inflammatory dermatoses patients, chamomile cream was as effective as hydrocortisone, superior to bufexamac and fluocortin butyl ester. Additionally, chamomile demonstrated antipruritic effects in mice, suppressing scratching behavior comparable to an antiallergic agent.

3. **Anxiety**

Studies on apigenin, a component of chamomile, showed anxiolytic activity in mice without sedation or muscle relaxant effects. Chamomile, which depresses the central nervous system, had significant sedative effects in mice.
In rats, inhalation of chamomile oil vapor resulted in a reduction of stress-induced elevations in plasma adrenocorticotropic hormone (ACTH) levels, It was proposed that the oil of chamomile may augment GABAergic activity within the central nervous system. The spasmolytic effects of chamomile were linked to compounds such as apigenin, apigenin-7-O-glucoside, and α-bisabolol.

4. **Chamomile and goats' milk**

In a study involving six groups of goats, different dietary supplements, including black cumin, chamomile, garlic, fenugreek, or absence of supplementation, were provided. Gouda cheese was produced using the milk from each treatment group, and monthly analysis was performed to assess parameters such as moisture, fat, total protein, salt content, acidity, and soluble nitrogen in the cheese, as well as sensory evaluation. The experimental cheeses, particularly those from goats fed diets containing black cumin seeds and chamomile flowers, displayed superior attributes compared to the control cheese, characterized by the absence of a goaty flavor [94].

Another study aimed to detect essential oils from chamomile and caraway seed in goat milk after feeding goats with chamomile. Despite feeding relatively large quantities of chamomile to goats over time, the characteristic essential oils of chamomile could not be detected in the milk [58].

Potential veterinary indications: Eyewash, mild sedative and anxiolytic, treatment for flatulence and mild colic in animals, source of antioxidants, topical wound therapy, effective for pruritic in mice and rats, odor reducer in goats' milk.[18]

Effect of German chamomile oil application on alleviating atopic dermatitis-like immune alterations in mice [59] [20]

The study investigated the effect of German chamomile (GC) oil on atopic dermatitis-like immune alterations in mice.
Atopic dermatitis is an immune-mediated disorder characterized by an imbalance favoring the type-2 helper T (Th2) immune response.

The study used a mouse model induced by the application of 2,4-dinitrochlorobenzene (DNCB) to induce atopic dermatitis-like symptoms. German chamomile oil, known for its anti-inflammatory and anti-histaminic effects, was applied topically, and its impact on immune parameters was evaluated.

Key findings of the study:

1. **Reduction in IgE Levels:** Serum IgE levels, which are elevated in atopic dermatitis, were significantly lowered in the GC oil application group after a 4-week period.

2. **Modulation of IgG Levels:** GC oil application led to a reduction in serum IgG1 levels compared to the control groups, suggesting an influence on Th2 cell activation.

3. **Decreased Histamine Levels:** Serum histamine levels, associated with allergic reactions, were lower in the GC oil group, indicating a potential anti-histamine effect.

4. **Suppression of IL-4 Production:** GC oil application resulted in a lower production of interleukin-4 (IL-4) from splenic T cells, contributing to the control of Th2 reactivity.

5. **Reduced Scratching Frequency:** Mice treated with GC oil exhibited a significantly lower frequency of scratching, indicating relief from itching.

6. **Decreased Inflammatory Cell Infiltration:** Histopathological examination revealed reduced inflammatory cell infiltration in the skin of mice treated with GC oil.

The study suggests that GC oil has immunoregulatory potential, influencing Th2 cell activation and alleviating atopic dermatitis-like immune alterations. The observed effects include reduced IgE and IgG1 levels, decreased histamine release, and relief from itching. The findings support the traditional use of GC oil in the treatment of skin disorders and propose its potential application in managing atopic dermatitis.

It's important to note that the study was conducted on mice, and further research, including clinical trials, would be needed to validate the effectiveness and safety of GC oil in human subjects. Additionally, identifying specific components of GC oil responsible for the observed effects could be a focus for future investigations.

Traditional usage[18]:

In the realm of history and traditional usage, chamomile has been acknowledged for its multifaceted therapeutic applications. Notably, pharmacopoeias and traditional medicinal systems have recognized its role as an adjuvant in addressing minor inflammatory conditions within the gastrointestinal tract [95]. Additionally, various historical sources have documented the herb as an antibacterial and antiviral agent, an emetic, and an emmenagogue [60].

Historically, chamomile's utilization extends to diverse contexts. For instance, it has been employed to alleviate eye strain and serves as an effective eyewash, as documented [61]. The dried flower heads of Matricaria recutita L. (Asteraceae) have found purpose in crafting spasmolytic and sedative teas, contributing to its historical significance [62].

The historical perspective is enriched by the insights of de Bairacli Levy [63], who characterizes chamomile as a female remedy and a pregnancy herb. The historical narrative includes intriguing applications, such as the suggestion to employ chamomile tea for soaking oat flakes in the hand-rearing of puppies. Furthermore, the herb’s historical role in bathing discharging eyes, treating patients with diarrhea and gastroenteritis, and its recommended dosage in these cases (2 tablespoons of tea three times daily) add depth to its traditional applications [63].

De Bairacli Levy [63] expands the historical discourse, advocating chamomile's efficacy in addressing inflamed gums, female ailments, wounds, and bruises. The herb's historical usage in tumor treatment as a poultice, and its role in managing blood and skin disorders, provide additional layers to its historical relevance. Even constipation, as noted in de Bairacli Levy's historical account (1963), is addressed through chamomile, with a specified dosage for therapeutic application.

In summary, the historical and traditional applications of chamomile, as documented by Weiss [64] [125-127], reveal a rich tapestry of therapeutic uses spanning gastrointestinal health, ocular care, pregnancy-related situations, and a spectrum of ailments and disorders. These historical insights contribute significantly to understanding the enduring significance of chamomile in traditional medicine.

Figure 12 (Left): Matricaria recutita (Wikipedia)[21]
Figure 13 (Right): Matricaria recutita (wildflowers of Israel: medicinal plants, photo by Sara Gold) [22]

3. **Silybum Marianum**

Other names: milk thistle, Holy thistle, Marian thistle, St. Mary’s thistle.

Family: Asteraceae.

Parts Used: Seed collected in late summer.

Background mechanism and clinical actions: Hepatoprotective, demulcent, cholagogue, galactagogue, antioxidant.[23]

Distribution in Israel: Golan, Hermon, Gallilee, Upper Jordan valley, Northern valleys, Gilboa, Carmel, Samarian mountains, Samarian desert, Judean mountains, Judean desert and Dead Sea valley, Ein Gedi, Sharon, Shefela, Northern Negev, Jordan Valley [24]

Flowering months in Israel: March – May [24]

Chemistry: Silymarin, a flavonoid complex composed of silibinin (Figure 14.), silidianin, and silichristine, is the primary focus of interest due to its perceived high activity, with silibinin likely accounting for the attributed benefits of silymarin. This compound is complemented by the presence of sterols, fixed oil, flavonoids (apigenin, quercetin, kaempferol), lignans, biogenic amines (tyramine, betaine), and mucilage.[23]

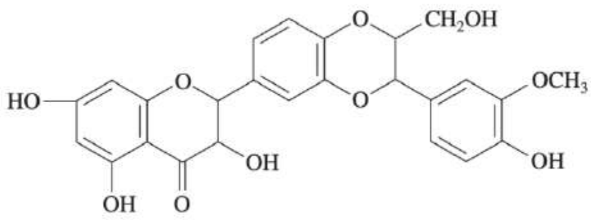


Figure 14: Silibinin.[23]

Veterinary medicine indications and its usage in Israel:

Published research indicates that silymarin, a compound derived from milk thistle, possesses diverse effects, acting as an antioxidant, inhibiting lipid peroxidation in hepatocyte plasma membranes, protecting against genomic injury, stimulating hepatocyte protein synthesis, suppressing NF-kappaB, chelating iron, stabilizing mast cells, slowing calcium metabolism, and decreasing activity of tumor promoters [65].

In the context of liver disorders, controlled clinical trials demonstrate that milk thistle, particularly in conditions such as toxin- and drug-induced hepatitis, alcoholic liver disease, viral hepatitis, and cirrhosis, may decrease aminotransferase activity and improve various clinical parameters inconsistently. Critical reviews on the treatment of hepatitis B and C with milk thistle and silymarin suggest no direct influence on viral infection but a potential attenuation of infection-induced damage [66] [128-129].

Concerning kidney diseases, silybin has shown to reduce oxidative damage to kidney cells in vitro, and in rat studies, silibinin prevented cisplatin-induced nephrotoxicity but had limited effects on cyclosporine-induced glomerular damage [67] [130-132].

In the realm of blood lipids, animal studies propose that silymarin may help control blood lipid levels, potentially by modulating cholesterol absorption. However, human studies in this area are limited [68] [133-134].

It's important to note that while these findings suggest potential therapeutic benefits of milk thistle and silymarin, further research, especially rigorous clinical trials, is necessary to establish their efficacy and mechanisms of action in various health conditions.

In the realm of pancreatic disorders, experimental damage to the pancreas in rats can be ameliorated with the use of silymarin, as demonstrated in studies [69].
Silibinin, a component of silymarin, has been found to protect the pancreas from cyclosporine toxicity in rat models. Notably, in human clinical trials involving alcoholics with hepatic cirrhosis and insulin-dependent diabetes, silymarin administration resulted in significant decreases in fasting glucose, glycosuria, and insulin needs over a six-month period [70] [135].

Silibinin and silymarin have shown promising results in animal studies regarding cancer prevention. In prostate cancer cells, these compounds alter cell cycle progression, inhibit cell survival signaling, mitogenic signaling, and synergize the effects of doxorubicin. Silibinin also exhibits inhibitory effects on growth and enhances apoptosis in implanted prostate tumor cells in nude mic [71]. Additionally, silibinin may aid in the repair of DNA damaged by UV radiation and inhibit chemical carcinogenesis when applied topically in mice [72] [137].

In veterinary trials, silymarin and silibinin have demonstrated positive effects in dogs given hepatotoxic chemicals, showing improvements in biochemical and histologic measures of hepatotoxicity and enhanced survival. Trials in postparturient cattle and broiler chicks have also indicated beneficial outcomes, such as increased milk production, reduced ketonuria, protection against aflatoxin B1, lower alanine aminotransferase (ALT) levels, and improved weight gain [73] [137-139].

Furthermore, silymarin has been investigated for its potential in treating giardiasis in dogs. A combination of silymarin and metronidazole demonstrated a significant reduction in infection levels compared to metronidazole alone, with no adverse effects on weight and liver measurements in dogs [74].

In terms of indications, milk thistle, specifically silymarin, is used for various liver diseases, especially as protection against toxic ingestion, such as in alcoholism. It is also employed for hypercholesterolemia, varicose veins, and, some herbalists recommend it for increasing lactation. In veterinary practice, potential uses include hepatitis, cholangiohepatitis, toxic liver injury (particularly aflatoxicosis), hepatic lipidosis, supplementary therapy for giardia treatment or during metronidazole administration, pancreatitis protection, safeguarding from drug-induced damage, managing hyperlipidemia, and promoting lactation while shielding dairy cows from ketonemia. No known contraindications have been reported, making milk thistle likely safe even for pregnant and lactating animals, although patients allergic to members of the daisy family may be sensitive to milk thistle [75] [140].

Special products in veterinary medicine in Israel [25]

In Israel, a very common product called WePatic© is commonly used in veterinary practice. This product consists of silibinin together with other compounds such as vitamins and antioxidants.

WePatic© gives effective protection for liver problems, tasty hepatoprotective tablets which consist of:

1. **SILIPHOS**, a complex comprising silybin and phosphatidylcholine, serves as a potent source of silybin with high activity and bioavailability, exhibiting inhibitory effects on free radicals and acting as an antihepatotoxic agent, safeguarding cells from detrimental influences. Notably, SILIPHOS enhances liver enzyme levels, promotes the generation

of new liver cells, and enhances the survival and histology of existing cells. Additionally, it augments protein synthesis while inhibiting the synthesis of inflammatory leukotrienes, thereby mitigating inflammation and fibrosis.

2. **ZINC** exhibits a comprehensive hepatoprotective role by inhibiting the production of free oxygen radicals, thereby safeguarding sulfhydryl groups from oxidation. Additionally, it acts as a copper chelator, contributing to the reduction of fibrosis. Its ability to inhibit lipid peroxidation stabilizes cell membranes, further enhancing its protective effects on hepatic tissues.

3. **SELENIUM**, as an essential element, functions as a cofactor for glutathione peroxidase, a crucial enzyme in mitigating the detrimental effects induced by free oxygen radicals. Furthermore, selenium exhibits an effect on reducing IL-6 transcription and expression, suggesting its role in modulating inflammatory processes.

4. **SAMe (S-ADENOSIL-L-METIONINA)** serves as a precursor molecule for thiols, elevating the concentration of glutathione, a pivotal factor in the activity of glutathione peroxidase and essential for defense against reactive oxygen species (ROS). WePatic® employs a gastroenteric coating to enhance bioavailability, ensuring optimal delivery and absorption of SAMe for its intended hepatoprotective effects.

5. **VITAMIN E** plays a crucial role in protecting against reactive oxygen species (ROS) and is a key component of the essential fat-soluble vitamin protection complex, working in conjunction with glutathione and vitamin C. When combined with selenium, it helps prevent the action of peroxidases in cell membranes, providing protection against the damaging effects of bile acids, particularly in cholestasis situations.

6. **VITAMIN C,** a water-soluble vitamin, primarily functions in the liver as an antioxidant, rendering reactive oxygen species (ROS) inert and contributing to the overall oxidative stress defense.

Figure 15: WePatic© [25].

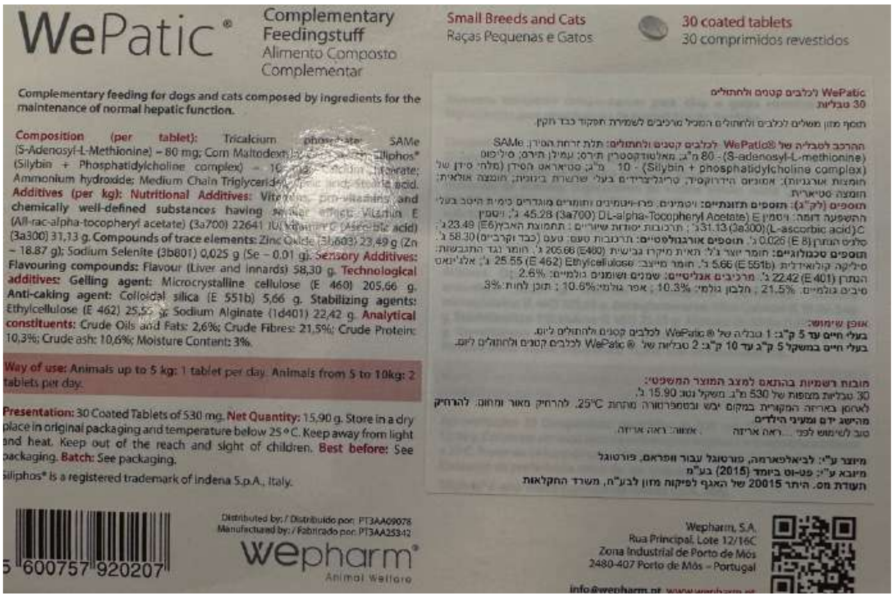


Figure 16: WePatic© [25] , photo taken by me, Tel Aviv, February 2024.

Traditional usage [23]:

The utilization of this plant dates back to ancient times, as evidenced by its mention in prominent herbals from the 16th and 17th centuries.
Gerard, a notable figure in herbal medicine, advocated its use for liver ailments, particularly melancholy.

While there is no historical record of its use among Native American populations in North America, European settlers introduced the plant to the region. It wasn't until 1898 that it became part of Eclectic medical practice. In Eclectic medicine, specific indications for its use included addressing conditions such as congestion in the spleen, liver, and kidneys, along with a pallid complexion.

Irregular appetite, nervous irritability, physical weakness, hypochondriac pain, pelvic tightness, coeliac axis congestion, and non-malarial splenic hypertrophy.

In Europe, the leaves were traditionally utilized in a manner akin to spinach, while the fruit, after removing the spines, was consumed similar to an artichoke.

4. **Marrubium vulgare**

Other Names: White horehound, hoarhound.

Family: Lamiaceae.

Parts used: aerial parts, leaves.

Background mechanism and clinical actions:
Used for chronic bronchitis, chronic obstructive pulmonary disease, feline asthma. [26]

Distribution in Israel: Golan, Hermon, Gallilee, Upper Jordan valley, Northern valleys, Carmel, Samarian mountains, Samarian desert, Judean mountains, Judean desert and Dead Sea valley, Ein Gedi, Sharon, Shefela, Northern Negev, Negev hills and Eilat, Jordan Valley. [27]

Flowering months in Israel: April-June

Chemistry: Diterpenoid lactones, including marrubiin, premarrubiin; phenolic acids, flavonoids, essential oil (containing alpha-pinene, sabinene, limonene, camphene, p-cymol, α-terpinolene), sterols, choline, alkaloids [26]

Veterinary medicine indications and its usage in Israel:

Horehound, a traditional remedy for diabetes, demonstrated notable efficacy in a double-blind trial involving individuals with inadequate control under conventional treatment [76].
The furane labdane diterpene marrubiin found in horehound exhibited analgesic effects in experimental pain models in mice [96] [153]. Moreover, laboratory animal studies have indicated potential antihypertensive activity associated with horehound [77] [142].
The herb exhibits antispasmodic and bronchial secretagogue activities, aligning with its traditional use for addressing dry cough. Additionally, it is employed for various purposes, including managing loss of appetite, nonulcerative dyspepsia, flatulence, and diabetes.

Traditional usage:

The plant has historical use among various Native American tribes, who employed it for kidney flushing, addressing breast complaints, and treating ailments such as cough, flu, sore throat, and colds. Among the Navajo, the plant was fed to sheep to impart bitterness to the meat. In the Eclectic tradition, horehound syrup was utilized for conditions like coughs, colds, asthma, chronic catarrh, and other pulmonary issues.

Figure 17 (left): Marrubium vulgare. [27]
Figure 18 (right): Marrubium vulgare, wild flowers of Israel, photo by Sara Gold. [28]

5. **Melissa officinalis L.**

Other Names: lemon balm, Melissa, Melissa balm, bee balm, honeyplant, sweet balm, Folium melissae being the dried leaves.

Family: Lamiaceae.

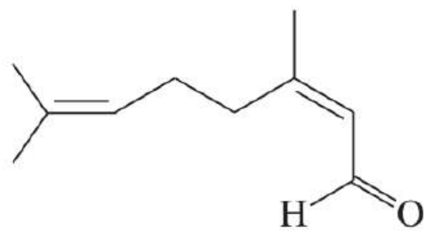
Parts Used: (Dried) leaves picked at or just prior to flowering.

Background mechanism and clinical actions: Indications for lemon balm include flatulence, depression, dementia, Alzheimer's disease, herpes simplex infection (topically), sleep disorders, tenseness, and irritability. In veterinary settings, potential indications include cognitive dysfunction, depression, anxiety related to cognitive dysfunction, and topical use for herpesviral infection and ringworm.[29]

Distribution in Israel: Golan, Gallilee, Upper Jordan valley, Northern valleys, Gilboa, Carmel, Samarian Mountains, Judean mountains, Sharon, Shefela[30]

Flowering months in Israel: May- September**.**

Chemistry: The primary constituents of the plant include hydroxycinnamic acids, with rosmarinic acid being the predominant one (<6%), along with p-coumaric, caffeic, and chlorogenic acids. The essential oil, constituting 1%-2% of the plant, comprises over 40% monoterpenes and more than 35% sesquiterpenes. Notable terpenoid components include citral - a mixture of neral and geranial isomers (figure18), citronellal, geraniol, nerol, linalool, farnesyl acetate, humulene (α-caryophyllene), β-caryophyllene, and eremophilene. Additionally, the plant contains flavonoids, tannins, bitter compounds, resin, and acidic triterpenes such as ursolic and oleanolic acids [83] [149-150].



Citral

Figure 19: Citral, The major terpenoid component of Melissa Officinalis plant.[29]

Veterinary medicine indications and its usage in Israel:

Published research highlights the therapeutic potential of lemon balm across various conditions[29]:
In a multicenter study involving 115 patients with herpes simplex infection, topical application of a 1% aqueous extract of lemon balm in a cream base significantly reduced the healing time of herpetic lesions, shortening it from 10 to 14 days to 6 to 8 days.
Another study demonstrated a significant reduction in the size of herpetic lesions within 5 days in patients treated with the same cream compared to a placebo [84] [151].

Lemon balm essential oil exhibited antimicrobial activity against 13 bacterial strains and 6 fungi, with notable efficacy against Shigella sonei and significant antifungal activity against Trichophyton species [85].

In a 4-month, placebo-controlled trial involving 42 patients with mild to moderate Alzheimer's disease, lemon balm extract, dosed at 60 drops daily, produced a significantly better cognitive function outcome than placebo. Agitation was also less common in the lemon balm extract group [86].

A randomized, placebo-controlled, double-blind study assessed the cognitive and mood effects of single doses of dried lemon balm leaf in 20 healthy participants. Higher doses (1600 mg) showed improved memory and increased "calmness," suggesting potential benefits for cognitive performance and mood, particularly in Alzheimer's disease [87].

Aromatherapy with lemon balm essential oil was investigated in a placebo-controlled trial for agitation in individuals with severe dementia. Results showed a 30% reduction in agitation in 60% of the active treatment group compared to 14% in the placebo group, with improvements in quality of life indices [88].

Traditional usage [29]:
Lemon balm has a longstanding tradition of oral consumption as a carminative for gastrointestinal disorders and as a sedative to address sleep disturbances related to nervous conditions [89] [152].

Additionally, traditional uses encompass the treatment of conditions such as amenorrhea, asthma, bee stings, cough, dizziness, dysmenorrhea, migraine headache, tachycardia, toothache, tracheobronchitis, and urinary incontinence [90].

Old European herbals historically documented lemon balm for its memory-improving properties, a notion that aligns with the identified cholinergic activities present in lemon balm extracts [82]. In Italy, folk use of lemon balm extended to promoting milk production in cows before or after calving [91].

Figure 20 (left): Melissa Officinalis. [29] Susan G. Wynn DVM, Barbara Fougere BVSc BVMS(Hons)-Veterinary Herbal Medicine-Mosby (2006), part IV, chapter 24, p. 590
Figure 21 (right): Melissa Officinalis. Flora of Israel and adjacent areas, by Prof. Avinoam Danin and Dr. Ori Fragman-Sapir, photo taken in Israel, Upper Galilee, Nahal Kziv, N of the Monfor, photo by Avinoam Danin.[31]

Figure 22: Melissa officinalis, Flora of Israel, and adjacent areas, by Prof. Avinoam Danin and Dr. Ori Fragman-Sapir, photo taken in Israel, The Botanical Garden, Mt. Scopus. photo by Avinoam Danin.[31]

6. **Artemisia judaica**

Other names: Judean wormwood.

Family: Asteraceae.

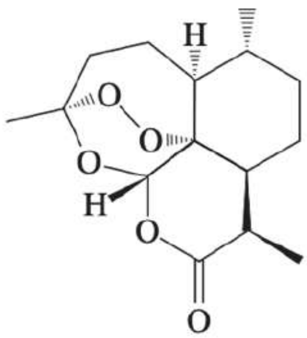
Parts used: aerial parts (Leaves collected in summer before blooming).

Background mechanism and clinical actions:
Artemisia judaica L., an aromatic medicinal plant abundant in Saint Katherine, Sinai, Egypt, has a rich history in traditional medicine. It is valued for its diverse therapeutic properties, including antibacterial, anthelmintic, antidiabetic, analgesic, and anti-inflammatory effects. Beyond Egypt, various Arabic regions have integrated it into their folk medicine practices, employing it to combat fungal infections, atherosclerosis, cancer, diabetes, arthritis, and inflammatory conditions[32].

Distribution in Israel: Negev hills and Eilat, Aravah[34].

Flowering months in Israel: March- April.

Chemistry: The plant contains sesquiterpene lactones, including artemisinin (Figure 22) and arteannuin B, as well as a volatile oil with components such as abrotamine and β-bourbonene. Additionally, flavonoids and vitamin A are present in the plant[32].



Artemisinin

Figure 23. artemisinin. Major sesquiterpene lactone component of Artemisia Judaica.[35]

Veterinary medicine indications and its usage in Israel:

Published Research about Artemisinin, a Sesquiterpene Derived from Quinhao (Artemisia annua) Qinghao plant, also known as Artemisia annua, has demonstrated efficacy against fungal skin diseases and leptospirosis in early Chinese research. It exhibits plasmodicidal activity, particularly against multiresistant strains of the malarial agent, Plasmodium falciparum [78].

The mechanism of action involves the reaction of artemisinin, a compound found in qing hao, with free intracellular iron through the endoperoxide bridge in the molecule. This reaction induces the production of free radicals, leading to cell death.

Both cancer cells and malarial parasites, which contain elevated iron levels, are targeted by artemisinin. It has been found to be as effective as conventional antimalarial drugs with variable efficacy and adverse effect profiles [79] [142].

In vitro studies have indicated artemisinin's antineoplastic activity. In a canine study, dihydroartemisinin, a derivative, inhibited tumor formation induced by canine oral papillomavirus. Additionally, artemisinin demonstrated inhibitory effects on Neospora caninum and Eimeria tenella in cell cultures and chicks, respectively, suggesting potential applications in treating viral and parasitic infections [80] [143-145].

Published research primarily focuses on artemisinin as a single extract. However, different plant harvests may contain variable levels of artemisinin, and some may not contain it at all.

Indications: Artemisinin derivatives hold potential for certain cancers. In the case of malaria, they are crucial for treating severe forms in areas with multidrug resistance, although long treatment courses and recrudescence may occur when used alone (WHO, 1998).[35]

Traditional usage[33]:

Artemisinin, derived from the Qinghao plant (Artemisia annua), has a long and rich history dating back to ancient China. Its antifever properties were first described in 340 AD.
Isolated by Chinese scientists in 1972, artemisinin has become a potent antimalarial drug, particularly effective when used in combination with other medications.
Marketed as artemether, it offers enhanced stability, pharmacokinetic properties, and potency compared to artemisinin.
This derivative is gaining importance in combating drug-resistant parasites.
[81] [146-148].

© **Photo:** Mori Chen

Figure 24 (left): Artemisia judaica, by Mori Chen. [36]
Figure 25 (right): Artemisia judaica, Flora of Israel, and adjacent areas, by Prof. Avinoam Danin and Dr. Ori Fragman-Sapir, photo taken in Israel, By Dr. Ori Fregman Sapir. [37]

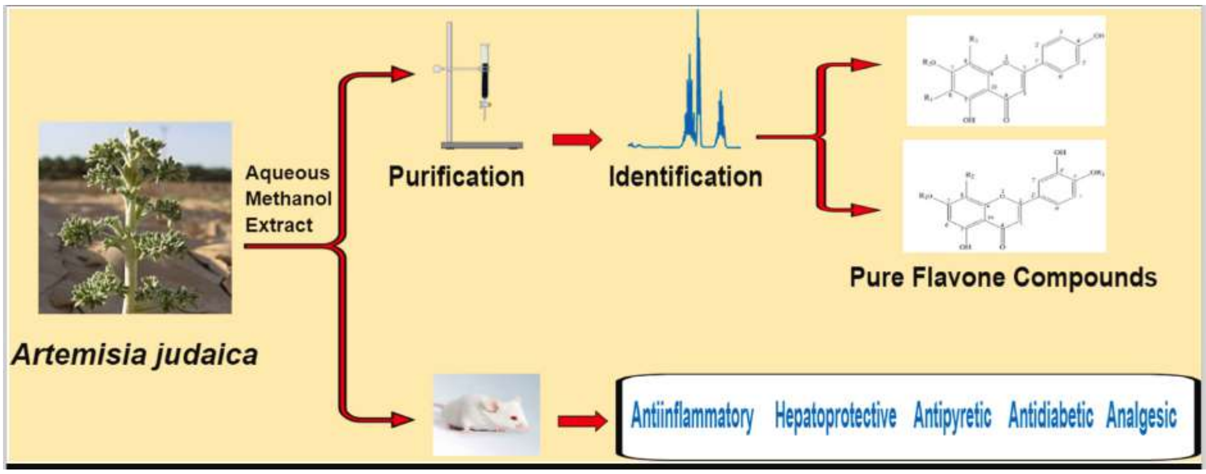


Figure 26: Evaluation of the effects of aqueous methanol extract (AME) by Fatma A. Moharram, L, Maii M. Nagy, Rabab A. El Dib, Mona M. el-Tantawy, Ghada G. El Hossary, Doaa G. El-Hosari (2021): Pharmacological activity and flavonoids constituents of Artemisia judaica L aerial parts.

The above study[32] aims to validate the traditional medicinal uses of Artemisia judaica by investigating its analgesic, anti-inflammatory, antipyretic, hepatoprotective, antidiabetic, and antioxidant properties. This will be accomplished by evaluating the effects of an 80% aqueous methanol extract (AME) of A. judaica aerial parts. Additionally, the study will focus on isolating and identifying the flavonoid content present in the extract.

7. Quercus ithaburensis

Other names: Mount Tabor Oak, Palestine Oak, Valonia Oak.

Family: Fagaceae.

Parts used: leaves.

background mechanism and clinical actions: Quercus species have a rich history in traditional medicine across various cultures, with different parts of the plant, including the fruit, bark, and leaves, utilized for their medicinal properties.

The plants are common for their antiseptic properties and for the treatment of gastrointestinal disorders, examples are diarrhea and hemorrhoids. Additionally, they have been used to address a wide array of conditions including gonorrhea, gastritis, asthma, fever, Parkinson's disease, as well as hepatoprotective conditions.

The bark derived from oak species, particularly from Quercus robur and Q. Petraea, exhibits anti-inflammatory, antibacterial, and antihemorrhagic activities, making it valuable in traditional medicine.

Leaves of Q. virginiana serve as antimicrobial agents and are utilized for gastrointestinal disorders. Galls of Q. infectoria are employed to restore uterine wall elasticity and treat inflammatory disorders, including wound infections after childbirth. In Indian and Asian traditional medicine, Quercus species are used for dental applications, management of infection diseases, skin conditions, and inflammatory disorders. In regions like Kumaun and Garhwal in India, Quercus leucotrichophora A. Camus is used to treat urinary infections, stomach pain, asthma, hemorrhages, diarrhea, and dysentery. The fruit, or acorn, of oak species is a significant source of energy and nutrition, consumed in various forms including roasted, boiled, or as an ingredient in coffee or bread production. Acorn oil, obtained from Quercus species, has been a staple in native diets for centuries, offering comparable nutritional benefits to other cooking oils. These traditional uses highlight the diverse medicinal and nutritional value of Quercus species in different cultures and regions.[40]

Primary Medicinal Activities:
For centuries, various countries and tribes have utilized Quercus species as traditional medicine, attributing them with a diverse range of biological effects including antioxidant, antidiabetic, anticancer, anti-inflammatory, and antibacterial properties. Recent phytochemical investigations into Quercus species have revealed the presence of phenolic acids (particularly gallic and ellagic acids and their derivatives), flavonoids (particularly flavan-3-ol), and tannins across the genus. These compounds, along with triterpenoids and flavonoids, have demonstrated positive effects on anti-inflammatory, antidiabetic, and anticancer activities, indicating their potential as candidates for the development of novel pharmaceutical agents.

However, further research is needed to explore other Quercus species' detailed chemical profiles and health effects. Additionally, comprehensive studies are required to assess the safety, potential side effects, and efficacy of Quercus extracts for therapeutic purposes.[39]

Common Uses: antioxidative, antidiabetic, anticarcinogenic, anti-inflammatory, and antibacterial characteristics. [92].

Distribution in Israel: Golan, Hermon, Galilee, Upper Jordan Valley, Northern Valleys, Gilboa, Carmel, Samarian mountains, Judean mountains, Sharon, Shefela.[38]

Flowering months in Israel: March- April

Chemistry:
The Quercus genus encompasses a wide array of compounds, including glycosides, terpenoids, flavonoids, phenolic acids, fatty acids, sterols, and tannins.
Among these, polyphenols play a significant role and are commonly found in all Quercus species. Notably, phenolic acids such as gallic and ellagic acids and their derivatives, flavonoids, particularly flavan-3-ol, and tannins, are prevalent across various species of Quercus. For instance, Quercus gilva Blume (QGB) has been found to contain picraquassioside D, quercussioside, (+)-lyoniresinol-90α-O-β-D-xylopyranoside, (+)-catechin, (−)-epicatechin, procyanidin B3, and procyanidin B4, suggesting its potential application in urolithiasis treatment. Similarly, Quercus incana has been reported to contain quercetin, methyl gallate, gallic acid, betulinic acid, (Z)-9-octadecenoic acid methyl ester, and β-sitosterol glucoside, with additional compounds such as eupatorin, cirsimaritin, betulin, and β-amyrin acetate observed in its leaves. These findings highlight the diverse bioactive compounds present in Quercus species, offering potential therapeutic applications across various ailments.[39]

Figure 27 (left). Quercus ithaburensis, A developing fruit. Israel, March 2023. Photo by Avinoam Danin.
Figure 28 (right). The lower leaf face (abaxial part) covered with dense short hairs. A stem carrying several young female flowers of the present year resembling buds. Isareal 2024, Photo by Avinoam Danin.

Conclusion

This study underscores several important points.
Firstly, Israel boasts a rich diversity of medicinal plants with significant therapeutic potential. An analysis of these plants reveals certain trends, notably the prevalence of treatments for wound healing, gastrointestinal issues, parasite management, and skin conditions. Anti-inflammatory, antioxidant, antibacterial, and antiparasitic properties emerge as common characteristics among these medicinal plants, with the Asteraceae and Lamiaceae families being particularly prominent.
However, it is evident that further research is needed to explore the medicinal potential of plants in Israel fully. Many aspects of medicinal plants remain poorly understood, including the validation of their ethnoveterinary uses and the extent of their efficacy. Given the complexity of plant compounds, much has yet to be discovered in this field, highlighting the need for continued investigation and exploration.

Summary

This review delves into the significance of medicinal plants, exploring the metabolites they contain and the active compounds responsible for their therapeutic properties.
Examining the historical use of medicinal plants worldwide sheds light on the potential medicinal benefits of plants found in Israel.
Key plants under discussion include *Calendula officinalis* (calendula arvensis), *Matricaria recutita* (wild chamomile), *Silybum marianum* (milk thistle), *Marrubium vulgare* (white horehound), *Melissa officinalis L*. (lemon balm), *Artemisia judaica* (Judean wormwood), and *Quercus Ithaburensis* (Mount Tabor oak).
Each plant is analyzed for its ethnoveterinary practices, phytochemical composition, and clinical implications of its major constituents, highlighting their respective effects.

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