

POISON OR REMEDY?

CASE REPORTS ON SELECTED PLANTS

Editor:
Ceyda Sibel Kılıç

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Poison or Remedy?

Case Reports on Selected Plants

Edited by

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FOREWORD

This e-book comprising 12 chapters covers the topics of unwanted and sometimes unexpected effects of some plants that have been used by different populations throughout the world for various purposes. Though most of these plants have ethnobotanical, medicinal, and culinary usage, they can still be a threat to human and animal health due to the toxic secondary metabolites they contain. Chapters include not only case reports but also botanical information, photographs, structures of chemical compounds responsible for the adverse effects, and ethnobotanical and/or medicinal usages.

Chapters include celery plant that is used for culinary purposes but also containing phototoxic components; the spice cinnamon, which can lead to unwanted effects due to some species' high coumarin content; Angel's trumpet having tropane alkaloids; *Gloriosa* and *Colchicum*, two important genera containing colchicine-type alkaloids; licorice plant; common ivy; *Heracleum* spp. having phototoxic components; nutmeg, a spice and a medicinal plant; oleander plant having significant cardiotoxicity; Syrian rue with harmine and harmaline; rhododendron and its product mad honey and finally castor oil plant that also have uses in the cosmetic industry.

I would like to congratulate the authors and especially the editor, Prof. Dr. Ceyda Sibel Kılıç, who is a former PhD student of mine, for their efforts. They provided important and current details with respect to the adverse effects of some well-known and commonly used plants/plant products that should be kept in mind.

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PREFACE

According to the data of World Health Organization (WHO), 80% of the population living in developing countries rely on herbal medicines for their health problems. It is known that plants contain hundreds of secondary metabolites resulting in various biological activities. However, they might also be responsible for various intoxications and/or adverse effects, either accidentally or on purpose, as many case reports confirm these occurrences.

Since plants can be our friends or foes, this book covers the unwanted effects of some plants (whether medicinal or not) in the form of case reports. We experience such side effects due to a lack of information about them and incorrect usage. Knowing these unwanted reactions will inform us about their adverse effects and will lead us to be cautious when we encounter/use these plants.

Each chapter contains botanical and phytochemical information related to the plant/plant product in question, including the structure of the common compounds responsible for the adverse effect(s). Case reports from different parts of the world are included along with the used parts and the intentions of the usage.

I would like to thank the authors for their contributions and would like to dedicate the book to Prof. Dr. Mekin Tanker from Ankara University (retired) for his contributions to the field of Pharmacognosy, who had passed away recently.

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CHAPTER 1***Apium graveolens* L. (Apiaceae)****Muhammed Mesud HÜRKÜL^{1,*} and Şeyda YAYLA¹**¹ Department of Pharmaceutical Botany, Ankara University, Faculty of Pharmacy, Tandoğan, Ankara, Türkiye

Abstract: *Apium graveolens* L. (Apiaceae; formerly Umbelliferae) is distributed from Europe to the Western Himalayas and from Micronesia to North Africa. The plant is called “celery” and is commonly consumed as a vegetable, also used as medicine, poison, and animal food. The plant has many pharmacological activities such as antioxidant, antimicrobial, hypocholesterolemic, cardiotonic, antidiabetic, antiulcer, hepatoprotective, antiplatelet, larvicidal, anti-spasmodic, anti-inflammatory, anticancer, analgesic and anti-infertility. However, many important health problems have also been reported with the use of celery. Case reports indicate that important conditions like anaphylactic shock, food-dependent exercise-induced anaphylaxis, hyperthyroidism, bipolar disorder, phototoxicity, and acute irritant contact dermatitis may occur due to the use of celery.

Keywords: *Apium graveolens*, Apiaceae, Umbelliferae, Celery, Case reports.

INTRODUCTION

Apium graveolens L. (Apiaceae; syn.: Umbelliferae), celery is distributed from Europe to the Western Himalayas and from Micronesia to North Africa (Fig. 1) [1 - 3]. *A. graveolens* is cultivated and generally used as a vegetable and eaten boiled. Furthermore, it is also used as medicine, poison, and animal food [2 - 4]. In recent years, celery has gained interest with respect to its pharmacological effects and various biological activities of celery have been reported, such as antioxidant, antimicrobial, hypocholesterolemic, antidiabetic, cardiotonic, antiulcer, hepatoprotective, antiplatelet, larvicidal, anti-spasmodic, anti-inflammatory, anticancer, analgesic and anti-infertility activities [5].

The plant is biennial, has a yellowish-green erect stem; angled, strongly sulcate, 30-100 cm, much branched above; leaflets (3-)5-7 per leaf, basal and lower cauline leaves deltate-rhombic, long-petiolulate, glabrous; greenish-white flowers up to 20 per umbellule having 4-12 unequal rays, without bracts and bracteoles;

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fruit broadly ovoid, blackish when ripe; flowering in April-August, in damp places, at an altitude up to ± 500 m [1 - 3]. The leaf stalks of the *A. graveolens* have a broad, sheath base and mostly consist of parenchyma and collenchyma bundles. Vascular bundles beneath the epidermis layer are prominently ridged on the abaxial surface of the leaf. The fruit of *A. graveolens* is known as a schizocarp, which splits into two single-seeded mericarps when ripe. Mericarps remain attached by a filament called carpophore. Fruits usually contain essential oil and abundant endosperm [6].

A. graveolens, whose natural habitat is swamps, is suitable for growing in tropical wetlands with high soil moisture and shallow water tables. Deep, humus-rich, light clay soils are preferred. It is important that the soil is well aerated and well drained. The pH should be slightly acidic or neutral (6.0-7.5). Sites with full sun are ideal. Partial shade can be tolerated, but full sun is important for optimum growth. Cool and temperate climates provide the most suitable environment. The temperature should be between 15-21°C. It should be protected from frost [7, 8].



Fig. (1). *Apium graveolens*

MAJOR ACTIVE SUBSTANCES OF THE PLANT

Celery is rich in volatile oil and phenolic compounds [9 - 11] and the main component of the volatile oil is *d*-limonene (50-80%) along with high amounts of β -selinene (10%) [9, 12, 13]. Moreover, coumarins and furanocoumarins (bergapten) are other main compounds that the plant contains [9, 10]. The seeds are rich in vitamin B and contain proteins (8%), volatile oil (1.5-3%), and fixed oil (5.8-14.2%) [10 - 14]. Leaves and stems are rich in flavonoids and contain apiin and apigenin as main compounds [9, 10]. Celery root contains ferulic acid, caffeic acid, and *p*-coumaric acid derivatives; additionally, coumarin, scopoletin, and aescoumlc acid [10]. The chemical structures of some of these major components are given in Fig. (2).

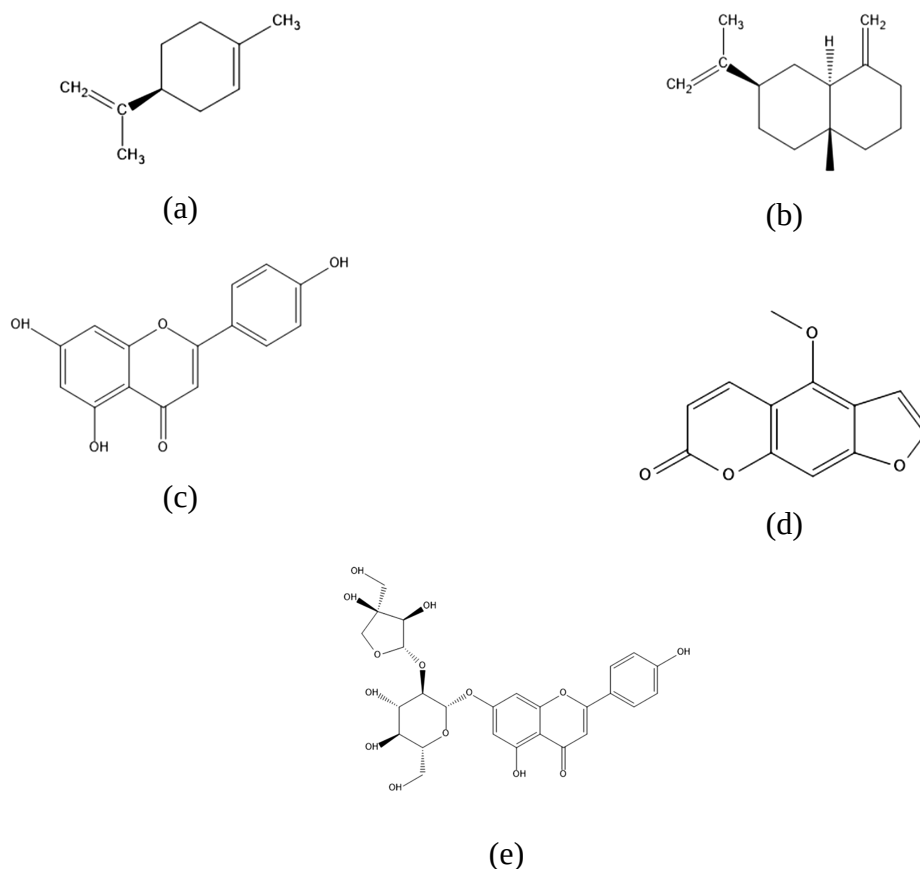


Fig. (2). Structures of (a) *d*-limonene, (b) β -selinene, (c) apiin; (d) bergapten, (e) apigenin (Structures are drawn with ChemDraw Ultra v. 12.0.2.1076)

CHAPTER 2

Cinnamomum sp. (Cinnamon and Cassia) (Lauraceae)

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Abstract: The genus *Cinnamomum* Schaeff. (Lauraceae) has more than 250 species, which consist of aromatic trees and shrubs, and only a few are used for the production of popular bioactive food ingredients cinnamon and cassia. They are made up of dried stem bark layers and are presented as quills or powders in the market. Essential oils from different parts of the plant are also used in the food, cosmetic and pharmaceutical industries. Traditional uses of this beneficial spice with respect to medicine include the treatment of respiratory and gynecological disorders, and digestive complaints including bloating, flatulence, and mild diarrhoea. Many recent studies have focused on different pharmacological activities of Cinnamon and Cassia such as anti-inflammatory, antimicrobial, anticancer, antioxidant, anti-hyperlipidemic, and antidiabetic activities.

Clinical benefits have contributed to cinnamon consumption; however, cinnamon may have some adverse effects, as well. Coumarin, a cinnamon component, is hepatotoxic and carcinogenic. It was discovered that cinnamaldehyde may disrupt respiratory homeostasis and sensitize skin. The safe daily cinnamon intake in Europe is 0.1 mg/kg/day. Contact dermatitis and chronic mucositis associated with cinnamon hypersensitivity were also observed.

Keywords: *Cinnamomum* sp., Cinnamon, Cassia, Coumarin, Case reports, Cinnamaldehyde, Essential oil, Lauraceae, Toxicity.

INTRODUCTION

Natural products, especially herbs, spices, and functional foods have gained huge popularity during the last three decades. They are preferred both for their nutritional and sensory properties and also for their potential health benefits. Spices and herbs are commonly used as food additives that maintain or improve

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taste, aroma, and colour [1 - 3]. Owing to their diverse chemical composition, they can extend the shelf life of foods and beverages. Many bioactive phytochemicals including terpenoids, volatile oils, flavonoids, alkaloids, polyphenolic compounds, and carotenoids are responsible for preventing foods from spoiling and giving them unique sensorial properties. Furthermore, the active ingredients of these products have several therapeutic and functional properties that provide numerous health benefits and reverse nutrient deficiency [4 - 6].

Although natural products have proven their therapeutic indications, in many cases unpredictable effects can be encountered. The majority of reported adverse reactions related to the use of herbal products are due to adulteration, poor product quality, or misuse. In addition to their undesirable effects and adverse reactions, medicinal plants are sometimes regarded as completely unsafe or underreported although they have been used traditionally for many years.

In this chapter, we took a closer look at *Cinnamomum* species that have been used as culinary ingredients for centuries and recently gained popularity as a complementary herbal drug to control diabetes and hyperlipidemia symptoms [7, 8].

Cinnamon is prepared from the inner barks of some *Cinnamomum* trees. Cinnamon and cassia have been widely used as a significant and irreplaceable element in every typical household kitchen due to their exotic aromas and tastes. Without any safety concerns for a long time, *e.g.*, cinnamon is the second most preferred spice in the United States and Europe, after black pepper [9]. Nevertheless, apart from monographs and various scientific papers about its hepatotoxic coumarin content, numerous case reports have been reported on adverse reactions of *Cinnamomum* spp. and their essential oils.

BOTANICAL SPECIFICATIONS

Cinnamomum Schaeff. genus (Lauraceae) comprising evergreen trees and shrubs is native to Tropical and Subtropical Asia to W. Pacific. The genus currently has the status of a tropical and subtropical region, existing in both hemispheres and also including Asiatic and New World species. The name *Cinnamomum* originates from the Greek “cinnamon” or “kinnamomon” a word meaning “sweet wood” [10 - 12].

Cinnamon and cassia are unique terms commonly used for several *Cinnamomum* trees. Although this genus has more than 250 species, only a few of them are used to obtain this popular bioactive food ingredient. Mainly *Cinnamomum verum* J.

Presl, *C. cassia* (L.) J. Presl (syn. *C. aromaticum* Nees), *C. burmanni* (Nees & T. Nees) Blume, *C. tamala* (Buch.-Ham.) T. Nees & Eberm. and *C. loureiroi* Nees are cultivated traditionally [13 - 15].

There is a big confusion in the use of cinnamon (Fig. 1a) and cassia (Fig. 1b) names. It is generally accepted that “Cinnamon” applies only to *C. verum* (Ceylon cinnamon, true cinnamon) while other commercial species such as *C. cassia* (Chinese cassia), *C. burmanni* (Indonesian cassia), *C. tamala* (Indian cassia) and *C. loureiroi* (Saigon or Vietnam cassia) are called “Cassia” or “Cassia cinnamons”. However, in the US, the FDA allows Ceylon cinnamon, Chinese, and Indonesian cassia to all be called cinnamon. Despite the high cost, Ceylon cinnamon is the most preferred type because of its low coumarin content and mildly sweet flavour [10, 16].



Fig. (1). Appearances of (a) *C. verum* (Ceylon cinnamon, true cinnamon) and (b) Cassia (Photos by. G. İşcan).

Ceylon-type cinnamon can be easily differentiated from the others based on the quill structure. True cinnamon sticks have many thin, easily breakable layers and are lighter in colour, whereas cassia-type sticks are mostly tenacious and deep reddish-brown, and they are rolled in only one layer. Sometimes, it can be found in different-sized broken pieces with cork layers, especially *C. cassia*. Moreover, ground cinnamon and cassia samples can only be recognized by microscopy and chromato-spectroscopic methods. Sclereids, needle-shaped crystals of calcium oxalate, starch granules in various sizes, and fibres, and the presence of cork fragments are important anatomical characters in microscopical differentiation [17 - 20].

Another point of contention is the origin of Vietnamese or Saigon cassia (*C. loureiroi*). Researchers have come to the unavoidable conclusion that *C. loureiroi*

CHAPTER 3

Datura* spp. / *Brugmansia* spp. (Solanaceae)*İlker ATEŞ¹ and Ceyda Sibel KILIÇ^{2,*}**¹*Department of Pharmaceutical Toxicology, Ankara University, Faculty of Pharmacy, 06560 Tandoğan, Ankara, Türkiye*²*Department of Pharmaceutical Botany, Ankara University, Faculty of Pharmacy, 06560 Tandoğan, Ankara, Türkiye*

Abstract: *Datura* L. and *Brugmansia* Pers. are two genera of the Solanaceae family, both known by the name Angel's Trumpet. Solanaceae family is well-known for its economic, ornamental, and medicinal plants that contain tropane alkaloids, and species of these two genera have been used since ancient times for their various activities. They also have illicit usage due to their hallucinogenic and euphoric effects, especially in young people. These plants are toxic due to atropine and scopolamine alkaloids that they contain in addition to accidental poisonings that are seen with the usage of members of these two genera. They are also involved in many hospitalizations and criminal cases such as rapes and robberies.

Keywords: Atropine, *Brugmansia* spp, Case report, *Datura* spp, Hyoscyamine, Scopolamine, Solanaceae, Tropane alkaloids.

INTRODUCTION

Datura L. and *Brugmansia* Pers. are two genera belonging to the family Solanaceae, a family containing economic, ornamental, and medicinal plants that have been used since ancient times for their various activities, also having psychotropic and toxic effects [1]. *Datura* species and especially *D. stramonium* L. are known by the names Angel's trumpet, Stinkweed, Locoweed, Devil's weed, Thorn apple, Jamestown weed, devil's cucumber, Hell's Bells, Apple of Peru, Green dragon, La Reina de la noche (the queen of the night), Mad apple, Trumpet lily, Torna-locas, Malpitte, Erba del diavolo (devil's grass), Erba maga (magic grass), Tatula, Domuz pıtırı, and Şeytan elması [2 - 6]. *Brugmansia* species, and especially *B. suaveolens* (Humb. & Bonpl. Ex Willd.) Bercht & J.Presl are known by the names Angel's Trumpet, Misha Colombo, Attana, and

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Cubung in different countries [7]. These plants have been known and used since ancient times for different purposes; *e.g.* *Datura* species have been used since the 16th century in love potions and intoxicants [8], and also as a poison especially for travelers, along with wine and tobacco [9]. Furthermore, due to their hallucinogenic and euphoric effects, these plants have gained popularity among teenagers and young adults since the mid-1970s, and became even more popular afterward due to easily accessible information *via* the internet [10 - 13]. Teenagers add plant extract to alcoholic beverages in order to increase the intoxicating effect [14]. Similarly, *Brugmansia* species are known for their hallucinogenic effects as well, and have been used in religious rites; *e.g.* the genus is known by the name “misha” in Northern Peru and used by Andean shamans and is still an important part of divinatory rituals and therapeutic applications today [15]. The plant was also used in witchcraft in ancient times due to its hallucinogenic effect; however, repeated use is considered to result in insanity [16].

Since the plants have been used for a long time, references to them can also be found in plays such as Hamlet from Shakespeare, Odessey from Homer, and Anthony and Cleopatra [2]. The literature also reports that *Datura* species are responsible for the death of a significant number of soldiers from Mark Anthony’s army in 36 B.C [17]. *Datura* sp. gained popularity among teenagers since it was mentioned in “The Teachings of Don Juan: A Yaqui Way of Knowledge” by Carlos Castenada [18].

These two genera resemble each other, and the genus *Brugmansia* was formerly included in the genus *Datura* as a subgenus or section; however, they are considered to be different genera today; *Datura* spp. as annual herbs and perennial shrubs, and *Brugmansia* spp. as arborescent species. These two genera are actually native to the American continent; however, they have been naturalized in tropical and temperate climates, and thus are considered to be cosmopolite genera [9, 19].

Both genera have funnel (trumpet) shaped and elongated corolla, however, their fruits are different; capsule-type fruits of the *Datura* genus bear spines, but the *Brugmansia* genus has elongated berry-type fruits without spines [20 - 22]. While *Datura* sp. has white flowers, *Brugmansia* sp. has white, yellow, pink, red, and orange flowers [20]. The general appearances of the species can be seen in Fig (1).

Due to the tropane alkaloids that they contain, these plants result in anticholinergic syndrome characterized by redness and dryness of the skin, hyperthermia, mydriasis, blurred vision, delirium, and other symptoms related to the central nervous system (CNS) [23]. In severe cases, especially when higher

doses are administered, respiratory failure, cardiovascular collapse, seizures, and hypoventilation can also be seen [13, 24]. Due to these alkaloids, these species are being used for medicinal purposes, as well. However, many cases of accidental poisoning especially in children and other populations can be found in the literature. For example, in 2003, buckwheat dishes led to poisoning in Slovenia and it was understood that *D. stramonium* plants were commonly growing at the edges of buckwheat fields, therefore contamination and poisoning occurred [4, 16, 25]. Furthermore, exposure to these alkaloids through milk and meat is also possible if tropane alkaloid-containing plants are found in animal feed [26].



Fig. (1). General appearances of: (a) *Datura* sp. (b) *Brugmansia* sp. (Photos by N. & Ö. Erdurak)

MAJOR ACTIVE SUBSTANCE(S) OF THE PLANT SPECIES

Datura and *Brugmansia* species are members of the Solanaceae family that contains crop plants, and poisonous and medicinal plants. Though members of the family have various primary and secondary metabolites, tropane alkaloids establish the major active substance group in this family and among them, atropine/hyoscyamine and scopolamine are major alkaloids [6, 9]. These alkaloids are synthesized in the roots and stored in vacuoles, reaching the highest amount during the flowering period [2]. Structures of atropine and scopolamine are given in Fig. (2).

D. stramonium is reported to contain scopolamine and atropine as major compounds that can pass the blood-brain barrier rapidly [24, 26]. *Datura* spp. are

CHAPTER 4

Gloriosa* spp. / *Colchicum* spp. (Colchicaceae)*Alper GÖKBULUT^{1,*}**¹ Department of Pharmacognosy, Ankara University, Faculty of Pharmacy, Tandoğan, Ankara, Türkiye

Abstract: Natural products, especially medicinal plants, play substantial roles in the management of health-related problems. Before the prevalence of modern medicine, phytotherapy was the predominant form of primary health care all over the world. However, it is well known that plants can do more harm than good if not handled with care. Many serious adverse effects that can result in death have occurred due to the misuse of unidentified plants and mindless usage. *Gloriosa* and *Colchicum* species are important medicinal plants that have diverse biological effects, and they contain alkaloids such as colchicine and their derivatives as the main active principles. Plants are used for medicinal purposes in traditional systems, particularly due to their anti-inflammatory, tonic, abortifacient, anthelmintic, analgesic, and laxative features. In addition to the important benefits of these two Colchicaceae plants, toxic effects due to their poisonous alkaloids have also been determined. In this study, an insight into the medicinal usage of *G. superba* and *C. autumnale* together with their toxicity in terms of case reports will be provided.

Keywords: Autumn crocus, Colchicaceae, *Colchicum autumnale*, *Gloriosa superba*, Glory lily, Toxicity.

INTRODUCTION

Gloriosa L. genus belonging to the Colchicaceae family has remarkably beautiful perennial species, which are widely distributed in Africa and Asia. Several species are recognized including *G. superba* L., *G. simplex* L., *G. lindenii* (Baker) J.C.Manning & Vinn., *G. katangensis* Maroyi, *G. littonioides* (Welw. ex Baker) J.C.Manning & Vinn., *G. flavovirens* (Dammer) J.C.Manning & Vinn., etc. Herein, the focus will be on *Gloriosa superba* L., which grows naturally in the tropical climates of Africa, along with Asia, Australia, and the Pacific Islands. This climbing plant with magnificent flowers reaches up to 5 m and is mostly called lily, glory lily, and superb lily [1]. Also in some Asian countries, *Gloriosa*

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is known by special traditional names among the natives such as Kalappaikillanku, Kembangtelang, Niyagala, and Karthigaipoo. Tamil Nadu, an Indian State, assigned this poisonous herb as its state plant [1, 2]. Every part of the species is used for medicinal purposes in Ayurvedic and Unani systems particularly due to its anti-inflammatory, tonic, abortifacient, anthelmintic, analgesic, and laxative activities [3].

Colchicum L. genus of the family Colchicaceae takes its name from “Colchis”, an ancient country on the Black Sea, which also indicates its origin. Autumn crocus, meadow saffron, and naked lady are common names of the species that have been used for the treatment of several ailments for centuries such as rheumatism, gout, prostate enlargement, gonorrhea, and several types of cancers. Dioscorides described *C. autumnale* L. in the first century BC, and the plant was suggested as a remedy to treat gout in De Materia Medica. Almost a hundred species of the genus are distributed throughout the world, and approximately half of them grow in Türkiye with a high endemism ratio [4]. In this chapter, mostly *C. autumnale* will be discussed among other species, as well.

Despite their narrow therapeutic indices, tropolone alkaloids such as colchicine and demecolcine are important secondary metabolites recommended for handling several ailments including Familial Mediterranean Fever (FMF), gout, Behcet’s Disease, myeloid leukemia and Hodgkin’s syndrome. Colchicine is a yellowish-white amorphous compound with a bad taste and contains a benzocycloheptanotropolone ring in the group of protoalkaloids. Colchicine and colchicine derivatives are responsible for various biological activities of *Gloriosa* spp. and *Colchicum* spp. which are rich in tropolone alkaloids [4, 5].

Although these plants have medicinal importance, they also come to the fore in many poisoning and suicide cases due to the toxic alkaloids that they contain [6]. *Gloriosa* spp. and *Colchicum* spp. are known as good sources of the aforementioned amino alkaloids and should be avoided by local people to prevent cases of intoxication.

TRADITIONAL USES

G. superba is an important tropical medicinal plant, which is being extensively used by local people. While the leaves of the plant are used to heal piles and ulcers, seeds are suggested for cancer treatment. In addition, the roots are consumed due to their antimicrobial features, especially for urinary tract infections. Leaves are applied directly to the chest to relieve symptoms of asthma in Congo and in Tanzania, ashes obtained by burning the leaves are recommended for wound healing. The plant juice is recognized as an effective antimalarial

agent. In other parts of Africa, tubers are used as an abortifacient agent and also as a means to commit suicide due to their high toxicity [1 - 3].

Both *G. superba* and *C. autumnale* were recommended as an important source of colchicine to combat gout in the sixth century. In the Unani System, *C. autumnale* is fundamentally used for the treatment of arthritis. Also, the plant is used for healing internal wounds and inducing deep sleep. It is a strong pain killer especially for muscular tissue, joint, and gastric pains [7].

Though *C. autumnale* is an important source of colchicine and demecolcine, many other taxa growing naturally in Anatolia are comparable to *C. autumnale* with respect to alkaloid contents, e.g. *C. balansae* Planch., *C. baytopiorum* C.D.Brickell, *C. bornmuelleri* Freyn, *C. kotschyi* Boiss., *C. macrophyllum* B.L.Burt, *C. speciosum* Steven, *C. triphyllum* Kunze, *C. turcicum* Janka, *C. umbrosum* Steven, *C. micranthum* Boiss., *C. chalconicum* Azn. are some of the Turkish *Colchicum* species, which have been studied previously for their colchicine and colchicine derivatives content and thus, they can be used to provide the same health benefits [8, 9].

ACTIVE SUBSTANCES

The presence of alkaloids, in *G. superba* and mainly colchicine makes it a significantly important medicinal plant; this alkaloid derives from phenylalanine and tyrosine amino acids. The whole plant, and especially the seeds are recognized as a potential commercial source of colchicine and colchicoside [1].

While *G. superba* contains 0.1-0.9% colchicines, Indian corms have less amount of this alkaloid [10]. Finnie and Staden reported 0.33–0.41% of colchicine in the stem, 1.18% in the flower, and 0.08% in the ovary [11]. In a previous study, four tropolone alkaloids (colchicine, lumicolchicine, 3- demethyl-N-deformyl-N-deacetyl colchicine, and 3-demethyl- colchicine) were isolated from the underground parts of the plant [12]. Tubers are considered to be significant sources of gloriosine and colchicine and contain tannins, colchicines, phenolic acids, and sterols, as well [13]. The main secondary metabolites of the leaves are superbine, colchicine, gloriosine, gloriosol, sterols, and stigmaterin [14]. Leaves also contain chelidonic acid, which is a heterocyclic organic acid with a pyran skeleton [15]. Some other colchicine derivatives that are identified as isomers exist in the leaves, as well [1].

Colchicum genus is reported to have substantial bioactive compounds, including tropolone and isoquinoline alkaloids, phenolic compounds, flavonoids, and tannins along with some minerals, carbohydrates, and proteins [7, 16 - 25]. Autumn crocus has been used medicinally for over 3000 years despite the fact that

CHAPTER 5***Glycyrrhiza glabra* L. (Fabaceae)****Aslı CAN AĞCA¹ and Sinem ASLAN ERDEM^{2,*}**¹ Department of Traditional, Complementary and Integrative Medicine, Ankara Yıldırım Beyazıt University, Institute of Public Health 06010 Etlik, Ankara, Türkiye² Department of Pharmacognosy, Faculty of Pharmacy, Ankara University, 06560 Tandoğan, Ankara, Türkiye

Abstract: *Glycyrrhiza glabra* L., commonly known as licorice, is a prominent medicinal plant of the Fabaceae family, recognised for its extensive therapeutic applications in various traditional systems of medicine. Licorice, including the roots and rhizomes of *Glycyrrhiza* spp., is known not only for its pharmacological properties but also for its use in cosmetics as a depigmentation agent and in foods as a flavouring and sweetener. *Glycyrrhiza glabra* is one of the main representatives of the drug “licorice,” whose main chemical constituents are triterpene saponins, flavonoids, and phenolic compounds. Licorice is cultivated throughout the world and is used in both conventional and traditional medicine.

The rhizomes and roots of licorice are used medicinally, either alone or in combination with other herbs, to treat a variety of conditions including stomach ulcers, hyperdipsia, flatulence, and colic, aside from respiratory conditions such as coughs, asthma, tonsillitis, and sore throats. Despite its long tradition and broad use, licorice is not without risk. A substantial number of side effects have been reported, predominantly with long-term use. Chronic or excessive use can lead to serious side effects, including hypokalemia, hypertension, and, in extreme cases, fatal cardiac events. This chapter also presents case reports that exemplify these adverse effects and highlight the importance of the cautious use of licorice in clinical practice. The findings suggest that while *Glycyrrhiza glabra* remains a valuable medicinal resource, its potential for toxicity requires careful administration and monitoring.

Keywords: Anti-inflammatory, Fabaceae, *Glycyrrhiza glabra* L., Glycyrrhizin (glycyrrhizic acid), Hypokalemia, Hypertension, Licorice.

INTRODUCTION

Roots and rhizomes of *Glycyrrhiza* species from the family Fabaceae give us licorice (Gan Cao). Among nearly 30 species, only *G. glabra* L., *G. inflata* Bat., and *G. uralensis* Fisch. ex DC. are defined as official sources of licorice, and the

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dried roots and rhizomes have been used as traditional medicine worldwide; especially in China, these three species have been recorded in the Chinese Pharmacopoeia. Licorice is used as a “guide drug” which harmonises the effect of other ingredients present in the formulation and is reported as one of the most prescribed herbs with a range of more than half in Traditional Chinese Medicine (TCM) [1 - 4].

Licorice is well-known and popular not only for its pharmacological effects but also for its use in the cosmetic field as a depigmentation agent and in the food industry for flavouring and sweetening products. Root fibers are used in insulation and the production of wallboards and boxboards [5, 6].

Licorice is widely used in various industries, and thus so many products contain licorice, however, the name of the species is not usually specified. Furthermore, three *Glycyrrhiza* spp. named *G. glabra*, *G. uralensis*, and *G. inflata* are all stated as licorice both in the Chinese and European Pharmacopoeias. In the United States and Japanese Pharmacopoeias, *G. uralensis* and *G. inflata* are referred to as licorice [7, 8].

The genus *Glycyrrhiza* originated from the Greek words glykos, meaning sweet, and rhiza, meaning root. The flowers are purple to pale white-blue and are placed in a hermaphrodite inflorescence. The fruit is an oblong legume, 2 to 3 cm long, and contains numerous seeds. The roots are horizontal, woody, stoloniferous, well-developed, and divided into three to five subsidiary roots. They are also taproot-type roots. Rhizomes and roots are brown-green to dark brown, and they can reach a depth of up to one meter. After reaching maturity in 3 to 4 years, the plants are harvested. The fragments of root appear as fractured fibrous bands, displaying the yellowish interior with a distinct flavour and scent [5, 7].

This chapter includes information on *G. glabra*, as the majority of case reports include this species.

PHYTOCHEMICAL COMPOSITION

The chemical composition of the plant is highly dependent on geographical conditions and the harvesting process. More than 400 compounds have been identified in *Glycyrrhiza* species, and the compositions of species vary remarkably. The chemical compounds identified in *G. glabra* mainly belong to triterpene saponins and phenolic compounds (including flavanones, chalcones, flavones, isoflavones, and isoprenylated flavonoids) [6, 9].

The plant grows naturally in many countries and is therefore used for different purposes to treat and/or prevent some ailments.

Triterpene Saponins

Glycyrrhizin (glycyrrhizic acid) (Fig. 1a) and its aglycone, glycyrrhetinic acid (Fig. 1b), are the major compounds of licorice roots and glycyrrhizin is found as a mixture of potassium and calcium salts of 18- β -glycyrrhizic acid. It is an oleanane-type triterpene saponin and is chemically named 20- β -carboxy-11--xo-30-norolean-12-en-3 β -yl-2-*O*- β -d-glucopyranurosyl- α -d glucopyranosiduronic acid. Glycyrrhizin, characterised by a significant sweet taste, is also named 18 β -glycyrrhizin or 18 β -glycyrrhizic acid. Both glycyrrhizin and glycyrrhetinic acid may exist as 18 α -isomer and 18 β -isomer. Almost 40 triterpene saponins and derivatives have been determined in *G. glabra* [2, 10 - 18].

Licorice saponin K2/H2, licorice saponin B2, and licorice saponin G2/yunganoside K2 were mentioned as metabolites primarily formed in *G. glabra*, and therefore they could be defined as biomarker molecules [19].

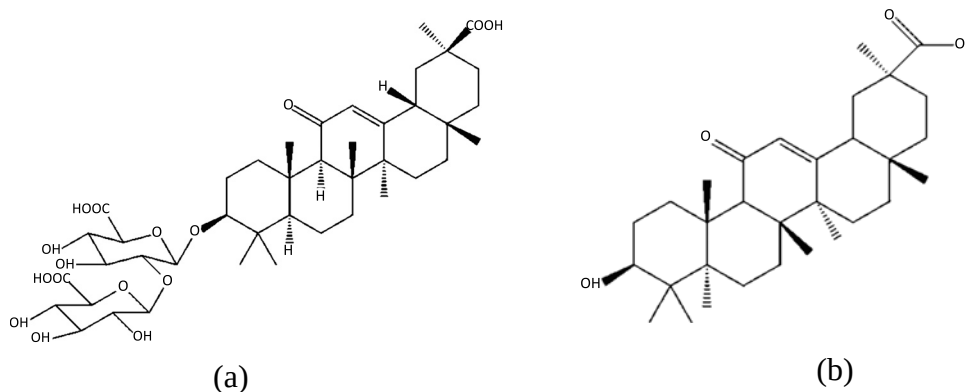


Fig. (1). Structures of major triterpene saponins of the species (a) Glycyrrhizic acid; (b) Glycyrrhetinic acid; Structures drawn with ChemDraw Ultra v. 12.0.2.1076)

Phenolic Compounds

Flavonoids isolated from *G. glabra* belong to different chemical structures such as flavanones, flavanone, chalcones, isoflavans and are responsible for the yellow colour of *G. glabra*. Isoliquiritigenin is the 2'-hydroxychalcone isomer of the flavanone liquiritigenin. The main flavonoids in *G. glabra* roots are stated to be glycosides of these compounds. The compounds with flavanone skeleton are; liquiritin, liquiritin apioside, neoliquiritin, glabrol, and liquiritigenin [5, 20, 21]. The chalcones isoliquiritin apioside, isoliquiritin, isoliquiritigenin, neoisoliquiritin, davidigenin, licocalchone A, licocalchone B and licuraside are also found. Licoisoflavone A, licoisoflavone B, gancaonin G, gancaonin H, hispaglabridin A, hispaglabridin B, glabridin, 3'-hydroxy-4'-O-methylglabridin, 4'-

CHAPTER 6***Hedera helix* L. (Araliaceae)****Gülnur EKŞİ BONA¹ and Gülderen YILMAZ^{2,*}**¹ Department of Pharmaceutical Botany, Faculty of Pharmacy, İstanbul University-Cerrahpaşa, İstanbul, Türkiye² Department of Pharmaceutical Botany, Faculty of Pharmacy, Ankara University, Ankara, Türkiye

Abstract: *Hedera helix* L., common ivy is a popular ornamental and medicinal plant that is generally known for its usages against respiratory tract diseases, and irritating cough. It also has various biological activities such as bronchospasmolytic, antileishmanial, antitumor, anti-inflammatory, antitrypanosomal, antimutagenic, molluscicidal, antioxidant, antimicrobial, analgesic, anthelmintic and antithrombin activities. The main active compounds responsible for these biological activities are triterpenic saponins. Common ivy is a widespread plant that contains strong irritants like polyacetylene compounds, falcarinol, and didehydrofalcarinol, which are powerful irritants that cause severe contact eczema in patients generally *via* dermal contact. It occurs mainly in spring when ivy grows rapidly and usually when it is pruned. Typical symptoms of ivy dermatitis are linear and vesicular eczema, allergic contact dermatitis on the hands, lateral parts of fingers, fingertips and forearms, neck, face, trunk, and lower legs. Additionally, commercial herbal supplements containing *H. helix* for respiratory tract diseases may cause unexpected side effects for children like moderate angular cheilitis and diaper dermatitis, mild vomiting, acute tubulointerstitial nephritis, and mild nausea. Especially allergic people are recommended to be careful when using the *H. helix* plant and the products prepared from the plant.

Keywords: Araliaceae, Case reports, *Hedera helix*, Ivy, Triterpene saponins.

INTRODUCTION

Hedera L. (Araliaceae) is a polyploid complex of woody vines with evergreen foliage, comprising 19 species and distinctive juvenile and adult life stages, naturally distributed in the Northern Hemisphere [1, 2]. The genus has a complicated taxonomy because of its unusual life cycle, broad geographic distribution, and its horticultural use [3 - 5].

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Hedera helix L. has up to 30 m height like trees, cliffs, and walls with its adventitious roots [6, 7]. It is known as ivy, common ivy, English ivy, true ivy, gum ivy, and woodbind [8]. Ivy is one of the most popular ornamental and medicinal plants distributed especially in Europe and Western Asia [1, 9 - 14]. The stem of *H. helix* is branched and may reach a diameter of 20 cm. Leaves are alternate, glabrous, dark green, glossy, and generally palmately lobed or ovate-rhomboid, around 8 cm long. Inflorescences are greenish-yellow, in the form of umbels that form semi-globular clusters. The flowering period is from Summer to late Autumn [13]. The general appearance and fruits of the plant are shown in Fig. (1).

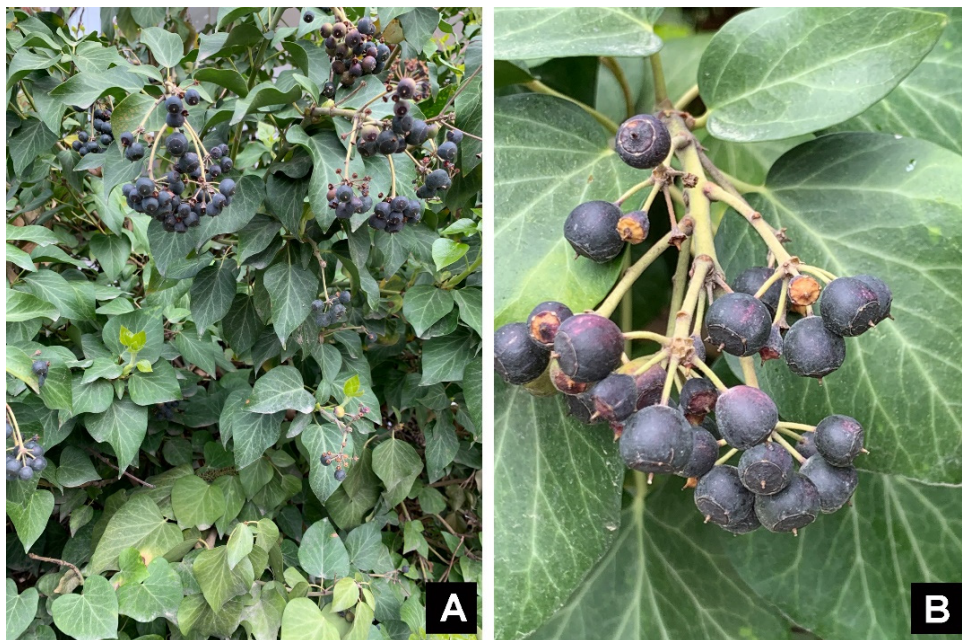


Fig. (1). General appearances of *H. helix* (A, B). (Photos by G. Yılmaz).

The fruit is a spherical, often 5-valved blackberry. It contains reniform, triangular, reddish-violet seeds at early stages that turn to dark brown and black later on [8, 13]. The parts that are used for medicinal purposes are the leaves and the berries [8]. The plant is also known by the synonyms *H. communis* Gray, *H. poetarum* Bertol. and *H. poetica* Salisb. [1].

Ivy is well-known for its medicinal use for treating respiratory tract conditions and irritable coughs. It also possesses a variety of biological properties, including the ability to inhibit bronchoconstriction, as well as antitumor, antileishmanial, anti-inflammatory, antitrypanosomal, antimutagenic, antioxidant, antimicrobial,

analgesic, anthelmintic, and antithrombin activities. [7-9, 13, 15, 19, 21-22,40, 47-55]. Ivy has strong irritants that might lead to contact eczema in certain people. The aim of this research is to compile case reports of the *H. helix*, which is widely used both decoratively and medically and may cause dermatitis in some people.

MAJOR ACTIVE SUBSTANCES

Triterpenic saponins, flavonoids, and phenolic compounds are the main active compounds responsible for the medicinal use of *H. helix* [7, 8, 15 - 23]. Major secondary metabolite groups isolated from the fruits of ivy are triterpene saponins with representative compounds such as helixoside A, helixoside B and hederagenin derivatives; polyacetylenes (falcarinon, falcarinol, panaxidol, (Z)-9,10-epoxy-1-heptadecene-4,6-diyn-3-one); fatty acids (petroselinic, oleic, *cis*-vaccenic, palmitoleic) and β -lectins [8, 9, 13, 19, 24 - 27]. Structures of some of these major components are shown in Fig. (2).

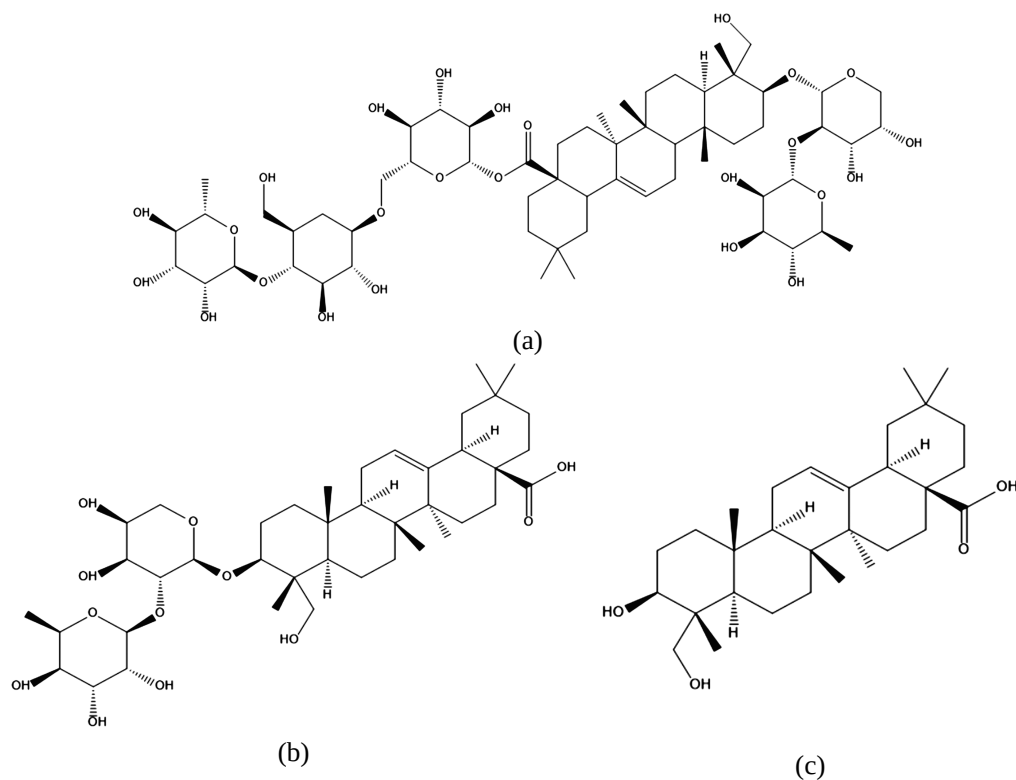


Fig. (2). Structures of (a) hederacoside C, (b) α -hederin, (c) hederagenin (Structures are drawn with ChemDraw Ultra v. 12.0.2.1076).

CHAPTER 7

Heracleum* spp. (Apiaceae)*Damla KIRCI^{1,*}, Büşra CUMHUR² and Safa GÜMÜŞOK³**¹ Department of Pharmacognosy, Faculty of Pharmacy, İzmir Katip Çelebi University, 35620 Çiğli, İzmir, Türkiye² Ankara University, Graduate School of Health Sciences, 06110 Dışkapı/Ankara, Türkiye³ Department of Pharmaceutical Botany, Faculty of Pharmacy, Ankara University, 06560 Tandoğan, Ankara, Türkiye

Abstract: *Heracleum* L. genus has been used for many years for medicinal purposes and also as food and spice. *Heracleum* species contain flavonoids, coumarins, lignans, sterols, and volatile compounds, and due to these secondary metabolites, members of the genus have many biological activities such as analgesic, anti-diabetic, vasodilator, and cytotoxic activities. *Heracleum* species are considered a public health hazard since they cause phototoxic reactions when skin is exposed to the sap and then UV rays. Compounds responsible for this effect in *Heracleum* species are furanocoumarins such as sphondin, bergapten, and pimpinellin. When we search the case reports found in the literature, we can see that the species responsible for toxicity are usually identified as *H. mantegazzianum* Sommier & Levier, *H. laciniatum* Desf. (Syn. *H. sphondylium* subsp. *sphondylium*), and *H. sphondylium* L. The most common adverse effects are blisters, skin burns, and erythema.

Keywords: Apiaceae, Case report, Furanocoumarin, *Heracleum* L., Phototoxicity.

INTRODUCTION

The genus *Heracleum* L., which is widespread in the Asian continent, is one of the largest genera of the Apiaceae family. *Heracleum* genus has been used for many years for medicinal purposes and as food and spice [1].

They are perennial or monocarpic, tall or stunted, usually aromatic plants, with rhizomes usually having a ring of thick, sometimes ribbon-like fibers. The stem is cylindrical, mostly corrugated. Lower leaves are simple and lobed or 1-2 pinnate or trisect-biternate, pubescent or glabrous. Bracts and bracteoles may be present or absent. Sepals are very small, and petals are white or sometimes pale green, regular or radial outside, tips bent, bilobed, usually glabrous. Narrowly coiled

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ringed stylopodium is conical, style filamentous, drooping in fruit, and usually glabrous. Fruits highly flattened on the back, hairy or glabrous, dorsal and lateral projections thin, 5; dorsal secretory ducts 4, filamentous or broadly clavate, separate intervacular base not elongated, secretory ducts 2-0 on opposite inner surfaces of mericarps [2-3]. The general appearance of a representative species, *H. platytaenium* Boiss., is given in Fig. (1).



Fig. (1). General appearance of *H. platytaenium* Boiss. (Photo by C.S. Kılıç)

The genus *Heracleum* L. is important as a medicinal plant because of its usage for inflammation, diarrhea, dysentery, sunstroke, infertility, gastrointestinal disorders, hemorrhoid, asthma, bronchitis, rheumatism, cancer, diabetes, wound, and headache [1].

ACTIVE SUBSTANCES

Heracleum species are known to contain flavonoids [4], coumarins [5], lignans [6], sterols [7], volatile compounds (oxygenated and oxygen-free monoterpenes), sesquiterpenes, and aliphatic esters. Octylacetate was identified as one of the major compounds of the essential oil [8, 9].

Table 1. Some flavonoids of *Heracleum* species.

Plant Name	Plant Part	Chemical(s)	Refs.
<i>H. mantegazzianum</i> Sommier & Levier	Stems	Cyanidin 3-sambubiosid	[10]
<i>H. moellendorffii</i> Hance	Leaves	Astragalin, hyperoside	[11]
<i>H. persicum</i> Desf.	Aerial parts and roots	Rutin, afzelin, astragalin, kaempferol, isorhamnetin-3- <i>O</i> - β - glucopyranoside, nicotiflorin, narcisin	[4]

Table 2. Some coumarins of *Heracleum* species.

Species Name	Plant Part	Chemical(s)	Refs.
<i>H. brunonis</i> (DC.) Benth. ex C.B. Clarke	Roots	Bergapten, imperatorin, heraclenol, columbianadin, columbianatin, pimpinellin, angelicin, xanthotoxin,	[12]
<i>H. canescens</i> Lindl.	Roots	heraclenin, imperatorin, heraclenol, isoheraclenin, isogospherol, alloisoimperatorin, psoralen, xanthotoxin	[13]
<i>H. cyclocarpum</i> K.Koch	Roots	sphondin, isopimpinelline, bergaptene, isobergaptene, pimpinelline, ostol	[5]
<i>H. mantegazzianum</i> Sommier & Levier	Fruits	Bergapten, xanthotoxin, isopimpinellin, imperatorin, pimpinellin, limettin, 5-methoxy-7-(3,3-dimethylalliloxy)-coumarin	[14]
	Fruits	impinellin, imperatorin, phellopterin, xanthotoxin	[15]
<i>H. laciniatum</i> Desf.	N/A	bergapten, isobergaptene, sphondin, isopimpinellin and pimpinellin	[16]
<i>H. persicum</i> Desf. ex Fisch.	Roots	sphondin, isopimpinelline, bergapten, isobergaptene, pimpinelline	[17]
<i>H. rapula</i> Franch.	Roots	moellendorffiline, rivulobirin B, rivulobirin A, 8-geranyloxypsoralen, heraclenin, imperatorin, R-heraclenol, <i>o</i> -isopropylideneheraclenol, bergapten, isopimpinellin, sphondin, isobergaptene, pimpinellin, angelical	[7]
<i>H. sphondylium</i> L.	Aerial parts, fruits, and roots	Bergapten, byakangelicol, imperatorin, isobergaptene, isopimpinellin, phellopterin, pimpinellin, sphondin, xanthotoxin	[18]

Myristica fragrans Houtt. (Myristicaceae)

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Abstract: In this present review work, nutmeg and mace from *Myristica fragrans* Houtt. were elaborated associated with their risks in use. Nutmeg, as a spice and medicinal preparation, is known and documented to be used as a carminative, expectorant, and analgesic and also used in infants. However, due to potential toxicological issues, as in the case reports, the use should be limited. Especially the narcotic effect, when consumed excessively, is associated with its components, myristicin and elemicin in particular. It is necessary to limit the use of nutmeg and be aware of potential drug interactions as well.

Keywords: Case reports, Mace, *Myristica fragrans* Houtt., Myristicaceae, Toxicity.

INTRODUCTION

Common names for nutmeg and mace (*Myristica fragrans* Houtt.) are jathikka, jaiphal, and javitri in India, as well as magic, muscdier, nux moschata, myristica, muskatbaum, etc., in various other countries. It is an evergreen tree among 72 *Myristica* spp. from the Myristicaceae family and is now mostly cultivated especially in Grenada in the West Indies, tropical zones of India, Asian Pacific countries, Sri Lanka, Ceylon, Malaysia, Taiwan, Vietnam, China, South America, and South Africa for world trade. The botanical origin of the species is the Banda Islands, Moluccas of Eastern Indonesia, where it is now rarely found in its natural habitats. The characteristic aromatic drupe-type fruits are single-seeded, fleshy, juicy, 6-9 cm long, and similar in appearance to the apricot. Also, a characteristic aromatic orange-yellow pericarp is formed when the fruit ripens, which is named mace [1 - 3]. *M. fragrans* fruits, mace, and their preparations have been demanded

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and used as a spice for centuries, which was and still is an important commercial Asian commodity in trade *via* the silk/spice road as in the former historical times.

It is important to highlight that nutmeg and mace are two separate parts; however, both originate from the fruit of *M. fragrans*. When the mature fruit opens, the stony endocarp, or seed, is visible, surrounded by a red, slightly fleshy web or grain; here, the dried grain alone is mace. The nuts are scraped and dried to produce nutmeg, which is the most available form of spice and condiment [1 - 4]. The general appearance of dried nutmeg seeds and aril or arillus named “mace” is illustrated in Fig. (1) Distributed worldwide, nutmeg, mace, and their preparations are usually available in herbal clinics, spice stores, and local markets. They are used as a flavoring agent in meals, condiments, bakery products, and desserts for their characteristic aroma.



Fig. (1). General appearance of (a) *M. fragrans* seeds and (b) mace aril (Photos by M. Karadağ).

M. fragrans preparations are prepared from the fruit yielding the seed and the surrounding aril (Myristicae macis), which are used in dried form, preferentially freshly ground in special mills as a spice. Although the *Myristica* tree leaves, barks, and other parts were also investigated, mostly nutmeg essential oil, mace essential oil, and nutmeg butter and fixed oil are consumed and sold in retail [1, 2]. However, ground nutmeg as a spice and its essential oil in aromatherapy, are the most utilized forms, along with flavorings and fragrances [4].

Nutmeg contains essential oil (5-15%), fixed oil (25-30%), proteins, fats, starch, and mucilage-type carbohydrates along with phenolic compounds, saponins, polyphenols, minerals, vitamins, *etc* [3 - 5].

It is known that *M. malabarica* and *M. argentea* are used for adulteration among others, which also have different flavours. Mostly organoleptically characterized, nutmeg fruits have a characteristic spicy fragrance and a slightly sweet taste with a flavor [4].

In this present review, the toxicological and narcotic effects of nutmeg/mace and its preparations are evaluated, which have been elaborated by current reviews and case reports worldwide despite its popular consumption as a spice.

MAJOR ACTIVE SUBSTANCES

Many reports on the essential oil chemistry of *M. fragrans* fruits from different origins have been published. In general, myristicin (10-25%) was characterized as the major component of the essential oil [4 - 9]. However, its essential oil also contains volatile components such as safrole and eugenol, which are reported as genotoxic and carcinogenic. Structures of myristicin, safrole, and eugenol are given in Fig. (2). There are reports on the reduction of toxic substances by techniques developed during the isolation of the essential oil [7, 8].

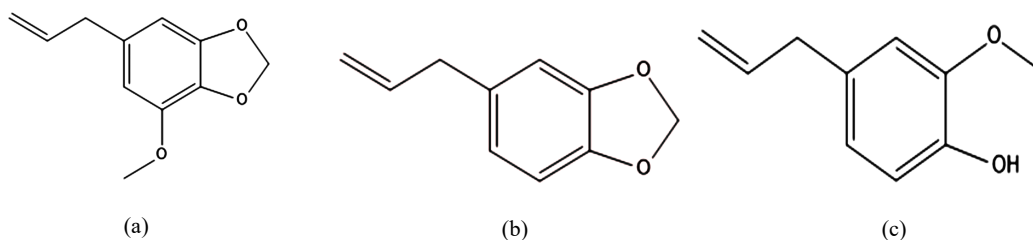


Fig. (2). Structures of: (a) myristicin, (b) safrole, (c) eugenol (Structures are drawn with ChemDraw Ultra v. 12.0.2.1076).

The antioxidant effect of the essential oils was experimented with by bioactivity-guided fractionation, where elemicin and terpinene-4-ol were characterized, which were the other major components of the oil responsible for biological activities [3 - 6]. Structures of the components are shown in Fig. (3).

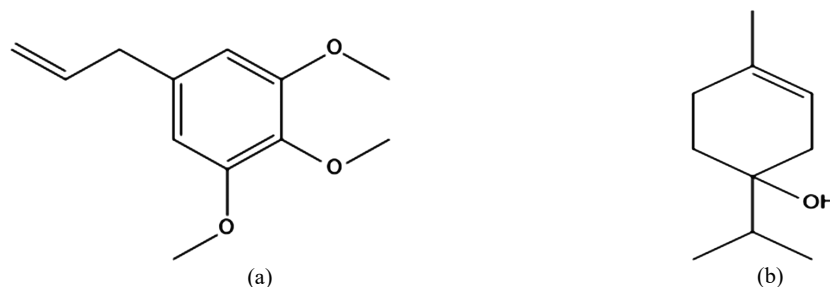


Fig. (3). Structures of: (a) elemicin, (b) terpinene-4-ol (Structures are drawn with ChemDraw Ultra v. 12.0.2.1076).

CHAPTER 9***Nerium oleander* L. (Apocynaceae)****Yavuz Bülent KÖSE^{1,*} and Nagehan SALTAN¹**¹ Department of Pharmaceutical Botany, Anadolu University, Faculty of Pharmacy, 26470 Tepebaşı, Eskişehir, Türkiye

Abstract: *Nerium oleander* L. is an evergreen shrub belonging to the Apocynaceae family. This species contains toxic cardiac glycosides and has been historically known as a poisonous plant. Oleander has been used in ethnomedicine for its cardiotonic, diaphoretic, diuretic, anticancer, antibacterial, antifungal, and expectorant effects.

Keywords: Apocynaceae, *Nerium oleander* L..

INTRODUCTION

Nerium oleander L. is an evergreen shrub of the Apocynaceae family and is up to 6 m high. It is known as Oleander, although taxonomically unrelated due to its superficial resemblance to *Olea* [1]. Leaves often in whorls of 3, very narrowly elliptic, acute, narrowed at base into a short petiole, 6-30 x 1-3 cm, coriaceous, with prominent midrib and very numerous fine parallel lateral veins. Flowers large, in terminal pedunculate cymes. Corolla infundibular, rose or red, but many different colored flower cultivars have been bred, such as purple, salmon, pink, lilac, and carmine. Calyx puberulent. Follicles 10-18 cm. Seeds hairy with apical coma [2, 3]. General appearance and a single flower are given in Figs. (1 and 2).

N. oleander is cultivated worldwide throughout the tropics and subtropics as an ornamental plant; it is native only to the Mediterranean region, Northwest Africa, the Iberian peninsula, the Arabian peninsula, southern Asia, and Yunnan region in southern parts of China [4, 5]. It prefers habitat-dried stream beds, waterfronts, and stony areas [6].

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MAJOR ACTIVE SUBSTANCES OF THE PLANT AND THEIR PHYSIOLOGICAL EFFECTS

N. oleander contains at least 2% cardiac glycosides. Neriin and oleandrin are glycosides with properties similar to digitalin, the main toxin of oleander. Olenadrigenin is another cardiac glycoside in oleander. Flavones (0.5%) and a small amount of essential oil, as well as rubber, fats, sugars, and hydrocyanic acid, were found in the leaves [7, 8]. The stem bark contains toxic glycosides, rosaginin and nerlin, volatile oil, and fixed oil. Also, flowers contain alkaloids, glycosides, carbohydrates, flavonoids, tannins, and phenolic compounds [9, 10].



Fig. (1). General appearance of the flowers and leaves.

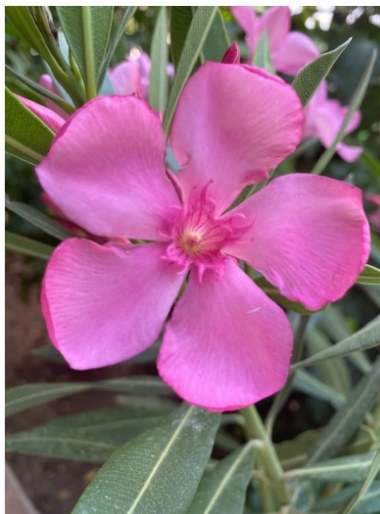


Fig. (2). Flower of *N. oleander*.

Cardiac Glycosides (Oleandrin, Nerioside, Oleandrogenin): These compounds are potent toxins that affect the heart and nervous system.

Bufadienolides (Bufalin, Bufotalin): These are another group of cardiac glycosides found in oleander. They have similar toxic effects to other cardiac glycosides, particularly on the heart.

Saponins: Oleandrin is sometimes classified as a saponin due to its structure. Saponins are compounds known for their foaming properties and are found in many plants. In oleander, saponins can contribute to its toxic effects, though they are not as potent as cardiac glycosides.

Alkaloids (α -amyrin, β -amyrin): These compounds are found in the leaves and stems of oleander. While they are not as toxic as cardiac glycosides, they may contribute to the overall toxicity of the plant.

The physiological effects of these substances include:

Cardiotoxicity: The most prominent effect is on the heart, leading to arrhythmias, bradycardia, tachycardia, and potentially fatal cardiac arrest.

Neurotoxicity: Symptoms such as seizures, tremors, confusion, dizziness, and coma can occur due to the impact on the nervous system.

Gastrointestinal effects: Ingestion of oleander can cause nausea, vomiting, abdominal pain, and diarrhea.

Skin irritation: Contact with oleander sap or other plant parts can cause skin irritation or dermatitis.

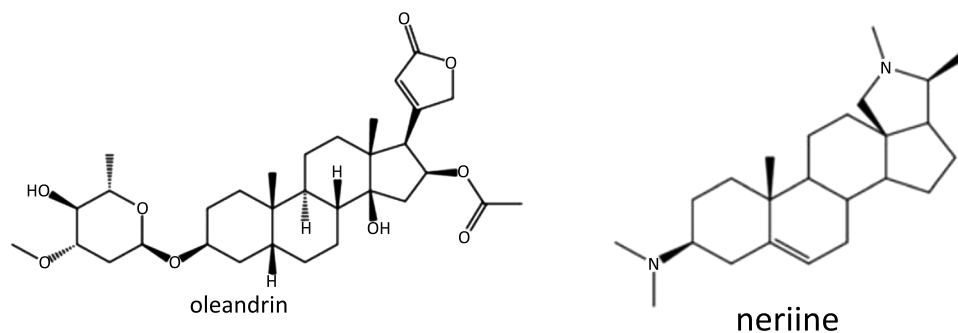


Fig. (3). Chemical structures of Oleandrin and Neriine.

CHAPTER 10

Peganum harmala L. (Zygophyllaceae)Betül DEMİRCİ^{1,*} and Gözde ÖZTÜRK¹¹ Department of Pharmacognosy, Faculty of Pharmacy, Anadolu University, 26470 Eskisehir, Türkiye

Abstract: *Peganum harmala* L. is a member of the Zygophyllaceae family, commonly known as ‘Harmal’, which grows spontaneously in Southeast Morocco, North Africa, and the Middle East, where its seeds are used traditionally for various purposes. Traditionally, in Anatolia, various shaped amulets are made by arranging the dried fruits on a decorative rope. The seed incense is commonly used against the evil eye, stressful conditions, and psychological disorders. *Peganum* seed and root preparations are reported for their antipyretic, narcotic, sedative, diaphoretic, and menstrual activities, usually used internally as an infusion (2-5%). The incense of *P. harmala* seeds is used against hemorrhoids. In addition to its traditional uses, there are several *in vitro* and *in vivo* studies on the antioxidant, antinociceptive, antimicrobial, antifungal, antidiabetic, antidepressant, and antitumor activities, among other biological activities. It is documented that its intended use as an abortifacient and emmenagogue may cause serious consequences and complications. Consuming *P. harmala* preparations at high concentrations may cause serious damage and life-threatening situations due to the secondary metabolites, harmaline alkaloids in particular, which is reviewed in this chapter with current literature data.

Keywords: Animal toxicity, β -carboline alkaloids, Biological activity, Human toxicity, *Peganum harmala* L., Zygophyllaceae.

BOTANICAL INFORMATION

Peganum harmala L., from the family Zygophyllaceae, is a branched, densely leafy, glabrous, perennial herb, also known as “Harmal, Syrian Rue, Turkish Rue, and Aspand, üzerlik”. It can spread up to 120 cm with a height of up to 60 cm; it generally appears round and bushy in its natural habitat [1, 2]. Leaves sessile, 4-8 cm long, irregularly and pinnatisectly dissected into acute segments that are 3-5 cm long, 2-3 mm broad, linear-lanceolate or sub-elliptic. Flowers white/yellowish white; 2-2.5 cm; pedicel filiform and 1.2 cm long; has 5 linear sepals, often exceeding the petals; petals 5, oblong/oblong-elliptic, subequal. Stamens with 4-5 mm long filaments are usually 15, rarely less, anthers dorsifixed and longer

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compared to filaments, and ovary 8-10 mm long, the upper 6 mm being triangular or three-keeled. Fruit is a 6-10 mm capsule, trigonous, depressed/retuse at the apex. Seeds triangular, blackish-brown, approximately 2 mm long. The flowering period is generally between April and October [1 - 4]. The general appearance of the plant is illustrated in Fig. (1).

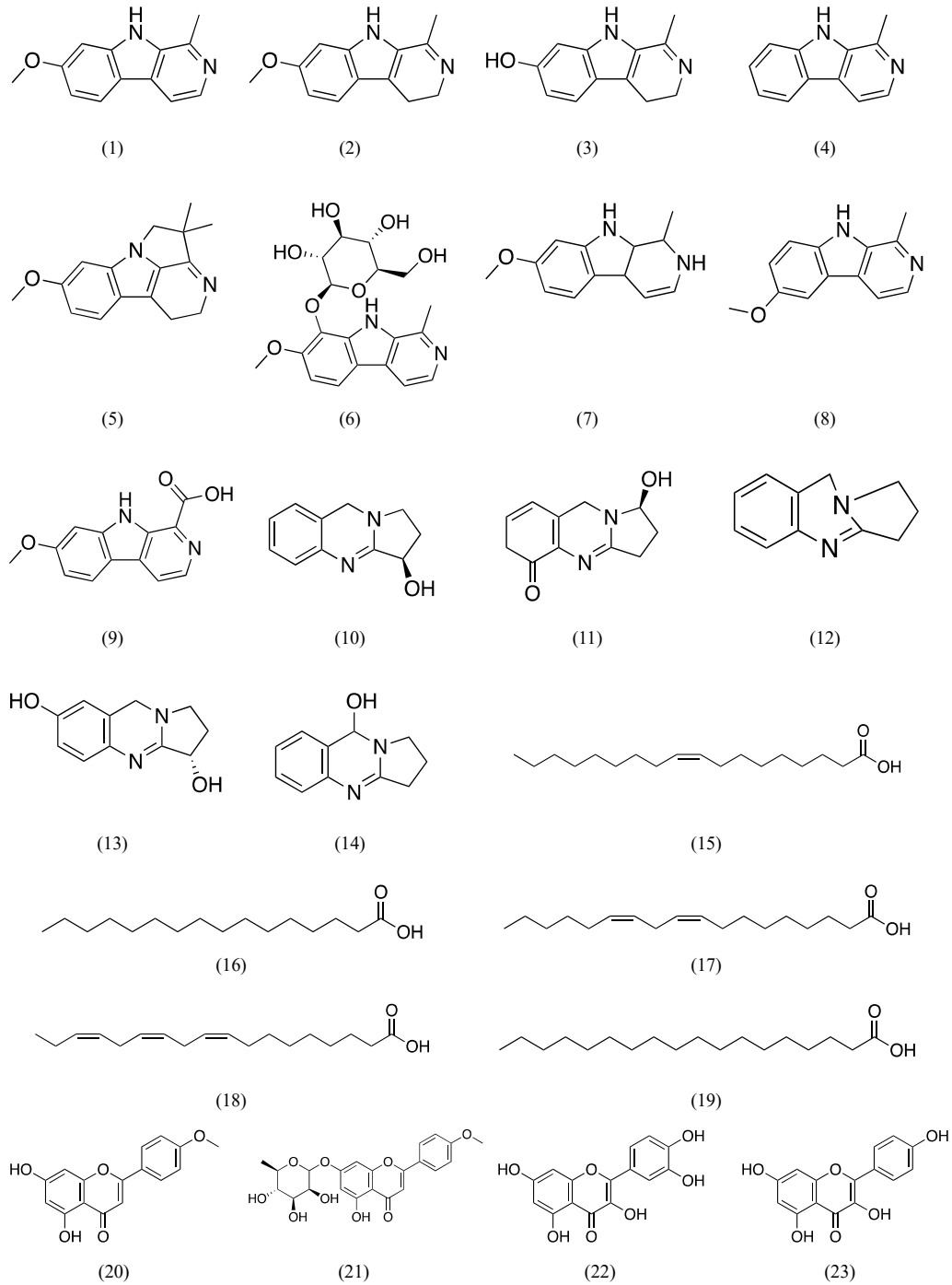


Fig. (1). (a) *P. harmala* in its habitat, (b) General appearance of *P. harmala* during the flowering period (Photos by G. Ozturk).

P. harmala grows in semi-arid rangelands, sandy soils, and steppe areas. The plant naturally grows in Africa, the Mediterranean, and the Middle East. Its traditional uses were reported in particular from Türkiye, Iraq, Iran, Uzbekistan, Tajikistan, China, Mongolia, Russia, Afghanistan, Pakistan, and India [3 - 6].

MAJOR ACTIVE SUBSTANCES

P. harmala contains a plethora of secondary metabolites, which are responsible for its diverse bioactivities. Important phytochemicals such as β -carboline and quinazoline alkaloids, phenolic substances, carbohydrates, volatile components, and fatty acids are major groups of reported constituents from *P. harmala* seeds [6 - 11]. Seeds also contain proteins, lipids, and mineral elements [4]. Similar alkaloids, phenolic substances, and amino acids are also among the reported secondary metabolites from aerial parts of *P. harmala* [5, 7, 11, 12]. Some of the major components of *P. harmala* (a-l) are illustrated in Fig. (2).



(Fig. 2) contd....

CHAPTER 11***Rhododendron* spp. (Ericaceae)****Şüheda Rumeysa OSMANLIOĞLU DAĞ^{1,*} and Ayşe Mine GENÇLER ÖZKAN²**¹ Department of Pharmaceutical Botany, Faculty of Pharmacy, Inonu University, Battalgazi, Malatya, Türkiye² Department of Pharmaceutical Botany, Faculty of Pharmacy, Ankara University, 6560 Tandoğan, Ankara, Türkiye

Abstract: *Rhododendron* L. is one of the largest dicotyledonous plant genera in the world, represented by more than 1.000 species, most of which grow naturally in the Northern Hemisphere. Many species and cultivars are also grown commercially, as rhododendrons are widely used in landscaping in many parts of the world due to their overall showy appearance and beautiful flowers. The first written information about these plants dates back to 401 BC and gives information about the toxicity of rhododendron honey. *Rhododendron* species and their products, such as honey, Labrador tea, edible flowers, and some medicines used in folk medicine, are known to cause poisoning cases due to human consumption. Some rhododendrons are also poisonous to grazing animals. Toxicological studies on *Rhododendron* species have addressed clinical observations and identified toxic components. Rhododendron and honey poisoning have been reported to be primarily associated with lipid-soluble grayanotoxins. These compounds affect sodium channels in cell membranes and cause a number of neurological, gastrointestinal, and cardiovascular dysfunctions. Grayanotoxins are found all over the plant, including flowers and nectar. Despite their toxic content and effects, rhododendrons and contaminated honey (mad honey) have been used in ancient systems of medicine, such as Traditional Chinese and Ayurvedic Medicines, as well as in European and North American Folk Medicine. However, mad honey is mostly consumed in Nepal and Türkiye as a recreational and traditional medicine. This review aims to present a comprehensive report on the toxicity of the *Rhododendron* genus after presenting the general botanical and ethnobotanical features.

Keywords: Case reports, Ericaceae, Mad honey, Phytochemistry, *Rhododendron* spp., Traditional uses.

INTRODUCTION

The first form of classification in the context of the plant-human relationship is a system based on needs, observation, and use. Characterized by a state of conti-

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nuous dynamic adaptation and change, this relationship has not always been mutually beneficial and has evolved with different degrees of interaction. If we follow the course of history regarding the description, evolution, naming, and taxonomy of plants, the first step in this sense undoubtedly begins with classifying plants into edible, poisonous, medicinal, and hallucinogenic categories [1, 2].

The unique three-way relationship between food, medicine, and toxin categories has existed in human history. Where one of these three categories is considered, the other two are invariably linked. For example, many foods commonly used worldwide are potentially toxic, either when ingested in large quantities or without some processing to reduce their toxic properties. The intersection between medicinal and poisonous plants is also widely recognized in world cultures. Because medicinal plant species are often chosen for the effects elicited by the active compounds they contain, many of them may have the capacity to cause harm when consumed in higher concentrations [3].

Plants belonging to the genus *Rhododendron* L. (Ericaceae), located in the middle of this remarkable food/medicine/poison triangle, are worth examining. Despite their toxicity, plants have been used in ancient therapeutic systems such as Traditional Chinese Medicine (TCM) and Ayurvedic Medicine, as well as in European and North American Folk Medicine. In addition, they are still known to cause numerous cases of poisoning, mainly due to contaminated honey consumption [4].

Name

The name *Rhododendron*, first described by Carl Linnaeus in 1753, comes from the Greek words “*rhodon*” meaning “a rose, rose garden” and “*dendron*” meaning “a tree”, possibly referring to the bunches of flowers. English vernacular names given to the species belonging to this genus are rose-tree, alpenrose, alpine rose, California rose-bay, *etc* [5, 6]. *Rhododendron ponticum* L. is known as komar, orman gülü (forest rose), kafil, kaful, kara ağ (black poison), and zelenika in Türkiye. Zifin, cifin, sarı ağ (yellow poison), and zifina are the names given to *Rhododendron luteum* [7] (Fig. 1).

Distribution

Rhododendrons mostly grow at high altitudes. Worldwide, it is estimated that there are about 1.200 *Rhododendron* species, mostly distributed in the Northern Hemisphere, especially in Asia. Major centers are western China (Yunnan), Papua New Guinea, northern Australia, Japan, eastern China, eastern Russia, the Himalayas, Afghanistan, Pakistan, the Caucasus, the Black Sea coast of Türkiye, eastern and central Europe, Spain, and eastern and western North America. China,

with 571 species (409 of which are endemic), has the most species. Besides, about 80 species, 14 varieties, and 10 subspecies exist in India [8 - 10]. The majority of these species, however, have been shown to be non-toxic [11].



Fig. (1). General appearances of (a) *Rhododendron ponticum* L. (Photo by D. ÇİÇEK POLAT), (b) *Rhododendron luteum* Sweet (Photo by N.G. MAMIKOĞLU).

Botany

Rhododendrons are usually evergreen, woody shrubs (1-8 m) or less often taller trees. Their thick and leathery leaves are essential for identification. Leaves are generally narrow, tapering both to the base and the apex. The leaf size varies by species. Some parts of the plant (the leaves, stems, flower stalks, *etc.*) may bear hairs or scales of various types. Those on the lower surface of the leaves are among the most critical diagnostic characteristics. In most species, shoots terminate in inflorescences located in the middle of a false leaf whorl. The calyx is usually reduced. The brightly colored corolla is the most striking part of the flower. It is mostly sympetalous with five lobes and campanulate, tubular or funnel-shaped. Stamens are generally 10 in number, but any number between 4 and 27 is possible. The ovary is usually round and cylindrical, with a single style at the top. Stigma consists of a sheath containing as many lobes as the number of chambers in the ovary. Nectar is usually found around the ovary's base or in the corolla's nectar sacs. The seeds are tiny and develop in capsule types that are conical, cylindrical, straight, or curved [12].

Mad Honey

Unlike regular commercial honey, rhododendron honey is contaminated with grayanotoxin (GTX) and causes poisoning. GTX is generally found in rhododendron plants growing in various countries like Türkiye, China, Tibet, Nepal, Myanmar, Japan, New Guinea, Indonesia, the Philippines, and also in

CHAPTER 12

Ricinus communis* L. (Euphorbiaceae)*Derya ÇİÇEK POLAT^{1,*} and Selen İLGÜN²**¹ Department of Pharmaceutical Botany, Faculty of Pharmacy, Ankara University, 06560 Tandoğan, Ankara, Türkiye² Department of Pharmaceutical Botany, Faculty of Pharmacy, Erciyes University, 38039 Talas, Kayseri, Türkiye

Abstract: *Ricinus communis* L. (Euphorbiaceae) is a medicinal plant known as castor oil plant and has highly toxic effects due to its ricin content. Root leaves and especially seeds of this plant, which has a wide distribution area in the world, are rich in terpenoids, phenolic compounds, and fatty acids. For this reason, the plant, used by the ancient people as a laxative for infections, inflammations, and toothache, has shown various biological activities. Antioxidant, anti-inflammatory, antimicrobial, and anticancer properties of the plant and its compounds have been determined in multiple studies. However, its seeds have toxic effects on humans and animals.

Keywords: Case report, Castor oil plant, Euphorbiaceae, Ethnobotany, *Ricinus communis* L.

INTRODUCTION

Ricinus communis L. (Euphorbiaceae) is a very important plant for the chemical industry due to its oil seeds; it is also known as the “castor oil plant”. The plant, sometimes also called the “Indian Bean”, can be grown in tropic and subtropical regions extensively [1, 2]. *R. communis*, which can grow very quickly in the form of trees and shrubs, are xerophytic and heliophile plants with a taproot system. These plants, which are also grown as ornamental plants, have magnificent leaves about 30-60 cm in diameter and contain 5-12 deep lobes. The flowers are monoecious and male flowers are 2 cm across. Perianth segments are ovate-lanceolate, anthers are densely present. While fruits are 1-2 cm, seeds are 0.8-1.5 cm, greyish, mottled brown [3, 4]. In addition to all these morphological features, such as the appearance of the plant, body color, leaves, seed color, and size, the oil content also varies according to the region where it grows. The leaves range from pale green to dark red, depending on their anthocyanin pigmentation

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content. The shape of the fruit is spherical and resembles a prickly capsule. The capsule surrounding the seeds cracks when fully mature (Fig. 1) [5, 6]. *R. communis*, which is an important part of agronomy, has been the subject of many medical studies thanks to its extracts with important pharmacological effects and effective secondary metabolites. It is a plant with high toxicity, especially due to ricin (known as ribosome-inactivating protein) and ricinine compounds [7, 8]. The oil obtained from the seeds of the castor oil plant can be used in ointments, nylon, varnishes, aircraft engine oils, hydraulic fluids, paints, detergents, plastics, paints, synthetic leather, cosmetics, and perfumes, and in the production of biofuel/biodiesel [9].



Fig. (1). General appearance (Photo by C.S. KILIÇ) and seeds of *R. communis* (Photo by D. ÇİÇEK POLAT).

ACTIVE SUBSTANCES

It has been determined that the compounds isolated from *R. communis* are mainly terpenoids, flavonoids, alkaloids, anthraquinones, tannins, saponins, polyuronides, glycosides, steroids, and reducing sugar [10].

Alkaloids

Alkaloids are among the secondary metabolites with important pharmacological effects. Ricinine (Fig. 2) is an important compound isolated from almost all parts of *R. communis* [3]. N-demethylricinine, 3-carboxy-4-methoxy N-methyl-2-pyridone, methyl 5-(3-cyano-1-methyl-2-oxo-1,2-dihydropyridine-4-yl) pentanoate, and 1-methyl-4-(4-methylpentiloxy) pyridine-2 (1H)-on are other important alkaloids isolated from the leaves and seeds of *R. communis* [11, 12]. In a study conducted in 2022, a new alkaloid ricicomin A was isolated from the leaves of *R. communis* [13].

Flavonoids and Benzoic Acid Derivatives

The flavonoids identified from the *R. communis*, especially with high antioxidant activity, are mainly quercetin and kaempferol derivatives. The most important of these compounds isolated from leaves and roots are quercetin-3-O- β -D-galactoside, quercetin-3-O- β -D-glucopyranoside, quercetin-3-O- β -D-xylopyranoside, quercetin-3-O- β -D-rutinoside, kaempferol-3-O- β -D-glucopyranoside, kaempferol-3-O- β -D-rutinoside, kaempferol-3-O- β -D-xylopyranoside, catechin, epicatechin, luteolin, and vitexin Fig. (2) [3, 14, 15]. The benzoic acid derivative compounds isolated from *R. communis* are ellagic, gallic, gentisic, and vanillic acids, and they also show high antioxidant activity [15].

Terpenoids

Terpenoids are an important group that is chemically rich and includes a wide variety of secondary metabolites. Some of the terpenoid compounds isolated from the *R. communis* plant are given in Table 1 and Fig. (2).

Table 1. Terpenoids from *R. communis* [3].

Compounds	
Thujone, 1,8-cineole, α -pinene, camphor, camphene, fusic acid	Monoterpenoids
(+)-beyerene, (+)-cembrene, (-)-kaurene, (+)-sandaracopimaradiene, callyspinol, (-)-trachylobane, Casbene, Phytol, (3E,7Z,11E)-19-hydroxycasba-3,7,11-trien-5-one, 6a-hydroxy-10b-methoxy-7a,8a-epoxy-5-oxocasbane-20,10-olide	Diterpenoids
Campesterol, β -sitosterol, stigmasterol, 3-O- β -D-glycosylsitosterol, 7-oxo- β -sitosterol, stigmasterol arachidate, stigmasterol oleate, stigmasterol stearate, stigmast-4-en-3-one, stigmast-4-en-6 β -ol-3-one, stigmast-4-en-3,6-dione, 3-O--d-glycosylstigmasterol	Sterols
Erandone, lupeol, 30-nor-lupan-3 β -ol-20-one, lup-20(29)-en-3 β ,15 α -diol-3-O-[β -D-glucuronopyranosyl-(1->3)- α -l-rhamnopyranosyl-(1->2) β -D-glucopyranosyl]-4 α ,20 α -di(hydroxymethyl)olean-12-en-28-oic acid	Triterpenoids

SUBJECT INDEX

A

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