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REVIEW ARTICLE / DERLEME MAKALE

AN OVERVIEW OF THE CHEMICAL COMPOSITION, BIOLOGICAL ACTIVITIES AND TRADITIONAL USES OF GENUS *ALKANNA* TAUSCH

ALKANNA TAUSCH CİNSİNİN KİMYASAL BİLEŞİMİ, BİYOLOJİK AKTİVİTELERİ VE GELENEKSEL KULLANIMLARINA GENEL BİR BAKIŞ

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ABSTRACT

***Objective*:** *This study summarizes some scientific studies conducted on the chemical contents and biological activities of the Alkanna genus, which is thought to be medically important and has various traditional uses among the public.*
***Result and Discussion*:** *Alkanna spp. have been used among the public since ancient times for the treatment of dermatological disorders, jaundice, kidney stones and for its wound healing, antinociceptive, anti-inflammatory, antibacterial, antiseptic and astringent effects. It has been observed that there are important biological activity studies on the chemical contents and active ingredients of Alkanna spp. and effective results have been obtained. According to the literatüre data, the Alkanna spp. may be an important candidate for drug development potential in the future.*
***Keywords*:** *Alkanna, biological activity, Boraginaceae, chemical content, traditional use*

ÖZ

***Amaç*:** *Bu çalışmada, tıbbi açıdan önemli olduğu düşünülen ve halk arasında çeşitli geleneksel kullanımları bulunan Alkanna cinsinin kimyasal içerikleri ve biyolojik aktiviteleri üzerine yapılan bazı bilimsel çalışmalar özetlenmiştir.*
***Sonuç ve Tartışma*:** *Alkanna türleri halk arasında eski çağlardan beri dermatolojik rahatsızlıklar, sarılık, böbrek taşı tedavisi ve yara iyileştirici, antinosiseptif, antiinflamatuar, antibakteriyel, antiseptik ve büzücü etkileri nedeniyle kullanılmaktadır. Alkanna türlerinin kimyasal içerikleri ve aktif bileşenleri üzerinde önemli biyolojik aktivite çalışmaları yapıldığı ve etkili sonuçlar elde edildiği gözlemlenmiştir. Literatür verilerine göre, Alkanna türleri gelecekte ilaç geliştirme potansiyeli için önemli bir aday olabilir.*
***Anahtar Kelimeler*:** *Alkanna, biyolojik aktivite, Boraginaceae, geleneksel kullanım, kimyasal içerik*

INTRODUCTION

The use of traditional medicine has spread internationally and grown in popularity. Herbal medicine is the most popular in usage on the big scale [1]. Plants are a rich natural source of chemical compounds that exhibit biological activities. They serve as reservoirs and sources for a wide range of

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secondary metabolites with therapeutic properties, such as alkaloids, flavonoids, tannins, and terpenoids [2,3]. Medicinal plants are still widely used by rural communities, with increasing popularity for treating or preventing various infections. The therapeutic efficacy of these products and their fewer side effects make them a good alternative source to synthetic drugs. Therefore, there is a great need for studies providing scientific data on the pharmacological and therapeutic effects of these traditional medicines [4-6].

The *Alkanna* genus has been used in traditional medicine since ancient times for its medicinal, pharmaceutical, and therapeutic properties. Additionally, plants from this genus have found applications in cosmetics, dye production, and food industries due to their bioactive compounds and natural pigments [7,8]. The genus has been cited as having great significance as a source of compounds that benefit health and are used for traditional medicine [3]. Especially, the root of the *Alkanna* is the most useful portion, and because of its intense red color, it is frequently used for cosmetic and beauty purposes. It has been demonstrated to cure skin damage beyond those uses; however, they may cause allergic and irritating reactions when applied topically. *Alkanna* root has been used for stomach ulcers, cancer, and diarrhea. In these situations, oral dosing was advised [4,5]. The root extract has also shown radical scavenging activity, which suggests it could have antiaging properties, however, in the scope there is very little clinical data available [9].

Alkanna root is used to treat and cure several ailments, according to the USDA (United States Department of Agriculture) National Nutrient [3]. Herein, information on the chemical content, various biological activity studies, and traditional uses of *Alkanna* spp., which are thought to have significant pharmaceutical potential, has been compiled. To date, such a comprehensive compilation study on *Alkanna* sp. has not been conducted. Chemical and biological activity studies on *Alkanna* spp. are generally summarized in the manuscript using the Web of Science, Mendeley, PubMed, and Scopus databases. In the literature, studies on traditional uses, chemical contents, and biological activities of *Alkanna* spp. and extracts have been compiled.

Distribution of *Alkanna* Tausch Genus

Alkanna Tausch, a Boraginaceae family member, commonly grows in the Mediterranean, Europe, and Western Asia and has spread worldwide to regions including the Caucasus, Iran, and Saudi Arabia. The genus is one of the large genera represented by approximately 60 spp. in the family [10] The genus Alkanna is represented by 36 spp. and 41 taxa in Türkiye. 30 of the *Alkanna* spp. are endemic, so it can be assumed that the Anatolian Peninsula is the gene center of the genus [11-13].

History and Traditional Uses of *Alkanna* spp.

Among the *Alkanna* spp., the use of *Alkanna tinctoria* Tausch as a red root dye dates back to 4000 BC. *Alkanna* spp. have a long history of usage in traditional Chinese medicine. The first known use of *Alkanna* roots was in the writings of the Greek physician and philosopher Hippocrates in the 4th and 5th century BC, who employed plant roots to heal ulcers [3,14]. In a study by Papagerogiou et al. (1999) alkannin was isolated for the first time from *A. tinctoria* root extracts and the wound-healing and antimicrobial properties of this extract were reported [12]. Greek physician Hippocrates also noted that the root of *A. tinctoria* could be used to treat various dermatological diseases . The botanist Theophrastus also indicated that it could be used as a medicine and dye. In addition, Dioscorides recommended *A. tinctoria* for treating multiple dermatological diseases [15]. Among the healing properties of the *Alkanna* spp., it has also been reported used in preparing traditional ointments and pastes for wound dressing. For example, Iranian folk medicine has mentioned its antinociceptive and anti-inflammatory activities for pain-related ailments. *A. tinctoria* has also been reported to be used ulcers, inflammatory wounds, jaundice, and kidney stones. It also has a deworming effect. Extracts of the root possess antibacterial, antiseptic, and astringent properties, so they are also used for varicose veins, bed sores, and itchy rashes [16,17]. Purple flowers of *Alkanna trichophila* var. *mardinensis* Hub. - Mor. are consumed as food in some regions of Türkiye [18]. In Table 1, different traditional uses of *Alkanna* spp. are mentioned in detail.

Table 1. Traditional uses of *Alkanna* sp.

Plant name	Plant part	Preparation	Method of application	Usage	Ref.
***Alkanna orientalis* Boiss.**	Root	Boiling with oil	External	*Tinea barbae* induced Dermatophyte	[19]
	Aerial part	Crushed, cooked with butter, and added beeswax		Wound healing Scar treatment Burn treatment Inflamed wounds Leg ulcer	
		Cooked with butter	External	Festering sore, ambustion	
		Boiled	External with pulp for one day	Ophthalmia	
	Leaves	Crushed	External	Ophthalmia	
		Decoction	Internal before breakfast	Asthma, Bronchitis, Stomach ailments	
***Alkanna cappadocica* Boıss. & Balansa**	Root	The roots are roasted in butter and made into an ointment	External	Wound healing	[16]
***Alkanna tinctoria* Boiss.**	Root	The roots are roasted in butter and made into an ointment	External	Kidney stone Bed sores Itching Rash	[6, 15, 20]
	Aerial parts	Cooking in oil Vinegar Decoction	Internal	Wound and burn treatment Inflamed wounds	
			External	Leprosy Antihelmintic Jaundice	
***Alkanna trichophila* Hub.-Mor.**	Base leaves, Flowers	Decoction	Internal	Anti-inflammatory	[21]
***Alkanna orientalis* (L.) Boiss.**	Root	Boiled	Internal	Anti-inflammatory	[22]
	Root	Boiled	External	Wounds Conjunctivitis Ambustion Scabies Earache	
	Aerial parts	Infusion	Internal	Diabetes Hypercholesteremia Analgesic Hemorrhoid	

Chemical Contents and Pharmacological Activities of *Alkanna* Sp.

Since ancient times, the genus *Alkanna* has been extensively known for its medical and pharmacological capabilities, based on its plant parts' chemical contents. The bark of the root, which contains dyeing chemicals, is the most essential portion of the plant [6,9,12,14,23]. Chemical and biological activity studies on *Alkanna* spp. are generally summarized in Figure 1. The chemical examination of these molecules revealed that the most prevalent components were aromatic diketones called naphthoquinones, also known as alkannins and shikonins. The double ring structure of these compounds, which give the deep red pigments, gives them their colour. These are lipophilic hydroxy

naphthoquinone red pigments that are widely employed in a variety of applications [9,12]. Various flavonoids, pyrrolizidine alkaloids, alkannin derivatives (isohexenylnaphtazarine), and fatty acids have been identified in phytochemical studies on the genus of *Alkanna* [24-27]. *Alkanna*'s roots and aerial parts were used as the primary materials for developing potentially effective extracts. Maceration and infusion techniques were employed for extraction, utilising solvents with varying polarities. The chemical contents of the extracts were analysed using HPLC, LC/MS GC/MS, and other spectrophotometric methods, identifying approximately 50 bioactive compounds, including phenolic acids, flavonoids, coumarins, and terpenes [8,28,29]. The chemical composition of *Alkanna* sp. is shown in Table 2.

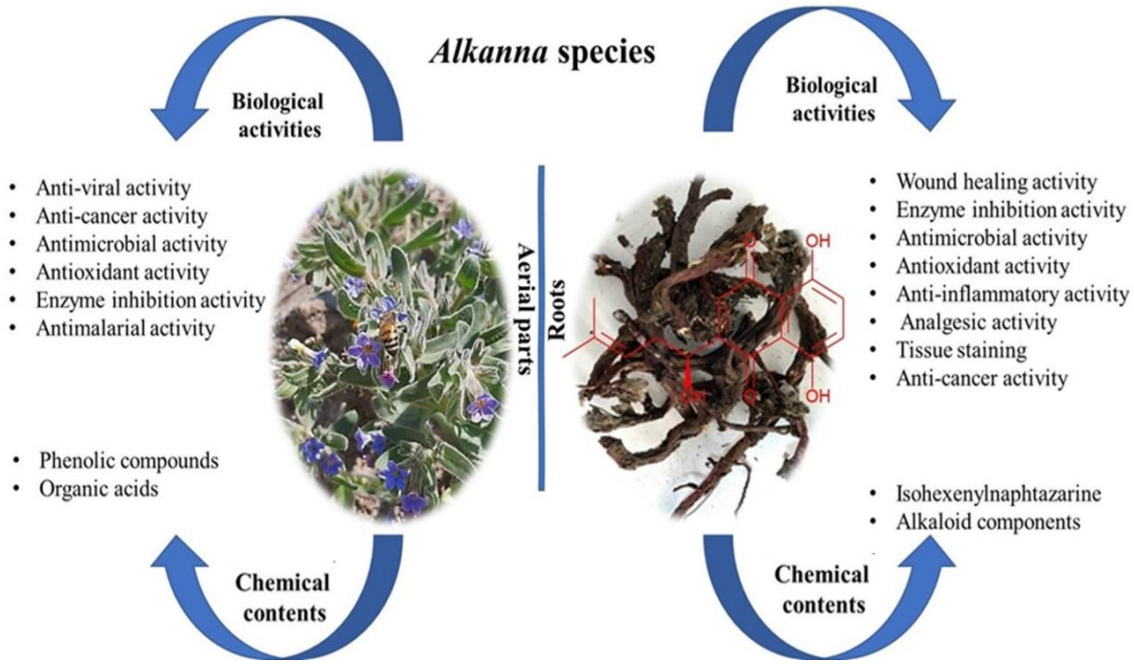

Figure 1. Highlights of chemical contents and biological activity studies of *Alkanna* spp.

Table 2. Chemical contents of *Alkanna* sp.

Plant name	Plant part	Active ingredient	Method	Extract	Ref.
***Alkanna corcyrensis* Hayek**	Root	Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl - α-methyl -*n*-butyl Alkannin	HPLC-PDA-MS	Hexane extract	[23]
***Alkanna tinctoria* Tausch**	Root	Alkannin Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl – α- methyl -*n*-butyl Alkannin	HPLC-PDA-MS	Hexane extract	

HPLC: High-Performance Liquid Chromatography; MPLC: Medium Pressure Liquid Chromatography; GLC: Gas-Liquid Chromatography; GC: Gas Chromatography; LC: Liquid chromatography; TLC: Thin-Layer Chromatography; VLC: Vacuum Liquid Chromatography; MS: Mass Spectrometry; H-NMR: Proton Nuclear Magnetic Resonance; DAD: Diode-Array Detection; FIB: Flame Ionization Detection PDA: Flame Ionization Detection

Table 2 *(continue)*. Chemical contents of *Alkanna* sp.

Plant name	Plant part	Active ingredient	Method	Extract	Ref.
***Alkanna methanaea* Hausskn.**	Root	Alkannin Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl - α -methyl -*n*-Butyl Alkannin	HPLC-PDA-MS	Hexane extract	[23]
***Alkanna orientalis* (L.) Boiss.**	Root	Alkannin Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl - α -methyl -*n*-Butyl Alkannin	HPLC-PDA-MS	Hexane extract	
***Alkanna calliensis* Heldr. ex Boiss.**	Root	Alkannin Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl – α- methyl -*n*-butyl Alkannin	HPLC-PDA-MS	Hexane extract	
***Alkanna graeca* Boiss. & Spruner**	Root	Alkannin Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl - α methyl -n-Butyl Alkannin	HPLC-PDA-MS	Hexane extract	
***Alkanna primuliflora* Griseb.**	Root	Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl - α methyl -n-Butyl Alkannin	HPLC-PDA-MS	Hexane extract	
***Alkanna stribrnyi* Velen.**	Root	Alkannin Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl - α methyl -n-Butyl Alkannin Teracryalkannin	HPLC-PDA-MS	Hexane extract	

HPLC: High-Performance Liquid Chromatography; MPLC: Medium Pressure Liquid Chromatography; GLC: Gas-Liquid Chromatography; GC: Gas Chromatography; LC: Liquid chromatography; TLC: Thin-Layer Chromatography; VLC: Vacuum Liquid Chromatography; MS: Mass Spectrometry; H-NMR: Proton Nuclear Magnetic Resonance; DAD: Diode-Array Detection; FIB: Flame Ionization Detection PDA: Flame Ionization Detection

Table 2 *(continue)*. Chemical contents of *Alkanna* sp.

Plant name	Plant part	Active ingredient	Method	Extract	Ref.
***Alkanna sieberi* A. DC.**	Root	Alkannin Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl - α methyl -n-Butyl Alkannin Teracryalkannin	HPLC-PDA-MS	Hexane extract	[23]
***Alkanna corcyrensis* Hayek**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	[30]
***Alkanna methanaea* Hausskn.**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	
***Alkanna pindicola* Hausskn.**	Root	Alkannin Acetyl Alkannin Isobutyl Alkannin Angelic Alkannin ß-ß dimethylacryl Alkannin Isovaleryl - α methyl -n-Butyl Alkannin	HPLC-PDA-MS	Hexane extract	
***Alkanna pindicola* Hausskn.**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	
***Alkanna graeca* Boiss.& Spruner**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	
***A. graeca* var. *versicolor* Boiss.**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	
***A. graeca* ssp. *Baeotica* (A.DC.) Nyman**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	
***Alkanna primuliflora* Griseb.**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	
***Alkanna stribrnyi* Velen.**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	
***Alkanna sieberi* A. DC.**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	
***Alkanna calliensis* Heldr. ex Boiss.**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	

HPLC: High-Performance Liquid Chromatography; MPLC: Medium Pressure Liquid Chromatography; GLC: Gas-Liquid Chromatography; GC: Gas Chromatography; LC: Liquid chromatography; TLC: Thin-Layer Chromatography; VLC: Vacuum Liquid Chromatography; MS: Mass Spectrometry; H-NMR: Proton Nuclear Magnetic Resonance; DAD: Diode-Array Detection; FIB: Flame Ionization Detection PDA: Flame Ionization Detection

Table 2 *(continue)*. Chemical contents of *Alkanna* spp.

Plant name	Plant part	Active ingredient	Method	Extract	Ref.
***Alkanna tinctoria* Tausch**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	[30]
***Alkanna noneiformis* Griseb.**	Root	Alkannin Shikonin	HPLC-DAD	Hexane extract	
***Alkanna tinctoria* Tausch**	Culture medium	Alkannin Shikonin Acetyl Alkannin ß-ß dimethylacryl Alkannin	HPLC TLC	Culture medium	[31]
Alkanna tinctoria* Tausch subsp. *tinctoria	Root	Alkannin	HPLC-DAD LC-MS	Hexane extract Methanol extract Chloroform extract	[32]
***Alkanna tinctoria* Tausch subsp. *anatolica* Hub.-Mor.**	Root	Alkannin	HPLC-DAD LC-MS	Hexane extract Methanol extract Chloroform extract	[32]
***Alkanna tinctoria* Tausch subsp. *subleiocarpa* (Hub.-Mor.) Hub.-Mor.**	Root	Alkannin	HPLC-DAD LC-MS	Hexane extract Methanol extract Chloroform extract	
***Alkanna pseudotinctoria* Hub.-Mor.**	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	[33]
Alkanna areolate* Boiss. var. *areolata	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	
***Alkanna pinardii* Boiss.**	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	
***Alkanna aucheriana* A.DC.**	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	
***Alkanna mughlae* H.Duman,Güner& Cagban**	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	
***Alkanna saxicola* Hub.-Mor.**	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	

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Table 2 *(continue)*. Chemical contents of *Alkanna* sp.

Plant name	Plant part	Active ingredient	Method	Extract	Ref.
***Alkanna macropjylla* Boiss.& Heldr.**	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	[33]
***Alkanna hirsutissima* (Bertol.) A.DC.**	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	
***Alkanna cordifola* K.Koch**	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	
Alkanna tinctoria* (L.) Tausch subsp. *subleiocarpa (Hub.-Mor.) Hub.-Mor.	Root	Alkannin	HPLC-DAD HPLC-PDA LC-MS	Hexane extract Methanol extract Chloroform extract	
***Alkanna trichophila* Hub.-Mor.**	Aerial parts	Gallic acid 3-Caffeoylquinic acid 5-Caffeoylquinic acid Vanilla acid Caffeic acid Syringic acid *p*- Coumaric acid Ferulic acid 3,5-Dicaffeoylquinic acid Naringin Rutin Hyperoside Kaempferol-3-glucoside Quercetin Quercitrin	HPLC-MS/MS	Methanol extract	[8]
***Alkanna orientalis* (L). Boiss**	Root	α-methyl-*n*- butyl Alkannin Alkannin acetate	TLC	Hexane extract	[34]
***Alkanna orientalis* (L.) Boiss.**	Aerial parts	ß- eudesmol α- eudesmol Isophorone β- caryophyllene	GC/GC-MS	Essential oil	[35]
***Alkanna primuliflora* Griseb.**	Aerial parts	7-Angeloylretronecine 9-Angeloylretronecine 7-Tigloylretronecine 9-Tigloylretronecine Triangularine Triangularicine Dihydroxytriangularine Dihydroxytriangularicine	GC-MS	Methanol extract	[27]

HPLC: High-Performance Liquid Chromatography; MPLC: Medium Pressure Liquid Chromatography; GLC: Gas-Liquid Chromatography; GC: Gas Chromatography; LC: Liquid chromatography; TLC: Thin-Layer Chromatography; VLC: Vacuum Liquid Chromatography; MS: Mass Spectrometry; H-NMR: Proton Nuclear Magnetic Resonance; DAD: Diode-Array Detection; FIB: Flame Ionization Detection PDA: Flame Ionization Detection

Table 2 *(continue)*. Chemical contents of *Alkanna* sp.

Plant name	Plant part	Active ingredient	Method	Extract	Ref.
***Alkanna graeca* Boiss. & Spruner**	Aerial parts	7-Angeloylretronecine 9-Angeloylretronecine 7-Tigloylretronecine 9-Tigloylretronecine Triangularine Triangularicine Dihydroxytriangularine Dihydroxytriangularicine	GC-MS	Methanol extract	[27]
***Alkanna orientalis* (L.) Boiss.**	Aerial parts	Kaempferol-3 - glucoside Kaempferol-3-rutinoside Quercetin-3-glucoside Quercetin-3- rutinoside Kaempferol-3,6-dimethyl ether 7-glucoside Kaempferol-3,6- dimethyl ether	Column Chromatography UV-Enzymatic Activity	Ethanol extract (70%)	[36]
***Alkanna orientalis* (L.) Boiss.**	Aerial parts	7- angeloylretronicin 9-angeloylretronicin Dihydroxytriangularin triangularine	H-NMR, ^{13}C-NMR, MS	Ethanol extract	[37]
***Alkanna orientalis* (L.) Boiss.**	Aerial parts	7-Angeloylretronecine 9-Angeloyretronecine 7-Senecioylretronecine 7-Angeloyl-9 (hydroxypropenoyl) retronecine Triangularicine Dihydroxytriangularicine Dihydroxytriangularicine	GLC-MS	0.5N HCl – with ultra thorax extraction	[38]
***A. tuberculate* Greuter**	Aerial parts	7-Angeloylretronecine 7-Tigloylretronecine 7-Angeloyl-9-(hydroxypropenoyl) retronecine 7-Tigloyl-9-(hydroxypropenoyl) Retronecine Triangularine Triangularicine Dihydroxytriangularicine Dihydroxytriangularicine	GLC-MS	0.5N HCl - with ultra thorax extraction	
***Alkanna bracteosa* Boiss.**	Aerial parts	β- eudesmol α- eudesmol Pulegone 1,8-cineole Farnesyl acetate Terpinyl acetate	GC-FID	Essential oil	[39]

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Table 2 *(continue)*. Chemical contents of *Alkanna* sp.

Plant name	Plant part	Active ingredient	Method	Extract	Ref.
***Alkanna sfikasiana* Tan, Vold and Strid**	Root and aerial parts	IsobutyrylAlkannin α- methylbutyrylalkanine Lanosterol Linoleic acid Rosmarinic acid Quercetin 3-O-rutinoside Quercetin 3-O-glucoside	-	-	[40]
***Alkanna tinctoria* Tausch**	Roots	Alkannin Acetyl-alkanine- 1H-benzotriazole, 4-nitro, 2-chloroethyl (methylsulfonyl) methanesulfonate and 2, 5-cyclohexadien-1-one, 4-diazo- (napthoquinone)	GC-MS	Ethanol (96%)	[41]
Alkanna tinctoria* Tausch subsp. *tinctoria		Pulegone 1,8-cineole α- terpinyl acetate Isophytol	GC-MS	Essential oil	[42]
***Alkanna sfikasiana* Tan, Vold and Strid**	Roots and aerial parts	Disodium rhabdosine Rosmarinic acid Linoleic acid Quercetin 3-O-β-D-Glucoside Quercetin 3-O-β-D-Rutinoside	VLC MPLC	Cyclohexane Dichloromethane Distilled water Methanol	[29]
***Alkanna orientalis* (L.) Boiss.** ***Alkanna* tinctoria Tausch** ***Alkanna kotschyana* A.DC.**	Aerial parts	Organic acid (Gluconic acid, Malic acid) Phenolic acid (Caffeic acid, Rosmarinic acid) Flavonol (Kaempferol-3-rutinoside, Quercetin-3-glucopyranoside) Flavone (Luteolin-7 rutinoside)	LC/Q-TOF-MS	Methanolic Extract	[28]
***Alkanna orientalis* (L.) Boiss**	Aerial parts	Sarothrin	HPLC	Methanol: water extract	[43]

HPLC: High-Performance Liquid Chromatography; MPLC: Medium Pressure Liquid Chromatography; GLC: Gas-Liquid Chromatography; GC: Gas Chromatography; LC: Liquid chromatography; TLC: Thin-Layer Chromatography; VLC: Vacuum Liquid Chromatography; MS: Mass Spectrometry; H-NMR: Proton Nuclear Magnetic Resonance; DAD: Diode-Array Detection; FIB: Flame Ionization Detection PDA: Flame Ionization Detection

Table 2 *(continue)*. Chemical contents of *Alkanna* sp.

Plant name	Plant part	Active ingredient	Method	Extract	Ref.
***Alkanna tubulosa* Boiss.**	Aerial parts	Salvianic acid A 9-Angeloylretronecine Jacoline Benzoic acid Caffeic acid Senecionine N-oxide Caffeoylshikimic acid Caffeoylshikimic acid Yunnaneic acid Rutin Rosmarinic acid Luteolin Naringenin Salvianolic acid C Dihydroxy-trimethoxy(iso)flavone derivates	HPLC LC-MS/MS	Ethyl acetate extract Ethanol extract Infusion Ethanol/Water extract	[44]
***Alkanna tinctoria* Tausch**	Root	Butanoic acid 3-hydroxy-3-methyl Arnebin 7 Dioctyl phthalate	GC-MS/MS	Ethanol extract Water extract	[45]
***Alkanna tinctoria* Tausch**	Root	1,4 naphthoquinones Alkannins Acetyl alkannin Isobutyl alkannin β,β-dimethyl acryl alkannin	HPLC	Methanol extract	[46]

HPLC: High-Performance Liquid Chromatography; MPLC: Medium Pressure Liquid Chromatography; GLC: Gas-Liquid Chromatography; GC: Gas Chromatography; LC: Liquid chromatography; TLC: Thin-Layer Chromatography; VLC: Vacuum Liquid Chromatography; MS: Mass Spectrometry; H-NMR: Proton Nuclear Magnetic Resonance; DAD: Diode-Array Detection; FIB: Flame Ionization Detection PDA: Flame Ionization Detection

According to Table 2, Alkannin derivatives (Acetylalkannin, Propionylalkannin, Isobutylalkannin, Angelylalkannin, Dimethylacryl-alkannin, Isovalerylalkannin, α-Methyl-n-Butylalkannin, and Hydroxyisovalerylalkannin etc.) were detected in chemical studies on *Alkanna* spp. These derivatives and the amounts that were detected varied between spp. and even within the same spp. when it was cultivated in various climates and altitudes [23]. Isohexanylnaphthazarine derivative substances are used as natural colorants for food, cosmetics, and textiles. The interest in isohexenylnaphtazarins has been increasing recently because of the strong anti-inflammatory [47,48], antifungal [49,50], antioxidant [39,40,51], cytotoxic [52–55], radical scavenging [48,52], and enzyme inhibitor properties. Besides these activities, scientific studies have shown that derivatives of isohexenylnaphtazarins play a role in topoisomerase I inhibition and are potential anticancer agents [40, 52]. *Alkanna* roots also include wax, tannins, and alkaloids. In addition, 11-deoxyalkannin and its derivatives (5-O-methyl-11-deoxyalkannin, 8-O-methyl-11-deoxyalkannin, 5-O-methyl-11-O-acetylalkannin, and 5-O-methyl-dimethylacrylalkannin) were isolated from *Alkanna cappadocica* Boiss. et Bal. and have been shown to have cytotoxic effects [52,53] .

Biological activities according to the part of the plant used (root, leaf, and aerial parts) and extraction method are shown in Table 3.

Table 3. Biological activity studies on *Alkanna* spp.

Plant name	Plant part	Extract	Biological activity	Method	Ref.
***Alkanna frigida* Boiss.**	Root	Ethanol extract	Anti-inflammatory Antinociceptive	Claw oedema from carrageenan Formalin test	[47]
***Alkanna orientalis* (L.) Boiss.**	Root	Ethanol extract	Anti-inflammatory Antinociceptive		
***Alkanna bracteosa* Boiss.**	Root	Methanol extract	Anti-inflammatory Analgesic	Claw oedema from carrageenan Formalin test	[48]
***Alkanna trichophila* Hub.-Mor.**	Root	Methanol extract	Anti-inflammatory Analgesic		
***Alkanna bracteosa* Boiss.**	Root	Methanol-water (8:2) extract	Antioxidant	DPPH FTC TBA	[24]
***Alkanna trichophila* Hub.-Mor.**	Root	Methanol-water (8:2) extract	Antioxidant		
***Alkanna frigida* Boiss.**	Root	Methanol-Water (8:2) extract	Antioxidant		
***Alkanna orientalis* (L.) Boiss.**	Root	Methanol-water (8:2) extract	Antioxidant		
***Alkanna orientalis* (L.) Boiss.**	aerial parts	Ethanol extract (70%)	Venom prophylaxis	Liver function test Hematological parameters Evaluation of internal hemorrhages in the rat abdominal cavity	[56]
***Alkanna orientalis* (L.) Boiss.**	Aerial parts	Ethanol extract	Anti-viral	*In vitro* Coxsackievirus	[37]
***Alkanna tinctoria* Tausch**	Root	-	*Staphylococcus aureus* induced eczema	Molecular docking	[57]
***A. cappadocica* Boiss. et. Bal.**	Aerial parts	Methanol extract	Anti-cancer Topoisomerase-I inhibition	*In vitro* cytotoxicity	[53, 58]
***A. pseudotinctoria* Hub.-Mor.**	*In vitro* culture medium	*In vitro* culture medium	Antibacterial (*Staphylococcus aureus, Mycobacterium smegmatis, Acinetobacter baumanii , Escherichia coli, Pseudomonas aeruginosa , Klebsiella pneumonia , Proteus spp ., Enterococcus hirae , Pichia guilliermondii ,Debaryomyces hansen*)	*In vitro* MIC	[59]

DPPH: 2,2-diphenyl-1-picrylhydrazy; FTC: ferric thiocyanate; TBA: Thiobarbituric Acid; MIC: Minimum Inhibitory Concentration; LDL: Low Density Lipoprotein; MBC: Minimal Bactericidal Concentration; PCR: Polymerase Chain Reaction; PV: Peroxidase Activity; CUPRAC: Cupric Reducing Antioxidant Capacity; FRAP: Ferric Reducing Antioxidant Power Assay; PPE: Porcine Pancreatic Elastase; SPF: Sun Protection Factor; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; ABTS: 2,2'-Azinobis [3-ethylbenzothiazoline-6-sulfonic acid]-diammonium salt

Table 3 *(continue).* Biological activity studies on *Alkanna* spp.

Plant name	Plant part	Extract	Biological activity	Method	Ref.
***A. cordifolia* K.Koch**	Roots	60% Methanol	LDL oxidation inhibitor	*In vitro* LDL oxidation and lipid peroxidation	[60]
***A. tinctoria* Tausch subsp. *subleicarpa* (Hub.-Mor.) Hub.-Mor.**	Leaves	Water extract Chloroform extract Ethanol extract Hexane extract	Antibacterial (*A. baumannii* , *E. coli* , *P. aeruginosa* , *S. aureus*)	Disk diffusion, MIC, MBC	[61]
***A. tubulosa* Boiss.**	Aerial parts and Roots	Methanol: water extract	Antimicrobial or efflux pump inhibitory activity (*Mycobacterium smegmatis*, *S. aureus*)	MIC	[43]
***Alkanna orientalis* (L.) Boiss.**	Roots	Butanol extract Petroleum ether extract	Antimutagenic	Ames *Salmonella* test	[62]
***Alkanna tinctoria* Tausch**	Roots	Ethanol extract (96%)	Antibacterial (*P. areuginosa* , *Bacillus subtilis* , *E. coli* and *S. aureus*	Disk diffusion and MIC	[41]
***Alkanna bracteosa* Boiss.**	Aerial parts	80% Methanol extract	Anticancer (Gastric cancer cell line)	Real-time PCR and Flow cytometry	[63]
***Alkanna tinctoria* Tausch**	Roots	Topical cream	Wound healing	Randomized, blinded, placebo-controlled study	[64]
***Alkanna tinctoria* Tausch**	Roots	%95 Ethanol extract	Antiproliferative Apoptosis induction	Cell proliferation analysis Cell cycle analysis Apoptotic analysis	[4]
***Alkanna orientalis* (L.) Boiss.**	Roots and aerial parts	Cyclohexane extract Dichloromethane extract Water extract Methanol extract	Antioxidant Enzyme inhibition activity	DPPH CUPRAC FRAP Phosphomolybdenum method Acetylcholine esterase inhibition Butyrylcholine esterase inhibition α -amylase inhibition	[29]
***Alkanna tinctoria* Tausch**	Roots	Ethanol extract (70%)	Histological staining of liver tissue	*In vivo* staining	[65]
***Alkanna orientalis* (L.) Boiss.**	Roots	Olive oil-Beeswax	Clinical trials	It was carried out in the burn unit with 64 patients.	[66]

DPPH: 2,2-diphenyl-1-picrylhydrazy; FTC: ferric thiocyanate; TBA: Thiobarbituric Acid; MIC: Minimum Inhibitory Concentration; LDL: Low Density Lipoprotein; MBC: Minimal Bactericidal Concentration; PCR: Polymerase Chain Reaction; PV: Peroxidase Activity; CUPRAC: Cupric Reducing Antioxidant Capacity; FRAP: Ferric Reducing Antioxidant Power Assay; PPE: Porcine Pancreatic Elastase; SPF: Sun Protection Factor; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; ABTS: 2,2'-Azinobis [3-ethylbenzothiazoline-6-sulfonic acid]-diammonium salt

Table 3 *(continue)*. Biological activity studies on *Alkanna* spp.

Plant name	Plant part	Extract	Biological activity	Method	Ref.
***Alkanna tinctoria* Tausch**	Aerial parts	Methanol extract	Antimicrobial, Antioxidant	Disk diffusion test β-Carotene-linoleic acid antioxidant test	[7]
***Alkanna tinctoria* Tausch**	Roots	-	Venous ulcer	Pressure-induced venous rabbit model	[67]
***Alkanna tinctoria* Tausch**	Aerial parts	Water extract Ethanol extract Chloroform extract	Prostate cancer	Cell proliferation analysis Isobologram analysis Apoptotic analysis	[68]
***Alkanna tinctoria* Tausch**	Roots	Water extract Methanol exrtact Hexane extract Acetone extract	Antioxidant Anti- elastase Sunscreen	DPPH PPE SPF calculation Antielaestase activity	[15]
***Alkanna sfikasiana* Tan, Vold and Strid**	Aerial parts	Water extract Ethanol extract Methanol extract	Antimalarial activity	Brine shrimp method *In vivo* antimalarial test	[69]
***Alkanna tinctoria* Tausch**	Root	Hexane extract	Wound healing activity	Clinical trial	[70]
***Alkanna tinctoria* Tausch**	Root	Dichloromethane extract	Antioxidant activity	PV	[9]
***Alkanna tinctoria* Tausch**	Root	Hexane extract	Cytotoxic and apoptotic activity	MTT test Hoechst and AO/EB staining	[54]
***Alkanna trichophila* Hub.-Mor.**	Aerial parts	Methanol extract	Antioxidant activity Enzyme inhibition activity	DPPH CUPRAC FRAP Phosphomolybdenum method Tyrosinase inhibition α-glucosidase inhibition Choline esterase inhibition α -amylase inhibition	[8]
***Alkanna tinctoria* Tausch**	Roots	Hexane extract	Tissue Staining	*In vivo* staining	[71]
***Alkana orientalis* (L.) Boiss**	Roots	Ointment with chloroform extract	Keratinolytic activity Wound healing.	Case-control, single-center, and pilot study that enrolled 60 patients	[72]
***Alkanna tinctoria* Tausch**	Roots	Ointment from extract	The burn was infected with *P. aeruginosa*	*In vivo* wound healing.	[73]

DPPH: 2,2-diphenyl-1-picrylhydrazy; FTC: ferric thiocyanate; TBA: Thiobarbituric Acid; MIC: Minimum Inhibitory Concentration; LDL: Low Density Lipoprotein; MBC: Minimal Bactericidal Concentration; PCR: Polymerase Chain Reaction; PV: Peroxidase Activity; CUPRAC: Cupric Reducing Antioxidant Capacity; FRAP: Ferric Reducing Antioxidant Power Assay; PPE: Porcine Pancreatic Elastase; SPF: Sun Protection Factor; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; ABTS: 2,2'-Azinobis [3-ethylbenzothiazoline-6-sulfonic acid]-diammonium salt

Table 3 *(continue)*. Biological activity studies on *Alkanna* spp.

Plant name	Plant part	Extract	Biological activity	Method	Ref.
***Alkanna tinctoria* Tausch**	Aerial parts	Water extract	Antimicrobial activity (Gram-negative and Gram-positive)	*In vitro* MIC	[74]
			DNA gyrase gene expression, cytotoxicity	*In vitro* MIC	
***Alkanna tubulosa* Boiss.**	Aerial parts	Ethyl acetate extract Ethanol extract Infusion Ethanol/Water extract	Antioxidant activity Enzyme inhibition activity Cytotoxic activity	DPPH ABTS CUPRAC FRAB MH PBD AChE activity BChE activity Tyrosinase inhibition α-Amylase inhibition α-Glucosidase inhibition Inhibition of carbonic anhydrases DU-145 (Prostate carcinoma) HGC-27 (Gastric carcinoma) DU-145 (Prostate carcinoma) MDA-MB- 231 (Breast carcinoma) HELA (Over carcinoma)	[44]
***Alkanna tinctoria* Tausch**	Root	Methanol extract	Antioxidant activity Antidiabetic activity	DPPH ABTS H_2O_2 activity α-amylase activity	[5]
***Alkanna tinctoria* Tausch**	Root	Ethanol extract	Antibacterial activity Wound Healing	Agar well diffusion method Wistar rats model	[75]
***Alkanna orientalis* (L.) Boiss**	Aerial parts	Aqueous ethanol extract (80%)	Anti-viral activity	*In vitro* (SARS-CoV M^{pro})	[76]
***Alkanna tinctoria* Tausch**	Root	Methanol extract	Antibacterial and antifungal activity Wound healing activity	Agar-well diffusion method *In vivo* (burn wound)	[46]
***Alkanna orientalis* (L.) Boiss**	Roots	Ointment	Clinical trials management of burn wounds	External application	[77]
***Alkanna strigosa* Boiss. & Hohen.**	Root	Hexane extract	Wound healing activity	*In vivo* wound	[78]

DPPH: 2,2-diphenyl-1-picrylhydrazy; FTC: ferric thiocyanate; TBA: Thiobarbituric Acid; MIC: Minimum Inhibitory Concentration; LDL: Low Density Lipoprotein; MBC: Minimal Bactericidal Concentration; PCR: Polymerase Chain Reaction; PV: Peroxidase Activity; CUPRAC: Cupric Reducing Antioxidant Capacity; FRAP: Ferric Reducing Antioxidant Power Assay; PPE: Porcine Pancreatic Elastase; SPF: Sun Protection Factor; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; ABTS: 2,2'-Azinobis [3-ethylbenzothiazoline-6-sulfonic acid]-diammonium salt

RESULT AND DISCUSSION

Medicinal plants are rich sources of natural chemical products used as traditional medicines and they produce many modern medicines from these plants. Secondary metabolites produced by plants are often responsible for the biological activities of plant spp. used worldwide. Nowadays, the medical and pharmaceutical importance of Alkanna has been understood and in this context, it has attracted the attention of many scientists and pharmaceutical companies. The main components of *Alkanna* spp. are Alkannin and its derivatives [53,78,79], as well as alkaloids, flavonoids, and other secondary compounds [24,28]. According to the scientific studies conducted on *Alkanna* spp. so far, it is thought that they can be a promising source for the discovery of a new herbal drug as an antimicrobial, antitumor, antioxidant, and anti-inflammatory agent [80]. In this context, focusing on standardization studies and supporting them with toxicity and clinical studies would be appropriate.

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AUTHOR CONTRIBUTIONS

Concept: S.Y., A.B.K.; Design: S.Y., A.B.K.; Control: A.B.K.; Sources: S.Y., A.B.K.; Materials: - ; Data Collection and/or Processing: - ; Analysis and/or Interpretation: - ; Literature Review: S.Y; Manuscript Writing: S.Y., A.B.K.; Critical Review: A.B.K.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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