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Phytochemicals of Artemisia Absinthium: Natural Antioxidant, Anticancer Agents, and its Characterizations

Artemisia absinthium'un Fitokimyasal Bileşenleri: Doğal Antioksidan ve Antikanser Etkiler ile Karakterizasyonları

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ABSTRACT

Artemisia absinthium L. (wormwood) is rich in bioactive constituents—including monoterpenes, sesquiterpene lactones, flavonoids, and phenolic acids that underpin documented antioxidant, antimicrobial, anti-inflammatory, and anticancer activities. Growing interest in plant-derived therapeutics has intensified the need for systematic evaluation of extraction strategies that maximize yield, stability, and bioactivity of these compounds. This review synthesizes current evidence on conventional and advanced extraction methods applied to *Artemisia absinthium* (*A. absinthium*) and relates the resulting phytochemical profiles to biological effects, with emphasis on antioxidant and anticancer outcomes. Additionally, it explores the integration of standardized wormwood extracts into modern controlled-release systems such as polymeric nanoparticles, liposomes, and nanoemulsions to enhance solubility, bioavailability, targeting precision, and therapeutic index. By bridging traditional uses with contemporary pharmaceutical technologies, this review highlights opportunities for method optimization, extract standardization, and rational formulation design, and outlines key research gaps to accelerate translation of *A. absinthium* into evidence-based drug delivery applications.

Key Words
Artemisia absinthium, extraction methods, phenolic compounds, antioxidant activity, anticancer activity.

ÖZ

Artemisia absinthium L. (pelin otu), monoterpenler, seskiterpen laktonlar, flavonoidler ve fenolik asitler gibi biyoaktif bileşenler bakımından zengindir. Bu bileşikler, belgelenmiş antioksidan, antimikrobiyal, antienflamatuvar ve antikanser aktivitelerin temelini oluşturmaktadır. Bitki kaynaklı tedavilere yönelik artan ilgi, bu bileşiklerin verimini, stabilitesini ve biyolojik aktivitesini en üst düzeye çıkaracak ekstraksiyon stratejilerinin sistematik olarak değerlendirilmesi gerekliliğini artırmıştır. Bu derleme, *Artemisia absinthium* (*A. absinthium*) üzerine uygulanan geleneksel ve ileri ekstraksiyon yöntemlerine ilişkin mevcut kanıtları sentezlemekte ve ortaya çıkan fitokimyasal profilleri biyolojik etkilerle ilişkilendirmektedir. Özellikle antioksidan ve antikanser sonuçlara vurgu yapılmaktadır. Ayrıca, standartlaştırılmış pelin otu ekstraktlarının çözünürlüğünü, biyoyararlanımını, hedefleme hassasiyetini ve terapötik indeksini artırmak amacıyla polimerik nanoparçacıklar, lipozomlar ve nanoemülsiyonlar gibi modern kontrollü salım sistemlerine entegrasyonu da incelenmektedir. Geleneksel kullanımları çağdaş farmasötik teknolojilerle birleştiren bu derleme; yöntem optimizasyonu, ekstrakt standardizasyonu ve rasyonel formülasyon tasarımı için fırsatları vurgulamakta, ayrıca *A. absinthium*'un kanıta dayalı ilaç taşıma uygulamalarına dönüştürülmesini hızlandırmak için temel araştırma boşluklarını ortaya koymaktadır.

Anahtar Kelimeler
Artemisia absinthium, ekstraksiyon yöntemleri, fenolik bileşikler, antioksidan aktivite, antikanser aktivite.

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INTRODUCTION

A. absinthium L., commonly known as wormwood, is a perennial herb that has been utilized in traditional medicine for centuries to treat a variety of ailments (Figure 1) [1]. Traditionally recognized for its intensely bitter taste, wormwood has a rich history of use in addressing digestive disorders [2], parasitic infections [3], and inflammatory conditions [4]. The pharmacological significance of *A. absinthium* is attributed to its diverse phytochemical profile, which includes monoterpenes, sesquiterpene lactones, flavonoids, and phenolic acids. Essential oils and extracts derived from the leaves and flowers of the plant are particularly rich in bioactive compounds, with major components such as thujone, davanone, camphor, p-cymene, and caryophyllene being commonly identified [5]. This complex chemical composition underpins a wide range of biological activities exhibited by *A. absinthium*, including antioxidant, antimicrobial, anti-inflammatory, and anticancer properties [6-7]. Numerous studies have emphasized its potent antioxidant activity, primarily attributed to the high content of phenolic acids and flavonoids present in its extracts. The radical scavenging ability of wormwood extract has been demonstrated through DPPH, ABTS, and FRAP assays, highlighting its potential role in mitigating oxidative stress-related disorders [8]. In addition to its antioxidant properties, wormwood exhibits strong antimicrobial effects against a broad spectrum of pathogens, including Gram-positive and Gram-negative bacteria [3]. Essential oils rich in thujone, camphor, and caryophyllene have shown significant inhibitory activity against bacterial strains such as *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, as well as several fungal species [9-10]. These findings suggest that *A. absinthium* may serve as a natural alternative for combating antibiotic resistance (Figure 2). The anti-inflammatory activity of wormwood has been linked to the modulation of pro-inflammatory cytokines and inhibition of enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX) [11-12]. This bioactivity supports its traditional use in the treatment of inflammatory conditions. Furthermore, increasing evidence supports

Figure 1. (a) Morphological parts of *A. absinthium* plant; (b) Global distribution map (GBIF data).

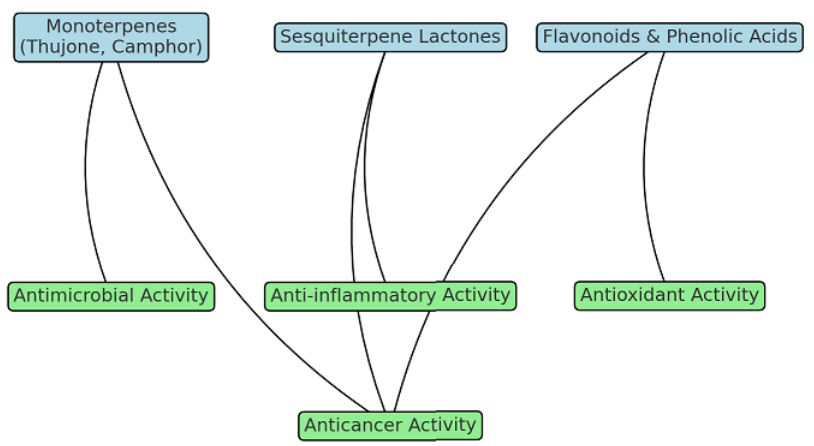

Figure 2. Biological activities of *A. absinthium* in relation to its phytochemical composition [5-6, 18].

the anticancer potential of *A. absinthium*. Studies have reported that extracts and isolated compounds from wormwood induce apoptosis, inhibit cell proliferation, and disrupt cancer cell cycle progression, particularly in colorectal, breast, and prostate cancer models [13-14]. These anticancer effects are thought to result from oxidative stress modulation, mitochondrial dysfunction, and regulation of key signaling pathways.

In recent years, there has been a growing interest in integrating wormwood extracts into controlled drug delivery systems to enhance the therapeutic potential and targeted release of its bioactive compounds. Controlled-release formulations, such as polymeric nanoparticles, liposomes, and nanoemulsions, have been developed to enhance the stability, bioavailability, and targeted delivery of *Artemisia*-derived bioactives [15-17]. These strategies aim to overcome the limitations associated with the poor solubility and bioavailability of phytochemicals, thereby maximizing their therapeutic potential. This review aims to provide an in-depth evaluation of the extraction methods, biological effects, and pharmaceutical applications of *A. absinthium*, with particular focus on its role in modern controlled drug delivery strategies.

MATERIALS and METHODS

We conducted a systematic literature survey to summarize extraction techniques and phenolic contents reported for *A. absinthium*. Searches were performed in PubMed, ScienceDirect, Google Scholar, and Web of Science for the period 2004–2025 using the keywords "*A. absinthium*" and "extraction." Records deemed relevant to the aims of this review were selected for detailed analysis. Eligible studies were evaluated for (i) extraction method(s) employed, (ii) phenolic composition/quantification, and (iii) assessment of antioxidant and anticancer activities. Findings from the included articles were synthesized to compare methodological approaches and reported phenolic profiles.

RESULTS and DISCUSSION

Phytochemical Compounds *of A. absinthium*

A. absinthium contains a wide array of secondary metabolites such as phenolic compounds. Major bioactive compounds include astragalin, cynaroside, ononin, rutin, quercetin, apigenin, kaempferol, luteolin, hyperoside, diosmetin, absinthin, and artabsin (Figure 3) [1-19].

The composition and biological activity of these compounds vary among different parts of the plant and depend on the extraction method and conditions. Various traditional and modern extraction techniques have been applied to isolate bioactive compounds from Artemisia absinthium efficiently.

Influence of Extraction Parameters

Solvent polarity, extraction temperature, and technique (e.g., maceration, ultrasound, enzymatic aid) critically determine both the yield and the chemical profile of Artemisia absinthium extracts (Table 1). Because solvent polarity dictates solubility, intermediate-polarity mixtures (typically 50–80% aqueous alcohols) are generally optimal for co-extracting polar phenolic acids/flavonoids together with moderately polar sesquiterpene lactones [20-21]. Consistent with this, an optimization study on Pakistan-grown wormwood reported that 80% methanol produced the highest extract yield (15.8 g/100 g) and the greatest totals of phenolics (84.2 mg GAE/g) and flavonoids (Barkat et al. 2024). Solvent choice also reshapes composition and bioactivity: when leaves were extracted with water versus ethyl acetate, the semi-polar ethyl acetate fraction showed far higher yield (15.95% vs. 0.67%) and greater total polyphenols (69.0 mg GAE/g) and flavonoids (25.8 mg QE/g), whereas the aqueous extract was richer in condensed tannins due to water's high polarity [22]. Even for a single target, polarity can be decisive—e.g., the sesquiterpene lactone anabsinthin was maximally recovered with 75% methanol and minimally with 25% methanol, underscoring how modest polarity shifts produce large efficiency changes [21]. Practically, tailoring the solvent system or using sequential/fractionated extraction allows selective enrichment of phenolics (medium polarity) versus terpenoids (low polarity; hexane/diethyl ether).

Temperature further modulates recovery by accelerating mass transfer but also risking thermal degradation. Studies testing 30–60°C indicate that while total phenolics peak near 60 °C, antioxidant activity (DPPH) may decline above ~45 °C—suggesting partial loss of thermo-labile antioxidants; consequently, ~45 °C often balances phenolic yield with functional activity [21]. In ultrasound-assisted workflows, moderate heating boosts diffusion and cell-wall disruption, yet

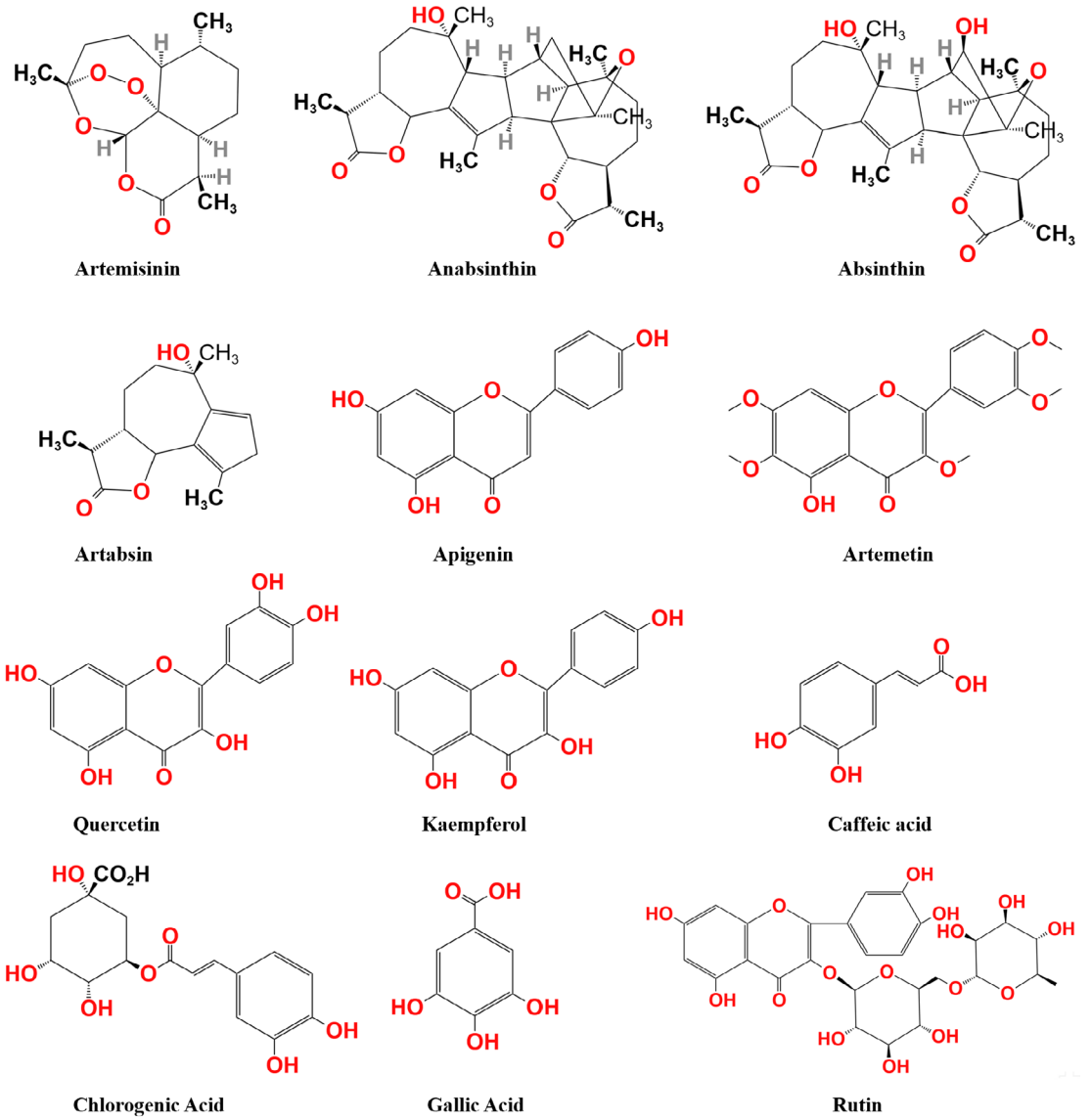

Figure 3. Chemical structures of major bioactive compounds identified in *A. absinthium*.

excessive temperatures (>70 °C) can degrade sensitive flavonoids; enzymatically assisted ultrasonication around ~50 °C has delivered maximal total flavonoids [21, 23]. Because volatile monoterpenes (e.g., thujone) and certain polyphenols can evaporate or transform at high temperatures, maintaining a moderate window (~40–60 °C) typically preserves bioactivity while sustaining efficient recovery of both phenolic and terpenic constituents [7, 21].

Characterization and Chemical Profiling

Accurate characterization of the extract is crucial for a reliable assessment of its biological activity. High-performance liquid chromatography (HPLC) and Fourier-transform infrared spectroscopy (FTIR) are key techniques for profiling *A. absinthium* extracts. HPLC allows quantification of flavonoids, phenolic acids, and sesquiterpene lactones such as absinthin/anabsinthin, enabling standardization of extract batches. [35-36].

HPLC Analysis

High-performance liquid chromatography (HPLC) is widely employed in the analysis of phenolic and more polar constituents of *A. absinthium* extracts. HPLC coupled with detectors operating in the UV-visible range such as diode-array detectors (DAD) or with mass spectrometry enables the identification of flavonoids, phenolic acids, and sesquiterpene lactones within the extract.

In a study by Hbika et al. 2022 [36], aqueous and ethyl acetate extracts prepared from *A. absinthium* leaves

Table 1. Overview of extraction methods, target cancer cell lines, concentration ranges, cytotoxic effects, and mechanisms.

Extraction Type	Target Cell Line	Concentration	Effect	Mechanism	References
Ultrasound assisted; Metanol:water (70:30)	MTT Analysis -HepG2 (ATCC HB-8065) -MCF-7 (ATCC HTB-22)	50–200 µg/mL	dose-dependent reduction in viability	Induced Apoptosis	24
Maceration; methanol	MTT Analysis -Calu-6	100-600 µg/ml	dose-dependent inhibitory effect	Induced apoptosis	25
Maceration; methanol	MTT Analysis -A549	5-100 µg/mL	dose-dependent inhibitory effect	-	26
Macroporous resin column chromatography	MTT Analysis -human esophageal carcinoma cells Eca109	10-100 µg/mL	IC50; 57.76 µg/mL	Induced mitochondrial dependent apoptosis	27
Maceration; 80% (v/v) of ethanol	MTT Analysis -Huh-7 (aggressive human liver cancer)-Vero (non-cancerous)	20 µL (1 mg/mL)	inhibited the growth of cancerous cell lines	-	28
Maceration; methanol	MTT Analysis -A2780 cell line ovarian cancer	50–500 µg/mL	dose-dependent inhibitory effect	dependent apoptosis	29
Soxhlet; methanol	MTT Analysis -human breast cancer cells MCF-7 -human colon cancer cells HCT 116	-	IC50 values for: MCF-7=80.96 ± 3.94 µg/ml HCT 116 = >200 µg/ml	inhibit the proliferation of MCF7 breast cancer cells but not HCT 116 cells	30
Maceration; ethanol	MTT Analysis -MCF-7, -MDA MB-231	100-500 µg/ml	IC50 values of whole parts of plant for: MCF-7=307.16 ± 20.4 µg/ml MDA MB-231 = 338.55 ± 15.7 µg/ml	-	31
Maceration; methanol	MTT Analysis -HCT-116	100-500 µg/ml	dose and time dependent	dependent apoptosis	32
Soxhlet; ethanol	MTT Analysis -MCF 7	10-50 µg/mL	dose and time dependent	dependent apoptosis	33
Maceration; Methanol:Water (80:20)	MTT Assay -DLD-1 -ECC-1	2-200 µg/ml	dose and time dependent	dependent apoptosis	34
Maceration; n-hexane and methanol	MTT Assay - Chronic myeloid leukemia cells (K562)	5-250 µg/ml	dose and time dependent	dependent apoptosis	35

were analyzed using HPLC-DAD to determine the major phenolic constituents. The results revealed that naringenin (a flavonoid aglycone) was the predominant compound in the aqueous extract, whereas caffeic acid was the main component in the ethyl acetate extract. These findings highlight both the compositional variation among extracts of different polarities and the effectiveness of HPLC in distinguishing such differences.

Other studies have identified compounds such as rutin, quercetin derivatives, apigenin glycosides, and sesquiterpene lactones like absinthin and anabsinthin in *A. absinthium* extracts using HPLC [37]. Notably, absinthin and anabsinthin are sesquiterpene lactones responsible for the plant's bitter taste, and their quantitative determination has been successfully performed via HPLC. For instance, Sariri et al. 2014 [37] reported that the highest concentration of anabsinthin (16.58 µg/g dry weight) was found in the extract obtained with 75% methanol.

HPLC is also a valuable tool for the standardization of *A. absinthium* extracts. To ensure consistent pharmacological activity across different extract batches, it is recommended that key reference compounds such as absinthin, rutin, and caffeic acid be quantitatively analyzed by HPLC (Table 2).

FTIR

FTIR aids in identifying functional groups present within the extract, thereby providing insights into the types of compounds it contains (Table 3). For instance, FTIR analysis of *A. absinthium* essential oil has revealed absorption bands around 3400 cm^{-1} corresponding to -OH groups (indicative of phenolic compounds), around 1700 cm^{-1} for carbonyl groups (from lactones or phenolic acids), and in the 1050–1150 cm^{-1} region for C–O stretching bands [15]. These spectral features suggest the presence of phenolic acids and terpene esters within the extract.

Jahan et al. [15] also analyzed a nanosuspension formulation of *A. absinthium* extract using FTIR and confirmed that the chemical integrity of the extract was maintained during the nanoformulation process. The main characteristic peaks, such as those corresponding to phenolic O–H and C=O groups, remained unchanged.

Antimicrobial Effects

The antimicrobial properties of *A. absinthium* are well-documented in the literature. Solvent-based extracts of the plant have demonstrated inhibitory activity against a variety of Gram-positive and Gram-negative bacteria, as well as fungi (Table 4). The antibacterial activity of *A. absinthium* extract is primarily attributed to its terpenoid and phenolic constituents, with particularly notable effects observed against Gram-positive bacteria. For instance, the essential oil obtained via hydro distillation has shown strong antibacterial activity against *Staphylococcus aureus*, *Bacillus spp.*, and *Micrococcus luteus*, exhibiting low minimum inhibitory concentration (MIC) values. In one study, the MIC value of wormwood essential oil against *S. aureus* was reported to be approximately 5 µg/mL, a potency comparable to that of standard antibiotics tested in the same experiment [6]. The same study also reported significant antifungal activity, with a MIC value of 4 µg/mL against the opportunistic yeast *Candida albicans*. In

Table 2. Major bioactive compounds in *A. absinthium* extracts with HPLC/LC–MS specifications.

Bioactive Components	RT (min)	LC–MS / HPLC Specification	DAD λmax (nm)	References
Quercitrin	22.50	C18 LC–MS	≈255, 353–356	39
Rutin	23.01	C18 LC–MS	≈255, 355–360	
Quercitrin	26.18	C18 LC–MS	≈255, 350–355	
Quercetin	30.38	C18 LC–MS	≈255, 370	
Luteolin	32.78	C18 LC–MS	≈255, 350	
Kaempferol	35.63	C18 LC–MS	≈266, 366	
Apigenin	36.91	C18 LC–MS	≈267, 336	
Cynaroside	≈14.08	C18 HPLC-UV	≈255, 345–350	40
Absinthin	—	HPLC-DAD-MS	—	41
Artabsin	—	HPLC-DAD-MS	—	
Quercetin/Rutin/etc.	—	HPLC-DAD-MS	—	42

Table 3. Key FTIR absorption bands and functional group assignments for *A. absinthium* constituents.

Bioactive Component	Key FTIR Bands (cm^{-1}) Assignments / Notes	References
Quercetin	O–H ~3400–3200; C=O (flavonol/flavone) ~1660–1650 Aromatic C=C ~1610–1600, 1560–1515; ring CH bend ~1460–1440; Phenolic C–O + O–H bend ~1280–1215 Ar–O ~1170–1110;Aromatic =C–H~835–810	43
Rutin	O–H ~3400–3200; C=O (flavonol/flavone) ~1660–1650 Aromatic C=C ~1610–1600, 1560–1515; ring CH bend ~1460–144; Phenolic C–O + O–H bend ~1280–1215; Ar–O ~1170–1110; Aromatic =C–H~835–810; Glycosidic C–O–C/C–O ~1150–1020; sugar C–O ~1075–1030; broad O–H (sugar) 3500–3200	
Kaempferol	O–H ~3400–3200; C=O (flavonol/flavone) ~1660–1650 Aromatic C=C ~1610–1600, 1560–1515; ring CH bend ~1460–1440; Phenolic C–O + O–H bend ~1280–1215; Ar–O ~1170–1110; Aromatic =C–H~835–810	44
Luteolin	O–H ~3400–3200; C=O (flavonol/flavone) ~1660–1650 Aromatic C=C ~1610–1600, 1560–1515; ring CH bend ~1460–1440; Phenolic C–O + O–H bend ~1280–1215 Ar–O ~1170–1110; Aromatic =C–H~835–810	45
Apigenin	O–H ~3400–3200; C=O (flavonol/flavone) ~1660–1650 Aromatic C=C ~1610–1600, 1560–1515; ring CH bend ~1460–1440; Phenolic C–O + O–H bend ~1280–1215; Ar–O ~1170–1110; Aromatic =C–H~835–810	46
Isoquercitrin/Hyperoside	O–H ~3400–3200; C=O (flavonol/flavone) ~1660–1650 Aromatic C=C ~1610–1600, 1560–1515; ring CH bend ~1460–1440; Phenolic C–O + O–H bend ~1280–1215 Ar–O ~1170–1110; Aromatic =C–H~835–810 Glycosidic C–O–C/C–O ~1150–1020; sugar C–O ~1075–1030 broad O–H (sugar) ~3500–3200	39
Absinthin (sesquiterpene lactone)	Lactone C=O ~1765–1735; conjugated C=C ~1660–1620 actone/ether C–O–C ~ 1450–1370; CH3 bends ~ 1240–1180 exocyclic =C–H ~ 980–900	41
Artabsin (sesquiterpene lactone)	As above	

Table 4. Minimum Inhibitory Concentrations (MIC), Minimum Bactericidal Concentration (MBC) and biofilm inhibition data for *A. absinthium* extracts and components.

Component / Extract	Bacterial Species	MIC / MBC (µg/mL)	References
Quercetin	*Staphylococcus aureus*	≈250 µg/mL (MIC)	48
Luteolin	*Staphylococcus aureus*	62.5 µg/mL (MIC)	49
Apigenin-7-O-glucoside	*S. aureus (biofilm)*	200 µg/mL (MBC)	50
Luteolin derivatives	*B. subtilis*	7.81 µg/mL (MIC)	51
Arborescin (isolated)	*Escherichia coli*	83 µg/mL (MIC)	52
Arborescin (isolated)	*Staphylococcus aureus*	166 µg/mL (MIC)	
A. absinthium methanol extract	*Escherichia coli ATCC 10536*	1255–2500 µg/mL (MIC)	53
Essential oil (*A. absinthium*)	*Pseudomonas aeruginosa*	≈390–1210 µg/mL (MIC)	6

contrast, Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* were found to be more resistant to wormwood essential oil, with MIC values exceeding 25 µg/mL in some strains [6]. This disparity is likely due to the structural characteristics of Gram-negative bacterial outer membranes and the presence of efflux pumps, which limit the penetration of essential oil components into the cell.

The major contributors to wormwood's antibacterial activity are its monoterpenes found in the essential oil. In an analysis of Iranian *A. absinthium* essential oil, camphor (14.8%), p-cymene (10.3%), and β-caryophyllene (6.9%) were identified as the dominant components, each of which demonstrated individual antibacterial activity against *S. aureus* [5]. Terpenes such as camphor and p-cymene are believed to exert their effects by targeting the bacterial cell membrane, increasing its permeability, and disrupting membrane protein structures, thereby inhibiting microbial growth. In addition, minor terpenes such as α-pinene and β-pinene, also present in wormwood, have been reported to possess antimicrobial potential and may contribute synergistically to the overall activity [5].

Beyond its volatile components, the polyphenolic compounds in *A. absinthium* including chlorogenic acid and caffeic acid derivatives may also contribute to its antimicrobial effects. These compounds are believed to act by inducing oxidative stress in microbial cells or by inhibiting key enzymatic functions.

The antimicrobial efficacy of *A. absinthium* extract is not limited to in vitro settings but has also been validated in animal models. In a preclinical study, topical application of wormwood extract was performed on rat skin wounds infected with *S. aureus*. The results showed that the bacterial load in the treated group was approximately 20 times lower than that in the untreated control group [47]. After eight days of treatment, the *S. aureus* count in untreated wounds was reported at an average of 7×10^6 CFU, whereas wounds treated with wormwood extract showed a significantly reduced count of 3×10^5 CFU [47]. This statistically significant reduction confirms the potent antibacterial effect of *A. absinthium* extract in vivo. The researchers attributed this activity to the major constituents of the extract, such as camphor, p-cymene, and caryophyllene, or possibly to their synergistic combinations [47]. Moreover, no signs of significant toxicity were observed during the wound healing process, suggesting that the extract may be safe for topical application.

The antimicrobial effects of *A. absinthium* extracts and essential oils are broad-spectrum in nature. Strong inhibitory effects have been reported against Gram-positive bacteria and various fungal species, whereas Gram-negative bacteria generally require higher concentrations for inhibition. The antimicrobial mechanisms of wormwood are believed to involve multiple pathways, including membrane disruption by terpenoids, enzyme inhibition by phenolic compounds, and induction of oxidative stress in microbial cells [5-6]. Consequently, *A. absinthium* extract has emerged as a promising natural antibiotic and preservative agent, with potential applications in developing novel strategies against multidrug-resistant bacterial strains.

Table 4 MIC and minimum biofilm inhibitory concentrations (MBIC) of *A. absinthium* bioactive components and crude extracts against a range of Gram-positive and Gram-negative bacteria. Among the phenolic constituents, luteolin exhibited the strongest activity against *Staphylococcus aureus* (MIC ≈ 62.5 µg/mL), followed by quercetin and apigenin-7-O-glucoside, the latter showing moderate antibiofilm inhibition (MBIC ≈ 200 µg/mL). Against *Bacillus subtilis*, luteolin and apigenin derivatives demonstrated very low MIC values (≈ 1.95–7.81 µg/mL), suggesting enhanced potency through structural modification. In contrast, crude methanolic extracts and essential oils required higher concentrations (1.2–2.5 mg/mL) to inhibit *E. coli* and *P. aeruginosa*, reflecting the generally lower susceptibility of Gram-negative bacteria. Interestingly, the isolated sesquiterpene lactone arborescin showed pronounced activity, with MIC values of 83 µg/mL against *E. coli* and 166 µg/mL against *S. aureus*. Overall, these results highlight that purified constituents generally display stronger antimicrobial effects than crude extracts, and that Gram-positive organisms tend to be more sensitive to *A. absinthium* phytochemicals.

The presented MIC data clearly indicate that quercetin, a flavonoid compound, demonstrates the strongest antibacterial activity among the tested substances, with an MIC of approximately 20 µg/mL against *S. aureus* and 31.2 µg/mL against *Bacillus spp*. This high potency is consistent with previous reports highlighting the ability of flavonoids to disrupt bacterial cell wall and membrane integrity even at micromolar concentrations. In contrast,

thujone and camphor, which are major monoterpenes found in the essential oils of *A. absinthium*, exhibit moderate activity against Gram-positive bacteria, with MIC values typically ranging from 500 to 800 µg/mL. Their antimicrobial effect is attributed to their lipophilic nature, which allows them to penetrate and destabilize bacterial membranes, causing leakage of cellular contents and protein denaturation.

Chlorogenic acid, a phenolic compound, displayed the weakest activity among the tested compounds, with MIC values reaching 1024 µg/mL for *S. aureus* and 40000 µg/mL for Bacillus spp. Such high concentrations suggest that its mechanism of action may rely more heavily on intracellular interactions, such as oxidative stress induction or enzyme inhibition, which require higher cellular uptake and may be less effective due to permeability barriers.

Interestingly, while essential oil components like α- and β-thujone and camphor have demonstrated rapid bactericidal effects sometimes comparable to or exceeding those of standard antibiotics such as gentamicin chlorogenic acid tends to be bacteriostatic rather than bactericidal, further underscoring the importance of compound class in determining antimicrobial potency.

Finally, although flavonoids such as quercetin are effective against resistant bacterial strains, their antifungal activity particularly against Candida albicans varies depending on their molecular structure and environmental conditions. Quercetin alone may not be fungicidal but has been shown to impair adhesion and biofilm formation in fungal pathogens, suggesting potential for use in combination therapies [54-60].

Anticancer Effects

In recent years, research on the anticancer effects of *A. absinthium* extract has gained increasing attention. Both the crude extract and isolated components of the plant have demonstrated cytotoxic and antiproliferative effects on various cancer cell lines (Table 1). The underlying mechanisms of these effects include inducing apoptosis (programmed cell death) in tumor cells, causing cell cycle arrest, and triggering oxidative stress [61].

A significant finding regarding the anticancer potential of *A. absinthium* is that extracts obtained using different solvents have been shown to suppress cancer cell growth and induce cell death. In a study by Wei et al. [61]. Three different organic phase extracts of *A. absinthium* (ethanol extract (AAEE) and its subfractions including petroleum ether (AAEE-Pe) and ethyl acetate (AAEE-Ea)) were investigated on hepatocellular carcinoma cell lines (H22 and BEL-7407). The results indicated that all extracts induced apoptosis and cell cycle arrest via endoplasmic reticulum stress and mitochondrial-dependent pathway. This was characterized by reduced mitochondrial membrane potential (Δψm), increased the release of cytochrome c, activated caspases (caspase-3, caspase-9), and promoted ROS production and ER stress. Finally, the extracts inhibited tumour growth in the H22 mouse model and improved survival without side effects. They also reported that the polysaccharide, flavone and triterpene content of AAEE, AAEE-Pe and AAEE-Ea was different, and that these were likely not the major antitumour components.

In a more recent study, *A. absinthium* was extracted using the ultrasound-assisted enzymatic hydrolysis method to enhance the total flavonoid content. LC-MS Analysis showed that major flavonoid constituents were astragalin, cynaroside, Ononin, rutin, Kaempferol-3-O-rutinoside, and luteolin. *A. absinthium* flavonoids and its active components, cynaroside and astragalin, inhibited the growth of the HeLa cervical cancer cell line in a dose-dependent manner, reducing cell viability after 24 hours of treatment (IC_{50} of 396.0 ± 54.2 µg/mL for cynaroside and 449.0 ± 54.8 µg/mL for astragalin). Furthermore, cynaroside and astragalin were shown to suppress the proliferation of cancer cells and induce apoptosis by promoting the accumulation of reactive oxygen species (ROS). These findings support the idea that the polyphenolic constituents of *A. absinthium* have good anti-cervical cancer activity.

The anticancer potential of *A. absinthium* extract has been demonstrated across various cancer models and is not limited to specific cancer types. For instance, Tsamesidis et al. evaluated the ethanolic extract of *A. absinthium* on HSC-3 cells, a human oral squamous cell carcinoma (tongue cancer) line. Their findings showed that, after 24 hours of treatment, the extract and artemisinin had significantly reduced the viability of HSC-3 cancer cells, decreasing it by 99% and 64%, respectively. Furthermore, an increase in the activity of Caspase 3 and Caspase 9 and inducing cancer cell death were observed. Notably, no significant cytotoxicity was

observed in human periodontal ligament stem cells (hPDLSCs) at the same dosage; cell viability remained at almost 100%. This selective cytotoxicity suggests that the extract can target cancer cells while sparing healthy tissues, making it a potential anticancer agent for treating tongue squamous carcinoma [13].

There is also evidence in the literature that *A. absinthium* has been investigated against breast cancer cells. In a recent study, Kauser et al. encapsulated the extract in pH-responsive polymeric nanoparticles and tested it on both estrogen receptor-positive (MCF-7) and triple-negative (MDA-MB-231) breast cancer cell lines [17]. The nanoparticle-loaded *A. absinthium* extract exhibited stronger anti-proliferative effects and greater inhibition of cell motility compared to the free extract. These effects were linked to disruption of microtubule structure and alterations in the expression of metastasis-associated proteins such as tubulin [17]. This study underscores the potential of targeted nanoformulations of *A. absinthium* to modulate multiple oncogenic pathways simultaneously.

At the molecular level, *A. absinthium* extract appears to act on multiple targets within cancer cells [9, 21]. Sohail et al. [62] investigated the effectiveness of methanol, ethanol and acetone extracts of *A. absinthium* on human hepatoma-derived (Huh7) liver cancer cell lines. They found that the methanolic leaf extract was the most effective, exhibiting 53% inhibition. Treatment of HUH-7 cells with a methanol extract resulted in a significant decrease in the expression of the TGFβ1 and MYC genes, as indicated by RT-PCR analysis. Decreased TGFβ1 expression signifies growth suppression in cancer cells. MYC is a proto-oncogene directly involved in cell proliferation and tumor growth. A reduction in MYC levels indicates hindered cancer cell proliferation. *Artemisia absinthium* extract has demonstrated promising anticancer activity in both in vitro cancer cell cultures and preclinical models. Inhibition of cell proliferation, induction of apoptosis, and suppression of metastatic characteristics have been consistently observed across different cancer types. This multifaceted activity is attributed to the extract's complex chemical profile and its potential to simultaneously target multiple cellular pathways [13, 61].

Application in Controlled Drug Delivery Systems

A considerable proportion of bioactive compounds in herbal extracts exhibit limited permeability across biological membranes, primarily due to their relatively large molecular structures and poor water solubility, which consequently restricts systemic absorption and reduces overall bioavailability. To overcome the solubility and bioavailability limitations of pharmaceutical compounds with low water solubility, various encapsulation techniques have been developed in recent years. These methods aim to increase the bioavailability of active compounds by increasing their solubility and to optimize the treatment dose. Various advanced drug delivery systems, such as polymeric nanoparticles, liposomes, nanoemulsions, and hydrogels, have been developed for herbal extracts and their bioactive constituents and extensively reported in the literature. *A. absinthium* extract, due to its diverse array of bioactive compounds, is a strong candidate for incorporation into controlled drug delivery systems. In recent years, various nanotechnological carriers have been explored for the delivery of wormwood extract, aiming to enhance efficacy while minimizing undesirable side effects [15-16].

Nanosuspensions and Nanoparticles

One widely used strategy to enhance the solubility and absorption of *A. absinthium* extract involves the development of nanosuspension formulations. Nanosuspensions are colloidal systems in which the active compound is dispersed in nanometer-sized particles. Jahan et al. [15] formulated and characterized a nanocrystalline suspension of ethanolic *A. absinthium* extract using the antisolvent precipitation technique. The optimized nanosuspension exhibited an average particle size of ~254 nm (with primary particles of ~25 nm based on AFM analysis), a zeta potential of –11.9 mV, and a narrow size distribution (PDI = 0.285). This formulation significantly improved the in vitro dissolution rate and enhanced the oral bioavailability of the extract by 1.13-fold in rats compared to the conventional suspension. Moreover, in a liver damage model, the nanosuspension showed superior hepatoprotective activity, evidenced by improved liver enzyme levels and histopathological outcomes relative to the crude extract group. These results suggest that nanosizing the wormwood extract enhances its biological efficacy and that controlled release can improve pharmacological outcomes [15].

Another promising carrier system for controlled release of *A. absinthium* is polymeric nanoparticles. Particularly in cancer treatment, the extract has been incorporated

into pH- or temperature-sensitive polymer matrices to achieve targeted delivery. Kauser et al. [17] developed pH-responsive polymeric nanoparticles composed of N-isopropylacrylamide, N-vinylpyrrolidone, and acrylic acid to encapsulate wormwood extract. These nanoparticles were designed to swell and release their contents in the acidic tumor microenvironment. In tests on breast cancer cell lines, the extract-loaded nanoparticles exhibited significantly higher apoptotic cell death and proliferation inhibition in both MCF-7 and MDA-MB-231 cells compared to the free extract. Interestingly, the encapsulated extract demonstrated enhanced cellular uptake and cytotoxicity in cancer cells, while maintaining low toxicity in normal cells—indicating an improved therapeutic index. Proteomics analyses further suggested that the nanoparticles disrupt microtubule dynamics and reduce cell motility, thereby potentially suppressing metastasis.

In a study conducted in 2025, Choudhary et al [63]. encapsulated essential oils (EOs) derived from Lantana camara and *A. absinthium* plants using chitosan-based polymeric nanoparticles via. EOs-loaded nanoparticles exhibited potent fumigant toxicity against the insect species Callosobruchus maculatus and Sitophilus granariu, significantly inhibiting AChE activity and resulting in high mortality [63].

Another innovative approach for delivering plant extracts such as wormwood involves nanoemulsions. These are kinetically stable systems consisting of nanometer-sized droplets of one phase dispersed in another, typically a lipid or aqueous phase. Karimi et al. (2024) developed both nanoemulsions (lipid nanodroplets) and nanoencapsulated formulations (polymeric nanocapsules) using *A. absinthium* and Urtica dioica (nettle) extracts, tested separately and in combination. The resulting nanoemulsions had particle sizes ranging from 10–50 nm, while nanocapsules ranged from 60–110 nm. These systems outperformed free extracts in several applications. For instance, the combined nanocapsule formulation (referred to as CCNW) inhibited bacterial biofilm formation—especially from *Klebsiella pneumoniae* and *Salmonella typhimurium*—with a maximum inhibition rate reaching 78% [16]. In antimicrobial testing, wormwood extract alone in nanoform showed significant activity, with an MIC of ~20 µg/mL against *S. typhimurium*, lower than that of the free extract.

In terms of anticancer activity, colon cancer (HCT116) cells were treated with both nanoemulsion and nanocapsule forms. While the IC_{50} of the free extract was ~170 µg/mL, it was ~312 µg/mL for the nanoemulsion and ~420 µg/mL for the nanocapsule [16]. Although the free extract appeared more potent at lower concentrations, the nanoemulsion and combined nanoformulations demonstrated superior cell-killing ability at higher doses (e.g., 500 µg/mL). Notably, the CCNW nanocapsule formulation—containing both extracts—was found to be the most effective for both antibacterial and anticancer outcomes. This synergistic effect is attributed to the controlled release of both phytochemicals within a compatible delivery system. These results indicate that nanoemulsification and nanoencapsulation technologies can significantly enhance the bioactivity of *A. absinthium* and may be suitable for both pharmaceutical and food-related applications.

Other Delivery Systems

Additional delivery systems reported in the literature include the integration of *A. absinthium* extract into biodegradable hydrogels, incorporation into fibrous carriers (e.g., electrospun nanofibers), and targeted liposomal or microcapsule formulations. In wound healing, bioactive films containing antimicrobial plant extracts are being explored. The incorporation of wormwood extract into chitosan- or alginate-based biopolymer films has been proposed to enable slow release at the wound site, enhancing both antimicrobial action and tissue regeneration [32].

Certain flavonoids in *A. absinthium* are prone to oxidation in the presence of light and oxygen or may undergo rapid metabolism in vivo. When encapsulated within a protective nanocarrier, these compounds can be stabilized and delivered intact to target tissues. In fact, Jahan et al. [15] reported that the antioxidant capacity of *A. absinthium* extract was slightly enhanced in nanosuspension form, likely due to improved preservation of active constituents. Furthermore, the strong bitterness of wormwood extract can be effectively masked through encapsulation, improving palatability and patient compliance.

CONCLUSION

A. absinthium extract holds significant value ranging from traditional use to modern pharmaceutical research, owing to its rich profile of bioactive constituents. This review has explored the multifaceted nature of *A. absinthium*, including its extraction, analytical characterization, antimicrobial and anticancer properties, and applications in controlled drug delivery systems. The current literature highlights several key points:

Rich and Complex Composition: *A. absinthium* extract contains diverse chemical groups, including monoterpenes (e.g., thujone, camphor, davanone), sesquiterpene lactones (e.g., absinthin, anabsinthin), flavonoids (e.g., rutin, quercetin derivatives), and phenolic acids (e.g., caffeic and chlorogenic acid derivatives). This complex composition underlies the extract's broad spectrum of biological effects. However, it also presents challenges for standardization and mechanistic understanding. Future studies should focus on establishing detailed profile–activity relationships to determine which constituents contribute most significantly to specific pharmacological effects.

Extraction and Standardization: The choice of extraction method has a direct impact on the chemical composition and biological activity of *A. absinthium* extract. Recent studies show that modern extraction techniques (e.g., ultrasonic-assisted, enzymatic, microwave-assisted) can yield more potent and bioactive-rich extracts. Moving forward, optimization of industrially scalable "green" extraction methods—such as supercritical fluid extraction or deep eutectic solvents—will be essential for *A. absinthium*. Given the chemical variability caused by geographic origin and harvest time, standardization strategies should be developed. This may involve defining threshold values for key marker compounds via HPLC or GC-MS and eventually integrating these into pharmacopeial standards.

Antimicrobial and Anticancer Potential: *A. absinthium* extract has demonstrated strong antimicrobial activity, particularly against Gram-positive bacteria and fungi. In vitro cancer studies show that the extract inhibits proliferation and induces apoptosis in various cancer cell lines. These findings position wormwood as a promising natural agent in both infectious disease and oncology research. Future studies should explore how these effects translate to in vivo models. Specifically in cancer therapy, investigations should include tumor suppression in animal models, synergy with chemotherapeutic agents, and toxicity profiles. Before clinical translation, the mechanisms of action must be thoroughly elucidated, and safety parameters clearly defined. Regarding antimicrobial use, the efficacy of the extract against resistant strains (e.g., MRSA, VRE) and the potential for resistance development should also be investigated.

Controlled Release and Formulation Development: Incorporation of *A. absinthium* into controlled release systems marks an important step toward the pharmaceutical development of natural products. Preliminary studies involving nanosuspensions, nanoparticles, and nanoemulsions have shown improvements in bioavailability and targeting efficiency. In the future, these formulations could be refined for clinical applicability. Topical systems such as hydrogels or wound dressings containing *A. absinthium* may provide dual benefits—antimicrobial and anti-inflammatory effects. For oral delivery, approaches like taste-masking and enteric-coated capsule/microsphere systems could enhance patient compliance and site-specific release. Inhalation delivery of the essential oil components for respiratory infections (e.g., via nebulized nanoemulsions) represents another promising research direction.

Safety and Toxicity Considerations: Although *A. absinthium* has been used in traditional medicine for centuries, high doses or prolonged use may lead to neurotoxic effects (e.g., seizures due to thujone). Therefore, the safety profile of any product developed from the extract must be rigorously evaluated. Particular attention should be given to its effects on the central nervous system, liver, and kidneys. Preliminary evidence suggests that controlled release systems may reduce toxicity to healthy cells. However, potential adverse effects and interactions must be carefully assessed in human trials. Future research should also address the safe dosage ranges of *A. absinthium* in its modern pharmaceutical forms versus traditional preparations.

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