Commentary Article

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Investigation of the physicochemical properties and pharmacokinetics of the active compounds in Quercus infectoria gall extract

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Abstract

The *Quercus genus*, known as oak trees, provides important bioactive compounds for pharmaceuticals. *Quercus infectoria* is recognized for its antimicrobial properties, containing Friedelin, Betulinic Acid, and Gallic Acid. The molecular weight, hydrophobicity, polarity, and solubility of these compounds play a key role in their biological activity and pharmacokinetics, which can be evaluated using SwissADME and PubChem. Lipinski's Rule of Five suggests that optimal molecular weights for oral bioavailability fall between 180 and 500 Da. Assessing the ability of compounds to penetrate the blood-brain barrier is crucial for neurological treatments. Friedelin, a pentacyclic triterpene with antimicrobial and anticancer properties, can penetrate cell membranes due to its hydrophobic nature, but absorption may be limited by its molecular weight. Betulinic acid, a triterpene with antiviral and anticancer properties, is well absorbed. Vanillic acid, a water-soluble phenolic compound, is easily absorbed but liver metabolism may affect its bioavailability. Ellagic acid, a polyphenol with antioxidant and anticancer properties, has complex pharmacokinetics due to conjugate formation and protein interactions. Gallic acid may impact its distribution, while phlorizin is being studied for its potential to inhibit glucosidase in diabetes management. Vescalagin's pharmacokinetics may be influenced by its sugar structure and conjugation sites, and low water solubility could limit its bioavailability. Breaking down *Quercus infectoria* into smaller compounds could enhance its therapeutic effects. Understanding the physicochemical properties and pharmacokinetics of new drugs and nutraceuticals is essential for evaluating their effectiveness, safety, absorption, and minimizing adverse effects. We study the pharmaceutical properties of *Quercus infectoria* bioactive compounds.

Keywords: *Quercus infectoria*, Jaft-E-Baloot, Antibacterial, Antifungal, Anti-parasite.

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1. Introduction

Quercus infectoria, also known as Aleppo oak, is a type of oak found in southern Europe and the Middle East. The tree is renowned for its medicinal galls, which are rich in tannins and used in traditional Asian medicine, leather softening, and dye production. These galls possess astringent and antiviral properties, making them effective in treating skin infections and gastrointestinal issues. They are also utilized in food, dental powders, gold sols, pharmaceuticals, and inks. The tannins from these galls have historically been used in leather tanning and post-childbirth treatments (1-3). The galls contain compounds such as flavonoids, alkaloids, and tannins with anti-inflammatory, antibacterial, antifungal, astringent, and antioxidant

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properties that may be beneficial in treating various health problems and potentially as food supplements, antimicrobial agents, and antioxidants (1-5).

1.1. Phytochemical Compound of Gall of Quercus Infectoria

The gall of *Quercus infectoria* contains phenolic acids like gallic and ellagic acid, as well as flavonoids such as quercetin, catechin, and naringin, contributing to its antioxidant properties. Hydrolyzable tannins found in the gall help protect the plant against herbivores and limit microbial growth (1, 2). Terpenoid metabolites like α-thujene, α-pinene, and limonene aid in plant growth and defense, while fatty acids such as palmitic, oleic, and linoleic acids are essential components of the gall. Some species also contain vitamins E and provitamin A. The composition of these compounds varies among Quercus species and is influenced by factors like season and collection time (6).

Phytochemical analysis of *Quercus infectoria* galls revealed the presence of gallotannic acids, carbohydrates, proteins, amino acids, saponins, phenolic compounds, and tannins, with the high tannin content enhancing their antibacterial properties. Both the aqueous extract and the gel exhibit significant antibacterial activity without causing skin irritation. *Quercus infectoria* galls are rich in tannins, containing 50-70% of these compounds. Tannins are classified into hydrolyzable and condensed types, with gallic and ellagic acids being present in the hydrolyzable tannins found in the galls. These compounds have various applications, including in dermatology, leather tanning, and treating inflamed or ulcerated tissues. Hydrolyzable tannins have traditionally been used to treat inflammation, ulceration, and diarrhea, and are listed in pharmacopoeias (6-8). The identification of bioactive compounds like friedeline, betulinic acid, and various acids highlights the potential of cork oak as a source of natural antioxidants and antibacterial agents (9, 10).

1.2. The Antioxidant and Biological Activities of Quercus Species

Quercus trees possess antioxidant properties and contain beneficial compounds such as gallic and ellagic acid, as well as ellagitannins. Compounds like ellagic acid, kaempferol, and quercetin in Quercus have demonstrated anti-inflammatory properties (9, 10). The ethanolic extract of Quercus infectoria galls, high in tannins, is a strong antioxidant. The high polyphenol content in galls provides antioxidant activity by neutralizing harmful reactive oxygen species (ROS) and protecting cells from oxidative damage. The extract shows strong antioxidant effects in vitro by scavenging free radicals like DPPH, ABTS, H_2O_2, and hydroxyl radicals. It shows strong reducing power and can chelate metal ions like iron and copper, which trigger ROS production. Studies indicate that the extract protects murine macrophages from oxidative stress, preserving their immune functions. *Quercus infectoria* galls may be a valuable natural source of antioxidants for preventing oxidative stress-related diseases (11).

1.3. Immunomodulatory Potential of Quercus infectoria Gall Extract

Macrophages play a crucial role in the body's defense against infections and inflammation by engulfing and digesting debris, foreign substances, and pathogens. The effect of *Quercus infectoria* gall extract on macrophage proliferation, phagocytic activity, and the production of nitric oxide (NO) and specific cytokines was studied. Macrophages treated with *Quercus infectoria* gall extract demonstrated increased proliferation and phagocytic activity compared to untreated ones, suggesting the extract's potential to enhance immune response. However, a decrease in nitric oxide production was noted at 64 µg/mL of the extract, indicating a possible regulatory effect on the immune system. The increase in cytokine levels (IL-2, IL-5, IL-10, IL-17A, IL-23, and

TGF-β1) in extract-treated macrophages suggests that *Quercus infectoria* gall extract may modulate immune responses. Its potential immunomodulatory activity indicates it can regulate the innate immune response, offering an alternative to cytotoxic drugs with fewer side effects (12).

1.4. Wound Healing Properties of Quercus Infectoria Galls

A wound is a break in the skin or mucous membrane that can allow microorganisms to enter, raising the risk of infection. Wound tissue can promote microbial growth due to hypoxia, necrosis, and a weakened immune response from damaged blood vessels. Wound healing is a complex process involving the repair of skin and soft tissue injuries. Traditional medicine utilizes various medicinal plants for wound care, many of which facilitate healing or possess antimicrobial properties. *Quercus infectoria* is a plant used by herbalists for treating sores and boils, with studies demonstrating its wound healing effectiveness in rat models. The galls of *Quercus infectoria* contain tannins, gallic, and ellagic acids, which have antioxidant properties. Research shows that its ethanol extract improves wound healing by enhancing skin tensile strength, accelerating epithelialization, and promoting collagen deposition. The extract boosts antioxidant enzymes (superoxide dismutase and catalase) that protect cells from oxidative damage, supporting the traditional use of *Quercus infectoria* galls for treating bacterial wounds and burns (1, 2, 13-15).

The effects of a *Quercus infectoria* gall hydroethanolic extract ointment on wound healing in diabetic mice were studied, as diabetes can impair healing due to poor circulation, nerve damage, and a weakened immune system. Diabetic patients are prone to chronic wounds and infections, necessitating effective treatments. *Quercus infectoria* gall hydroethanolic extract significantly improves wound healing in diabetic mice. Both 5% and 10% concentrations of the *Quercus infectoria* gall hydroethanolic extract ointment show potential for healing diabetic wounds by reducing inflammation, promoting apoptosis of damaged cells, enhancing antioxidant properties, and boosting cellular proliferation. Further research could improve wound management for diabetics and enhance their quality of life by reducing complications from chronic wounds (16).

Many bacterial species were found to be resistant to common antibiotics like Gentamicin, Ampicillin, and Doxycycline. The in vitro antibacterial activity of aqueous, ethanol, and methanol extracts of *Quercus infectoria* against these resistant strains from surface wounds was evaluated. The ethanolic extract of *Quercus infectoria* exhibited the strongest antibiotic effect against Staphylococcus aureus at 3.125 mg/ml, while its impact on *Escherichia coli*, *Klebsiella pneumoniae*, and *Citrobacter freundii* was lower at 25 mg/ml. The aqueous, methanolic, and ethanolic extracts were effective at this concentration. *Quercus infectoria* extracts may serve as potential alternative therapies for wound infections, particularly against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, with effective concentrations of 25 mg/ml (13-15, 17).

1.5. Central Nervous System (CNS) Depressant Properties of Quercus Infectoria Galls

Quercus infectoria galls exhibit a wide range of pharmacological properties, as demonstrated in animal studies. These properties include hypoglycemic activity in rabbits and central nervous system depressant effects, such as decreased treadmill activity and enhanced barbiturate-induced sleep. Additionally, the galls show antitremorine activity, delaying the onset of tremorine-induced tremors and reducing their severity. Moreover, they have local anesthetic effects, effectively blocking the conduction of the isolated frog sciatic nerve. These findings highlight the diverse pharmacological potential of *Q. infectoria* galls (1, 2).

1.6. Antimicrobial and Antibacterial Properties of Quercus Infectoria Gall Extract

The extract of *Quercus infectoria* galls demonstrates strong antifungal activity against *Candida glabrata* and *Candida krusei*, as well as antibacterial effects against *Staphylococcus aureus*, *Streptomyces griseolus*, and *Pseudomonas citronellosis* at a concentration of 250 µg/mL. It has the potential to serve as a natural source of antioxidants and antimicrobial agents for food preservation and pharmaceuticals. The methanol extract exhibits the highest antimicrobial activity, followed by ethanol and aqueous extracts, with minimum inhibitory concentrations against MRSA strains ranging from 63 to 250 µg/ml. Transmission electron microscopy reveals that the ethanol extract, ethyl acetate fraction, and tannic acid cause clumping of partially divided cocci with thickened cell walls in MRSA cultures, suggesting they may target the organism's cell wall structure as part of their antibacterial mechanisms. Chloroform and hexane extracts have the least activity. Scanning electron microscopy shows morphological changes in all bacterial strains treated with *Quercus infectoria* galls extract, highlighting its potential as an antimicrobial agent (13, 14, and 17).

The antibacterial activity of *Quercus infectoria* galls against oral bacteria related to dental caries and periodontitis was studied. Methanol and acetone extracts were tested on *Streptococcus mutans*, *Streptococcus salivarius*, *Porphyromonas gingivalis*, and *Fusobacterium nucleatum*. Both extracts exhibit similar antibacterial effects against the tested oral pathogens, with *Streptococcus salivarius* being the most susceptible. The antibacterial effects of *Quercus infectoria* gall extracts on multidrug-resistant bacteria were also examined, showing significant inhibitory effects against MRCoNS and MRSA. The extracts display promising *in vitro* antibacterial activity, especially against MDR Gram-positive bacteria, indicating their potential as antimicrobial agents (19).

Additionally, the antibacterial activity of *Quercus infectoria* gall extracts on dental pathogens like *Streptococcus mutans*, *Streptococcus sanguis*, *Streptococcus salivarius*, *Lactobacillus acidophilus*, and *Staphylococcus* spp. was investigated, with the methanolic extract showing the largest zone of inhibition against all bacteria. *Quercus infectoria* galls could be effective antibacterial agents against dental pathogens, supporting their traditional use in dental powders for treating toothache and gingivitis. Overall, plant extracts like *Quercus infectoria* may hold promise as sources of new antimicrobial agents for combating infectious diseases (19, 20).

1.7. Q. Infectoria in Treating Various Gynecological Disorders

Infectoria plays a crucial role in traditional medicine for treating gynecological disorders, primarily utilizing two parts: the fruit hulls ("Jaft-E-Baloot") and the galls ("Mazo"). Both parts have similar biological activities, mainly due to tannins (50-70%), which possess astringent, antimicrobial, anti-inflammatory, and anticancer properties, making them versatile for addressing female health issues. While most studies focus on Mazo, there is one clinical study on Jaft-E-Baloot related to vaginal laxity. Jaft-E-Baloot is more prevalent in Iran and globally, while Mazo receives more research attention. Both have proven effective for women's ailments such as vaginal infections, cervicitis, utero-vaginal prolapse, vaginal laxity, and cancer. Although most studies on anti-cancer and vaginal infections are experimental, clinical and animal studies have validated their effectiveness for cervicitis, utero-vaginal prolapse, and vaginal laxity. Large-scale clinical trials are essential to evaluate the efficacy of Jaft-E-Baloot and Mazo extract with vegetable oils in pessary form for treating vulvovaginal candidiasis, given their traditional uses. Infectoria, which contains Jaft-E-Baloot and Mazo, shows promise for

female health. Their tannins may help manage infections, inflammation, prolapse, laxity, and cancer, but further large-scale clinical trials are needed to validate their efficacy and safety in treating gynecological disorders (21). The ethanolic extract of *Quercus infectoria* gall effectively inhibited vaginal pathogens, particularly *Streptococcus agalactiae* and *Staphylococcus aureus*, and achieved 100% growth inhibition of *Trichomonas vaginalis*, suggesting its potential for treating vaginitis. Further studies are needed to confirm efficacy (22).

1.8. Quercus Infectoria for the Treatment of Candidiasis

Candidiasis, caused by Candida species, is becoming increasingly concerning due to the rise of non-albicans infections and antifungal resistance. *Quercus infectoria*, a traditionally used medicinal plant, may offer potential as an alternative treatment. Its tannin content, as well as gallic and ellagic acids, have anti-inflammatory, antibacterial, and antifungal properties, demonstrating anti-Candida potential. The methanol and aqueous extracts of Infectoria galls may provide safe, cost-effective, and efficient antifungal agents against the increasing cases of candidiasis (23).

1.9. Antileishmanial Activities of Quercus Infectoria Olivier Extract

The antileishmanial and cytotoxic properties of *Quercus infectoria* Olivier extract were investigated for its effectiveness against *Leishmania major*, the cause of cutaneous leishmaniasis, both *in vitro* and *in vivo*. The oak extract effectively inhibited the growth of promastigote and amastigote forms of the parasite, reduced lesion size and parasite load in infected male BALB/c mice, and exhibited strong antioxidant properties without cytotoxic effects on murine macrophage cells (23). Additionally, the antileishmanial, antioxidant, and cytotoxic activities of *Quercus Infectoria* fruit hull extract were studied. The extract significantly inhibited the growth of promastigote and amastigotes of *Leishmania major* in a dose-dependent manner in infected male BALB/c mice. Major recovery rates of 91.6%, 66%, and 50% radical inhibition were observed in treated mice with 20, 10, and 5 mg/kg of oak extract. The DPPH test showed that inhibition increased with higher oak concentrations. These findings suggest oak may be a promising alternative for leishmaniasis treatment (24).

1.10. Anti-leptospiral Activity

Leptospirosis, caused by Leptospira species, is a global infectious disease affecting animals and humans, with over 500,000 annual cases reported. Misdiagnosis is common due to varied symptoms, especially in tropical regions like Malaysia. Treatment typically involves penicillin and doxycycline, but their effectiveness in preventing complications and death is uncertain. Researchers have investigated herbal alternatives like *Quercus infectoria* gall extract, which has demonstrated antimicrobial properties against various bacteria and yeast strains, including drug-resistant ones. The gall contains tannins with natural antimicrobial and anti-inflammatory effects. Infectoria gall extract effectively inhibits *Leptospira serovars* at a minimum inhibitory concentration of 0.125 mg/mL, suggesting its potential as an alternative treatment for leptospirosis in conjunction with current antibiotics (25).

1.11. Treatment of Malaria with Quercus infectoria

Quercus infectoria, a medicinal plant, is utilized to alleviate high fever caused by malaria. Galls produced by insect bites contain antibacterial, antifungal, antiviral, antioxidant, and anti-inflammatory properties. In vitro and in vivo studies have shown effectiveness against parasites. Researchers tested four extracts on the chloroquine-sensitive 3D7 strain of *Plasmodium falciparum*. Acetone

and methanol extracts, rich in phenolic compounds like tannic, gallic, and ellagic acids, exhibited promising antimalarial activity. Ellagic acid, particularly effective in the parasite maturity stage, indicates that *Quercus infectoria* galls could be a potential source of antimalarial treatment. Further research, including *in vivo* studies, optimization of extraction methods, and identification of active compounds, is necessary for validation. Successful findings could lead to the development of new global antimalarial treatments (26).

2. Materials and Methods

2.1. Predicting Physicochemical Properties and Pharmacokinetics

The SwissADME web tool is a valuable resource for drug development researchers, providing a simple and efficient platform to predict crucial parameters such as physicochemical properties and pharmacokinetics. Its user-friendly design, along with reliable predictive models like BOILED-Egg and iLOGP, can be accessed for free at http://www.swissadme.ch. The research greatly benefited from its intuitive interface and accurate predictions, significantly improving our study outcomes (27-33).

2.2. Methods

For this study, we conducted a narrative review by searching for "*Quercus infectoria*" in Google Scholar, PubMed, Scopus, and Web of Science databases. We utilized PubChem and SwissADME software to analyze the pharmacological and physicochemical properties of compounds, as well as their antimicrobial properties. Models such as BOILED-Egg, iLOGP, and other pharmaceutical indexes were calculated (31).

3. Results

3.1. Physicochemical properties of the studied compounds

Each compound displays unique characteristics in terms of molecular weight, hydrophobicity, polarity, and solubility in physiological fluids, which significantly influence their pharmacokinetics and potential applications. Vescalagin, with a molecular weight of 934.63 and 67 heavy atoms, is the heaviest compound studied. Despite not being absorbed through digestion, it has a specific effect on the digestive system. Its high molecular weight and complex structure may contribute to its limited absorption in the gastrointestinal tract.

Phlorizin, weighing 436 Daltons, has low digestive absorption but high polar surfaces and excellent solubility in physiological fluids. Gallic Acid, with a low molecular weight of 170 Daltons, is highly soluble in physiological fluids. However, it has very low hydrophobicity, which may limit its potential for certain pharmaceutical applications. Its multiple polar levels, on the other hand, could be advantageous for compounds that require interaction with various biological targets. Ellagic Acid, weighing 330 Daltons, features four hydrophobic rings in its core and functional groups such as hydroxides on the sides. The hydrophobic core allows for better penetration and passage through biological membranes, while the hydrophilic functional groups on the periphery contribute to its good solubility in physiological fluids. This balance of properties could make Ellagic Acid a versatile candidate for various pharmaceutical applications. Vanillic Acid, the lightest compound in the study, consists of a small aromatic and hydrophobic ring alongside a central aromatic ring, enabling it to pass through biological membranes effectively. Its hydroxyl functional groups provide good solubility in physiological fluids. This combination of properties could make Vanillic Acid a promising candidate for applications where membrane penetration and solubility are essential factors. The molecules of Friedelin have high molecular weights and consist of five hydrophobic aromatic rings, resulting in very low solubility in physiological fluids. Their properties limit their digestive absorp-

tion and availability in the bloodstream. However, their high hydrophobicity allows for potential absorption through the skin, making them suitable for transdermal drug delivery systems or topical applications (Table 1, 2).

3.2. Pharmacological Properties of the Studied Compounds

The study highlights the pharmacokinetic properties of compounds extracted from *Q. infectoria* gall, including Vanillic Acid, Ellagic Acid, Gallic Acid, Phlorizin, Vescalagin, and Betulinic Acid. These compounds exhibit diverse absorption and distribution characteristics within the body. In terms of digestive absorption, Vanillic Acid, Ellagic Acid, and Gallic Acid show high levels of absorption. However, none of the studied compounds

Table 1. Includes the CID number, IUPAC name of compounds in the study, secondary structure, and radar diagram of the physicochemical properties of the compounds being studied

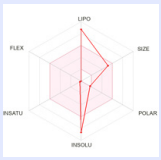
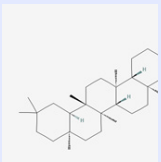
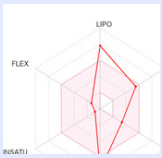
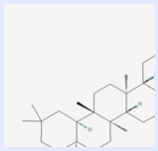
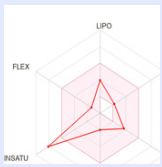
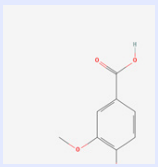
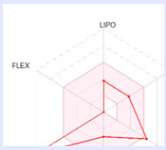
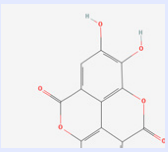
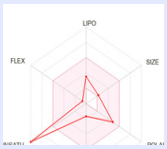
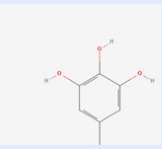
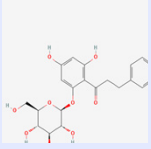
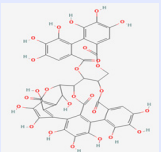
Name	CID Number	IUPC	Radar scale of physicochemical properties	2D Chemical structure
Friedelin	91472	(4R,4aS,6aS,6aS,6bR,8aR,12aR,14aS,14bS)-4,4a,6a,6b,8a,11,11,14a-octamethyl-2,4,5,6,6a,7,8,9,10,12,12a,13,14,14b-tetradecahydro-1H-picen-3-one		
Betulinic Acid	64971	(1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-prop-1-en-2-yl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a]chrysene-3a-carboxylic acid		
Vanillic Acid	8468	4-hydroxy-3-methoxybenzoic acid		
Ellagic Acid	5281855	6,7,13,14-tetrahydroxy-2,9-dioxatetracyclo[6.6.2.04,16.011,15]hexadeca-1(15),4,6,8(16),11,13-hexaene-3,10-dione		
Gallic acids	370	3,4,5-trihydroxybenzoic acid		
Phlorizin	6072	1-[2,4-dihydroxy-6-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyphenyl]-3-(4-hydroxyphenyl)propan-1-one		
Vescalagin	168165	7,8,9,12,13,14,25,26,27,30,31,32,35,36,37,46-hexadecahydroxy-3,18,21,41,43-pentaoxanonacyclo[27.13.3.138,42.02,20.05,10.011,16.023,28.033,45.034,39]hexatetraconta-5,7,9,11,13,15,23,25,27,29(45),30,32,34(39),35,37-pentadecaene-4,17,22,40,44-pentone		

Table 2. Physicochemical properties of the studied compounds.

Molecule	Friedelin	betulinic acid	Vanillic Acid	Ellagic Acid	gallic acids	Phlorizin	vescalagin
Formula	C30H50O	C30H48O3	C8H8O4	C14H6O8	C7H6O5	C21H24O10	C41H26O26
MW	426.72	456.7	168.15	302.19	170.12	436.41	934.63
Heavy atoms	31	33	12	22	12	31	67
Aromatic heavy atoms	0	0	6	16	6	12	30
Fraction Csp3	0.97	0.9	0.12	0	0	0.38	0.15
Rotatable bonds	0	2	2	0	1	7	0
H-bond acceptors	1	3	4	8	5	10	26
H-bond donors	0	2	2	4	4	7	16
MR	134.39	136.91	41.92	75.31	39.47	106.14	211.49
TPSA	17.07	57.53	66.76	141.34	97.99	177.14	455.18
iLOGP	4.5	3.83	1.4	0.79	0.21	1.25	1.15
XLOGP3	9.8	8.21	1.43	1.1	0.7	0.54	0.94
ESOL Log S	-8.66	-7.71	-2.02	-2.94	-1.64	-2.71	-6.56
ESOL Solubility (mg/ml)	0	0	1.6	0.343	3.9	0.85	0.0003
ESOL Solubility (mol/l)	0	0	0.0095	0.0011	0.0229	0.002	0
ESOL Class	Poorly soluble	Poorly soluble	Soluble	Soluble	Very soluble	Soluble	Poorly soluble

can cross the blood-brain barrier, indicating their limited impact on the central nervous system. Phlorizin and Vescalagin are actively transported out of cells by the Pgp protein (P-glycoprotein). The study also reveals that Ellagic Acid inhibits Cytochrome CYP1A2 and CYP3A4, while Betulinic Acid inhibits Cytochrome CYP2C9. Cytochromes play a crucial role in drug metabolism, and understanding their interactions with various compounds is essential for predicting drug efficacy and potential side effects. The bioavailability score, which indicates the proportion of a drug reaching its target site without structural alterations, is 85% for both Betulinic Acid and Vanillic Acid. This suggests that these compounds have a high likelihood of exerting their intended pharmacological effects. Regarding skin absorption, the study found that Friedelin has the highest absorption rate among the studied compounds. This information is valuable for researchers and pharmaceutical companies working on topical drug delivery systems or transdermal drug formulations. The pharmacokinetic properties of these compounds provide essential insights into their potential applications in various therapeutic areas. Understanding these properties is crucial for optimizing drug design, predicting drug-drug interactions, and ensuring the safe and effective

Table 3. Pharmacological Properties of the Studied Compounds.

Molecule	Friedelin	Betulinic acid	Vanillic Acid	Ellagic Acid	Gallic acids	Phlorizin	Vescalagin
GI absorption	Low	Low	High	High	High	Low	Low
BBB permeant	No	No	No	No	No	No	No
Pgp substrate	No	No	No	No	No	Yes	Yes
CYP1A2 inhibitor	No	No	No	Yes	No	No	No
CYP2C19 inhibitor	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	Yes	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	Yes	No	No
log Kp (cm/s)	-1.94	-3.26	-6.31	-7.36	-6.84	-8.58	-11.33
Bioavailability Score	0.55	0.85	0.85	0.55	0.56	0.55	0.17
Synthetic Accessibility	5.17	5.63	1.42	3.17	1.22	4.93	7.58

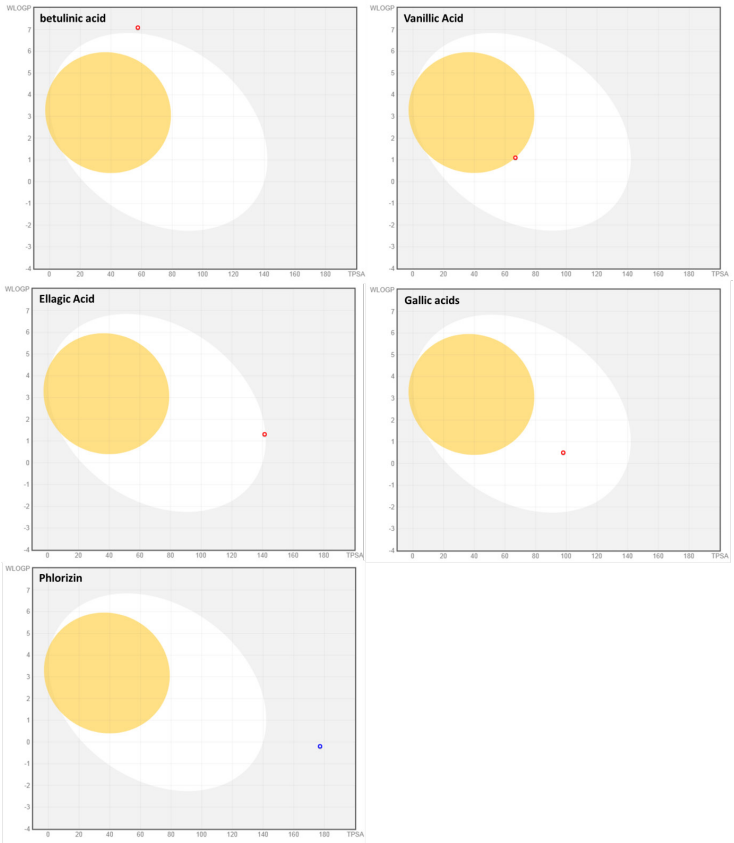


Figure 1. Illustrates the blood-brain barrier and the digestive absorption of ligands. Yellow areas indicate compounds that can pass through the barrier passively, while white areas represent those that can be absorbed by the digestive system. Blue dots represent compounds entering the central nervous system via P-glycoproteins, and red dots indicate compounds being removed by glycoproteins. This visual representation aids in understanding the complex processes involved in compound absorption and elimination within the body. The Friedelin and Vescalagin compounds are not included within the range depicted in the diagram.

use of these compounds in medical treatments (Table 3) (Figure 1.).

4. Discussion

Quercus species exhibit a wide range of beneficial properties due to their antioxidant, antibacterial, antifungal, anti-inflammatory, and anticancer components. The primary antioxidant compounds found in these species include gallic and ellagic acid, along with ellagitannins like castalagin, vescalagin, and roburin. These species have various applications in industries such as cosmetics, pharmaceuticals, and food products, and can also serve as natural disinfectants and decontaminants for chicken eggs. The antioxidant activity of Quercus species is mainly attributed to their high tannin content and polyphenol presence. Quercus extracts have been found to possess potent antioxidant properties, protecting cells from oxidative damage by neutralizing reactive oxygen species and scavenging free radicals. Additionally, Quercus species have demonstrated antileishmanial, anti-toxoplasma, antiadipogenic, vasodilatory, and antiosteoporotic effects, further expanding their potential uses in treating various health issues (1-31).

The studied compounds vary in molecular weight and heavy atom counts, which impact their solubility and membrane permeability. Friedelin, with a molecular weight of 426.72 and 31 heavy atoms, is hydrophobic and has limited solubility in physiological fluids. Betulinic Acid, with a molecular weight of 456.7 and 33 heavy atoms, is less polar than Friedelin and has higher water solubility. Va-

nillic Acid, the lightest compound at 168.15 Daltons, is highly hydrophilic. Ellagic Acid contains a hydrophobic core with aromatic rings, while Gallic Acid is soluble in water due to its polar structure. Phlorizin is large and polar, which affects its membrane permeability. Vescalagin is the largest molecule with poor solubility in physiological fluids.

The radar diagram visually represents the physicochemical properties, emphasizing polar surface area and logP values as key indicators of hydrophilicity and hydrophobicity. In terms of pharmacological properties, Vanillic Acid, Ellagic Acid, and Gallic Acid demonstrate high absorption rates, while Friedelin and Betulinic Acid have low rates. None of the compounds can cross the blood-brain barrier, and Phlorizin and Vescalagin are P-glycoprotein substrates. Ellagic Acid inhibits key enzymes in drug metabolism, potentially interacting with other medications. Gallic Acid and Betulinic Acid also show inhibitory activity against drug-metabolizing enzymes. Bioavailability scores suggest Betulinic Acid and Vanillic Acid may be effective orally. Log Kp values indicate Friedelin's high skin permeability. The synthetic accessibility of these compounds impacts their feasibility for pharmaceutical production. None of the studied compounds are BBB-permeant, which is crucial information for researchers developing treatments for CNS disorders.

5. onclusion

Understanding the physicochemical and pharmacokinetic properties of the studied compounds is crucial for future research on potential therapeutic applications, drug development, and interaction considerations. Their diverse biological effects, such as antioxidant and antimicrobial properties, underscore their significance in various industries and health-related issues.

Author's Contributions

All processes in this study were carried out by Roohallah Yousefi.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Şöhretoğlu, D., & Renda, G. (2020). The polyphenolic profile of Oak (Quercus) species: A phytochemical and pharmacological overview. Phytochemistry Reviews, 19(6), 1379-1426.
2. Sorathiya S. To Formulate Film Forming Spray using Quercus Infectoria (Oak Gall) for Wound Healing Activity. *IJISRT*. 2023;8(11): 734-762.
3. Pars A, Karadag R. Applications of laser radiation on cotton fabrics Dyed gall oak (quercus infectoria olivier). *Tekstil ve Mühendis.* 2022;29(127):161-7.
4. Elham A, Arken M, Kalimanjan G, Arkin A, Iminjan M. A review of the phytochemical, pharmacological, pharmacokinetic, and toxicological evaluation of Quercus Infectoria galls. *J Ethnopharmacol.* 2021 Jun 12;273:113592. doi: 10.1016/j.jep.2020.113592. Epub 2020 Nov 17. PMID: 33217520.
5. Askari SF, Azadi A, Namavar Jahromi B, Tansaz M, Mirzapour Nasiri A, Mohagheghzadeh A, et al. A comprehensive review about Quercus infectoria G. Olivier gall. *Res J Pharmacogn*. 2020; 7(1): 67-75.
6. Taib M, Rezzak Y, Bouyazza L, Lyoussi B. Medicinal Uses, Phytochemistry, and Pharmacological Activities of Quercus Species. *Evid Based Complement Alternat Med.* 2020 Jul 31;2020:1920683. doi: 10.1155/2020/1920683. PMID: 32802116; PMCID: PMC7415107.
7. Khatamifar M, Fatemi SJ, Torkzadeh-Mahani M, Mohammadi M, Hassanshahian M. Green and eco-friendly synthesis of silver nanoparticles

by Quercus infectoria galls extract: thermal behavior, antibacterial, antioxidant and anticancer properties. *Particul Sci Technol.* 2022 Apr 3;40(3):281-9.

8. Yusof WNSW, Abdullah H. Phytochemicals and Cytotoxicity of Quercus infectoria Ethyl Acetate Extracts on Human Cancer Cells. *Trop Life Sci Res.* 2020 Apr;31(1):69-84. doi: 10.21315/tlsr2020.31.1.5. Epub 2020 Apr 7. PMID: 32963712; PMCID: PMC7485533.

9. Burlacu E, Nisca A, Tanase C. A Comprehensive Review of Phytochemistry and Biological Activities of Quercus Species. *Forests*. 2020; 11(9):904.

10. Othón-Díaz ED, Fimbres-García JO, Flores-Sauceda M, Silva-Espinoza BA, López-Martínez LX, Bernal-Mercado AT, et al. Antioxidants in Oak (Quercus sp.): Potential Application to Reduce Oxidative Rancidity in Foods. *Antioxidants*. 2023; 12(4):861.

11. Nikitina Olha O. Pharmacognostic Study of the galls of wild representatives of Quercus robur L., created by insects. *Res J Pharm Tech*. 2021; 14(1):122-128. doi: 10.5958/0974-360X.2021.00022.6

12. Wan-Nor-Amilah WAW, Syifaa'-Liyana ML, Azlina Y, Shafizol Z, Nurul AA. In Vitro Immunomodulatory Activity of Aqueous Quercus infectoria Gall Extract. *Oman Med J.* 2021 May 31;36(3):e265. doi: 10.5001/omj.2021.63. PMID: 34113461; PMCID: PMC8167420.

13. Amilah WA, Mohamad AN, Izani NJ, Arizam MF. Antimicrobial activities of Quercus infectoria gall extracts: A scoping review. *J Herb Medicine*. 2022 Mar 1;32:100543.

14. Başyiğit B, Sağlam H, Köroğlu K, Karaaslan M. Compositional analysis, biological activity, and food protecting ability of ethanolic extract of Quercus infectoria gall. *J Food Process Preserv.* 2020 Sep;44(9):e14692.

15. Hanon NA, Abd FN. The Antimicrobial Activity of Quercus Infectoria Extracts Against Bacteria Isolated from Wounds Infection. *Al-Mustansiriyah J Sci.* . 2021 Feb. 24 [cited 2024 Nov. 17];32(1):1-4.

16. Dardmah F, Farahpour MR. Quercus infectoria gall extract aids wound healing in a streptozocin-induced diabetic mouse model. *J Wound Care*. 2021 Aug 2;30(8):618-625. doi: 10.12968/jowc.2021.30.8.618. PMID: 34382850.

17. Basri DF, Fan SH. The potential of aqueous and acetone extracts of galls of Quercus infectoria as antibacterial agents. *Indian J Pharmacol.* 2005 Jan 1;37(1):26-9.

18. Chusri S, Voravuthikunchai SP. Detailed studies on Quercus infectoria Olivier (nutgalls) as an alternative treatment for methicillin-resistant Staphylococcus aureus infections. *J Appl Microbiol*. 2009 Jan;106(1):89-96. doi: 10.1111/j.1365-2672.2008.03979.x. Epub 2008 Dec 19. PMID: 19120622.

19. Kováč J, Slobodníková L, Trajčíková E, Rendeková K, Mučaji P, Sychrová A, et al. Therapeutic Potential of Flavonoids and Tannins in Management of Oral Infectious Diseases-A Review. *Molecules.* 2022 Dec 24;28(1):158. doi: 10.3390/molecules28010158. PMID: 36615352; PMCID: PMC9821998.

20. Dsouza MR, Aishwarya BS, Supriya SS. Anticariogenic activity of galls of Quercus Infectoria Olivier against oral pathogens causing dental caries. *Int J Pharm Sci Res.* 2020;11:1711-8.

21. Mahboubi M. Quercus infectoria fruit hulls and galls and female genital disorders. Clinical Phytoscience. 2020 Jul 7;6(1):44.

21. Mahboubi M. Quercus infectoria fruit hulls and galls and female genital disorders. **Clin Phytosci**. 2020;6(1):44.

22. Mehri Ardestani M, Aliahmadi A, Toliat T, Dalimi A, Momeni Z, Rahimi R. Antimicrobial Activity of Quercus infectoria Gall and Its Active Constituent, Gallic Acid, against Vaginal Pathogens. *Trad Integr Med.* 2019;4(1):12-21.

23. Kheirandish F, Delfan B, Mahmoudvand H, Moradi N, Ezatpour B, Ebrahimzadeh F, et al. Antileishmanial, antioxidant, and cytotoxic activities of Quercus infectoria Olivier extract. *Biomed Pharmacother.* 2016 Aug;82:208-15. doi: 10.1016/j.biopha.2016.04.040. Epub 2016 May 12. PMID: 27470357.

24. Ozbilgin A, Durmuskahya C, Kayalar H, Ertabaklar H, Gunduz C, Ural IO, et al. Antileishmanial Activity of Selected Turkish Medicinal Plants. *Trop J Pharm Res* 2014; 13(12):2047-2055 doi: 10.4314/tjpr.v13i12.15

25. Mustafa H, Ismail N, Wahab WNAWA. Anti-microbial Activity of Aqueous Quercus infectoria Gall Extract against Pathogenic Leptospira. *Malays J Med Sci.* 2018 Jul;25(4):42-50. doi:

10.21315/mjms2018.25.4.4. Epub 2018 Aug 30. PMID: 30914846; PMCID: PMC6422538.
26. Zin NNINM, Mohamad MN, Roslan K, Abdul Wafi S, Abdul Moin NI, Alias A, et al. In Vitro Antimalarial and Toxicological Activities of Quercus infectoria (Olivier) Gall Extracts. *Malays J Med Sci.* 2020 Jul;27(4):36-50. doi: 10.21315/mjms2020.27.4.4. Epub 2020 Aug 19. PMID: 32863744; PMCID: PMC7444841.
27. Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, et al. PubChem Substance and Compound databases. *Nucleic Acids Res.* 2016 Jan 4;44(D1):D1202-13. doi: 10.1093/nar/gkv951. Epub 2015 Sep 22. PMID: 26400175; PMCID: PMC4702940.
28. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep.* 2017 Mar 3;7:42717. doi: 10.1038/srep42717. PMID: 28256516; PMCID: PMC5335600.
29. Daina A, Michielin O, Zoete V. iLOGP: a simple, robust, and efficient description of n-octanol/water partition coefficient for drug design using the GB/SA approach. *J Chem Inf Model*. 2014 Dec 22;54(12):3284-301. doi: 10.1021/ci500467k. Epub 2014 Nov 25. PMID: 25382374.
30. Daina A, Zoete V. A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *ChemMedChem.* 2016 Jun 6;11(11):1117-21. doi: 10.1002/cmdc.201600182. Epub 2016 May 24. PMID: 27218427; PMCID: PMC5089604.
31. Yousefi R, Mokarmian S, Jamshidi A. Efficacy of Beta-Secretase-1 Enzyme Inhibitors in Alzheimer's Disease. *J Adv Pharm Res.* 2023; 7(4): 243-250. doi: 10.21608/aprh.2023.230890.1234