A Comprehensive Review of Phytochemistry and Biological Activities of Quercus Species

Ema Burlacu 1,†, Adrian Nisca 2,† and Corneliu Tanase 2,*

1 Residency Department, “George Emil Palade” University of Medicine, Pharmacy, Sciences and Technology of Târgu Mures, 38 Gheorghe Marinescu Street, Târgu Mures, 540139 Mures, Romania; morariuemma@yahoo.com
2 Department of Pharmaceutical Botany, “George Emil Palade” University of Medicine, Pharmacy, Sciences and Technology of Târgu Mures, 38 Gheorghe Marinescu Street, Târgu Mures, 540139 Mures, Romania; adyt97@yahoo.com
* Correspondence: corneliu.tanase@umfst.ro; Tel.: +40-744-2155-43
† These authors share the first authorship.

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Abstract: The Quercus genus provides a large amount of biomaterial with many applications in fields like pharmaceutics, cosmetics, and foodstuff areas. Due to the worldwide dissemination of the genus, many species were used for centuries in traditional healing methods or in the wine maturing process. This review aims to bring together the results about phytoconstituents from oak extracts and their biological applicability as antioxidants, antimicrobial, anticancer, etc. The literature data used in this paper were collected via PubMed, Scopus, and Science Direct (2010–June 2020). The inclusion criteria were papers published in English, with information about phytoconstituents from Quercus species (leaves, bark and seeds/acorns) and biological activities such as antioxidant, antibacterial, antiobesity, anti-acne vulgaris, antifungal, anticancer, antiviral, antileishmanial, anti-diabetic, anti-inflammatory. The exclusion criteria were the research of other parts of the Quercus species (e.g., galls, wood, and twigs); lack of information about phytochemistry and biological activities; non-existent Quercus species reported by the authors. The most studied Quercus species, in terms of identified biomolecules and biological activity, are Q. brantii, Q. infectoria and Q. robur. The Quercus species have been reported to contain several phytoconstituents. The main bioactive phytochemicals are phenolic compounds, volatile organic compounds, sterols, aliphatic alcohols and fatty acids. The, Quercus species are intensely studied due to their antioxidant, anti-inflammatory, antimicrobial, and anticancer activities, provided by their phytochemical composition. The general conclusion is that oak extracts can be exploited for their biological activity and can be used in research fields, such as pharmaceutical, nutraceutical and medical.

Keywords: Quercus; oak; phenolic compounds; bark; acorn; antioxidant; antibacterial; antitumoral

1. Introduction

The Quercus genus is an evergreen or deciduous tree, belonging to the Fagaceae family. These genus contain about 450 species and represent an important tree group widespread in Europe, Asia, North Africa, North, Central and South America. The white oaks (section Quercus), live oaks (series Virentes) golden cup or intermediate oaks (section Protobalanus) and red oaks (section Lobatae) are present in America. The cycle cup oaks (subgenus Cyclobalanopsis) are found in Asia and the white oaks along with black oaks (section Cerris) are extended into Eurasia [1–3].

Quercus species are widespread in Northern Hemisphere, in temperate seasonally dry forests, and tend to be distributed in well-drained upland areas and often in montane areas and some species...
are able to tolerate some degree of flooding (Q. *lyrata* and Q. *laurifolia*). The most common deciduous broad-leaved trees are Q. *ilex*, Q. *dentata*, Q. *acutissima*, Q. *variabilis*, Q. *acuta*, Q. *glauca*, Q. *serrata* and Q. *salicina*. The most studied oaks are the European oaks, principally Q. *robur* (english oak) and Q. *petraea* (sessile oak or durmast oak) [4,5].

The *Quercus* species produce a universally known fruit (acorn) and, together with bark and leaves, has been used in traditional medicine, applied as antiseptic or in gastrointestinal disorders. Due to their nutritional role acorns are used as food for both humans and animals. The oak wood has important role in wine maturation in oak barrels and in the wood industry for the wood color, durability, and protection against fungal decay [1,6–8].

Large areas of oak forests (Europe, Asia, North Africa, North America, Central and South America), large amounts of forest waste (oak bark and leaves) resulting from wood processing, high availability and their drought resistance make *Quercus* species important sources of bioactive compounds. In the same time, the diversity of folk uses and the richness of phytochemicals found in *Quercus* species make this genus interesting for assessing biological activities and toxicological effects.

The aim of this review is to update the literature data (2010–June 2020) about phytochemistry and biological activities of *Quercus* species and to discuss their potential as antioxidants, antimicrobials, anti-inflammatories, and other activities.

2. Phytochemistry

The *Quercus* species have been reported to contain several phytoconstituents with significant differences between species due to the high variability. Even so, there are some classes of compounds that are ubiquitous in all *Quercus* species (Figure 1). The main bioactive phytochemicals are phenolic compounds, commonly found as glycosides [9]. Other compounds that can be found in *Quercus* species are volatile organic compounds, vitamins (especially vitamin E), sterols, aliphatic alcohols and fatty acids [9,10].

![Phytochemicals and biological activities of Quercus sp.](image)

**Figure 1.** The main phytochemical compounds and biological activities of *Quercus* sp.

Phenolic compounds (Figure 2) are one of the largest groups of secondary metabolites in the plants with great importance due to their occurrence and the pharmacological properties [11]. These compounds show a large diversity of structures from simple molecules (e.g., phenolic acids) to polyphenols (e.g., stilbenes, flavonoids, and derived polymers) [12]. These compounds protect
the plants against some herbivores and affect positively mammals (humans included) due to the antioxidant, antimicrobial, anti-inflammatory and anticancerogenic activities [13]. Even though, phenolic compounds display a large variety of biological activities, most of them are secondary effects of the antioxidant activity, which has several proposed mechanisms of actions. The general idea is that phenolic compounds may provide an electron to be donated or the whole hydrogen atom, from the O–H bond, to be transferred to free radical molecules, thus transforming the free radicals into harmless species. This process also transforms the phenolic into a radical, with an odd electron, but because of the aromatic structure the odd electron has the possibility to be spread over the entire molecule, resulting in a radical stabilization [14].

![Chemical structures of the main phenolic compounds found in Quercus species.](image)

**Figure 2.** Chemical structures of the main phenolic compounds found in *Quercus* species.

The investigation of phenolic compounds *Quercus* species shows their presence in all organs (leaves, bark, and acorn). There is a complex variation in the production of individual phenolic compounds across *Quercus* species. Significant differences exist between absolute and relative concentration of polyphenols. For example, the ellagitannin production in white *Quercus* leaves may be characterized as products of castalagin and vescalagin [15], whereas in the black *Quercus* species these compounds are in relatively lower amounts without derivatives. These differences between oak phenolic compounds explain ecological differences between species [15].

The phenolic compounds identified in the *Quercus* species are mostly flavonoid and non-flavonoid phenolic constituents that intermediate the phenylpropanoid metabolism by shikimate pathway [16]. The resulting hydroxycinnamic acids and esters participate in reductase, oxygenase and transferase processes, resulting in a characteristic pattern of secondary metabolites for each plant species. For example, flavan-3-ols, flavonols and acylated kaempferol glucosides were identified and quantified in *Quercus* extracts (Table 1) are phenolic acids (e.g., gallic acid, vanillic acid, syringic acid, ferulic acid, quercetin, kaempferol). These compounds are identified especially in the leaves of *Quercus glauca*, *Q. incana*, *Q. ilex*, *Q. mongolica*, *Q. salicina*, *Q. petraea*, and *Q. robur* [18–20] with differences between the quantities of each compound. In the leaves of *Quercus resina* the presence of epicatechin, vanillic, p-coumaric acid, benzoic acid, salicylic acid, syringic acid, gallic acid, p-hydroxybenzoic acid, catechin, vanillin acid, chlorogenic acid, 4-hydroxy-3-methoxybenzoic acid, and caffeic acid have been shown [21].

The *Quercus* bark can be considered a possible renewable source of bioactive compounds due to the large quantities of polyphenols. The main phenolic compounds identified in *Quercus* bark extracts (Table 1) are phenolic acids (e.g., caffeic acid, ellagic acid, gallic acid, and protocatechuic acid),
tannins (ellagitannins, roburins) and flavonoids. The *Quercus* species in which the phenolic profile of the bark extracts was analyzed are *Q. acutissima*, *Q. alba*, *Q. macrocarpa*, *Q. petrea*, *Q. robur* and *Q. sideroxyla* (Table 1). Hosam et al. [22] showed the presence in bark extracts of catechin, caffeic acid, ellagic acid, epicatechin, epigallocatechin, epigallocatechin gallate, gallic acid, and in *Q. acutissima*, the presence of caffeic acid, ellagic acid, epicatechin, epigallocatechin, gallic acid and protocatechuic acid in *Q. macrocarpa* and the presence of catechin, ellagic acid, gallic acid, protocatechuic acid and vanillic acid in *Q. robur* [22].

The *Quercus* species produce a widely known fruit, identified as an acorn [9]. Traditionally, acorns have been used in animal feed. The nutritional value and the high content in phytochemical compounds with biological activity led to the use of acorns in the human diet [23]. There are a considerable number of publications dedicated to phytochemical compounds in acorns, which are integrated in the review of Vinha et al. [23]. The main phenolic compounds identified in *Quercus* acorns extracts are phenolic acids (gallic acid, ellagic acid, and their derivatives), flavonoids (quercetin, catechin, naringin) and tannins. These compounds have been identified in acorns of *Q. brantii*, *Q. floribunda*, *Q. glauca*, *Q. incana*, *Q. mongolica*, *Q. robur* (Table 1). Thus, it is reported that *Quercus* acorns had an important content of carbohydrates, amino acids, proteins, lipids, and various sterols [24]. The terpenoid metabolites are involved in plant growth and development but predominantly for more specialized chemical interactions and protection in the abiotic and biotic environment [25]. For example, terpenes like α-thujene, α-pinene, camphene, sabinene, α-pinene, myrcene, β-phellandrene, β-terpinene, limonene, cis-β-ocimene, trans-β-ocimene, γ-terpinene, p-cymene, linalool, 3-methyl-3-buten-1-ol, 3-methyl-3-buten-1-yl acetate were identified in *Q. ilex* leaves [26] while β-arylmethane, betulinic acid, lupeol, betuline oleanolic acid, hederagenin, palmettoic acid, arjunic acid, were found in the sapwood of *Q. faginea* [27]. A study published in 2009 [28] showed that *Q. robur* emits a high amount of isoprene, but also low amounts of α-pinene, camphene, myrcene, β-pinene, in some cases 1,8-cineole and limonene could also be identified. Welter et al. [29] showed *Q. canariensis* almost exclusively emitted isoprene, while *Q. suber* exclusively emitted monoterpenes (mainly α-pinene, β-pinene, sabinene, myrcene and limonene), occasionally β-ocimene was identified in the emissions of both species, while traces of α-thujene, camphene, α-terpinene, γ-terpinene and terpinolene were found only in *Q. suber* [29].

The *Quercus* genus may also contain other compounds, like fatty acids, for example, palmitic, oleic and linoleic acids being the most abundant fatty acids in the acorns (Table 1). The kernel oil obtained from *Q. robur* and *Q. cerris* also rich in these fatty acids, stearic, arachidic and α-linolenic acids being also present, but in smaller quantities [30].

Other studies have shown that acorns may also contain vitamins (vitamin E and provitamin A) [9]. Rabhi et al. [31] showed that *Q. ilex* and *Q. suber* oils contain 2 vitamins of vitamin E, those being α-tocopherol and γ-tocopherol, the second being present in a significantly higher concentration. The same study analysed the content of sterols and aliphatic alcohols in *Q. ilex* and *Q. suber*, the major sterol being β-sitosterol followed by lower amounts of campesterol, stigmasterol, clerosterol, Δ5-avenasterol, Δ5,24-stigmastadienol, Δ7-stigmastenol and Δ7-avenasterol [31]. Similar compounds were identified in the sapwood of *Q. faginea* the most abundant aliphatic alcohol being docosanol followed by tetracosanol, octadecanol, pentacosanol, hexacosanol and hexadecanol, while the most abundant sterol was β-sitosterol; campesterol, stigmasterol, stigmastanol, γ-sitostenone and stigmastane-3,6-dione could also be identified in the sapwood of this species [27].

### 3. Biological Activity of Quercus Extracts

The ethnobotanical data show that *Quercus* spp. can be valuable plants, especially for the treatment of gastrointestinal disorders, skin and urinary tract infections (e.g., *Q. ilex*, *Quercus oblongata* D. Don) [32,33]. The *Quercus* acorns are edible (animal feed or human diet), astringent and diuretic, used in diarrhea, indigestion and asthma [23]. The wood can be used for timber, fuel or in agricultural tools (handles of plough, axes, gun buts, and walking sticks) [34,35]. Starting from ethnobotanical
results, the researchers performed numerous experiments to demonstrate the biological activity of phytochemicals found in Quercus species.

3.1. Antioxidant Activity

Due to the biomolecules variety present in different parts of oaks, their power as an antioxidant and their beneficial aspects in multiple applications has been reported [36].

Some studies showed a highly and significant correlation between phenolic contents and antioxidant activity and that may be the reason for stronger radical scavenging activities [37]. Nedamani et al. [38] concluded that antioxidant activity showed by Q. brantii extract’s reducing power is related to their total phenolic content, and Tuyen et al. [39] showed a strong correlation between phenolic content in Q. mongolica ssp. crispa leaves and bark extract and its antioxidant power. Many other studies showed the antioxidant effect of oak tannins in somatic cells beside other effects [40,41]. Kim et al. [42] reported that methanolic extract of Q. acuta showed the highest radical scavenging activity and total phenolic content, while the reducing power was the highest in the water extract. Along with the type of extract, it was showed that the radical scavenging activity was increased by increasing concentrations of Q. brantii leaf extract [43].

As to applicability, Ferreira et al. [44] revealed the protective effect of acorn extract of Q. ilex against oxidative degradation of lipids and proteins carbonylation. These effects are probably related to the intense antioxidant activity of polyphenols from acorns and so they may be used as preservatives in the alimentary industry, in nutraceutical and pharmacology activities. Another applicability of antioxidant power is noted by Horvathova et al. [45]. The Q. robur extract showed stimulation of antioxidant enzymes, decreasing damage to proteins and lipids, and a moderate increase in the total antioxidant capacity of plasma on human subjects. The authors concluded that the extract can be used as a natural supplement for improving the life quality in humans.

The most common antioxidant compounds in Quercus species are gallic and ellagic acid. Gallic acid (3,4,5-trihydroxybenzoic acid) is a most popular phenolic compound, a natural antioxidant that is basically a secondary metabolite [46]. The ellagic acid is a polyphenol that occurs largely in woody eudicotyledons plants [47]. This phenolic acid is one of the highly investigated phytochemicals, with antioxidant, antimutagenic, and anticancer properties [48]. Thus, the antioxidant activity of Quercus extract can be attributed and to gallic and ellagic acid. Other common phenolic compounds from Quercus species are ellagitannins, including castalagin, vescalagin and roburin. It has been previously demonstrated that these compounds have potent antioxidant activity [49].
Table 1. The biological activities of natural extracts obtained by *Quercus* (Fagaceae) species.

| Quercus Species: Scientific and Common Name | Raw Materials | Extract Type | Main Compounds Identified | Biological/Pharmacological Activities | References |
|--------------------------------------------|---------------|--------------|---------------------------|--------------------------------------|------------|
| *Quercus acuta* Thunb.—Japanese evergreen oak | Leaf | Hexane, Ethyl acetate, Acetone, Methanol, Ethanol, Water extract | Cinnamic acid, phytol, α-linolenic acid, α-tocopherol, β-sitosterol, β-amyрин, and friedelin-3-ol | - Antioxidant activity (methanolic extract showed the highest radical scavenging activity and total phenolic content, while the reducing power was the highest in the water extract); - Antibacterial activity against *Staphylococcus aureus*, *Salmonella typhimurium*, *Escherichia coli*, *Micrococcus luteus* and eight Meticilin Resistant *Staphylococcus aureus* (MRSA) and strains shown by ethyl acetate extract | [42] |
| | Leaf | Ethyl acetate extract | Vitamin E, loliolide, sesquiterpene (neophytadiene), triterpene (α-amyrin, friedelin), Phytosterol (stigmastanol), palmitic acid, linolenic acid, flavonoids (quercetin, luteolin, apigenin) | - Antioxidant activity; - Antihyperuricemic and xanthin oxidase inhibitory activity - Hyperuricemic mice demonstrated that leaf extract could inhibit hepatic xanthin oxidase activity and significantly alleviate hyperuricemia to a similar extent to allopurinol | [50] |
| *Quercus acutissima* Carruth.—sawtooth oak | Acorn shell | Water and methanol extract | Phenolic compounds | - Antioxidant activity; - Anti-adipogenic activity | [51] |
| | Acorn | Ethanol extract | - | - Antiobesity effect—quercus fruit extract attenuated increasing lipid droplet size in retroperitoneal fat tissue and hepatic lipid accumulation induced by high-fat diet in mice | [52] |
| | Bark | Water extract | Flavonoids, gallo-tannin, ellagittin | - Anti acne vulgaris—inhibited androgen-related pathogenesis of acne, testosterone conversion, and sebum synthesis partially through inhibition of 5α-reductase activity and testosterone-induced sebum synthesis in rats | [53] |
| | | Methanol extract | Phenolic acids (caffieic acid, ellagic acid, gallic acid, and protocatechuic acid) | - Antibacterial activity against *Pseudomonas aeruginosa*, *Bacillus cereus*, *Listeria monocytogenes*, *Escherichia coli*, *Staphylococcus aureus*, *Mariniluteicoccus flaveus*; - Antifungal activity against *Aspergillus flavus*, *Aspergillus ochraceus*, *Aspergillus niger*, *Candida albicans*, *Penicillium fenisolans*, *Penicillium ochrochloron*; - Anticancer activity against breast cancer cell line, cervical cancer cells, human T lymphocyte cells, human colon cancer cell line, human embryonic kidney cells | [22] |
| Quercus Species: Scientific and Common Name | Raw Materials | Extract Type | Main Compounds Identified | Biological/Pharmacological Activities                                                                 | References |
|-------------------------------------------|--------------|--------------|---------------------------|-------------------------------------------------------------------------------------------------------|------------|
| **Quercus alba L.—white oak**             | Bark         | Methanol extract | Ellagitannins, procyanidins, triterpenes | **Antibacterial activity against Streptococcus aureus,** *Acinetobacter baumannii,* *Klebsiella pneumoniae,* *Pseudomonas aeruginosa,* *Acinetobacter baumannii,* *Staphylococcus epidermidis;**  
**Antibiofilm activity against Staphylococcus aureus** | [54]         |
|                                          | Water extract | -            | -                         | **Antibacterial activity against Staphylococcus aureus**                                             | [55]       |
| **Quercus brantii Lindl.—Brant’s oak**    | Acorn        | Ethanol extract | Phenolic compounds | **Antiviral activity against Herpes Simplex Virus type 1 (HSV-1)**                                    | [56]       |
|                                          |              | Methanol extract | Phenolic compounds | **Antioxidant activity showed by extract’s reducing power related to their total phenolic content**    | [38]       |
|                                          |              | Ethyle alcohol extract | Phenolic compounds | **Antiproliferative activity—crude ethyle alcohol extract and the n-butanol and chloroform fractions of Q. brantii suppress the proliferation of cancer cells through induction of early apoptosis** | [57]       |
|                                          |              | Ethanol extract | Phenolic compounds | **Antioxidant activity;**  
**Antibacterial activity against *Staphylococcus aureus* and *Enterococcus faecalis***                     | [58]       |
|                                          | Powder and hydro-alcoholic extract | Phenolic compounds | -                         | **Antioxidant activity;**  
**Anti-inflammatory activity**                                                                        | [59]       |
| **Leaves**                                | Alcoholic extract | Polysaccharide | -                         | **Antioxidant activity—the radical scavenging activity was increased by increasing concentration of leaf extract;**  
**Antibacterial activity against *Salmonella typhi,* *Staphylococcus aureus;***  
**Antifungal activity against *Candida albicans,* *Flavococcus citri***                                 | [43]       |
| **Acorn**                                 | Hydro-alcoholic extract | -            | -                         | **Antifungal activity against vaginal candidiasis; results of the Q. brantii extract vaginal douche are the same as the clotrimazole vaginal cream** | [60]       |
| Quercus Species: Scientific and Common Name | Raw Materials | Extract Type | Main Compounds Identified | Biological/Pharmacological Activities | References |
|-------------------------------------------|---------------|--------------|---------------------------|---------------------------------------|------------|
| *Quercus castaneifolia* C.A. Mey—chestnut - leaved oak | Acorn | Methanol extract | - | Anti-toxoplasma activity | [61] |
| *Quercus cerris* L.—Turkey oak, Austrian oak | Seed | Water extract | flavonoids, ellagic acid, gallotannins, ellagitannins, α-tocopherol | Antioxidant activity | [62] |
| | Leaves | Water extract | - | Antibiofilm activity against *Staphylococcus aureus* | [63] |
| *Quercus coccifera* L.—kermes oak | Bark and lower stems | Methanol extract | Lignan (lyoniresinol), cocciferoside, chlorocatechin, polydatin | α-glucosidase inhibitory activity; Tyrosinase inhibitory activity | [64] |
| *Quercus crassifolia* Bonpl.—mexican oak | Bark | Ethanol and water extract | Polyphenols (flavonoids, hydroxycinnamic acids) | Antioxidant activity | [65] |
| | | | | Antioxidant activity; Antibacterial activity against *Escherichia coli*; Toxic activity on kidney was observed associated with short-term repeated administration of *Q. crassifolia* bark extract in rats | [66] |
| *Quercus mongolica* ssp. *crispula* (Blume) Menitsky—mizunara | Leaves and bark | Ethanol extract | Ellagic acid, chlorogenic acid, benzoic acid | Antioxidant activity—strong correlation between phenolic content in studied extract and its antioxidant power | [39] |
| | Leaves | 80% acetone extract | - | Potent anti-inflammatory activity; Anti-Acne Vulgaris Effects | [67] |
| *Quercus floribunda* Lindl. Ex A. Camus | Acorn | Water, Methanol, N-Hexane, Chloroform extracts | Flavonoids, quercetin, gallic acid, catechin and chlorogenic acid, pyrocatechol | Antioxidant activity; Anticancer activity against human liver cancer cell line and monocytic leukemia cell line; Antibacterial activity—mildly active against *Bacillus subtilis, Escherichia coli, Klebsella pneumoniae* and *Staphylococcus aureus*; Antidiabetic activities—mild to moderate α-amylase inhibition; Antileishmanial activity | [68] |
| Quercus Species: Scientific and Common Name | Raw Materials | Extract Type | Main Compounds Identified | Biological/Pharmacological Activities | References |
|------------------------------------------|--------------|--------------|---------------------------|--------------------------------------|------------|
| Quercus gilva Blume—red-bark oak         | Leaves and bark | Aqueous acetone extract | Cathechins, tannins | - Antioxidant activity; - Anti-uro lithiasis effect | [69]       |
| Quercus glauca Thunb.—ring cupped oak, Japanese blue oak, | Bark | Ethanolic extract | Lignans, lignanoids, triterpenoids, flavonoids | - Antioxidant activity | [70]       |
| Quercus ilex L.—evergreen oak, holy oak | Acorn pulp | Acetone and water extract | Phenolic compounds | - Antioxidant activity | [44]       |
| | Acorn | Water extract | Phenolic compounds | - Antidiarrheal activity | [71]       |
| | Leaves | Hydro-methanol extract | Phenolic acids—(gallic, protocatechuic, ellagic acid derivatives, and ellagic acid), flavonoids, (catechin, epicatechin, and quercetin) | - Ant-inflammatory activity—extract decreased neutrophil infiltration and reduced the inflammatory cytokines in ulcerative colitis rats | [72]       |
| | Bark | Water and methanol extract | Flavonoids, catechins | | | |
| Quercus incana Bartran—bluejack oak, cinnamon oak | Bark | Methanol extract | Flavonoids, tannins | - Antioxidant activity; - Antibacterial activity against Bacillus subtilis, Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli; - Antifungal activity against Candida glabrata, Candida albicans, Aspergillus niger, Aspergillus flavus, Fusarium solani, Microsporus canis | [74]       |
| | Leaves | Chloroform, Methanol n-hexane extract | Flavonoids (eupatorin), triterpene (betulin) | - Anticancer activity—inhibition observed by betulin against large cells lung cancer was dose- and time-dependent; betulin has completely eradicated cancer cells even after 15 days of incubation in culture media during colony formation assay compared to the control | [75]       |
| Quercus infectoria G. Olivier—aleppo oak | Acorn | Ethanolic extract | Phenolic compounds | - Anti-biofilm activity on MRSA and MSSA (Meticilin Susceptible Staph. aureus) | [76]       |
| | Methanolic extract | Tannins, phenols and flavonoids | | - Antioxidant activity | [77]       |
| | Ethanol and water extract | p-hydroxybenzoic acid, pyrogallol, catechol, caffeine, catechine, e-vanillic, 3-hydroxythyrno-sol, naringin, rutin | | - Antibacterial activity against Escherichia coli, Salmonella Typhimurium, Pseudomonas aeruginosa, and Staphylococcus aureus; - Antifungal activity—against Candida albicans | [78]       |
| Quercus Species: Scientific and Common Name | Raw Materials | Extract Type | Main Compounds Identified | Biological/Pharmacological Activities | References |
|------------------------------------------|--------------|--------------|---------------------------|--------------------------------------|------------|
|                                          |              | Water extract | Tannins                   | Antibacterial activity against MRSA through interference of various metabolism and function of the bacterial proteome | [79]       |
|                                          |              | Methanol extract | Alkaloids, flavonoids, steroids, tannins | Analgesic activity | [80,81] |
|                                          |              | Water extract | -                         | Anti-inflammatory activity and non-toxic activity on acute and chronic administration in rats | [82]       |
| Bark                                    |              | Acetone extract | Phenolic compounds | Anti-quorum sensing activity—reduced the pyocyanin, protease, elastase production and biofilm formation in *Pseudomonas aeruginosa* | [83]       |
|                                          |              | Hidroalcoholic extract | - | Antiangiogenic activity—the extract prevented the formation of endothelial tubular structures by endotelial cells, inhibited the ability of cellular migration and decreased the vascular endothelial growth factor secretion | [84]       |
| Acorn                                   |              | Acetone and methanol extract | - | Antibacterial activity of acorn extract in combination with Vancomycin against two strains of MRSA. The time-kill curves showed a faster killing rate than Vancomycin alone and a synergic interaction | [85]       |
|                                          |              | Ethanol extract | -                         | Antifungal activity against *Candida albicans* compared with fluconazole | [86]       |
|                                          |              | Aqueous extract | -                         | Antibiofilm activity against *Pseudomonas aeruginosa* | [87]       |
|                                          |              | Ethanol extract | Phenolic acids (tannic acid, gallic acid, ellagic acid), flavonoids | Anti-inflammatory activity—extract treatment ameliorated the inflammatory phenotype of bone marrow derived macrophages induced by prediabetic or diabetic environments | [88]       |
|                                          |              | Water extract | Gallic acid, syringic acid | Antiosteoporotic—*Q. infectoria* semipurified fractions combined with osteoporotic drug pamidronate induce bone formation in human fetal osteoblast cell model, and increase the efficiency of pamidronate acting on osteoblast cell. | [89]       |
| Quercus Species: Scientific and Common Name | Raw Materials | Extract Type | Main Compounds Identified | Biological/Pharmacological Activities | References |
|------------------------------------------|--------------|--------------|---------------------------|---------------------------------------|------------|
| Quercus laurina Bonpl.—mexican oak       | Bark         | Ethanollic and water extract | - | - Antioxidant activity | [65] |
|                                          | Bark         | -            | Mono-terpenoids (1,8-cineol, γ-terpine), sesquiterpenoids, aliphatic aldehydes | - Antimicrobial activity and sinergic effect against *Streptococcus pyogenes* | [90] |
| Quercus oblongata D. Don—banj oak        | Acorn        | -            | Palmitic and stearic acids | - Antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* | [91] |
|                                          | Leaves       | -            | Carbohydrates, protein | - Nutritional support for sustaining the minimal level of production (milk, meat) and increased food intake, nutrient digestibility in winter time on cattle | [92] |
| Quercus macrocarpa Michx.—bur oak        | Bark         | Methanol extract | Caffeic acid, ellagic acid, protocatechuic, gallic acid, epicatechin, epigallocatechin | - Antioxidant activity; - Antibacterial activity against *Pseudomonas aeruginosa*, *Bacillus cereus*, *Listeria monocytogenes*, *Escherichia coli*, *Staphylococcus aureus*, *Mariniluteicoccus flaveus*; - Antifungal activity against *Aspergillus fischeri*, *Aspergillus ochraceus*, *Aspergillus niger*, *Candida albicans*, *Penicillium feniculorum*, *Penicillium ochrochloron*; - Anticancer activity against breast cancer cell line, cervical cancer cells, human T lymphocyte cells, human colon cancer cell line, human embryonic kidney cells | [22] |
|                                          | Leaves       | Acetone extract | Tannins, flavonoids | - Anti-inflammatory activities | [93] |
|                                          | Leaves       | Acetone extract | Catechin, epigallocatechin, quercetin, kaempferol, glucopyranoside | - Antioxidant activity | [94] |
| Quercus mongolica Fisch. ex Ladeh.—Mongolian oak | Acorn (cups) | Ethanol extract | Ellagic acid, kaempferol | - Hypoglycemic activity. After 15 days of oral administration in alloxan-induced diabetic rats, fasting blood glucose levels, cholesterol and triglyceride levels were significantly decreased; - Antioxidant activity; - Superoxide dismutase activity in heart, liver, spleen and kidney were significantly improved | [95] |
| Quercus Species: Scientific and Common Name | Raw Materials | Extract Type | Main Compounds Identified | Biological/Pharmacological Activities | References |
|-------------------------------------------|--------------|--------------|---------------------------|--------------------------------------|------------|
| **Quercus petraea (Matt.) Liebl.—sessile oak** | Twigs, leaves, acorn | Water extract | Catechin, tannins, flavonoids, proanthocyanidin | Antioxidant activity | [1] |
| | Bark | Alcohol extract | Tannins (vescalagin, castalagin, grandinin and roburin E) | Antioxidant and antiinflammatory activity | [96] |
| **Quercus phillyreoides A.Gray—ubame oak** | Bark | Water extract | Alkaloids, flavonoids, saponins, tannins, terpenoids, antraquinone | Antifungal activity against Lasiodiplodia theobromae, Aspergillus niger, Sclerotium rolfsii, Penicillum oxalicum, Rhizoctonia solani, Fusarium oxysporum | [97] |
| **Quercus pyrenaica Wild.—Pyrenean oak** | Bark | Water/acetone and methanol extract | Vescalagin, castalagin, grandinin and roburin E | nutraceutical and cosmetic applications | [98] |
| **Quercus robur L.—common oak/pedunculate oak/European oak/English oak** | Bark | Water extract | Gallic acid, ellagic acid, castalin/Vescalin granidinin/roburin E | Antioxidant activity | [99] |
| | | Tannins (roburins) | Improvement in energy, tiredness and tension level associated with reduction of oxidative stress | | [100] |
| | | Phloroglucinol dihydrate, 4-propylresorcinol, pyrogallol | Antibacterial activity against Chromobacterium violaceum | | [101] |
| | | Carotenoids, proanthocyanidin, tannins, flavonoids | Antioxidant activity | | [1] |
| | Bark | Water extract | | Antioxidant activity | | [102] |
| | | Roburins | Antioxidant activity | | [45] |
| | | Ellagitanins | Antiinflammatory activity | | [103] |
| | | Ellagic acid | Antioxidant activity | | [104] |
| | Acorn | Water extract | | Antioxidant activity | | [105] |
| | Bark | Water extract | vanillin, coniferaldehyde, acetovanillone and syringaldehyde | Flavouring activity of grapewine | [106] |
| Quercus Species: Scientific and Common Name | Raw Materials | Extract Type | Main Compounds Identified | Biological/Pharmacological Activities | References |
|-------------------------------------------|--------------|--------------|---------------------------|--------------------------------------|------------|
| **Quercus Species:**                      |              |              |                           |                                      |            |
| **Scientific and Common Name**            |              |              |                           |                                      |            |
| **Methanol extract**                      |              |              | Alkaloids, anthraquinones, saponins, tannins and terpenoids | - Antioxidant activity; - Antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis* and *Bacillus subtilis* | [107]      |
| **Ellagic acid, gallic acid, protocatechuic acid and vanillic acid** |              |              |                           | - Antioxidant activity; - Antibacterial activity against *Pseudomonas aeruginosa*, *Bacillus cereus*, *Listeria monocytogenes*, *Escherichia coli*, *Staphylococcus aureus*, *Mariniluteococcus flavus*; - Antifungal activity against *Aspergillus flavus*, *Aspergillus ochraceus*, *Aspergillus niger*, *Candida albicans*, *Penicillium fenisuliform*; - Anticancer activity against breast cancer cell line, cervical cancer cells, human T lymphocyte cells, human colon cancer cell line, human embryonic kidney cells and human urinary bladder cancer cells | [22]      |
| **-**                                     |              |              |                           | Production of styrene by cultivating a fungus (*Penicillium expansum*) on forest waste biomass (oak bark) as a feeding substrate along with potato dextrose and yeast extract | [108]      |
| **-**                                     |              |              |                           | Supplementation of diets in dairy cows with *Q. robur* extract reduced urinary N excretion and increased the concentration of α-linoleic acid in milk | [109]      |
| **Acorn**                                 | Methanol/water extract | Phenolic compounds |                           | Inhibitory effect on α-synuclein fibrillation, protein that its fibrillation is the causative factor of Parkinson’s disease | [110]      |
| **Bark**                                  | Ethanol extract |              | Gallic acid, castalagin, vescalagin, granidin, roburin E | - Antidiabetic activity determined by α-glucosidase inhibition assay | [111]      |
| **Quercus salicina Blume**                | Leaves and bark | Ethanol extract | Gallic and vanillic acids, flavonoids | - Antioxidant activity | [39]      |
|                                           |              |              |                           | - Vasodilatator effect on porcine endothelium coronary artery | [112]      |
Table 1. Cont.

| Quercus Species: Scientific and Common Name | Raw Materials | Extract Type | Main Compounds Identified | Biological/Pharmacological Activities | References |
|--------------------------------------------|---------------|--------------|---------------------------|---------------------------------------|------------|
| Quercus scytophylla Liebm.—mexican oak     | Bark          | Ethanolic and water extract | -                         | - - Antioxidant activity              | [65]       |
| Quercus serrata Murray—jolcham oak         | Leaves and bark | Ethanol extract | syringic acid, cinnamic acids, flavonoids | - Antioxidant activity | [39]       |
|                                            | Seeds         | Ethanol extract | Triterpenoid comounds fractions | - Anti-neuroinflammatory activity   | [113]      |
| Quercus sideroxyla Bonpl.                  | Bark          | Ethanol extract | Gallic acid, catechin, epicatechin, gallocatechin, dimeric procyanidins | - Antihiperglycemic activity—maintaining the glucose levels to more stable levels by inhibiting the α-amylase enzyme | [114,115] |
|                                            | Aqueous acetone extract | Gallic acid, catechin, epicatechin, gallocatechin, procyanidins, proanthocyanidins | - Antioxidant activity | [114]       |
| Quercus suber L.—cork oak                  | Bark          | Hidroalcoholic extract | Gallic acid, ellagic acid, vescalagin, castalagin, B-O-ethylvescalagin | - Antioxidant activity              | [116]      |
|                                            | Acetone extract | Phenolic acids, proanthocianidins, | - Antifungal activity against *Trichophyton verrucosum*, *Trichophyton mentagrophytes* | [37]       |
|                                            | water extract | - | - Antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* | [117]       |
| Quercus variabilis Blume—Chinese cork oak  | Acorn cups and shell | Ethanol and water extract | Ellagic acid, tannins | - Antioxidant activity; - Antibacterial activity against *Staphylococcus aureus*, *Salmonella paratyphi*, *Salmonella typhimurium*, *Salmonella enteritidis*, *Listeria monocytogenes* | [118]       |
3.2. Antibacterial and Antifungal Activity

Since ancient times, the traditional use of oak bark in medicine field was well known and applied topically to burns and wounds to prevent infection, or applied orally for gastrointestinal diseases. The Quercus extract (especially bark extract) contains important antimicrobial compounds such as gallic acid, ellagic acid, vescalagin or castalagin [119,120]. Due to its history of antibacterial uses, Deryabin and Tolmacheva [101] used Q. robur cortex against Chromobacterium violaceum. The results showed an anti-quorum sensing effect determined by the extract’s bioactivity.

The antimicrobial activity is sustained by diverse results of experiments reported against Streptococcus aureus, Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa. Thus, Q. alba bark extracts inhibited growth in the strains of Acinetobacter baumannii and growth of Staphyloccus epidermidis and showed antibiofilm activity against Staphyloccus aureus [54]. Not only the oak bark but the leaves of Q. brantii have antibacterial and antifungal activity, as shown by Tahmouzi [43]. Acorn extract of Q. brantii showed antifungal activity against vaginal candidiasis [60] and Q. floribunda acorn extract showed mildly antibacterial activity against Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus.

The antibacterial and antifungal activity can be the result of extract type, harvesting time, oak tree species, and the instrument quality and measurement methods. Tayel et al. [86] showed the antifungal activity against Candida albicans of the Q. infectoria acorn ethanolic extract. The acorns are concentrated in tannins (ellagitannins) more than other parts of oak trees and the antibacterial and antifungal activity can be attributed to these compounds [76]. Tannins have been shown to inhibit growth in a wide range of bacteria, fungi and viruses, inactivating the microbial enzymes, sequestering essential metal ions in complexes and inhibition of membrane transport [121]. Zhou et al. [118] showed antibacterial activity of Q., variabilis acorn extract, destroying the bacteria’s wall cell and inhibits their normal growth and cellular metabolism. Khairon et al. [79] showed the antibacterial activity against MRSA of Q. infectoria acorn water extract through the interference of various metabolisms and functions of the bacterial proteome. Tannins also act as biofilm inhibitors by binding to matrix proteins [122]. Chusri et al. [76] highlighted the anti-biofilm activity on MRSA and MSSA due to Q. infectoria extract effect on Staphilococcus aureus cell wall and cell surface hydrophobicity.

Another use of oak extracts is in the cosmetic and pharmaceuticals industries [90], or in alimentary industry. The Quercus extract can be applied as a natural disinfectant and decontaminant for chicken eggs or for helping farmers to avoid fungicides due to their human and environmental hazards [97].

3.3. Anti-Inflammatory and Anticancer Activity

Along the time, more anticancer treatment were developed, but recently the evolving of cancer resistancy and side effects of the chemoterapic therapy, demands new chemicals with high potency, low side effects, and high selectivity at molecular level [75].

The Quercus genus is intensely studied due to its high potency against inflammation and proliferation of cancer cells. The main anticancer compounds identified in Quercus species are ellagic acid, kaempferol and its glycosides, quercetin, myricetin [123–126]. Farhad et al. [57] describe antiproliferative activity of Q. brantii crude extract that suppresses the proliferation of cancer cells through induction of early apoptosis as mechanism. The betulin compound found in Q. incana leaves extract by Hasan et al. [75] has completely eradicated large cells’ lung cancer even after 15 days of incubation in culture media during colony formation assay compared to the control. Different cancer cells as MCF-7 (breast cancer cell line), HeLa (cervical cancer cells), Jurkat (human T lymphocyte cells), HT-29 (human colon cancer cell line), HEK 293 (human embryonic kidney cells) and T24 (human urinary bladder cancer cells) were tested by Elansary et al. [22] with great regression done by Q. macrocarpa and Q. robur bark extracts.

There are several studies showing anti-inflammatory activity. Castejón Martínez et al. [72] describe that phenolic extracts from Q. ilex leaves decreased neutrophil infiltration and reduced the inflammatory cytokines in TNBS-induced ulcerative colitis rats. Chokpaisarn et al. [88] have described the Q. infectoria
acorn extract amelioration of inflammatory phenotype of bone marrow-derived macrophages induced by prediabetic or diabetic environments, potentially by inhibiting the Set-7/NF-κB pathway.

The phenolic compounds (e.g., ellagic acid) improves anti-inflammation through isolated compounds from Q. mongolica bark extract which showed inhibitory activities towards inflammatory cytokines and chemokines induced in ultraviolet B (UVB)-irradiated keratinocytes by increasing the cell migration ability of cells and enhancing their regeneration when exposed to UVB, and these compounds can be further developed for treating the chronic inflammatory skin diseases, like atopic dermatitis and psoriasis [127].

3.4. Antidiabetic Activity

Diabetes mellitus is a metabolic disorder distinguished by a failure of glucose homeostasis with disturbances of carbohydrate, fat and protein metabolism as a result of defects in insulin secretion [128]. Phloridzin is a dihydrochalcone glycoside detected at higher concentrations in Quercus leaves, (e.g., Q. resino) [129]. This compound is recognized for its astringent properties and antidiabetic effects [129]. For example, an effect of Q. coccifera bark extracts is inhibition of α-glucosidase. This effect could be important in the treatment of diabetus mellitus, as Sari et al. [64] and Muccilli et al. [111] concluded. The other antidiabetic phenolic compounds from Quercus species can be ellagic acid, rutin or vescalagin [127,130,131]. The Q. floribunda acorn extract has mild to moderate α-amylase inhibition and this strategy is an essential target to manage blood glucose level in noninsulin dependent diabetes mellitus, as found by Soto et al. [115]. Another way to treat diabetes is observed after 15 days of oral administration of Q. mongolica acorn extract in alloxan-induced diabetic rats by Yin et al. [95]. They reported a hypoglycemic activity, but also the fasting blood glucose, cholesterol and triglyceride levels were significantly decreased.

Thus, the significant antidiabetic effect of the Quercus phenolic compounds could be due to the presence of the phenolic compounds, which could act synergistically or independently to enhance the activity of glycolytic enzymes.

3.5. Other Activities

Wine taste is clearly defined by the infusion of phytochemical components found in Quercus species such as Q. petraea, by Sindt et al. [132], who determined that the taste of three compounds extracted from oak bark, that were described for their bitterness and their influence in wine and brandy, increased in bitterness during oak aging. Jiménez-Moreno et al. [106] exhibit more clearly that the wine flavor which was in contact with oak bark displayed a more intense wood and spicy aroma, and more body and persistence in the mouth than the control wine, obtained after applying the toasted oak extract of Q. robur.

Antileishmanial activity against Leishmania tropica by Q. floribunda was studied with interest by Kheirandish et al. [77] who found that promastigotes treated with oak extracts were able to infect only 33.2% of the peritoneal macrophages and their infectiveness reduction was 51.3%. After 4 weeks of Q. infectoria acorn extract treatment, a decrease in the number of parasites compared to the control group was observed. Daryani et al. [61] showed anti-toxoplasma activity of Q. castaneifolia acorn methanolic extract by increasing the survival rate of the mice compared to the mice in the untreated infected control.

Antiadipogenesis is crucial for the prevention of obesity because adipogenesis occurs progressively throughout human life [133]. The antiadipogenic activity was revealed by Q. acutissima acorn extract, which decreased the intracellular lipid droplets in fat tissue and hepatic lipid accumulation and downregulates the diglyceride acyltransferase 2 gene expression as found by Youn et al. [51] and Hwang et al. [52]. The Youn et al. [51] speculated that inhibitory activities of aqueous/methanolic Q. acutissima acorn extracts and particularly the gallic acid, is mediated by regulation of the cell cycle and insulin signaling in the early stage of adipogenesis. Therefore, further study regarding the precise mechanism for the anti-adipogenic activity of acorn shell extracts is required.
Antiacne activity was found by Koseki et al. [53], which explained that *Q. acutissima* bark extract inhibited androgen-related pathogenesis of acne through inhibition of α-reductase activity in testosterone-induced sebum synthesis in rats.

*Q. brantii* acorn ethanol extract showed antiviral activity against HSV-1 (Herpes Simplex Virus type 1) by modulating the replication mechanism as suggested by Karimi et al. [56].

One of the interesting effects is shown by *Q. salicina* leaves and bark extract as the vasodilatator effect on porcine endothelium coronary artery, experienced by Park et al. [112]. *Q. gilva* leaves and bark extract inhibits the development of urolithiasis in the animal models, as described by Youn et al. [69], and *Q. infectoria* can be used as analgesic for mild pain relief [79] or for its antiosteoporotic activity, shown by Abdullah et al. [89].

The nutritional role is reminded by Paswan and Sahoo [92] for sustaining the minimal level of production (milk, meat) in wintertime by using *Quercus oblongata* leaves’ extract.

Finally we have some reports regarding the toxicity of obtained extracts. The *Q. infectoria* acorn water extract showed non-toxic activity on acute and chronic administration in rats and no significant adverse effects [82]. One the other hand, the *Q. crassifolia* bark water extract appears to have toxic activity on kidney and was associated with short-term repeated administration in rats, as Valencia et al. [65] discovered.

4. Conclusions and Future Directions

This review unified results about biological activities of *Quercus* extracts and its isolated compounds. Most bioactivity studies were focused on antioxidant, antimicrobial and anticancer effects. Thus, the *Quercus* extracts are a great source of phytoconstituents, especially polyphenols. The general conclusion of scientists is that these extracts can be exploited for their antioxidants, antimicrobial and anticancer potential activities and can be used in diverse research fields, such as pharmaceutical, nutraceutical, medical, and for improving the wine sensory quality. Most of the pharmacological effects of *Quercus* genus can be explained by the high amount of phenolic compounds’ content, especially tannins and their antioxidant potential. The pharmacological studies have mostly been performed in vitro and in vivo, and clinical studies are very limited. Thus, clinical studies are needed to confirm in vitro and in vivo results for a rational use in phytotherapy. These studies should be continuously developing newer techniques for treating multidrug resistance and quorum sensing activity as a bacterial biofilm formation. New anticancer therapies should be continuously developed because of the tendency of resistance to classical treatments. That is why more studies should concentrate on in vivo experiments. More studies are needed to show the link between the chemical compound and bioactivity and to discuss their action mechanism. Even if *Quercus* products are generally safe, more toxicological data are needed.

Large areas of oak forests, large amounts of forest waste (oak bark and leaves) resulting from wood processing, high availability and their drought resistance make *Quercus* species important sources of bioactive compounds.

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