A Comprehensive Review on Pharmacological activity of *Quercus* species

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Abstract:

Quercus species represent a significant group of evergreen or deciduous trees from temperate and tropical climatic areas. Quercus species are mostly known as oak and belong to family of the Fagaceae. Quercus leucotrichophora is a medium-sized tree, usually attaining about 15 m in height, occasionally 24 m. It is widely distributed in temperate forests of the northern hemisphere and tropical climatic areas. Many of its members have been used in traditional medicine to treat and prevent various human disorders such as asthma, hemorrhoid, diarrhea, gastric ulcers, and wound healing. The multiple biological activities including anti-inflammatory, antibacterial, hepatoprotective, antidiabetic, anticancer, gastroprotective, antioxidant, and cytotoxic activities have been ascribed to the presence of bioactive compounds such as triterpenoids, phenolic acids, and flavonoids. This paper aimed to provide available information on the medicinal uses, phytochemicals, and pharmacology of species from Quercus. However, further investigation is needed to fully clarify the mode of action of its bioactive compounds and to evaluate in vivo chronic toxicity, before exploring their potential use as a supplement in functional foods and natural pharmaceutics.

***Keywords**: Quercus species; Pharmacological Activity; Phytochemistry; Hepatoprotective; Anti-inflammatory.*

1. Introduction:

Quercus species represent a significant group of evergreen or deciduous trees from temperate and tropical climatic areas. Quercus leucotrichophora is a medium-sized tree, usually attaining about 15 m in height, occasionally 24 m (Sati et al., 2016). Seedlings under two years old are very shade-tolerant, but beyond that, the tree needs moderate to full sun. Although it thrives in relatively rich soils, such as clays generated from shale and clay loams, the plant does not fare well in arid areas. Ripe seed may linger on trees for many months after it has ripened since the timing of when it matures varies from region to region. The banj oak grows in the Himalayas at elevations ranging from 1500 to 2400 metres above sea level. (Kumar et al., 2011).

1.1 Morphology: Quercus lucotrichophora Full, rounded canopies characterise A. Camus. At first, the bark is smooth and tan-brown, but it becomes somewhat furrowed and corky as it ages. Ovals with sharp teeth form the leaves, alternately arranged on the stems. White hairs on the underside of the leaves give the leaves a silvery grey appearance as they grow (hence the name leucotrichophora, meaning "which has white hairs"). On the tops of the branches, the male inflorescences (catkins) are found, while the small spherical female flowers may be seen on the underside of the leaves. The acorns are orange-tan and the size of marbles. (Joshi &Juyal, 2017; Semwal et al., 2018).

1.2 Chemical constituents: Quercus plants contain various secondary plant metabolites, including terpenoids, flavonoids, phenols, steroids, tannins (ellagitannins and hydrolysable tannins), and many others. Standard flavonoid quercetin and its 3-O-disaccharide have been reported from the leaves of Q. leucotrichophora. The flavonoids, namely 7-methoxy kaempferol, 3-O-[{α-l rhamnopyranosyl-(1‴ → 4″)} {α-l-rhamnopyranosyl-(1″″ → 6″)}]-β-d-glucopyranosyl quercetin and flavon-5, 3′,4′-trihydroxy 7-O-β-d-glucopyranosyl (6″ → 1″)-β-d-glucopyranoside have also been isolated from the stem bark of Q. leucotrichophora. The gas chromatography-mass spectroscopy (GC–MS) analysis of a volatile extract of stem bark of Q. leucotrichophora showed the presence of 86.36% monoterpenoids, 6.53% sesquiterpenoids and 0.11% of aliphatic aldehydes. The GC–MS study of fruits oil of Quercus brantii growing in southwestern Iran revealed the presence of oleic acid (52.99–66.14%), linoleic acid (10.80–11.11%), Palmetic acid (8.08–10.06%), stearic acid (0.74–1.57%), α-linolenic acid (0.19–0.35%), erucic acid (0.12–0.15%)and arachidic acid (0.12–0.15%). (Sati et al., 2016).

1.3 Geographical distribution: Quercus leucotrichophora is distributed in Northern India, Nepal, Myanmar, Pakistan, and Sri Lanka. In Nepal, it naturally occurs at 1,500–2,700 metres (4,900–8,900 feet) in forested areas associated with Rhododendron arboreum, Lyonia ovalifolia, and Myrica esculenta. (Manandhar et al., 2002); (Thadani et al.,1995).
It is found in Himalayas Mountain in Pakistan, particularly in Dir, Chitral, Swat, Hazara, Tirah, Kurram Agency, Murree Hills and Azad Kashmir.In Northern India, found in central Himalaya Mountain of Uttarakhand and Himachal Pradesh. Quercus leucotrichophora is commonly known as Banjh oak, Banj oak (Uttarakhand) and Ban oak (Himachal). In Nepal,

it is known as Banjhi, Rainj, Khasarant, Tikhebhanjh in standard Nepali and Sulsing in Tamang language. (Dhyani et al., 2020)

1.4 Traditional uses:

1. Banj oak is a primary source of fuel supply and a large fodder tree in the Himalayan region. QL leaves, seeds and bark are used in the human and animal health care system(Ajo et al., 2013).
2. The seeds act as astringent, diuretic agents, and urinary disorders and are also used in treating indigestion, diarrhoea and asthma in humans (Semwal et al., 2018).
3. The bark of the plant (25g in 100ml) is used as a gargle for tonsillitis and to cure toothache and piles. (Kumari et al., 2011)
4. The leaves are used as an astringent in treating diarrhoea, while the gum resin is used for Stomachache. (Joshi &Juyal, 2017)
5. The gum resin of the plant by making its paste to cure Gonorrheal, asthma, haemorrhages, diarrhoea, and dysentery and the dry resin is taken with water for stomach pain (Sati et al., 2016).

2. Pharmacological Activities: Researchers have validated the usage of several species within the Quercus genus as medicinal treatments due to their investigation into the biological activities traditionally attributed to the Quercus species. Extracts and single compounds have been shown to display a variety of pharmacological actions, such as antioxidant, antibacterial, anti-inflammatory, and cytotoxic activity, according to the research conducted.

2.1 Antioxidant activity: It has been shown that members of the Quercus genus exhibit antioxidant activity. Arina and Harisun conducted research (Arina et al., 2019) in which they investigated the impact that different extraction temperatures had on the tannin content and antioxidant activity of Quercus infectoria (Manjakani). The results indicate that the extract has a high DPPH scavenging ability, as measured by an IC50 value of 0.064 mg/ml when extracted at a temperature of 75 degrees Celsius. Another research demonstrated that the Thermo treatment and extraction method significantly impacted the amount of antioxidant activity that Quercus cerris L. wood possessed (Cetera et al., 2019). Using three different solvents, researchers looked at the antioxidant capabilities of the leaves and acorn of the Q. super tree (hexane, methanol, and water). In this particular instance, the DPPH and ABTS tests revealed that the aqueous extracts exhibited the most significant levels of antioxidant activity. In the acorn extracts, phytochemical components such as phenolic compounds have been hypothesised to be responsible for this antioxidant effect (Tejerina et al., 2011). To provide one example, Sánchez-Burgos et al. (Sánchez-Burgos et al., 2013) demonstrated that aqueous extracts derived from the leaves of several white Quercus species (Q. grisea, Q. Laeta, Q. obtusata, and Q. resinosa) displayed strong radical scavenging ability against (DPPH) and HO• radicals.

2.2 Activity against harmful bacteria: Investigations on the antibacterial properties of Quercus have been conducted using Gram-positive and Gram-negative bacteria and multidrug-resistant bacterial pathogens as test subjects. An aqueous extract of the leaves of four different species of white oaks (Quercus resinosa, Quercus Laeta, Quercus grisea, and Quercus obtusata) was tested for its antimicrobial activity against a variety of bacteria and yeast, including Escherichia coli, S. epidermidis, K. pneumoniae, P. mirabilis, P. Hauser, and P. Vulgaris (C. Albicans). In addition, they observed that every aqueous extract of oak that was examined showed signs of being susceptible to K. pneumoniae (ATCC 13883). These researchers also reported that Q. resinosa and Q. grisea demonstrated antimitotic activity against these organisms (Sánchez-Burgos et al., 2013). On the other hand, Bahador and Baserisalehi (Bahador et al., 2011) investigated the antibacterial activity of the fruit of Q. castaneifolia against Gram-negative bacteria (E. coli, Salmonella typhimurium, and Shigella dysent S. dysenteriae were more sensitive than other strains, with a zone of 18 millimetres and a minimum inhibitory concentration (MIC) value of 2.5 x 10-4. The MIC values for E. coli extracts were the lowest of any tested organism. The antibacterial activity of a gold nanoparticle generated from the leaves of Quercus incana was assessed against human pathogens in research conducted by Sarwar et al. (Sarwar et al., 2018). (Pseudomonas pickettii, Salmonella setubal, Staphylococcus aureus, Bacillus subtilis, Aspergillus flavus, and Aspergillus niger). The findings demonstrated improved antibacterial efficacy against the whole spectrum of bacterial infections. In addition, ethanolic extracts of Q. persica were tested against S. aureus, B. subtilis, E. coli, and K. pneumoniae. All of these bacteria were shown to be susceptible to the extracts (Nourafcan et al., 2013)

2.3 Cytotoxic and Anticancer Activity: The cytotoxic and anticancer activity of a broad range of extracts from Quercus species has been established by several studies against various cancer cell lines. The cytotoxicity of the MeOH and water extracts of the barks of Quercus cerris var. cerris, Quercus macranthera subsp. syspirensis and Quercus aucheri were tested on the Hep-2 human larynx epidermoid carcinoma cell line. The results showed that all three of these bark extracts exhibited significant cytotoxicity. According to the findings, the aqueous and methanolic extracts of Q. macranthera subsp. syspirensis showed the highest level of cytotoxicity against the tested cell line, with IC50 values of 165.29ug/ml and 273.771ug/ml, respectively. This was demonstrated by the fact that both of these extracts had values of 165.291ug/ml (Wan Abdul Wahab et al., 2012). In addition, the cytotoxic potential of the ethanolic extract of Quercus ilex has been investigated using the MTT test at doses of 250, 500, and 1000 mg/mL. According to the findings, the treatment affected cell viability in a dose- and time-dependent way (Ramos-Gomez et al., 2017). The results suggested that the therapy inhibited cell viability. The researchers Perez and colleagues (Perez and colleagues, 2017) investigated the cytotoxic activity of 17 triterpenoids isolated from the oak heartwood of Quercus robur against human prostate cancer (PC3) and human estrogen-dependent breast adenocarcinoma (MCF-7) cell lines as well as lymphocytes derived from human peripheral blood. The acquired data show that breast cancer cells (MCF7) were most impacted by triterpenoids, with roburgenic acid being the most active chemical (IC50 = 19.7 M). This was shown by the fact that triterpenoids were found to be the most effective treatment. In addition, the scientists observed the selectivity of some triterpenoids against lymphocytes, with an IC50 value of more than 200 M, whereas the same compounds were active against cancer cells.

Furthermore, the genotoxicity of Q. resinosa leaves extracts was evaluated on HeLa cells by the single-cell electrophoresis assay (comet assay). The results showed that the phytochemical compounds present in the extracts obtained from their decoctions increase the oxidative process as well as other damage to DNA in transformed human cells (Rocha-Gomez et al ., 2009) Yarani and colleagues (Yarani and colleagues, 2013) investigated the antiangiogenic activity of the Quercus infectoria acorn shell and found that it was effective. The treatments demonstrated that the extract exhibited antiangiogenic potential. This potential exerts its inhibitory impact primarily via the down-regulation of critical mediators such as VEGF and MMPs.

2.4 Anti-inflammatory and Neuro protective Activity: Inflammation is a typical pathological process that may be associated with several different illnesses. Numerous studies have been conducted on the anti-inflammatory properties possessed by the Quercus species. MorenoJimenez et al. (MorenoJimenez et al. 2015) examined the anti-inflammatory activity in HT-29 cells from the leaves infusion of Q. sideroxyla, Q. durifolia, and Q. eduardii. MorenoJimenez as al. published their findings in the journal MorenoJimenez et al., 2015. According to the findings, Q. sideroxyla modulated the expression of NF-Kb, which resulted in a reduction in the levels of the inflammatory indicators COX-2 and IL-8.

In addition, research conducted in vitro has shown that the triterpenes extracted from the acorns of the Quercus Serrata var. brevipetiolata species block the formation of nitric oxide (NO) and other proinflammatory cytokines (Huang et al., 2016). In addition, the efficacy of lupeol extracted from white oak leaves (Quercus resinosa, Q. grisea, Q. laeta, and Q. obtusata) to inhibit COX-1 and COX-2 enzymes was investigated using an in vitro colorimetric COX (ovine) inhibitor test. In this particular investigation, lupeol derived from Q. obtusata exhibited a unique ability to suppress COX-2 without having the same impact on COX1 (Sanchez-Burgos et al., 2013.)

2.5 Hepatoprotective: Xu et al. (J. Rocha-Guzman et al., 2018) reported that acorns (Quercus liaotungensis) and their galloyl triterpenes exhibited more substantial antiproliferative effects against t-HSC/Cl6 cells than the reference silymarin, suggesting its potential for being developed into an anti hepatic fibrosis food or medicine. This study was In the same year, Singh and Bisht (Medina-Torres et al., 2018) investigated in vivo hepatoprotective activity of the root extract of Q. oblongata D. DON. Their findings unequivocally demonstrated the beneficial effect of the ethanolic extract when administered at a dose of 300 mg/kg in comparison to the standard silymarin. In a similar vein, it was indicated that the administration of 300 mg/kg of the Q. dilatata extract demonstrated a protective effect against the hepatotoxicity generated by bisphenol A (BPA-). This was accomplished by returning hepatic inflammation to normal levels (Zhao et al., 2018). Toori et al., 2013 studied the hepatoprotective effects of acorn extracts on rats with carbon tetrachloride-induced liver injury. They found that the extracts prevented liver damage from occurring. According to their research findings, the aqueous extract at doses of 250 and 500 mg/kg exhibited outstanding hepatoprotective capability. This indicates that this solvent is a superior option since it has no adverse effects. Additionally, several researches have shown that Quercus spp. has hepatoprotective properties (Naim et al., 2017).

2.6 Antidiabetic Effect: Diabetes is a chronic condition distinguished by high blood glucose levels, which directly result from the body's inability to make insulin (Triplitt et al., 2015). Inhibiting carbohydrate-hydrolysing enzymes (such as alpha-amylase and beta-glucosidase) is one potential strategy for treating diabetes. This strategy involves delaying the absorption of glucose in the body (Yin et al., 2018)

Researchers Custodio et al. (2015) investigated the inhibitory impact of Quercus suber leaves and acorns on essential enzymes related to hyperglycemia. These enzymes include -amylase and -glucosidase. According to their research findings, the most outstanding results were achieved with the methanol and water extracts of the leaves, which had values of 89 and 97 per cent, respectively. This might most likely be related to the high phenolic content of the water and methanol extracts. Additionally, the -glucosidase inhibiting the activity of the extract from the bark of Q. coccifera was significantly higher than that of acarbose, which was found to have an IC50 value of 50.45 0.20 g/ml. This finding was based on the extract having an IC50 value of 3.26 0.08 g/mL. (Sariet al., 2019) In a separate piece of research, triterpenoids extracted from the nuts of the Quercus liaotungensis tree were investigated for their ability to inhibit the activities of three different enzymes: -glucosidase, -amylase, and protein-tyrosine phosphatase 1B. According to the researchers' findings, all substances had significant inhibitory effects on PTP1B and -glucosidase; however, the authors did not notice any inhibition of -amylase (Xu et al., 2018). In addition, research has shown that the polyphenol fraction derived from acorn leaves (Quercus liaotungensis) inhibits the activities of both -glucosidase and PTP1B. (Xu et al., 2018). Similarly, Yin et al. (Yin et al., 2018) discovered that Mongolian oak cups could be a source of ellagic acid (EA), which exhibits critical inhibitory actions against beta-glucosidase beta-amylase, and the development of advanced glycation end products (AGEs). According to the findings of other researchers, the antidiabetic activity of the chloroform extract of Quercus dilatata was at its highest, inhibiting -amylase by 21.61 1.53 per cent when it was dosed at 200 g/ml (Ahmadi et al., 2017). In addition, the condensed tannin fractions that were extracted from the leaves of Quercus phillyraeoides exhibited powerful -glucosidase inhibitory activities, with IC50 values that ranged from 2.60 to 3.14 g/ml, respectively (Indrianingsih et al., 2016) In addition, Lin et al. (Lin et al., 2018) determined that the decreased digestibility of the acorn of Quercus fabrei Hence is caused by hydrolysable tannins in the acorn. These findings provide even more credence to the notion that acorns might be used to create dishes with a low glycemic index. According to the results of one research (Ahmadi et al., 2019), prebiotics derived from acorns has the potential to improve HFD-induced abnormalities in glucose metabolism via the beneficial regulation of the gut-microbiome-brain axis. Using female C57BL/6 mice, Gamboa-Gomez et al. (Yadavet al., 2017) demonstrated the antihyperglycemic and antioxidant benefits of oak leaf infusions and fermented drinks derived from Quercus convallata and Q. arizonica. This research was conducted in both in vitro and in vivo settings. According to their findings, oak leaf infusions and fermented drinks displayed significant inhibition of -amylase (8–15 per cent and 5–9 per cent, respectively). -glucosidase was also inhibited by these products (98 per cent and 99 per cent, respectively).

In general, species of Quercus might be a possible alternative source of antidiabetic compounds. Still, these in vitro results need to be validated by more research in both in vivo and clinical settings.

2.7 Skin Disorder: Melanin is the primary pigment that determines hair and skin colour. It is essential in warding off the potentially damaging effects of ultraviolet (UV) radiation on the skin. On the other hand, a high concentration of melanin may cause several skin conditions supported by evidence from complementary and alternative medicine. Alternative Medicine 15 dermatological conditions, including skin hyper pigmentation and cosmetic issues (Rocha-Guzman et al., 2003). Tyrosinase is an essential enzyme in the process of making melanin. According to research by Carrico et al. 2018, it concluded that it inhibiting this enzyme reduces both the generation and deposition of melanin.

The extract obtained from the leaves of Quercus species was shown to be efficient in preventing photo-induced oxidative stress in the skin by scavenging various ROS and RNS (Almeida et al., 2008). In addition, Koseki et al. (Koseki et al. 2015) demonstrated that an extract of Quercus acutissima Cortex decreased androgen-related pathogenesis of acne, testosterone conversion, and sebum generation, in part by inhibiting 5'-reductase. This research was published in the journal Koseki et al. As a direct result of this, one can conclude that the Quercus species has the potential to be an essential component of the cosmetic product.

3. Conclusion: For a long time, Quercus species have been used as a traditional medicine in various countries and tribes. The bark, fruit, and leaves of the species from the genus were reported to possess a broad spectrum of biological effects, such as antioxidant, antidiabetic, anticancer, anti-inflammatory, and antibacterial. The current phytochemical studies of the species from the genus Quercus showed that phenolic acids (particularly gallic and ellagic acids and their derivatives), flavonoids (particularly flavan-3-ol), and tannins are somehow ubiquitous in all Quercus species. From these researches, phenolic compounds, triterpenoids, and flavonoids have a positive effect on anti-inflammatory, antidiabetic, and anticancer actions which can be considered as promising candidates for the development of novel pharmaceutical agents. For this, additional research on other Quercus species need much attention from biochemists for studying their detailed chemical profile and health effect, and also more studies are required to evaluate the safety, side effect, and efficacy of extracts.

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