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Phytochemistry and biological activities of the genus *Rubus*

Rubus cinsinin fitokimyası ve biyolojik aktiviteleri

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ABSTRACT

The genus *Rubus*, a member of the Rosaceae family, includes important species with both food and medicinal uses. With an emphasis on the anti-inflammatory, anti-cancer, antioxidant, and antibacterial properties of the main chemicals present in *Rubus* species, this review aims to synthesize the results of recent studies in order to better understand the biological activity and chemical composition of these species and their value as natural bioactive resources. This work also seeks to identify future directions for research that could enhance the clinical applications of *Rubus*-based bioactive compounds. For this purpose, NCBI, MDPI, ScienceDirect, Google Scholar, MEDLINE and Springer Nature Link databases were searched for recent articles on phytochemical and biological activity studies on *Rubus* species. The results showed that *Rubus* species are rich in compounds belonging to different chemical groups (phenolic acids, tannins, flavonoids, anthocyanins, etc.) and extracts and/or secondary metabolites of these species have important biological activities such as antioxidant, antimicrobial, anti-inflammatory, and anticancer effects.

Keywords: *Rubus* species, phytochemistry, biological activity

ÖZET

Rosaceae ailesinin bir üyesi olan *Rubus* cinsi, hem gıda hem de tıbbi kullanımları olan önemli türleri içerir. Bu derleme, *Rubus* türlerinde bulunan ana kimyasalların anti-inflamatuar, anti-kanser, antioksidan ve antibakteriyel özelliklerine vurgu yaparak, bu türlerin biyolojik aktivitesini, kimyasal bileşimini ve doğal biyoaktif kaynaklar olarak değerlerini daha iyi anlamak için son çalışmaların sonuçlarını analiz etmeyi amaçlamaktadır. Bu çalışma ayrıca *Rubus* bazlı biyoaktif bileşiklerin klinik uygulamalarını geliştirebilecek araştırmalar için bir rehber olma niteliğini amaçlamaktadır. Bu amaçla NCBI, MDPI, ScienceDirect, Google Scholar, MEDLINE ve Springer Nature Link veri tabanlarında *Rubus* türleri üzerinde yapılan fitokimyasal ve biyolojik aktivite çalışmalarını içeren güncel makaleler taranmıştır. Sonuçlar, *Rubus* türlerinin farklı kimyasal gruplara ait bileşikler (fenolik asitler, tanenler, flavonoidler, antosiyaninler, vb.) açısından zengin olduğunu ve bu türlerin ekstraktlarının ve/veya sekonder metabolitlerinin antioksidan, antimikrobiyal, anti-inflamatuar ve antikanser etkiler gibi önemli biyolojik aktivitelere sahip olduğunu göstermiştir.

Anahtar kelimeler: *Rubus* türleri, fitokimya, biyolojik aktivite

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Introduction

Plants not only form the basis of many medicines used in the treatment of various diseases, but have also found their place in many fields from textile production to food and cosmetics (Bhatt et al., 2023). Through the experiences recorded from past generations to the present, plants have gained significant importance in our lives due to their therapeutic effects.

One of the existing plant species, *Rubus* species traditionally used worldwide for their food and medicinal properties. *Rubus* species belong to the Rosaceae family, with approximately 1,500 species worldwide. In Türkiye, 16 species grow naturally (Güner et al., 2012). The common ones are *Rubus idaeus, Rubus sanctus* and *Rubus saxatilis*. *Rubus* species are commonly known as 'blackberry, raspberry, wild grape'. Plants of this genus can spread from sea level to an altitude of 4500 meters (Bhuyan & Dutta, 2021).

Some of the plants belonging to this genus have woody stems with thorns, similar to roses. The leaves are mostly palmate or pedate compound, sometimes pinnate. The leaves are compound, consisting of 3 to 5 leaflets, with the central leaflet being the largest; leaf edges range from serrated to irregularly toothed. Small flowers, measuring 0.5-1.5 cm and varying in color from white to pink, begin to emerge in the second year after planting. The stipules are mostly narrow and they may be directly attached to the petiole. Most of the plants in this genus are perennial and they are shrubby plants. Except for *Rubus chamaemorus*, the majority of species are hermaphrodites, meaning that both male and female reproductive parts are present in the same flower. The color of the fruit varies from white to black. Fruits of many of the species in this genus are edible. In many countries, the fruit is primarily grown for fresh consumption. Processed *Rubus* fruit, on the other hand, is widely utilized in the food and beverage sectors to create products such as wine, beer, soft drinks, jam (Davis & Meikle, 1972).

Rubus species are adapted to very extreme conditions such as cold/hot climate conditions, and high altitude etc. (Wairegi et al., 2024). The phytochemicals found in plants of the *Rubus* genus, such as tannins, flavonoids, phenolic acids, terpenoids, anthocyanins, lignans and vitamins make this genus an important and ideal subject for scientific research. Numerous cultures, despite lacking awareness of the specific chemical compounds, have recognized the medicinal qualities of *Rubus* and utilized them in various applications owing to their significant nutritional and medicinal benefits.

Rubus species have been commonly utilized either on their own or as part of traditional Chinese and Indian medicine (Hummer, 2010). In Indian medicine, leaves and barks of *Rubus* species are used for its astringent and diuretic properties (Hummer, 2010). In traditional Chinese medicine, *Rubus* is utilized to strengthen and stabilize the kidneys, helping to conserve vital energy and treat liver and kidney deficiencies (Hummer, 2010).

It has been applied to enhance vision, reduce lower back pain, stop frequent urination or treat blurred vision, and prevent cancers of the uterus, cervix, and colon (Hummer, 2010). In ancient Greek, Hippocrates recommended applying stems and leaves of blackberries steeped in white wine as an astringent remedy to heal wounds and facilitate childbirth (Hummer, 2010).

The aim of this review is to compile recent phytochemical and biological activity studies on *Rubus* species by searching NCBI (National Center for Biotechnology Information), MDPI (Multidisciplinary Digital Publishing Institute), ScienceDirect, Google Scholar, MEDLINE and Springer Nature Link databases and to reveal the phytochemical richness and medicinal importance of the species belonging to this genus.

1. Phytochemistry of *Rubus* species

1.1. Anthocyanins

Anthocyanins are phenolic compounds responsible for the coloration in many plants, flowers, and fruits. These compounds are also highly valued for their pharmacological properties. Different anthocyanins such as cyanidin pentoside, cyanidin-3-*O*-glucoside and cyanidin-*O*-hexoside were found by chromatographic examination of *Rubus fruticosus* (Vega et al., 2021). By using chromatografhic techniques, the anthocyanin profile in methanol extracts from the fruits of hybrids (*R. idaeus / R. occidentalis*) and five cultivars *of R. occidentalis* was determined. Research findings indicated that *Rubus* spp. (Shuofeng) has a high anthocyanin content and identified cyanidin and pelargonidin as the primary anthocyanin components in this plant (Zhao et al., 2023). In a study using edible berries including *R. fruticosus*, *R. palmatus*, *Rubus* x *medius*, *R. trifidus*, *R. hirsutus*, *R. idaeus*, *R. microphyllus*, anthocyanin contents of berries were analyzed by using quantitative NMR spectroscopy. Among these berries, *R. hirsutus* had the highest total anthocyanin concentration, according to an NMR spectroscopy examination. The two main anthocyanins found are cyanidin-3-glucoside and pelargonidin-3-glucoside (Kumazawa et al., 2024). The anthocyanin content in *Rubus coreanus* known as Korean black raspberries was measured quantitatively through liquid chromatography.

According to the research findings, cyanidin-3-*O*-rutinoside, phelagonidin-3-*O*-glucoside and cyanidin-3-*O*-glucoside are the primary anthocyanins present in *R. coreanus* (Kim et al., 2024). The Chinese raspberry, or *Rubus chingii*, is a plant that grows widely throughout Asia, including China, Japan and Korea. The primary anthocyanins in *R. chingii* consist mainly of cyanidins, including glucosides, sophorosides, rutinosides, sambubiosides, and glucosylrutinosides (Hua et al., 2023). Cyanidin-3-rutinoside and cyanidin-3-glucoside are the two main anthocyanins found in *Rubus discolor*, also known as wild blackberry, according to an examination of its anthocyanin content (Kopjar et al., 2024).

1.2. Tannins

Tannins are widely dispersed, naturally occurring phenolic chemicals that have an astringent quality. They are commonly found in various plant parts and are primarily categorized into hydrolysable tannins, which break down in water, and condensed tannins which are generally more resistant to hydrolysis (Pizzi, 2021). Bolatkyzy's research showed that the major tannin compound in *Rubus vulgaris* is tannic acid (Bolatkyzy et al., 2024). The analysis of tannin content *of Rubus adenotrichos* was indicated that the major tannin compound in the plant is composed of ellagic acid (Schmidt-Durán et al., 2023). A chemical examination of the unripe fruits of *R. chingii* revealed the presence of four ellagitannins: pedunculagin, casuariin, casuarinin, and casuarictin (Li et al., 2019). Phytochemical analysis of leaves of *Rubus chamaemorus* was showed that 4-*O*-*α*-L-arabinofuranosylellagic acid and epicatechin (one of the components of the tannin) are the tannins isolated (Whaley et al., 2021). The primary constituents of the tannin content of *Rubus ellipticus*, also referred to as the yellow Himalayan raspberry, were determined to be ellagitannins, specifically lambertianin C and sanguiin H6 (Burlando et al., 2023). The presence of many tannin compounds was discovered by the phytochemical investigation of *Rubus ulmifolius*. The hydromethanolic extract of *R. ulmifolius* fruits sourced from Italy includes chlorogenic acid (one of the components of the tannin). On the other hand, the ethanolic extract of *R. ulmifolius* fruits collected from the same region contains hydrolyzable tannins, including compounds like pedunculagin and geranin (Candela et al., 2021).

1.3. Terpenoids

Terpenoids are found in large quantities in the kingdom of plants and have a number of uses. Phytochemical analysis of leaves of *R. suavissimus* and *R. chingii* Hu was indicated that rubusoside which is diterpenoid glycoside found in the plants. Rubusoside is used as bioactive sweetener (He et al., 2023; Liu et al., 2024). One of *R. chingii*'s distinctive diterpenes is goshonoside. While goshonoside G is found solely in fruits, goshonoside F1, F2, F3, F4, and F5 are only found in leaves (He et al., 2023; Z. Liu et al., 2023). A study using a steam distillation extract of *R. idaeus* leaves revealed that the sesquiterpene β-caryophyllene and β-linalool, geraniol, 1,8-cineole and α-citral found terpenoids in the plant (De Santis et al., 2022). Linalool, α-terpineol, and geraniol are the main monoterpenes found in *Rubus rosifolius* essential oil profiles, whereas δ-cadinene has been determined as a sesquiterpene (Rambaran & Ginigini, 2020). In a research on anti-*toxoplasma* activity and chemical compositions of aquatic extract of *Rubus idaeus* L., m-cymene and carvone were identified as monoterpenes whereas anethole has been identified as sesquiterpenes (Mohammad Rahimi et al., 2020).

1.4. Phenolic acids and flavonoids

The plant tissues of *Rubus* species are abundant in phenolic compounds, which contain an aromatic structure with one or more hydroxyl groups that can be free or substituted. A study analyzing *R. fruticosus* L.'s cultivars indicated that kaempferol-3-*O*-glucoside, myricetin, ellagic acid, catechin, chlorogenic acid, *p*-coumaric acid, quercetin-3-*O*-rutinoside, kaempferol, quercetin-3-*O*-glucoside, and hydroxybenzoic acids detected in these cultivars (Čechovičienė et al., 2024). HPLC analysis of *R. ellipticus* indicated that kaempferol was one of the main compounds was identified (Muniyandi et al., 2019). Studies on the aerial parts of *Rubus niveus* indicated that gallic acid, quercetin and rutin are major compounds were detected (Pancholi & Rana, 2020). In a study of chemical composition of *Rubus ulmifolius* Schott indicated that gallic acid was the major phenolic acid identified. Also, the flavonoids with the highest quantities were quercetin and isoquercitrin (Schulz et al., 2019). Analysis of chemical composition identification of *Rubus glaucus* Benth examined that β-sitosterol and campesterol are the phytosterols existing in the extract prepared from fruits of *R. glaucus* Benth (Álvarez & Hurtado, 2024). Study analyzing of chemical composition of *Rubus caesius* indicated that rutin, hyperoside, naringenin 7-*O*-glucoside**,** tiliroside, astragalin and luteoloside are the flavonoid glycosides identified from the ethanolic extract prepared from *R. caesius* leaves (Hering et al., 2022).

2. Biological activities of *Rubus* species

2.1. Antidiabetic activity

One strategy to control blood glucose levels in diabetic patients is to inhibit enzymes that hydrolyze carbs, such as pancreatic α-amylase, which lowers the gastrointestinal system's absorption of glucose. In a study using the root parts of *R. sanctus*, potential α-amylase inhibitory activity was found in methanol, aqueous, acetone, and hexane fractions; IC_{50} values ranged from 20.12 to 50.9 μg/ml. The α-amylase inhibitor acarbose was used to compare this effect. The most active fraction; methanol, had an IC_{50} value of 20.12 μg/ml, while acarbose had an IC_{50} value of 6.56 μg/ml. These extracts were found to have nearly the same α-amylase inhibitory potential as acarbose (Jaradat et al., 2021a).

Also, with an approximate IC_{50} of 269.94 μg/mL, methanol extract from *R. ellipticus* leaves demonstrated a moderate level of α-amylase inhibition. The authors proposed that the antidiabetic properties of this species might result from its antioxidant properties (Subba et al., 2019).

In another study using a polyphenol-enriched extract of the fruits of *R. chingii* Hu claims that *R. chingii* may help mice with streptozotocin (STZ)-induced diabetes by reducing a number of diabetes symptoms including preventing the pancreas from being destroyed by streptozotocin, lowering hyperglycemia, reversing the atrophy of skeletal muscle and weight loss. Mice with STZ-induced diabetes were given aqueous extract of *Rubus chingii* fruits as 30 mg/kg every day for 18 days, and the anti-diabetic effects were evaluated. In comparison to mice given STZ alone, the anti-diabetic effects of *R. chingii* extract (30 mg/kg) given daily for 18 days to STZ-induced diabetic mice were assessed. These study findings imply that *R. chingii* may be an effective treatment for the symptoms of diabetes and hyperglycemia (Huo et al., 2021).

Furthermore, the antidiabetic qualities of fruit extracts from *R. fruticosus* L. at various stages of maturity were studied by Akyüz in 2022. Study findings demonstrated significant inhibitory effects on the enzyme α-amylase, which are essential for postprandial glucose management. Ethanol and water extracts of the immature, intermediate, and ripening phases of *R. fruticosus* L. showed antidiabetic benefits through different levels of α-amylase enzyme inhibition. Strong α-amylase inhibition was shown by water extracts, especially in the intermediate stage. Acarbose, an antidiabetic medication, was also used to compare the extracts' inhibitory properties. Based on fruit ripeness, the results indicate that *R. fruticosus* fruit extracts are effective natural antidiabetic agents that may be used to treat postprandial hyperglycemia (Akyüz, 2022).

Two varieties *Rubus rosifolius* were studied by Rambaran in order to investigate the hypoglycemic effect of fruit extracts made of *n*-hexane, ethyl acetate, and methanol. Fasting blood glucose levels were examined. 50 mg/kg of the extracts were administered orally to each animal, while 15 mg/kg of metformin served as a positive control. Analyses showed that, out of all the extracts, *n*-hexane extract had the strongest hypoglycemic activity. The oxidized triacylglycerol extracted from the *n*-hexane extract shown more activity and was more effective at reducing blood glucose levels than metformin and hypoglycemic medications. The oxidized triacylglycerol had a notable hypoglycemia effect over metformin for the first half hour (Rambaran et al., 2020).

2.2. Hepatoprotective activity

In a study conducted with ethanolic extract prepared from all parts of *R. sanctus* oral administration of 40% ethanol over 21 days followed by a single subcutaneous injection of CCl_4 caused significant hepatocellular damage in rats. A significant rise in the rats' serum enzyme activity (ALT, AST, ALP, and γ-GT) indicated this damage. These increased enzyme levels were decreased after the administration of ethanolic extract orally. The effects of *R. sanctus*'s ethanolic extract were comparable to those seen in the silymarin-treated group (Badr et al., 2009).

In another study done by VandenAkker (2020), the hepatoprotective effect of *R. idaeus* enriched diet on obese rats was observed. Eight weeks of an 8% *R. idaeus*-enriched diet were followed by measurements of plasma triglycerides (TGs), total cholesterol, High density lipoprotein cholesterol (HDL-C), Non-high density lipoprotein cholesterol (non-HDL-C), and hepatic triacylglycerol (TG) concentration. A diet supplemented with *R. idaeus* was found to diminish hepatic TG accumulation in obese rats while decreasing plasma TG, plasma cholesterol and HDL-C (VandenAkker et al., 2021).

2.3. Antimicrobial activity

R. idaeus leaves extracts were tested for antimicrobial activity against two strains of yeast (*Saccharomyces cerevisiae* and *Candida albicans*) and four Gram-negative (*Enterobacter aerogenes, Escherichia coli*, *Salmonella typhimurium* and *Pseudomonas aeruginosa*) as well as four Gram-positive (*Enterococcus faecali*, *Staphylococcus aureus*, *Listeria monocytogenes* and *Bacillus subtilis*) bacteria. Gram-positive bacteria were effectively inhibited by the extracts, as evidenced by inhibition zones ranging from 9.0 to 21.0 mm. However, they did not demonstrate any antibacterial action against Gram-negative bacteria, with the exception of *S. typhimurium,* which had inhibition zones between 9.0 and 18.3 mm. Notably, *E. coli* and *E. aerogenes* showed resistance to the extracts. Furthermore, there was no biological activity of raspberry plant components against *S. cerevisiae, E. aerogenes*, *E. coli* and *C. albicans* (Ispiryan et al., 2024).

In addition, ethanolic extract from *R. fruticosus* L. fruits was used against both Gram-negative (*E. coli, P. aeruginosa, Vibrio harveyi,* and *Proteus mirabilis*) and Gram-positive (*S. aureus, B. subtilis*, *Enterococcus hirae*, and *Enterococcus faecalis*) bacteria. The antibacterial activity assessment was carried out using a well- diffusion assay. Every extract that was tested shown efficacy against the bacterial species that were examined in this investigation. With inhibition zones measuring 8.53 mm and 9.85 mm, respectively, *S. aureus* and *E. coli* were the Gram-positive and Gram-negative bacteria that reacted most favorably to these treatments (Salah-Eldin et al., 2024).

Furthermore, antibacterial activity against *S. aureus* and *E. coli* was tested in aqueous and methanol extracts of the leaves, flowers, fruit, and stem of *Rubus ellipticus* known as Himalayan yellow Raspberry. The antibacterial activity of plant extracts were evaluated using the agar well diffusion method and the minimum inhibitory concentration (MIC) assay. *R. ellipticus* methanol fruit and leaf extracts demonstrated antibacterial activity against *S. aureus* with 19 mm and 7 mm zones of inhibition, respectively. Effective antibacterial activity against *S. aureus* was demonstrated by *R. ellipticus* methanol leaf and fruit extracts, with MIC values of 0.203 mg/ml and 0.813 mg/ml, respectively (Das et al., 2021).

The antibacterial properties of methanolic and aqueous extracts of leaves and stems as well as juice of *Rubus canescens* DC. were investigated against a range of Gram-positive and Gram-negative bacteria using the disc-diffusion method. Gram-positive bacteria *Streptococcus pneumonia*e and Methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacteria *E. coli* and *Klebsiella pneumoniae*, were the bacterial isolates that were used. *K. pneumoniae* and *S. pneumoniae* were not affected by fruit juice, leaf and stem aqueous and methanolic extracts, or both. Fruit juice was the only substance that reduced *E. coli* growth, with an average inhibition zone of 18 mm. The antibacterial activity of *R. canescens* DC leaf aqueous extract against MRSA was found to have an average inhibition zone of 46 mm (Assafiri et al., 2020).

Ethanol, acetone, methanol, and aqueous extracts of the fruits of *Rubus discolor* were tested for their antibacterial properties against *Micrococcus flavus*, *E. coli, L. monocytogenes, P. aeruginosa,* and *S. typhimurium*. Ampicillin was the positive control for the assay. The minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of the extracts ranged from 1.2 to 5.0 mg/mL, whereas ampicillin showed values between 0.2 and 1.2 mg/mL. Gram-positive bacteria were more susceptible to the effects of all extracts than Gram-negative bacteria. The most susceptible Gram-positive and Gram-negative bacteria, respectively, to the ethanol extracts were *L. monocytogenes* and *S. typhimurium* (Veličković et al., 2021).

2.4. Antioxidant activity

Studies on the antioxidant activity of the Siberian raspberry, *Rubus matsumuranus* H. Lev. & Vaniot, were conducted. A methanol extract of *R. matsumuranus* leaves was prepared for the DPPH scavenging experiment. The scavenging ability of the *R. matsumuranus* methanol extract (1000 µg/mL) against DPPH was investigated using a microplate spectrophotometric test. The microplate spectrophotometric assay demonstrated excellent scavenging action with an IC_{50} value of 24.68 µg/mL (Kashchenko et al., 2021).

In a study conducted with extracts and fractions of *R. caesius* leaves, (water, 50% methanol, ethyl acetate, chloroform /diethyl ether, methanol and *n*-butanol) antioxidant capacity is analyzed by 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assays. Ethyl acetate fraction of *R. caesius* leaves exhibited the strongest antioxidative activity, while the water extract showed the lowest activity (Grochowski et al., 2019). In another study, the ferric reducing power (FRAP), metal chelating assay, and ABTS radical scavenging test were used *in vitro* models to evaluate the antioxidant property of an aqueous extract prepared from the aerial parts of *R. sanctus*. Trolox served as the control in the $ABTS^{\bullet+}$ radical scavenging activity assessment, and *R. sanctus* extract showed ABTS radical scavenging activity of 98.9%, which was comparable to Trolox's (99.9%). Ferrozine creates colored complexes with Fe^{2+} ions. However, the presence of an efficient chelating agent disrupts this complex formation, which lowers the complexes' red color intensity. EDTA was used as positive control (99.7 %). *R. sanctus* has cheating ability at 3 mg/mL with 90.1%. According to ferric reducing power assay (FRAP), reducing capacity of *R. sanctus* at 3 mg/mL was found 2.281 which is higher than ascorbic acid's reducing capacity. Ascorbic asid was used as control the reducing ability at 3 mg/mL was found 2.199 (Deliorman Orhan & Hoşbaş Coşkun, 2019).

Shoukat et al., focused on the the antioxidant activity of both *R. idaeus* and *R. strigosus* fruits by the help of two methods; free radical cleansing and ferric reducing antioxidant power methods. The antioxidant properties measured by the radical scavenging method and ferric reducing antioxidant power showed similar results. For both species examined, the free radical scavenging percentage in *R. idaeus* ranged from 55.2 mg/mL at the immature stage to 81.4 mg/mL at full maturity. In *R. strigosus*, this percentage ranged from 56.1 mg/mL at the immature stage to 89.2 mg/mL at full maturity. There was a significant difference in antioxidant activity across stages immature, semi-ripe, and fully mature in both species. However, in the mature stage, the free radical scavenging percentage did not significantly differ between the two species (Shoukat et al., 2022).

The antioxidant activity of *R. fruticosus* L. was analyzed by applying DPPH and FRAP assay. Ethanol, acetone, methanol and acetonitrile extracts were prepared. According to both the FRAP and DPPH techniques, the extract prepared with acetonitrile had the maximum antioxidant capacity. The DPPH radical is less effectively bound by components extracted with higher polarity solvents (e.g. ethanol polarity index: 0.654) than by those extracted with lower polarity solvents (e.g. acetonitrile polarity index: 0.460) (Albert et al., 2022).

Furthermore, the antioxidant potential of distilled water extracts from *Rubus apetalus* Poir. and *Rubus steudneri* Schweinf. leaves was investigated in rats with diabetes induced by alloxan. The animals were separated into groups as normal control, diabetic control, tested groups and diabetic animal receiving antidiabetic drug glibenclamide. Animals tested were feeded after intraperitoneally injection of alloxan monohydrate in saline. Animals received oral treatments oral administration of leaf extracts from *R. steudneri* Schweinf. and *R. apetalus* Poir. as 150 mg/kg and 300 mg/kg was administered to the animals. The animals' organs were dissected for study and blood samples were gathered. The livers of both normal and treated animals were examined for levels of glutathione (GSH), malondialdehyde (MDA), superoxide dismutase (SOD), total thiols, and catalase (CAT). *R. apetalus* and *R. steudneri* leaf extracts both enhanced the antioxidant activity with increased SOD, GSH, total thiols, and catalase findings (Hi, 2019).

2.5. Anti-inflammatory activity

A new pectin polysaccharide that was obtained from *R. chingii* Hu was tested for its anti-inflammatory properties in mice with colitis produced by dextran sulfate sodium (DSS). Following the administration of polysaccharides and anti-inflammatory medications, the findings of the DAI score showed that the test group receiving high-dose polysaccharide treatment was able to successfully reduce the symptoms of colitis. Inflammatory factors IL-6 and TNF-α in colon tissue was remarkably elevated. Inflammatory factors IL-6 and TNF-α are much lower in the high dosage polysaccharide treatment group than in the DSS-induced colitis mice group. According to the findings, polysaccharides can reduce intestinal inflammation by preventing inflammatory agents (Kong et al., 2022).

By identifying COX-2 inhibitory activity and anti-hyaluronidase activity, the anti-inflammatory properties of an aqueous extract made from the leaves of the *R. fruticosus* cultivars Chester, Loch Ness, Loch Tay, and Ruczaj were examined. One of pro-inflammatory compounds is hyaluronidases. The anti-hyaluronidase activity of each of the four cultivars of water extracts was assessed. The Ruczaj and Loch Tay varieties had the most activity with IC_{50} values of 129.30 and 127.36 μg/mL, respectively. The percentage of COX-2 inhibition of was similar for all tested variants. The best results are shown by the strongest COX-2 inhibition and the lowest IC_{50} (Paczkowska-Walendowska et al., 2021).

In an investigation carried out with leaves of *Rubus suavissimus* S. Lee, the inhibitory effect of ethanolic extract on H_2O_2-induced inflammation in retinal pigment epithelial cells was anayzed**.** Present study has demonstrated that H_2O_2 administration induces inflammation in ARPE-19 cells. ELISA was used to assess the secretion of TNF-α, IL-1β, and IL-6 in cell culture, showing that these inflammatory markers were significantly elevated in ARPE-19 cells. Treatment with RS extract reversed H_2O_2-induced cytokine expression, leading to a decrease in proinflammatory cytokine production (Liu et al., 2023).

In another study, the impact of reducing inflammation of aqueous extract prepared from fruits of *R. coreanus* on atopic dermatitis which is chronic inflammatory skin disease was examined using HaCaT cells. TNF-α (Tumor Necrosis Factor Alpha), IL-6 (Interleukin 6), and IL-1β (Interleukin 1β) are proinflammatory cytokines that help cause systemic inflammation. Expression levels of all genes were examined using real-time PCR. In TNF-α/IFN-γ-stimulated HaCaT cells, the mRNA expression levels of these cytokines markedly elevated. However, treatment of these stimulated cells with RCW led to a dose-dependent reduction in the mRNA expression of TNF-α, IL-6, and IL-1β.

These findings indicate that RCW effectively reduces inflammation (Pyeon et al., 2021).

In a study conducted with ethanolic extacts of mature and immature fruits of *R. occidentalis*, the extracts were used on pain management in an operated rat model. The rats received an intraperitoneal injection of several doses of ethanolic extracts of both mature an immature fruits of *R. occidentalis* two hours following the plantar incision. Rats' blood samples were taken after injection, and tests for TNF-α, IL-1β, and IL-6 were conducted. The study's findings showed that intraperitoneal administration of ethanolic extracts of *R. Occidentalis*'s immature fruits had a dose-dependent analgesic effect in the rat model. At 24 and 48 hours following surgery, ethanol extracts from *R. occidentalis* immature fruits dramatically decreased proinflammatory cytokine levels, and compared to mature *R. occidentalis* fruits, ethanolic extracts of immature fruits showed a greater anti-inflammatory activity (Choi et al., 2023).

2.6. Cytotoxic activity

In a cytotoxicity investigation with aqueous, hexane, methanol and acetone fractions prepared from the root of *R. sanctus*, the cytotoxicity evaluation was conducted on the Hep3B cell line. The impact of these extracts on Hep3B cells' cell cycle stages was investigated. The methanol fraction was identified as the most potent inhibitor due to its ability to extend the G2-M phase over time, thereby reducing the rate of cell proliferation. Furthermore, it was demonstrated that extracts from the roots of *R. sanctus* reduced the secretion of a important marker, α-fetoprotein, by decreasing the cell population in the G1 and S phases while inducing an extended duration of the G2-M phase. Hep3B cells treated with aqueous, methanol, acetone, and hexane fractions showed a drop in average levels of α-fetoprotein (AFP) from 1205 ng/ml to 355, 530.6, 237, and 268 ng/ml, respectively. The greatest notable suppression of α-fetoprotein secretion was observed in the acetone fraction (Jaradat et al., 2021b).

In another study, the MTT test was used to evaluate the cytotoxic effects on the MCF-7 cell line of methanolic extract and hexane, ethyl acetate, and methanol fractions prepared from *Rubus hyrcanus* roots and leaves. Over the course of 48 hours, the MCF-7 cell line was exposed to each sample at different concentrations. The ethyl acetate fractions from roots and leaves had the strongest cytotoxic effects on the MCF-7 cell line, with IC_{50} values of 247 and 227 μg/mL, respectively (Yousefbeyk et al., 2022).

The acetone extract of *Rubus fairholmianus* roots was tested on the human breast cancer cell line MCF-7 for cytotoxicity study. From this extract, two main components were identified: 1-(2-hydroxyphenyl)-4-methylpentan-1-one (C1), 2-[(3-methylbutoxy) carbonyl] benzoic acid (C2) (George & Abrahamse, 2019). MCF-7 cell viability was shown to decrease after treatment with chemicals C1 and C2. The impact of these substances on cell survival was assessed using the trypan blue viability test. Both C1 and C2 produced a dose-dependent reduction in cell viability, with IC_{50} values determined at 4.69 μg/mL for C1 and 8.36 μg/mL for C2. MCF-7 cells treated with a higher concentration of compound C1 showed a significant decrease in cell count, with cell viability of 21.75%, while those treated with a higher concentration of compound C2 showed cell viability of 48.25% (George & Abrahamse, 2019).

The conducted study with the methanolic seed extract of *Rubus idaeus* L., cytotoxic effects of methanol extracts from *R. idaeus* L. seeds on several human cancer cell lines were evaluated (Simonovic et al., 2021). According to the National Cancer Institute guideline, crude extracts with an IC_{50} value below 30 μg/mL are considered active (Mbaveng et al., 2019). At effective concentrations (IC_{50}<30 μg/mL), the methanol extract of *R. idaeus* L seeds was found to inhibit the growth of A-549 lung cancer cells (Simonovic et al., 2021).

The cytotoxic effects of methanol extracts from *R. idaeus* fruits were evaluated on the hormone-dependent ovarian cancer cell line CHO-K1 using the MTS assay. Methanol extracts were prepared using two different extraction techniques: soxhlet and microwave-assisted extraction, with their efficiencies in producing phytochemical extracts being compared. *R. idaeus* extract obtained through the soxhlet method showed cytotoxicity toward CHO-K1 cells at a concentration of 50 μg/mL. However, the extract produced via microwave-assisted extraction did not show cytotoxicity at 1000 μg/mL (Ryan Deweese et al., 2021).

Conclusions

This review has explored the findings related to the chemical composition and biological effects of *Rubus* species. In numerous studies, the bioactive components of *Rubus* species, including ellagitannins, phenolic acids, flavonoids and anthocyanins, have been demonstrated anti-inflammatory, anti-cancer, anti-microbial, and antioxidant properties. These compounds are the main contributors to the biological activities of *Rubus* species. The chemical diversity within *Rubus* species enhances their potential therapeutic effects and supports the pharmacological use of extracts obtained from these plants.

Better understanding of the structural and functional aspects of these bioactive compounds highlights the importance of *Rubus* species in promoting public health and suggests their promise in future drug discovery. Additionally, further researches on the bioavailability and biotransformation of these compounds is essential to increase their effectiveness and supporting their clinical applications.

Author contributions

Deniz Oylumlu, Ali Şen: Collection and compilation of data, writing of the manuscript. Ali Şen: Review and editing of the manuscript. Deniz Oylumlu, Ali Şen: Correction and analysis of chemical compounds. Deniz Oylumlu, Ali Şen: Designing, supervising and editing of the manuscript. Deniz Oylumlu, Ali Şen: All authors read and approved the final manuscript.

Declaration of interests

The authors declare that there is no conflict of interest.

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